DOI: 10.1111/imr.13108

INVITED REVIEW

Immunological Reviews WILEY

Routine SARS-CoV-2 vaccination for all children*

Kristina De Paris[1] | Sallie R. Permar[2]

[1]Department of Microbiology and Immunology, Center for AIDS Research, and Children's Research Institute, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[2]Department of Pediatrics, Weill Cornell Medicine/ New York Presbyterian, New York, New York, USA

Correspondence
Sallie R. Permar, Department of Pediatrics, Weill Cornell Medicine, 525 East 68th Street, M-622, Box 225, New York, NY 10065, USA.
Email: sap4017@med.cornell.edu

Funding information
This study received funds from NIH NIAID 7P01AI117915 "Early Life Vaccination to Prevent HIV acquisition during Adolescence," awarded to SRP and KDP.

Summary

The SARS-CoV-2 pandemic has resulted in unprecedented health and economic losses. Children generally present with less severe disease from this virus compared with adults, yet neonates and children with COVID-19 can require hospitalization, and older children can develop severe complications, such as the multisystem inflammatory syndrome, resulting in >1500 deaths in children from COVID-19 since the onset of the pandemic. The introduction of effective SARS-CoV-2 vaccines in school-age children and adult populations combined with the emergence of new, more highly transmissible SARS-CoV-2 variants has resulted in a proportional increase of infections in young children. Here, we discuss (1) the current knowledge on pediatric SARS-CoV-2 infection and pathogenesis in comparison with adults, (2) the data on vaccine immunogenicity and efficacy in children, and (3) the benefits of early life SARS-CoV-2 vaccination.

KEYWORDS
children, infant immunity, MIS-C, SARS-CoV-2, vaccines

1 | INTRODUCTION

The SARS-CoV-2 pandemic has touched and changed our lives in many unforeseen ways and exposed the strengths and weaknesses of our societies. Leveraging our scientific knowledge and resources, we were able to introduce effective SARS-CoV-2 vaccines with unprecedented speed. At the same time, health inequalities, misinformation, and political complexities hampered efficient vaccine implementation. Currently, according to the Kaiser Family Foundation, <70% of the eligible world population has received at least one vaccine dose, many fewer have received the recommended booster vaccinations. Therefore, considering the continued emergence of new SARS-CoV-2 variants with higher transmission potential, inequity in vaccine distribution, and widespread vaccine hesitancy, vaccine coverage is suboptimal to curb the pandemic.

Several vaccines have been approved for use in adults, only few in adolescents, and so far just one, the Pfizer-BioNTech vaccine, has received emergency use authorization (EUA) for children 5 to 11 years,[1] but none yet for children under age 5. This lack of access to a vaccine in the youngest age group more than 1.5 years since a SARS-CoV-2 vaccine was approved for human use represents a health disparity for children. Both Pfizer-BioNTech and Moderna have submitted clinical trial data to the US FDA to obtain EUA for vaccination of infants aged 6 months to 5 years. Yet, delays in clinical testing of vaccines in this age group led to the vaccine efficacy being tested when circulating variants were more transmissible and could evade vaccine immunity, resulting in expected reduced efficacy that has clouded the vaccine approval process. Thus, even when approved, the opinion is expected to remain divided about the use of a pediatric SARS-CoV-2 vaccine for young children.[2] Here, we will attempt to provide a fair assessment of the importance of SARS-CoV-2 vaccine implementation in the pediatric population.

2 | POTENTIAL INNATE IMMUNE FACTORS CONTRIBUTING TO REDUCED DISEASE SEVERITY IN CHILDREN

The observation that children present with less severe disease and mortality compared with adults was surprising as many other

*This article is part of a series of reviews covering SARS-CoV-2 Immunity appearing in Volume 309 of *Immunological Reviews*.

© 2022 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

infectious diseases, including respiratory infections such as influenza, present with higher morbidity in infants compared with adults. Several reasons may account for the relatively mild disease outcomes in the pediatric population. An obvious explanation would be lower expression of the receptors for SARS-CoV-2 in relevant target tissues and cells. The literature on this topic remains controversial. Several studies have indeed reported that angiotensin converting enzyme 2 (ACE-2) mRNA levels increase with age in nasal epithelium and lung and are lowest in children.[3-6] Another study, however, reported that neonates have lower mRNA levels of ACE-2 and transmembrane serine protease 2 (TMPRSS2) in nasal scrape samples,[7] whereas children <18 years of age present with higher ACE-2 and comparable TRMPSS2 mRNA levels compared with adults.[8,9] Yet another study utilizing human lung tissue, revealed that ACE-2 expression on lung epithelial cells is low in the neonate, but higher in infants up to 1 year of age compared with children ages 1–17 years or adults up to 45 years of age.[10] In endothelial cells or other cell types of the lung, ACE-2 mRNA expression, however, is higher in adults compared to children of all ages.[10] These different findings might be due to the type of sample collected, the cellular composition of these samples, and/or the assay type for receptor expression. It should also be noted that most studies are limited in sample size and report a high inter-individual variation in ACE-2 mRNA expression. The fact that SARS-CoV-2 viral loads in nasal or nasopharyngeal samples of children and adults are of similar magnitude[4,11,12] argues against reduced infectivity due to lower receptor expression as cause for milder disease in children. Furthermore, studies have been unable to detect a relationship between viral load and ACE-2 expression.[11]

Infants receive many vaccines in the first year of life and it has been proposed that these frequent vaccinations could heighten innate immune responses, known as "trained immunity".[13-16] Indeed, live-attenuated vaccines such as measles, polio, and BCG have been associated with the induction of trained immunity.[17] Although the live attenuated polio and BCG vaccines are no longer administered in many high-income countries, the MMR, chickenpox and rotavirus live attenuated vaccines are included in the routine pediatric vaccine schedule; in low- and middle-income countries (LMICs), live attenuated polio and BCG vaccines are still widely distributed. Therefore, it is feasible that trained immunity aspects contribute to better control of SARS-CoV-2 infection in children,[13-16] but a causal relationship cannot be established.

There is evidence, however, that innate immune responses to SARS-CoV-2 infection differ between children and adults. Gene expression analysis of nasal swab samples revealed a strong induction of innate immunity and type I interferon (IFN) responses in infants, whereas in adult samples a bias toward higher metabolic activity was noted.[11] A more recent study confirmed higher local IFN in children compared with adults.[12] Increased IFN levels in children were, at least in part, ascribed to a higher pre-activation state of the IFN response in many epithelial cell types, but also in immune cells.[12] The SARS-CoV-2-induced IFN response, however, was more effectively induced in adults, both in the upper and lower airways and systemically.[12] Adults also presented with stronger systemic inflammatory responses, in particular elevated levels of D-Dimer and C-reactive protein (CRP) compared to children.[11] In contrast, a recent study did not find differences in type I IFN responses between adults and children <15 years of age with asymptomatic or mild disease, but also noted distinct gene expression pattern in nasal samples.[18] In the latter study, the cellular composition in acute SARS-CoV-2 infection changed from a predominance of epithelial cells to an increasing number of immune cells[18] and gene expression data confirmed increased activity in pathways associated with chemotaxis, neutrophil activation, and T-cell activation in adults, but not in infant samples. Consistent with these findings, higher frequencies of cells with cytotoxic potential, including NK cells, $CD8^+$ T cells, but also $CD4^+$ T cells, were found in adult compared to infant samples.[12] Furthermore, in adults the formation of neutrophil extracellular traps (NET) has been associated with COVID-19 disease severity.[19] Infants, however, have an impaired ability to form NETs.[20] Overall, these data imply a bias towards a stronger inflammatory response in adults, both locally and systemically, whereas infants may contain virus replication rapidly via type I IFNs at local entry sites and mount somewhat lower systemic inflammatory responses effectively resulting in reduced pathogenesis in most infants infected with SARS-CoV-2. Following up on these findings is important for development of potential therapeutic to reduce the severity of other respiratory pathogens that commonly cause severe disease in infants, such as respiratory syncytial virus.

Finally, children in general also have fewer comorbidities than adults, such as diabetes, cancer, and obesity, and thus fewer risk factors for severe COVID-19 than adults. Yet, children with severe disease and who have died from SARS-CoV-2 infection frequently have co-morbidities, with obesity as the most common co-morbidity associated with severe disease in adolescents.[21,22] With obesity affecting nearly 20% of the US childhood population, vaccination is an important tool to prevent infection in these high-risk populations.

3 | SEVERE DISEASE FROM COVID DOES NOT OCCUR FREQUENTLY IN CHILDREN, YET COVID-19 HAS BECOME A LEADING CAUSE OF DEATH IN CHILDREN

It will be essential to balance health benefits with potential risks to justify the introduction of a pediatric SARS-CoV-2 vaccine. What do the data tell us so far? According to WHO, SARS-CoV-2 infections have exceeded 500 million cases and resulted in >6 million deaths.[23] Children and adolescents account for about 21% of cases and 0.4% of deaths. For the purpose of this article, we will define children as being <18 years of age. Generally, pediatric SARS-CoV-2 infection is associated with less severe disease outcomes compared with adults.[24-28] However, over 1500 U.S. children have died from this infection since 2020, which is considerably higher than deaths that occurred annually from many viruses that we routinely vaccinate against, including influenza and varicella.[29] Moreover, severe complications, including the

pediatric inflammatory multisystem syndrome, temporally associated with SARS-CoV-2 (PIM-TS) and the multisystem inflammatory syndrome in children (MIS-C), have been observed in a subset of children.[30] Are these numbers sufficiently high and the disease outcomes severe enough to warrant a strong impetus on vaccination of the pediatric population? We could argue every life is worth saving. Skeptics raise alarm about potential long-term consequences.[2] As of May 2022, in the US alone, 8 million children ages 5 to 11 years have completed a two-dose SARS-CoV-2 vaccine regimen. The exceptional data on the safety and immunogenicity of the vaccines in these recipients should suffice to overcome any doubts on vaccine safety. While long-term outcome data on vaccine safety are indeed missing, yet vaccine safety events have never occurred at such a late juncture with previous vaccine platforms. Furthermore, the rare cases of myocarditis and pericarditis that have been observed in adolescents and young adults receiving SARS-CoV-2 vaccines[31-34] seem to be dose-dependent and have yet to be reported with lower dose pediatric vaccines in younger populations. Follow-up data demonstrated that all subjects had recovered and were asymptomatic,[35] and while some patients still presented with slight cardiac abnormalities, these occurred at a significantly lower rate than after SARS-CoV-2 infection.[36] The number of participants in clinical trials conducted in young infants (<5 years) is too low to detect rare events but given the lower doses being used in this population and relatively rare occurrence of myocarditis in this age group in general, a vaccine-associated risk for myocarditis in infants 6 months to 5 years of age is unlikely to be identified.

A French study reported that a hyperinflammatory syndrome after vaccination of 12 to 17 year old occurred at a rate of 1.5 per one million total vaccine recipients (95% CI 0.8, 2.6).[37] In contrast, 113 cases of MIS-C were observed among one million SARS-CoV-2 infections in the same age group.[37] Evidence is starting to emerge that vaccination can reduce the risk of MIS-C.[38] Prevention of MIS-C is important because affected infants and adolescents may face long-term health sequalae that are not yet known. Neurological manifestations have been seen in about 20% of MIS-C patients.[39] Although, as pointed out above, many patients appear to fully recover, fatal MIS-C outcomes due to encephalomyelitis or other causes have occurred.[40,41] It should be noted that the CNS is still developing in infants and adolescents, and thus, any damage can potentially be detrimental and long-lasting. Importantly, exact data on global SARS-CoV-2 infections in LMICs are often not available, especially when estimating pediatric cases. In fact, only recently a first study on MIS-C was reported from South Africa.[42] Therefore, on the global level, pediatric complications due to SARS-CoV-2 infection are most likely underreported and will continue to occur given the considerably lower vaccine coverage in LMICs.[42] In high income countries, such as the USA, the risk for MIS-C is increased in Black and Hispanic children.[30,41] This disparity could be due to socio-economic and health care access inequities, but genetic and environmental risk factors are still being explored. Yet should the latter be the case, we would expect a higher MIS-C incidence in South American and African countries.

4 | ROBUST IMMUNITY TO SARS-COV-2 INFECTION AND VACCINATION IN CHILDREN

Infants and children mount robust plasma and nasal antibody responses, and of similar magnitude as adults, against SARS-CoV-2.[11] A comparative study of children and adults demonstrated that antibodies in infants were preferentially targeting the spike protein and less frequently the N protein, whereas antibodies to both proteins were easily detectable in adults.[43] These findings have implications for serology testing approaches to confirm prior SARS-CoV-2 infection. There is conflicting evidence regarding the functional capacity of the antibody responses in children, while some studies reported neutralizing antibody responses of lower magnitude in children,[43,44] other studies observed comparable plasma antibody responses and neutralizing antibody titers in children and adults.[45,46]

Several studies have documented that SARS-CoV-2-specific T cell responses are reduced in children compared with adults.[46,47] Both the frequencies of $CD4^+$ and $CD8^+$ T cell responses to SARS-CoV-2 structural and ORF1ab proteins are lower in infants compared with adults when IFN-γ production or T cell activation are assessed, and infants also have lower frequencies of effector memory $CD4^+$ T cells.[47] There is, however, no age-dependent difference in overall polyfunctionality of the T cell response.[47] T cell responses persist and increase with time post infection in both age groups.[47] The impact on disease severity on T cell responses requires further clarification as both reduced[46] and stronger[48] T cell responses have been observed in children with MIS-C compared with children with mild COVID-19.

Pediatric immunity to SARS-CoV-2 mRNA-LNP vaccination has also proven to be robust, as demonstrated in the Pfizer and Moderna mRNA-LNP dosing studies in children ages 5-11 where vaccine doses of half or less than that used in adults were able to achieve similar spike-specific IgG responses and neutralizing titers.[49,50] Moreover, pre-fusion stabilized Spike mRNA-LNP vaccination of 2 month-old nonhuman primates at a lower dose than studied in pre-clinical adult nonhuman primate vaccines achieved high magnitude and durable binding and neutralizing antibody responses.[51] Finally, recent data released from Moderna on phase II/III studies in children ages 6 months to 6 years indicated that responses to a low dose mRNA-LNP vaccine that is a quarter of the adult dose elicited responses that were similar to that elicited in adolescents and young adults with the adult vaccine dose.[52] Further, Pfizer-BioNTech released preliminary information from their phase II/III trial in the same age group reporting that a low dose mRNA-LNP series of three immunizations was tolerable, immunogenic, and demonstrated 80% efficacy during a time when the Omicron variant was circulating.[53]

Prevention methods against SARS-CoV-2 infection in young infants include maternal vaccination. Despite being originally left out in clinical trials, pregnant women have significantly benefitted from vaccination.[54-56] Moreover, mothers vaccinated prior to or during pregnancy will transfer SARS-CoV-2 specific antibodies to their babies transplacentally and via breastmilk.[57,58] However, this passive protection is only going to protect the infant in the first 6 to 12 months of life prior to waning of maternal antibodies, and with the low durability and ongoing virus evolution, maternal antibodies are likely to only protect neonates for a few months. Even when breastfeeding is continued into the 2nd year of life, the decline of vaccine-induced antibodies and limited uptake of antibodies from breast milk into circulation would likely result in titers too low to protect the infant against infection. Importantly, vaccine authorization is unlikely to be granted prior to 6 months of life as infants under age 6 months have not been included in clinical trials. Yet, neonates are one of the most frequently hospitalized pediatric population from SARS-CoV-2 infection[59] and hospitalization of infants under 1 year of life increased during the Omicron waves of SARS-CoV-2 infection,[59] most of which did not have underlying conditions. Thus, it is likely that protection against severe COVID disease for all children will require vaccination at younger than 6 months of age. However, it is yet unknown whether pre-existing maternal antibodies against SARS-CoV-2 in infants will interfere with responses to mRNA-LNP or other SARS-CoV-2 vaccines, and this should be studied in both pre-clinical models and human trials.

5 | BENEFITS FAR OUTWEIGH THE RISKS: ADVANTAGES TO ROUTINE EARLY LIFE VACCINATION AGAINST SARS-COV-2

The benefits of childhood vaccination with SARS-CoV-2 vaccines far outweigh the risks of acquiring the infection when unvaccinated, placing the vaccine among the most important to child health as other routine vaccines, as well as seatbelts and car seats to prevent severe injury and death from motor vehicle accidents. Moreover, there are a host of reasons for SARS-CoV-2 vaccines to become part of the routine pediatric vaccine schedule starting in the first year of life. Advantages to early life immunization against SARS-CoV-2 include the following: (a) protection against infection and severe acute COVID disease for infants and children; (b) protection against COVID post-infectious inflammatory syndromes such as MIS-C; (c) potential protection against long lasting sequelae of COVID and long COVID; (d) reduction in transmission among households and congregate settings for children, including schools; (e) high magnitude and durable antibody responses can be elicited in early life via existing SARS-CoV-2 vaccines at lower doses, reducing side effects and adverse events; and (f) initiation of foundational immunity against SARS-CoV-2 and related coronaviruses in early life.

6 | REMAINING GAPS AND TASKS

The SARS-CoV-2 pandemic was preceded by the earlier outbreaks of SARS-CoV-1 in 2003 and the middle east respiratory syndrome (MERS) in 2013. We should assume that other coronaviruses will eventually evolve and jump species from their original hosts to humans.[60-64] To prevent future devastating outbreaks, continued basic science research in the area of virus evolution and immunity to protect against evolving strains is needed. The emergence of new variants of concern (VOCs) during the SARS-CoV-2 pandemic further emphasizes this point and also stresses the urgency for the development of a pan-coronavirus vaccine.

Right now, many questions about SARS-CoV-2 pathogenesis and prevention remain unanswered. Our knowledge about factors resulting in severe COVID-19 outcomes is still limited. What specific host immune mechanisms prevent severe disease in children, adolescents, and adults? Among those, which ones are common across all ages, and which one are age-specific. There is a need to identify biomarkers that can predict the emergence of late complication, such as MIS-C or long COVID. Why do some patients develop severe neurological symptoms, including lesions within the brain? In adults, male sex has been linked to higher morbidity and mortality, this has not been observed in children. What are the underlying reasons, do they include sex-specific regulation of gene expression? These are just a few of the areas that will require intensive research. We are only starting to gather data on long-term outcomes and such data need to be interpreted in the context of the relevant viral variant at the time of data collection. While many VOCs have demonstrated increased transmissibility, higher infection rates did not always translate into increased disease severity. Do we need age-specific diagnostic, treatment, and prevention strategies? The next few years will provide large population data to conclusively assess durability of vaccine-induced immunity and protective efficacy, data that will inform the need for additional vaccine boosts to protect against potentially newly emerging VOCs. The parallel real-world assessment of vaccine safety and risk is a necessary part of this evaluation, especially as COVID vaccines are rolled out in our youngest children. Without a doubt, new variants will continue to emerge, and in the opinion of the authors, we will be unable to end ongoing devastating effects of the pandemic if we do not ensure the wide-spread implementation of a safe and effective vaccination across all age groups.

7 | CONCLUDING REMARKS

The statistics on COVID-19 speak for themselves, as of May 16, 2022, globally SARS-CoV-2 infections have exceeded 500 million cases and resulted in >6 million deaths (covid19.who.int). Yet, less than 60 per 100 persons are fully vaccinated and <25 have received recommended booster doses.[23] Effective vaccines have

been developed, and it is up to the governing bodies of the global community to devise and implement the means to ensure sufficient vaccine production, distribution, and uptake across populations of all ages in high-, middle-, and low-income countries, in urban and rural areas, and at a cost that is affordable. To be successful in these efforts, we also need to overcome vaccine hesitancy, including for children. Therefore, politicians, health care providers, and scientists must work together and provide the critical real-world data on vaccine safety and effectiveness, as well as a uniform message on the importance of vaccination to ensure protection against effects of the COVID-19 pandemic for all populations. We have to clearly communicate in lay terms what vaccines are available, how they work, what their limitations are, and why the benefits outweigh the risks. Moreover, we should build on global successes of routine pediatric vaccine schedules for protection against and elimination of a number of previous pandemic pathogens. Thus, we conclude that the SARS-CoV-2 vaccine should become a routine pediatric vaccine recommended and available worldwide, providing the highest chance of success in putting the unprecedented global effects of the SARS-CoV-2 virus behind us.

AUTHOR CONTRIBUTIONS

KDP and SRP equally contributed to conceptualization and writing of the manuscript.

ACKNOWLEDGEMENTS

There is an enormous amount of literature on SARS-CoV-2 infection, pathogenesis, treatment, and vaccination. We realize that our references are often only touching upon the sheer number of papers available and apologize to all the authors we have not cited and want to emphasize that every contribution to the fight against COVID-19 is greatly appreciated.

CONFLICT OF INTEREST

Dr. Permar serves a consultant to GSK, Merck, Pfizer, Moderna, Hoopika, and Dynavax on their vaccine programs for cytomegalovirus (CMV), and has a sponsored program on CMV vaccine development with Moderna and Merck. Dr. Permar also serves as an educator on CMV for Medscape.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Sallie R. Permar https://orcid.org/0000-0003-1438-4554

REFERENCES

1. Creech CB, Walker SC, Samuels RJ. SARS-CoV-2 Vaccines. *JAMA*. 2021;325:1318-1320.
2. Lavine JS, Bjornstad O, Antia R. Vaccinating children against SARS-CoV-2. *BMJ*. 2021;373:n1197.
3. Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA*. 2020;323:2427-2429.
4. Yonker LM, Neilan AM, Bartsch Y, et al. Pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): clinical presentation, infectivity, and immune responses. *J Pediatr*. 2020;227:45-52.e5.
5. Muus C, Luecken MD, Eraslan G, et al. Single-cell meta-analysis of SARS-CoV-2 entry genes across tissues and demographics. *Nat Med*. 2021;27:546-559.
6. Steinman JB, Lum FM, Ho PP, Kaminski N, Steinman L. Reduced development of COVID-19 in children reveals molecular checkpoints gating pathogenesis illuminating potential therapeutics. *Proc Natl Acad Sci USA*. 2020;117:24620-24626.
7. Heinonen S, Helve O, Andersson S, Janer C, Suvari L, Kaskinen A. Nasal expression of SARS-CoV-2 entry receptors in newborns. *Arch Dis Child Fetal Neonatal Ed*. 2022;107:95-97.
8. Hasan MR, Ahmad MN, Dargham SR, et al. Nasopharyngeal expression of angiotensin-converting enzyme 2 and transmembrane serine protease 2 in children within SARS-CoV-2-infected family clusters. *Microbiol Spectr*. 2021;9:e0078321.
9. Plaas M, Seppa K, Gaur N, Kasenomm P, Plaas M. Age- and airway disease related gene expression patterns of key SARS-CoV-2 entry factors in human nasal epithelia. *Virology*. 2021;561:65-68.
10. Inde Z, Croker BA, Yapp C, et al. Age-dependent regulation of SARS-CoV-2 cell entry genes and cell death programs correlates with COVID-19 severity. *Sci Adv*. 2021;7:eabf8609. doi:10.1126/sciadv.abf8609
11. Pierce CA, Sy S, Galen B, et al. Natural mucosal barriers and COVID-19 in children. *JCI Insight*. 2021;6:e148694. doi:10.1172/jci.insight.148694
12. Yoshida M, Worlock KB, Huang N, et al. Local and systemic responses to SARS-CoV-2 infection in children and adults. *Nature*. 2022;602:321-327.
13. Gursel M, Gursel I. Is global BCG vaccination-induced trained immunity relevant to the progression of SARS-CoV-2 pandemic? *Allergy*. 2020;75:1815-1819.
14. Mantovani A, Netea MG. Trained innate immunity, epigenetics, and Covid-19. *N Engl J Med*. 2020;383:1078-1080.
15. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? *Nat Rev Immunol*. 2020;20:335-337.
16. Netea MG, Giamarellos-Bourboulis EJ, Dominguez-Andres J, et al. Trained immunity: a tool for reducing susceptibility to and the severity of SARS-CoV-2 infection. *Cell*. 2020;181:969-977.
17. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci USA*. 2012;109:17537-17542.
18. Koch CM, Prigge AD, Anekalla KR, et al. Age-related differences in the nasal mucosal immune response to SARS-CoV-2. *Am J Respir Cell Mol Biol*. 2022;66:206-222.
19. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. *J Exp Med*. 2020;217:e20200652. doi:10.1084/jem.20200652
20. Yost CC, Cody MJ, Harris ES, et al. Impaired neutrophil extracellular trap (NET) formation: a novel innate immune deficiency of human neonates. *Blood*. 2009;113:6419-6427.
21. Harwood R, Yan H, Talawila Da Camara N, et al. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: a systematic review and individual patient meta-analysis. *EClinicalMedicine*. 2022;44:101287.
22. Choi JH, Choi SH, Yun KW. Risk factors for severe COVID-19 in children: a systematic review and meta-analysis. *J Korean Med Sci*. 2022;37:e35.
23. Organization WH. 2022. covid19.who.int. Accessed May 16, 2022.
24. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch Dis Child*. 2020. doi:10.1136/archdischild-2020-320338. Epub ahead of print.

25. Zimmermann P, Curtis N. COVID-19 in children, pregnancy and neonates: a review of epidemiologic and clinical features. *Pediatr Infect Dis J*. 2020;39:469-477.
26. Zimmermann P, Curtis N. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in children. *Pediatr Infect Dis J*. 2020;39:355-368.
27. Butt AA, Dargham SR, Loka S, et al. COVID-19 disease severity in children infected with the omicron variant. *Clin Infect Dis*. 2022. doi:10.1093/cid/ciac275. Epub ahead of print.
28. Blanchard-Rohner G, Didierlaurent A, Tilmanne A, Smeesters P, Marchant A. Pediatric COVID-19: immunopathogenesis, transmission and prevention. *Vaccines (Basel)*. 2021;9:1002. doi:10.3390/vaccines9091002
29. CDC. 2022. Flu & Young Children, *on* CDC. cdc.gov. Accessed May 16, 2022.
30. Moss WJ, Gostin LO, Nuzzo JB. Pediatric COVID-19 vaccines: what parents, practitioners, and policy makers need to know. *JAMA*. 2021;326:2257-2258.
31. Morton Z, Green D, Grisham M. A case of myopericarditis following administration of the Pfizer COVID-19 vaccine. *Arch Clin Cases*. 2022;9:1-5.
32. Wu CT, Chin SC, Chu PH. Acute fulminant myocarditis after ChAdOx1 nCoV-19 vaccine: a case report and literature review. *Front Cardiovasc Med*. 2022;9:856991.
33. Asaduzzaman M, Purkayastha B, Alam MMJ, Chakraborty SR, Roy S, Ahmed N. COVID-19 mRNA vaccine-associated encephalopathy, myocarditis, and thrombocytopenia with excellent response to methylprednisolone: a case report. *J Neuroimmunol*. 2022;368:577883.
34. Ahmed SK. Myocarditis after BNT162b2 and mRNA-1273 COVID-19 vaccination: A report of 7 cases. *Ann Med Surg (Lond)*. 2022;77:103657.
35. Hadley SM, Prakash A, Baker AL, et al. Follow-up cardiac magnetic resonance in children with vaccine-associated myocarditis. *Eur J Pediatr*. 2022;1-5. doi:10.1007/s00431-022-04482-z. Epub ahead of print.
36. Patel T, Kelleman M, West Z, et al. Comparison of multisystem inflammatory syndrome in children-related myocarditis, classic viral myocarditis, and COVID-19 vaccine-related myocarditis in children. *J Am Heart Assoc*. 2022;11:e024393.
37. Ouldali N, Bagheri H, Salvo F, et al. Hyper inflammatory syndrome following COVID-19 mRNA vaccine in children: a national post-authorization pharmacovigilance study. *Lancet Reg Health Eur*. 2022;17:100393. doi:10.1016/j.lanepe.2022.100393:100393
38. Nygaard U, Holm M, Hartling UB, et al. Incidence and clinical phenotype of multisystem inflammatory syndrome in children after infection with the SARS-CoV-2 delta variant by vaccination status: a Danish nationwide prospective cohort study. *Lancet Child Adolesc Health*. 2022. doi:10.1016/S2352-4642(22)00100-6. Epub ahead of print.
39. LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. *JAMA Neurol*. 2021;78:536-547.
40. Duarte-Neto AN, Caldini EG, Gomes-Gouvea MS, et al. An autopsy study of the spectrum of severe COVID-19 in children: from SARS to different phenotypes of MIS-C. *EClinicalMedicine*. 2021;35:100850.
41. Encinosa W, Figueroa J, Elias Y. Severity of hospitalizations from SARS-CoV-2 vs influenza and respiratory syncytial virus infection in children aged 5 to 11 years in 11 US States. *JAMA Pediatr*. 2022;176:520-522.
42. Butters C, Abraham DR, Stander R, et al. The clinical features and estimated incidence of MIS-C in Cape Town, South Africa. *BMC Pediatr*. 2022;22:241.
43. Weisberg SP, Connors TJ, Zhu Y, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. *Nat Immunol*. 2021;22:25-31.
44. Pierce CA, Preston-Hurlburt P, Dai Y, et al. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. *Sci Transl Med*. 2020;12:eabd5487. doi:10.1126/scitranslmed.abd5487
45. Lau EHY, Tsang OTY, Hui DSC, et al. Neutralizing antibody titres in SARS-CoV-2 infections. *Nat Commun*. 2021;12:63.
46. Singh V, Obregon-Perko V, Lapp SA, et al. Limited induction of SARS-CoV-2-specific T cell responses in children with multisystem inflammatory syndrome compared with COVID-19. *JCI Insight*. 2022;7:e155145. doi:10.1172/jci.insight.155145
47. Cohen CA, Li APY, Hachim A, et al. SARS-CoV-2 specific T cell responses are lower in children and increase with age and time after infection. *Nat Commun*. 2021;12:4678.
48. Conway SR, Lazarski CA, Field NE, et al. SARS-CoV-2-specific T Cell responses are stronger in children with multisystem inflammatory syndrome compared to children with uncomplicated SARS-CoV-2 infection. *Front Immunol*. 2021;12:793197.
49. Creech CB, Anderson E, Berthaud V, et al. Evaluation of mRNA-1273 Covid-19 vaccine in children 6 to 11 years of age. *N Engl J Med*. 2022;386:2011-2023. doi:10.1056/NEJMoa2203315
50. Walter EB, Talaat KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. *N Engl J Med*. 2022;386:35-46.
51. Garrido C, Curtis AD 2nd, Dennis M, et al. SARS-CoV-2 vaccines elicit durable immune responses in infant rhesus macaques. *Sci Immunol*. 2021;6:eabj3684. doi:10.1126/sciimmunol.abj3684
52. investors.modernatx.com. Moderna announces its COVID-19 vaccine phase 2/3 study in children 6 months to under 6 years has successfully met its primary endpoint. 2022. https://www.accesswire.com/694300/Moderna-Announces-its-COVID-19-Vaccine-Phase-23-Study-in-Children-6-Months-to-Under-6-Years-Has-Successfully-Met-Its-Primary-Endpoint. Accessed May 16, 2022.
53. Pfizer. Pfizer-BioNTech COVID-19 Vaccine demonstrates strong immune response, high efficacy and favorable safety in children 6 months to under 5 years of age following third dose. 2022. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-biontech-covid-19-vaccine-demonstrates-strong-immune#:~:text=search%20results%20for-,Pfizer%2DBioNTech%20COVID%2D19%20Vaccine%20Demonstrates%20Strong%20Immune%20Response%2C,of%20Age%20Following%20Third%20Dose&text = NEW%20YORK%20%26%20MAINZ%2C%20Germany%2D%2D(BUSINESS%20WIRE)%2D%2D%20Pfizer%20Inc. Accessed May 14, 2022.
54. Giles ML, Gunatilaka A, Palmer K, Sharma K, Roach V. Alignment of national COVID-19 vaccine recommendations for pregnant and lactating women. *Bull World Health Organ*. 2021;99:739-746.
55. Shook LL, Fallah PN, Silberman JN, Edlow AG. COVID-19 vaccination in pregnancy and lactation: current research and gaps in understanding. *Front Cell Infect Microbiol*. 2021;11:735394.
56. Butt AA, Chemaitelly H, Al Khal A, et al. SARS-CoV-2 vaccine effectiveness in preventing confirmed infection in pregnant women. *J Clin Invest*. 2021;131:e153662. doi:10.1172/JCI153662
57. Collier AY, McMahan K, Yu J, et al. Immunogenicity of COVID-19 mRNA vaccines in pregnant and lactating women. *JAMA*. 2021;325:2370-2380.
58. Beharier O, Plitman Mayo R, Raz T, et al. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. *J Clin Invest*. 2021;131:e154834. doi:10.1172/JCI154834
59. Marks KJ, Whitaker M, Agathis NT, et al. Hospitalization of infants and children aged 0–4 years with laboratory-confirmed COVID-19 - COVID-NET, 14 states, March 2020–February 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71:429-436.

60. Menachery VD, Yount BL Jr, Debbink K, et al. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med*. 2015;21:1508-1513.
61. Menachery VD, Yount BL Jr, Debbink K, et al. Author correction: a SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med*. 2020;26:1146.
62. Morens DM, Breman JG, Calisher CH, et al. The origin of COVID-19 and why it matters. *Am J Trop Med Hyg*. 2020;103:955-959.
63. Ge XY, Li JL, Yang XL, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature*. 2013;503:535-538.
64. Li W, Shi Z, Yu M, et al. Bats are natural reservoirs of SARS-like coronaviruses. *Science*. 2005;310:676-679.

How to cite this article: De Paris K, Permar SR. Routine SARS-CoV-2 vaccination for all children. *Immunol Rev*. 2022;309:90-96. doi: 10.1111/imr.13108