COVID-19 Vaccines Have Moved Out of Neutral, but Still Gearing Up in Children

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We agree that optimal drug doses in those ≥12 years of age have been similar to those identified for adults.[1, 2] Neither of our articles addressed the complexity of pediatric drug development.[3, 4] Importantly, the bar for vaccine licensure in healthy children is different from that for administration of a potentially lifesaving therapeutic. Additionally, classic pharmacokinetic data (e.g., clearance, volume of distribution) do not exist for locally administered vaccines. As such, we need to determine the vaccine dose and schedule from clinical trial data. While we can utilize "our present understanding of the developing human body"[2] as a starting point for rational clinical trials, we owe our children data on which to base vaccine licensure. Children change dramatically during adolescence. For example, the median boy undergoes puberty between 12 – 17 years of age and has a >60% increase in weight (median of ~40kg to ~65 kg).[5] Data support 2 doses of HPV vaccine in younger children, but 3 in those ≥16 years of age.[6] Data about the dosing of COVID-19 vaccines in children (including those 12 – 17 years of age) are needed and required by the US Food and Drug Administration (FDA) before vaccine approval. The FDA has noted that the "epidemiology and pathogenesis of COVID-19, and the safety and effectiveness of COVID-19 vaccines, may be different in children compared with adults" and such studies will help ensure compliance with the Pediatric Research Equity Act.[7] Recently, Pfizer-BioNTech announced preliminary data that antibody levels observed in 12 – 15 year olds post vaccination were greater than those observed in 16 – 25 year olds, but with similar tolerability.[8] Moderna also completed enrolling 12 – <18 year olds (NCT04649151). Thus, data are available that can combat vaccine hesitancy and the impression that the vaccines were 'rushed,' particularly for the new mRNA and vector-based COVID-19 platforms. Unfortunately, many advocated delaying pediatric COVID-19 vaccine clinical trials awaiting adult safety and efficacy data. Such delays were not warranted as vaccines have been studied and licensed in children without adult efficacy data (e.g., rotavirus, pneumococcal). In the meanwhile, the

number of US deaths due to COVID-19 in children now exceeds the maximum number of influenza-related deaths in children observed in any single season.[9, 10] In the future, such delays could be avoided by sponsors being more innovative (in conjunction with the FDA) in writing adaptive trials that incorporate vulnerable populations (e.g., pregnant women, children) without compromising protections. It would be possible to start trials in relatively healthy adults and then expand into these populations based upon pre-specified criteria.

Despite these delays, vaccine clinical trials are finally shifting into gear in children. Recently, both Pfizer-BioNTech (NCT04816643) and Moderna (NCT04796896) announced studies for children 6 months – <12 years of age, and other manufacturers are initiating trials. Such trials are powered for safety and immunogenicity, but may not provide efficacy. Ensuring transparency in these studies and their data will be critical in combatting vaccine hesitancy if data support the expansion of COVID-19 vaccines into children.

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EJA has received personal fees from Medscape, Pfizer, and Sanofi Pasteur for consulting, and his institution receives funds to conduct clinical research unrelated to this manuscript from MedImmune, Regeneron, PaxVax, Pfizer, GSK, Merck, Novavax, Sanofi-Pasteur, Janssen, and Micron. He also serves on a safety monitoring board for Sanofi-Pasteur and Kentucky BioProcessing, Inc.

WO is a member of the Scientific Advisory Board for Moderna Inc. and a member of the DSMB for AstraZenica Vaccines.

JDCs institution receives funds to conduct clinical research unrelated to this manuscript from Merck, GSK, Pfizer, and Sanofi. He is currently an investigator on federally funded COVID-19 research with products manufactured by Moderna, Gilead, Eli Lilly, and EMD Serono. He serves pro bono on a data and safety monitoring board for Sanaria.

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