ACCELERATING THE DEVELOPMENT OF COVID-19 VACCINES AND THERAPEUTICS FOR EVERYONE

By Richard Jefferys and Lindsay McKenna

The COVID-19 pandemic has spurred a massive global research effort to develop therapeutics and biomedical prevention interventions (particularly vaccines, because they're believed to be the best hope for curtailing the pandemic and returning society to normalcy). The U.S. government is investing heavily through the National Institutes of Health (NIH) Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private research partnership and the puerilely named "Operation Warp Speed" program, which aims to accelerate vaccine development. The urgency has prompted implementation of novel adaptive clinical trial designs intended to rapidly weed out ineffective therapies, along with widespread use of concertinaed vaccine research timelines that combine typically discrete phases, leading to an abundance of phase I/II and II/III studies.

As more candidates enter the latter stages of efficacy testing, it's increasingly important that trial participants reflect the diverse populations that will need interventions. This is a necessary step—along with work on pricing, distribution, and accessibility—toward ensuring that rollout can happen rapidly for all people who stand to benefit.

Who is most at risk?

The increased susceptibility of older people and people with comorbidities to worse outcomes from COVID-19 is well described. In the U.S., studies have shown that there is a disproportionate risk of COVID-19 among Black and Latinx people, and while the data are more limited, this might also be the case for American Indian, Alaska Native, and Pacific Islander populations.[1] (For more on these disparities, see Madoori, et al. p. 15) Recent evidence indicates that racial disparities are even greater among young people,[2] and while this is a group at lower risk for severe disease and mortality, studies have found that a proportion of younger people with COVID-19 require hospitalization and mechanical ventilation.[3]

Overall, women face a lower risk of morbidity and mortality from COVID-19 than men, likely because of sex differences in immune responses.[4] However, evidence indicates that pregnant women face significantly higher risks than nonpregnant women (see textbox p. 15).

Ensuring inclusion

An example of advocacy to ensure broad representation in COVID-19 research is the recent response to exclusion of people with HIV from vaccine efficacy trials conducted by Moderna and Pfizer. After the circulation of sign-on letters and statements from community activists (including TAG) and professional medical organizations, both companies amended their protocols to allow the participation of people with HIV.[5] In Pfizer's case, this involved expanding its trial from 30,000 to 44,000 participants to facilitate inclusion of people with HIV, hepatitis B, and hepatitis C.[6]

Updates on enrollment in several vaccine efficacy trials have included information on participant diversity. At the time of writing, Moderna had reported that 28,043 people have joined its study, approaching the 30,000-person target. While the company notes that 33% are from "diverse communities," the most recently available breakdown is far from optimal: 72% of participants are white, 16% Hispanic or Latinx, 7% Black or African American, 3% Asian, 1% more than one race, 0.4% American Indian or Alaska Native, and 0.2% Hawaiian or other Pacific Islander.[7] The COVID-19 Prevention Network (CoVPN), which is collaborating with Moderna, is undertaking initiatives aimed at improving participant diversity.[8] Enrollment trends by week suggest that these efforts are having a positive impact.[7]

Pfizer has enrolled 36,576 participants, including at sites outside the U.S. The company notes that about 42% have diverse backgrounds (28% in the U.S.): 28% Hispanic or Latinx, 9% Black, 4% Asian and 0.6% Native American.[9]

Persistent gaps

Neither company appears to provide a breakdown of participants by sex and/or gender identity, and a recent analysis (not yet peer reviewed) has found that this is a common problem in COVID-19 research. Among 2,484 trials registered in ClinicalTrials.gov, only 16.7% cited sex/gender as a recruitment criterion and 4.1% made reference to sex/gender in their descriptions of planned analyses. Of the 11 clinical trials with published results as of June 2, 2020, none reported results disaggregated by sex/gender. The authors of the paper write: "Given the biological relevance and the potential risks of unwanted side effects, we urge researchers to focus on sex-disaggregated analyses already at the planning stage of COVID-19 trials."[10]

Among a multitude of therapeutic trials, two major randomized controlled studies have demonstrated reductions in recovery time or mortality in hospitalized people with COVID-19. The antiviral drug remdesivir was associated with an improvement in recovery time of five days on average,[11] while the immune-suppressive corticosteroid dexamethasone reduced 28-day mortality in people receiving either invasive mechanical ventilation or oxygen alone.[12] Information on the demographics of participants in these trials is shown in Table 1. No information on race/ethnicity of participants was provided for the dexamethasone study, which was conducted in the UK, but the published results note that a prespecified subgroup analysis by race will be forthcoming when data collection is completed.

Relatively few COVID-19 clinical trials are including children. An early review of research conducted in China found only three studies enrolling people under 16 years old (out of 63 evaluating conventional therapies).[13] Researchers have issued a call for more pediatric trials, with a set of recommendations including central coordination and an emphasis on multicenter studies to increase sample sizes.[14] Gilead Sciences, the manufacturer of remdesivir, has launched a pediatric study,[15] and an expert panel has made preliminary recommendations on the use of the drug in this population.[16]

Similarly, inclusion of children in COVID-19 vaccine trials is limited. AstraZeneca is assessing the safety of its candidate in the 5 to 12 age group. Based on information in online registries, two studies in China allowed enrollment of people as young as 6 months (no data have yet been presented), and one study in India has a lower age bound of 12.[17]

Table 1: Demographics for participants enrolled in major randomized controlled studies of therapeutics for COVID-19

	remdesivir (U.S.)	dexamethasone (UK)
Total # of participants	1062	6425
Women	378 (35.6%)	2338 (36.4%)
Race		
American Indian or Alaska Native	7 (0.7)	N/A
Asian	135 (12.7)	N/A
Black or African American	226 (21.3)	N/A
Multi-Racial	3 (0.3)	N/A
Native Hawaiian or Other Pacific Islander	4 (0.4)	N/A
White	566 (53.3)	N/A
Unknown	121 (11)	N/A
Ethnicity		
Hispanic or Latinx	250 (23.5)	N/A
Not Reported/ Unknown	57 (5,4)	

Conclusion

As scientific research progresses toward the goal of effective therapies and biomedical prevention options for COVID-19, there is clearly much work to do to ensure that there is robust information on the effects of candidate interventions in diverse populations. To chart the path forward, it's essential that there be maximal transparency regarding plans for generating the data necessary for rapid approval and distribution for all.

A regrettable component of the emerging maelstrom of information related to COVID-19 is limited disclosure of new trial results via press release. TAG concurs with researchers who have outlined a minimum set of requirements for the disclosure of new study results, including participant demographics.[33]

SPOTLIGHT: ETHICAL INCLUSION OF PREGNANT PARTICIPANTS IN RESEARCH

In 2019, 1.9 billion women were of childbearing age (15–49 years old) globally.[18] Surveys in the United States have found that nearly 50 percent of women age 15–44 expect to have a child in the future and that from 2011 to 2015, 85 percent of women 40–44 reported ever having given birth.[19,20] In fact, there are nearly 4 million births every year in the U.S.[21] Many women of childbearing potential are part of the essential workforce, including healthcare workers. A disproportionate share of low-wage essential jobs are held by Black and Latinx women, populations that also have higher rates of pregnancy conditions such as gestational diabetes and hypertension, both risk factors for COVID-19-related complications.[22,23]

An analysis of surveillance data collected by the U.S. Centers for Disease Control and Prevention (CDC) found that Hispanic and non-Hispanic Black pregnant women were disproportionately affected by SARS-CoV-2 infection during pregnancy. Further, among women of childbearing age with SARS-CoV-2 infection, those who are pregnant are more likely to be hospitalized, be admitted to the intensive care unit, and receive mechanical ventilation compared with nonpregnant women.[24,25] Yet, 65 percent of COVID-19 therapeutic clinical trials[26] and 100 percent of COVID-19 vaccine clinical trials exclude pregnant people.[27]

In many ways the exclusion of pregnant people from COVID-19 clinical research is the legacy of decades of researchers misguidedly seeking to protect pregnant people and fetuses from research, rather than through their participation in research. Still, it's inexcusable, especially when considering that for some of the therapeutic interventions under investigation for COVID-19 (e.g., chloroquine/hydroxychloroquine, lopinavir/ritonavir), safety data exist in pregnancy from use for other indications. Additionally, a number of platforms under investigation for COVID-19 vaccines have been tested previously and found safe in studies of pregnant animals (e.g., ChAdOx1 for Rift Valley fever disease in pregnant sheep, gorilla adenovirus-vectored vaccines for Zika virus in pregnant mice).[28,29,30]

To ensure that all populations can benefit from ongoing research efforts, developmental and reproductive toxicology (DART) studies necessary to include women of childbearing potential and pregnant people in clinical trials must be an urgent priority, especially ahead of phase III trials. Developers of vaccines and therapeutics should be transparent about their plans to conduct DART studies and assess their candidates in pregnant people.

Following people enrolled in trials who become pregnant is another important way to capture data; the efficacy trial protocols for the Moderna and Pfizer COVID-19 vaccines have recently been disclosed publicly, and both include guidance on reporting and following any cases to capture outcomes.[31,32]

Endnotes

1. Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and racial/ethnic disparities. JAMA. 2020 Jun 23;323(24):2466–7. doi: 10.1001/jama.2020.8598. https://jamanetwork.com/journals/jama/fullarticle/2766098.

2. Bixler D, Miller AD, Mattison CP, et al., SARS-CoV-2-associated deaths among persons aged <21 years - United States, February 12–July 31, 2020. Morb Mortal Wkly Rep. 2020 Sep 18;69(37):1324–9. doi: 10.15585/mmwr.mm6937e4. https://www.cdc.gov/mmwr/volumes/69/wr/mm6937e4.htm.

3. Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study BMJ 2020;370:m3249. doi: 10.1136/bmj.m3249. https://www.bmj.com/content/370/bmj.m3249.

4. Takahashi T, Ellingson MK, Wong P, et al. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature. 2020 Aug 26. doi: 10.1038/s41586-020-2700-3. Online ahead of print. https://www.nature.com/articles/s41586-020-2700-3.

5. Tech2 News Staff. "Moderna, Pfizer move to include HIV-positive volunteers in phase 3 trials of COVID-19 vaccines." Firstpost. 2020 August 10. https://www.firstpost.com/health/moderna-pfizer-move-to-include-hiv-positive-volunteers-in-phase-3-trials-of-covid-19-vaccines-8690821.html.

6. Pfizer (Press Release). Pfizer and BioNTech propose expansion of pivotal COVID-19 vaccine trial. 2020 September 12. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-propose-expansion-pivotal-covid-19.

7. Moderna, Inc. Enrollment update. 2020 October 2. https://www.modernatx.com/cove-study.

8. COVID-19 Prevention Network (CoVPN) (Press Release). New national faith-based community engagement initiative to partner with key communities around COVID-19 and CoVPN clinical trials. 2020 September 10. https://www.newswise.com/coronavirus/new-national-faith-based-community-engagement-initiative-to-partner-with-key-communities-around-covid-19-and-covpn-clinical-trials.

9. Pfizer. Our progress in developing a potential COVID-19 vaccine. 2020 October 5. https://www.pfizer.com/science/coronavirus/vaccine.

10. Brady E, Nielsen MW, Andersen JP, Oertelt-Prigione S. Lack of consideration of sex and gender in clinical trials for COVID-19. medRxiv. 2020 Sep 14. 2020.09.13.20193680. https://doi.org/10.1101/2020.09.13.20193680.

11. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Oct 8:NEJMoa2007764. doi: 10.1056/NEJMoa2007764. https://www.nejm.org/doi/full/10.1056/NEJMoa2007764.

12. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson J, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med. 2020 Jul 17:NEJMoa2021436. doi: 10.1056/NEJMoa2021436. https://www.nejm.org/doi/full/10.1056/NEJMoa2021436.

13. Qiu R, Wei X, Zhao M, et al. Outcome reporting from protocols of clinical trials of Coronavirus Disease 2019 (COVID-19): a review. medRxiv 2020.03.04.20031401; doi: https://doi.org/10.1101/2020.03.04.20031401.

14. Campbell JI, Ocwieja KE, Nakamura MM. A call for pediatric COVID-19 clinical trials. Pediatrics. 2020 Aug;146(2):e20201081. doi: 10.1542/peds.2020-1081. https://pediatrics.aappublications.org/content/146/2/e20201081.

15. Gilead Sciences (Press Release). Gilead Sciences statement on phase 2/3 clinical trial of remdesivir in pediatric patients hospitalized with COVID-19. 2020 June 17. https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-clinical-trial-of-remdesivir-in-pediatric-patients.

16. Chiotos K, Hayes M, Kimberlin DW, et al. Multicenter interim guidance on use of antivirals for children with COVID-19/SARS-CoV-2. J Pediatric Infect Dis Soc. 2020 Sep 12:piaa115. doi: 10.1093/jpids/piaa115. https://academic.oup.com/jpids/advance-article/doi/10.1093/jpids/piaa115/5904884.

17. Branswell H. "Will Covid-19 vaccines be safe for children and pregnant women? The data, so far, are lacking." STAT News. 2020 August 19. https://www.statnews.com/2020/08/19/will-covid-19-vaccines-be-safe-for-children-and-pregnant-women-the-data-so-far-are-lacking/.

18. World Health Organization. Women of reproductive age (15–49 years) population (thousands). 2019. https://www.who.int/data/maternal-newborn-child-adolescent/indicator-explorer-new/mca/women-of-reproductive-age-(15-49-years)-population-(thousands).

19. Daugherty J, Martinez G. Birth expectations of U.S. women aged 15–44. NCHS Data Brief No. 260. U.S. Department of Health and Human Services. October 2016. https://www.cdc.gov/nchs/data/databriefs/db260.pdf.

20. Martinez GM, Daniels K, Febo-Vazquez I. Fertility of men and women aged 15–44 in the United States: national survey of family growth, 2011–2015. National Health Statistics Reports, No. 113. U.S. Department of Health and Human Services. July 2018. http://www.cdc.gov/nchs/data/nhsr/nhsr113.pdf.

21. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: final data for 2018. National Vital Statistics Reports. 2019 Nov 27;68(13). https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_13-508.pdf.

22. Jin Rho H, Brown H, Fremstad S. A basic demographic profile of workers in frontline industries. Center for Economic and Policy Research. 7 April 2020. https://cepr.net/a-basic-demographic-profile-of-workers-in-frontline-industries/.

23. Panagiotakopoulos L, Myers TR, Gee J, et al. SARS-CoV-2 infection among hospitalized pregnant women: reasons for admission and pregnancy characteristics - eight U.S. health care centers, March 1–May 30, 2020. Morb Mortal Wkly Rep. 2020;69(38):1355–9. Epub 2020 Sep 23. https://www.cdc.gov/mmwr/volumes/69/wr/mm6938e2.htm.

24. Ellington S, Strid P, Tong VT, et al. Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status – United States, January 22–June 7, 2020. Morb Mortal Wkly Rep. 2020 Jun 26;69(25):769–75. https://www.cdc.gov/mmwr/volumes/69/wr/mm6925a1.htm.

25. Delahoy MJ, Whitaker M, O'Halloran A, et al. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19 – COVID-NET, 13 states, March 1–August 22, 2020. Morb Mortal Wkly Rep. ePub: 2020 September 16;69(38);1347–54. doi: http://dx.doi.org/10.15585/mmwr.mm6938e1.

26. Pastick KA, Nicol MR, Smyth E, et al. A systematic review of treatment and outcomes of pregnant women with COVID-19 – a call for clinical trials. Open Forum Infect Dis. 2020 Aug 13;7(9);ofaa350. https://doi.org/10.1093/ofid/ofaa350.

27. Farrell R, Michie M, Pope R. Pregnant women in trials of COVID-19: a critical time to consider ethical frameworks of inclusion in clinical trials. Ethics Hum Res. 2020 Jul;42(4):17–23. doi: 10.1002/eahr.500060. https://onlinelibrary.wiley.com/doi/10.1002/eahr.500060.

28. Dashraath P, Nielsen-Saines K, Madhi SA, Baud D. COVID-19 vaccines and neglected pregnancy. Lancet. 2020 Sep 5;396;10252:E22. doi: https://doi.org/10.1016/S0140-6736(20)31822-5.

29. Stedman A, Wright D, Wichgers Schreur PJ, et al. Safety and efficacy of ChAdOx1 RVF vaccine against Rift Valley fever in pregnant sheep and goats. npj Vaccines. 2019 Oct 18;4:44(2019). https://doi.org/10.1038/s41541-019-0138-0.

30. Hassan AO, Dmitriev IP, Kashentseva EA, et al. A gorilla adenovirus-based vaccine against Zika virus induces durable immunity and confers protection in pregnancy. Cell Rep. 2019;28(10):2634–46.e4. doi:10.1016/j.celrep.2019.08.005. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6750284/.

31. Moderna, Inc. A phase 3, randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine in adults aged 18 years and older. 2020 August 20. https://www.modernatx.com/sites/default/files/mRNA-1273-P301-Protocol.pdf.

32. Pfizer. A phase 1/2/3, placebo-controlled, randomized, observer-blind, dose-finding study to evaluate the safety, tolerability, immunogenicity, and efficacy of SARS-CoV-2 RNA vaccine candidates against COVID-19 in healthy individuals. 2020 September. https://pfe-pfizercom-d8-prod.s3.amazonaws.com/2020-09/C4591001_Clinical_Protocol.pdf.

33. Siedner MJ, Gandhi RT. Proposing minimum requirements for announcing clinical trial results during the COVID-19 pandemic. Clin Infect Dis. 2020 Jul 8:ciaa945. doi: 10.1093/cid/ciaa945. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa945/5868929.