Covid-19 vaccines in children: be careful

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Summary
• Salary from University of Maryland & The BMJ
• Public, foundation, and non-profit funding of academic research
• Reimbursement (e.g. lodging, travel) from non-profits
• No industry funding
Trial evidence: what do we know so far?

- Harms outweighed benefits in Pfizer trial of 12-15 year olds
- Benefits were rare & short term side-effects were common
- We know nothing about long term effects

5.3 Known Risks

In individuals 12-15 years of age, there were higher frequencies of solicited local adverse reactions/systemic adverse events and lymphadenopathy in vaccine recipients than placebo recipients. Overall (after any dose), common solicited adverse reactions and events after BNT162b2 vaccination included injection site pain (90.5%), fatigue (77.5%), headache (75.5%), chills (49.2%), muscle pain (42.2%), fever (24.3%), joint pain (20.2%), injection site swelling (9.2%), injection site redness (8.6%), all of which were generally mild to moderate and lasted a few days. Severe solicited local adverse reactions and systemic adverse events occurred in 0.0%-2.4% of 12-15-year-old BNT162b2 recipients; such events were more frequent after BNT162b2 Dose 2 than after BNT162b2 Dose 1 and more frequent in BNT162b2 recipients than age-matched placebo recipients. Among recipients of BNT162b2, severe solicited adverse reactions/events in 12-15-year-olds occurred less frequently than in 16-25-year-olds.

Figure source: FDA EUA memorandum (pp. 38-39) [https://www.fda.gov/media/148542/download#page=38](https://www.fda.gov/media/148542/download#page=38)
Why do so few children enjoy any benefit?

• Covid-19 was a rare event in the trial (18 cases among ~1000 placebo)
• Many U.S. children have already had SARS-CoV-2 infections
• Immunity following natural infection is strong and long lasting

<table>
<thead>
<tr>
<th>Age group</th>
<th>Estimated Infections (February 2020-March 2021)</th>
<th>Total Population (2019)</th>
<th>Proportion with past SARS-CoV-2 infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 yrs</td>
<td>4,466,773</td>
<td>19.6m</td>
<td>~23%</td>
</tr>
<tr>
<td>5-17 yrs</td>
<td>22,203,414</td>
<td>53.5m</td>
<td>~42%</td>
</tr>
</tbody>
</table>

Sources:
   https://doi.org/10.1038/s41586-021-03647-4 & Breton et al. bioRxiv [preprint]. Dec 2020
“There’s not been a serious side effect in history that hasn’t occurred … within six weeks of getting the dose.”

Not so simple!

- Pandemrix – narcolepsy discovered ~9 months later (Aug 2010)
- mRNA vaccine – myocarditis discovered ~4 months later (April-June 2021)

Long-term harms (all we can do is theorize at this point e.g. by considering mechanism of action, biodistribution and other studies)

Not just about biological timeline, but pharmacovigilance timeline

It’s about discovering an AE early enough to prevent harm to others

Sources:
2. Wastila et al. Citizen Petition (June 1, 2021; Docket ID: FDA-2021-P-0521) https://downloads.regulations.gov/FDA-2021-P-0521-0001/attachment_1.pdf (see Pfizer and Moderna biodistribution studies, Tables 1a, 1b, 2)
Indirect protection: vaccinating children to benefit adults?

• Current status
  • Lavine et al.: “vaccinating children is likely to be of marginal benefit in reducing the risk to others” ... “Once most adults are vaccinated, circulation of SARS-CoV-2 may in fact be desirable, as it is likely to lead to primary infection early in life when disease is mild, followed by booster re-exposures throughout adulthood as transmission blocking immunity wanes but disease blocking immunity remains high.”¹
  • Remains an unproven hypothetical benefit that could be tested in an RCT

• However even if proven:
  • To authorize or approve a medical product in a population (e.g. children), the benefits must outweigh the risks in the same population (irrespective of the effects in population Y)
  • It’s an ethically questionable proposition

Conclusion: we must avoid a fiasco

• There is no covid-19 emergency in children (therefore EUA criteria not met)

• So far, demonstrated risks far outweigh demonstrated benefits in children (therefore BLA criteria not yet met)

• There is no “unmet need” and there is no need to rush to approve

• Medium and long-term safety is unknown (we have reason to be cautious: narcolepsy/Pandemrix, myocarditis/mRNA Covid-19 vaccine, and biodistribution studies)

• Expanded Access Programs can be used prior to BLA, for parents who wish to vaccinate their children before it’s demonstrated that benefits outweighs risks

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