COVID-19 Vaccine Clinical Trial Updates

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Why Do We Need COVID-19 Vaccines in Children?

1. Direct effects
   - At least 322 children in the U.S. have died from COVID[1]
   - The pandemic also has taken a toll on:
     - Children's mental and emotional health[2]
     - Social well-being, and[2,3]
     - Educational experience[3]
2. Indirect effects
   - For the week ending 27 May 21, children were 24.0% of new reported weekly COVID-19 cases[4]
   - More than 3.9 million children in the U.S. have been infected with SARS-CoV-2[4]
   - Children known to be good spreaders of other respiratory viruses (ex influenza)[5]
     - Block infections in children can block transmission in adults.

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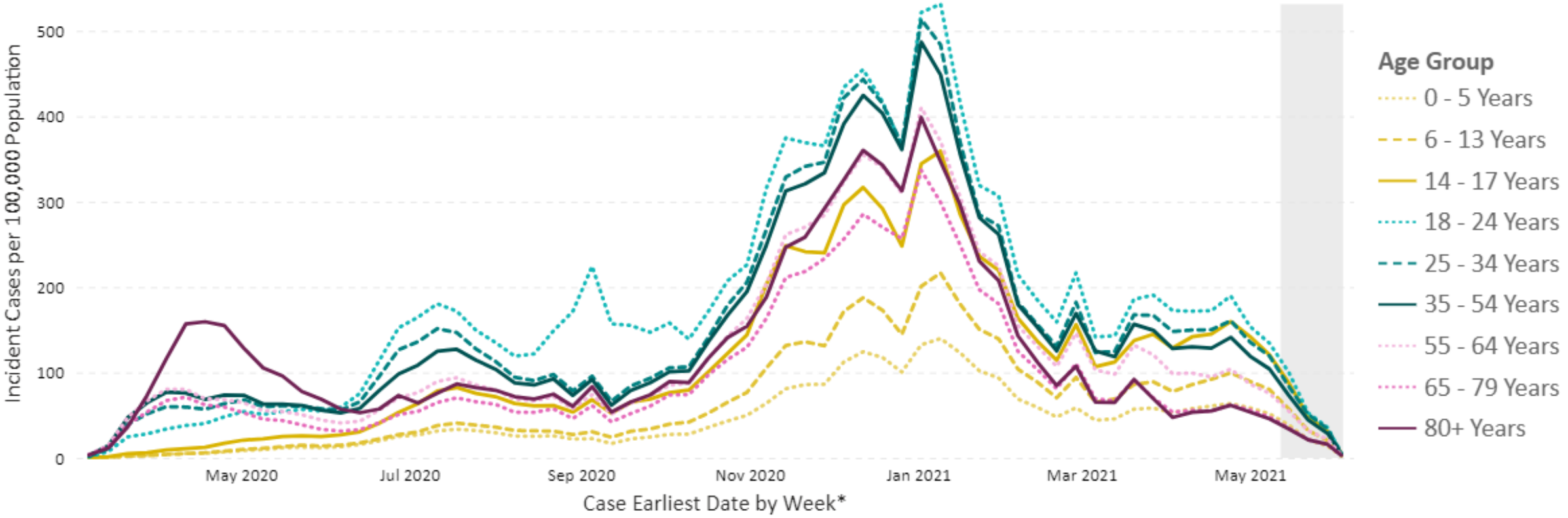
1. AAP News: Moderna reports COVID-19 vaccine for teens safe, effective. https://www.aappublications.org/news/2021/05/06/moderna-covid-vaccine-teens-050621. Accessed May 2021. 2. AAP News: Updated guidance focuses on mental health risks, needs during pandemic. https://www.aappublications.org/news/2021/03/15/ebhguidance3-15-21. Accessed May 2021. 3. AAP News: Updated COVID-19 guidance addresses physical distancing in schools, emotional toll on students. https://www.aappublications.org/news/2021/03/25/covid-school-guidance-update-032521. Accessed May 2021. 4. AAP Children and COVID-19: State-level data report. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/. Accessed May 2021. 5. Speakers' opinion.

Incidence of COVID-19 in US by Age



COVID Data Tracker; CDC.gov, Jun 3, 2021

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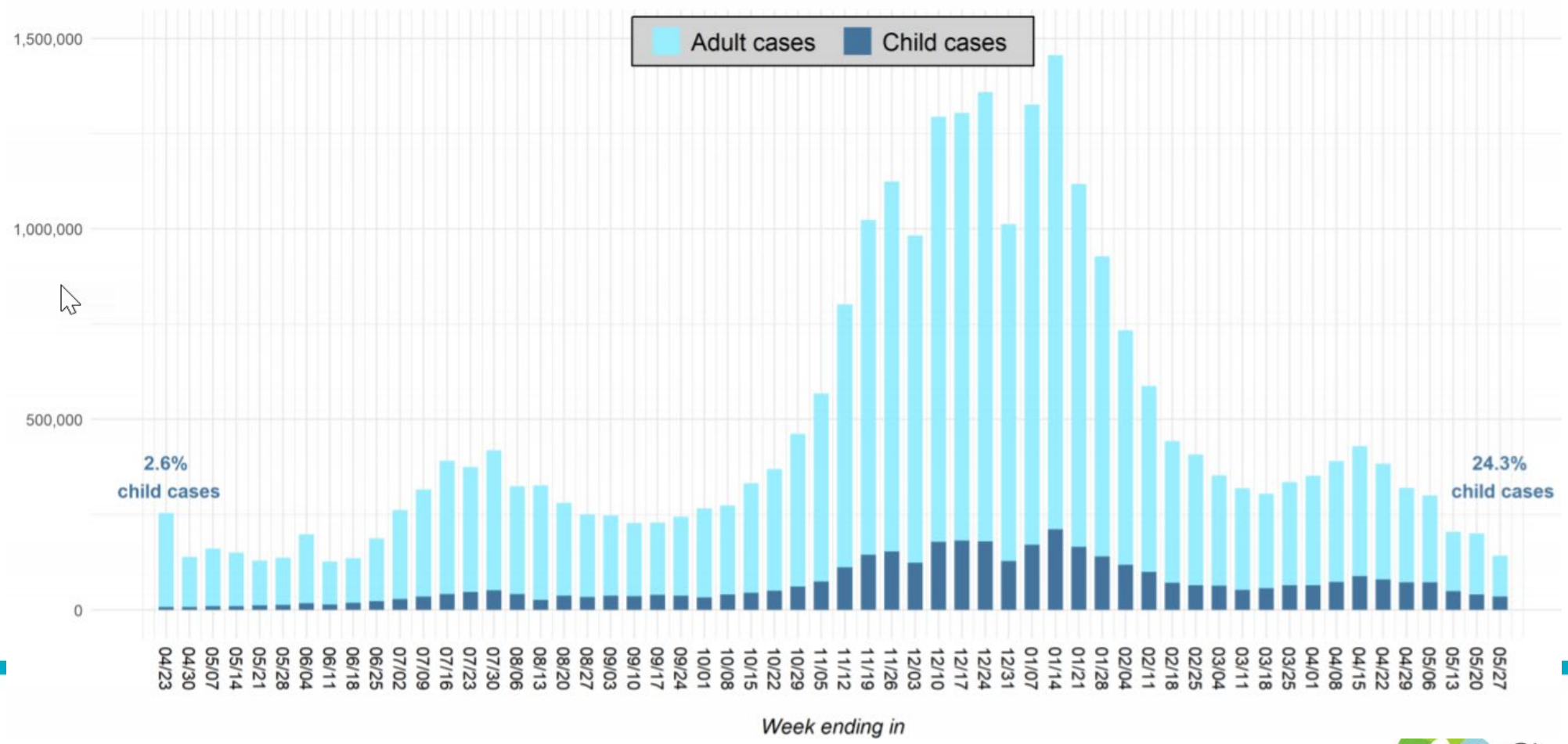
Number of COVID-19 Cases in US per Week for Children and Adults



CDC and AAP/Children's Hospital Association. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/ Downloaded 6Jun2021

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Projected Pediatric Hospitalizations Based on Infection Rate

SCENARIO: Percent of All Children Infected	Projected Number of Infected Children	Projected Number of Severely Ill Children	Projected Number of Critically Ill Children	Projected Number of Severely + Critically Ill Children
0.5	369,833	882	109	991
1.0	739,666	1,764	217	1,981
5.0	3,698,331	8,821	1,086	9,907
10.0	7,396,662	17,642	2,173	19,815
15.0	11,094,993	26,462	3,259	29,722
20.0	14,793,324	35,283	4,346	39,629
25.0	18,491,655	44,104	5,432	49,536
30.0	22,189,986	52,925	6,519	59,444
35.0	25,888,317	61,746	7,605	69,351
40.0	29,586,648	70,566	8,692	79,258
45.0	33,284,979	79,387	9,778	89,165
50.0	36,983,310	88,208	10,865	99,073
55.0	40,681,640	97,029	11,951	108,980
60.0	44,379,971	105,849	13,038	118,887

Pathak et al. JPubHealthManag. 2020

Pediatric Hospitalizations and Deaths in US from COVID vs Selected Viral Illness', Pre-vaccination

Virus	Hospitalizations (per 100,000)	Death per year
COVID	22 (0-17 yrs old)	322 (as of May 27, 2021)
Influenza	34-92 (<4 yrs old) 20-41 (5-17 yrs old)	110-192 (2016-2020)
Varicella	4-13 (0-20 yrs old)	50 (1970-1994)
Rotavirus	1500 (≤ 5 yrs old)	20-60 (1999-2007)
Rubella	Not available	17 (1966-1968)
Hepatitis A	<1 (0-15 yrs old)	3 (1990-1995)

Courtesy of Evan Anderson

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Clinical Infectious Diseases

Article Contents

ACCEPTED MANUSCRIPT

Warp Speed for COVID-19 Vaccines: Why are Children Stuck in Neutral? FREE

Evan J Anderson ✉, James D Campbell, C Buddy Creech, Robert Frenck, Satoshi Kamidani, Flor M Munoz, Sharon Nachman, Paul Spearman

Clinical Infectious Diseases, ciaa1425, https://doi.org/10.1093/cid/ciaa1425

Published: 18 September 2020 **Article history** ▼

Pediatric Vaccine Trials: Past Guidance

- WHO and EMA guidance on conducting vaccine trials in pediatric populations follows a ‘de-escalation’ approach, depending on the perceived benefit and risk of vaccination[1,2]

- A de-escalation approach was previously used during the 2009 H1N1 pandemic[3–6]
- **Immunobridging** trials may be considered instead of efficacy trials when a different age group or posology is proposed, unless it is expected that the immune response to the vaccine may differ[2]

EMA, European Medicines Agency; WHO, World Health Organization.
1. WHO: Guidelines on clinical evaluation of vaccines: regulatory expectations. https://www.who.int/biologicals/Clinical_guidelines_27_January_2016.pdf. Accessed May 2021. 2. EMA: Guideline on clinical evaluation of vaccines. 3. GSK: Pandemic (H1N1) 2009 Influenza Update: Experience of GSK’s H1N1 adjuvanted vaccine, Pandemrix™, and preliminary paediatric results. https://www.gsk.com/en-gb/media/press-releases/pandemic-h1n1-2009-influenza-update-experience-of-gsk-s-h1n1-adjuvanted-vaccine-pandemrix-and-preliminary-paediatric-results/. Accessed May 2021. 4. GSK: Pandemic 2009 Influenza Update: Pandemrix™ data in children and adolescents from 3 to 17 years of age. https://www.gsk.com/en-gb/media/press-releases/pandemic-2009-influenza-update-pandemrix-data-in-children-and-adolescents-from-3-to-17-years-of-age/. Accessed May 2021. 5. ClinicalTrials.Gov NCT00971321 https://clinicaltrials.gov/ct2/show/NCT00971321. Accessed May 2021. 6. ClinicalTrials.Gov NCT00964158. https://clinicaltrials.gov/ct2/show/NCT00964158. Accessed May 2021.

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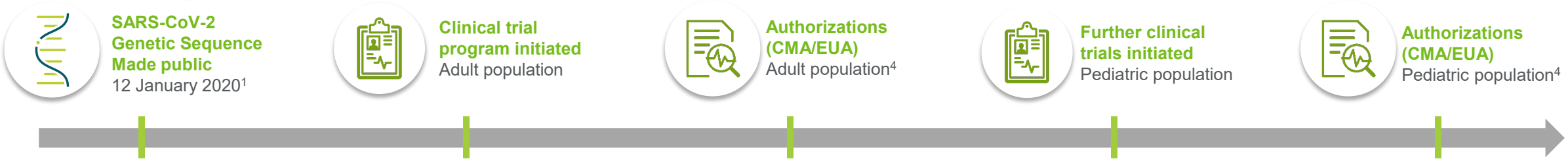
NIH Bioethics Panel (25Aug2020) Stated

- There is sufficient safety data in adults to justify initiating pediatric trials now.
- Trials should first enroll small numbers of older children with no underlying health conditions.
  - Subsequent trials de-escalating in age of participants
- Trials need to ensure that participants reflect the geographic and demographic diversity of populations affected by the pandemic.

Overview of Vaccine Development



Pfizer-BioNTech BNT162b2	**Phase 1:** Mar 2020[2] **Phase 3:** Jul 2020[3]	**EMA, FDA, Swissmedic, UK MHRA** 1–21 Dec 2020	**12–15 years:** Oct 2020[5] **<12 years:** Mar 2021[6]	**FDA, Health Canada, Aus TGA, Singapore*** **12–16 years:** 5–11 May 2021
Moderna mRNA-1273	**Phase 1:** Mar 2020[7] **Phase 3:** Jul 2020[8]	**EMA, FDA, Swissmedic, UK MHRA** 18 Dec – 12 Jan 2020	**12–17 years:** Dec 2020[9] **<12 years:** Mar 2021[10]	Targeting FDA Submission* 12–17 years: Early June 2021[11]
Oxford/Astrazeneca ChAdOx1 nCoV-19	**Phase 1:** Apr 2020[12] **Phase 3:** May 2020[13]	**EMA, UK MHRA**** 30 Dec – 12 Jan 2020	**6–17 years:** Mar 2021[14]	
Novavax NVX-CoV2373	**Phase 1:** May 2020[15] **Phase 3:** Sep 2020[16]	Targeting Regulatory Submissions* Q3 2021[17]	**12–17 years:** May 2021[18]	
Janssen Ad26.COV2-S	**Phase 1:** July 2020[19] **Phase 3:** Sep 2020[20]	**EMA, FDA, Swissmedic** 27 Feb – 22 Mar 2021	**12–17 years:** Apr 2021[21]	

***Not currently authorized in Switzerland or the EU. **Not currently authorized in Switzerland**

CMA, conditional marketing authorization; EMA, European Medicines Agency; EUA, emergency use authorization; FDA, Food & Drug Administration; MHRA, Medicines and Healthcare products Regulatory Agency; TGA, Therapeutic Goods Administration.

1. World Health Organization. Novel Coronavirus – China. https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/ Accessed May 2020. 2. ClinicalTrials.gov NCT04368728 https://clinicaltrials.gov/ct2/show/NCT04368728/ Accessed April 2021. 3. ClinicalTrials.gov NCT04816643. https://clinicaltrials.gov/ct2/show/NCT04816643. Accessed April 2021. 4. Regulatory Affairs Professionals Society (RAPS). https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker/ Accessed May 2021. 5. BioNTech. https://investors.biontech.de/news-releases/news-release-details/pfizer-biontech-announce-positive-topline-results-pivotal-covid/ Accessed April 2021. 6. ClinicalTrials.gov NCT04816643. https://clinicaltrials.gov/ct2/show/NCT04816643. Accessed April 2021. 7. Jackson LA, et al. NEJM 2020;383:1920-31. 8. ClinicalTrials.Gov. NCT04470427 https://clinicaltrials.gov/ct2/show/NCT04470427/ Accessed May 2021. 9. ClinicalTrials.Gov. NCT04649151. http://clinicaltrials.gov/ct2/show/NCT04649151/ Accessed April 2021. 10. ClinicalTrials.Gov. NCT04796896. https://clinicaltrials.gov/ct2/show/NCT04796896/ Accessed April 2021. 11. Moderna https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-teencove-study-its-covid-19-vaccine Accessed May 2021. 12. ClinicalTrials.Gov. NCT04324606. https://clinicaltrials.gov/ct2/show/NCT04324606/ Accessed April 2021. 13. ClinicalTrials.Gov. NCT04400838. https://clinicaltrials.gov/ct2/show/NCT04400838/ Accessed April 2021. 14. Cochrane COVID-19 Study Register. ISRCTN15638344 HTTPS://COVID-19.COCHRANE.ORG/STUDIES/CRS-16897279/ Accessed April 2021. 15. ClinicalTrials.gov. NCT04368988. https://clinicaltrials.gov/ct2/show/NCT04368988/ Accessed May 2021. 16. ClinicalTrials.gov. NCT04583995. https://clinicaltrials.gov/ct2/show/NCT04583995/ Accessed May 2021. 17. PMLive. https://www.pmlive.com/pharma_news/novavax_announces_further_delays_for_regulatory_filings_of_covid-19_vaccine_1369844/ Accessed May 2021. 18. Novavax. https://ir.novavax.com/news-releases/news-release-details/novavax-initiates-pediatric-expansion-phase-3-clinical-trial/ Accessed May 2021. 19. ClinicalTrials.Gov. NCT04436276 https://clinicaltrials.gov/ct2/show/NCT04436276/ Accessed May 2021. 20. ClinicalTrials.gov. NCT04505722. https://clinicaltrials.gov/ct2/show/NCT04505722/ Accessed May 2021. 21. Janssen. https://www.janssen.com/johnson-johnson-expands-phase-2a-clinical-trial-covid-19-vaccine-candidate-include-adolescents/ Accessed May 2021.

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Adolescent COVID-19 Vaccine Trials

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Pfizer/BioNTech mRNA Vaccine

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Pfizer COVID-19, 16-17 Year Old Study

- Approximately 900 randomized 1:1 vaccine to placebo. Incorporated into main Phase 3 study
- 2 doses 3 weeks apart, 30 ug dose
- Blood collected baseline and 1 month after 2nd dose
- Local and systemic reactogenicity collected for 7 days after each dose
- SAEs and unsolicited AEs collected for 6 months after dose 1.
- Immunogenicity safety and efficacy compared with 16–25 year-olds
- Participant asked to contact site if had COVID-like illness

Frenck et al. NEJM 27May 2021

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Pfizer COVID-19 12-15 Year Old Study

- 2260 adolescents 12-15 yrs old randomized 1:1 vaccine to placebo
- 2 doses 3 weeks apart, 30 ug dose
- Blood collected baseline and 1 month after 2nd dose
- Local and systemic reactogenicity collected for 7 days after each dose
- SAEs and unsolicited AEs collected for 6 months after dose 1.
- Immunogenicity safety and efficacy compared with 16–25 year-olds
- Participant asked to contact site if had COVID-like illness

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Geometric mean ratio of 50% neutralizing titers 1 mo after dose 2, 12–15 vs 16–25 years of age

Assay	BNT162b2				12–15/16–25 years of age	
	12–15 years of age		16–25 years of age			
	n	GMT (95% CI)†	n	GMT (95% CI)†	GMR (95% CI)†	Met noninferiority objective‡
SARS-CoV-2 neutralization assay (NT50)	190	1239.5 (1095.5, 1402.5)	170	705.1 (621.4, 800.2)	1.76 (1.47, 2.10)	Yes

Frenck et al. NEJM 27May 2021

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Pfizer COVID-19 Vaccine Efficacy, 12–15 years of age

Efficacy endpoint	SARS-CoV-2 infection status	BNT162b2		Placebo		VE (95% CI[§])
		n1* (N)	Surveillance time[†] (n2[‡])	n1* (N)	Surveillance time[†] (n2[‡])	
First COVID-19 occurrence from 7 days after dose 2	Without evidence of infection prior to 7 days after dose 2	0 (1005)	0.154 (1001)	16 (978)	0.147 (972)	100.0% (75.3, 100.0)
First COVID-19 occurrence from 7 days after dose 2	With or without evidence of infection prior to 7 days after dose 2	0 (1119)	0.170 (1109)	18 (1110)	0.163 (1094)	100.0% (78.1, 100.0)

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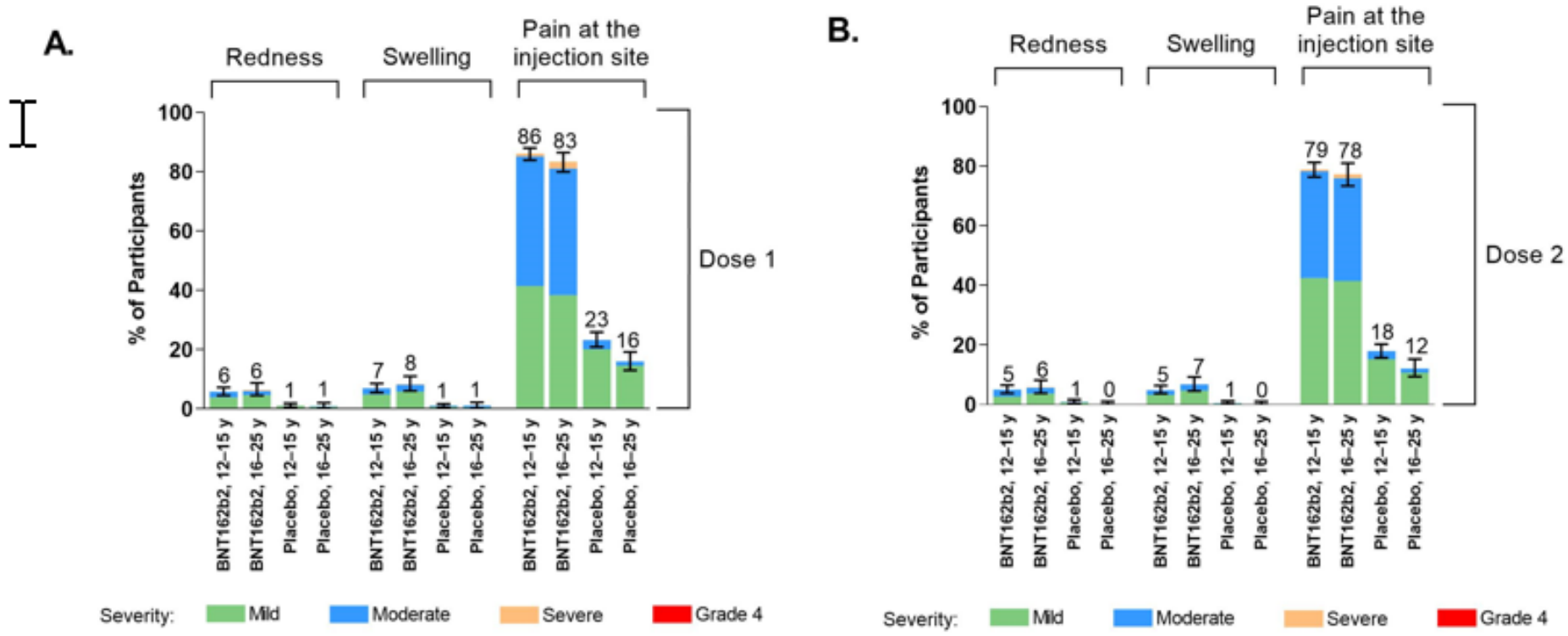
Pfizer COVID-19 Vaccine, Local AEs, 12-15 yr old vs 16-25 yr old



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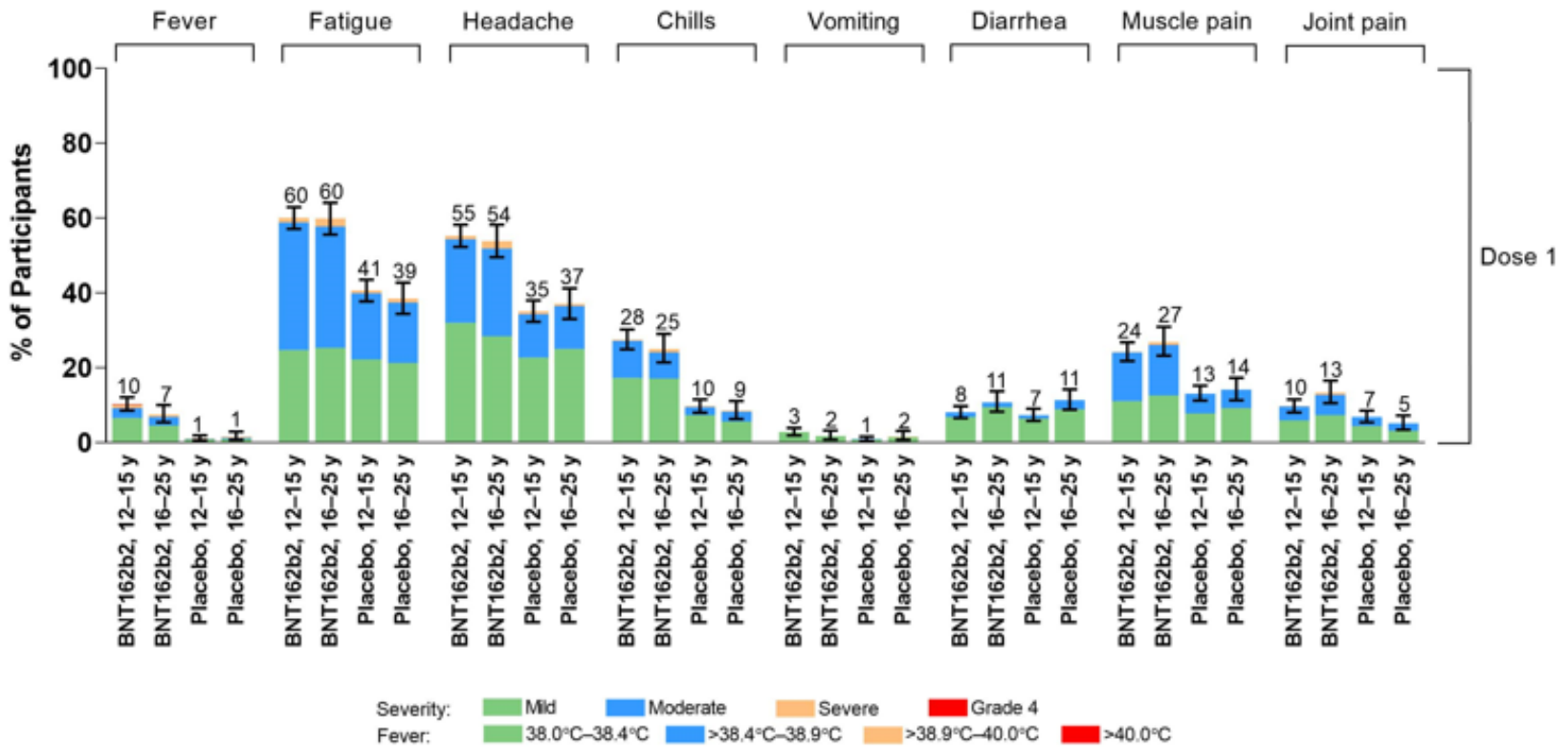
Pfizer COVID-19 Vaccine, Systemic AEs, 12-15 yr old vs 16-25 yr old, Dose 1



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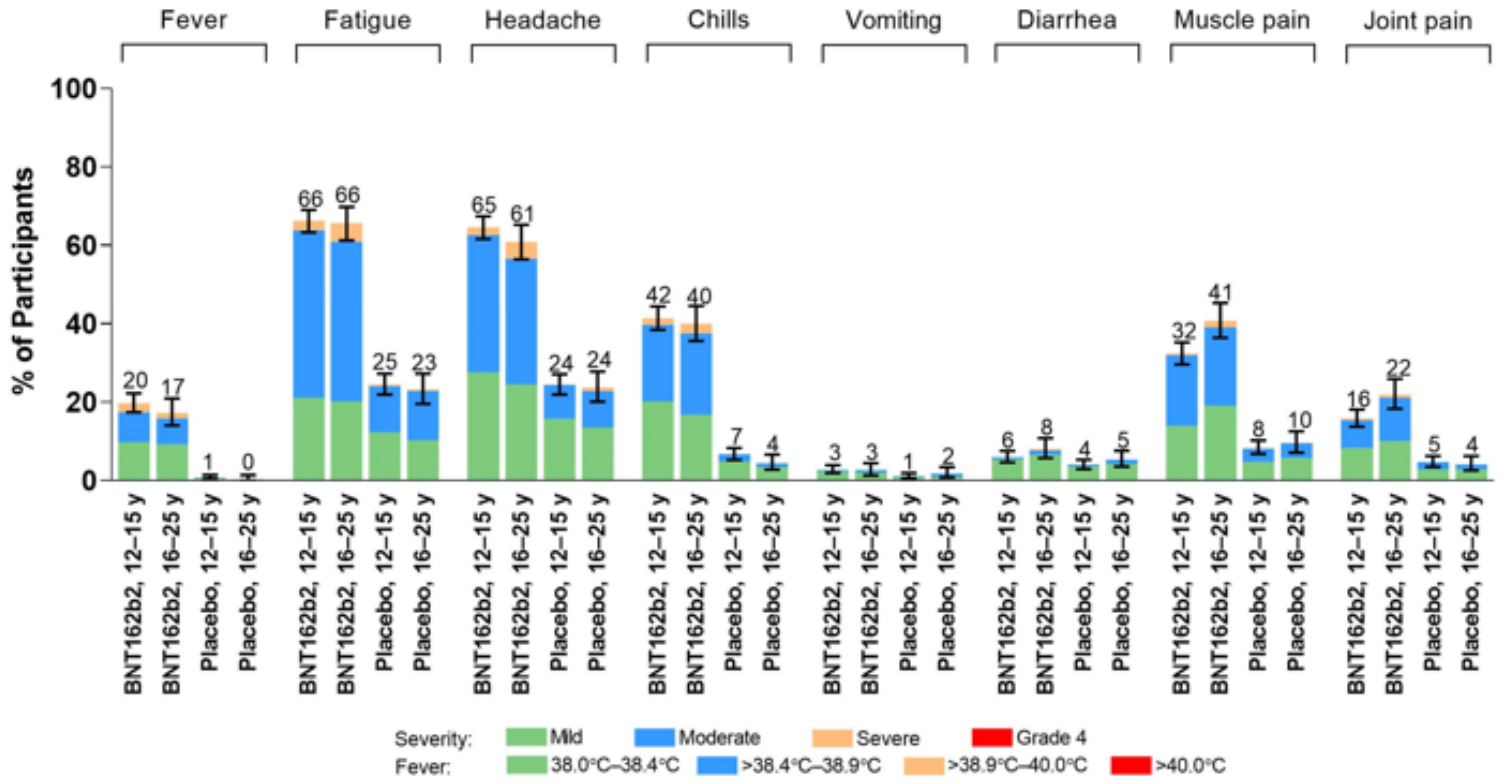
Pfizer COVID-19 Vaccine, Systemic AEs, 12-15 yr old vs 16-25 yr old, Dose 2



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Moderna mRNA Vaccine

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Moderna, TeenCove Study (12-<18 yrs old)

- 3732 participants, 2:1 randomization (vaccine:placebo)
- Receive 2 doses of vaccine (100 ug dose) 28 days apart
- Nasal swab collected prior to each vaccine and if have COVID-like symptoms
- Blood collected at baseline and 28 days after 2nd vaccine
- Local and systemic adverse reactions collected for 7 days after each dose
- SAEs and unsolicited AEs collected for 6 months after dose 1.

Moderna, TeenCove Study (12-<18 yrs old), Results

- Immunogenicity of adolescents was non-inferior to the Phase 3 study adult comparator group
- After two doses, no case of COVID-19 in vaccine group vs 4 cases in the placebo group.
- Using CDC definition (1 symptom and pos PCR), vaccine efficacy of 93% beginning 14 days after first dose.
- Injection site pain most common solicited local adverse event.
- Headache, fatigue, myalgia and chills most common solicited systemic adverse events.

Moderna press release, May 25, 2021

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Astra Zeneca Adenoviral Vectored Vaccine

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AstraZeneca Pediatric Study

- 6-17 years of age
- Single-blind, randomized
- N=300, 240 vaccine, 60 MCV4 as active control
- Currently on hold pending safety evaluation in adults (blood clots in the brain and low platelets)

Oxford University extends COVID-19 vaccine study to children. https://www.ovg.ox.ac.uk/news/oxford-university-extends-covid-19-vaccine-study-to-children. Accessed May 2021.

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Janssen

Ad26.COV2-S

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Janssen Pediatric Expansion to Phase 2a Study

- 12–17-year-olds
- Adolescents being added to the Phase IIa adult trial.
- To evaluate the reactogenicity and immunogenicity of Ad26.COV2-S at one-, two- and three-month intervals
- Initially “small number” of adolescents aged 16-17, then expanded to younger adolescents in a step-wise manner
- Two doses will be evaluated but specific dose not announced.

Janssen. Johnson & Johnson Expands Phase 2a Clinical Trial of COVID-19 Vaccine Candidate to Include Adolescents. https://www.janssen.com/johnson-johnson-expands-phase-2a-clinical-trial-covid-19-vaccine-candidate-include-adolescents/ Accessed May 2021.

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Novavax

NVX-CoV2373

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Novavax Pediatric Expansion (12-17 years old)

- To evaluate the efficacy, safety and immunogenicity of NVX-CoV2373
- 3000 participants, randomized 2:1 (vaccine:placebo)
- Two doses, 21 days apart
- A blinded crossover is planned to take place 6 months after the initial vaccination
- Outcome measures
  - Number of participants symptomatic COVID-19
  - Reactogenicity incidence and severity in the 7 days after vaccination
  - Incidence and severity of unsolicited AEs.
  - Medically attended adverse events through day 49

Novavax Initiates Pediatric Expansion for Phase 3 Clinical Trial of COVID-19 Vaccine. https://ir.novavax.com/news-releases/news-release-details/novavax-initiates-pediatric-expansion-phase-3-clinical-trial. Accessed May 2021. 2. ClinicalTrials.Gov. https://clinicaltrials.gov/ct2/show/NCT04611802. Accessed May 2021.

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Pediatric COVID-19 Vaccine Trials

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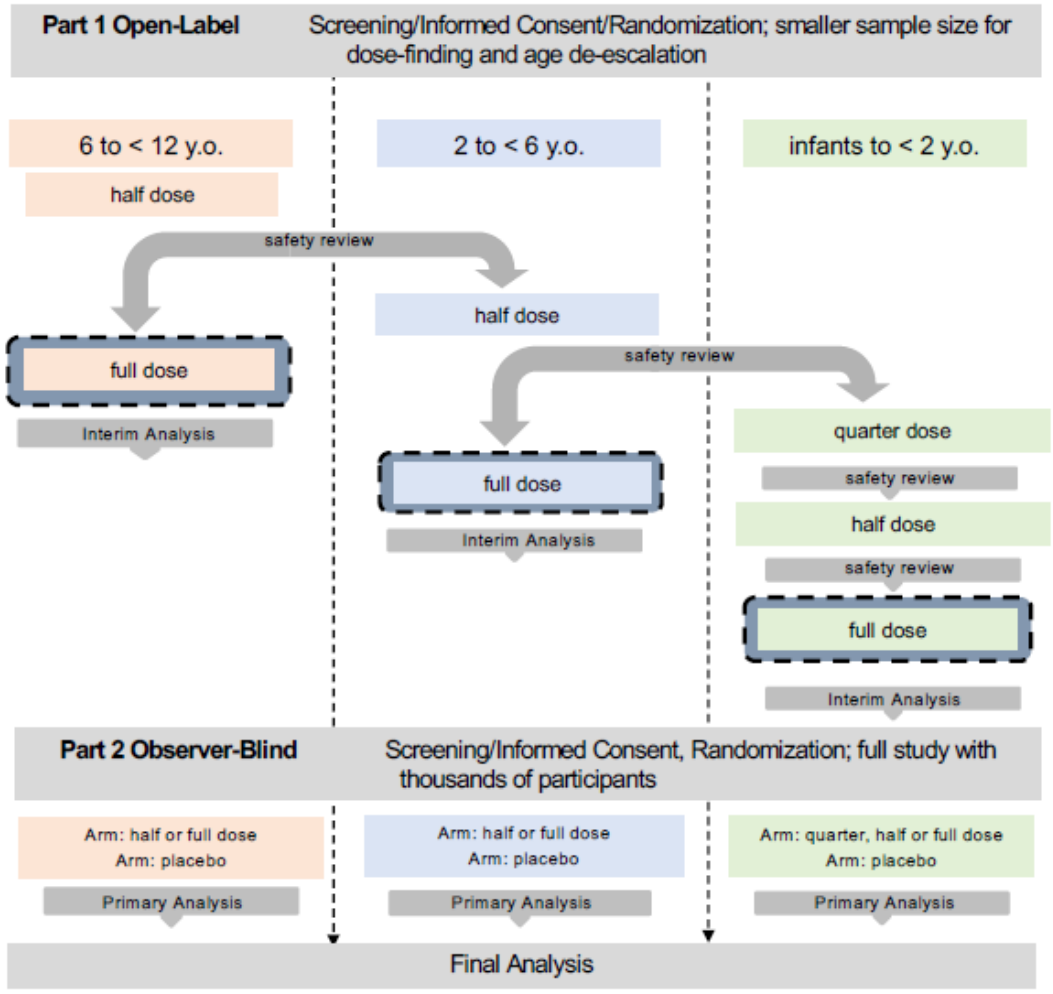
Example: dose-ranging study in children, infants to <12 years

- Protocols in development
- 3 age groups:
  - 6 to <12 years
  - 2 to < 6 years
  - Infants to < 2 years
- May relatively large N for safety if novel platform
- May test multiple dose levels
  - Full, half, and quarter doses considered by age group



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Pfizer/BioNTech mRNA Vaccine

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Pfizer Phase 1/2/3 Pediatric Trial (NCT04816643)

- Three age ranges
  - 5 years - <12 years
  - 2 years - <5 years
  - 6 mo - < 24 months
- Part 1, dose finding, Phase 1 (n=48 for each age range)
  - 10ug, 20ug, 30 ug to be evaluated
- Part 2, placebo controlled, expanded cohort (Phase 2/3)
  - Randomized 2:1 (vaccine:placebo)
  - Optimal dose used from Part 1
  - n=2250 (5-11), n=1125 (6-24 mo, 2-5 yr)

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ClinTrials.gov

Pfizer Phase 1/2/3 Pediatric Trial (NCT04816643)

- Outcome measures
  - Safety and tolerability
  - Immunobridging within each age group to 16-25 year age group in Phase 3
  - Efficacy (if sufficient cases)

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Moderna mRNA Vaccine

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Moderna KidCove

- Three age ranges
  - 6 years - < 12 years
  - 2 years - < 6 years
  - 6 mo - < 2 years
- Part 1, dose finding, Phase 1
  - n= 375 each dose (6- <12 yrs), 75 each dose (2-6 yrs), 150 each dose (6 mo- <2 year)
  - 50 ug, 100 ug dose (also 25 ug for 6-24 month group)
- Part 2, placebo controlled, expanded cohort (Phase 2/3)
  - 3:1, vaccine:placebo
  - n=1700 (6- <12), n=2000 (6-24 mo, 2- <6 yr)
  - Use dose from Phase 1

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Moderna KidCove

- Outcome measures
  - Safety and tolerability
  - Immunogenicity
  - Efficacy (if sufficient cases)

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Conclusions

- SARS-CoV-2 negative impacts children's health, social wellbeing and education, and indirectly children may contribute to transmission of the virus
- Pediatric studies are ongoing for BNT162b2, mRNA-1273, NVX-CoV2373, Ad26.COV2-S and ChAdOx1
- BNT162b2 is authorized for 12 and above
- Moderna plans FDA submission for 12–18 year olds by early June

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