Pediatric COVID-19 Vaccines

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02JUN2021
POTENTIAL CONFLICTS AND DISCLOSURES:

- Financial compensation to Emory for clinical research:
  - Pfizer, Merck, GSK, Sanofi Pasteur, Novavax, Regeneron, PaxVax, MedImmune, Janssen, and Micron unrelated to this talk.
  - Pfizer – pediatric trial

- I have served as consultant:
  - Medscape, Sanofi Pasteur, Janssen, and Pfizer

- Safety monitoring committee
  - Kentucky BioProcessing, Inc
  - Sanofi Pasteur

- NIH funded
  - Local PI for the Moderna mRNA-1273 Phase I and variant studies
  - Local PI for the Moderna mRNA-1273 Phase 3 study
  - Local PI for the Janssen Ad26-Spike protein Phase 3 study
  - Local PI for the Moderna mRNA-1273 KidCOVE
>40 in clinical trials
>150 in preclinical eval

2 mRNA
- Pfizer mRNA BNT162b2; Phase 3: ~44K
- Moderna mRNA-1273; Phase 3: 30K

2 viral-vectored
- AstraZeneca ChAd-Spike; Phase 3: Data released, future uncertain, doses released by the US
- Janssen Ad26-Spike; Phase 3: Approved

2 S protein-based
- Novavax NVX-CoV2373 – started end of Dec 2020, data pending
- Sanofi/GSK-delayed Insufficient antigen, Phase 2 study

https://media.defense.gov/2020/Aug/13/2002476369/-1/-1/0/200813-D-ZZ999-100.JPG
SARS-CoV-2 Vaccines: Status Report

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https://doi.org/10.1016/j.immuni.2020.03.007

Current stage: Development of vaccine candidates and pre-clinical testing

- RNA vaccines
- DNA vaccines
- Recombinant protein vaccines
- Vectors
- Live attenuated vaccines
- Inactivated vaccines

Time frame unclear. 6-18 months. Maybe longer?

Vaccine candidates:
- Pfizer
- Moderna
- Novavax
- Sanofi
- AstraZeneca
- Janssen
- VSV-backbone Ebola
- LAIV, Rotavirus, MMRV, OPV
- Vaccinia
- PCV13, HIB, Hep B, HPV
- Hep A, IPV
Do We Need a Vaccine for Children?

- Initial Impression: Children don’t transmit virus
- Less frequently symptomatic, uncertainty about impact of school closures
- Current Knowledge: Children do transmit SARS-CoV-2, just relatively less frequently
Do We Need a Vaccine for Children?

- Initial Impression: Children don’t get sick (e.g., inadequate hosp., inadequate deaths)
- Current Knowledge: Substantial burden of hospitalizations in children


**Table: Hospitalizations/Year**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Hospitalizations/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19</td>
<td>53.9 per 100,000 age 0-4 yrs</td>
</tr>
<tr>
<td></td>
<td>33 per 100,000 age 5-17 yrs</td>
</tr>
<tr>
<td></td>
<td>Through 4/24/2021</td>
</tr>
<tr>
<td>Varicella</td>
<td>4–31 per 100,000</td>
</tr>
<tr>
<td></td>
<td>Age &lt;20 yrs</td>
</tr>
<tr>
<td></td>
<td>Years 1988–1995</td>
</tr>
<tr>
<td>Rubella</td>
<td>Not available</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>107 hospitalized children</td>
</tr>
<tr>
<td></td>
<td>Age &lt;15 yrs</td>
</tr>
<tr>
<td></td>
<td>Year 2005</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>55,000–70,000 children</td>
</tr>
<tr>
<td></td>
<td>Age &lt;5 yrs</td>
</tr>
<tr>
<td></td>
<td>Years 1993–2002</td>
</tr>
<tr>
<td>Influenza</td>
<td>34–92 per 100,000 age 5–17 yrs for 2016–2020 seasons</td>
</tr>
</tbody>
</table>

Do We Need a Vaccine for Children?

• Initial Impression: Children don’t get sick (e.g., inadequate hosp., inadequate deaths)
Do We Need a Vaccine for Children?

• **Initial Impression:** Children don’t get sick (e.g., inadequate hosp., inadequate deaths)

• **Current Knowledge:** Substantial number of COVID-19-related deaths in children

<table>
<thead>
<tr>
<th>Virus</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19</td>
<td>332 children</td>
</tr>
<tr>
<td></td>
<td>Age ≤18 yrs</td>
</tr>
<tr>
<td></td>
<td>Through 5/5/2021</td>
</tr>
<tr>
<td>Varicella</td>
<td>50 children per year</td>
</tr>
<tr>
<td></td>
<td>Age &lt;15 yrs</td>
</tr>
<tr>
<td></td>
<td>Years 1970–1994</td>
</tr>
<tr>
<td>Rubella</td>
<td>17 children per year</td>
</tr>
<tr>
<td></td>
<td>All ages</td>
</tr>
<tr>
<td></td>
<td>Years 1965–1968</td>
</tr>
<tr>
<td>Hepatitis A†</td>
<td>3 children per year</td>
</tr>
<tr>
<td></td>
<td>Age &lt;20 yrs</td>
</tr>
<tr>
<td></td>
<td>Years 1990–1995</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>20–60 children per year</td>
</tr>
<tr>
<td></td>
<td>Age &lt;5 yrs</td>
</tr>
<tr>
<td></td>
<td>Years 1999–2007</td>
</tr>
<tr>
<td>Influenza</td>
<td>110–198 children per year</td>
</tr>
<tr>
<td></td>
<td>Years 2015–2020</td>
</tr>
</tbody>
</table>

https://data.cdc.gov/NCHS/Provisional-COVID-19-Deaths-Focus-on-Ages-0-18-Years-nr4s-juj3
https://gis.cdc.gov/grasp/fluview/fluview/pedfludeath.html
Do We Need a Vaccine for Children?

- Initial Impression: Children don’t get sick (e.g., inadequate hosp., inadequate deaths)

- Substantial non-medical direct impact upon children by COVID-19
  - Education (e.g., online learning), extracurricular activities (e.g., sports, drama, music, social events), economic, and the emotional and psychological development of children
Why pediatric studies?

- Differences in height, weight, body surface area, muscle mass, and fat distribution in children
- Need to understand reactogenicity, safety, and immunogenicity in children + establish the dose

Delay in starting pediatric studies from the experts:

“...begin pediatric studies after safety and efficacy is established in adults...”

Perspective:

- Adult phase 1/2 COVID-19 studies conducted in parallel with animal studies → expediting of Phase 3
- Vaccine development typically starts with a small Phase 1 study of healthy young adults
- Phase 2 and 3 studies in children usually occur without large studies of adult safety / efficacy
  - Pediatric vaccines licensed BEFORE substantial adult safety/efficacy data
    - Rotavirus (RV1, RV5), polio, PCV7/13, HIB, MMR
  - Multiple live-attenuated RSV vaccines in children currently with very minimal adult data
Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents

Robert W. Frenck, Jr., M.D., Nicola P. Klein, M.D., Ph.D., Nicholas Kitchin, M.D., Alejandra Gurtman, M.D., Judith Absalon, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Emmanuel B. Walter, M.D., Shelly Senders, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Hua Ma, Ph.D., Xia Xu, Ph.D., Kenneth Koury, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Timothy Jennings, D.O., Donald M. Brandon, M.D., Stephen J. Thomas, M.D., Özlem Türeci, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Ülger Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group

A Local Events, Dose 1

<table>
<thead>
<tr>
<th></th>
<th>Redness</th>
<th>Swelling</th>
<th>Pain at Injection Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT162b2, 12-15 Yr</td>
<td>6</td>
<td>7</td>
<td>85</td>
</tr>
<tr>
<td>BNT162b2, 16-25 Yr</td>
<td>5</td>
<td>8</td>
<td>83</td>
</tr>
<tr>
<td>Placebo, 12-15 Yr</td>
<td>1</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Placebo, 16-25 Yr</td>
<td>1</td>
<td>1</td>
<td>16</td>
</tr>
</tbody>
</table>

B Local Events, Dose 2

<table>
<thead>
<tr>
<th></th>
<th>Redness</th>
<th>Swelling</th>
<th>Pain at Injection Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT162b2, 12-15 Yr</td>
<td>5</td>
<td>7</td>
<td>79</td>
</tr>
<tr>
<td>BNT162b2, 16-25 Yr</td>
<td>6</td>
<td>1</td>
<td>78</td>
</tr>
<tr>
<td>Placebo, 12-15 Yr</td>
<td>0</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Placebo, 16-25 Yr</td>
<td>0</td>
<td>0</td>
<td>12</td>
</tr>
</tbody>
</table>
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Table 2. SARS-CoV-2 Serum Neutralization Assay Results 1 Month after Dose 2 of BNT162b2 among Participants without Evidence of Infection.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No. of Participants</th>
<th>Geometric Mean 50% Neutralizing Titer (95% CI)†</th>
<th>Geometric Mean Ratio (95% CI), 12 to 15 Yr vs. 16 to 25 Yr.‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–15 yr</td>
<td>190</td>
<td>1239.5 (1095.5–1402.5)</td>
<td>1.76 (1.47–2.10)</td>
</tr>
<tr>
<td>16–25 yr</td>
<td>170</td>
<td>705.1 (621.4–800.2)</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 3. Vaccine Efficacy against Covid-19 in Participants 12 to 15 Years of Age.

<table>
<thead>
<tr>
<th>Efficacy End Point†§</th>
<th>BNT162b2</th>
<th>Placebo</th>
<th>% Vaccine Efficacy (95% CI)‡∆</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants with Event/Total No.§</td>
<td>Surveillance Time (No. at Risk)¶</td>
<td>No. of Participants with Event/Total No.§</td>
</tr>
<tr>
<td>Covid-19 occurrence at least 7 days after dose 2 in participants without evidence of previous infection</td>
<td>0/1005</td>
<td>0.154 (1001)</td>
<td>16/978</td>
</tr>
<tr>
<td>Covid-19 occurrence at least 7 days after dose 2 in participants with or without evidence of previous infection</td>
<td>0/1119</td>
<td>0.170 (1109)</td>
<td>18/1110</td>
</tr>
</tbody>
</table>

† Results are for the efficacy population that could be evaluated, which included all eligible 12- to 15-year-old participants who received two doses of BNT162b2 or placebo as randomly assigned, with dose 2 received within the prespecified window, and had no major protocol deviations.

‡ Participants without evidence of previous infection were those who had no serologic or virologic evidence of past SARS-CoV-2 infection before 7 days after dose 2 (i.e., N-binding antibody testing [serum] negative at vaccination visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at vaccination visits 1 and 2) and had negative NAAT results (nasal swab) at any unscheduled visit before 7 days after dose 2.

§ The 95% confidence interval for vaccine efficacy was derived on the basis of the Clopper–Pearson method with adjustment for surveillance time.

¶ The number of participants with a first occurrence of Covid-19 at 7 or more days after dose 2 and the total number of participants with data are shown.

∆ Total surveillance time in 1000 person-years for the given end point across all participants within each group of participants who were at risk for the end point is shown. The period for Covid-19 case accrual was from 7 days after dose 2 to the end of the surveillance period.
Pediatric Update

- Pfizer 12 – 17 year old study data
  - March 31 Pfizer press release
  - April 9 Pfizer submitted data to FDA for expansion of their EUA (12 – 15 year olds)
  - May 10 FDA expanded the EUA
  - May 12 reviewed and approved by ACIP

- Moderna also have 12 – 17 year old study data (TeenCOVE): 3,700 participants (2:1) 100 mcg
  - 0 cases in vaccine versus 4 in placebo 14 days after vaccination = 100% efficacy
    - 93% efficacy after the first vaccination
    - Pain, headache, fatigue, myalgia, chills (especially after second dose)
  - 06MAY2021 and 25MAY2021 press releases of the data
  - Reportedly submitting data to FDA for expansion of their EUA (12 – 17 year olds) in JUNE
  - ___ FDA review
  - ___ ACIP review
Pediatric Update

• Studies for those <12 years of age
  • Age de-escalation
  • Dose escalation/finding studies
• Pfizer – NCT04816643:
  • September for data for 2 – 11 year olds

• Moderna - NCT04796896
  • No timeline stated
Pediatric Update

- Studies for those <12 years of age
  - Janssen?
  - Novavax?

- Some uncertainty about whether the FDA will grant an EUA for those <12 years of age.

- Distribution challenges: Pfizer

- Ongoing safety data review:
Should We Mandate a COVID-19 Vaccine for Children?

The zeal to develop and implement a vaccine to prevent coronavirus disease 2019 (COVID-19) infection has been exceptional. Operation Warp Speed, the Trump administration’s proposal, seeks to produce hundreds of millions of doses of a vaccine by January 2021. Recent polls show as many as 70% of adults in the United States plan to get vaccinated against COVID-19 once a vaccine is available. And thousands of adults have registered to participate as volunteers in human challenge trials to speed up the development of a new vaccine.

We anticipate that this fervor will eventually lead to discussions about making a COVID-19 vaccine mandatory. An obvious group to target for mandatory vaccination is children. Not only do we already mandate several vaccines for them to attend school, but strategies to reopen schools or keep them open may be predicated on it.

A few might suggest the current US approach to influenza vaccine should inform our approach to a COVID-19 vaccine. No state requires influenza vaccination for children to attend school. The analogy is understandable because the virus that causes COVID-19 may be the only way to achieve the high herd immunity threshold needed to provide wide community protection. Consider the measles virus. It has an R0 of 12 to 18; as a result, approximately 92% to 94% of the population must be immune to prevent spread. This has been achieved by requiring 2 doses of measles vaccine for children in all states before enrollment in school, with only very limited ways to opt out.

Rather than resort to analogies, we can use 9 standard criteria that can help guide whether a COVID-19 vaccine for children should be mandated (Box). These criteria can be divided into 3 categories: 4 criteria related to the vaccine, 2 related to the disease, and 3 related to implementation. Ordinarily, each of these categories would be considered in determining whether a vaccine should be mandated for children, although the weight given to each criterion may differ. In times of great public health need, such as the present pandemic, however, we propose that each criterion continue to be evaluated in making vaccine policy, but 5 criteria should be prioritized.

The criterion that should be prioritized over all others is the first. There must be evidence that a COVID-19

Box. Criteria to Consider When Evaluating Antigens for Inclusion in Mandatory School Immunization Programs

1. **Vaccine related**: Experience to date with the vaccine containing this antigen indicates that it is safe and has an acceptable level of adverse effects.
2. **Vaccine related**: The antigen is effective as measured by immunogenicity and population-based prevention.
3. **Vaccine related**: The vaccine containing this antigen is as cost-effective from a societal perspective as other vaccines used to prevent disease.
4. **Vaccine related**: The vaccine containing this antigen should bear some relationship to increasing safety in the school environment.
5. **Disease related**: The vaccine containing this antigen prevents disease(s) with significant morbidity and/or mortality in at least some subset of the population.
6. **Disease related**: Vaccinating the infant, child, or adolescent against this disease reduces the risk of person-to-person transmission.
7. **Implementation related**: The vaccine is acceptable to the medical community and the public.
8. **Implementation related**: The administrative burdens of delivery and tracking of vaccine containing this antigen(s) are reasonable.
9. **Implementation related**: The burden of adherence for the vaccine containing this antigen is reasonable for the parent/caregiver.

Adapted from Washington State Board of Health, Immunization Advisory Committee.

Adapted from Opal et al.

Nevertheless, with these criteria as a framework, the only logical conclusion is that we currently know too little about the performance of any of the candidate COVID-19 vaccines or the epidemiology of SARS-CoV-2 in children to make any firm judgments about whether a COVID-19 vaccine should be mandatory in children. Yet, it is not too early to begin integrating these criteria into our planning to help ensure we get this decision right. Our nation’s children deserve as much.
Summary

Substantial burden in children including hospitalization, MIS-C, and death

Substantial other impacts upon children (educational, social, psychological)

Pediatric Vax data extending down to age 12, EUA for Pfizer, ongoing safety evaluations

Pfizer and Moderna have ongoing trials in those <12 years of age