

COMMENTARY

 OPEN ACCESS



Resolving sex and gender bias in COVID-19 vaccines R&D and beyond

Lavanya Vijayasingham^a, Shirin Heidari^{b,c}, Jean Munro^d, Saad Omer^e, and Noni MacDonald^f

^aGender and Health Hub, United Nations University- International Institute for Global Health, Kuala Lumpur, Malaysia; ^bGENDRO, Geneva, Switzerland; ^cGlobal Health Centre, Graduate Institute of International and Development Studies, Geneva, Switzerland; ^dGender Equality, GAVI Vaccine Alliance, Geneva, Switzerland; ^eYale Institute for Global Health, Yale University, New Haven, CT, USA; ^fDepartment of Pediatrics, Dalhousie University, Halifax, NS, Canada

ABSTRACT

The influence of sex and gender in immune response and vaccine outcomes is established in many disease areas, including in COVID-19. Yet, there are notable gaps in the consideration of sex and gender in the analysis and reporting of COVID-19 vaccines clinical trial data. The push for stronger sex and gender integration in vaccines science should be championed by all researchers and stakeholders across the R&D and access ecosystem – not just gender experts. This requires joint action on the tactical framing of customized value propositions (based on stakeholder motivations), the stronger enforcement of existing regulation, tools, and commitments, and aligning the overall agenda to parallel calls on intersectionality, equity diversity and inclusion.

ARTICLE HISTORY

Received 29 November 2021
Revised 12 January 2022
Accepted 25 January 2022

KEYWORDS

COVID-19; sex; gender;
vaccines research

The case for better sex and gender considerations in COVID-19 vaccine science is strong, as it is for vaccines R&D in general. The combination of biological sex differences – the genetic, cellular, biochemical, physiological, and immunological differences within and beyond the reproductive systems, and gender – the differences in sociocultural norms, roles, power relations and access to resources between women, men, and people of other gender identities, can influence vaccines outcomes, uptake and access.

On the biological side, there are known sex-differences in immune responses to viral infections, including respiratory tract infections such as influenza, SARS, and MERS.^{1,2} There is documented research that women tend to mount a higher antibody response than men after receiving equal doses of influenza, yellow fever, rubella, measles, mumps, hepatitis A and B, herpes simplex 2, rabies, smallpox and dengue vaccination.^{2,3} Post-vaccination adverse events are more common in women,⁴ as are adverse events from pharmaceutical medications more broadly.⁵ One explanation for this is that there are inadequate considerations of sex-differences in early pharmacokinetics, bioavailability and dosing studies.⁵ In children too, nonspecific effects (protective and detrimental effects from vaccination) such as susceptibility to other infections, and all-cause deaths are found to be related to vaccine-type and sex.³ Of course, real-world safety surveillance of COVID-19 vaccines suggested a potential sex-dimension in the proportions of rare allergic reactions (mRNA vaccines) and thrombosis (nonreplicating viral vector vaccines) in women, and equally rare but serious adverse events-cardiac complications in young men and boys (mRNA vaccines).⁶

Known gender-related or disproportionate barriers such as access to credible information, influence vaccine uptake decisions, and equitable access.^{7,8} For instance, there is lower COVID-19 vaccine acceptance among women in low-and-

middle-income countries,⁹ and among pregnant women, particularly in high-income countries, who hesitate to vaccinate on account of safety fears, and the lack of conclusive data in pregnancy.¹⁰ However, only 5 of 58 countries with COVID-19 vaccine policies (March 2021) refer to gender in these documents,⁷ and in countries such as Gabon, Somalia, and Timor-Leste, women account for less than 35% of those who have received at least one dose of a COVID-19 vaccine (June 2021).¹¹

Despite these points, sex and gender considerations continue to be neglected in COVID-19 vaccine R&D.¹² At the start of the pandemic, there was attention on gender in many other domains of the COVID-19 response, including men's higher risk of severe infections and death. Yet, amidst the need for speed, scale, and solidarity to develop vaccines, sex and gender considerations were relegated in global research agendas and evaluations guidelines. While women and men are generally well represented in late phase COVID-19 vaccine trials, there is a mixed record of how well sex-disaggregated and gender-specific data or considerations feature in the outcomes reporting, analysis, and evaluations processes.¹² While there are many preexisting commitments toward sex considerations and reporting from journals, such as implementing the SAGER guidelines,¹³ this has not been adequately enforced across all COVID-19 studies.¹⁴

If the value and importance are clear, then the implementation gap of sex and gender considerations in COVID-19 and all other vaccines R&D should not be the responsibility of only a niche group of sex and gender experts. Champions across all stakeholder groups are needed to negotiate for better considerations at every stage of research, evaluation, and decision-making along the vaccine development process. So how do we, as a collective of champions, do better?

Resolving resistance and changing minds: tactical framing to achieve critical mass for normative shifts

As an approach, we need to communicate the value through tactful language that is ‘understood’ through the motivations and conditionings of the various stakeholders. The evidence base to support better integration of sex and gender across many clinical medicine and laboratory science fields exists, but it needs a ‘story’- a compelling narrative and a ‘value proposition.’ Here are some brief talking points:

First, it contributes to better science. Sex and gender analysis helps identify protective benefits that can support translation, innovation, and development of vaccines that benefit everyone. Neglect and blind spots can mean potential discoveries have been overlooked, where unmet need, medical harm and increased distrust toward vaccines and therapeutics across populations is perpetuated. Second, serving these unmet needs creates value for health systems, economies, and societies, including through human capital gains from healthier and more gender-equal societies. Third, it facilitates ethical, inclusive, and human rights-based innovation, which in turn can contribute to social and distributive justice and individual bodily autonomy to pursue the highest attainable health.

While publicly calling out specific gaps and biases are necessary, isolating or overtly ostracizing approaches using frames of references that are not meaningful to other stakeholders may not serve the objective. Identification of gaps should be coupled with suggestions of solutions or alternative practices that can be considered. Repeated messaging and persistent enquiry of the absence of necessary considerations can catalyze the critical mass required to make pronounced and longstanding changes.

As an example, framing the value in terms of commercial interests and economic gains is likely to appeal to the rationales and motivations of private investors and scientist-entrepreneurs. Strong sex and gender considerations can contribute to the development of precision medicine, more effective and potentially more cost-effective products that can provide a potential competitive edge over other therapeutic and prophylactic options in the market. Value of information analysis for instance,¹⁵ can be applied to model and assess the anticipated payoffs from the investments associated with the additional sex and gender considerations. Additionally, there are commercial merits in building a public image as socially conscious companies that are course-correcting away from the legacy of sexism and androcentrism in R&D, especially in the eyes of the media, socially conscious impact investors and consumers of products.

Holding ‘feet to fire’: establishing and enforcing regulatory policies that promote accountability toward new and existing tools, strategies & recommendations

Calls for stronger sex and gender considerations at structural and policy levels, to address the persistent biases in medicine is not new. There are ample existing resources to shift norms, build capacity, and raise targeted awareness amongst stakeholders. For COVID-19 vaccines for example, there are specific global tools and recommendations to collect relevant data

variables and analyze sex-disaggregated safety surveillance data, such as the WHO background paper on critical sex and gender considerations for equitable research, development and delivery of COVID-19 Vaccine,¹⁶ and the interagency developed guidance note and checklist for tackling gender-related barriers to equitable COVID-19 vaccine deployment developed by SDG 3 Global Action Plan.⁸ We now need to discuss and facilitate its implementation, especially in the long-term, and in resource-limited settings.

Here, a foresight-driven, mutually serving, and sustainable strategy should be co-shaped by all stakeholders, including industry innovators who are agentic actors that are driven by good science, economic value, and social impacts. Co-shaping the approach is important for ownership, and buy-in. Stakeholder pushback, reservations, and anticipated challenges can be identified and resolved early, so that interventions are not ‘side-stepped’ in its implementation.

Indeed, the need for more resources, for example the time, financing, and capacity to recruit study participants to achieve strength of evidence is acknowledged. Here, we can draw on past lessons on how incentives such as tax breaks, patent extensions, and rebates on evaluation fees encouraged industry investments and innovations in areas of unmet therapeutic and data needs. This includes the approach of how greater investments in rare and neglected tropical diseases were facilitated. Conversely, a balanced penalty-based approach, such as through delays or rejections in approvals can also be considered. Innovators, as market-driven commercial entities would respond to social and structural shifts in the ecosystem to remain competitive in the market.

Regulatory processes, and networks such as the WHO pre-qualification mechanism, and the International Council for the Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) can shape these normative standards that need to be adhered to for positive regulatory decisions. Drawing from parallel regulatory levers, the establishment of national requirements for local data in countries such as in Japan, India and China drove the conduct of clinical trials in these countries.¹⁷ The implementation of internationally adopted guidelines and standards for the evaluation and regulation of pediatric products, and national incentives facilitated the pursuit of formal indications and better data in children.¹⁸ In the case of sex and gender considerations, the ICH should consider revisiting a 16-year old assessment that specific guidelines are not necessary on how sex should be included, and reported in studies, through an updated review on the role of sex factors across disease areas, and gaps in guideline recommendations, implementation and enforcement in global product evaluations and standardized regulatory dossiers.

Aligning call to parallel conversations on intersectionality, equity, diversity, and inclusion

Ultimately, there is a broader problem with the scientific approach to COVID-19 vaccine science and its distribution – its exclusionary paradigm. Consider the current global vaccine R&D trends – who ‘does, leads, influences and ‘benefits’ from the science? We need to also anchor the work of addressing sex and gender biases in health and medical research in these

broader conversations about intersectionality, equity, diversity, and inclusion.⁶ For instance, target product profiles, R&D agendas and ‘end-to-end’ product planning, market entry and lifecycle management must integrate sex and gender considerations, as well as more diverse voices on domains such as user preferences, acceptability, willingness-to-pay and value-assessments, including from countries and markets with lower ability to pay, to serve the pursuit of timely and equitable access and affordability.

We also need more women in decision-making positions in R&D, regulatory and industry leadership.^{6,17} However, tokenistic representation is not enough. Systemic change is required. Broader structural barriers and biases are pervasive, such as in the case of scientific meritocracy systems that are shaped by legacies of sexism, racism and other category and process-based biases that privilege-specific types of achievements, ways of work, epistemic networks, scientific paradigms, and life roles. This perpetuates the divide in the distribution of scientific resources, and capacity. We need to align with and extend the goal to dismantle and disrupt the unjust systems that have left various groups behind.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work is led by The Gender and Health Hub at UNU-IIGH, which receives grant funding from the Bill and Melinda Gates Foundation.

ORCID

Lavanya Vijayasingham  <http://orcid.org/0000-0002-4424-4491>

Data availability statement

This article is inspired by an online panel discussion – *Sex and gender in COVID-19 vaccines: data, policy, and communication organized by GAVI, GENDRO and UNU-IIGH*. <https://www.genderhealthhub.org/articles/sex-and-gender-in-covid-19-vaccines-data-policy-and-communication/>

References

- Ursin RL, Klein SL. Sex differences in respiratory viral pathogenesis and treatments. *Annu Rev Virol* [Internet]. 2021;8:393–414. [accessed 2021 Jul 2]. <https://www.annualreviews.org/doi/10.1146/annurev-virology-091919-092720>.
- Klein SL, Pekosz A. Sex-based biology and the rational design of influenza vaccination strategies. *J Infect Dis*. 2014;209:114–19. doi:10.1093/infdis/jiu066.
- Aaby P, Benn CS, Flanagan KL, Klein SL, Kollmann TR, Lynn DJ, Shann F. The non-specific and sex-differential effects of vaccines. *Nat Rev Immunol*. 2020;20:464–70. doi:10.1038/s41577-020-0338-x.
- Flanagan KL, Fink AL, Plebanski M, Klein SL. Sex and gender differences in the outcomes of vaccination over the life course. *Annu Rev Cell Dev Biol*. 2017;33:577–99. doi:10.1146/annurev-cellbio-100616-060718.
- Zucker I, Prendergast BJ. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol Sex Differ*. 2020;11:32. doi:10.1186/s13293-020-00308-5.
- Heidari S, Durrheim DN, Faden R, Kochhar S, MacDonald N, Olayinka F, Goodman TS. Time for action: towards an intersectional gender approach to COVID-19 vaccine development and deployment that leaves no one behind. *BMJ Global Health*. 2021;6:e006854. doi:10.1136/bmjgh-2021-006854.
- Evagora-Campbell M, Borkotoky K, Sharma S, and Mbuthia M. From routine data collection to policy design: sex and gender both matter in COVID-19. *The Lancet*. 2021;397(10293):2447–2449. [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(21\)01326-X/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01326-X/fulltext).
- SDG3 Global Action Plan for Healthy Lives and Well-Being: Gender Equality Working Group, Gender and Health Hub, United Nations University International Institute for Global Health. Guidance note and checklist for tackling gender-related barriers to equitable COVID-19 vaccine deployment [Internet]. 2021 [accessed 2021 Apr 21]. <https://www.genderhealthhub.org/articles/guidance-note-and-checklist-for-tackling-gender-related-barriers-to-equitable-covid-19-vaccine-deployment/>.
- Solis Arce JS, Warren SS, Meriggi NF, Scacco A, McMurry N, Voors M, Syunyaev G, Malik AA, Aboutajdine S, and Adejojo O, et al. COVID-19 vaccine acceptance and hesitancy in low- and middle-income countries. *Nat Med*. 2021;1–10. <https://globalhealth5050.org/the-sex-gender-and-covid-19-project/the-data-tracker/?explore=variable>.
- Skjefte M, Ngirbabul M, Akeju O, Escudero D, Hernandez-Diaz S, Wyszynski DF, Wu JW. COVID-19 vaccine acceptance among pregnant women and mothers of young children: results of a survey in 16 countries. *Eur J Epidemiol*. 2021;36:197–211. doi:10.1007/s10654-021-00728-6.
- Global Health 50/50. The COVID-19 sex-disaggregated data tracker: vaccinations-at least one dose [Internet]; 2021. <https://globalhealth5050.org/the-sex-gender-and-covid-19-project/the-data-tracker/?explore=variable&variable=Vaccinations>. Accessed on 30 June 2021.
- Heidari S, Palmer-Ross A, Goodman T. A systematic review of the sex and gender reporting in COVID-19 clinical trials. *Vaccines*. 2021;9:1322. doi:10.3390/vaccines9111322.
- Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and gender equity in research: rationale for the SAGER guidelines and recommended use. *Res Integrity Peer Rev*. 2016;1:2. doi:10.1186/s41073-016-0007-6.
- Palmer-Ross A, Ovseiko PV, Heidari S. Inadequate reporting of COVID-19 clinical studies: a renewed rationale for the sex and gender equity in research (SAGER) guidelines. *BMJ Glob Health*. 2021;6:e004997. doi:10.1136/bmjgh-2021-004997.
- Fenwick E, Steuten L, Knies S, Ghabri S, Basu A, Murray JF, Koffijberg (Erik) H, Strong M, Schmidler GDS, Rothery C. Value of information analysis for research decisions—an introduction: report 1 of the ISPOR value of information analysis emerging good practices task force. *Value Health*. 2020;23:139–50. doi:10.1016/j.jval.2020.01.001.
- Heidari S, and Goodman T. Critical sex and gender considerations for equitable research, development and delivery of COVID-19 vaccines: background paper [Internet]; 2021. https://cdn.who.int/media/docs/default-source/immunization/sage/covid/gender-covid-19-vaccines-sage-background-paper.pdf?sfvrsn=899e8fca_15&download=true. Accessed on 10 August 2021.
- Ravindran SK, Teerawattananon Y, Tannenbaum C, and Vijayasingham L. Making pharmaceutical research and regulation work for women. *Br Med J*. 2020;371:1–5. doi:10.1136/bmj.m3808.
- Turner MA, Catapano M, Hirschfeld S, Giaquinto C. Paediatric drug development: the impact of evolving regulations. *Adv Drug Deliv Rev*. 2014;73:2–13. doi:10.1016/j.addr.2014.02.003.