

# Sex differences in vaccine responses: toward personalized vaccinology

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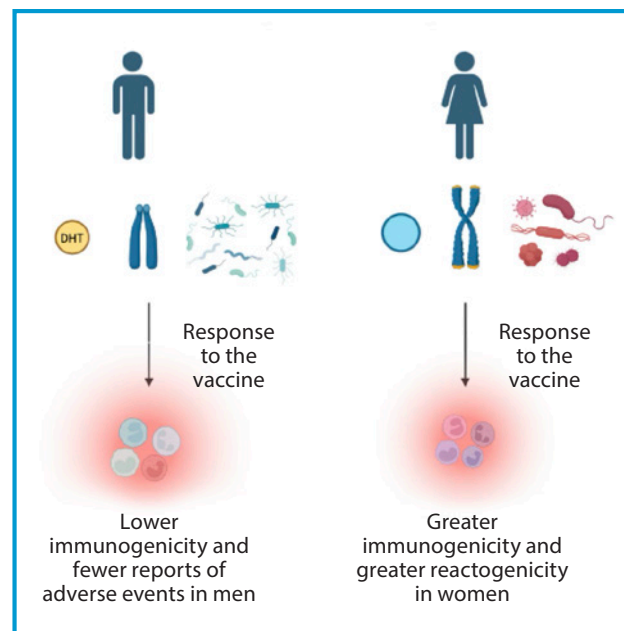
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**Summary.** Understanding and recognizing the importance of sex differences in the immune response to vaccines is critical to establishing their efficacy, safety, and long-term protection. Extensive literature indicates that women mount a more vigorous humoral and cellular immune response than men, a difference driven by hormonal influences, genetic determinants, and gut microbiota-related mechanisms. Along with such stronger responses also comes a greater incidence of reactogenicity and adverse events associated with vaccines. On the other hand, men generally show lower immunogenicity after vaccination, and they tend to report fewer adverse events. Different stages of the life course, including puberty, pregnancy, menopause, and aging, also influence sex-based differences. The COVID-19 pandemic has provided a unique opportunity to analyze sex-based patterns on a large scale. The need to conduct sex-disaggregated analyses at all vaccine development stages, including clinical trials and drug safety monitoring phases, emerges very clearly. Such analyses should include both biological sex and gender-related behaviors as well as sociocultural variables. A move toward a sex-based approach will increase equity in vaccination, maximize vaccine efficacy, and reduce avoidable adverse effects in the population.

**Key words.** Vaccines, sex/gender differences, personalized vaccinology.

Immunological research has focused increasingly on sex differences in immune responses to vaccines. These differences are not limited to efficacy but extend to safety and reactogenicity, and, in a broader sense, also impact public health strategies. The scientific literature demonstrates that women mount stronger humoral and cellular immune responses compared to men but report higher rates of adverse events following vaccination. These differences are the result of the combined effects of biological sex and psychosocial, behavioral, or cultural factors. Indeed, women exhibit significantly greater antibody production as well as a significantly greater incidence of adverse effects across all types of vaccines, including those for SARS-CoV-2 and hepatitis B.<sup>1</sup> The scientific literature has consistently documented that women mount more robust responses than men to immunization, while simultaneously reporting more adverse effects (Figure 1).

The evidence that women produce higher antibody titers than men is available for influenza vaccines,<sup>2</sup> as well as for MMR (measles, mumps, and rubella) and BCG (Bacillus Calmette-Guérin) vaccines.<sup>3</sup> A stronger immunological response in women arises from a complex interaction between hormonal, genetic, and cellular factors. Differences in immune response measures and distinct antibody production patterns between men and women do not necessarily result in different levels of protection against infection. Although these immune response measures are commonly used as surrogates to estimate vaccine effectiveness, the evidence linking sex-related differences in immunogenicity to differences in clinical outcomes is inconsistent or insufficient for many illnesses. Thus, it is commonly assumed that vaccines confer comparable protection in women and men.



**Figure 1.** Biological differences between men and women influencing vaccine response. In men, the immunosuppressive effects of androgen hormones, the XY chromosome configuration and specific characteristics of the gut microbiota contribute to a lower immunogenicity and a lower frequency of adverse events. In women, the immunostimulatory effects of estrogens, the presence of two X chromosomes, and the differences in the gut microbiota favor a more intense immune response, albeit associated with greater reactogenicity (figure created with BioRender.com.).

Yet, there are numerous measurable cellular-level differences. For example, estrogens enhance the proliferation and activation of B and T lymphocytes, as well as the production of proinflammatory cytokines, whereas testosterone tends to downregulate immune activation.<sup>2,3</sup> Additionally, an impressive number of immune-related genes reside on the X chromosome. Since women have two X chromosomes, this confers a much broader diversity of gene expression, possibly explaining a stronger basal immune activation and a more vigorous response to immunological challenges.<sup>4</sup> In addition, newly emerging evidence is documenting sexually dimorphic differences in gut microbiota composition, impacting sex-specific immune maturation and vaccine responsiveness.<sup>5</sup>

The same mechanisms underlying enhanced immune responses in women also contribute to higher rates of reactogenicity. Across vaccine studies, including those for influenza and COVID-19 mRNA vaccines, women consistently report higher rates of local and systemic adverse events than men.<sup>4,6</sup> Commonly reported symptoms include injection-site pain, fever, malaise, arthralgia, and fatigue. Due to their enhanced immunogenic response, women might experience more intense inflammatory reactions. Furthermore, women tend to report their symptoms more frequently or seek medical attention sooner. Conversely, men may underreport symptoms due to sociocultural norms, stigma, or delayed healthcare-seeking behavior.<sup>3</sup>

Another critically important aspect is the duration of protection conferred by vaccines. Studies indicate that women tend to maintain higher and more sustained antibody levels compared to men, suggesting a possible longer persistence of vaccine-induced immunity.<sup>3</sup> From a practical standpoint, this has implications for a more accurate estimate of the best timing for booster administration. However, this stronger or more prolonged immune response in women could theoretically contribute to an immune dysregulation in susceptible individuals.<sup>7</sup>

The COVID-19 pandemic provided an unprecedented opportunity to study sex differences in real time and on a worldwide scale. Systematic reviews have established that, despite the comparable efficacy of mRNA vaccines, women consistently experienced more adverse events than men, albeit mostly mild to moderate in severity.<sup>4,6,8</sup>

Sex differences stretch beyond biological sex and encompass gender-related behavioral factors. Women more frequently seek health-related information, comply with medical advice, and take part in vaccine campaigns; they are also likely to report adverse events more accurately than men. On the other hand, men may underreport symptoms or postpone medical evaluation, thereby influencing the evaluation of sex-based risk factors or the estimation of vaccine safety.<sup>4</sup> Hence, for any type of study

on sex-related differences, biological sex, gender identity, and sociocultural influences should all be considered within a multidisciplinary approach.

Life-course hormonal fluctuations are potent modulators of immune responses. Puberty, pregnancy, and menopause trigger significant endocrine changes that regulate immunity and dictate vaccine efficacy.

Despite the profound immunological changes during pregnancy, vaccines recommended for pregnant women demonstrate comparable safety and effectiveness.<sup>3</sup> With aging, the situation becomes more complex: immunosenescence exhibits sex-specific patterns that influence vaccine response, susceptibility to infections, and the optimal timing of booster doses.<sup>9</sup> All these aspects are crucial for designing strategies to ensure effective protection through different life stages.

Recent developments in immunology and vaccinology have highlighted the importance of sex as a variable. Despite the growing recognition of the importance of sex-disaggregation in health-related research, sex-disaggregated data are still inconsistently reported across vaccine clinical trials, post-marketing surveillance studies, and real-world evidence. Comparative analyses of vaccines by sex tend to be exploratory in nature, possess low statistical power, or are based on incomplete data regarding sex-specific variables. A closely related issue is the persistent underrepresentation of women in vaccine clinical trials. This limits the ability to thoroughly investigate how vaccines work differently for men and women. In the past, for example, researchers often excluded women of childbearing potential during the study, as there was insufficient preclinical data regarding the reproductive safety of vaccines. As a result, data obtained from a variety of sources may not be comparable, and translating observed differences into general recommendations for clinical and public health practice may be difficult.

Overcoming these regulatory and methodological barriers would support trial designs that include a wider and more representative range of participants.

Several experts now advocate for clinical trials to systematically disaggregate data by sex, assess sex-specific immunogenicity and safety profiles, and factor in sex-based distinctions when establishing vaccination schedules.<sup>3,4</sup> Failure to adopt such an approach could result in women receiving less accurate or even inappropriate vaccine recommendations.

While analyzing sex-based differences facilitates a better understanding of vaccine responses, biological sex alone may not be sufficient to determine an individual's ideal dose. Immune responses to diseases and vaccines can vary significantly, even among individuals of the same sex. Factors such as genetics, epigenetics, prior exposure to infectious agents, comorbidities, past immunological experiences, and the gut microbiome all influence these reactions. A more comprehensive under-

standing of sex differences in immunity – encompassing genetics, hormones, gut microbiota, and aging – will be instrumental in developing next-generation vaccines.

From a translational perspective, the principles outlined here provide insights into the development of sex-specific vaccination strategies in clinical practice (e.g., calibrating the duration of antibody responses, providing education about expected reactogenicity, and improving systems to monitor sex-specific safety signals). Additionally, translating these concepts into socially-informed behaviors could lead to higher compliance, mitigate vaccine hesitancy, and improve communication strategies.

However, vaccination outcomes are impacted not only by biological differences, but also by gender-related behaviors, as well as by factors such as healthcare access and attitudes toward vaccination. In low- and middle-income countries, structural and sociocultural barriers often limit women's access to vaccine and booster shots, as well as their ability to report adverse events. It is important to consider these aspects when implementing sex- and gender-informed immunization programs to create more equitable and effective health interventions. By integrating biological sex, gender-related characteristics, and life course biology together, we could really pave the way for personalized vaccination strategies that maximize effectiveness while reducing adverse reactions.

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