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Effect of sex on vaccination outcomes: important but frequently overlooked

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It is well established that vaccination does not affect males and females equally. For example, females generally mount greater antibody responses to vaccination than males, but also suffer more adverse events following vaccination, probably as a result of more robust immunity. Despite this, most researchers in the field of vaccinology do not take biological sex into account when conducting their studies. This omission is likely to lead to a loss of important information in terms of both reactogenicity and immunogenicity following vaccination as well as those suffering adverse events. It also suggests that the vaccine dose in males and females may need to be different in order to achieve the same outcome of protective immunity while minimising reactogenicity.

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Introduction

It is widely accepted that the biological sexes differ in their responses to vaccination [1••,2••] but the mechanisms and clinical significance remain uncertain [3] (Figure 1). Despite this, few vaccine studies analyse their results by biological sex making it difficult to determine how important this factor is. Until we have these data, males and females will continue to be recommended the same schedule and dose of vaccines throughout life. Herein, we review the evidence for sexual dichotomy in vaccination outcomes published over the last two years and discuss the implications for vaccine policy.

Antibody responses to vaccination

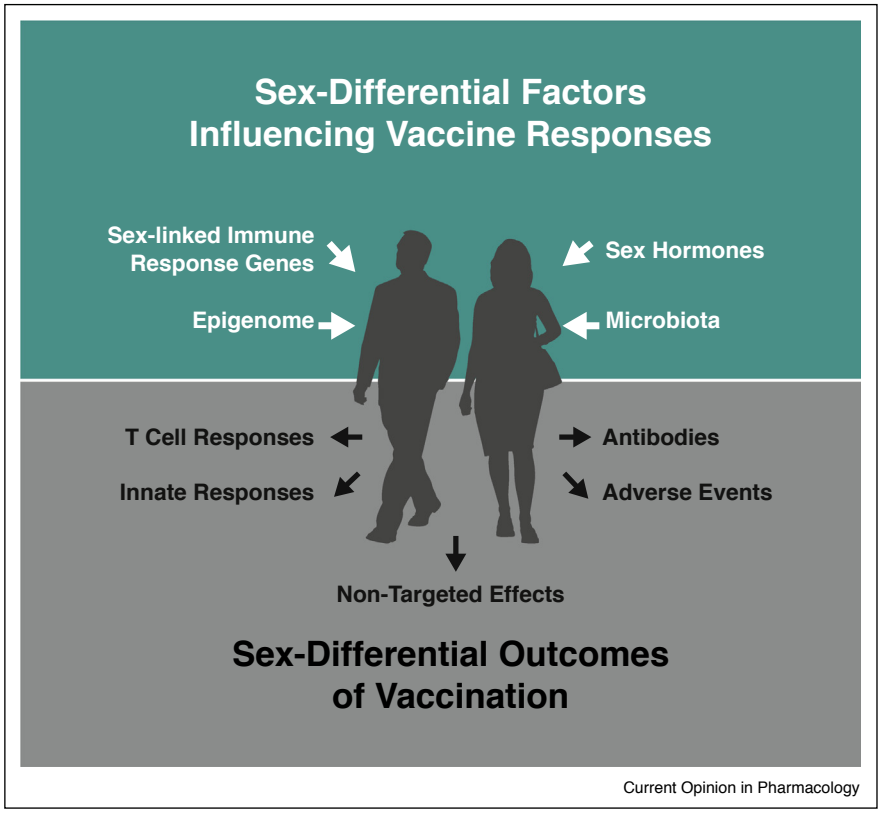
Antibody responses serve as the accepted correlate of protection for most vaccines. On the whole, females mount greater antibody responses to vaccination than their male counterparts from birth to old age [1••] (Table 1). This includes greater antibody responses in females following vaccination with the inactivated diphtheria, hepatitis B, influenza, rabies, pertussis and pneumococcal vaccines and the live measles vaccine [1••]. Murine studies also show that antibody isotype profile may vary by sex [4]. However, males may have greater antibody responses than females to certain vaccines or both sexes have equivalent responses. For example, elderly males >65 years mount greater antibody responses to influenza, tetanus-low dose diphtheria (Td) and Td-acellular pertussis (Tdap) vaccines than corresponding elderly females [1••]. A recent meta-analysis for sex differences in IgG responses across six Dutch studies found slightly higher vaccine-stimulated pneumococcal titres in females following vaccination with the pneumococcal conjugate vaccines (PCV7, PCV10, PCV13) but otherwise no sex differences in responses to the Pentavalent vaccine (diphtheria-tetanus-acellular pertussis [DTaP], inactivated polio vaccine [IPV], *Haemophilus influenzae* type b [Hib]) [5]. An analysis for sex differences in antibody responses to measles vaccination in three cohorts totalling 2872 children found no evidence for sex differences [6].

Innate immune responses to vaccination

The early innate immune response plays a key role in vaccine immunogenicity since it can predict subsequent protective antibody and T cell responses [7]. Sex differences have been described for multiple components of the innate immune system [2••], with adult females considered to have greater innate immunity than males [8]. However, the opposite is true in childhood and old age when males tend to have the greater innate inflammatory capacity [2••].

Few studies have analysed for sex differences in innate immunity following vaccination (Table 1), although one showed marked differences in innate signatures after yellow fever vaccination of healthy adults, with many more toll-like receptor (TLR) signaling genes expressed in females compared to males [1••]. An Australian study of neonatal bacille Calmette-Guérin (BCG) vaccination showed an increase of macrophage migration inhibitory factor (MIF) in females and decrease in males to multiple innate stimuli [9]. Males also had lower IL-10 production

Figure 1



Summary of the sex-differential outcomes of vaccination and the causative factors. Sex differences in vaccination have been described for a number of outcomes, as shown in the lower half of the figure. Key factors thought to drive these sex differences include sex hormones and sex-linked immune response genes, as shown in the upper half of the figure. A role for sex-differential epigenetic effects of vaccines and sex differences in the microbiota are speculative and yet to be confirmed.

to TLR2 stimulation *in vitro* and lower monocyte chemoattractant protein-1 (MCP-1) to TLR4 [9]. BCG vaccinated low-birth weight African neonates had sex-differential enhanced reactivity to TLR1/2 and 7/8 stimulation *in vitro* supporting enhanced innate immunity [10]; but another African study showed no effect of BCG vaccination of six-week-old infants on TLR ligand reactivity [11]. A study investigating the innate effects of measles or diphtheria-tetanus-whole cell pertussis (DTwP) vaccination of nine-month-old Gambian infants showed decreased *in vitro* TLR4 reactivity in DTwP vaccinated females and increased TLR4 reactivity in measles vaccinated males [12]. Furthermore, DTwP vaccinated females downregulated expression of multiple genes involved in interferon signaling and dendritic cell maturation 4 weeks after vaccination as opposed to males who had no innate gene changes [12].

T cell responses to vaccination

The evidence for sex differences in memory T cell responses to vaccination is less clear-cut since most vaccine studies focus on antibodies, and those analysing T cell responses rarely take biological sex into account. However, the multiple sex differences in adaptive T cell immunity [2••] would suggest that T cell responses to vaccination would differ in males and females. Females have higher CD4 T cells and greater T cell activation and proliferation while males have higher CD8 T cell frequencies [2••]. Females tend to be polarised towards Th2 type responses, while males are more Th1 biased and have more regulatory T cells (Tregs) [2••]. Infant studies suggest that males have greater cellular mediated immunity (CMI) to BCG and rubella vaccination, while females mount better cellular responses to HSV-2 vaccination [1••] (Table 1).

Adverse events following vaccination

Adverse events following immunisation (AEFIs) range from mild local reactions to more severe systemic or allergic reactions. Many countries have AEFIs reporting and surveillance systems, however, the data are often *ad hoc* and incomplete. Despite this, the overriding experience is that females experience more AEFIs than males [1••] (Table 1). A recent Spanish analysis of >13 million vaccination episodes found a significantly higher AEFI rate to multiple vaccines among females (59.6%)