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

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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

Slide B

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[3]

Age group	Estimated Infections (February 2020-March 2021)[1]	Total Population (2019)[2]	Proportion with past SARS-CoV-2 infection
0-4 yrs	4,466,773	19.6m	~23%
5-17 yrs	22,203,414	53.5m	~42%

Sources:

1. CDC https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html
2. US Census https://www2.census.gov/programs-surveys/popest/tables/2010-2019/national/asrh/nc-est2019-syasexn.xlsx
3. Dan et al. Science. Feb 2021 http://doi.org/10.1126/science.abf4063 & Turner et al. Nature. May 2021. https://doi.org/10.1038/s41586-021-03647-4 & Breton et al. bioRxiv [preprint]. Dec 2020 http://doi.org/10.1101/2020.12.08.416636 & Hall et al. Lancet. Apr 2021. http://doi.org/10.1016/S0140-6736(21)00675-9

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"There's not been a serious side effect in history that hasn't occurred … within six weeks of getting the dose."[1]

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[2])

Not just about biological timeline, but pharmacovigilance timeline

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

Sources:

1. Offit P. What Are the Long-term Side Effects of COVID-19 Vaccine? Jan 2021. https://www.chop.edu/centers-programs/vaccine-education-center/video/what-are-the-long-term-side-effects-of-covid-19-vaccine
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)

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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**

Source: Lavine JS, Bjornstad O, Antia R. Vaccinating children against SARS-CoV-2. BMJ. 2021 May 13;373:n1197. https://doi.org/10.1136/bmj.n1197 PMID: 33985969.

Slide E

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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