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Sex-Differential and Non-specific Effects of Vaccines Over the Life Course

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Abstract

Biological sex and age have profound effects on immune responses throughout the lifespan and impact vaccine acceptance, responses, and outcomes. Mounting evidence from epidemiological, clinical, and animal model studies show that males and females respond differentially to vaccination throughout the lifespan. Within age groups, females tend to produce greater vaccine-induced immune responses than males, with sex differences apparent across all age groups, but are most pronounced among reproductive aged individuals. Females report more adverse effects following vaccination than males. Females, especially among children under 5 years of age, also experience more non-specific effects of vaccination. Despite these known sex- and age-specific differences in vaccine-induced immune responses and outcomes, sex and age are often ignored in vaccine research. Herein, we review the known sex differences in the immunogenicity, effectiveness, reactogenicity, and non-specific effects of vaccination over the lifespan. Ways in which these data can be leveraged to improve vaccine research are described.

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1 Introduction

Biological sex (i.e., differences between males and females based on sex chromosome complement, reproductive tissues, and sex steroid concentrations) and age contribute significantly to differences in vaccine acceptance, induced immune responses, and clinical outcomes (Klein et al. 2010). Although females are often less likely to accept vaccines (Pulcini et al. 2013), they tend to develop greater antibody and cell-mediated immune responses following vaccination than males (Klein et al. 2010; Umlauf et al. 2012; Zhang et al. 2008) (Fig. 1). After vaccination against influenza, yellow fever, rubella, measles, mumps, hepatitis A and B, herpes simplex 2, rabies, smallpox, dengue viruses, and SARS-CoV-2, protective antibody responses can be as much as twice as high in adult females as compared with males (Klein et al. 2010; Nam et al. 2022). Females are also more likely to develop severe adverse reactions, including local and systemic pain, inflammation, fever, and allergic reactions (Furman et al. 2014; Klein et al. 2010; Poland et al. 2009). It has often been assumed that greater adverse events among females reflects a gender difference (i.e., socio-cultural construct that defines behavioral, occupational, and even decision-making strategies) rather than a biological difference, as data on adverse events are often obtained through passive reporting, and females may be more likely to report adverse events than males (Klein and Morgan 2020, Morgan and Klein 2019). Data for COVID-19 mRNA vaccination illustrate that females are more likely to report non-serious adverse events and experience more local reactions (e.g., rash at injection site) and anaphylaxis than males (Blumenthal et al. 2021; Shimabukuro et al. 2021). In response to COVID-19 adenovirus-vectored vaccines, females < 50 years of age are more likely to experience thrombosis and thrombocytopenia (Lai et al. 2021; Li et al. 2022) and males < 50 years of age are more likely to develop myocarditis (Pepe et al. 2021). Many of these more serious adverse events cannot merely be attributed to reporting biases and likely reflect biological differences between the sexes. Furthermore, studies from low-income settings with high infectious disease pressure have revealed that routine childhood vaccines may affect all-cause mortality in such settings, to a degree that is not explained by the vaccine-specific effects, i.e., vaccines also have so-called non-specific effects (“off-target” or “heterologous” effects). Intriguingly, these effects differ greatly between boys and girls, both beneficial and harmful non-specific effects being strongest for girls. These differences are indicative of biological differences in vaccine response already in childhood.

The biology of males and females is not static throughout the life course, but instead reflects the changes that occur in genetic and epigenetic factors, hormones, and environmental interactions over the lifespan (Bronikowski et al. 2022, Fischer et al. 2018,He et al. 2021, Klein and Flanagan 2016); however, minimal consideration is given to how these sex-specific shifts in biology over the life course contribute to vaccine-induced immunity (Fig. 1). The goal of this review is to highlight the breadth of sex differences in vaccine-induced immunogenicity, reactogenicity, and protection against vaccine-preventable diseases as well as non-specific effects on other diseases and all-cause mortality over the life course and provide recommendations to improve pre-clinical and clinical vaccine trials. We propose that all future vaccine studies should evaluate the impact of sex and age on immunological responses and vaccination outcomes.

2 Effects of Biological Sex on Vaccine Responses Over the Life Course

2.1 Birth to 5 Years of Age

As the immune system is not fully developed in neonates, they are particularly vulnerable to microbial infections. Infants have an anti-inflammatory skewed immune response that is characterized by high levels of circulating IL-10, adenosine, and regulatory T cells (Tregs); suboptimal immunological memory; reduced reactivity of innate immune cells; and a Th2-biased adaptive immune response (Burl et al. 2011, Kollmann et al. 2012, Levy et al. 2006, Ndure et al. 2014, Noho-Konteh et al. 2016, Papaioannou et al. 2019, Tsafaras et al. 2020, Zazara and Arck 2019).

Neonates and infants are the target recipients of many vaccines (Fig. 1a). Starting in 1974, the World Health Organization initiated the Expanded Program on Immunization (EPI), through which they have developed standardized vaccination schedules recommended for neonates, infants, and children (World Health Organization 2021).

Antibody responses to many childhood vaccines are greater in females with some exceptions (Flanagan et al. 2015). Females who are vaccinated with the hepatitis B vaccine (HBV) or the combined measles, mumps, rubella vaccine (MMR) by one year of age, but not after, showed greater and longer lasting antibody responses compared to males (Flanagan et al. 2015; Kontio et al. 2016; Trevisan et al. 2020). No sex differences are observed in antibody response to HBV and MMR when children were vaccinated at 5 months or at 18 months of age, respectively (Kontio et al. 2016; Trevisan et al. 2020). Greater antibody responses to diphtheria, pertussis, hepatitis A, HBV, pneumococcus, rabies, human papilloma virus (HPV), and rubella vaccines as well as to the candidate malaria vaccine RTS,S/ASO2 are observed in females compared to males (Boef et al. 2018, Flanagan et al. 2015, Noho-Konteh et al. 2016). In a meta-analysis of individual data from vaccine trials, antibody responses to *Haemophilus influenzae* type b (Hib) and tetanus toxoid vaccines were found to be comparable among younger aged males and females under 3 years of age (Voysey et al. 2016). Individual studies, however, reveal that females following infant vaccination have moderately higher IgG levels against Hib and tetanus compared to males, while no sex differences are observed in antibody responses to diphtheria and pertussis vaccines (Boef et al. 2018). In a meta-analysis of the published clinical trial data on the quadrivalent HPV vaccine (qHPVV), antibody titers are greater in children (<16 years of age) than in adults, and qHPVV is more immunogenic in females across all age groups than in males (Aldakak et al. 2021). Further, stronger sex differences are observed in vaccine responses against low-risk HPV strains (6 and 11) compared to high-risk strains (16 and 18) (Aldakak et al. 2021).

Compared to humoral responses, data regarding the effect of biological sex on cell-mediated responses to childhood vaccination lag further behind and show no clear trend in sex-specific responses. Studies have reported a male bias in cell-mediated immune responses as evidenced by larger bacille Calmette-Guérin (BCG) scars and tuberculin skin test reactivity in infants under one year age (Burl et al. 2010; Diness et al. 2007) and greater rubella-specific lymphoproliferation (Mitchell 1999) in males aged 15 years old as compared to females. Females have greater herpes simplex 2 virus (HSV-2)-specific CD4+ T cell

responses following HSV-2 vaccination (Zhang et al. 2008). Studies of tuberculosis and measles, however, report no sex differences in either *M. tuberculosis*-specific Th1 or Th2 responses (Sartono et al. 2010) or in measles-specific in vitro cytokine responses (Noho-Konteh et al. 2016).

Limited data are available on adverse events following childhood vaccination (Weber et al. 2014). BCG-associated vaccine adverse events such as osteitis/osteomyelitis and suppurative lymphadenitis are rare, but higher in males compared to females and in individuals vaccinated at age < 6 months compared to children vaccinated at a later age in Japan (Okuno et al. 2022). In general, MMR vaccines cause more adverse events, such as fever, parotitis, meningitis in infant females (Khalil et al. 2003), but more males are affected with MMR-associated thrombocytopenic purpura among children < 5 years old (France et al. 2008). The available data suggest that the sex and age of children can affect the adverse events following childhood vaccination.

Although sex differences in antibody responses following childhood vaccination are reported, it is unclear whether these differences have any clinical relevance as differences in antibody titer may not matter once protective levels are achieved. While many studies of vaccine efficacy in children include equal numbers of both sexes, very few studies stratify their data according to sex. In Guinea-Bissau, measurements of hospitalization rates due to measles showed that measles vaccination was more efficacious in female children below 4 years old compared to males following infant vaccination (Martins et al. 2014). There are contradictory reports on sex differences in the efficacy of the HBV vaccine. In one study, male sex was found to be associated with non-responsiveness to HBV (Zuckerman 2006), while a retrospective follow-up study of Gambian adults vaccinated against HBV during infancy showed no evidence of sex differences in vaccine efficacy (Peto et al. 2014). Another study found that only infant females produced anti-HBV antibody responses above the threshold for protection, predicting that females were likely to be better protected than males (Bocsan et al. 2005). A study in Spain suggested that BCG vaccination efficacy is greater in infant males than females (Altet et al. 1992); there were, however, no sex differences in protective efficacy against TB during a 15-year follow-up study in India (Narayanan 2006). These results highlight a need for sex-disaggregated clinical data on vaccine responses, efficacy, and non-specific effects in children as it may inform both sex-specific timing and sequencing for childhood vaccines and the use of sex-specific doses.

There are limited data available regarding the immunogenicity, reactogenicity, and effectiveness of COVID-19 vaccines in children and infants. Moreover, no studies have presented sex-disaggregated data, so it is unclear whether sex differences in response to COVID-19 vaccination exist in these age groups (Frenck et al. 2021; Sacco et al. 2022). One complication arising from childhood infection with SARS-CoV-2 that is specific to children is that they are at risk of developing multi-systemic inflammatory syndrome (MIS-C), with males having a higher risk than females for MIS-C. Two studies that evaluated the risk of multi-systemic inflammatory syndrome (MIS-C) in hospitalized children report that vaccination with either mRNA-1273 or BNT162b2 is associated with > 90% effectiveness against developing MIS-C (Levy et al. 2022; Zambrano et al. 2022); however, these studies did not disaggregate their data based on sex, so it is unclear if vaccination equally protects

male and female children against MIS-C. It is evident that adult females mount greater antibody responses and report more adverse events to the SARS-CoV-2 vaccines than males; whether COVID-19 vaccine-induced immunity and reactogenicity also differs between the sexes at different childhood ages, must be considered.

2.2 Puberty and Adulthood

In contrast to the limited number of sex-stratified studies of vaccination in children, sex differences in vaccine responses after puberty and adulthood are well documented (Fig. 1a). Following vaccination against influenza virus, measles, mumps, rubella, hepatitis A and B, yellow fever virus, dengue viruses, herpes simplex 2, rabies, and COVID-19, greater antibody responses in females compared to males have been reported (Cook 2008; Klein et al. 2016; Nam et al. 2022). In the context of influenza vaccines, females (18–49 years of age) who received either a full or half dose of the trivalent-inactivated vaccine (TIV) had higher neutralizing antibody and hemmaglutination inhibition (HAI) antibody titers against H1N1, H3N2, and influenza B antigens than males (Engler et al. 2008; Furman et al. 2014). In fact, females who received the full dose are observed to have HAI titers that are twice as high as males, while the antibody titers produced by females who received the half-dose vaccine are equivalent to males who received the full-dose vaccine (Engler et al. 2008). This suggests that the effective vaccine dose for influenza is lower in females compared to males and that sex-specific vaccine dosing regimens warrant additional evaluation. In The Netherlands, a large retrospective cohort study found that in healthy adult workers (16–70 years of age) who received the standard three-dose vaccination regimen of HBV, females had higher rates of seroconversion post-vaccination, while males had a greater prevalence of non-response to HBV (Vermeiren et al. 2013). Similar studies in Serbia, Pakistan, and Brazil all found that rates of non-response to HBV were greater among males compared to females (Motta-Castro et al. 2009; Rosic et al. 2008; Zeeshan et al. 2007). In a study of healthy volunteers vaccinated against yellow fever virus, adult females had greater transcriptional activity of toll-like receptor signaling-associated genes than males (Klein et al. 2010). In response to infection, it is well documented that adult females tend to produce more robust antibody responses than adult males (Ursin et al. 2021). Taken together, vaccination may elicit stronger innate and adaptive immune responses in females compared to males.

While most vaccination studies highlight a predominance of female-biased greater vaccine-induced immunity, there are documented instances in which either a male-bias is reported or where conflicting data exist. In a US meta-analysis of smallpox vaccination, males have approximately 27% greater antibody titers after smallpox vaccination than females (Troy et al. 2015), while another study reported that males had greater vaccinia-specific cytokine responses following vaccination compared to females (Haralambieva et al. 2013). In Thailand, vaccination against Japanese encephalitis virus (JEV) with the mouse brain-derived inactivated JEV vaccine (MBDV) was introduced as part of the National Immunization Program beginning 1990 (Sudjaritruk et al. 2022). In an age-stratified seroepidemiological study, despite vaccination, JEV seroprotection, as measured by neutralizing antibody responses, only persists in ~ 50% of the population (Sudjaritruk et al. 2022). Moreover, in adults (21–67 years of age), males have greater neutralizing antibody responses than females (Sudjaritruk et al. 2022). Adolescent males (10–20 years

of age) and older males (>51 years of age) have greater neutralizing antibody responses as compared to younger adult males (21–50 years of age) reflecting a pattern of high antibody responses following vaccination, waning immunity, and boosted responses in older adults from JEV exposure (Sudjaritruk et al. 2022). Interestingly, following implementation of JEV vaccines in Thailand, the age distribution of JEV cases shifted from children to adults, likely due to the lower levels of seroprotection among young adults (Sudjaritruk et al. 2022). In a cohort of 748 adolescents (11–19 years of age) who received two doses of the MMR-II vaccine, greater neutralizing antibody titers were observed in females compared with males (Riggenbach et al. 2022). In contrast, isolated peripheral blood mononuclear cell (PBMC) cultures from male participants that were stimulated ex vivo with mumps virus secreted greater levels of inflammatory cytokines (e.g., MIP-1α, MIP-1β, TNFα, IL-6, INF-γ, and IL-1β) than PBMCs isolated from female participants (Riggenbach et al. 2022). These results not only suggest that humoral and cell-mediated immunity may be regulated by different processes, but also suggest that they are regulated in a sex-dependent manner (Riggenbach et al. 2022).

From the onset of the COVID-19 pandemic it was clear that, on a global scale, males were more likely to experience severe disease, require ICU admission, require invasive ventilation, and were 30% more likely to die due to COVID-19 than females, all effects that were exacerbated with increasing age (Jacobsen et al. 2021, The Sex and Gender COVID-19 Project 2022). This resulted in two major shifts in the approach to studying sex differences in response to COVID-19 vaccines. The first is that each of the major manufacturers of COVID-19 vaccines (i.e., Moderna—mRNA-1273, Pfizer-BioNTech—BNT162b2, Johnson & Johnson—Ad26.COV2.S, and AstraZeneca—ChAdOx1) ensured that their clinical trials included an equal number of male and female participants (Jensen et al. 2022). BNT162b2, mRNA-1273, and Ad26.COV2.S vaccine trials included sex-disaggregated efficacy data showing no statistical differences between males and females (Jensen et al. 2022). Sex- and age-disaggregated data, however, are only reported for the BNT162b2 and mRNA-1273 vaccines (Baden et al. 2021; Polack et al. 2020). The second shift came from within the research community as an unprecedented number of peer-reviewed studies evaluated sex- and age-specific efficacy, safety, and durability of SARS-CoV-2-specific immunity post-vaccination and boosting as new SARS-CoV-2 variants emerged. Noteworthy, adverse event data were not reported by sex.

Overall, adult females have been shown to have greater COVID-19 vaccine-induced antibody titers and durability of immunity against both mRNA and adenovirus-vectored vaccine platform; mRNA vaccines and heterologous vaccine schedules elicit greater antibody responses in both males and females than adenovirus-vectored platforms (Collatuzzo et al. 2022; Hvidt et al. 2022; Nam et al. 2022; Steensels et al. 2021). Furthermore, adult individuals who receive the mRNA-1273 vaccine compared to BNT162b2 mRNA vaccine consistently have greater antibody responses both post-initial vaccine dose and post-boosting, likely attributable to the greater mRNA dose in the former vaccine (Collatuzzo et al. 2022; Hvidt et al. 2022; Lo Sasso et al. 2021; Nam et al. 2022; Steensels et al. 2021).

Reports of sex-specific adverse events in adults following COVID-19 vaccination have been varied. In general, greater reactogenicity (i.e., local reactions and systemic pain, fever, headache, and fatigue) following both the first and second doses of the BNT162b2, mRNA-1273, and ChAdOx1 vaccines is reported for adult females compared to adult males (Hoffmann et al. 2021, Ogawa et al. 2022). In one study, younger adults (median age of 33 years) reported greater adverse events than middle-aged adults (median age of 43 years) (Wi et al. 2021). While serious adverse reactions are rare following COVID-19 vaccination, some studies have shown that 70% of serious adverse reactions are reported in females and that females are at greater risk for development of anaphylaxis (Blumenthal et al. 2021; Shimabukuro et al. 2021; Somiya et al. 2021) and vaccine-inducted thrombotic thrombocytopenia (VITT) (Greinacher et al. 2021; Lai et al. 2021). The observation of VITT is primarily associated with the adenovirus-vectored vaccines ChAdOx1 and Ad26-COV2.S (Greinacher et al. 2021; Li et al. 2022). Despite a predominance of adverse events reported in females, adolescent and young adult males (12–39 years of age) are at 10 times greater risk for developing myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines (Bozkurt et al. 2021; Klein et al. 2021; Pepe et al. 2021). Given the extent and range of sex-specific immunogenicity and reactogenicity of each COVID-19 vaccine platform, each platform must be carefully evaluated for sex- and age-associated efficacy and safety.

In addition to COVID-19 vaccination, adverse events are generally more common in adult females than males for several vaccines, including influenza, hepatitis B, and yellow fever vaccines (Klein et al. 2015). Females requiring yellow fever, diphtheria, tetanus toxoids, oral polio, and oral typhoid vaccines prior to traveling report more adverse events than males (Philipps et al. 1996). While generally considered safe, the prevalence of death due to viscerotropic disease following yellow fever vaccination is higher in young adult females (19–34 years of age) than males (Seligman 2011). However, analysis of reporting data in the US from 2000 to 2006 found that males reported more serious adverse events following yellow fever vaccination (Lindsey et al. 2008).

While vaccine-induced antibody production is often utilized as a correlate of protection (Klein et al. 2010), it is important to note that vaccine-induced immune responses and vaccine efficacy are not the same. One example of this difference is evident from two double-blind phase 3 randomized efficacy trials of the herpes simplex type 2 (HSV-2) glycoprotein-D-adjuvant subunit vaccine with adult participants (>18 years of age) from four countries (Stanberry et al. 2002). In this study, researchers reported no sex differences in humoral and cell-mediated immune responses following vaccination, but initially found that the vaccine was not efficacious against HSV infection when the data were not stratified by sex and prior exposure to HSV (Stanberry et al. 2002). However, further analysis determined that the vaccine was effective at preventing HSV infection in ~ 70% of females that were seronegative for both HSV-1 and HSV-2, but was not effective at preventing infection in seronegative males (Stanberry et al. 2002). In combined analysis of four influenza virus challenge studies, individuals were assessed for pre-existing antibody titers to influenza prior to viral challenge; while females had overall higher pre- and post-challenge HAI and neutralizing antibody titers compared to males, males had consistently higher neuraminidase inhibition (NAI) titers than females both pre- and post-challenge (Giurgea et al. 2022).

Importantly, females were more likely to develop symptoms than males post-challenge (Giurgea et al. 2022). Thus, these studies highlight that while immunogenicity may be either higher in one sex or equivalent between sexes, efficacy can also vary which adds an additional layer of complexity to these issues.

The use of animal models can provide insights into sex differences in vaccine efficacy. Adult females of diverse species tend to have greater antibody responses than males (Klein et al. 2016). In adult non-human primates, following vaccination against simian immunodeficiency virus (SIV), females show increased local IgA antibody titers, numbers of memory B cells, and numbers of plasma cells as compared to males (Mohanram et al. 2016;Tuero et al. 2015). SIV-vaccinated females also have elevated levels of virus-specific IgG1, IgG2, and IgG3 antibodies as compared to males, with anti-SIV IgG3 antibody levels correlating with antibody-mediated cytotoxicity and phagocytic activity, suggesting that the quality of the antibody response is greater in females than males (Mohanram et al. 2016). Studies in mice further illustrate that following vaccination or challenge, females develop greater systemic and mucosal antibody responses than males (Dhakal et al. 2021; Lorenzo et al. 2011). When immunized with an H1N1 or H3N2 influenza virus, adult female mice mount greater neutralizing and total antibody responses than males (Lorenzo et al. 2011). Following vaccination, female mice are better protected against lethal challenge with a novel influenza strain than males (Lorenzo et al. 2011, Ursin et al. 2022).

2.3 Aged Individuals

Overall, antibody responses tend to be lower in aged adults (>65 years of age) than younger adults (18–64 years of age) (Haq et al. 2014; Poland et al. 2014; Shapiro et al. 2022a, b). The occurrence and magnitude of sex differences in vaccine responses in aged individuals, however, differ greatly by vaccine antigen. Aged females (65–74 years of age) have greater antibody responses following vaccination with the seasonal and pandemic 2009 H1N1 (pH1N1) influenza vaccines than males (Booy et al. 2011; Furman et al. 2014; Khurana et al. 2012; Loeb et al. 2020; Talaat et al. 2010) and are reported to have seroconversion and seropositivity rates 2–3 times higher than age-matched males (Kao et al. 2010; Moehling et al. 2020). While aged females had greater antibody responses to the pH1N1 vaccine, males generated antibodies with greater avidity (Khurana et al. 2012). Among aged as well as adult females, greater seroconversion of neutralizing antibody responses to the pH1N1 vaccine is associated with greater circulating concentrations of estradiol (Potluri et al. 2019). In a longitudinal study of adults over 75 years of age who were vaccinated with a high-dose influenza vaccine in at least four out of six influenza seasons, pre-vaccination HAI titers against H3N2 and influenza B (but not H1N1) decreased with age in males and remained constant in females (Shapiro et al. 2021a, b). This decline in the durability of humoral immune responses in males may explain why males are more susceptible to influenza B infection and hospitalization (Wang et al. 2015; Wong et al. 2019) and highlights a need to consider sex-specific vaccine strategies in older adult populations (Klein and Pekosz 2014).

In contrast to influenza vaccination, aged males produce greater antibody responses to pneumococcal vaccines than females (Brandão et al. 2004; Cook et al. 2007; Goldblatt et al. 2009). In older adults (50–80 years of age) who received the two-dose seven-valent

pneumococcal vaccine, aged males not only had higher serotype-specific IgG antibodies following each dose than females, but also had a greater increase in their antibody response following receipt of the second dose than females (Goldblatt et al. 2009). In long-term care residents who received the 23-valent pneumococcal vaccine, IgG antibody responses against all four of the pneumococcal serotypes analyzed were greater in aged males than females (Brandão et al. 2004). Greater male responses to Td/Tdap vaccines (tetanus, diphtheria, pertussis) in aged individuals has also been reported (Bayas et al. 2001; Hainz et al. 2005; Marlovits et al. 2000).

Whether there are sex differences in aged individuals in response to COVID-19 vaccines is not clear as there are several conflicting reports. In a study that compared immune responses of long-term care residents (median age of 88 years) in Ontario, Canada, who received two doses of either the BNT162b2 or mRNA-1273 vaccine, females had greater anti-spike IgG, anti-spike RBD IgG, and neutralizing antibodies titers following the initial vaccine dose than males, but this sex difference was not apparent following the second dose (Abe et al. 2021). Notably, individuals who received the mRNA-1273 had greater neutralizing antibody titers (2.95-fold) to the vaccine strain and broader neutralization capacity against other SARS-COV-2 variants than those who received the BNT162b2 (Abe et al. 2021). One key difference between the mRNA-1273 and BNT162b2 vaccines is that the mRNA-1273 contains a higher dose of mRNA (i.e., 100 μg) than the BNT162b2 vaccine (i.e., 30 μg) (Centers for Disease Control and Prevention 2022). Similar to influenza vaccination, high-dose COVID-19 vaccines may be more effective for people over 65 years of age. In a study comparing SARS-CoV-2 naïve healthcare workers (HCWs, median age of 48 years) and SARS-CoV-2 naïve long-term care residents (median age of 76 years) in Ohio, long-term care residents had lower post-vaccination titers following receipt of the second dose of BNT162b2 compared to HCWs (Canaday et al. 2021). No sex differences were noted following receipt of the initial vaccine doses, but a strong negative correlation between age and antibody titers was observed (Canaday et al. 2021). In aged individuals who received both doses of the BNT162b2 and also had prior SARS-CoV-2 infections, post-vaccination antibody levels were greater in females than males (Canaday et al. 2021). This study also found that older individuals who were assessed as being frail produced 75% lower antibody responses than healthy, aged adults (Canaday et al. 2021). In contrast, in a study examining vaccine responses following three dose of either mRNA-1273 or BNT162b2 in older adults (75–98 years of age) compared to younger healthcare workers (18–74 years of age) in the Baltimore area, it was reported that aged females produce greater anti-spike IgG, anti-spike RBD IgG and neutralizing antibody titers than aged males following receipt of the initial vaccine series (Shapiro et al. 2022a, b). When results were evaluated to determine the sex-specific effects of age on humoral responses, age-associated reductions in humoral immune responses are greater in males than females following receipt of the first two vaccine doses (Shapiro et al. 2022a, b). Receipt of the third booster dose eliminated these sex differences (Shapiro et al. 2022a, b).

Among aged individuals, females aged 65 and older are more likely to report systemic adverse reactions (i.e., fever, headache, myalgia, redness, swelling, and injection site pain) in response to the pneumococcal vaccines, the herpes zoster vaccine, influenza vaccines, Td/Tdap, and COVID-19 vaccines (Fink et al. 2015, Hoffmann et al. 2021, Klein et al.

2021). It is unclear whether these differences in adverse reactions reflect a sex difference in reactogenicity or a gender bias in reporting. Interestingly, reporting of serious adverse reactions following COVID-19 vaccination is higher in younger adults than older, and serious adverse reactions are more common in adult females than males (Xiong et al. 2021). However, while fewer serious adverse reactions are reported in aged individuals, men have more serious adverse reactions (including permanent disability and death) than females for individuals 65 years of age and older (Xiong et al. 2021).

There are a limited number of studies evaluating vaccine efficacy in the elderly that include sex-disaggregated data. In a study of older community-dwelling adults in Taiwan who received the seasonal influenza vaccine, an association between higher HAI titers and lower rates of hospitalization and reduced risk of mortality was found in females (Wang et al. 2002). Influenza vaccine effectiveness, determined by all-cause mortality, is also reportedly higher in aged females than males in Spain (Vila-Córcoles et al. 2007), England (Fleming et al. 1995), and the USA (Nichol et al. 2007). Similarly, several retrospective analyses have shown that among older adults who received herpes zoster or pneumococcal vaccines, aged females are better protected against disease and mortality than males (Hillebrand et al. 2015). In Germany, hospitalization rates for herpes zoster infection were found to be higher in older vaccinated males than females (Hillebrand et al. 2015). A study evaluating the cause of death registered on the US death certificates discovered that there was a significant decline in pneumonia-associated mortality among aged females compared to males following the introduction of the 23-valent pneumococcal vaccine in 1983 (Soneji et al. 2011). Similarly, older females were reported to be better protected against hospitalization due to community-acquired *Streptococcus pneumoniae* infection in the USA and Europe (Wiemken et al. 2014). While the amount of sex-disaggregated data on vaccine efficacy are certainly limited, these studies seem to suggest that vaccine efficacy is generally higher among aged females than males.

3 Sex Differences in Non-specific Effects of Vaccines

3.1 Epidemiological Studies

The sexes differ in the non-specific effects (NSEs) (also called off-target or heterologous effects) following vaccination. NSEs of vaccines are best defined as effects on morbidity and mortality (either increase or decrease) that are unrelated to prevention of the disease targeted by that vaccine (Aaby et al. 2014). Many studies have demonstrated sex-differential NSEs of vaccines, and in keeping with the trends showing greater antibody responses and adverse events in females following vaccination, females are generally more susceptible to NSEs (Aaby et al. 2020, Aaby et al. 2014, Benn et al. 2020, Flanagan et al. 2017, Flanagan et al. 2013).

The first evidence of NSEs of vaccines was discovered in randomized controlled trials (RCTs) of the high-titer measles vaccine (HTMV) that occurred in the late 1980s (Aaby et al. 2003). This vaccine was administered to infants (4–6 months of age) in measles endemic areas to determine whether the HTMV vaccine was as effective in younger infants as the standard dose MV that was given to infants > 9 months old (Aaby et al. 2003). While initial reports showed that the HTMV vaccine-induced antibody responses that were as effective as

the standard dose given after 9 months of age, additional studies found a two-fold increase in the mortality among female recipients of HTMV compared to male recipients (Aaby et al. 2003; Knudsen et al. 1996). This was the first evidence that a vaccine could be protective against its targeted pathogen while have non-specific deleterious effects on susceptibility to other pathogens in a sex-differential manner (Aaby et al. 2003).

Subsequent studies evaluating other childhood vaccines have shown that many vaccines have sex-differential NSEs. Overall, the current evidence suggests that live vaccines are associated with beneficial NSEs with improved morbidity and mortality, while non-live vaccines are associated with deleterious NSEs (Aaby et al. 2014, Flanagan et al. 2017, Flanagan et al. 2013). Both the beneficial and the deleterious NSEs are generally most pronounced in females. The live BCG vaccine is one of the best characterized vaccines in relation to NSEs. A number of observational studies and RCTs have shown that neonatal BCG vaccination is associated with reduced overall infant mortality as compared to infants who did not receive the vaccine (Flanagan et al. 2013; Shann 2010). Several recent RCTs in Guinea-Bissau of BCG vaccination of low-birth weight neonates, a group normally excluded from BCG vaccination, found BCG associated with a 38% (CI = 17–54%) decrease in mortality in the first four weeks of life (Biering-Sørensen et al. 2017). It was determined that BCG vaccination protected these neonates from respiratory infections and sepsis which are the most common causes of neonatal mortality among low-birth weight children in low-income countries (Aaby et al. 2011). A recent Ugandan RCT showed that neonatal BCG vaccination reduced physician-diagnosed non-tuberculous infectious disease incidence by 29% (95% CI = 5–47%) in the first 6 weeks of life as compared to BCG naïve infants (Prentice et al. 2021). Interestingly, the studies in Guinea-Bissau and another study in The Gambia found that the decrease in mortality following BCG vaccination was greater in females compared to males (Aaby et al. 2011; Garly et al. 2003). The male mortality reduction followed a different time-course to the female reduction, being in the first week of life for males but weeks 2–4 for females at which time the effect had waned for males (Biering-Sørensen et al. 2018). However, a systematic review by the Strategic Advisory Group of Experts (SAGE) on vaccination at the WHO indicated that the BCG effects were not convincingly sex-differential (Higgins et al. 2016). A fascinating observation is that maternal BCG status, as evidenced by the presence of a maternal BCG scar, provides sex-differential vertical protection to the newborn with improved male survival, particularly against sepsis (Schaltz-Buchholzer et al. 2022).

Live standard dose measles vaccine has consistently been associated with stronger reductions in all-cause mortality in females than in males. The systematic WHO/SAGE review analyzed two RCTs and ten observational studies and concluded that measles vaccine was associated with a 54% (95% CI 22–94%) more beneficial effect on all-cause mortality in females than in males (Higgins et al. 2016). Another live vaccine, smallpox vaccine, has also been associated with stronger NSEs in females than in males. The presence of a smallpox vaccination scar is linked with protective NSEs with improved long-term survival in Danish (Rieckmann et al. 2017) and West African adults (Jensen et al. 2006). The latter study showed a greater survival benefit to females, and another smallpox scar study also showed that smallpox vaccination was associated with protection against HIV-1 infection in women but not in men (Rieckmann et al. 2019).

The live oral polio vaccine (OPV) is the only live vaccine which seems to have more beneficial NSEs in males. It has been linked with sex-differential NSEs with lower mortality in boys receiving OPV plus pentavalent vaccine as compared to unvaccinated infants (Pfeiffer et al. 2017). The same more beneficial effect of OPV in males vs. females has been seen in studies of OPV campaigns (Andersen et al. 2021, 2018). In an RCT of BCG + OPV vs. BCG-alone at birth, following children until the time of OPV campaigns, receiving OPV-BCG vs. BCG-alone was associated with 32% (95% CI 0–55%) reduction in all-cause mortality, the beneficial effect being separately significant for males (45% 95% CI 5–68%) (Lund et al. 2015). In a Russian RCT of 1,115 adult volunteers, OPV protected against laboratory confirmed COVID-19 as compared to the placebo group (Yagovkina et al. 2022). The data were not analyzed by sex. In a Guinean RCT of 3,726 individuals aged 50 years and older, OPV was associated with a 29% (95% CI = 2–49%) reduction in the risk of mortality, admissions, and consultation for infections in males during the COVID-19 pandemic, whereas it had no effect in females (Fisker et al. 2022). Thus, while the live BCG, MV, and smallpox vaccines seem to be associated with more beneficial NSEs in females than in males, OPV seems to be associated with more beneficial NSEs in males.

Several inactivated vaccines including diphtheria-tetanus-whole cell pertussis (DTwP), HBV, and inactivated polio vaccine (IPV) have been associated with harmful non-specific effects (Aaby et al. 2012, 2007, 2016; Garly et al. 2004). Observational studies have shown an increase in mortality in children who received the DTwP vaccine, especially in females compared to males (Aaby et al. 2012; Shann 2010), although a more recent study found no such effect, possibly due to the confounding effects of lower mortality rates, high BCG coverage, and OPV campaigns (Sørensen et al. 2022).

The RTS,S malaria vaccine, which is based on hepatitis B surface antigen plus the malarial circumsporozoite protein in ASO1 liposome-based adjuvant, was found in phase III clinical trials to be associated with higher all-cause mortality in girls (mortality ratio 1.91, 95% CI 1.30–2.79, $p = 0.0006$), but no such effect was observed in boys (mortality ratio 0.84, 95% CI 0.61—1.17, $p = 0.33$) in two age groups (6–12 weeks and 5–17 months). This highly significant sex-differential effect (p = 0.001) suggests that the vaccine has deleterious NSE in female recipients in keeping with other non-live vaccines and warrants further investigation given its relatively poor efficacy of 18–36% against clinical malaria (Klein et al. 2016).

The deleterious effects of DTP and other non-live vaccines in females are seen as long as the vaccine is the most recent vaccine. Upon scrutiny, it was discovered that the HTMV vaccine itself was not deleterious to females, but that the combination of receiving HTMV and then subsequent vaccination with either the DTwP vaccine, IPV, or the DTwP-IPV vaccine is what led to the increased risk of mortality (Aaby et al. 2003). The findings that the NSEs are sex-differential and strongest as long as a given vaccine is the most recent vaccine open the possibility that males and females may benefit from different routine vaccination schedules. A schedule that ensures that females in particular have a live vaccines for most of their childhood would likely be associated with lower all-cause mortality alongside specific protection against the vaccine-targeted diseases (Shann 2021).

3.2 Immunological Mechanisms for Sex-Differential NSE of Vaccines

The biological and immunological mechanisms that underpin sex differences in NSEs of vaccines have been unclear (Flanagan et al. 2017; Flanagan et al. 2013), but mechanistic explanations are starting to emerge in the literature (de Bree et al. 2018a, b). Biologically, it makes sense that NSEs of vaccines would be sex-differential given the myriad of X-linked immune response genes and microRNAs (Fish 2008); the opposing effects of male and female sex hormones on the immune system (Klein and Flanagan 2016); and the finding that even the microbiome is sex-differential (Vemuri et al. 2019).

Several studies have shown that BCG vaccination causes epigenetic and metabolic reprogramming leading to enhanced innate immunity, a process called trained immunity (Bekkering et al. 2021; Netea et al. 2020). Epigenetic effects of BCG vaccination in humans were initially demonstrated in adults (Kleinnijenhuis et al. 2012) but have also been confirmed in neonates. An Australian study showed epigenetic remodeling of circulating monocytes persisting to greater than 1 year post-BCG vaccination (Bannister et al. 2022), and a Ugandan neonatal study found significantly lower histone trimethylation at the TNF promoter in BCG-vaccinated infants compared to a BCG naïve group (Prentice et al. 2021). An immunological study of low-birth weight infants immunized with BCG in Guinea-Bissau found that the protective NSEs of BCG were associated with enhanced innate immune responses at 4 weeks of age, with better enhancement in infant females compared to males (Jensen et al. 2015), at the age when females were observed to benefit most from BCG (Biering-Sørensen et al. 2018). A study of Australian newborns found that BCG + HBV vaccination at birth led to decreased IFN-γ in males 7 days after vaccination as compared to unvaccinated infants and increased IFN-γ production in female neonates (Nissen et al. 2018; Pittet et al. 2022). A study of the impact of the sex hormones estrogen and dihydrotestosterone on the training of monocytes by BCG suggests that they are unlikely to play a role in innate immune training, and thus, other mechanisms for sex-differential NSE of BCG should be sought (de Bree et al. 2018a, b).

A Gambian infant study found that measles vaccination increased pro-inflammatory innate immune responses in male infants, whereas DTwP vaccination suppressed T cell and innate immune responses in infant females but not males (Noho-Konteh et al. 2016). In a study in Guinea-Bissau, infant females vaccinated against measles were found to have increased plasma concentrations of IL-1ra, CXCL8, and CCL2 compared to males (Jensen et al. 2014). Whether DTwP and measles vaccines cause epigenetic changes has not been explored but clearly warrants investigation. In a small study, oral polio revaccination was associated with changes in gut and upper respiratory microbiomes of infants (Medeiros et al. 2022). The study was too small to assess sex differences, but the findings may help to explain why the OPV-induced immune response seems to play a role against pathogenic gut bacteria by reducing etiology-specific bacterial diarrhea in male infants (Upfill-Brown et al. 2017). Taken together, these results highlight the fact that vaccines can lead to sex-differential innate and adaptive immunological changes which can account for the observed NSE. These warrant further urgent investigation to understand the biological interactions that govern sex-specific NSEs. Harnessing the mechanisms whereby vaccines augment heterologous immunity could be used to improve vaccine design and vaccine campaign strategies leading

to better protective immunological responses in both adults and children. Indeed, BCG and OPV were both studied in the early stages of the COVID-19 pandemic for their potential to provide non-specific protection against the disease prior to the advent of effective COVID-19 vaccines (Aaby et al. 2022, O'Neill et al. 2020). BCG failed to protect healthcare workers against COVID-19 in a trial conducted in South Africa (Upton et al. 2022), but may have reduced all-cause mortality among participants across trials (Aaby et al. 2022). None of these studies reported by sex, but there is every reason to believe that the effects would be sex-differential and many of the BCG studies investigating their protective effect against SARS-CoV-2 are yet to report their findings The beneficial effects of live vaccines therefore have the potential to be harnessed for future pandemic infections before specific vaccines can be developed. Importantly, understanding why some vaccines induce deleterious NSEs is critical for finding ways to overcome or circumvent these undesirable effects.

4 Concluding Remarks

It is evident that over the life course, males and females experience differences in the immunogenicity, reactogenicity, protection, and NSEs following vaccination. While the overall trend is that young adult females produce greater antibody responses, have higher correlates of protective immunity, and report more adverse events following vaccination compared to males, older adults, and children, this is not true in all instances. In fact, collapsing these observations of sex differences in response to vaccination over the life course in this way is almost as problematic as the lack of sex-disaggregated data that examines immune responses to vaccination over the lifespan. In the data that we have summarized, it is clear that nuance exists based on the type and dose of vaccine and antigen, the age of the vaccinee, prior exposure to either infection or repeated (seasonal) vaccination, and perhaps other host factors that include, but are not limited to, circulating sex steroid concentrations, genetics, and comorbidities. Differences between males and females in circulating sex steroid hormones (Fig. 1b) as well as immune responses (Fig. 1c) are dynamic and the nature of these sex differences changes both between and within the sexes throughout the lifespan. There is a greater need for research (including pre-clinical and clinical trials) that evaluates vaccine responses and vaccine efficacy as well as non-specific effects of vaccines to include sex and age as biological variables instead of controlling for them (Shapiro et al. 2021a, b). While the mechanisms mediating sex differences in immunological responses are still unknown, vaccine design and vaccine strategies should be sex- and age-specific in order to both improve immunogenicity, mitigate adverse events, promote beneficial NSEs, and limit detrimental ones.

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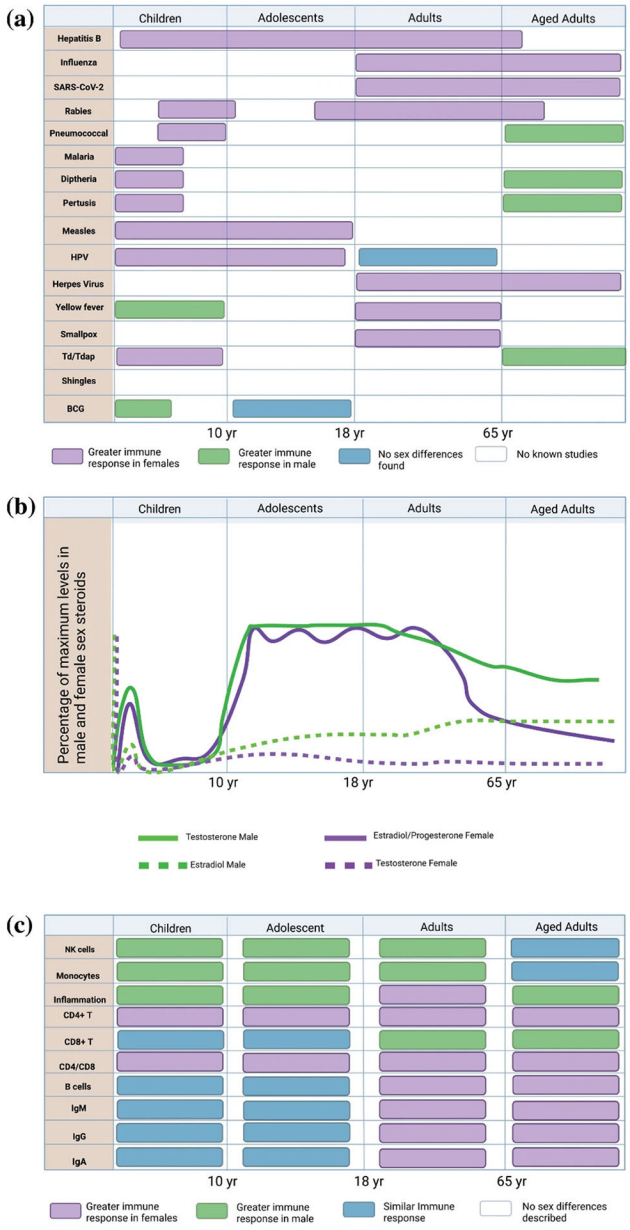

Fig. 1.

Vaccine-induced immunity, sex steroids, and immunological responses change over the lifespan. **a** Immunization tables recommend that certain vaccines are given during particular ages, with greater antibody responses observed in males (green) or females (purple) at different life stages. Concentrations of circulating sex steroids (**b**) and sex differences in cell-mediated immune responses (**c**) also change over the life course, reflecting two possible biological mechanisms that impact sex differences in vaccine-induced immunity