Safety of BNT162b2 COVID-19 Vaccine in Adolescent Patients of UP-PGH

Roxanne J. Casis Hao, MD and Mary Anne R. Castor, MD

Division of Allergy and Immunology, Department of Pediatrics, Philippine General Hospital, University of the Philippines Manila

ABSTRACT

Background. In response to the pandemic brought about by COVID-19, vaccines were developed immediately. Together with adhering to safety protocols, vaccines are needed to help decrease the mortality and morbidity. As with any other, COVID-19 vaccines are evaluated based on efficacy and safety. Real world data is important in the recommendation of vaccines.

Objectives. This study aims to assess the short-term safety of BNT162b2 COVID-19 vaccines administered to Filipino adolescents from October 15, 2021 to December 15, 2021 at the Philippine General Hospital. The number and type of local and systemic reaction within 7 days of vaccination were determined.

Methods. This is a retrospective cohort study. The review of the recorded events was done through an electronic diary that was accessed from the official Electronic Medical Records of University of the Philippines-Philippine General Hospital (UP-PGH). This included solicited and prespecified local and systemic reactions that occurred within 7 days of receipt of vaccine dose. Descriptive statistics was used to present the data.

Results. Out of the 1,756 BNT162b2 vaccines administered (Dose 1- 890; Dose 2- 866), 13% (N=221) indicated having adverse reaction. Injection site pain was the overall most common reaction with majority (81%) experiencing it within 7 days of vaccination. Systemic reactions made up 60% of the reactions after Dose 1 and 85% of the reactions after Dose 2. This includes tiredness, headache and fever. None of the reactions required hospitalization or further workup.

Conclusion. BNT162b2 vaccine has a good safety profile among adolescents vaccinated at UP-PGH, since most of the reported adverse events within 7 days of vaccination were local and systemic reactogenic reactions that did not necessitate hospitalization or work-up. No serious adverse events were reported. Further follow-up is suggested to assess longer term safety.

Keywords: COVID-19 vaccine, mRNA vaccine, BNT162b2 vaccine, adverse events following immunization

INTRODUCTION

In January 2020, an enveloped RNA coronavirus was isolated in the patients affected and was determined to be caused by a zoonotic novel coronavirus, eventually named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] By March, the World Health Organization has recognized that coronavirus disease-2019 (COVID-19), caused by this virus, is a public health concern and declared it a pandemic.[2,3]

SARS-CoV-2 contains single stranded positive sense RNA genome which encodes for viral replication and structural proteins like the spike surface glycoprotein. SARS-COV-2 gains entry into the host cell thru its spike proteins (S proteins). The S proteins are composed of 2 sub units.[4] S1 subunit contains the receptor binding domain (RBD)

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Corresponding author: Roxanne J. Casis Hao, MD
Division of Allergy and Immunology
Department of Pediatrics
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: rjcasishao@up.edu.ph
ORCiD: https://orcid.org/0000-0003-4094-7736

which is crucial for attachment to the host cell receptor. On the other hand, S2 subunit facilitates subsequent fusion and intracellular movement in the host cell. SARS-CoV-2 utilizes angiotensin converting enzyme II (ACE2) receptor to invade the host cell in the heart, intestine, kidney, and the endothelial and type II alveolar host cells.[5,6] Once it gains entry, an immune response ensues which leads to the clinical features seen in COVID-19 patients.

In children and adolescents, fewer cases have been reported compared to adults. They are also noted to have mostly milder symptoms and lower death rates.[1] The reason for this variation in incidence and severity has not yet been established and multiple factors have been cited.[1] Some have postulated that this may be due to the lower binding affinity of the ACE2 receptors or decreased receptor expression in the younger age group.[6,7] Trained immunity from recurrent infections and vaccinations are also being alluded to as possible cause. Since children often get infected with common viruses, they may have cross-reactivity to SARS-CoV-2 which leads to an increase in the antibodies and increased innate immune response to these pathogens.[2,6] On the other hand, mandatory vaccinations in childhood, particularly Bacillus Calmette-Guérin (BCG), have also been considered to contribute to the age-related difference in COVID-19 severity.[6] However, this may be unlikely as there are countries who do not include BCG in their national immunization schedule. Lastly, children are almost always at home since the start of the pandemic which means exposure is less likely.

The average incubation period in children is between 3 and 7 days after which they may or may not develop symptoms.[8] Most common symptoms are still fever, cough, sore throat and nasal congestion. Although children rarely present with critical illness that requires hospital admission or intensive care, an inflammatory response similar to Kawasaki Disease (KD) has been reported.[2,9,10] Multi-system inflammatory syndrome (MIS-C) is a rare post COVID-19 infection commonly seen 2-6 weeks after an acute infection.[11,12] Similar to KD, they present with high fever, abdominal pain, vomiting, conjunctivitis, mucocutaneous symptoms and rash. The presence of gastrointestinal symptoms, shock and coagulopathy make it different from KD. Moreover, laboratory results may show elevated levels of ferritin, D-dimers, troponin, procalcitonin and C-reactive protein.[13,14]

Some of the factors identified that may lead to more severe conditions in children are male sex (about 60%), comorbidities (36-50%) such as immunosuppression, respiratory, cardiovascular and oncologic disorders, signs and symptoms of lower respiratory tract involvement on presentation (73%), viral coinfection (15%) and radiologic findings suggestive of pneumonia or ARDS (24-30%).[8,12,15-19] For adolescents, approximately one-third of those hospitalized receive intensive care while 4.9% are in need of mechanical ventilation.[20] They may also play a part in the transmission of COVID-19 and their vaccination would be important in achieving herd immunity.[21-23] Moreover, once adults are vaccinated, the younger age group would make up the remaining number of COVID-19 infections.[24,25] Additionally, the pandemic has had an impact on the students' schooling and social development, and has affected their caregivers as well.[26-28] Therefore, it is crucial that safe and efficacious vaccines be administered not just to adults but also to the younger age group.

Aside from adhering to safety protocols, vaccines are needed to decrease morbidity and mortality associated with COVID-19. There are several types of vaccines that have been developed but among those, only the mRNA (BNT162b2 and mRNA-1273) vaccines have received an emergency use authorization from our Philippine Food and Drug Administration (FDA) for administration to adolescents.[29]

In the phase 2-3 randomized placebo-controlled trial of mRNA-1273 SARS-CoV-2 Vaccine, which included 3732 healthy adolescents, concluded that the vaccine had an acceptable safety profile. The most common solicited adverse reaction from the vaccination group was injection site pain (93.1% of Dose 1 and 92.4% of Dose 2). This was followed by headache (Dose 1- 44.6%; Dose 2 – 70.25%) and fatigue (Dose 1- 47.9%; Dose 2 -67.8%). There were no serious adverse events reported.[30]

Likewise, in the randomized placebo-controlled trial of BNT162b2 COVID-19 vaccine including 2260 healthy adolescents, the authors concluded that the vaccine had a favorable safety and side-effect profile. The adverse reactions were mainly reactogenic that presented as injection site pain (79-86%), fatigue (60-66%), headache (55-65%). There were no serious adverse events, as well.[23]

As for studies on safety in adolescents with comorbidities, there was a survey done in the United Kingdom with 533 patients aged less than 16 years old given one or two doses of COVID-19 vaccine. Sixty percent of the patients received 2 doses of either Pfizer-BioNTech, AstraZeneca or Moderna. From this, only 2% had medically attended adverse events after Dose 1 and also 2, and these include headache and fever/flu-like symptoms.[31] A retrospective case series of Bickel et al. included 31 eligible patients that were admitted at a pediatric long term care facility and was given BNT162b2 vaccine. Most (Dose 1 – 26/31; Dose 2 – 23/31) did not report any side effect. The side effects that were recorded were mild and transient. The most common was agitation/discomfort (Dose 1- 3/31; Dose 2 – 4/31).[32]

The Center for Disease Control in the United States also tracks down adverse events using their Vaccine Adverse Event Reporting system (VAERS) and through v-safe (a smartphone-based surveillance system).[33] Adverse events reported from December 14, 2020-July 16, 2021 were collated. Out of the 8.9 million adolescents given BNT162b2 COVID-19 vaccine, there were 9246 reports of adverse events received through VAERS. Of these, most were non-serious (90.7%); 9.3% were serious adverse events including 4.3% for myocarditis. Out of the 129,000 enrolled adolescent in

v-safe, 63.4% reported local reaction while there were 48.9% systemic reactions. Common reactions include dizziness (20.1%), syncope (13.3%) and headache (11.1%).

Based on the Health Technology Assessment Council (HTAC) recommendation dated October 1, 2021, Pfizer-BioNTech and Moderna were found to be effective, can potentially reduce symptomatic and severe COVID-19 infection for the adolescent population.[29] On safety, the HTAC assessed, from available trials and real world data in other countries, that Pfizer-BioNTech and Moderna vaccines had acceptable short term safety profiles. The council added that follow up data from longer term studies and real world studies are still needed.

In October 15, 2021, the vaccination for adolescents with comorbidities in the Philippines was started. Initially eight key hospitals were identified to administer the vaccines which included UP-PGH. As the evidence on the management of COVID-19 continues to evolve, a local real world study looking into the safety of the COVID-19 vaccines administered to Filipino adolescents is important. It can address vaccine hesitancy because of perceived adverse reactions as well as prepare and educate healthcare workers in managing the possible reactions.

METHODS

This is a retrospective cohort study of patients aged 12-17 years old given BNT162b2 vaccine at the UP-GH from October 15, 2021 to Dec 15, 2021. BNT162b2 vaccine was the only vaccine provided to the adolescent patients of UP-PGH. This is a single center study.

This study aims to assess the short-term safety of BNT162b2 vaccine administered to Filipino adolescents from October 15, 2021 to December 15, 2021 at the Philippine General Hospital. The number and type of local and systemic reaction within 7 days of vaccination were determined.

The patients included were from the different subspecialty clinics of the UP-PGH Department of Pediatrics. The vaccination was offered to patients who were eligible based on stipulated operational guidelines on COVID 19 vaccination of the Pediatric Population Ages 12-17 years old with comorbidities (DOH department circular 2021-0464B) 34– this include/s document/s to prove filiation. Adolescents aged 12-17 years old with the following comorbidities were included: medical complexity (long term dependence on technical support), genetic conditions, neurologic conditions, metabolic/endocrine diseases, cardiovascular diseases, HIV, obesity, tuberculosis, chronic respiratory diseases, renal disorders, hepatobiliary diseases, and immunocompromised state due to disease or treatment. Exclusion criteria or rescheduling or deferment of vaccination as per DOH guidelines included the following: 1) presence of fever/ chills, headache, cough, colds, sore throat, myalgia, fatigue, weakness, loss of smell/taste, diarrhea, shortness of breath/ difficulty in breathing and rashes; 2) history of exposure to a confirmed or suspected COVID-19 case in the past 2 weeks; 3) confirmed COVID-19 patients with less than 90 days from the last isolation or treatment; 4) received convalescent plasma or monoclonal antibodies for COVID19 in the last 90 days; 5) received any other vaccine in the past 2 weeks. The patient's age, sex, history of allergies and other comorbid conditions were collected and tabulated during the health screening and assessment prior to vaccination which was done by a pediatric resident or fellow.

After vaccination, the patients and caregivers were instructed to fill up an electronic diary in digital form (Google form). This form included solicited, prespecified local reactions (injection site pain, swelling and redness), systemic events (anaphylaxis, tiredness, headache, muscle pain, fever, chills, joint pain, nausea, feeling unwell, swollen lymph nodes, difficulty breathing, dizziness, weakness, pruritus, loss of appetite, runny nose, nasal congestion, sore throat, others) and hospital admission during the first 7 days after receipt of each vaccine dose. This list of reactions was also as recommended in the DOH operational guidelines.[31] The patients and caregivers were instructed to indicate or choose the applicable symptoms that they have (if any) at any point within 7 days after receiving their dose. The UP-PGH COVID-19 Vaccine Adverse Event Following Immunization (AEFI) Management and Surveillance team also assisted by phone call or short message service (SMS) in reminding and assisting the patients if they had difficulty completing the form. A hotline number was also given to the patients in case of emergency or queries. Once a patient submits a response in the google form, an electronic mail will be sent to and alerts the members of the AEFI team. The pediatricians in the team contact the patient and assess the symptoms and need for further management. The responses submitted in the google form and further details gathered by the pediatrician were coordinated.

For this study, the authors were only able to review the recorded adverse events-saved in an anonymized Microsoft Excel file - extracted from the electronic diary. From data reviewed, the investigators were unable to differentiate the manner of how the data was collected - whether actively (patients answering directly through google forms) or passively (with a physician assisting). The authors did not have access to the data of the other vaccinees who did not have adverse reactions.

Sample Size

Slovin's formula was used to compute the minimum sample size. This was based on 1756 population size, 5% margin of error, and 95% confidence interval. Using the sample size equation below:

Sample size

$$n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$$

The sample size computed is 316.

Statistical Analysis

Descriptive statistics (percentages and counts) was used to analyze the data. Presentation of results were through graphs and tables.

Ethical Considerations

Conflict of Interest

There are no conflicts of interest in any form—financial, proprietary and professional with the study, primary investigator and the site to be declared.

Privacy and Confidentiality

The informed consent and assent provided by DOH prior to vaccination include the authorization for the release of data as needed for public health purposes, including vaccine registries.[31] However, since this is a retrospective study, consent for use of the data specifically for this study was not included. Hence, the records that were retrieved were anonymized and no patient identifiers were included in this final research paper. Moreover, the investigators were only allowed access to the data once the study was approved by the University of the Philippines Manila Research Ethics Board (UPMREB). The data was taken from the official Electronic Medical Records of UP-PGH, thus, the researchers complied with RA 10173 or Data Privacy Act of 2012. The electronic diary from where data was extracted was created and deployed by the surveillance nurse from the AEFI surveillance team. UP-PGH Hospital Infection Control Unit (HICU) owns this data and as such, only they can give access by sharing the google link through the surveillance nurse. Generally, only the members of the AEFI surveillance team are given access to the data which is dependent on the approval of HICU. This group of individuals is composed of the surveillance nurse from HICU, one pharmacist, UP Health Service Chair and Head Nurse, Department of Emergency Medicine representative, Division of Allergy representative, and Division of Pediatric Infectious Disease representative. Only select members of the surveillance team from HICU are "editors" or are allowed to input data while the rest who are granted access are only allowed as "viewers" and cannot change any of the data. Upon approval of the study by the UPMREB, the surveillance nurse designated by HICU provided the google link to the data set that is included in the study only and with no patient identifiers. The investigators were only allowed to view the data. The data is part of the national AEFI surveillance and it complements the vaccination program of the DOH. AEFI surveillance is applied up to 1 year from date of vaccination. However, monthly evaluation of the shared access is done to ensure that allowed persons are regularly updated. The investigator was allowed access while the study data collection was ongoing. All hard copies of data obtained by the investigator are kept under lock and key. Soft copies are in a password protected USB that is stored in the Division of Allergy and Immunology office at the Philippine General Hospital for 5 years. All of this may only be accessed by the research investigators with permission from the primary investigator. All data collected and forms used will be deleted from the primary investigator's laptop permanently a year after the study has ended. Results of the study will be disseminated through publication in a scientific journal after completion of the research and finalization of the manuscript. This study underwent the assessment and approval of the UPMREB prior to research implementation.

There was no direct benefit to the participants from this study and it will mainly be societal.

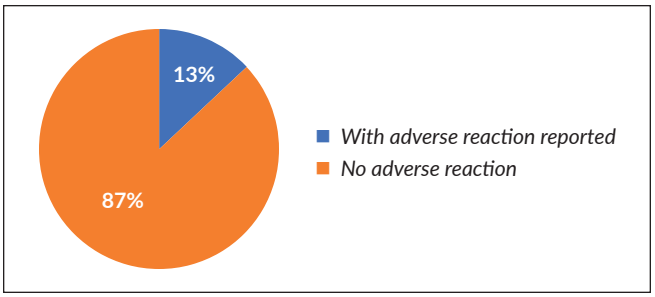

Figure 1. Percentage of adverse reactions among the total vaccines administered.

RESULTS

A total of 1,756 vaccines (Dose 1- 890; Dose 2 - 866) were administered to adolescents between October 15, 2021 and December 15, 2021. From this, 221 (13%) patients reported adverse reactions within 7 days of receipt of vaccine (Figure 1). These adverse reactions occurred, mostly (213/221), after Dose 1. The demographic profile of the patients with adverse reactions are as follows: 50.7% females, mean and median age of 15, with interquartile range of 3, 22.6% had a history of allergy, and 87% with noted comorbid conditions with some participants having more than one condition (Table 1).

There was a total of 497 adverse reactions reported (Dose 1(N) = 471; Dose 2 (N)=26) with some patients reporting more than one reaction. Over all, injection site pain was the most common adverse reaction reported by majority of the vaccinees. Local reactions (injection site pain, injection site swelling, injection site redness) made up 39% (193/497) of the total reactions (Table 2). Majority or 189 of 193 (97%) reported after Dose 1. None of the local reaction necessitated hospital admission or medical work up.

Systemic reactions made up 61% (N= 304) of the total reactions. Tiredness, headache, and fever were the most frequently reported event (Table 3). There were 282 systemic reactions after Dose 1 and 22 systemic reactions after Dose 2. Anaphylaxis was not reported by any of the participants. Similar to local reactions, none of the systemic reactions warranted admission or needed medical work up.

DISCUSSION

As the COVID-19 pandemic rapidly spread across the world, several vaccines of different platforms were developed in record time. Although the vaccines have been shown to be beneficial in mitigating the virus, the decision to get vaccinated not just involves its efficacy but the safety as well. A vaccine's safety profile includes all adverse events that may have been caused or worsened at any time after the vaccination.[32]

The results of the study showed higher rates of adverse events compared to the report by CDC (13% vs 0.1%).[32] Although the study revealed higher rates of total adverse events, it had zero serious adverse events compared to the 9.3% from the CDC VAERS.

It is also important to consider that reported adverse events may include reactogenic reactions. From the review of the records, all of the adverse events are reactogenic reactions since none of them necessitated further management and work up. Reactogenic reactions are the clinical signs and symptoms produced by the body's immune response to the vaccine.[33] These reactions are expected to happen since the vaccines contain antigens that are designed to elicit that immune response in order to provide the much-needed protection against the disease.

Reactogenicity may present as injection pain, redness, swelling, fever, headache, and myalgia.[33] Similarly, the most common elicited reactions in the study include injection site pain, tiredness, fever, and headache. Although majority of the reactions occurred within 7 days after the first dose, vaccine adherence was high with 97% of the patients getting the second dose. Furthermore, there were no serious adverse events reported.

Another reason for the higher adverse events reported may also be due to the nature of the electronic diary that used solicited responses as opposed to the passive surveillance used in the Vaccine Adverse Event Reporting System (VAERS)

Table 1. Demographic characteristics of participants

Characteristic	
***Sex** – N (%)*	
Male	109 (49.3)
Female	112 (50.7)
***Age at vaccination** (years)*	
Mean	15
Median	15
***Reported Allergy History** – N (%)*	
Yes	50 (22.6)
Drug	10 (4.5)
Food	21 (9.5)
Insect	1 (0.5)
Pollen	3 (1.4)
Multiple	12 (5.4)
Others	4 (1.8)
Animal dander (2) Mold (1) Housedustmite (1)	
No	168 (76)
***Comorbid conditions** – N (%)*	
Yes	191 (86)
Diabetes Mellitus	8
Allergic Rhinitis &/or Asthma	72
Urticaria/Atopic Dermatitis	9
Hypertension	8
On anticoagulant	1
Immunocompromised	7
Autoimmune condition	5
Neurologic	50
Cardiac conditions	16
Hematologic conditions	6
Tuberculosis	6
Renal Conditions	11
Obesity	10
Psychiatric Conditions	3
Genetic conditions	7
Endocrinologic/Metabolic conditions	13
Others	4
Hyperacidity (1) Hirschsprung's disease (1) Polycystic ovary syndrome (1) Pre hypertension (1)	
No	30 (14)

Table 2. Frequency of local reactions

Local Reaction	Dose 1	Dose 2	Total
Injection site pain	175	4	179
Injection site redness	3	0	3
Injection site swelling	11	0	11
Total	189	8	193

Table 3. Frequency of systemic reactions

Systemic Reaction	Dose 1	Dose 2
Anaphylaxis	0	0
Tiredness	58	1
Headache	41	3
Muscle pain	16	2
Chills	14	2
Joint pains	9	1
Fever	31	3
Nausea	3	0
Feeling unwell	18	2
Swollen lymph nodes	0	0
Difficulty of breathing	5	0
Dizziness	17	2
Weakness	11	2
Pruritus	2	0
Loss of Appetite	7	0
Runny nose	12	0
Nasal congestion	11	0
Sore throat	6	0
Others	21	4
Total	282	22

of CDC. It has been mentioned that solicited reactions are reported to a greater extent than when participants are asked to do it spontaneously.[32] Aside from the solicited reactions, the active surveillance of the AEFI team who called/contacted the patients having difficulties and queries increased the reporting.

This study has several limitations. The severity of the reactions was not classified and the duration of the reactions were not noted in the electronic diary. It is also recommended that long term safety studies be done in larger populations.

CONCLUSION

Among Filipino adolescents in UP-PGH, BNT 162b2 vaccine has a good safety profile since most of the reported adverse events within 7 days of vaccination were local and systemic reactogenic reactions that did not necessitate hospitalization or work up. No serious adverse events were reported.

Statement of Authorship

Both authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising, and final approval of the version to be published.

Author Disclosure

Both authors declared no conflicts of interest.

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REFERENCES

1. World Health Organization, COVID-19 disease in children and adolescents. [Internet]. 2021 [cited 2022 Feb]. Available from https://www.who.int/publications/i/item/WHO-2019-nCoV-Sci_Brief-Children_and_adolescents-2021.1
2. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020 Jun; 145(6):e20200702. doi: 10.1542/peds.2020-0702.
3. Karia R, Gupta I, Khandait H, Yadav A, Yadav A. COVID-19 and its Modes of Transmission. SN Compr Clin Med. 2020;2(10):1798-1801. doi: 10.1007/s42399-020-00498-4.
4. Fani M, Teimoori A, Ghafari S. Comparison of the COVID-2019 (SARS-CoV-2) pathogenesis with SARS-CoV and MERS-CoV infections. Future Virol. 2020 May; 15(5):317-323 doi: 10.2217/fvl-2020-0050
5. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Mar;579(7798):270-273. doi: 10.1038/s41586-020-2012-7.
6. Borrelli M, Corcione A, Castellano F, Fiori Nastro F, Santamaria F. Coronavirus Disease 2019 in Children. Front Pediatr. 2021 May;9:668484. doi: 10.3389/fped.2021.668484.
7. Fang F, Luo XP. Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives. Zhonghua Er Ke Za Zhi. 2020 Feb;58(2):81-85. doi: 10.3760/cma.j.issn.0578-1310.2020.02.001.:.
8. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspa M, Lancella L, Calò Carducci FI, et al,. COVID-19 Study Group. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health. 2020 Sep;4(9):653-661. doi: 10.1016/S2352-4642(20)30177-2.
9. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15;395(10223):497-506 doi: 10.1016/S0140-6736(20)30183-5.
10. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020 Jun;20(6):689-696. doi: 10.1016/S1473-3099(20)30198-5.
11. World Health Organization, Multisystem Inflammatory Syndrome in Children and Adolescents Temporally Related to COVID-19 [Internet]. 2020 [cited 2022 Feb]. Available from https://www.who.int/publications/i/item/multisystem- inflammatory- syndrome- in-children- and- adolescents- with- covid- 19
12. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: A systematic review. EClinicalMedicine. 2020 Jun;24:100433. doi: 10.1016/j.eclinm.2020.100433.
13. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. Multisystem Inflammatory Syndrome in Children Associated with Severe Acute Respiratory Syndrome Coronavirus 2 Infection (MIS-C): A Multi-institutional Study from New York City. J Pediatr. 2020 Sep;224:24-29. doi: 10.1016/j.jpeds.2020.06.045.
14. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C). Cell. 2020 Nov;183(4):982-995.e14. doi: 10.1016/j.cell.2020.09.034.
15. Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. Pediatrics. 2020 Oct;146(4):e2020009399. doi: 10.1542/peds.2020-009399.
16. Derespina KR, Kaushik S, Plichta A, Conway EE Jr, Bercow A, Choi J, et al. Clinical Manifestations and Outcomes of Critically Ill Children and Adolescents with Coronavirus Disease 2019 in New York City. J Pediatr. 2020 Nov;226:55-63.e2 doi: 10.1016/j.jpeds.2020.07.039.
17. Christophers B, Gallo Marin B, Oliva R, Powell WT, Savage TJ, Michelow IC. Trends in clinical presentation of children with COVID-19: a systematic review of individual participant data. Pediatr Res. 2022 Feb;91(3):494-501. doi: 10.1038/s41390-020-01161-3.
18. Garazzino S, Montagnani C, Donà D, Meini A, Felici E, Vergine G, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Euro Surveill. 2020 May;25(18):2000600. doi: 10.2807/1560-7917.ES.2020.25.18.2000600.
19. Mannheim J, Gretsch S, Layden JE, Fricchione MJ. Characteristics of Hospitalized Pediatric Coronavirus Disease 2019 Cases in Chicago, Illinois, March-April 2020. J Pediatric Infect Dis Soc. 2020 Nov;9(5):519-522. doi: 10.1093/jpids/piaa070.
20. Havers FP, Whitaker M, Self JL, Chai SJ, Kirley PD, Alden NB, et al. COVID-NET Surveillance Team. Hospitalization of Adolescents Aged 12-17 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 1, 2020-April 24, 2021. MMWR Morb Mortal Wkly Rep. 2021 Jun;70(23):851-857. doi: 10.15585/mmwr.mm7023e1.
21. Rumain B, Schneiderman M, Geliebter A. Prevalence of COVID-19 in adolescents and youth compared with older adults in states experiencing surges. PLoS One. 2021 Mar 10;16(3):e0242587. doi: 10.1371/journal.pone.0242587.
22. Szablewski CM, Chang KT, Brown MM, Chu VT, Yousaf AR, Anyalechi N, et al. SARS-CoV-2 Transmission and Infection Among Attendees of an Overnight Camp - Georgia, June 2020. MMWR Morb Mortal Wkly Rep. 2020 Aug;69(31):1023-1025. doi: 10.15585/mmwr.mm6931e1.
23. Frenck RW Jr, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021 Jul;385(3):239-250. doi: 10.1056/NEJMoa2107456.

24. The White House, Press briefing by White House COVID-19 response team and public health officials [Internet]. 2021 Apr 5 [cited 2022 Feb]. Available from: https://www.whitehouse.gov/briefing-room/press-briefings/2021/04/05/press-briefing-by-white-house-covid-19-response-team-and-public-health -officials-24/
25. Centers for Disease Control and Prevention, COVID data tracker [Internet]. 2021 [cited 2022 Feb] Available from: https://covid.cdc.gov/covid-data-tracker/#trends _dailytrendscases
26. Buonsenso D, Roland D, De Rose C, Vásquez-Hoyos P, Ramly B, Chakakala-Chaziya JN, et al. Schools Closures During the COVID-19 Pandemic: A Catastrophic Global Situation. Pediatr Infect Dis J. 2021 Apr;40(4):e146-e150. doi: 10.1097/INF.0000000000003052.
27. Masonbrink AR, Hurley E. Advocating for Children During the COVID-19 School Closures. Pediatrics. 2020 Sep;146(3):e20201440. doi: 10.1542/peds.2020-1440.
28. Townsend E. Debate: The impact of school closures and lockdown on mental health in young people. Child Adolesc Ment Health. 2020 Nov;25(4):265-266. doi: 10.1111/camh.12428.
29. Republic of the Philippines Health Technology Assessment Department of Health, Evidence summary on pediatric vaccination for the prevention of COVID-19. [Internet] 2021 Oct 28. [cited 2022 Feb]. Available from: https://hta.doh.gov.ph/2021/11/05/pediatric-vaccination-for-the-prevention-of-covid-19-12to17/
30. Ali K, Berman G, Zhou H, Deng W, Faughnan V, Coronado-Voges M, et al. Evaluation of mRNA-1273 SARS-COV-2 Vaccine in Adolescents. N Engl J Med. 2021 Dec; 385(24):2241-51. doi: 10.1056/NEJMoa2109522.
31. Aiano F, Campbell C, Saliba V, Ramsay ME, Ladhani SN. COVID-19 vaccine given to children with comorbidities in England, December 2020-June 2021. Arch Dis Child. 2022 March; 107(3):e16. doi: 10.1136/archdischild-2021-323162.
32. Bickel S, Harris C, Huxol H, Morton R. COVID-19 Vaccination Outcomes at a Pediatric Long-Term Care Facility. Pediatr Infect Dis. 2021 July 1; 40(7):e281-e283. doi: 10.1097/INF.0000000000003185.
33. Hause A, Gee J, Baggs J, Abara W, Marquez P, Thompson D, et al., COVID-19 Vaccine Safety in Adolescents Aged 12–17 Years - United States, December 14, 2020–July 16, 2021. [Internet] 2021 Aug 6 [cited 2022 Feb]. Available from: https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7031e1-H.pdf
34. Republic of the Philippines Department of Health Kagawaran ng Kalusugan, Department Circular No. 2021-0464-B: Further Amendment to DC 2021-0464 entitled "Interim Operational Guidelines on the COVID-19 vaccination of pediatric population ages 12-17 years old with comorbidities" [Internet]. 2022 Feb 11[cited 2022 Feb]. Available from: https://doh.gov.ph/covid19/amendment-to-dc2021-0464-B
35. Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da Silva F. The how's and what's of vaccine reactogenicity. NPJ Vaccines. 2019 Sep;4:39. doi: 10.1038/s41541-019-0132-6.