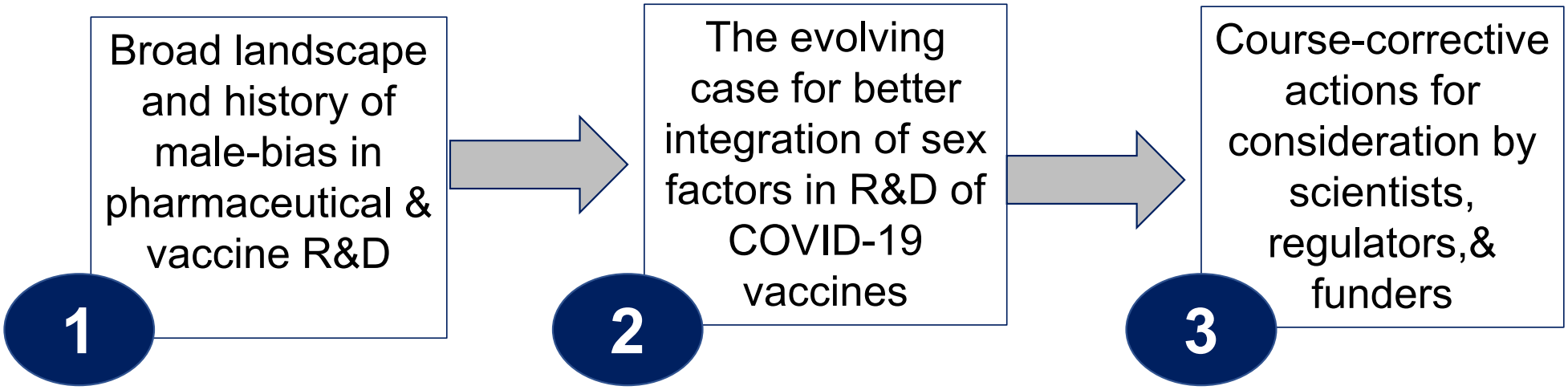
Sex in COVID-19 Vaccines R&D, Regulation, and Real-World Outcomes:

An opportunity for regional leadership to course-correct

Dr Lavanya Vijayasingham

Biological Sex:
The biological characteristics and profiles of
females, males, intersex, and gender-diverse individuals,
such as their anatomical, physiological & biochemical profiles in reproductive & other systems, genetic composition & expression.

Sex matters for everyone,
but there is unmet need for R&D on **women's** sex-related issues



1 Why are biological sex factors and sex-disaggregated data important for R&D, regulation and real-world data monitoring?

Women & men have different disease:

- risks
- symptoms
- clinical signs
- prognosis
- rates of progress
- severity
- mortality rates

Across multiple therapeutic areas:

- cardiology
- neurology
- pain management
- infectious and immune-system related diseases

Women & men respond to pharmaceutical treatment differently based on:

- body size & fat distribution
- reproductive systems
- concentrations of hormones, enzymes, & pharmaceutical-target molecules
- hormonal changes in menstrual cycles, pregnancy, breastfeeding, contraception use & menopause
- gut absorption,
- blood concentration,
- liver, and kidney clearance rates
- genetics

TK Sundari Ravindran et al. BMJ 2020;371:bmj.m3808
https://www.bmj.com/content/371/bmj.m3808

1 Gaps in practice along the broader pharmaceutical research and regulation pathway

Pre-clinical →

Many studies still:

- do not analyze & report data by sex
- do not justify the use of male-only studies
- cite hormonal variability of females as a reason for their exclusion.

Clinical studies →

Many studies still:

- do not analyze & report data by sex
- purposefully leave out females- citing:
  - *pursuits of restricted indications*
  - *difficulties in enrolment*
  - *resource limitations*
  - *weak expectations of reaching clinically meaningful outcomes*
- lag in representation of elderly, pregnant & lactating women

Regulatory decision-making →

- problem with enforcement
- bias & variability in decisions
- scarce economic value research on sex-differences

Post-market / real-world

- women report higher adverse events, including those that require hospitalization
- sex-differentiated dosing may be required in some cases

References available from
TK Sundari Ravindran et al. BMJ 2020;371:bmj.m3808
https://www.bmj.com/content/371/bmj.m3808

2 Many of these gaps were unaddressed and sex-responsive practices were relegated within the R&D and regulation of COVID-19 vaccines

Low proportion of sex-disaggregated reporting and analysis of all COVID-19 studies, and in vaccine-specific studies.

- Of 75 clinical trials on COVID-19 vaccines identified in April 2021, **24% reported their sex-disaggregated main outcome data, and 13% discussed of the sex-related implications of their findings.** *Heidari et al 2021-https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8622702/*

Global guidance did not require/request for sex-disaggregation of trial data for regulatory evaluation and approval, and sex-related factors under considered in the R&D agenda

- For example, WHO's "Considerations for evaluation of COVID-19 vaccines (November 2020)" only calls for sex-disaggregation of efficacy data, and not safety and adverse events data from trials.

2 Sex factors in vaccines, immune system response and therapeutics

What we knew prior to COVID-19:

Efficacy/Effectiveness:
Women mount higher immune response with same dose as men in influenza A, yellow fever and hepatitis A and B vaccines- this difference diminishes after menopause; sex hormones influence vaccine outcomes.

Adverse events:
Women- disproportionate adverse events in multiple vaccine disease areas:

Human Papillomavirus (HPV), yellow fever, rubella, measles, mumps, hepatitis A, hepatitis B, herpes simplex type 2, rabies, smallpox, and dengue

Heidari et al (2021) Time for action: towards an intersectional gender approach to COVID-19 vaccine development and deployment that leaves no one behind. BMJ Global Health 6, e006854.https://gh.bmj.com/content/6/8/e006854

2 Sex factors in COVID-19 vaccines: *Adverse events (very rare)*

What we know about COVID-19 vaccines:

- Early concerns about blood clots-women disproportionate in initial days; communication that contraception use induced higher risk opens up further questions of risk profiles women experience

- Cardiac complications (myocarditis and pericarditis) from mRNA vaccines use in young men and adolescent boys

- **US VAER system-** more women tend to report more post-COVID-19 vaccine adverse events, but among older adults, older men were more likely to report more a serious adverse events.

- **COVID-19 Citizen Science (mRNA vaccine)-** being a woman, Asian or pregnant, use of marijuana and having a prior SARS-COV-2 infection, was associated with higher odds of an adverse event report.

2 Sex factors in COVID-19 vaccines: Prioritized R&D on Pregnant and Lactating Women

- Pregnant women with COVID-19 are known to have a higher risk of preeclampsia/ eclampsia, severe COVID-19 infections, intensive care unit admission, requiring mechanical ventilation, maternal mortality and having a preterm birth.

- Yet, they were excluded from earlier phase 3 trials; initial safety outcomes were established through tracking in the post-market phase.

- Similar experiences were reported during the Ebola crisis. Even though there was disproportionate mortality amongst pregnant women, they were excluded from clinical trials for vaccines, thereby indirectly leading to many avoidable deaths.

3

Opportunity to do better
What are the suggestions?

R&D: Questions remain

Does safety, efficacy, optimal dosing, and protective duration of the different COVID-19 vaccines differ by sex, age, pregnancy and lactating status?

R&D: Unmet needs

- Study design that considers, anticipates, and is adequately powered to detect sex differences in safety, efficacy and effectiveness of vaccines
- Disaggregated analysis and reporting
- Responsive R&D and evidence generation that address the concerns of women, to support science communication

Regulatory levers and enforcement

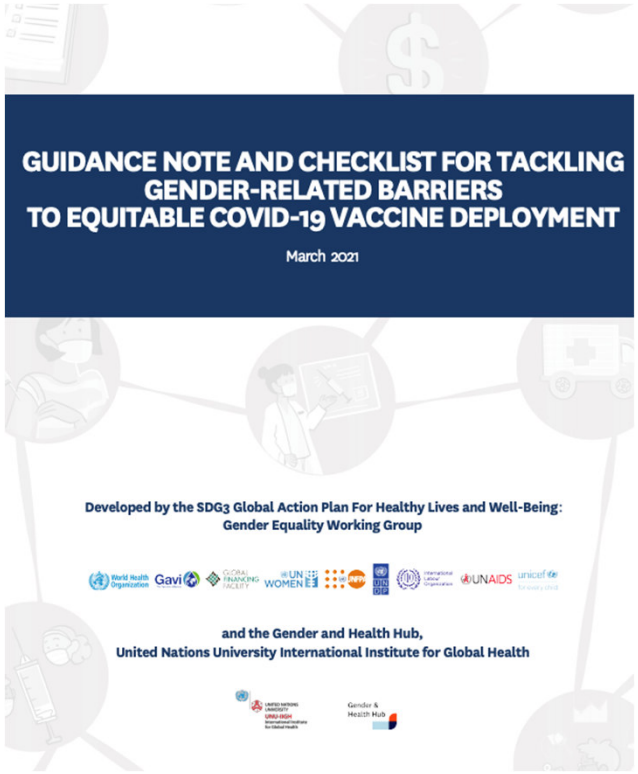
✓ **Make sex and age disaggregated data on pre- and post-market vaccine trials an essential requirement for expedited approval and emergency regulatory approval procedures (*and now full authorization*)**

- Approval should not be delayed if disaggregated data is not available immediately but agree on a timeframe for its provision and consider imposing penalties if this data is not provided within the agreed time period.

Real-world effectiveness and safety surveillance

✓ **Mechanisms for both active and passive reporting should capture sex and age disaggregated data, pregnancy/lactating status, frequency, and severity of adverse events following immunization**

Guidance note and checklist for tackling gender-related barriers to equitable COVID-19 vaccine deployment



*Available at: https://www.genderhealthhub.org/articles/guidance-note-and-checklist-for-tackling-gender-related-barriers-to-equitable-covid-19-vaccine-deployment/

3 Opportunity for regional leadership in implementing sex-responsive R&D, regulation and real-world monitoring

- Champions beyond the gender experts- addressing resistance, value-framing, engaging in dialogue to co-develop shifts in practice
- Engaging with different groups of women at various points in R&D to understand and address concerns through evidence generation
- Regulatory and funding enforcement to drive consistent and cohesive practice
- Strengthening data systems, analytical capabilities and real-time reporting/communication