

COVID-19 Vaccine in Children: Current Evidence and Recommendations

Vacinação contra a COVID-19 nas Crianças, Evidencia e Recomendações Atuais

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Resumo

A vacinação contra a COVID-19 constituiu uma estratégia fundamental no controlo da pandemia e o seu benefício foi maior nos grupos de maior risco e com maior mortalidade.

As crianças e adolescentes com COVID-19 apresentam, em geral, doença ligeira e frequentemente assintomática, mas existem manifestações clínicas graves respiratórias e/ou inflamatórias associadas em que há necessidade de internamento hospitalar e, em cerca de um terço dos casos, em unidades de cuidados intensivos (UCI).

A mortalidade por COVID-19 das crianças e adultos jovens é baixa e a existência de doenças crónicas ou condições médicas subjacentes tem relevância para a gravidade clínica e para o prognóstico.

Atualmente, após declaração do final da pandemia em Maio de 2023, a vacinação das crianças em Portugal deixou de abranger crianças saudáveis, mas inclui as crianças com imunossupressão e doenças crónicas. Seguindo as recomendações da OMS, vários países europeus adotaram uma estratégia semelhante. Outros países como os Estados Unidos da América mantêm vacinação de crianças saudáveis como parte da estratégia de saúde pública para controlo da doença e melhoria da imunidade.

Em Portugal, a vacinação das crianças pertencentes aos grupos de risco implica o envolvimento dos pediatras, que nas várias áreas seguem crianças com doenças crónicas e que poderão ter um papel relevante contrariando a hesitação vacinal, resultado de desconhecimento, má informação e de uma perceção errada de baixo risco.

Abstract

Vaccination against COVID-19 (coronavirus disease 2019) was a fundamental tool in the pandemic control strategy and its benefits were greater in the groups at higher mortality risk.

Children and adolescents with COVID-19 generally present with mild and often asymptomatic disease, but they may have severe respiratory and/or inflammatory clinical manifestations resulting in hospital admission with around one-third requiring intensive care. Mortality from COVID-19 in children and young adults is low and the existence of chronic diseases or underlying medical conditions is relevant to clinical severity and prognosis.

Currently, after the end of the pandemic was declared in May 2023, vaccination of children in Portugal no longer covers healthy children, but includes children with immunosuppression and chronic diseases. Following WHO recommendations, several European countries have adopted a similar strategy. Other countries, such as the United States of America (US), continue to vaccinate healthy children as part of the public health strategy to control the disease and improve immunity.

In Portugal, the vaccination of children belonging to risk groups requires the involvement of pediatricians, who are involved in the care of children with diverse chronic diseases in various areas and who may play a relevant role in overcoming vaccine hesitancy of the parents that results from lack of knowledge, misinformation or a mistaken perception of low risk.

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Introduction

COVID-19 is a respiratory disease caused by SARS-CoV-2, an RNA virus that is transmitted primarily by human contact via droplets and aerosols. Clinically, infection often presents with headaches, fatigue, coughing, myalgias and, in severe cases, it can progress to pneumonia, respiratory failure, multiorgan dysfunction syndrome and death.

The dissemination of the virus led to the outbreak being declared a pandemic in March 2020 and triggered an unprecedented scientific movement, contributing to an extensive understanding of the disease and the development of treatment and prevention means, including vaccines. Scientific, industrial and political institutions joined efforts to make vaccination available.

The assignment of risk levels to population groups led to the definition of differentiated vaccination priorities and schedules.

National vaccination strategies followed recommendations from regional and global organizations (WHO).¹ Since vaccines have become available, the priority has been protecting the more susceptible and then achieving herd immunity, protecting the population and restoring normality.

There is a large disproportion between the severity and mortality of the disease in adults and in children, as shown by UNICEF data (COVerAGE database),² which allows us to estimate that, between 2020 and 2022, children and adolescents up to 20 years of age (30% of the study population at risk) accounted for 21% of reported cases and 0.4% of deaths.

Immunosuppression and chronic diseases like diabetes, obesity, chronic lung, cardiac and neurologic diseases are commonly identified as risk factors for developing serious illness³ in adults and children.

More than a year after the pandemic was declared over in Europe, in Portugal Direção Geral de Saúde (DGS)⁴ recommends primary vaccination of children 6 months to 17 years with risk factors or pre-existing conditions, considered within the medium-risk group by WHO,¹ changing previous guidelines.

This review aims to find evidence for current recommendations, regarding the severity of the disease in the general pediatric population and in children with underlying health risks and the efficacy and safety of vaccines.

Methods

The narrative review search strategy was carried out in PubMed/Medline database (October 12, 2024) using the key terms "COVID-19 vaccine" AND "children" OR "child" OR "adolescent", in all fields.

The review includes systematic reviews and meta-analyses, randomized controlled trials, retrospective studies, prospective cohort studies and case series.

Only articles published in English were included and papers published before 2020 December (the beginning of COVID-19 vaccination) or papers reporting poor/non-extractable data were excluded. WHO, UNICEF, DGS, and CDC websites were also consulted (October 12, 2024).

Results

Clinical spectrum in children and adolescents

Children and adolescents with COVID-19 generally present with mild respiratory and often asymptomatic disease,⁵ although severe cases, including hospitalization in intensive care units (ICU) and deaths, were also reported in this group.

A recent review⁶ presented an interesting comparison between yearly incidence rates, admissions and number of deaths from COVID-19 with other childhood diseases pre-vaccine licensure, showing dramatically higher numbers for COVID-19, thus illustrating the relevance of pediatric COVID-19 (Table 1).

Table 1. Comparison between data of influenza and COVID-19⁶

	Incidence (years considered)	Admissions (years considered)	Deaths (years considered)
Influenza	20-30/100 000 (2010-2021)	20/100 000 (2017-2018)	171 (2017-2018)
COVID-19	100-1900/100 000 (2020-2023)	9-34/100 000 (2017-2018)	2320 (2020-2023)

In a cohort study in the United States (US),⁷ that included 20 714 children and adolescents 18 and younger with COVID-19, from March to October 2020, only 11.7% required hospitalization

and 3.6% in an ICU. The presence of a chronic condition compared to none was a risk factor, adjusted OR (odd ratio) 3.27 (95% confidence interval (CI) 2.44-4.37) (Table 2).

Table 2. Outcome of pediatric COVID-19, hospitalization and ICU⁷

	Pediatric covid cohort (n/%)	With hospitalization (n/%)	With ICU (n/%)
Total/ % of total	20714/ 100	2430/ 11.7	756/ 3.6
Presence of 1 or more chronic condition*	Yes- 6047 (29.2) No- 14667 (70.8)	1659 (68.3) 771 (31.7)	630 (84.3) 117 (15.7)

*Chronic Condition Indicator Refined (CCIR) for ICD-10-CM

Comparisons were often made between COVID-19 and flu. A multicenter study in the US compared pediatric patients admitted to ICU with severe COVID-19 and severe influenza,⁸ showing a similar proportion of patients requiring mechanical ventilation (30.2% in both) and a similar mortality rate (2.9% and 2.2%, $p=0.32$). Most patients in both groups had an

underlying medical condition (78.5% of the COVID-19 group, versus 66.4% of the influenza group), most frequently respiratory disease. The difference between influenza and COVID-19 was significant for immunosuppression and obesity which were more frequent in the COVID group, as shown in Table 3.

Table 3. Underlying Conditions in pediatric patients in ICU with influenza and COVID-19⁸

Characteristics	Influenza (n=179)	COVID-19 (N=381)	p value
Underlying condition, n (%)			
At least 1 underlying condition	119 (66.4)	299 (78.5)	0.002
Respiratory (including asthma)	71 (39.7)	143 (37.5)	0.63
Oncologic/immunosuppressive	3 (1.7)	47 (12.3)	<0.001
Body mass index-based obesity, n (%)	27/126 (21.4)	147/348 (42.2)	<0.001

In a series of 48 children with COVID-19 admitted to ICU,⁹ 40 (83%) had preexisting comorbidities; 35 (73%) presented with respiratory symptoms and 18 (38%) required invasive ventilation. Eleven patients (23%) had a failure of 2 or more organ systems and 2 patients (4%) died. Nineteen patients (40%) were classified as medically complex, defined as dependent on long-term technology support (including tracheostomy) associated to development delay and/or genetic anomalies.⁹

While the more common presentation is respiratory, a wide range of inflammatory conditions associated with COVID-19 infection present in childhood, including multisystem

inflammatory syndrome (MIS-C) a rare but severe condition involving various organs including the heart, a few weeks after acute infection.¹⁰

A prospective, observational study¹¹ in critical ill children hospitalized in 18 countries (n=557) found that mortality was 10% - 15% in children < 2 years - (odds ratio 1.94, 95% CI 1.08-3.49). Presentation without MIS-C (respiratory phenotype) had 13% mortality (49/367) vs 3.2% (6/188) with MIS-C and most who died had comorbid conditions.

A mortality study that analyzed data from the US, England and Spain, found an age-related U-shaped pattern of COVID-19

mortality, with the lowest rate between 3-10 years (newborns and infants having a high rate similar to the twenty year olds).¹²

In a national English study over a 22-month surveillance period,¹³ the 185 deaths in young people under 20 within 100 days of a SARS-CoV-2 positive test were analyzed and 81 were attributed to COVID-19. SARS-CoV-2 was responsible for 1.2% (81/6790) of all deaths in this population and for 0.7/100 000 infections. In this study 75% had significant underlying health conditions, mainly severe neurodisability and immunocompromised conditions. Many authors found the association with underlying conditions to clinical severity to be relevant.

Risk factors- chronic diseases and conditions

The CDC published an extensive albeit not exhaustive list of underlying medical conditions stratified into 3 levels of increased risk according to the strength of existing clinical evidence: higher risk (conclusive); suggestive of higher risk; and mixed evidence (non-conclusive). Underlying conditions for which there is evidence of higher risk in pediatric patients currently include neurologic conditions and disabilities including Down syndrome.¹⁴

A systematic review and meta-analysis which included 17 studies and was published in 2021 by Choi *et al*¹⁵ searched for evidence related to risk factors for severe COVID-19 in children and found: obesity (relative risk (RR) 1.43; 95% CI 1.24-1.64), diabetes (RR 2.26; 95% CI 1.95-2.62), chronic lung disease, (RR 2.62; 95% CI 1.71-4.0), heart disease (RR 1.82; 95% CI 1.58-2.09), neurologic disease (RR 1.18; 95% CI 1.05-1.33) and immunocompromised status (RR 1.44; 95% CI 1.01-2.04).

Woodruff,¹⁶ in a series of 3106 children hospitalized in 14 states in the US, differentiated relevant risk factors associated to severe COVID-19 by age. Under 2 years old, chronic lung disease (adjusted relative risk (aRR) 2.2 95% CI 1.1-4.3), neurologic disorders (aRR 2; 95% CI 1.5-2.6), cardiovascular disease (aRR 1.7; 95% CI 1.2-2.3), and prematurity (aRR 1.6; 95% CI 1.1-2.2) were shown to be relevant, whereas feeding tube dependence (aRR 2.0; 95% CI 1.5-2.5), diabetes mellitus (aRR 1.9; 95% CI 1.6-2.3) and obesity (aRR 1.2; 95% CI 1.0-1.4) were relevant among children and adolescents aged 2-17 years.

Gonzalez Dambraskas *et al*, in a multicenter, observational study including children with COVID-19 in ICU identified factors associated with mortality: cardiac disease (adjust OR (aOR) 2.89 (95% CI 1.20-6.94), pulmonary (not asthma) aOR 4.43 (95% CI 1.7-11.5), liver disease (aOR 12.2 (95% CI 2.82-53.3), malignancy (aOR 5.9 (95% CI 2.04-17) and malnutrition (aOR: 2.93 (95% CI 1.26-.,8)).¹¹

Underlying chronic respiratory disease is one of most frequently referred risk factors and includes various conditions and different associated risks.

In a survey¹⁷ promoted by the European Respiratory Society (ERS) with 174 participating centers, 945 children were included and underlying conditions were entered in 185 cases. Reported respiratory diseases were asthma (63), cystic fibrosis (CF) (14), non-CF bronchiectasis (10), bronchopulmonary dysplasia (BPD) (9), pulmonary hypertension (3) laryngomalacia (1), interstitial lung disease (2), tracheostomy (2) and other rare pulmonary conditions (7). Among the 185 children, 84 had other underlying conditions such as cardiac, oncologic, neurologic, renal, and miscellaneous diseases, including genetic and rare disorders. Thirty-five patients were hospitalized in ICU, and 17 had respiratory underlying disease. In the asthmatic group, 33 needed hospitalization, 5 were admitted to ICU care and no deaths were reported.

Data concerning asthma as a risk factor was controversial but a Scotland population study¹⁸ brought some clarification: children aged 5–17 years with poorly controlled asthma had a higher risk (HR) of COVID-19 hospital admission compared with those without asthma (previous asthma hospital admission HR 6.4; 95% CI 3.27-12.53) or ≥ 2 courses of oral corticosteroids (HR 3.53 (95% CI 1.87-6.67)).

In addition to the associated risks of more severe COVID-19, children with chronic diseases were also impacted by the disruption of their usual management and follow-up plan.¹⁹

Children vaccination- safety and efficacy data

A systematic review and meta-analysis²⁰ analyzed 88 studies with children and adolescents from 27 countries including the US, China, Australia, Argentina, Italy, Israel, France, Denmark and South Korea.

Comparing a partially vaccinated group (one dose) with a fully vaccinated group (two doses), vaccine effectiveness against infection was 42.87% vs 63.33%; against COVID-19, 60.65% vs 75.77% and hospitalization due to COVID-19 72.74% vs 82.78%. The incidence rates of any adverse event after the first dose were all over 30%, and the incidence rates of the more frequent adverse events were tenderness (52.77%), injection site pain (50.98%), fatigue/asthenia/tiredness (24.04%), headache (20.3%) and myalgia/muscle pain and chills (12.19%).

The incidence rate of myocarditis or pericarditis was 2.42/100 000 and 3.86/100 000 for acute allergic reactions. Children aged 5 or less had a lower incidence of adverse events compared with children 6-11 and 12-18 years.

Both the Food and Drug Administration (FDA) and EMA (European Medicines Agency) expanded the Emergency use Authorization for COVID-19 vaccines to include adolescents 12 years and older in 2021 and further extended it to children 5 to 11 years old in 2022. Monitoring systems are fundamental to safeguard safety and efficacy issues. From two safety monitoring systems in the US,²¹ with data concerning 172 032 vaccinated 12 to 17 year olds, most reported reactions following vaccine BNT-162b2 were mild to moderate, occurring most frequently on the day after vaccination and were more common after the second dose, compared with the first one. A total of 20 240 adverse events were reported and 91.5% were non-serious. The relevant adverse events were 40 cases of multisystem inflammation syndrome in children (1.2 cases per million vaccinations), 34 (85%) of which had evidence of prior severe COVID-19 infection and 570 cases of myocarditis (17.7 cases per million vaccinations), 77% of which were fully recovered at the time of the report.

Many studies report an increased risk of developing myocarditis after COVID-19 vaccination, particularly in male adolescents and young adults, although a systematic review published in 2022 indicated a 7-fold higher risk of myocarditis after SARS-CoV-2 infection than after COVID-19 vaccination.²² This difficulty in establishing the more relevant factor in developing myocarditis results from the inherent biases of observational studies. Currently, with almost universal infection and/or vaccination a decline in myocarditis cases is expected.²³

An English risk-benefit analysis²⁴ included 12-17 year old adolescents between July 2020 and March 2021, in a high incidence context of 680 cases per 100 000 showed: 169 412 cases which led to 1390 hospital admissions, 91 ICU admissions, 11 deaths and 6776 long COVID cases (4%). Vaccine-associated myocarditis/pericarditis were 6.72 cases per million after the first dose and 62.75 per million after the second dose in boys; and 0 cases after the first dose and 8.62 after the second dose in girls. Even in an incidence scenario of 50/100 000/week, vaccination would prevent 70 admissions and two deaths in 16 weeks.

An US case control study²⁵ involving 1185 patients and 1627 controls, from July 2021 to February 2022, showed vaccination to be effective at reducing the risk of hospitalization in both children and adolescents and reducing critical illness in adolescents. The risk of omicron-associated hospitalization was reduced by two-thirds among children 5 to 11 years of age. Among adolescents 12 to 18 years of age the two doses provided lower protection against omicron-associated hospitalization (40%) compared to delta-associated hospitalization (93%), but prevented critical illness caused by either variant.

Fayad⁶ reviewed safety data from VAERS and CISA and various studies concerning the efficacy of the 3 currently available vaccines in EU and concluded that they are safe, efficacious and effectively protect against COVID-19 and prevent severe disease in children and adolescents.

Vaccination strategy 2024 in Portugal

In Portugal, in 2024, the COVID-19 vaccination strategy of DGS⁴ is based on WHO guidelines and includes a primary vaccination schedule for children and young people 6 months to 17 years with risk disease criteria.

The risk disease criteria are active malignant neoplasm, transplantation, immunosuppression, HIV infection, neurological diseases (including neuromuscular diseases and cerebral palsy), severe and profound intellectual development disorder, trisomy 21, diabetes, obesity, cardiovascular disease, chronic renal failure on dialysis or stage III, IV and V and chronic lung disease. This last group includes chronic respiratory disease with long-term oxygen therapy or ventilation, severe asthma under systemic corticosteroid therapy, bronchiectasis, cystic fibrosis and alpha1 antitrypsin deficiency.

Seasonal booster vaccination is indicated for children 6 months to 4 years with severe to moderate immunosuppression and for older children with risk disease criteria, as indicated for the primary schedule.

Currently, a previous medical prescription on the electronic medical prescription (PEM) platform is necessary to vaccinate children who meet the vaccination criteria.

Recommendations in other countries / regions 2023-2024

The World Health Organization's current recommendation regarding post-pandemic vaccination recognizes healthy children and adolescents aged 6 months to 17 years as belonging to a low-priority group and considers their vaccination to have a low public health impact. The recommendation makes an allowance for national health authorities to consider vaccination of this group based on disease burden, cost-effectiveness and other public health priorities.¹

Children aged 6 months to 17 years with obesity or comorbidity that increases the risk of severe COVID-19 (without specifying diseases) are included in a medium-priority group, with an indication for a dose of vaccine. The WHO recommends taking risk groups into account for the selection of children to be vaccinated.

In Portugal, the current COVID-19 vaccination strategy, which is set out in standard 8/2024, recommends the vaccine for children with eligibility criteria that include a set of conditions and chronic diseases.

In other European countries, the recommendations are similar.²⁶ In Spain children 6 months to 12 years old with risk factors are vaccinated. France, Germany and Italy vaccinate people with 6 months or more and risk factors.

England indications (Greenbook) include only children with immunosuppression as a risk group for whom vaccination is indicated.²⁷

In September 2023, in the US the Advisory Committee on Immunization Practices (ACIP) issued a universal recommendation for the vaccination of people over 6 months of age with updated vaccines.²⁸

Vaccine hesitancy

Vaccine hesitancy is a relevant phenomenon that has been measured and characterized. COVID-19 vaccination in children occurred after adult vaccination and met with greater resistance. The willingness to vaccinate children was variable and one correlation described was with the country's rate of vaccination of the adult population as shown by Goldman.²⁹ Also vaccination of children is strongly influenced by the age and vaccination status of adults in the same household.³⁰

Regarding the vaccination of children with chronic diseases, in a survey in Italy involving parents of 5–11-year-old children, only 38.8% expressed an intention to vaccinate their children.³¹

Discussion

Circulating variants of the SARS-CoV-2 virus and their characteristics can impact COVID-19-associated risk but also the effectiveness of available vaccines, leading to the need for updating specific guidelines over time. Agencies like WHO, EMA and FDA continue to monitor safety and confirm a favorable risk-benefit profile and their recommendation are also based on the current hybrid immunity that naturally has been changing over time.

The number and quality of studies involving pediatric patients with COVID-19 compared to those for the adult population constitute a limitation in the complete definition of the risk factors associated with severe COVID disease. For many diseases, the presumption of risk is extrapolated from adult patients with the same condition.

It should be noted that the terms “medical complexity”, “cardiovascular disease” or “chronic lung diseases” are unavoidably vague and may cover a variable number of specific diseases. There may be, for example, no available data for certain rare diseases and conditions with a low prevalence which will not allow for an objective assessment of the risk they pose. The scarcity of pediatric evidence for most conditions is very impressive and probably due to the lower numbers of children affected. Nevertheless, the studies confirmed the significance of both severe disease and mortality in children and its association with pre-existing comorbidities.

Children with chronic diseases have care and follow-up plans with variable complexities that generally include immunizations. While the recommendation regarding flu vaccination is well-established, it is similarly important to follow recommendations regarding COVID-19 for chronically at-risk patients.

In Portugal, pediatricians who take care of children with chronic diseases/high-risk underlying conditions, have an important role in recognizing this risk, overcoming vaccine hesitancy and prescribing the vaccine.

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TND: Pesquisa, Análise dos dados, escrita de versão preliminar, revisão crítica

JBP: Análise dos dados, revisão crítica, perspectivas de reflexão

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