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Prophylaxis of SARS-CoV-2 Viral Infection in Childhood

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ABSTRACT

A vast number of scientific studies has already been carried out about the novel coronavirus, yet most of the studies date back to pre-omicron period. The current evidence is unequivocally suggesting a mild disease course and excellent prognosis among the pediatric population. Despite high contagiousness, the currently dominant omicron variant is evidently causing milder symptoms than earlier variants of concern. Therefore, assessment of currently available prophylactic measures against coronavirus disease 2019 among pediatric population with their advantages and disadvantages according to the most recent evidence-based studies was carried out.

Omicron's rapid replication and oftentimes asymptomatic course has made early identification challenging, which is exacerbated by prioritization of risk groups in limited testing facilities. Prolonged social distancing with remote school policies looks to have serious adverse effects on physical and mental health and should not be applied during omicron-predominance. Hand hygiene is a cost-effective method to fight against wide range of microbes but its isolated effect against coronavirus disease 2019 is less clear. Face masks suitable for children give weak protection against infection, thus the role is limited to prevent transmission, making them suboptimal given the side effects and dubious adherence in younger children.

Effectiveness of vaccines against infection with omicron variant is weak but similarly to infection, they stimulate long-lasting cellular immunity that gives robust protection against severe form of the disease. However, the studies are showing increased post-vaccination risk of myocarditis in male adolescents, particularly after the second dose. While risks of complications from infection appear more serious than potential side effects of vaccinations in non-immune children, individualized pediatric vaccination schedules addressing child's sex, immune status, and presence of comorbidities are required. Owing to increasing prevalence of cellular immunity in Western countries, future prophylaxis in childhood should be centered around vaccinations at this stage of the pandemic.

Keywords: children, COVID-19, myocarditis, omicron, prophylaxis, vaccination.

INTRODUCTION

Following Chinese authorities' initial report of the novel coronavirus to the World Health Organization (WHO) on December 31, 2019 and subsequent outbreak of epidemic on all continents, a global pandemic was declared on March 11, 2020. (1). As of May 6, 2022, a total of 513,955,910 confirmed cases of COVID-19 and 6,249,700 deaths were confirmed globally. (2) The exact number of positive cases among children and adolescents worldwide is not established as testing is generally prioritized for adults and those with severe illness. In the United States (US), Centers for Disease Control and Prevention (CDC) reported 72,682,838 confirmed cases on May 5, 2022, of which 16.7% were from individuals aged less than 18 years. (3) This is depicted in figure 1; the pediatric age group appears

largely underrepresented in confirmed COVID-19 cases. Moreover, the data from UNICEF reveals that merely 0.4% of COVID-19 deaths globally are attributable to the children and adolescents under 20 years of age (4), while in the US the mortality is less than 0.1% in children under 18 years of age. (3)

Age Group	Percent of cases	Count of cases	Percent of US population
0-4 Years	3.3	2 349 055	6
5-11 Years	6.7	4 839 319	8.7
12-15 Years	4.8	3 422 361	5.1
16-17 Years	2.8	2 009 504	2.5

Figure 1. COVID-19 cases by age group in United States as of May 5, 2022.
Note. Attached from 'Demographic Trends of COVID-19 cases and deaths in the US reported to CDC.' (https://covid.cdc.gov/covid-data-tracker/#demographics)

Since early stages of the pandemic, there have been reports of milder symptoms and more favorable prognosis among children with COVID-19 compared to adult population (5). At present, the most commonly expressed COVID-19 symptoms among children include fever, cough, stuffy and runny nose, headache, diarrhea, nausea, vomiting and sore throat. (6) Also seizures and shortness of breath have been observed among unvaccinated children (7) although more than 30% of pediatric cases might remain asymptomatic. (8) Estimates for COVID-19-associated hospitalization vary between countries and pediatric age groups. CDC reported a peak weekly hospitalization rate of 7.1 per 100,000 children in January 2022, with higher risk for getting hospitalized observed among 0–4 years old children. (9) Based on Danish data collected before the surge of currently dominant omicron variant, the risk for hospitalization among people younger than 18 years was 0.49% whereas risk for ICU admission was 0.01%. (10) Management of COVID-19 in children primarily relies on symptomatic care although monoclonal antibodies combined with corticosteroids and biological agents may be used in more severe cases. For diagnosis, nucleic acid amplification through polymerase chain reaction (PCR) remains a gold standard with commercial alternatives available as discussed later. (11)

Zimmerman et al. suggest several theories and mechanisms that might contribute to the differences in severity and mortality of COVID-19 between adults and children. Most notably, children have more robust innate immune response with increased amount of natural killer cells. (12) Earlier coronavirus infections in adults may also result in immunological memory that hampers, rather than enhances, the antigen-specific immune response to a neoantigen such as SARS-CoV-2. (13) Children also have higher reserve of lymphocytes and absolute numbers of T and B cells – especially the large repertoire of naïve T cells has been hypothesized to contribute to a strong T cell-mediated immune response. That said, a retrospective study using medical records from hospital system in New York City showed adults mounting a stronger T cell response to the viral spike protein compared to pediatric patients, yet the children had shorter hospitalization, required less mechanical ventilation, and faced lower mortality

compared to adults. (14) Hence, it currently appears that innate immune responses in the upper respiratory tract may be more effective in children but prior and more frequent common coronavirus infections in adults result in immunological memory, that forms a dysregulated, antigen-specific immune response to a novel microbe such as SARS-CoV-2. However, a full understanding of differences in immunity is still evolving.

The ongoing pandemic has also provided a platform for several mutations in SARS-CoV-2. When mutations change the characteristics of the virus permanently and become part of the viral genome, the result is a variant. A group of variants with similar genetic changes may be designated by public health organizations as a variant of concern (VOC). (15) WHO designates five VOCs, of which mostly omicron is currently circulating. (16) Figure 2 outlines time and place of the earliest documented samples and main characteristics of each of the five VOCs.

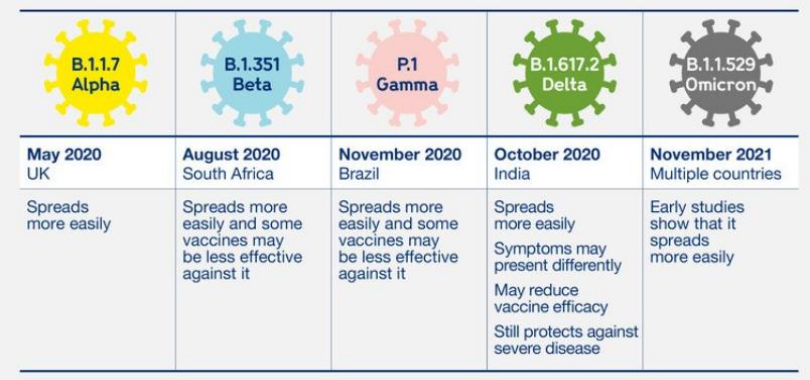

Figure 2. Variants of Concern.
Note: Attached from Wellcome, a global charitable foundation. (https://wellcome.org/news/what-variant-expert-explains)

Of the variants of concern, delta overtook the global dominance from alpha by July 2021, mainly due to its higher transmissibility (17). The first sequenced omicron case was reported from Botswana on November 11, 2021, and a few days later another sequenced case was detected in Hong Kong in a traveler from South Africa. South Africa's daily COVID-19 incidence grew rapidly from 280 to 800 cases per day in the following week, suggesting an considerably higher infectivity than that of delta. (18) The researchers in Hong Kong later found that omicron infects and multiplies 70 times faster than earlier VOCs in human bronchus, allowing faster transmission between humans than previous variants. In contrast, the replication time was more than 10 times lower in the human lung tissue than the original SARS-CoV-2 variant. (19) The researchers assumed this to result in lower severity of disease and later evidence is suggesting omicron to preferably infect and replicate in the upper respiratory tract, as opposed to delta and other VOCs which prefer the lower respiratory tract. (20) Indeed, recent studies with adult population show that infection with omicron yields only 1.9% probability for hospitalization while disease course is also shorter with a median duration of 5.0 days. (21)

The biophysical base for the rapid transmission is omicron's higher binding affinity to ACE-receptors found in human mucosa, thought to result from increased quantity and quality of interactions with omicron's spike protein and ACE-2 receptor. (22) The rapid replication rate made omicron to replace delta as the dominant variant in several countries by the end of January, 2022. (23) Moreover, omicron's structural characteristics contribute to its unique features. It has up to 36 genetic mutations in the spike protein (24) while delta only has two. (25) The high number of mutations in the spike protein not only allows omicron to invade ACE-receptors more easily, but it also seems to facilitate escape from vaccine-induced humoral immunity since the currently approved COVID-19 vaccines are targeting virus's spike protein.

In summary, the latest evidence is suggesting lower incidence and mortality from COVID-19 among children and adolescents compared to adults with generally mild clinical presentation. Moreover, the globally dominant omicron variant is known to be more infectious than the previously dominant delta but is causing less severe clinical picture due to its preference to replicate in the upper respiratory tract instead of lungs. The highly mutated spike protein of omicron may also cause current spike protein targeted vaccinations to provide impaired protection against breakthrough infections. In the following chapters, a narrative literature review is provided to assess the currently available alternatives for prophylaxis against COVID-19 in childhood in the setting of omicron-predominant environment, followed by discussion of advantages and disadvantages attributable to each prophylactic measures.

LITERATURE SELECTION STRATEGY

A search of the literature on Google Scholar and PubMed websites was carried out between February 20 and May 11, 2022, by using specific keywords found generally in headings of this review. A review of relevant peer-reviewed studies and pre-prints was conducted with preference given to novel articles published in 2022 that specifically dealt with the omicron variant. Hierarchy of evidence was generally honored when choosing the relevant articles for references although the number of systematic reviews and meta-analyses published in 2022 was limited. For general information and recommendations, information available at CDC and WHO was prioritized. The use of data lacking a primary data collection, such as personal viewpoints, other narrative reviews, comments, correspondences, was generally avoided. The search was limited to only include source material available in English language. It is noteworthy that this study does not represent a systematic review of all the scientific literature on prophylaxis of SARS-CoV-2 viral infection in childhood. Thus, data search methods and even conclusions to some extent may be subject to unintentional bias.

PROPHYLACTIC INFECTION CONTROL MEASURES

Different measures to prevent COVID-19 infection among pediatric population are classified here according to the epidemiologic triad, a traditional model explaining how disease results from the interaction between agent and susceptible host in an environment that supports transmission of the agent to the host. (26) This is illustrated in figure 3. Prophylactic medications including monoclonal antibodies for pre- and post-exposure prophylaxis are not in the scope of this review.

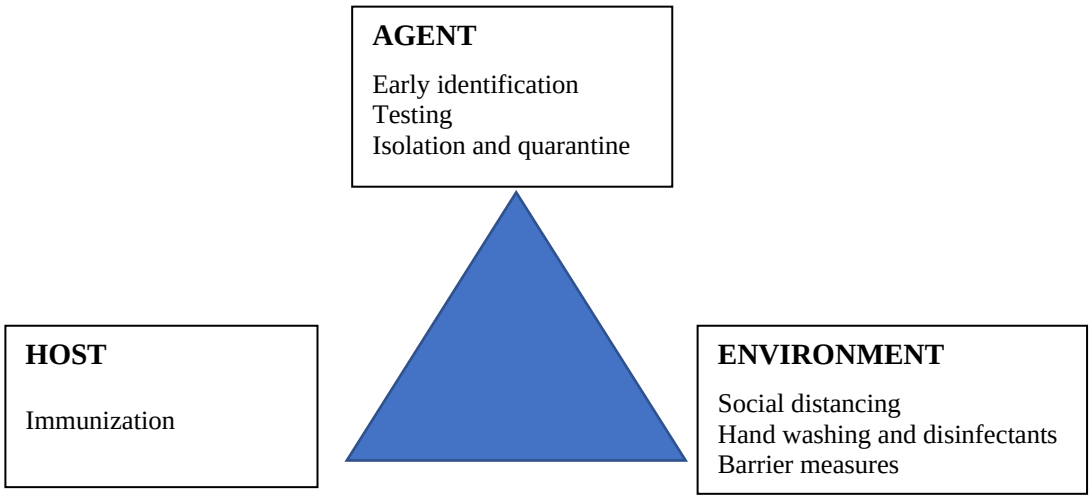

Figure 3. Causation of COVID-19 according to the epidemiologic triad.
Note: Adapted from CDC: Lesson 1: Introduction to Epidemiology.
(https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section8.html)

EARLY IDENTIFICATION

One aspect in general prevention measures is to target for early identification of potential SARS-CoV-2 carriers. Nevertheless, due to mild and oftentimes asymptomatic clinical picture among children with COVID-19 the early identification may be challenging due to difficulties in proactive identification, testing, and self-isolation of those exposed to or showing typical symptoms of SARS-CoV-2. This is particularly problematic since asymptomatic but infected people have spread the virus already from the start of the pandemic. (27) Based on the latest evidence, the average asymptomatic incubation period from the exposure to the onset of symptoms is between 3.6 and 3.7 days. (28) (29) that is much shorter than incubation period of 6.3 days for the original SARS-CoV-2 variant. (28)

Early identification of COVID-19 during omicron predominance requires parents to be aware of the most typical symptoms of omicron variant described earlier, ideally followed by prompt testing and isolation from social contacts. Whether a confirmed exposure should result in self-quarantine automatically remains debatable due to high contagiousness of the omicron variant, and limited resources available for tracing activities, but a known exposure should make the adolescents and parents of the younger children to look up for typical COVID-19 symptoms. Due to rapidly spreading omicron

variant, WHO urges to weigh any interruption in tracing policy against healthcare capacity, population immunity against omicron and socioeconomic priorities. (30) Overall, amid omicron dominance, the early identification and timely tracing have become troublesome due to higher incidence rates and less pathognomonic clinical picture.

TESTING

Testing bridges the gap between early identification of potential carriers and subsequent isolation. Nasal swab is generally preferred over oropharyngeal swab as it yields a significantly higher viral load, resulting in more robust sensitivity. (31) With the introduction of COVID-19 home test kits for commercial use that detect pieces of proteins that make up the SARS-CoV-2 virus instead of genetic material the conventional PCR tests do, this approach could be adopted to children attending school and kindergartens which may be considered as high-risk environments for virus transmission, owing to the limited opportunities for proper social distancing. However, while the home testing increases the number of tests available, and frees up healthcare industry's resources elsewhere, its sensitivity is much lower than that of a PCR test, allowing false negative cases to spread the virus more frequently. Obtaining a quality specimen and the performance of the test itself may also be problematic with home tests. (32)

Despite the mild clinical picture and difficulties in tracing during omicron predominance, influential organizations such as American Academy of Pediatrics (AAP) still recommend testing all children who either show typical symptoms of COVID-19 and those with a close contact to confirmed or probable SARS-CoV-2 infection. Asymptomatic children who have had laboratory-confirmed SARS-CoV-2 infection in the past three months may still be exempt from testing after exposure. (33) On the other hand, WHO recognizes that in situations where SARS-CoV-2 incidence is very high, it may not be possible to identify, monitor and quarantine all contacts. The organization recommends prioritizing health and care workers who are at highest risk of spreading the virus to vulnerable people, and contacts at highest risk for development of severe disease, such as immunocompromised individuals and elderly. (30) Consequently, while testing potential pediatric carriers is beneficial *per se*, other groups should be prioritized if the testing capacity is limited.

ISOLATION AND QUARANTINE

Isolation means that a person with an infectious disease is isolated from those who are healthy to avoid possible further transmissions. The term is sometimes interchangeably used with quarantine that more specifically refers to isolation of an asymptomatic person who have been in close contact with someone with confirmed infection. Its purpose serves to prevent the transmission of an infectious disease by keeping the exposed people apart from others. Quarantine may be either voluntary or mandatory. In

event of the latter, usually a communicable disease control physician orders the asymptomatic person to be quarantined. (34) (35)

The length of isolation and quarantine varies between countries and individual characteristics, such as vaccination status and recent travelling history, might also affect the required length of isolation and quarantine respectively. Amid the dominance of rapidly replicating and less severe omicron variant, some countries have opted for reducing the required length of isolation. For example, the CDC announced in December 2021 that it shortens the recommended isolation time from 10 days 5 days for COVID-19 positive individuals who have been fever-free for at least 24 hours before the end of the isolation. The policy change was motivated by findings that SARS-CoV-2 transmission occurs primarily in the first two days prior to onset of symptoms and 2–3 days after. For fully vaccinated, asymptomatic individuals exposed to COVID-19 quarantine is not required. (36) United Kingdom (UK) went even further by changing the mandatory isolation of COVID-19 positive individuals to recommendation to self-isolate from April 1, 2022 onwards. (37)

SOCIAL DISTANCING

Social or physical distancing is determined by the WHO as a distance of at least 1 meter from each other while avoiding spending time in crowded places or in groups. (38) A physical distance of at least 1 meter is also what UNICEF recommends for children. (39) The aim of social distancing is to stop chains of transmission and prevent new ones from appearing, based on the current etiopathogenetic understanding of COVID-19. WHO recognizes that the virus can spread both in small liquid particles that transmit through coughs, sneezes, speaks, sings, or breathes, and also in short-range aerosols when infectious particles that pass through the air are inhaled at short range. (40)

The current evidence supports the idea of lower transmission of betacoronaviruses when applying physical distancing of 1 meter or more compared with a distance of less than 1 meter. (41) People living in communities with the greatest social distancing opportunities face significantly lower risk of getting infected with COVID-19. (42) Moreover, social distancing along with lockdown strategies appears to effectively slow down the spreading of other infectious diseases as well and reduce the hospital admissions among children. (43)

However, strict application of social distancing is found to result in adverse mental health outcomes. (44) In addition, social and risky behavioral problems, such as substance abuse, suicide, relationship problems, academic issues, and absenteeism from work among children and adolescents may result. (45) Social distancing has also been shown to decrease children's physical activity and the decline appears greater among those participating in organized team sports. (46) Aside from distancing-related

disadvantages, it is debatable how effectively social distancing practices can be adopted in crowded establishments, such as schools and kindergartens, or how well younger children comply with enforced social distancing policies. During the omicron era, the role of social distancing in disease prevention is questionable.

HAND WASHING AND DISINFECTANTS

Good hand hygiene is a highly cost-effective public health measure and protects against a range of diseases other than COVID-19, such as diarrhea and pneumonia. (47) It has been estimated that hand hygiene has a 24% to 31% likelihood of decreasing the spread of a communicable disease. (48) Particularly the start of COVID-19 pandemic raised global awareness of hand hygiene and hand cleansing. Currently, CDC recommends washing hands with soap and water for at least 20 seconds or using a hand sanitizer with at least 60% alcohol to clean hands before and after touching the eyes, nose, mouth, face mask or any item or surface that may be frequently touched by other people. (49) Disinfectants should only be used only when soap and water are not readily available. On the other hand, alcohol-based hand sanitizers with moisturizers have less irritancy potential as opposed to soaps and synthetic detergents. (48)

The isolated effect of handwashing in prevention of COVID-19 is not extensively researched. Thus, while good hand hygiene has an established position in prevention of communicable diseases in general, its exact role in prophylaxis of SARS-CoV-2 remains less clear, since SARS-CoV-2 is also known to remain viable in the air for a minimum of 3 hours, making airborne transmission possible. (50) In fact, the viral load in exhalations of those infected with omicron variant may be ten-fold higher than with the original variant in 2020. (51) A disadvantage with very intensive handwashing is potential development of hand eczema among children although it is preventable to some extent with well-established prophylactic skin care, such as using emollient cream following handwashing. (52)

BARRIER MEASURES – FACE MASKS

A face mask is a product that covers the wearer's nose and mouth. Types of face masks include barrier face mask coverings and surgical face masks. Face masks are for use as source control by the general public and health care personnel, and are not personal protective equipment unlike respirators, such as N95s, which have not been tested for broad use in children. (53)

Face masks have been used for decades for prevention of viral infections especially for health cares but only the global spread of SARS-CoV-2 resulted in extensive efforts to study the effectiveness of face masks among the general population. Earlier in the pandemic it was commonly accepted that SARS-CoV-2 spreads primarily with contact routes and respiratory droplets with a diameter of 5–10 μm while

airborne transmission, referring specifically to microorganisms in droplet nuclei less than 5 μm, was a topic of more controversy. As discussed earlier, later evidence has shown SARS-CoV-2 to be viable in aerosols for hours, with the omicron-infected individuals releasing a copious amounts of viral aerosols compared to earlier VOCs which is also thought to support the higher transmissibility. While the data concerning face mask efficacy from the era of omicron-predominance remains scarce, a recently published systematic review using studies from pre-omicron period concluded that only N95 or equivalent respirators seem to give statistically significant protection against infection with coronaviruses while the efficacy of medical and surgical masks against coronavirus infections remains weak, highlighting the insufficient evidence on the effectiveness of medical or surgical masks in community settings. (54) However, the authors pointed out that medical and surgical masks, also suitable for the pediatric population, might be useful in preventing transmissions by capturing the virus in the droplets of an infected person.

Ahead of improving epidemiologic situation in Western countries towards the summer season, many countries have recently lifted face mask restrictions. For instance, until lately the CDC recommended children ages 2 years and older to wear a face mask in public indoor spaces but is currently guiding individuals of all ages to wear a face mask based on personal preference. (55) WHO continues to recommend children to wear face masks indoors, yet stresses that no child should be denied access to school or activities because of lack of a mask. (56)

A widespread face mask use may be associated with adverse psychological and developmental effects. An Italian study found that mask use negatively influenced the ability to infer facial expressions at any age. Also, capacity to read emotions from facial configurations became reduced, and the impact was pronounced in children aged between 3 and 5 years old. (57) A similar finding was made in the US in a joint school–university project for children aged 9 to 10 years who showed significant problems in reading the emotion disgust, frequently misperceived as sadness. (58) These findings complement earlier identified physical side effects of face mask use that include headaches, acne, nasal bridge, facial itching, rash, and discomfort related to increased facial temperatures. (59) The physical side effects appear slightly more common in N95 respirator users than those wearing a surgical face mask, which might explain lower adherence among N95 users. (60) Nevertheless, it is noteworthy that face mask use and impaired emotional perception among younger children is related to widespread face mask use among adult population, not pediatric population itself. The efficacy of face masks among pediatric population also requires more studies from omicron-predominant era.

IMMUNIZATION

On December 2, 2020, seven months after the start of clinical trials, UK became the first country in the Western world to allow the use of a COVID-19 vaccine. (61) Currently, European Medicines Agency's (EMA) has authorized five vaccines against COVID-19, developed by BioNTech and Pfizer, Moderna, AstraZeneca, Janssen Pharmaceutica NV, and Novavax respectively. (62) The approved COVID-19 vaccines may further be classified according to their mechanism of action – the common feature is that they all use a harmless version of a spikelike structure on the surface of the SARS-CoV-2, called an S protein. (63)

The first administered COVID-19 vaccine was based on messenger ribonucleic acid (mRNA) technology, becoming the first mRNA vaccine authorized for use against any disease in humans. (64) Currently, vaccines from Pfizer-BioNTech and Moderna are utilizing this technology. (63) In short, genetically engineered mRNA with information on how to encode for SARS-CoV-2 specific S protein is formed in laboratory settings and injected to human bodies, causing the cell to produce for S protein which results in activation of immune system and subsequent production of antibodies. The other types of COVID-19 vaccines are vector vaccines and protein subunit vaccines. In a vector vaccine, an inactivated virus, instead of mRNA is inoculated with extraction of genetic material from SARS-CoV-2 spike protein. (63) This technology is utilized in vaccines from Janssen and AstraZeneca. In protein subunit vaccines, spike protein from SARS-CoV-2 is cultivated into yeast, bacteria, or animal cells that then produce S proteins, which are then purified and combined with substances, forming a protein subunit to be injected. The method aims to ensure that the injectable protein subunits include only the parts of the virus that best stimulate immune system. Novavax is currently the only vaccine using protein subunit technology.

In addition to elicitation of antibody production, effectiveness of vaccines is also based on activation of cellular immunity. The S protein presentation on the cell surface activate various immune cells, including T-helper (Th) cells that begin to produce cytokines which then stimulate Th cells to differentiate to memory T cells and B cells into plasma cells. These plasma cells are responsible for antibody production. (65) Also memory B cells are generated during primary responses to T-dependent vaccines. When re-exposed to antigen, they can differentiate into antibody producing plasma cells, resulting in rapid increase to higher titers of antibodies that have a higher affinity for antigen than antibodies generated during primary responses. (66)

The neutralizing antibody titers decrease substantially during the first 6 months, waning the humoral response, although this can temporarily be overcome with administration of booster shots. However, durability of memory T and B cells responsible for the cellular response is longer. The current evidence

suggests that number of SARS-CoV-2–specific memory B cells continue to increase up to 6 months after vaccination. (67) The exact lifespan of SARS-CoV-2 specific immune memory cells is still under investigation but the most recent studies report generation of memory responses up to 9–12 months after infection (68) (69). Prior infection with other VOCs and vaccination with Pfizer-BionTech also appear to elicit robust T cell immune responses against the omicron variant through cross-reactivity. (69) (70). The frequency of variant cross-binding memory B cells seems to be higher after vaccination than after mild SARS-CoV-2 infection. (67) The clinical relevance of activation of immune cell memory is the decreased risk of developing a severe disease and subsequent hospitalization.

The range of appropriate and safe vaccines for pediatric population is limited to mRNA technology. In Europe, Pfizer-BioNTech's vaccine, marketed as *Comirnaty,* and Moderna's vaccine, marketed as *Spikevax,* are authorized for use in children older than 5 and 6 years respectively with reduced doses for children under 12 years of age. In the US, Comirnaty currently remains the only option for the pediatric population. Pfizer-BioNtech's trial in children 6 months through 4 years of age has been ongoing for several months and Moderna also filed for authorization of Spikevax for children under 6 years of age in April 2022 (71) (72) with authorizations in the US expected in June 2022. (73) Both mRNA vaccines produce memory T cells and B cells that are comparatively stable over 6 months. (74)

In general population, mRNA vaccines have a reputation of being effective against severe COVID-19 disease while providing lower protection against infection with omicron variant. According to a recently published case-control study, the effectiveness of Comirnaty within pediatric population after two doses was 40% against hospitalization for COVID-19, 79% against critical COVID-19, while yielding only 20% protection against noncritical COVID-19 among 12–18 years old children. For 5–11 years old children two doses of Spikevax gave higher protection of 68%. The isolated, vaccine-related protection against hospitalization from infection with delta variant was significantly higher, above 90%, highlighting omicron's capability to evade from immunity. (75) A similar finding was made in a non-peer reviewed study conducted in New York that identified a significantly decreasing effectiveness of Comirnaty against infection. Vaccine effectiveness against infection within 28–34 days of second dose for children 12-17 years was 56% and for children 5-11 years merely 12%. The decrease in efficacy was more rapid among children 5–11 years compared to children 12–17 years, possibly resulting from reduced vaccine dosing among 5–11 years old children. (76)

In the US, the safety of vaccines is primarily monitored through reported adverse effects to national Vaccine Adverse Event Reporting System (VAERS). Based on VAERS data, the most common adverse effects attributable to Comirnaty were pain at the injection site, fatigue, and headache in the age group 5–11 years. In the age group 12–15 years, chills and new or worsened muscle pain were also frequently reported. Other less frequently reported side effects in pediatric population included injection site

redness and swelling, diarrhea, arthralgia and fever. (77) For Moderna's Spikevax, the most common adverse effects in the adult population were similar but more frequently reported than those attributable to Comirnaty. (78)

Post-marketing data of Comirnaty and Spikevax demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. This has been an area of intensive research lately. Males aged 12–24 years appear to be at greatest risk, but majority of symptoms resolve with conservative management. (77) (78) According to a VAERS-based, non-peer-reviewed retrospective study, the median age of patients with vaccine-induced myocarditis was 21 years with males comprising 82% of cases. Up to 96% of such patients required hospitalization but majority of symptoms were resolved upon hospital discharge. (79) It also seems that risk of developing myocarditis is associated to mRNA vaccines, at least when comparing to inactivated virus-based technology used in Chinese CoronaVac vaccine. (80)

The exact incidence of vaccine-induced myocarditis varies between studies, with many basing the data on non-pediatric patients. One of the earliest study conducted in England estimated the incidence of vaccine-induced myocarditis to be only 1 to 1,000,000 after the first dose of Comirnaty and 6 and 10 to 1,000,000 after first and second dose of Comirnaty respectively. (81) An Israeli study found slightly higher incidence of 2.7 cases per 100,000 people with Comirnaty (82). The most recently published pan-Scandinavian study included four cohort studies from Sweden, Denmark, Norway, and Finland, including a total of 23,122,522 people aged 12 years or older. The adjusted incidence rate ratio (IRR) for myocarditis was 1.75 after the second dose of Comirnaty and 6.57 for Spikevax. For 16–24 years old males the IRRs after second dose were considerably higher: 5.31 with Comirnaty and 13.83 with Spikevax, equivalent to 5.55 and 18.39 extra events per 100,000 vaccinations respectively. For comparison, extra cases of myocarditis after confirmed SARS-CoV-2 infection were merely 1.37 per 100,000 individuals among unvaccinated males between 16 and 24 years. The risk for myocarditis was highest during the first 7 days and when two mRNA vaccines combined. (83)

The potential side effects of mRNA vaccines need to be balanced against known health risks from COVID-19 infection. As previously discussed, the clinical picture among the pediatric population is generally milder than that of the adults. Nevertheless, a new life-threatening syndrome called Multisystem Inflammatory Syndrome in Children (MIS-C), has appeared in children during the COVID-19 pandemic. Its exact pathogenesis is still not fully understood, yet the syndrome has been shown to have a temporal relationship to SARS-CoV-2 infection with patient's median age being 8.6 years. MIS-C carries mortality of 1.5% and with up to 68% requiring treatment in intensive care unit. (84) Using pre-omicron data, the estimated incidence in the US was 0.03% in patients younger than 21 years and 0.05% in Denmark in patients under 18 years. (85) (10) Recent information from preprint

case studies is predicting mitigation of MIS-C with the omicron variant. This is understood to be due to a missing binding motif that is known to modulate interleukin-1β in immune cells. (86) On the other hand, a Norwegian pre-print did not identify statistically significant difference in the risk for MIS-C between infections from omicron and delta variants among unvaccinated children, which would bode for significantly higher incidence of MIS-C in the omicron era. (87)

A retrospective multicenter study across 16 hospitals in patients aged 12–21 years of age in the US both assessed the association between mRNA vaccines and myocarditis and compared the severity of clinical picture of vaccine-induced myocarditis to MIS-C-induced myocarditis. The results showed statistically significant association between myocarditis and mRNA vaccine administration. However, the clinical picture of vaccine-induced myocarditis was mild with overall favorable short-term prognosis while clinical picture of myocarditis among patients with MIS-C was more serious with significantly impaired left ventricular ejection fraction. (88)

One method to assess necessity of COVID-19 vaccination among the pediatric population is to perform a risk-benefit analysis, in which risks from known vaccine-related adverse effects are weighed against the established benefits of active immunization. Such risk-benefit analysis with a complex design was recently published, utilizing VAERS-data on vaccination of 12–17 years old adolescents. (89) Incidence of vaccination-induced myopericarditis was stratified by age and vaccination dose. Then benefits of one and two doses of Comirnaty vaccination in adolescents to prevent COVID-19 hospitalization were weighed separately against risks of vaccination-induced myopericarditis. Additional risk stratification by age, sex, prior infection history, dominant COVID-variant and medical comorbidity status was also performed.

The results showed that benefit of one vaccination outweighed the risk of vaccine-induced myopericarditis in nonimmune boys and girls regardless of the variant, even at the highest estimated myopericarditis rates. On the contrary, for boys with prior COVID-19 infection and no underlying medical comorbidity, the risk of myopericarditis exceeded the expected risk of hospitalization even with the first dose. For boys without medical comorbidity the risks for myopericarditis after the second dose appeared to exceed the risk of hospitalization, regardless of the variant. The risk of myocarditis from second dose was 2.8 times higher than the 120-day COVID-19 hospitalization risk, even at very high disease prevalence scenario. Nevertheless, the authors acknowledged that COVID-19 has adverse effects beyond myocarditis and hospitalization, such as MIS-C and even pediatric deaths. Several limitations were also highlighted, such use of passive VAERS-reporting tool subject to bias and ignorance of the indirect benefits of vaccination. Despite the flaws, the results are pointing out to more individualized vaccination strategies for children against SARS-CoV-2.

DISCUSSION

The outbreak of COVID-19 pandemic has produced a vast number of related scientific articles during the last two years with many publishers providing free access. The nature of the pandemic is evolving rapidly, not only because of the large amount of new information being produced but also due to the constantly mutating characteristics of the virus. The currently dominant omicron variant appears to have unique characteristics in terms of higher transmissibility, lower severity, and increased ability to evade from active immunization in comparison to earlier dominant variants of concern, making plenty of earlier findings and recommendations outdated.

Omicron's shorter replication time and higher contagiousness has made the once effective find, test, trace, isolate, support system less practical since many infections go unnoticed before the clinical symptoms arise. Omicron's intrinsic properties have also resulted in steep increase in COVID-19 incidence rates, partly by virtue of its higher capability for breakthrough infections (90). This has widely put testing resources to limits and for example United Kingdom has limited the free COVID-19 testing only for healthcare personnel and people with immunosuppression and major comorbidities. (91) Children rarely are prioritized in any country despite being capable of spreading the virus. This highlights the importance of quick self-isolation upon known exposure or presentation of typical symptoms if decision-maker's goal is to slow down the propagation of SARS-CoV-2.

Of the environmental prophylactic infection control measures, social distancing is difficult to properly adopt to younger children's everyday life who normally spend the business hours in crowded schools or kindergartens, gaining social skills for the future. Proper monitoring of social distancing also requires additional resources. Most importantly, the adverse effects of prolonged isolation on mental and physical health of children and adolescents should be addressed better in the future. With increasing immunity through vaccinations and infections, lockdowns or remote schools should not have a role in the prophylaxis against SARS-CoV-2 viral infection at this stage of pandemic.

Regular and thorough handwashing with detergent is an excellent method to prevent transmission of communicable diseases among the pediatric population. It is affordable, widely available even in less developed countries and relatively straightforward to carry out even for a young child. The main drawback with intensive handwashing is dermatitis, that may be more pronounced in countries with cold climate. The problem is partly preventable by using moisturizing creams. Hand sanitizers may also occasionally be used instead of running water, although use of disinfectants should generally be done under adult supervision for children less 6 years old. From epidemiologic point of view, the role of handwashing in prevention of COVID-19 is still not entirely established as omicron appears to increase the risk for airborne transmission instead, highlighting the role of face masks and respirators.

When used on grand scale, face coverings suitable for pediatric population may indeed protect individuals from infectious respiratory particles containing SARS-CoV-2 or other viruses that are targeting the upper respiratory tract. Such widespread use during the epidemiologically challenging winter season with pediatric population involved could potentially save lives of immunocompromised people and those with major comorbidity. However, the appropriate use among the youngest ones might be challenging, and extensive use among the adult population may expose to undesirable psychological and developmental effects, which remains a topic for further studies. The protective effect of surgical face masks appears weak in the light of the latest evidence as they do not sit tightly enough on the face, allowing viral particles to enter the airways from sides. One alternative for the future is to exempt younger children from strict face mask policy and encourage teens and adolescents to use FFP2 respirators in public settings, as older age will increase the risk of complications from COVID-19 anyway. That said, it remains to be seen whether an enforced face mask policy will any have a role in prophylaxis of COVID-19 outside the healthcare facilities as the cellular immunity against SARS-CoV-2 is increasing rapidly, giving adequate protection against severe COVID-19.

The first vaccines against SARS-CoV-2 for adults became available in Western countries in less than a year into the pandemic, followed by approvals of mRNA vaccines for pediatric use during 2021. Despite the very rapid development process, efficacy of mRNA vaccines was initially very good against the earlier variants. However, omicron's heavily mutated spike protein substantially decreased effectiveness of COVID-19 vaccinations against infection, making the breakthrough infections common. Incidence rates along with hospital admissions have increased in many countries, including United States, but simultaneously hospital stays have been shorter, ICU admissions fewer and mortality rates relatively lower (92). Along with the earlier data on children's mild clinical manifestation of COVID-19, the post-marketing findings about clinically significant association between mRNA vaccination and myocarditis have questioned the rationale of mass vaccinations in childhood.

There are valid arguments for and against vaccinating the children and adolescents. Vaccine-associated myocarditis appears to be a genuine problem especially among the male adolescents, while the post-infection MIS-C, potentially preventable by vaccinations, is more prevalent in the age group 5–11 years with median age of 8.3 years. (93) The arguments against vaccinating children without comorbidities are mostly based on addressing the risk of vaccine-induced myocarditis that, despite its generally favorable clinical course, is still associated with high hospitalization rates. Several myocarditis cases may also go undetected due to the relatively mild course.

A frequently used argument for pediatric vaccinations is that complicated infection is more serious than side-effects of vaccination. With vaccinations, children and adolescents gain cellular immunity, which

appears to protect well against the severe form of COVID-19, potentially caused by more dangerous variants in the future. However, the cellular immunity is also gained through COVID-19 itself. The *primum non nocere* should be honored and the significant side-effect of myocarditis among pediatric population observed in the national recommendations of pediatric COVID-19 vaccination programs. Similarly, AstraZeneca's vector virus vaccine was temporarily withdrawn in several countries in 2021 after rare events of blood clots among female individuals who had earlier received *Vaxzevria.* (94)

Regarding pediatric COVID-19 vaccinations, additional studies may be required to more accurately define the length of cellular immunity which appears central in prevention of severe disease that is infrequently seen in children and adolescents. Without a confirmed infection with COVID-19, the benefits of first dose of vaccination will very likely outweigh any potential vaccine-related side effects. Nevertheless, many pediatric infections go unnoticed both due to high proportion of asymptomatic infection and because of prioritization of testing facilities for the adult population. For healthy children with underlying immunity from prior infection, additional vaccination may unnecessarily raise the risk of myocarditis without delivering clinically significant added benefits, as incidence of myocarditis is shown to be higher after the second dose. The risk for adverse effects is even higher if history of prior infection is ignored in the vaccination schedule, which is the case currently in the US where two to three doses of vaccines are still recommended to pediatric population, regardless of the immune status. The CDC justifies its policy with studies showing a lesser risk for reinfection among those with history of primary infection and subsequent vaccination. (95) It is worth noticing that studies referred to are from pre-omicron time. To alleviate the risk of vaccine-induced myocarditis the organization encourages males ages 12–39 years to have an 8-week interval between the first and the second dose instead of the standard 3 weeks. (96)

One aspect to refrain from unnecessary rounds of vaccinations for non-risk groups is the restrained and uneven distribution of vaccinations between developed and developing countries. The latter have served as a platform for new variants, supposedly due to low primary vaccination coverage. In these countries, the proportion of young people is higher than in developed countries, and the burden of epidemics could be lowered with appropriate supply of primary doses. The extra mRNA vaccines earmarked as booster shots for the healthy children in developed countries might be more beneficial in in the countries of the Third World.

CONCLUSIONS

The pandemic has reached a phase when prophylaxis against SARS-CoV-2 in childhood should be based on vaccinations. The main goal of prophylaxis programs should be to achieve as high immunity level as possible. Vaccines, along with confirmed COVID-19 infection, give a long-term cellular

immunity which seem protects well against the severe form of COVID-19. The clinical picture of COVID-19 among children is generally mild and self-limited with excellent prognosis, thus other forms of prophylaxis may not be quintessential in the future. The main reason to actively provide vaccinations to healthy children is the higher likelihood of complications from COVID-19 primary infection in infection-naïve children. Especially MIS-C is an undesirable, potentially lethal condition, the risk of which can effectively be mitigated through vaccination. Moreover, the well-documented post-marketing risk of vaccine-induced myocarditis, child's immune status, sex and presence of comorbidities need to be better addressed in vaccination schedules of the future, making them more individualized. More studies are required about length of the expected cellular memory against SARS-CoV-2 and how often children will require boosters, or whether they benefit from them at all.

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