

Vaccine safety and vaccination against COVID-19 in adolescents



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Caution: Summary is a preliminary report of work by Pandemic Scientific Response team. It will be continuously updated accordance to the unfolding of events and emerging of scientific evidence.

In Brief

- The proportion of infection in the Malaysian population < 18-year-old was **17.3%** (322,694/1,862,187), and the fatality rate was **0.25%** (47/18,491) as of 6 September 2021. Similar increasing trend is observed worldwide partly due the Delta variant and the relative lower proportion of vaccination in this population group.
- The COVID-19 infection rates were generally < **3%** among the adolescents between 12 to 17-year-old and < **1%** among the children below 12-year-old.
- The young people with COVID-19 showed mild symptoms such as fever, dry cough, pneumonia and more gastrointestinal symptoms; whereas the adolescents presented more with dizziness, chills and myalgia.
- Among those infected, about **20%** would be hospitalised, about **2%** admitted to intensive care unit (<80% had comorbidities), and < **0.1%** died.
- Less than 1% of those infected experienced Multisystem Inflammatory Syndrome in Children (MIS-C) or Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) which is a severe, heterogeneous disease preponderant for males, adolescents, and racial and ethnic minorities.
- Generally, > **97%** recovered without any sequelae and about **2%** may experience the Long COVID syndrome for more than 3 months.
- The Pfizer-BioNTech vaccine safety profile in the U.S. adolescents aged 12–17 years during December 2020 to July 2021 reported **0.1%** (9,246/8.9 million) adverse events after vaccination.
- Out of those reported adverse events, about 90% of these were non-serious and **9.3%** were serious including myocarditis (**4.3%**) and death (**0.15%, n=14**).
- The non-serious vaccine reactions were mainly local to the injection site (about 60%), fatigue (about 35%), headache (about 30%) and myalgia (about 25%) felt the next day after both dose 1 and 2.
- Systemic reactions were about 50-55% after dose 1 and increase to 65-70% after dose 2. The common non-serious conditions included dizziness (about 20%), syncope (about 13%), headache (about 10%), fever, fainting, excessive sweating, fatigue and about 15% required an emergency evaluation.
- Comparing the potential harms of COVID-19 and the lesser adverse reactions from the vaccination, much biophysical-social benefits of vaccination beside relative higher antibody titre in the young, it is highly encouraged that the adolescent to be vaccinated.

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Summary

The COVID-19 infection rates in children and adolescents have been reported in several countries¹: **0.3%** in 1 to 4-year-old and **0.1%** in 5 to 17-year-old in the Americans, **1.2%** of 22,512 COVID-19 cases in Italy, and among the Australians **3%** were in 10 to 19-year-old and **1%** of all COVID-19 cases were aged under 10 years.

Whereas in Malaysia (according to a report in an online daily) among those infected < 18-year-old (n= 322,694, **9.9%**), 47 (**0.015%**) had died of COVID-19. The proportion of infection in this population was **17.3%** (322,694/1,862,187 number of infection in the country as of 6 September 2021), and the fatality rate was **0.25%** (47/18,491 deaths in the country as of 6 September 2021). Increasing trend is observed worldwide partly due the Delta variant and the relative lower proportion of vaccination in this population group, with the young population account for up to 20% of new COVID-19 cases in the US².

Population by age (0 to 19-year-old), 2020		2020	2021
Total population (all age groups)	32,657,300		
0 - 4	2,542,200		
5 - 9	2,554,000		
10 - 14	2,504,100		
15 - 19	2,835,700		
https://mysidc.statistics.gov.my/index.php?lang=en#			
Total infected (assuming there are 10,000,000 for 0 to 17-year-old in 2020-2021)		12,620 (0.12%) (6 died)	310,074 (3.1%) (41 died)
Infant & children < 5-year-old		3,180 (3 died)	81,168 (15 died)
Children 5-6-year-old		1,227 (0 died)	32,996 (1 died)
Children 7-12-year-old		4,071 (1 died)	106,823 (9 died)
Children 13-17-year-old		4,142 (2 died)	89,087 (16 died)

<https://www.nst.com.my/news/nation/2021/09/723745/47-children-under-18-died-covid-19-start-pandemic> (accessed on 6 September 2021)

An overview of SARS-CoV-2 global pandemic among the children of all age groups with COVID-19 in 266 English literature between January 2019 until August 2020 reported the following findings³:

1. From a total of 72,314 cases by the Chinese Center for Disease Control and Prevention less than **1%** were younger than 10 years old
2. Children have milder symptoms or even asymptomatic carriers, may be a reason of misdiagnosis or underdiagnosis. These might be due to children have powerful innate immune response and rarely have risk factors or underlying chronic conditions except obesity. This explains why they had faster recovery and better prognosis compared to adults.
3. Common presenting symptoms are similar to that in the adults which are the fever, dry cough, pneumonia but fewer children seem to have severe pneumonia and a sizeable of children had gastrointestinal

symptoms. This may be related with elevated expression or different functions of ACE-2 in their gastrointestinal tract. Fever in children with SARS-CoV-2 tends to ease within three days and is not a predictive marker of the final outcome as seen in adults where high-grade fever on admission was linked with ARDS and death. These trivial symptoms may mimic common childhood illnesses such as viral fever, bronchiolitis or acute gastroenteritis and thus overlooked that they become a source of COVID-19 transmission. The symptomatology is slightly different among the adolescents with dizziness, chills and myalgia were more commonly reported¹.

4. The average incubation period is approximately 6.5 days (compared to 5.4 days in adults)
5. **5.7%–20%** of children with COVID-19 were hospitalized, and **0.6%–2%** were admitted to intensive care unit (compared to 10%–33% were hospitalized and admitted to an intensive care unit in adults).
6. Compared to that in adult COVID-19, chest imaging in children are atypical with more localized ground glass opacities and scarce interlobular septal thickening. The most common finding is unilateral or bilateral sub-pleural bilateral ground glass opacity. Also, asymptomatic children have been reported to demonstrate abnormal CT findings. The plain chest radiography frequently missed lesions or important features in children. This cautions that timely thoracic CT imaging is needful in the young patients. Most lesions in children would fully resolve in a week but the lung changes in infected adults would only gradually be absorbed in 2 weeks.
 - a. The initial imaging may be normal, abnormalities are likely to be observed on CT following 6 days after symptoms onset. The adult patterns of multifocal peripheral patchy ground glass opacities or mixed consolidation, and when improved will appear as fibrotic stripes.
7. Leucocytosis and raised creatine kinase MB isoenzyme (CK-MB) appeared to be more common in children in contrary to adults. However, increased inflammatory markers and lymphocytopenia were less common in children.
8. Life-threatening and fatal cases were very rare (<0.1%) among the young patients and they were mostly in those with underlying chronic diseases. In a study of 48 children, 83% admitted to intensive care units had comorbidities and the case fatality rate was 4.2%.
9. Management of COVID-19 in children is also predominantly symptomatic and supportive as no specific therapy is currently available. In severe cases, intravenous immunoglobulin can be administered as compared to the use of methylprednisolone in adults. This was shown to reduce mortality.



It is noted that vaccination and effective treatment for COVID-19 should be based on actual physiological need and not purely based on the administratively driven definition of age ie children as < 12- or 18-year-olds or ascribing non-existent of mature physical sexual characteristics. Extra cautions and consideration as in case-by-case basis are needed in order to minimise the negative impact of the classification in the prevention and treatment of COVID-19 in minors⁴.

Multisystem Inflammatory Syndrome in Children (MIS-C) or Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS)

PIMS-TS/MIS(-C) has caused > 4100 cases in the US, with 37 deaths². Of the currently used case definitions, the WHO definition is preferred, as it is more precise, while encompassing most cases.

This serious complication usually presents

- At a median age of 8 years⁵
- In males (58.9%)
- In ethnic minorities (37.0% Black)
- Those with obesity (25.3%)
- Characterized by fever (99.4%), gastrointestinal (85.6%) and cardiocirculatory manifestations (79.3%), and increased inflammatory biomarkers, 50.3% present respiratory symptoms.
- Over half of patients (56.3%) present with shock
- Majority of the patients (73.3%) need intensive care treatment, including extracorporeal membrane oxygenation (ECMO) in 3.8%
- Mortality is about 1.9%

In a UK study of admission to 21 PICUs between April 1 and May 10, 2020⁶, 78 cases of paediatric PIMS-TS were reported in children (aged <18 years). Historical data for similar inflammatory conditions showed a mean of one (95% CI 0.85-1.22) admission per week, compared to an average of 14 admissions per week for PIMS-TS and a peak of 32 admissions per week during the study period.

The data over the first 4 days of admission showed a serial reduction in C-reactive protein (from a median of 264 mg/L on day 1 to 96 mg/L on day 4), D-dimer (4030 µg/L to 1659 µg/L), and ferritin (1042 µg/L to 757 µg/L), whereas the lymphocyte count increased to more than 1.0×10^9 cells per L by day 3 and troponin increased over the 4 days (from a median of 157 ng/mL to 358 ng/mL)⁶.

- 36 (**46%**) of 78 patients were invasively ventilated
- 65 (**83%**) needed vasoactive infusions
- 57 (**73%**) received steroids
- 59 (**76%**) received intravenous immunoglobulin
- 17 (**22%**) received biologic therapies
- 28 (36%) had evidence of coronary artery abnormalities (18 aneurysms and ten echogenicity)
- **Three** children needed extracorporeal membrane oxygenation
- **Two** children died



Long COVID in the young

In a recent Swiss study⁷ estimating the overall prevalence and burden of Long COVID symptoms in children and adolescents reported within 6 months (in March to May 2021) after SARS-CoV-2 serologic testing in October or November 2020, 4 of 109 seropositive participants (**4%**) vs 28 of 1246 seronegative ones (**2%**) reported at least 1 symptom lasting beyond 12 weeks (tiredness, difficulty concentrating, increased need for sleep, congested or runny nose, stomachache and chest tightness). The most frequently reported symptoms lasting more than 12 weeks among seropositive children were tiredness (3/109, **3%**), difficulty concentrating (2/109, **2%**), and increased need for sleep (2/109, **2%**). Similar proportions of seropositive and seronegative children reported excellent or good health.

In another similar study⁸ in UK in a cohort of PCR-confirmed SARS-CoV-2 infection compared to test-negative controls and age-, sex- and geographically-matched 11-17-year-old children and young people, at 3 months post-testing 66.5% of test-positives (n=3,065) and 53.3% of test-negatives (n=3,739) had any symptoms, with 30.3% and 16.2% had ≥ 3 symptoms, respectively. These indicated that about **10-15%** of the young COVID-19 people continue to experience some symptoms after recovery.

The assessed symptoms:

1. Fever
2. Chills
3. Persistent cough
4. Tiredness
5. Shortness of breath
6. Loss of smell
7. Unusually hoarse voice
8. Unusual chest pain
9. Unusual abdominal pain
10. Diarrhoea
11. Headaches
12. Confusion, disorientation or drowsiness
13. Unusual eye-soreness
14. Skipping meals
15. Dizziness or light-headedness
16. Sore throat
17. Unusual strong muscle pains
18. Earache or ringing in ears
19. Raised welts on skin or swelling
20. Red/purple sores/blisters on feet
21. Others

COVID-19 Vaccine Effectiveness

BNT162b2 (Pfizer–BioNTech) vaccine containing nucleoside-modified messenger RNA encoding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein has been tested and approved for use in healthy adults including those aged ≥ 16 years old.

Further study⁹ has shown that the observed vaccine efficacy was **100%** (95% CI, 75.3 to 100) against confirmed COVID-19 (onset ≥ 7 days after dose 2) among 12 to 15-year-old who received two injections, 21 days apart, of 30 μg of Pfizer's BNT162b2 (n= 1131) compared to those who received placebo (n=1129). The geometric mean ratio of SARS-CoV-2, 50% neutralizing titers after dose 2 in 12-to-15-year-old participants relative to 16-to-25-year-old participants was 1.76 (95% confidence interval [CI], 1.47 to 2.10), which met the noninferiority criterion of a lower boundary of the two-sided 95% confidence interval greater than 0.67.

Other vaccines that have been used among the adolescents include Moderna and Sinovac. Moderna vaccines has demonstrated similar safety and efficacy data to that of the BNT162b2 (Pfizer–BioNTech) in children aged 12 to 17-year-old. It has received the European Medicines Agency approval and pending the FDA's. Both companies are conducting studies in younger children spanning ages 6 months through 12 years. Meanwhile, the Sinovac (CoronaVac) vaccine has also been tested of its safety, tolerability, and immunogenicity in healthy children and adolescents (3 to 17-year-old) in clinical trials¹⁰. The study reported almost 100% seroconversion of neutralising antibody with only mild and moderate adverse reactions such as injection site pain, fever, headache, fatigue, etc.

COVID-19 Vaccine Safety in Adolescents Aged 12-17 Years

Looking into the Pfizer-BioNTech vaccine safety profile in the US through their Vaccine Adverse Event Reporting System (VAERS) and adverse events and health impact assessments reported in v-safe (a smartphone-based safety surveillance system)¹¹, a total of 9,246 (**0.1%**, out of approximately 8.9 million vaccinated) adverse events were reported after the vaccination in U.S. adolescents aged 12–17 years during December 14 year 2020 to July 16 year 2021. Out of this, 90.7% of these were non-serious adverse events and 9.3% were serious adverse events, including myocarditis (4.3%) and death (0.15%, 14). It was noted that the vaccine-related myocarditis was self-limited, uneventful recovery mostly in older boy within the first week after vaccination. However, it was reported that there were more myocarditis (2.3%) from COVID-19 disease and therefore vaccine is protective against COVID myocarditis².

The most frequently reported reactions after either dose were injection site pain (about 60%), fatigue (about 35%), headache (about 30%) and myalgia (about 25%). Common non-serious conditions included dizziness (1,862; 20.1%), syncope (1,228; 13.3%), and headache (1,027; 11.1%), fever, fainting, excessive sweating, fatigue and 145 (16.1%) were transported to an emergency department for further evaluation. The serious conditions include chest pain (56.4%), increased troponin levels (41.7%), myocarditis (40.3%), increased c-reactive protein (30.6%), and negative SARS-CoV-2 test results (29.4%). CDC reviewed 14 reports of death after vaccination. Among the decedents, four were aged 12–15 years and 10 were aged 16–17 years. The possible causes of death were pulmonary embolism (two), suicide (two), intracranial hemorrhage (two), heart failure (one), hemophagocytic lymphohistiocytosis and disseminated Mycobacterium chelonae infection (one), and unknown or pending further records (six).

During the week after receipt of dose 1, local (63.9%) and systemic (48.9%) reactions were commonly reported by adolescents aged 12–15 years; systemic reactions were more common after dose 2 (63.4%) than dose 1 (48.9%). Reporting trends were similar for adolescents aged 16–17 years: systemic reactions were reported among 55.7% after dose 1 and 69.9% after dose 2. For each dose and age group, reactions were reported most frequently the day after vaccination. The most frequently reported reactions for both age groups after either dose were injection site pain, fatigue, headache, and myalgia.

In another study¹² in Israel that analysed risk ratios and risk differences at 42 days after vaccination versus those unvaccinated, and comparing the same to those SARS-CoV-2-infected persons matched to uninfected persons, reported that the risk of serious adverse events was substantially higher after SARS-CoV-2 infection compared to that after vaccination (except in lymphadenopathy, herpes zoster and acute appendicitis) even though there was an increased risk after vaccination (see table below).

Adverse Events Associated with SARS-CoV-2 Vaccination and COVID-19

	Vaccination Analysis		COVID-19 Analysis	
	Vaccinated Group (N=884,828) vs. Control Group (N=884,828)	SARS-CoV-2- Infected Group (N=173,106) vs. Control Group (N=173,106)	Risk Ratio (95% CI)	Risk Difference per 100,000 persons (95% CI)
Acute Kidney Injury	0.44 (0.23 to 0.73)	-4.6 (-7.8 to -1.8)	14.83 (9.24 to 28.75)	125.4 (107.0 to 142.6)
Appendicitis	1.40 (1.02 to 2.01)	5.0 (0.3 to 9.9)	[1.10 (0.9 to 1.9)]	4 (unknown)
Arrhythmia	0.89 (0.74 to 1.04)	-6.1 (-14.7 to 1.8)	3.83 (3.07 to 4.95)	166.1 (139.6 to 193.2)
Deep Vein Thrombosis	0.87 (0.55 to 1.40)	-1.1 (-4.5 to 2.7)	3.78 (2.50 to 6.59)	43.0 (29.9 to 56.6)
Herpes Zoster Infection	1.43 (1.20 to 1.73)	15.8 (8.2 to 24.2)	[0.95 (0.85 to 1.04)]	-9 (unknown)
Intracranial Hemorrhage	0.48 (0.20 to 0.89)	-2.9 (-5.6 to -0.5)	6.89 (1.90 to 19.16)	7.6 (2.7 to 12.6)
Lymphadenopathy	2.43 (2.05 to 2.78)	78.4 (64.1 to 89.3)	[1.02 (0.9 to 1.7)]	3 (unknown)
Myocardial Infarction	1.07 (0.74 to 1.60)	0.8 (-3.3 to 5.2)	4.47 (2.47 to 9.95)	25.1 (16.2 to 33.9)
Myocarditis	3.24 (1.55 to 12.44)	2.7 (1.0 to 4.6)	18.28 (3.95 to 25.12)	11.0 (5.6 to 15.8)
Pericarditis	1.27 (0.68 to 2.31)	1.0 (-1.6 to 3.4)	5.39 (2.22 to 23.58)	10.9 (4.9 to 16.9)
Pulmonary Embolism	0.56 (0.21 to 1.15)	-1.5 (-3.6 to 0.4)	12.14 (6.89 to 29.20)	61.7 (48.5 to 75.4)

[] indicates estimated numbers extracted from graphs

Are children with COVID-19 really have mild disease, and there is no point immunizing them and exposing them to the vaccine adverse reactions?

Children and the young people in the population have the COVID-19 infection rate of **15-20%**, up to **4%** could be hospitalised, up to **0.4%** admitted into intensive care unit and about **0.002%** fatality rate. In addition to the much unquantifiable psychological, physical and financial effects to the family due to the infection, during quarantine, hospitalisation and treatment of the minors.

The current data showed that the potential harms of COVID-19 infection would be small comparing to the COVID-19 vaccine adverse reaction rate is about **0.1%**, serious ones is about **0.01%** and death due to the vaccine is about **1 in a million**. Instead, the risk of the same illnesses and complications were many more and higher in COVID-19. In addition to the benefits of vaccination, relatively higher antibody titre was induced among the younger population¹³, vaccination would allow social activities, enable engagement in educational activities, sports and emotional well-being for the children and the young people in the family as well.

Therefore, it is highly encouraged that all parents to come forward to have their 12 and 17-year-old adolescents vaccinated against the COVID-19. We shall wait for more data in those younger than 12-year-old. Unfortunately, we will not have long-term safety data to assist us in our decision during this span of pandemic.

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