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REVIEW

Evidence and rationale for vaccinating children and adolescents against SARS-CoV-2: a comprehensive narrative review

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Abstract

Vaccines remain the most rigorous and cost-effective weapon of the public health care system against infectious diseases. The development of safe and effective vaccines against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) emerged as an imperative response to the unprecedented morbidity and mortality of the Coronavirus Disease 2019 (COVID-19) pandemic and the subsequent immense pressure on health care systems, families and global society. Despite the typically mild disease course of SARS-CoV-2 in minors, the associated rare but potentially life-threatening complications, as well as the emergence of new highly transmissible variants, led promptly to the extension of COVID-19 vaccine clinical trials in children and adolescents. To date, various COVID-19 vaccine candidates have been successfully trialed in pediatric populations, followed by their incorporation into corresponding vaccination campaigns in both high- and low-income countries. However, the universal COVID-19 vaccination of children and adolescents remains a matter of debate, along with skepticism about their overall safety and benefits in this age group. In this narrative review, we attempt to summarize the multi-faceted burden of COVID-19 on minors, highlighting the favourable safety/effectiveness profile of COVID-19 vaccines in this age group, elucidating the raised concerns and presenting the current implemented vaccination strategies.

Keywords

SARS-CoV-2; Viral vaccines; mRNA vaccines; Vaccine development; Vaccination hesitancy; Minors; Communicable diseases; Public health

1. Introduction

In late 2019, a novel coronavirus emerged in the heartland of China causing an alarming outbreak of lower respiratory tract infections, followed by a rapid global spread [1, 2]. In the first trimester of 2020, the World Health Organization (WHO) declared this situation as a pandemic [3]. Since then, the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has led to tens of millions of hospitalizations and more than 6.1 million deaths worldwide, affecting mostly the elderly and patients with chronic conditions or multiple comorbidities [4, 5]. Although children and adolescents represent essential nodes of the transmission chain in the community, they tend to experience a mild disease course in most cases [6, 7]. Nevertheless, there are reported cases among children with Coronavirus Disease 2019 (COVID-19) requiring treatment or hospitalization, while a low but not negligible number of them need critical care or even die [8–10]. Moreover, as a result of the current pandemic, several aspects of everyday life, including education and social activities, have been compromised during lockdown periods with unknown effects in the cognitive and emotional development of minors, apart from the uncertainty of the possible long term effects of COVID-19 [11–14]. Simultaneously, rare but severe post-infectious complications, such as the so-called Multisystem Inflammatory Syndrome in Children (MIS-C), underline the essential need of protecting this vulnerable age group [15].

Apart from preventive non-pharmacological interventions, such as social distancing, face masks and hand hygiene, vaccines appear to be the most efficacious way to control the spread of the pandemic [16, 17]. However, vaccine hesitancy in combination with the raising dilemma of justification of COVID-19 vaccination in minors, given the typically mild course of SARS-CoV-2 infection in these subjects, emphasize the need for redefining the burden of the COVID-19 pandemic among the pediatric population, as well as the crucial role of COVID-19 vaccination in preventing devastating infectious complications [18–20]. Hence, the aim of this narrative review is to illustrate these points, clarifying aspects of the favourable safety/effectiveness profile of COVID-19 vaccines in chil-

dren and adolescents, and providing a comprehensive list of COVID-19 vaccine candidates trialed in children worldwide.

2. Methods

2.1 Outcome

The expected outcome of this narrative review is to qualitatively summarize: (1) the clinical and socio-psychological impact of the SARS-CoV-2 pandemic on children and adolescents, (2) the scientific data available regarding COVID-19 vaccination in minors reported in literature, describing their safety and effectiveness profile both in clinical trials and in real world settings, and (3) the current vaccination strategies implemented in this age group worldwide.

2.2 Search strategy

Two authors independently conducted a search in three different medical literature databases: PubMed, ScienceDirect, and UpToDate, in an attempt to identify the most representative papers published in English from 1 January 2020 to 7 January 2022, covering the three thematic axes outlined above. Independently of the sub-specific topic of each query, as elaborated in the Outcome section, the search strategy was based on the search string: ((“COVID-19”(MeSH Terms) OR “SARS-CoV-2”(MeSH Terms)) AND (“Minors”(MeSH Terms) OR “Child”(MeSH Terms) OR “Adolescent”(MeSH Terms))), or its equivalent combination of the following keywords and Boolean operators: (“COVID-19” OR “SARS-CoV-2” OR “2019-nCoV” OR “Novel coronavirus”) AND (“minors” OR “children” OR “adolescent” OR “infant” OR “neonate”), in order to restrict the COVID-19 related search results to the age group of interest.

Subsequently, for the first query, varying combinations of the following terms: (“clinical manifestations” or “symptoms”), (“immune response” or “immune dysregulation” or “immunological dysregulation”), (“epidemiology” or “morbidity” or “mortality”), (“social impact” or “psychological impact” or “mental health”), (“education” or “school” or “school closure”), (“MIS-C” or “Multisystem Inflammatory Syndrome” or “Hyperinflammation” or “Kawasaki-like”), and/or (“Long COVID” or “post COVID-19” or “post SARS-CoV-2 infection”), were added in the original search string, to gain insight into the multiple aspects of the burden of COVID-19 in minors.

Regarding the further two queries, we utilized the recently introduced MeSH term “COVID-19 Vaccines”, as well as the keywords “vaccines”, “vaccine strategies”, “vaccine policies”, “vaccine clinical trials”, “vaccine development”, “vaccine authorization” in addition to the original search string. Furthermore, taking into consideration that COVID-19 vaccine development and authorization is a rapidly evolving and dynamic process, along with the fact that writing and publishing a scientific article is a time-consuming stepwise process, demanding meticulous peer review and hence being incapable to cover thoroughly the latest scientific advances and political developments, we also performed a relevant search in: (1) press and media sources, widely acknowledged as credible (*e.g.*, Reuters, The New York Times, Washington Post, The Guardian, British Broadcasting Corporation—BBC, Cable News Network—CNN), (2) the official websites of medical/health agencies, such as the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC) and the European Medical Agency (EMA), (3) the official websites of the pharmaceutical companies involved in the development of COVID-19 vaccines, and (4) international and national clinical trial registries (ClinicalTrials.gov, European Union Drug Regulating Authorities Clinical Trials Database—EudraCT, Chinese Clinical Trial Registry—CCTR, Clinical Trial Registry of India—CTRI, Cuban Public Registry of Clinical Trials—RPCEC).

3. The burden of SARS-CoV-2 infection on minors

3.1 Clinical manifestations of acute COVID-19 in children

In the vast majority of pediatric cases, infection with the novel coronavirus SARS-CoV-2 causes mild to moderate acute febrile respiratory illness, manifesting with symptoms predominantly from the upper respiratory tract (URT) and less frequently from the lower respiratory tract (LRT) [21, 22]. The most common clinical manifestation is fever, presented in more than half of the infected children, followed by coughing (41%), nasal congestion (17%), pharyngitis/sore throat (16%), and rhinorrhea (14%), as reported in a recent systematic review and meta-analysis [23]. The presence of dyspnoea, hypoxemia, signs of respiratory distress and other symptoms associated with pneumonia, which appears to be the main clinical hallmark of COVID-19 in adults, tends to be less common in pediatric patients. However, it is associated with unfavorable outcomes, namely the development of acute respiratory distress syndrome (ARDS), requiring invasive mechanical ventilation [23–27]. Regarding pulmonary imaging, the chest computed tomography (CT) scan findings are mild or slightly atypical in most children with real-time reverse transcription–polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection, whereas ground-glass opacities, multiple patchy shadows and consolidations—in either unilateral or bilateral distribution—are indicative of more extensive lung involvement, hence more severe clinical features [21, 28–30].

SARS-CoV-2 can also affect the gastrointestinal tract, with consistently elevated incidence in children compared to adults [24]. The most commonly reported gastrointestinal symptoms include (in order of descending prevalence) diarrhea, nausea and vomiting, abdominal pain, anorexia and/or other feeding difficulties, leading potentially to dehydration due to insufficient fluid intake and excessive gastrointestinal losses, especially when combined with fever [21, 23, 24, 31]. In addition, gastrointestinal manifestations may precede the typical systemic and respiratory symptoms, delaying the timely diagnosis of COVID-19 and the appropriate management of these patients [24, 27, 31–33].

Other extrapulmonary COVID-19 manifestations demonstrated in the pediatric population involve renal

(acute kidney injury, uraemia, haematuria), cardiovascular (hypovolemic shock, hypertroponinemia, tachyarrhythmias), and neurological complications (irritability, lethargy, altered mental status, headache, muscular weakness, meningism, seizures), exhibited either during acute SARS-CoV-2 infection or in the context of the associated post-infectious multisystem inflammatory syndrome in children (MIS-C) [34–36]. Moreover, apart from Kawasaki-resembling mucocutaneous lesions, pediatricians should not neglect erythema multiforme- and urticaria-like eruptions, or chilblain-like lesions, particularly on the lower extremities of adolescents, as these cutaneous manifestations have been associated with COVID-19 in minors [37–40].

3.2 Laboratory and immunological features of pediatric COVID-19

During the course of acute infection in children, the peripheral white blood cell counts are usually within normal range values, whereas lymphopenia—an unfavorable prognostic factor—is observed in a relatively small percentage of infected children (16%), in contrary to adults (43–57%) [23, 27, 41]. Elevation in liver (alanine aminotransferase—ALT, aspartate aminotransferase—AST), muscle (creatine phosphokinase—CPK) and cardiac (creatine kinase-myoglobin binding—CK-MB, troponin) enzymes has been reported with variable frequency and severity among pediatric series of COVID-19 [23, 27, 42–44]. Furthermore, the elevation of acute-phase reactants (C-reactive protein—CRP, lactate dehydrogenase—LDH, procalcitonin, ferritin) and other inflammatory markers (erythrocyte sedimentation rate—ESR, interleukin-1—IL-1, IL-6) is more profound in severe cases [21, 27, 41, 45–48]. Regarding coagulation tests, children in need of respiratory support and critical care show a trend towards longer prothrombin time and higher D-dimer concentrations [21, 49, 50].

The reported dysregulated immune responses in adult COVID-19 patients rapidly progressing into invasive mechanical ventilation indicate the vivid interaction between SARS-CoV-2 and the host immune system [51, 52]. Data from pediatric studies suggests that severe COVID-19 in children is also characterized by sustained robust activation of T-lymphocytes, with the expansion of the usually quiescent effector and memory T-cell subsets [53–55]. In severe MIS-C, the expansion of memory T-cell compartments is accompanied by the expansion of SARS-CoV-2-specific IgG-secreting plasmablasts, which bear autoimmune potential [53, 56]. Notably, recent studies have demonstrated that even mild SARS-CoV-2 infection can trigger the production of a wide variety of auto-antibodies, associated with discrete clinical features of the spectrum of post-acute COVID-19 sequelae [57, 58].

3.3 Morbidity and mortality of pediatric COVID-19

Initially, the increased prevalence of asymptomatic or mildly symptomatic pediatric patients with molecularly confirmed SARS-CoV-2 infection was reassuring about the impact and prognosis of COVID-19 in minors [21]. As the pandemic escalated, COVID-19—associated hospitalization rates among minors aged 0–17 years surged, coinciding with the emergence and increased circulation of new highly transmissible SARS-CoV-2 variants [59, 60]. Noticeably, in the USA, more than one-fifth of hospitalized children and adolescents required intensive care unit (ICU) admission during the Delta- and Omicron-predominant periods [60]. Excluding the Omicron-predominant period, the reported percentage of ICU admission in Europe was 6.7% of hospitalized pediatric COVID-19 cases, surpassing the corresponding percentage for influenza-related pediatric hospitalizations in 2019–2020 [60, 61].

Risk factors for unfavorable outcomes in pediatric COVID-19 cases and ICU admission include neonatal or infantile age, non-Caucasian ethnicity, and the presence of non-communicable disease comorbidities, such as obesity, hypertension, diabetes mellitus, chronic respiratory disease, or hematological disorders [61–63]. In this context, it becomes evident the disproportionate burden of COVID-19 in children and adolescents from socioeconomically deprived communities, where multiple background comorbidities are prevalent and critical care resources are limited [62, 64].

As of February 2022, according to the Max Planck Institute for Demographic Research (MPIDR) COVerAGE-DB database, over 12,800 COVID-19—related deaths occurred in minors under 20 years of age [65, 66]. Despite the low overall COVID-19 mortality rate in children and adolescents, excess mortality rates were observed mainly but not exclusively in resource-limited critical care settings, and were associated with the presence of ARDS or organ dysfunction at admission, as well as select underlying comorbidities [26, 61, 62, 64, 67–69]. In addition to the direct impact of the pandemic on pediatric mortality, the potentially indirect effects of COVID-19 on mortality in this vulnerable age group, stemming from disruptions to health services and preventative measures like routine immunization, should not be neglected [66, 70–72].

3.4 MIS-C

As early as the spring of 2020, a new hyperinflammatory entity with multi-organ involvement in association with a preceding SARS-CoV-2 infection was observed in children and adolescents in the United Kingdom [73]. This novel condition, which is currently officially known as Multisystem Inflammatory Syndrome in Children (MIS-C), bears a striking resemblance to Kawasaki disease [74]. This syndrome has also been described in the following terms: pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), pediatric inflammatory syndrome or pediatric inflammatory shock. However, the term“MIS-C” has prevailed in the medical community [75].

According to the CDC Health Advisory, the case definition for MIS-C includes any individual aged $<$21 years presenting with fever $\geq$ 38.0°C lasting $\geq$ 24 hours, who meets all of the following diagnostic criteria:

•laboratory evidence of inflammation—including elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), as well as elevated neutrophils, reduced lymphocytes and low albumin; AND

•evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND

•no alternative plausible diagnoses; AND

•positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms [76, 77].

On the other hand, the WHO case definition for MIS-C, despite including similar clinical laboratory criteria, does not necessarily require cases to experience serious illness or need hospitalization [78]. Nevertheless, it should be admitted that MIS-C, even if rare, is a serious post-infectious complication of COVID-19 in children and adolescents, frequently requiring intensive care unit admission and critical support of vital functions [79, 80]. As of end of February 2022, the CDC has recorded 7459 MIS-C cases and 63 MIS-C—related deaths [81].

The treatment of the syndrome is based on supportive measures and the administration of corticosteroids, intravenous immune globulin (IVIG) and anticoagulants, as in the well-known Kawasaki disease. Recent studies suggest that there are no differences in the outcome after treating patients with corticosteroids, IVIG or their combination [82]. Although the incidence of the syndrome is low, namely 2 cases per 100,000 [83], its severity along with the high prevalence of SARS-CoV-2 infection in children, is one of the major causes that led many countries to encourage the vaccination of children and adolescents [20].

With the progression of the COVID-19 pandemic, both the case definitions for MIS-C and the suggested therapeutic algorithms are evolving. Several scientific associations recommend the long term follow up of recovered patients.

3.5 Long-COVID in minors

In the pediatric scientific community, there has been a lot of research focused on the so called “long-COVID syndrome”. This syndrome has already been described in adults and is characterized by the persistence or appearance of symptoms from various systems (respiratory, cardiovascular, nervous and others) after acute SARS-CoV-2 infection, even in people who initially experienced a mild disease course. The terminology used also includes the terms: post-COVID, COVID syndrome, and COVID long-haulers, whereas clear case definitions and universally accepted diagnostic criteria for the syndrome do not yet exist. In late 2021, the World Health Organization adopted a clinical case definition for long-COVID in adults after a Delphi consensus, noting that the corresponding case definition may differ in children [84]. Following this initiative, a similar methodological approach was implemented for the clinical case definition of long-COVID in children and adolescents by Terence Stephenson and his colleagues, who proposed the following definition: “Post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with one or more persisting physical symptoms for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after COVID-19 infection, and may fluctuate or relapse over time” [85].

In recently published studies, both the frequency and duration of the syndrome, as well as the clinical manifestations, vary a lot [86–88]. There are significant difficulties in documenting the syndrome in children, as: (1) in newborns and young children the presence of long-COVID—associated features may be overestimated or underestimated by their guardians; (2) in older children and adolescents the reported features may not be due to a post-COVID condition, but presumably due to the indirect effects of the pandemic on families (lockdown, school closures, restriction of activities and the social life of children and their families); and (3) there are children and adolescents who may have been infected from SARS-CoV-2 with little or no symptoms and in which no molecular diagnosis has been established, therefore they may escape the probable diagnosis of long-COVID. The Achilles’ heel of most published studies attempting to describe the features of long-COVID, is the lack of a matched control group, leading inevitably to inconclusive results [89].

It is now well evident that SARS-CoV-2 infection is much milder in children and adolescents than in adults and is less likely to lead to serious illness, hospitalization, need for intensive care or death. Therefore, the possible long term complications of the disease constitute a critical parameter which influences the parents’ decision to vaccinate their children or not [90]. Hence, it is very important to obtain a clear picture of the severity and frequency of long-COVID syndrome in these age groups. However, it is important to note that it is still unknown if vaccines against SARS-CoV-2 are also effective in preventing long-COVID in children, whereas recent adult studies suggest that the risk can be reduced but not eliminated [91, 92].

3.6 Psychosocial impact of the current pandemic on children

The COVID-19 pandemic, in addition to its direct impact on health outcomes, has also had significant indirect effects on the daily life of children and their families. Children and adolescents, especially during the quarantine period, stopped attending school, as well as many of their usual outdoor activities, and were confined indoors for prolonged time intervals, staying away from their friends and loved ones, and hence developing an addiction to social media in compensation for loneliness [93, 94]. Distance learning was used to fill the gap in lifelong learning where possible, further enhancing the use of digital technologies in peer social interactions [95, 96]. As reported by recent studies, children and their families experienced elevated levels of stress during lockdown, with the less privileged being disproportionately affected [11, 94]. According to an extensive United Nations International Children’s Emergency Fund (UNICEF) report, the multifaceted effects of the ongoing pandemic on children are not yet completely understood. Thus, societies should use all available interventions and resources in order to minimize and alleviate the psychosocial burden of the COVID-19 pandemic in minors [97].

4. COVID-19 vaccines in children and adolescents

Undoubtedly, despite the tremendous progress in drug discovery and development in recent decades, vaccines remain the most rigorous and cost-effective weapon of public health care systems against infectious diseases [98]. The immense pressure of the COVID-19 pandemic on public health systems worldwide led to generous government funding for the development of vaccines against SARS-CoV-2. Through a coalition that embodied the global scientific community, pharma industry and governments, safe and effective novel vaccines were developed, trialed, authorized for emergency use and distributed at accelerated speed, more precisely, in less than a year from the official onset of the current pandemic [99]. As soon as the initial encouraging results emerged from COVID-19 vaccine clinical trials in adults [100–103], followed by their emergency use approval (EUA) by regulatory authorities, their safety and immunogenicity began to be evaluated in minors [104–109]. A comprehensive list of the COVID-19 vaccines approved or being trialed for use in children and adolescents is depicted in Table 1, whereas Table 2 includes information on their approval status for this specific age group among various countries.

There is large heterogeneity regarding the vaccine technology used; from traditional (protein subunit, inactivated) to novel ones (mRNA-based, viral vector-based, DNA-based). It is important to note that the first two approved COVID-19 vaccines for emergency use in adolescents are mRNA-based [104, 106], proving the prophetic prediction that "mRNA-based vaccines can fill the gap between emerging pandemic infectious disease and a bountiful supply of effective vaccines" (Zhang *et al.*, 2019) [110].

Remarkably, according to published results of vaccine clinical trials in minors, no serious adverse events related to vaccination were reported, whereas injection site reactions and fever were the most frequently encountered adverse events. Furthermore, solid evidence of their immunogenicity and effectiveness in preventing confirmed COVID-19 in each corresponding age group was well established [104–109]. In real world settings, vaccinating children and adolescents against SARS-CoV-2 has been proven to contribute essentially towards preventing severe disease and COVID-19—related hospitalization, as well as MIS-C [20, 111].

During the Omicron-predominant period, real-world data on BNT162b2 effectiveness demonstrated waning protection against asymptomatic and symptomatic Omicron infection among fully vaccinated children and adolescents [112, 113]. However, two doses of BNT162b2 significantly protected eligible minors against COVID-19—associated emergency department encounters, as well as critical illness, irrespectively of the causing SARS-CoV-2 variant [113–115].

5. Current strategies for the use of COVID-19 vaccines in minors across the globe

Currently, the only FDA-and-EMA-approved COVID-19 vaccine for emergency use in children and adolescents, aged between 5–17 years, remains the mRNA-based BNT162b2, which has been successfully incorporated into COVID-19 vaccine campaigns in minors in the USA [116], Canada [117], Australia [118], Israel [119], Japan [120], and the majority of European Union (EU) countries [121]. Despite its preliminary skepticism toward the universal COVID-19 vaccination of both the 12–15 and 5–11 years age groups, offering initially COVID-19 vaccines exclusively to vulnerable minors, the UK's Joint Committee on Vaccination and Immunization (JCVI) recently extended the vaccination program to also include healthy children older than 5 years [122, 123]. However, Sweden has decided against the universal COVID-19 vaccination of children aged 5–11 years, proclaiming that the clear benefits in this specific age group do not definitely outweigh the potential risks [121, 124].

On the other hand, China has succeeded in mass COVID-19 vaccination of children aged 3–17 years with its inactivated Sinovac and Sinopharm vaccines, after declaring it as mandatory for school attendance [125–127]. In addition, India and Cuba have already vaccinated a significant percentage of their pediatric population with their indigenously developed and trialed COVID-19 vaccines [128, 129].

6. Discussion

The current review highlights the intensive COVID-19 vaccine research, focusing on the pediatric population, and its visible and impressive achievements within a short timeframe. The development of safe and effective vaccines against SARS-CoV-2 arose as a public health imperative due to the immense pressure of the pandemic on health care services globally [130–133]. During the last two years, the pandemic has imposed unique multi-faceted challenges on international society, inflicting an unprecedented high death toll and an excessive surge in demand for hospital and critical care services [4].

Taking these implications into consideration, the observed relative sparing of children and adolescents by severe COVID-19 has definitely constituted a saving grace [134]. Nevertheless, the emergence of new highly transmissible SARS-CoV-2 variants, along with the rare but potentially fatal clinical entity of MIS-C, has gradually revealed that minors are not invincible. Sequentially, as illustrated comprehensively in Table 1, various COVID-19 vaccine candidates have been trialed in pediatric populations to date, not only in high-income but also in resource-limited countries, such as India and Cuba, denoting the disproportionate burden of the pandemic in socioeconomically deprived settings and thus the essential need for active preventive measures, in order to shield particularly, but not exclusively, vulnerable children and adolescents. Biomedical and clinical research flourished and, eventually, resulted in emergency-approved COVID-19 vaccines that were tested to be safe and effective in pediatric clinical trials [104–106]. Their favourable safety profile and their high effectiveness in preventing severe COVID-19 in the long term have also been confirmed in real-world settings, especially in adolescents older than 12 years of age, after millions of doses were administered to this age group [135].

TABLE 1. List of COVID-19 vaccines being trialed for use in children and adolescents.

Vaccine	Sponsor/Manufacturer	Type of vaccine	Age group of minors	Dose	Dosage schedule	ClinicalTrials.gov identifier
BNT162b2	Pfizer/BioNTech SE (USA/Germany)	mRNA	16–18 years	30 μg	2-dose, separated by 21 days, schedule	NCT04368728 Phase 1/2/3
			12–15 years	30 μg	2-dose, separated by 21 days, schedule	NCT04368728 Phase 1/2/3
			5–11 years	10 μg	2-dose, separated by 21 days, schedule	NCT04816643 Phase 1/2/3
			6 months–5 years	3 μg	2-dose, separated by 21 days, schedule or 3-dose schedule, with the third dose 2 months after the second one	NCT04816643 Phase 1/2/3
mRNA-1273	Moderna TX, Inc. (USA)	mRNA	12–17 years	100 μg	2-dose, separated by 28 days, schedule	NCT04649151 Phase 2/3
			6 months–11 years	NA/ND	2-dose, separated by 28 days, schedule	NCT04796896 Phase 1/2/3
ChAdOx1nCoV-19 (AZD1222)	Astrazeneca-University of Oxford (UK)	Non replicating viral vector	6–17 years	5×10^{10} virus particles	2-dose, separated by 28 days, schedule or 3-dose schedule (0, 28, 84 weeks)	ISRCTN15638344 (Phase 2)^
Ad26.COV2.S	Janssen Vaccines & Prevention B.V. (USA)	Non replicating viral vector	12–17 years	NA/ND	1-dose schedule or 2-dose schedule (56-day interval)	NCT05007080 (Phase 2/3)
Gam-COVID-Vac	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation (Russia)	Non replicating viral vector	12–17 years	NA/ND	2-dose, separated by 21 days, schedule	NCT04954092 (Phase 1/2/3)
BBIBP-CorV	Sinopharm/Beijing Institute of Biological Products (China)	Inactivated	3–17 years	4 μg	2-dose, separated by 28 days, schedule	ChiCTR2000032459 (Phase 1/2)*
CoronaVac	Sinovac Biotech Co., Ltd (China)	Inactivated	3–17 years	3 μg	2-dose, separated by 28 days, schedule	NCT04551547 (Phase 1/2) NCT04884685 (Phase 2b) NCT04992260 (Phase 3) NCT04992208 (Phase 4)
			6–35 months	NA/ND	2-dose, separated by 28 days, schedule	NCT04992260 (Phase 3)

TABLE 1. Continued.

Vaccine	Sponsor/Manufacturer	Type of vaccine	Age group of minors	Dose	Dosage schedule	ClinicalTrials.gov identifier
BBV152	Bharat Biotech International Limited (India)	Inactivated	2–18 years	NA/ND	2-dose, separated by 28 days, schedule	NCT04471519 (Phase 1/2) NCT04918797 (Phase 2/3)
ZyCoV-D	ZydusCadila (India)	DNA (needle-free)	12–18 years	2 mg	3-dose, separated by 28 days, schedule (0–28–56 days)	CTRI/2021/01 /030416 (Phase 3)**
NVX-CoV2373 (Nuvaxovid)	Novavax (USA)	Protein subunit (nanoparticle)	12–17 years	5 μg	2-dose, separated by 21 days, schedule	NCT04611802 (Phase 3)
CIGB-66	Center for Genetic Engineering and Biotechnology—CIGB (Cuba)	Protein subunit	3–18 years	50 μg	3-dose, separated by 14 days, schedule (0–14–28 days)	RPCEC00000381 (Phase1/2)*** RPCEC00000390 (Phase 2)***
FINLAY-FR-2	Finlay Institute of Vaccines (Cuba)	Protein subunit	3–18 years	25 μg	2-dose, separated by 28 days, schedule, followed by a 56-day booster dose of FINLAY-FR-1A	RPCEC00000374 (Phase1/2)*** RPCEC00000384 (Phase 2)***
FINLAY-FR-1A	Finlay Institute of Vaccines (Cuba)	Protein subunit	2–18 years	50 μg	1 dose (booster)	RPCEC00000391 (Phase1/2)***

*^International Standard Randomised Controlled Trial Number Registry (ISTRCN); *Chinese Clinical Trial Registry (CCTR); **Clinical Trial Registry of India (CTRI); ***Cuban Public Registry of Clinical Trials (RPCEC); NA/ND: Not announced/Not determined.*

TABLE 2. Approval status of COVID-19 vaccines being trialed in minors worldwide.

Vaccine	Age group	Status of approval or recruitment	Comments	DOI of published results
BNT162b2	16–18 years	Approved on 23 August 2021, by FDA for the prevention of COVID-19 disease in individuals 16 years of age and older. On 11 December 2020, the FDA had issued the first emergency use authorization (EUA) for BNT162b2 for the aforementioned purpose, while on 21 December 2020, EUA was granted by the EMA.	153 minors aged 16–18 years old were included in Phase 2/3 as part of the 16–55 years of age group (77 in the BNT162b2 group and 76 in the placebo group – 1:1 ratio). Observed vaccine efficacy in the 16–17 years of age subgroup: 100% (95% CI, −3969.9 to 100.0).	10.1056/NEJMoa2034577
	12–15 years	On 10 May 2021, the FDA expanded the EUA for BNT162b2 to include adolescents aged 12–15 years old. The same authorization was granted in the EU by the EMA on 28 May 2021. In Australia, the Australian Technical Advisory Group on Immunization (ATAGI) extended the previously recommended vaccination using BNT162b2 to include all adolescents over 12 years old on 23 July 2021. In Israel, the BNT162b2 vaccine was approved for use in adolescents in June 2021. In addition, it is currently approved for use in adolescents >12 years old in New Zealand, Japan, the Philippines, Mexico, Brazil, Chile, Canada, South Africa, Jordan, Hong Kong and Singapore. In the UK, as well as in Norway, all adolescents 12–15 years old are to be offered a single vaccine dose of BNT162b2. However, on 10 January 2022, the National Health Service (NHS) England decided to offer second doses to this age group.	2260 adolescents 12 to 15 years of age received injections, with 1131 receiving BNT162b2 and 1129 receiving placebo (1:1 ratio). No vaccine-related serious adverse events. Observed vaccine efficacy: 100% (95% CI, 75.3 to 100.0).	10.1056/NEJMoa2107456
	5–11 years	On 29 October 2021, the FDA expanded the EUA for BNT162b2 to include children aged 5–11 years old, whereas the same approval was granted in the EU by the EMA on 25 November 2021. In Australia, the use of BNT162b2 in the 5–11 years old age group was approved by Therapeutic Goods Administration (TGA) on 5 December 2021, followed by the final recommendations of ATAGI on 9 December 2021. The UK regulatory authorities approved the use of BNT162b2 in 5-to-11-year-old children on 22 December 2021, whereas NHS England recommended that the vaccination should be offered only to vulnerable children of this age group.	During the Phase 2/3 trial, 2268 children 5 to 11 years of age received injections, with 1517 receiving BNT162b2 (10 μg) and 751 receiving placebo (2:1 ratio), whereas a safety expansion group of an additional N 2250 participants was recruited later. Favourable vaccine safety profile without serious adverse events. Observed vaccine efficacy in the initial enrollment group: 90.7% (95% CI, 67.7 to 98.3).	10.1056/NEJMoa2116298

TABLE 2. Continued.

Vaccine	Age group	Status of approval or recruitment	Comments	DOI of published results
	6 months–5 years	Still recruiting. Ongoing study.	The Phase 1/2/3 trial of BNT162b2 in children initially enrolled up to 4500 children <12 years old, which were divided into three age groups: ages 5 to 11 years; ages 2 to 5 years; and ages 6 months to 2 years. On 17 December 2021, the press release from Pfizer provided information about the interim immunogenicity analysis, in which non-inferior efficacy was demonstrated in the 6-to-24-month-old age group but not in the 2-to-5-year-old age group. No safety concerns were identified. The aforementioned results led to the decision to evaluate a three-dose vaccination scheme in this population (6 months through 4 years of age), with the third dose provided at least two months after the second dose of the original two-dose scheme.	No results published
mRNA-1273	12–17 years	On 23 July 2021, the EMA granted an extension of the EUA for mRNA-1273 to include adolescents aged 12–17 years. In June 2021, Moderna filed for EUA from the FDA to expand the use of mRNA-1273 to adolescents 12–17 years old. However, the FDA has delayed the corresponding decision, in order to check if the vaccine could increase the risk of myocarditis in this age group. ATAGI provisionally extended the use of mRNA-1273 in adolescents 12–17 years old on 4 September 2021.	3732 adolescents 12 to 17 years of age received injections, with 2489 receiving mRNA-1273 and 1243 receiving placebo (2:1 ratio). Observed vaccine efficacy: 93.3% (95% CI, 47.9 to 99.9).	10.1056/NEJMoa2109522
	6 months–11 years	Still recruiting.	The Phase 2/3 study is expected to enroll 6750 healthy pediatric participants less than 12 years of age.	No results published
ChAdOx1 nCoV-19 (AZD1222)	6–17 years	No longer recruiting—Terminated.	In February 2021, a Phase 2 study of ChAdOx1 nCoV-19 Covid-19 vaccine in children and adolescents was launched, enrolling 300 minors, with 240 of them receiving the vaccine. However, in April 2021, this pediatric vaccine trial was prematurely terminated due to rare but serious Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) events in adults.	No results published

TABLE 2. Continued.

Vaccine	Age group	Status of approval or recruitment	Comments	DOI of published results
Ad26.COV2.S	12–17 years	Still recruiting.	Estimated enrollment: 3300 participants.	No results published
Gam-COVID-Vac	12–17 years	Still recruiting.	Estimated enrollment: 3000 participants to be randomized to two groups—vaccine and placebo—in a 4:1 ratio.	No results published
BBIBP-CorV	3–17 years	In August 2021, both China and the United Arab Emirates approved the EUA of BBIBP-CorV for children and adolescents aged 3–17 years old. Argentina issued similar approval in October 2021. Ongoing Phase 3 trials in this age group.	288 participants, divided into three age cohorts (3–5, 6–12, and 13–17 years), were randomly assigned to vaccine or control group in a 3:1 ratio (216 *vs.* 72). Phase 1/2 trial completed, supporting the use of a 4 μg dose and two-shot regimen BBIBP-CorV in phase 3 trials in children 3–17 years to further ascertain its safety and efficacy against COVID-19.	10.1016/S1473-3099(21)00462-X
CoronaVac	3–17 years	On 28 May 2021, China approved the EUA of CoronaVac for children and adolescents aged 3–17 years old, while in June 2021 CoronaVac was approved for use in adolescents aged 12–17 years old by Indonesian authorities. In early September 2021 Chile's Institute of Public Health approved the emergency use of CoronaVac for children and adolescents aged 6–17, whereas in early October 2021 Malaysia granted conditional approval for CoronaVac to be used on adolescents aged between 12–17 years. In September 2021 Sinovac announced the launch of a Phase 3 trial of CoronaVac on children and adolescents aged 6 months to 17 years in South Africa.Phase 1/2 and 3 trials still recruiting.	550 participants aged 3–17 years old in Phase 1/2 trial (71 for Phase 1 and 479 for Phase 2). Preliminary results from ongoing Phase 1/2 trial supported the use of 3 μg dose with a two-regimen schedule for further studies in children and adolescents above 3 years of age. Estimated enrollment in Phase 3 trial: 14,000 participants (including 200 participants aged 6–35 months, 3800 participants aged 3–5 years, 5000 participants aged 6–11 years and 5000 aged 12–17 years) to be randomized to two groups—vaccine and placebo—in a 1:1 ratio.	10.1016/S1473-3099(21)00319-4
	6–35 months	Still recruiting.	Estimated enrollment: 200 participants aged 6–35 months to be randomized to two groups—vaccine and placebo—in a 1:1 ratio.	No results published
BBV152	2–18 years	On 13 October 2021, in India the Subject Expert Committee approved the use of BBV152 for the beneficiaries aged 2–18 years old. Ongoing Phase 2/3 trials.	The Phase 2 clinical trial included 14 adolescents aged between 12–18 years: 10 in the 3 μg with Algel-IMDG group and 4 in the 6 μg with Algel-IMDG group. Participants aged 12–18 represented 3.7% of the total participants (n = 380), requiring follow-on studies on this population. Ongoing Phase 2/3 trial of BBV152 on children 2–18 years old in India, divided in three age groups: 2–6, 6–12 and 12–18 years. Estimated enrollment: 525 participants (175 in each age group), who receive two doses of BBV152 28 days apart.	10.1016/S1473-3099(21)00070-0 (results from Phase 1/2 trial only for adolescents 12–18 years old, who represented a very small proportion of the total participants)

TABLE 2. Continued.

Vaccine	Age group	Status of approval or recruitment	Comments	DOI of published results
ZyCoV-D	12–18 years	On 20 August 2021, ZyCoV-D received EUA from the Drug Controller General of India for use, apart from adults, in adolescents in the 12–18 years age group. Ongoing Phase 3 trials.	The Phase 3 trial in 28,216 subjects aged 12 years and above is currently ongoing. The number of participants aged 12–18, who were enrolled in the study, is not announced. Interim results in July 2021 demonstrated an overall efficacy of 67% against symptomatic SARS-CoV-2 infections (subgroup analysis regarding vaccine efficacy in adolescents is not announced).	No results published
NVX-CoV2373 (Nuvaxovid)	12–17 years	The company is going to submit applications to global regulatory authorities for the expansion of NVX-CoV2373 use in adolescents during the first trimester of 2022, after being approved for adult use in Europe in December 2021, as well as in the UK, Australia and New Zealand, in February 2022.	The Phase 3 trial included 2247 adolescents aged 12–17 years old (vaccine *vs.* placebo). Reported efficacy: 80%; 82% effective against the Delta variant.	No results published in peer-reviewed scientific journal
CIGB-66	3–18 years	On 01 July 2021, Cuba's National Regulatory Authority (Center for State Control of Medicines and Medical Devices—CECMED) authorized parallel Phase 1/2 trials for CIBG-66 in children above 3 years of age. The trials began on July 15. Still recruiting.	Target sample size for Phase 1/2 and 2 trials: 592 and minimum 700 children aged 3–18 years, respectively. The Phase 2 trial is a single arm study without a control group.	No results published
FINLAY-FR-2	3–18 years	On 14 June 2021, the recruitment of eligible participants for Phase 1/2 trials was initiated, after getting the proper approval of CECMED on June 10. On 14 July 2021, Phase 2 trials for the use of FINLAY-FR-2 in children aged 3–18 years began. Still recruiting. On 03 September 2021, the EUA of FINLAY-FR-2 was expanded to children aged 2–18 years old in Cuba.	In the preliminary stage of Phase 1/2 trials, 50 volunteers aged 3–18 years were enrolled (25 aged 12–18 and 25 aged 3–11). Safety of the vaccine was confirmed in the 12–18 years age group, before proceeding to the vaccination of the 3–11 years age group. Target sample size for Phase 1/2 and 2 trials: 350 and 425 children aged 3–18 years, respectively. Both trials are single arm studies without control groups.	No results published
FINLAY-FR-1A	2–18 years	Still recruiting.	Target sample size: 520 children aged 2–18 years. Single arm study without control group.	No results published

DOI: Digital Object Identifier; FDA: Food and Drug Administration; COVID-19: Coronavirus Disease 2019; EMA: European Medical Agency; CI: Confidence Interval; EU: European Union.

The initial concerns about the risk of COVID-19 vaccine-associated anaphylaxis soon diminished, as the widespread uptake of COVID-19 vaccines was not accompanied by a relatively higher incidence of severe vaccine-associated allergic reactions [136]. While mass COVID-19 vaccination in adults was advancing, myocarditis post mRNA-based vaccination arose as a rare but concerning adverse event [137, 138]. However, even the low numbers of mRNA-vaccine-related myocarditis cases observed mainly in young males were mild without persistent clinically important changes in the ejection fraction [139]. In addition, the risk of myocarditis following mRNA COVID-19 vaccination remains significantly lower compared to the risk of COVID-19-related cardiac injury, indicating clearly that the benefits of COVID-19 vaccination far outweigh the above risk [140, 141]. Moreover, the 5 times higher risk of myocarditis after the mRNA-1273 compared to the BNT162b2 was followed by the suspension of the administration of the Moderna vaccine in adolescents in multiple countries [142]. This fact demonstrates that the evaluation of vaccine safety is a dynamic process on a continuous basis, ensuring the efficacy of post-marketing surveillance and the integrity of the international pharmacovigilance systems [143–145].

The rapid development and distribution of COVID-19 vaccines has raised concerns in parents and public circles about the rationale of childhood vaccination against SARS-CoV-2, given the typically mild disease course in this age group [146–148]. Despite enabling this rapid development in the context of pandemic emergency, the novel mRNA vaccine platforms have triggered conspiracy theories, further aggravating the above dilemma and inevitably contributing to vaccine skepticism [149]. In addition, the universal COVID-19 vaccination of children and adolescents, as well as its mandatory component, remains demonstratively a matter of scientific and political debate [90, 146, 150–153].

It has to be admitted that the expeditious development of COVID-19 vaccines remains a major matter of concern. The accelerated speed of COVID-19 vaccines development is attributed to the unparalleled global coalition of academia, pharmaceutical companies and governments, which has mobilized abundant human and economic resources, and facilitated—to an unprecedented extent—the seamless exchange of medical data, scientific knowledge and biotechnology experience [145]. The legacy of the previous coronavirus epidemics (SARS-CoV, MERS-CoV), along with the evidence-based potential of novel vaccine platforms, reinforced and accelerated the development of vaccines against SARS-CoV-2 [154, 155]. Simultaneously, the government-endorsed front-load funding enabled the mass production of the vaccine candidates before their final approval, shifting the risk in terms of costs and failure from industry to governments [156]. This dynamic process was further assisted by the regulatory model of rolling review. The agility of the particular regulatory process, followed by the EMA, contributed to the substantial shortening of the COVID-19 vaccines approval timeline, but without bypassing any of the necessary steps that ensure the rigorous assessment of safety and effectiveness [157, 158]. To briefly explain the rolling review process, whenever the researchers had a predefined part of the clinical trial results available, they submitted it to the Committee for Medicinal Products for Human Use (CHMP), which examined it thoroughly in a prompt manner [145]. As a result, at the end of Phase III clinical trials, the volume of information to be evaluated was significantly reduced and more manageable, leading to shorter review time for conditional marketing authorization [159]. It is, therefore, obvious that the shorter approval timeline of COVID-19 vaccines by regulatory authorities was not under any circumstances the result of a "discount" in terms of safety or efficacy, which was an additionally alleged concern.

In contradiction to the expressed concerns, the overall safety of the approved COVID-19 vaccines in minors has been proven both in the short and long term, in the absence of serious side effects, especially compared to the complications of severe acute illness and MIS-C [104–106, 135, 140, 141]. Considering that vaccines have been approved for the pediatric population against diseases with comparatively lower mortality than COVID-19, the usefulness of vaccinating this age group is indicated, in order to shield them from the rare but potentially catastrophic complications of SARS-CoV-2 infection [160].

In real world settings, vaccinating children and adolescents against COVID-19 has been proven not to contribute essentially in blocking the transmission chain of SARS-CoV-2, especially under the prism of the emergence of the Delta and Omicron variants. [111, 161]. However, it is important to note that the currently approved vaccines have been developed based on the original strain of SARS-CoV-2, justifying their waning effectiveness at preventing infection and transmission over time [161]. Nevertheless, they retain their efficacy in preventing severe disease and MIS-C, which constitutes the basis for their recommendation in minors [20, 111].

Now that we have attained safe and effective "weapons" to combat the ongoing COVID-19 pandemic, there is still hesitation about vaccinating minors, not only from people who are systematically vaccine opponents, but also from people who, despite being vaccinated themselves, remain skeptical about vaccinating their children against SARS-CoV-2. Even at a national level, some countries have extended promptly their COVID-19 vaccination campaigns to adolescents and children aged 5–11 years, whereas others, such as the UK and Sweden, are more dubious. We should not omit to mention underprivileged countries which lack resources and infrastructure to vaccinate children. This raises ethical issues of healthcare inequities and poses, simultaneously, a major risk to public health, as the virus continues to spread and mutate. Initiatives, such as COVID-19 Vaccines Global Access—COVAX [162], have addressed these coverage gaps, declaring that "with a fast-moving pandemic, no one is safe, unless everyone is safe".

To put it concisely, in the interests of minors' health and welfare, along with the state of public health, vaccinating children and adolescents against SARS-CoV-2 represents a prudent decision.

This narrative review provides a comprehensive overview of the multi-faceted burden of COVID-19 on minors, highlighting the favourable safety/effectiveness profile of COVID-19 vaccines in this age group, based on the best available evidence, at the time of publication. The strength of our narrative review lies in the extensive and clearly defined literature-search methodology. To the best of our knowledge, this is one of

the first studies to include a comprehensive list of COVID-19 vaccine candidates trialed in children worldwide, underlining the intensity of all the current global scientific efforts towards the development of safe and effective COVID-19 vaccines for this particular age group. In addition, it provides evidence-based information regarding their accelerated but transparent approval for emergency use in minors, addressing raised safety concerns.

However, this review has limitations due to the lack of a systematic approach. Despite our efforts to search extensively for peer reviewed and non-academic literature, the rapidly evolving landscape of COVID-19 vaccine development and authorization might have contributed to the possible absence of some relevant articles.

Due to the narrative structure of the review, the quantitative evaluation of the efficacy of COVID-19 vaccines in minors is outside the scope of the present study, justifying the need for a future systematic review and meta-analysis.

7. Conclusions

Eventually, throughout the ongoing Odyssey of the COVID-19 pandemic, safe and effective COVID-19 vaccines are available for emergency use in children and adolescents. Despite the fact that the SARS-CoV-2 infection has typically a mild course in minors, severe acute COVID-19, with a disproportionate burden in underprivileged settings, the potentially fatal MIS-C, as well as the uncharted territory of long-COVID in this age group, highlight the essential need for active preventive measures and communication strategies, addressing both skepticism and access inequities. Under this prism, the rationale behind vaccinating children and adolescents against SARS-CoV-2 is justified and now attainable.

AUTHOR CONTRIBUTIONS

NK—conceptualized and designed the study, administered the project, defined the project outline, performed the literature search and study selection, wrote the original draft, reviewed and edited. AG—designed the study, developed the search strategy, performed the literature search and study selection, wrote the original draft, constructed the tables, reviewed, edited and corrected English. DI—contributed to the literature search, validated the data in the tables and edited. EV—designed the study, supervised, reviewed and edited. EK—performed the search in clinical trial registries, reviewed and edited. MK—reviewed and edited. AV—reviewed and edited. MS—supervised and reviewed. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Eleni Volakli, Maria Sdougka and Asimina Violaki are serving as the Guest editors of this journal. We declare that Eleni Volakli, Maria Sdougka and Asimina Violaki had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to DB.

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