Ethical Challenges during COVID-19: Research with Vulnerable Populations

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December 1st, 2023

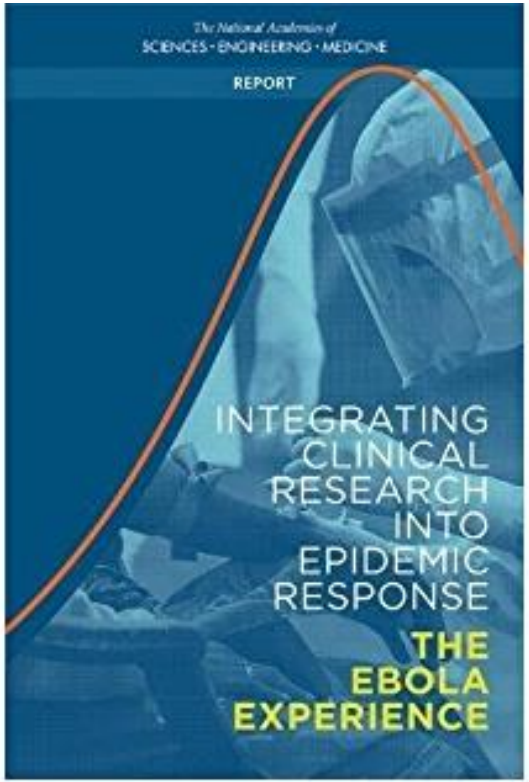
Disclaimer

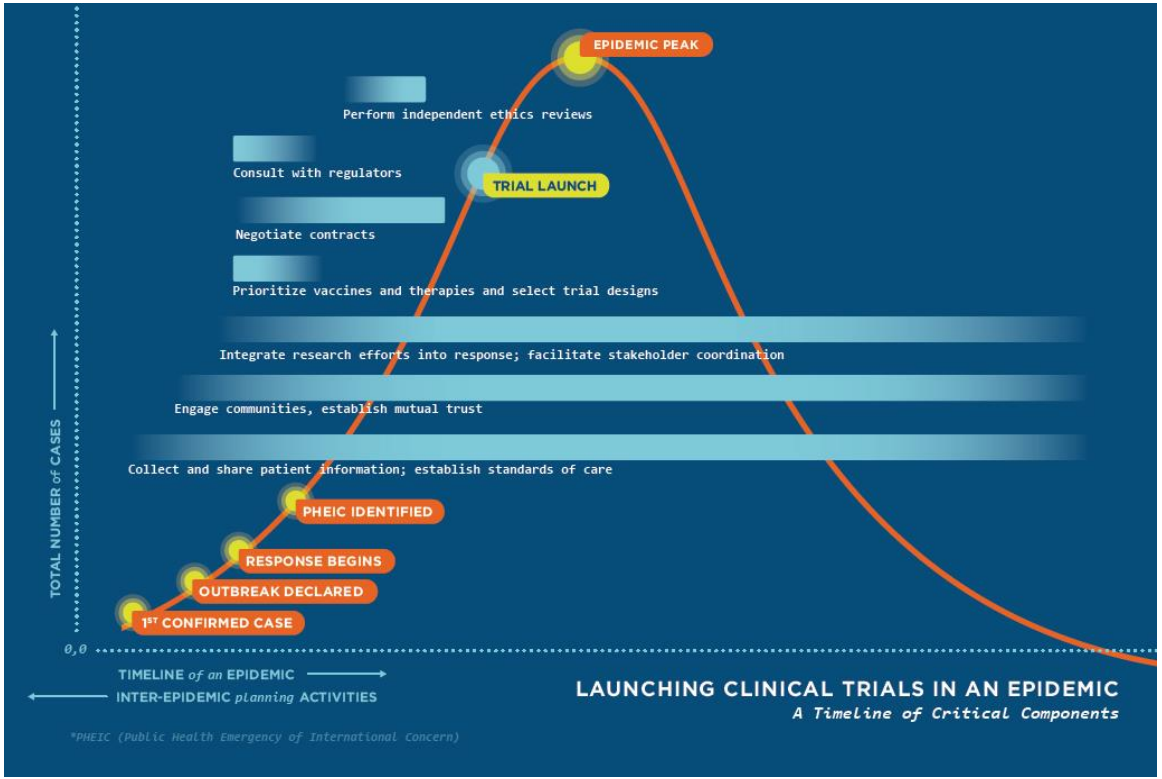
- The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance from the Food and Drug Administration (FDA) or the Department of Health and Human Services (HHS).

Key Messages

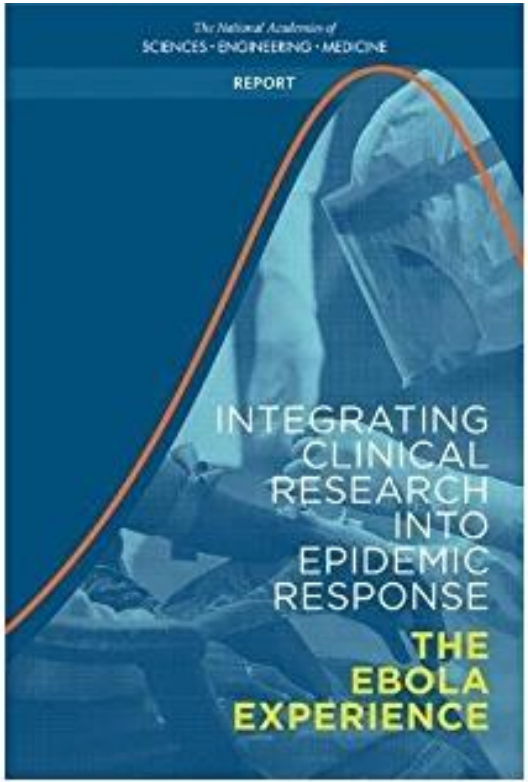
- Ethical principles underlying the conduct of clinical research remain the same in a public health emergency.
- Every effort should be made to maintain Good Clinical Practice standards to assure human subject protections and data validity.
- Too often, vulnerable populations are inappropriately excluded from trials or trials specific to these populations are delayed.
    - The additional protections afforded these populations under FDA and HHS regulations are intended to ensure they can be included in clinical research in a way that assures their protection.
    - Excluding these individuals can lead to additional disease burden and uncertainty as they decide whether to take a treatment that has not been studied in similar individuals.
- For these reasons, the DOH principles hold true for public health emergencies without revision.

Speed is of the essence, so time for debate must be minimized





Sound design principles remain in epidemics…



"The committee concludes that the randomized controlled trial (RCT) was an ethical and appropriate design to use, even in the context of the Ebola epidemic, stating that RCTs are the most reliable way to identify the relative benefits and risks of products being studied. Except when rare circumstances are applicable, every effort should be made to implement RCTs during epidemics."

Though speed is essential, requirements for participant protection must also be maintained, including for vulnerable populations

What are vulnerable populations?

- The HHS Common Rule does not explicitly define, but offers examples
- “children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons” (45 CFR 46.107(a))

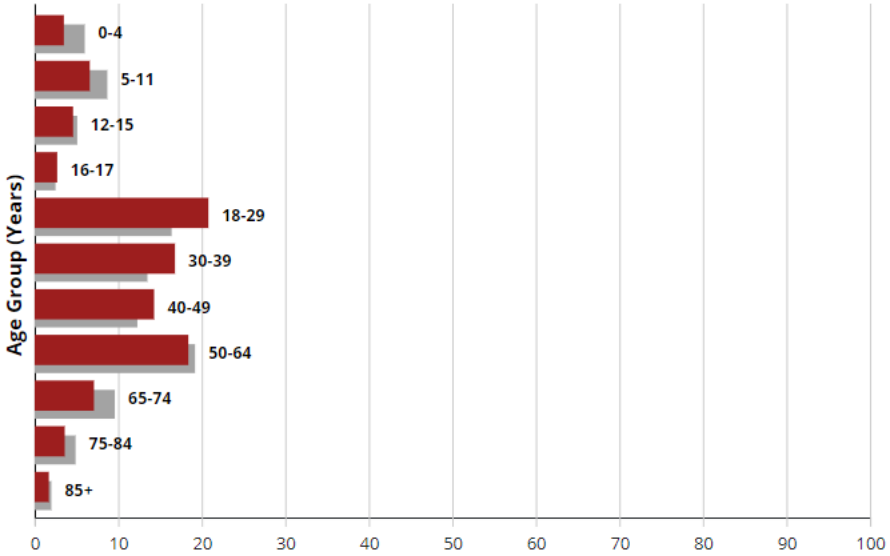
Two populations of specific interest in public health emergencies

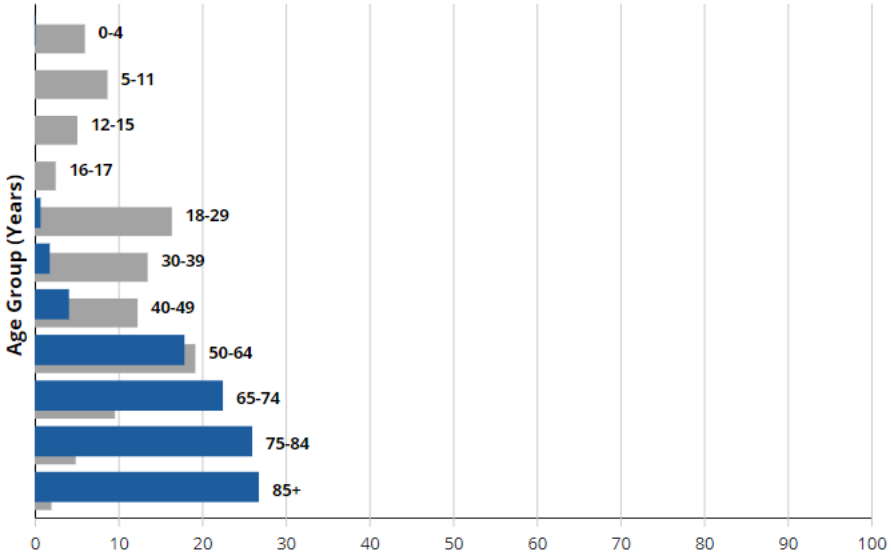
- Pediatric populations
- Pregnant people (in US, often not considered vulnerable, but frequently excluded from research nonetheless)

Two populations of specific interest in public health emergencies

- **Pediatric populations**
- Pregnant people

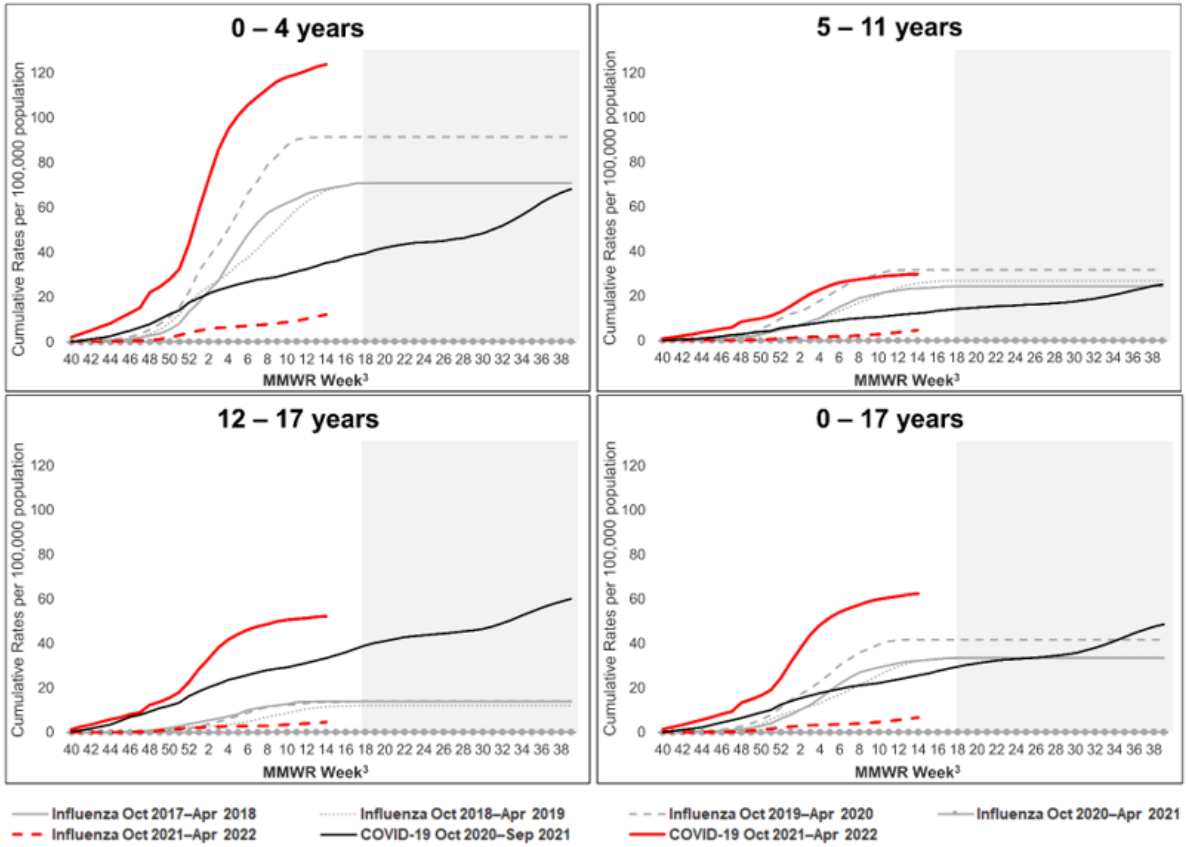
COVID is a larger threat to adults, but pediatric morbidity and mortality exists





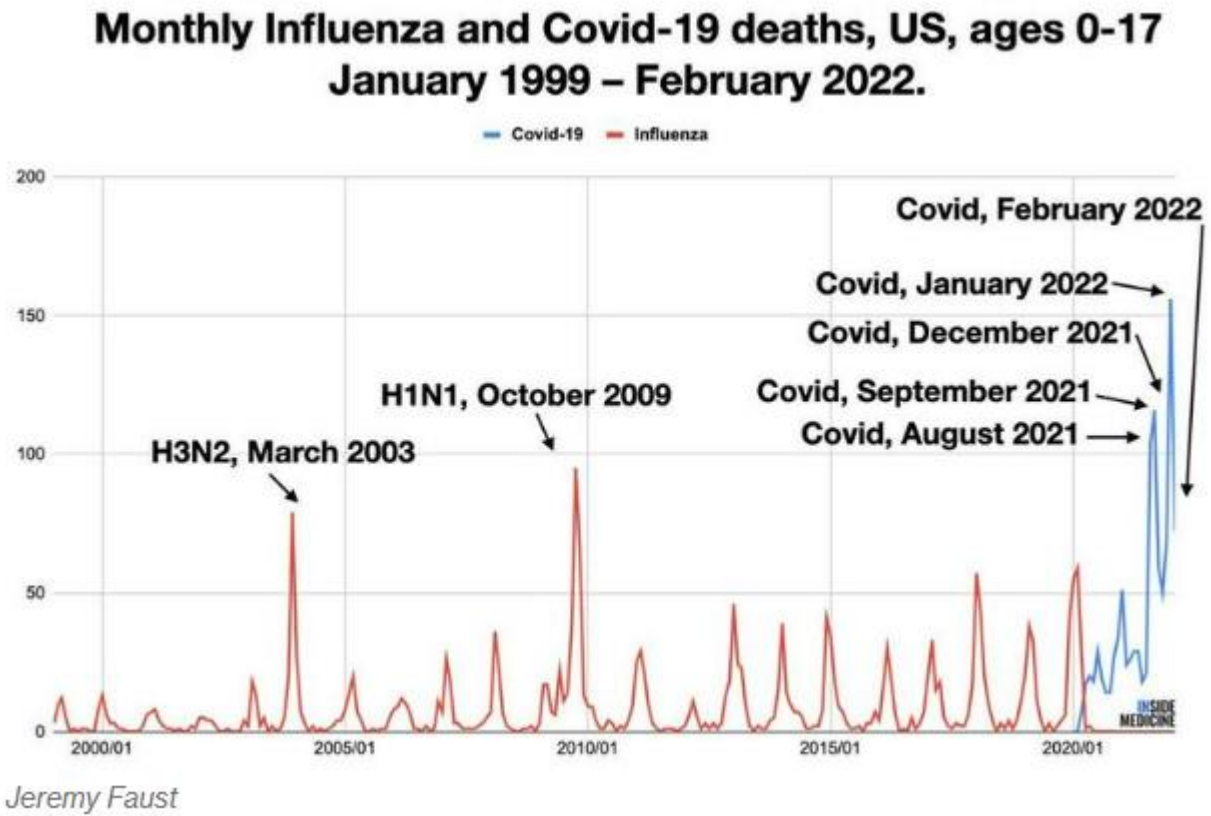
Source: cdc.gov, COVIDNET as of 9.24.22

In fact, in the US, COVID hospitalizations surpassed influenza



Source: M Delahoy et al. *Clin Inf Dis* May 20, 2022.

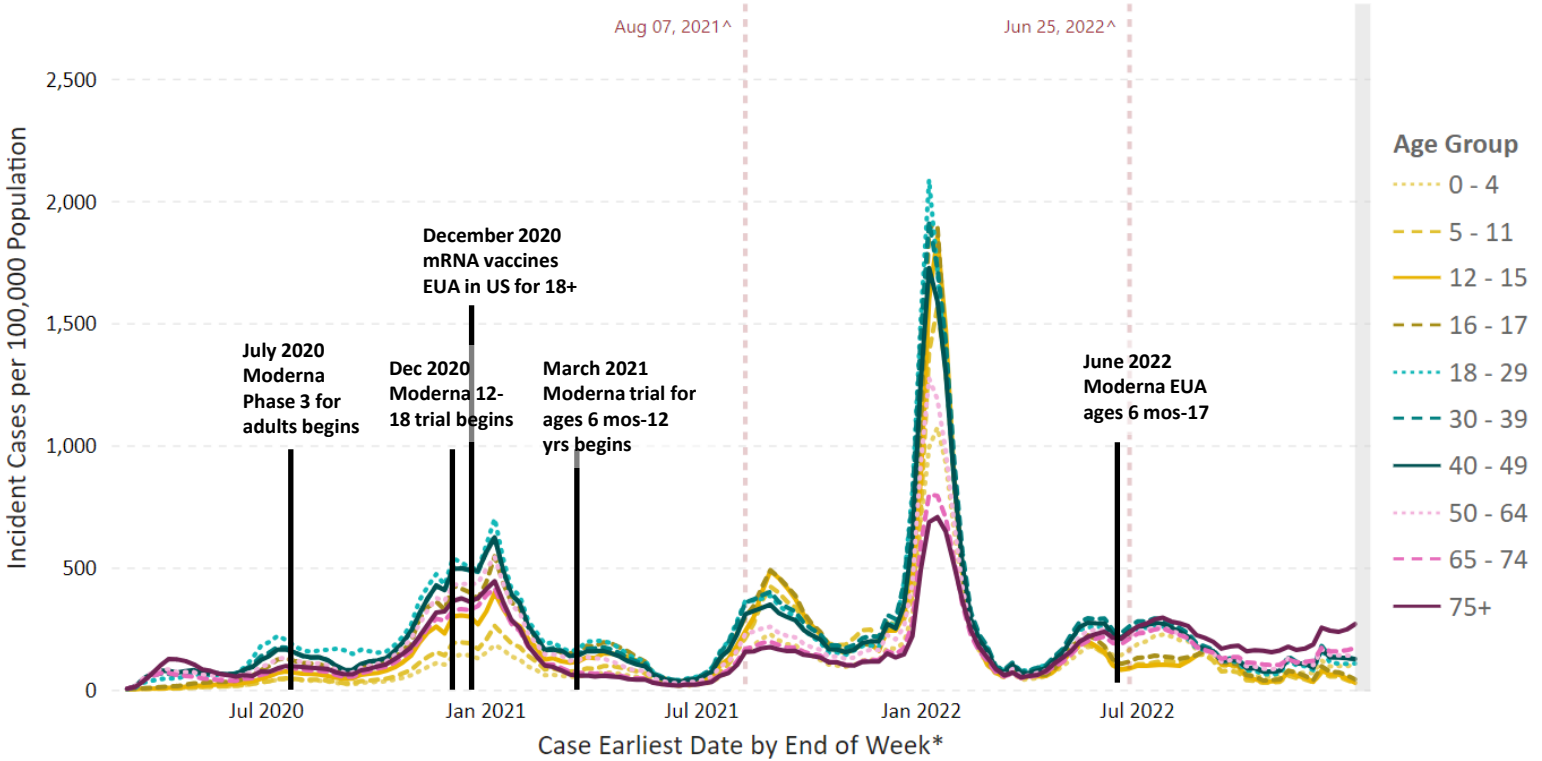
As did COVID deaths



Source: https://insidemedicine.bulletin.com/delta-and-omicron-killed-far-more-children-than-flu-ever-does

COVID-19 Weekly Cases per 100,000 Population by Age Group, United States

March 01, 2020 - December 31, 2022*



*Moderna dates displayed for illustrative purposes

US: Includes data up to the week ending on Nov 11, 2023. Percentage of cases reporting age by date - 99.92%.

US territories are included in case and death counts but not in population counts. Potential six-week delay in case reporting to CDC denoted by gray bars. Weekly data with five or fewer cases have been suppressed. *Case Earliest Date is the earliest of the clinical date (related to illness or specimen collection and chosen by a defined hierarchy) and the Date Received by CDC. The date for the current week extends through Saturday. ^Case rates for South Dakota during the week ending Aug 07, 2021, and Texas during the week ending Jun 25, 2022, are reflective of a data reporting artifact. Surveillance data are provisional, and as additional clinical date data becomes available, the case rates over time are subject to change.

Source: CDC COVID-19 Case Line-Level Data, 2019 US Census, HHS Protect; Visualization: Data, Analytics & Visualization Task Force and CDC CPR DEO Situational Awareness Public Health Science Team

Treatment Considerations for Children With COVID-19

Currently, no results from pediatric clinical trials that evaluated the treatment of COVID-19 have been published. Data evaluating the use of pharmacologic therapy in children with COVID-19 are limited largely to descriptive reports.[1,2] Therefore, more high-quality randomized trials, observational studies, and pharmacokinetic studies are urgently needed. Whenever possible, clinical trials of therapeutics and multicenter observational cohorts should enroll children with COVID-19.

The current recommendations for treating COVID-19 in children have been mostly extrapolated from recommendations for adults with COVID-19, recommendations for children with other viral infections, and expert opinion.[3-5] Applying adult data from

Source: NIH Treatment Guidelines

Conducting ethical studies in children

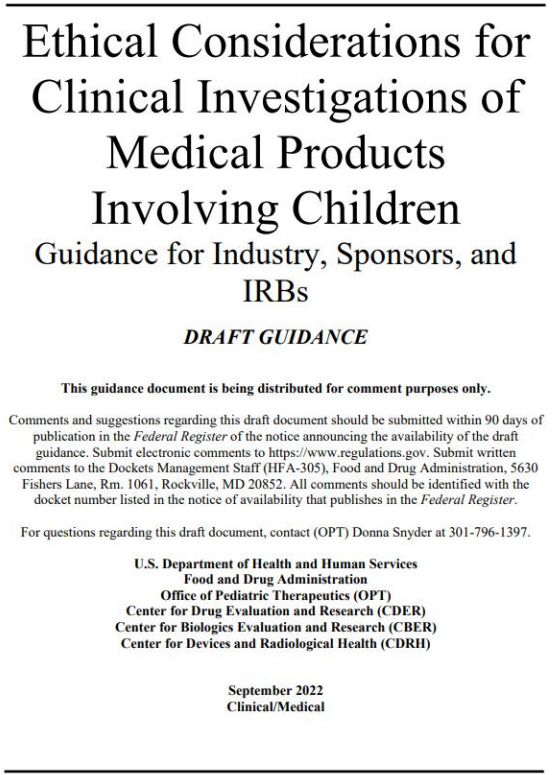
- Close review of the consent document (parental permission) to assure it is balanced and written in plain language
- Children cannot consent for themselves, adequate provisions for soliciting a child's assent need to be made when a child is capable of providing assent
- Additional risk mitigation efforts in protocol design
- Additional oversight by safety monitors, DMC, IRBs and the FDA
- Novel trial designs such as an adaptive enrollment practices in order to enroll less vulnerable populations first before broadening the pool of subjects enrolled

Additional Protections

- Review of the protocol and recruitment practice to assure that there is a fair selection of subjects. The scientific goal of the study should be the basis for determining the individuals that will be enrolled in the research and that the targeted population is not exploited due to their condition or vulnerability.
- Pre-specified stopping rules
- Consideration of including IRB members knowledgeable about and experienced in working with populations vulnerable to coercion or undue influence - 21 CFR 56.107(a)
- Community consultation to assess the opinion of those likely to be enrolled (done in emergency research under 21 CFR 50.24(a)(7)(i))
- Public Disclosure of the research to assure transparency (e.g. ClinicalTrials.gov, and emergency research under 21 CFR 50.24(a)(7)(ii) and (iii))

Ethical Considerations for Pediatric Clinical Trials

- Children are a vulnerable population who cannot consent for themselves and who therefore are afforded additional safeguards when participating in a clinical investigation.
- When finalized, this draft guidance will describe the ethical framework for protecting children in clinical research, and steps for considering enrollment.
- The draft guidance provides a detailed description of the additional human subject protection regulations that are included in 21 CFR 50, subpart D (Additional Safeguards for Children in Clinical Investigations).



Ethical Considerations for Clinical Investigations of Medical Products Involving Children

Guidance for Industry, Sponsors, and IRBs

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OPT) Donna Snyder at 301-796-1397.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Pediatric Therapeutics (OPT)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

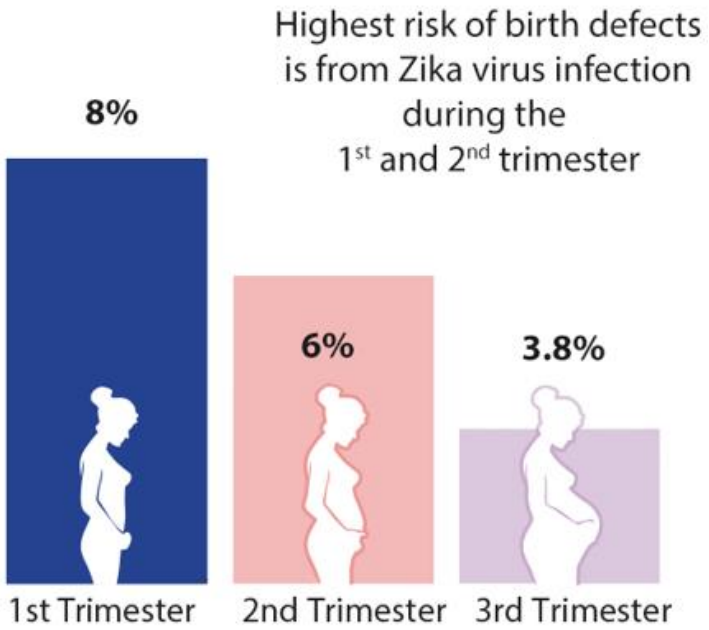
September 2022
Clinical/Medical

Adapted from Melanie E. Bhatnagar

Two populations of specific interest in public health emergencies

- Pediatric populations
- **Pregnant people**

Zika pandemic impacted pregnancy directly, but pregnant people were generally excluded from vaccine trials



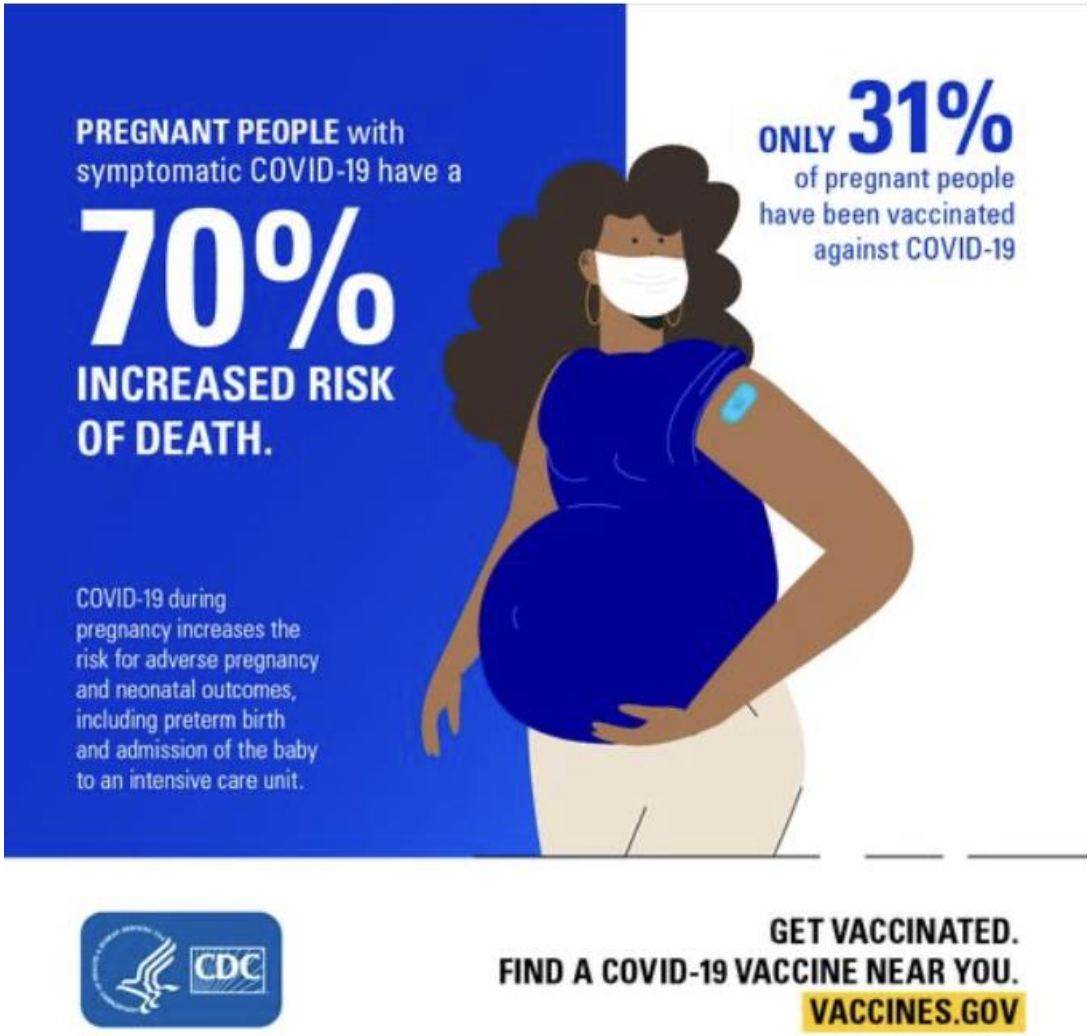
NIH Zika DNA Vaccine: Phase 2/2b Study Population

- Healthy men and women ages 15-35 years in areas at risk of Zika infection
  - *Negative result pregnancy test (hCG)*
  - *Agree to use effective means of birth control to avoid pregnancy through 12 weeks after last vaccination (all pregnancies will be followed for outcome)*
  - *Not breastfeeding*
- No history of confirmed Zika infection (subject self-report)
- 24 months of follow up
  - Scheduled visits every 2 weeks *and* for any possible Zika symptoms

VRC Clinical Trial Program

Adapted from Karin Bok, NIAID

Risk of COVID in pregnancy well known



Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

N = 30,420
Ages 18 and older

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

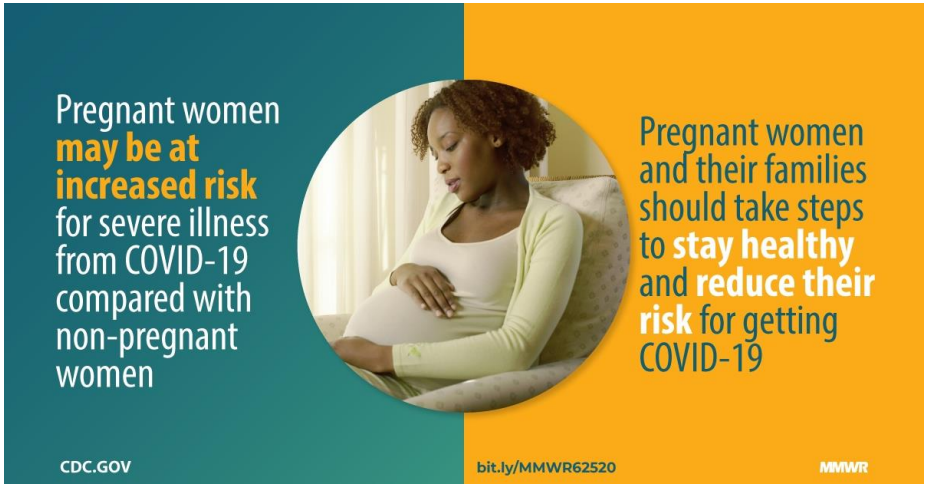
Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

N = 43,548
Ages 16 and older

CDC Recommends, WHO Disagrees

Pregnant Women Get Conflicting Advice on Covid-19 Vaccines

The W.H.O. and the C.D.C. provide differing views, and experts partly blame a lack of data because expectant mothers have been excluded from clinical trials.



Published Jan. 28, 2021

The W.H.O. drops opposition to vaccinations for pregnant women.

Give this article

A pregnant woman being vaccinated in Tel Aviv. Jack Guez/Agence France-Presse — Getty Images

Published Jan. 29, 2021

Ethical Considerations for Pregnant Populations

- Pregnant people need to be able to make informed decisions regarding treatments and preventive modalities.
- It is important to gather data on the benefits and risks of **new** therapeutics and vaccines for pregnant people intentionally and in a systematic way, allowing for appropriate follow up of diverse outcomes
- Pregnant people and fetus/newborn should also be able to benefit from new vaccine technologies addressing previously unmet medical needs
- The benefit of vaccination should be balanced against lack of data/theoretical risk of unknown outcomes
- Pregnant people are unlikely to be included in efficacy trials during a pandemic/emergency
- Developmental & Reproductive Toxicity (DART) study should be conducted expeditiously, ideally with other toxicology studies

Adapted from Karin Bok, NIAID

Special considerations for resource poor environments in emergencies

Resource Poor Environment as Vulnerability

- Need to assure that the goals of the research are in line with the public health needs of the host country(ies)
- Efforts are needed to assure prospective subjects are not exploited due to their condition or environment
- Consideration should be given to building research capacity in the host country(ies) through collaborative partnership(s)*
- Consideration should be given to facilitating post trial access when appropriate
- The targeting of high-risk population for COVID trials should be done with great care to assure that the health needs of each individual are addressed

* Emanuel EJ et al. What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research. The Journal of Infectious Diseases, Volume 189, Issue 5, 1 March 2004

Summary:

- Ethical principles outlined in the Declaration of Helsinki hold true in public health emergencies
- In fact, the urgency of the moment often tests our resolve to maintain protections, making joint understanding of this imperative all the more important
- Regarding vulnerable populations, excluding them unnecessarily can lead to a paucity of data to guide practice and care. They *can* be enrolled, but existing guidance on participant protection should be consulted

Acknowledgements

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- Adam Berger
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