Sex and Gender Impact Immune Responses to Vaccines Among the Elderly

In response to the recommended vaccines in older-aged individuals, sex differences occur in response to those that protect against influenza, tetanus, pertussis, shingles, and pneumococcal infections. The efficacy of vaccines recommended for older-aged adults is consistently greater for females than for males. Gender differences as well as biological sex differences can influence vaccine uptake, responses, and outcome in older-aged individuals, which should influence guidelines, formulations, and dosage recommendations for vaccines in the elderly.

Aging of the Immune System

With age, there is a progressive functional decline in the immune system (17) that is assumed to occur equally in males and females. One of the most well characterized attributes of an aging immune system is an aberrant chronic low-grade pro-inflammatory state (16), which may occur to a greater extent in females than in males (40). The activity of innate immune cells that are associated with inflammation, including dendritic cell (DC) subsets, macrophages, and neutrophils, also becomes dysregulated with age (2, 15, 60, 112). While inflammatory responses are necessary to orchestrate responses that clear pathogens and repair tissues, dysregulation or chronicity of inflammatory responses can contribute to tissue damage and disease.

In the United States, as well as in most developed countries in the world, the population is aging, largely due to the “baby boomers” who began turning 65 in 2011. Based on data analyses from the U.S. Census Bureau, the projections for 2050 are that the population of people over the age of 65 will almost double the 2012 estimated population of 43.1 million (85). With growth in the population of older-aged individuals comes public health concerns about the care and treatment for chronic as well as acute diseases, including infectious diseases. In developed countries, women tend to outlive men (41a, 72). Although sex and gender differences in mortality rates among individuals 65 years and older are well documented, the extent to which the sexes differ in response to diseases that either are specific to older age or worsen with age has not been adequately considered. The risk of severe outcome from infectious diseases, in particular, becomes greater for older-aged individuals in developed countries (FIGURE 1), with vaccines serving as a primary prophylactic treatment, when available. In this review, we will show that sex (i.e., biological differences) and gender (i.e., social and cultural norms) affect the responses to and outcome of recommended vaccines in older-aged individuals (i.e., 65 years and older). We will further demonstrate that male-female differences in the responses to vaccines alter the efficacy of vaccines for protecting aging individuals equally. Consideration will be given to specific vaccines and possible biological mechanisms that could differentially influence vaccine uptake, response, and outcome in older-aged males and females.
Sex Differences in Immune Function

There exists a growing body of literature illustrating that both innate and adaptive immune responses differ between the sexes following exposure to immunological stimuli, but this is currently not considered in the design or dosing of recommended vaccinations at any age. In both humans and preclinical animal models, most studies typically utilize young adults, with little to no consideration of whether sex differences in immune function change over the course of life. Innate immune responses differ between the sexes, at least among young adults. Studies conducted using young adult mice illustrated that the activity of pattern recognition receptors (PRRs), production of inflammatory proteins (e.g., IFN-α, IFN-γ, TNF-α), antigen presentation, and phagocytic capacity of macrophages is reportedly higher in females than in males in response to diverse antigens and pathogens (9, 26, 38, 77, 90, 111). Whether these innate immune system differences between the sexes are still present in aged individuals has not been adequately addressed, but some data suggest that elevated production of inflammatory proteins in females compared with males persists among aged individuals (40).

Females also exhibit elevated humoral and cell-mediated immune responses to antigenic stimulation, vaccination, and infection than do males (38). Both basal levels of immunoglobulin (Ig) (14) as well as antibody responses to viruses and vaccines are consistently higher in females than in males among both young and aged individuals (23, 65, 66). Men also reportedly have lower absolute CD3+ T-cell counts, absolute numbers of CD4+ T cells, CD4+-to-CD8+ T-cell ratios, and helper T-cell type 1 (Th1) responses (3, 27, 108, 115). Among older individuals, there are limited data indicating that reductions in adaptive immune responses with age, including numbers of T and B cells and cytokine production, are more dramatic in males than in females (51).

Vaccine Design Should Consider Both Sex and Age

Vaccination Rates are not Consistently Analyzed for Male-Female Differences Among Aged Individuals

Although some vaccines are widely distributed in the elderly population, the uptake of others is much less common. In the U.S., the seasonal influenza vaccine is routinely offered to persons 65 years of age and older, and 61% of this population is vaccinated, which is almost double the vaccination rate among young adults (20, 34, 115a). Similarly, the vaccination rate for the pneumococcal

**FIGURE 1.** Among adults, susceptibility to infection increases with older age

For infectious diseases in which vaccines are available, vaccines are the primary prophylactic treatment for the prevention of disease. Antibody responses as well as the efficacy of vaccines decrease with older age and to a greater extent among males than females. In addition to immunological changes that occur with older age, endocrinological changes occur in both males and females, in which both estrogen and testosterone levels decline, which may contribute to increased susceptibility to infections and reduced efficacy of vaccines in older-aged individuals.

Influenza

Tetanus-Diphtheria-Pertussis

Pneumococcal

Herpes Zoster

<table>
<thead>
<tr>
<th>Recommended schedule</th>
<th>Influenza</th>
<th>Tetanus-Diphtheria-Pertussis</th>
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<tr>
<td>Vaccination rate</td>
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<td>Pandemic H1N1</td>
<td>Td/Tdap</td>
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</tr>
<tr>
<td>Adverse reactions</td>
<td>1 dose/year</td>
<td>1 dose Tdap + Td booster/10 yr</td>
<td>1 dose 65+</td>
<td>1 dose 65+</td>
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<tr>
<td>Antibody response</td>
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<td>M = F</td>
<td>M &gt; F</td>
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<tr>
<td>Efficacy</td>
<td>F &gt; M</td>
<td>F &gt; F</td>
<td>F &gt; M</td>
<td>F &gt; M</td>
</tr>
<tr>
<td>References</td>
<td>10, 11, 21–23, 25, 32, 35–37, 39, 40, 49, 57, 58, 63, 64, 81–83, 105–107, 109</td>
<td>7, 42, 52, 74, 104, 113</td>
<td>12, 24, 47, 95, 96, 101, 102, 114</td>
<td>54, 55</td>
</tr>
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Influenza Tetanus-Diphtheria-Pertussis Pneumococcal Herpes Zoster

Seasonal Pandemic H1N1 Td/Tdap PPSV23/PCV13 HZV

1 dose/year 1 dose Tdap + Td booster/10 yr 1 dose 65+ 1 dose 65+

Table 1. Sex differences in vaccination for the elderly

females; M, males; NA, not available.

pneumococcal bacteria; PCV13, pneumococcal conjugated vaccine against 13 types of pneumococcal bacteria; HZV, herpes zoster vaccine; F, Td, tetanus and diphtheria; Tdap, tetanus, diphtheria, and pertussis; PPSV23, pneumococcal polysaccharide vaccine against 23 types of pneumococcal bacteria; PCV13, pneumococcal conjugated vaccine against 13 types of pneumococcal bacteria; HZV, herpes zoster vaccine; F, females; M, males; NA, not available.

Vaccination rate M/F

Adverse reactions F/M

Antibody response F/M

Efficacy F/M

References 10, 11, 21–23, 25, 32, 35–37, 39, 40, 49, 57, 58, 63, 64, 81–83, 105–107, 109

Sex-specific differences in the rate of vaccination for distinct vaccines have been reported in the elderly (Table 1). It is widely documented both in the U.S. and in several European countries that rates of vaccination for both the seasonal and pandemic influenza vaccines are greater for elderly males than for their female counterparts (4, 8, 21, 33, 35, 40, 59, 98, 106). In contrast, receipt of both the herpes zoster and pneumococcal vaccines tends to be higher among females than males (54, 70). To date, there are no studies that partition and analyze tetanus, diphtheria, and pertussis (Tdap) or tetanus and diphtheria (Td) vaccination rates by sex.

Multiple factors play a role in the acceptance of vaccines by aged individuals, including gender-associated differences in beliefs and general knowledge regarding vaccination (33). Females report more adverse reactions to vaccination and have more concerns regarding vaccine safety and efficacy than males, which may contribute to the observed differences in the uptake of influenza vaccines among aged males and females (33, 40). In other cases, a lack of public awareness about the availability and benefits of vaccines (e.g., the pneumococcal and herpes zoster vaccines) or a lack of partitioning and analysis of epidemiological data for sex differences (e.g., Tdap and Td) may result in a misconception that the receipt of vaccines is equivalent for males and females among aged individuals.

Vaccine is higher in the aged population (59.7%) compared with young adults (18.5%), whereas the rates of vaccination for the tetanus vaccine are similar between the aged and young adult populations at 53.4% and 64%, respectively (19). Although the elderly have a higher uptake of both the seasonal influenza and pneumococcal vaccines, neither meets the target vaccination coverage rate of 90% in the U.S. (29a).

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Adverse Reactions to Vaccines are Greater in Aged Females Than in Males

The U.S. Food and Drug Administration (FDA)-approved vaccines may elicit mild to moderate adverse reactions that include both local and systemic reactions. Aged females consistently report more adverse reactions than males in response to the seasonal and pandemic influenza vaccines (10, 22, 25, 32, 36, 49, 57, 58, 82), the pneumococcal vaccines (24, 101), the herpes zoster vaccine (55), and the tetanus and pertussis vaccines (7, 42, 113). While both males and females experience similar types of adverse reactions, the proportion of female vaccinees reporting local reactions, such as injection site pain, redness, and swelling, as well as systemic reactions, including joint or muscle pain, headache, back and abdominal pain, fever, chills, and hypersensitivity reactions is consistently greater than for males (Table 1). Whether differences in adverse reactions among aged males and females reflect a gender-based reporting bias or a sex difference in inflammation has not been resolved. Data on adverse reactions to vaccines are typically collected through the U.S. Vaccine Adverse Event Reporting System (VAERS), which relies on passive reporting of adverse reactions. Thus females may be more likely to report adverse reactions to VAERS than males. Limited analyses of local erythema and induration, which are measures of inflammation, at the site of seasonal influenza vaccination illustrate that aged females have significantly larger (≥6 mm) injection site reactions to the vaccine than their male counterparts (18). Future studies must continue to develop methods for accurate assessment of the qualitative as well as the quantitative reactions to vaccines to better understand whether differences in adverse reactions to vaccines reflect a sex, gender, or both form of biases. Furthermore, the impact of dose
and route of administration on reducing adverse reactions in females has not been documented.

**Antibody Responses to Vaccines Differ Between the Sexes Among Aged Individuals**

Most vaccines provide protection through the induction of antibodies, which has historically been used as a relative correlate of protection (91, 92). The magnitude of the antibody response to vaccines depends on many factors, including the age and sex of the vaccinee. In general, antibody responses are lower in aged males and females compared with their younger adult counterparts (FIGURE 1) (29, 53, 94). In some cases, this has resulted in reformulation of vaccines, such as the development of the high-dose influenza vaccine for annual vaccination of individuals 65 years and older, regardless of sex.

Sex differences in the antibody response depend on the specific vaccine (Table 1). Aged females consistently have higher antibody responses to influenza vaccines than males (11, 23, 37, 40, 63, 64, 105). As noted above, the high-dose seasonal influenza vaccine was introduced to overcome the overall lower antibody production in aged compared with young adults. Sex differences in hemagglutination inhibition (HAI) antibody titers to either the standard-dose or high-dose influenza vaccine are apparent, in which antibody responses are significantly higher in older females than in males against each of the three influenza strains (H1N1, H3N2, and Influenza B) (37). Similar to the seasonal influenza vaccines, older females were reported to have higher HAI antibody titers against the monovalent pandemic 2009 H1N1 (pH1N1) inactivated vaccine than males, resulting in a two to three times higher seroprotection and seroconversion rate in females than in males (63). Although older females produced higher antibody responses to the pH1N1 vaccine, the avidity of their antibodies after pH1N1 vaccination was significantly lower than that of older males (64). If higher avidity is a measure of a superior antibody response in the elderly, then these data suggest that the quality of the antibody response might be better for males than for females. If females have lower antibody avidity than males, then this may suggest that cross-reactivity of antibody to novel strains of influenza is higher for aged females than males, which has been demonstrated in a murine model of heterosubtypic influenza challenge (71).

In contrast to influenza vaccines, aged males have higher antibody responses to both the pneumococcal vaccine and the Td/Tdap vaccines than females (7, 12, 24, 42, 47, 52, 74, 95, 96, 104, 113). In a study evaluating the immunogenicity of the 23-valent pneumococcal vaccine in nursing home residents, both pre- and post-vaccination IgG titers against all four serotypes analyzed were higher in males than in females (12). In a similar study, when aged individuals were administered the 7-valent pneumococcal vaccine, males were found to have consistently higher levels of serotype-specific IgG both pre- and post-vaccination. Antibody concentrations were 19% higher in males than in females 6 wk after the first dose, and 30% higher 6 wk after the second dose (47). Few studies have analyzed antibody response to Tdap vaccines for sex-specific differences. The available studies suggest that, although there are varying trends depending on the vaccine antigen and study population, males tend to have higher antibody titers to both tetanus and diptheria than females (42, 52, 74, 104). This is in contrast to what has been reported for younger adults, in which females consistently have higher antibody titers than males in response to live attenuated, subunit, and inactivated vaccines, including the pneumococcal, influenza, yellow fever, rubella, measles, mumps, hepatitis A and B, herpes simplex 2, rabies, smallpox, and dengue vaccines (66, 99).

The lack of consistently higher antibody responses among aged females compared with males may be caused by both biological and social differences between the sexes. The dose of a vaccine may also contribute to the difference in antibody response, since high doses of a vaccine could potentially mask or reverse sex-specific differences in the immune response. Historically, if aged males ever served in the military, then they will likely have higher rates of immunization than females who were not in the military (42, 45). Similarly, females of child-bearing age have only been able to participate in phase 1 and 2 clinical trials since 1977, which may also explain the bias for a higher number of men willing to participate in vaccine trials (100). Data from influenza vaccines are a notable exception because these vaccines are administered annually and, therefore, present the largest body of literature from which to analyze sex- and age-based differences in the correlates of vaccine protection.

**Vaccine Efficacy is Greater for Aged Females Than for Males**

Vaccine efficacy refers to the percent reduction in disease incidence in a vaccinated population under ideal conditions (110). Efficacy is measured in randomized, controlled clinical trials where there is active monitoring of disease, vaccination status, and lab confirmation of the infection. In addition, efficacy studies often include monitoring hospitalization, medical visits, and mortality (110). Vaccine efficacy is often misinterpreted as vaccine effectiveness, which refers to the ability of a vaccine to...
prevent disease in a population-wide, real-world setting.

Following receipt of influenza vaccines, vaccine efficacy is typically measured by hospitalization and mortality rates post-vaccination. Most studies of influenza vaccine efficacy, however, do not disaggregate data by sex. Among older community-dwelling adults in Taiwan that received the standard seasonal influenza vaccine, higher HAI titers were associated with lower rates of hospitalization and mortality in females than males in logistic regression models, suggesting that the efficacy of the influenza vaccine in older adults might be higher for females (109). Vaccine effectiveness, as measured as all-cause mortality, was also measured in a large study of community-dwelling elderly in Spain and was higher in seasonal influenza-vaccinated aged females than males (107). During the 1989-1990 influenza epidemic in England, a review of over 10,000 elderly patient records revealed that vaccination was better at preventing mortality in aged females than males (39). Finally, several large studies have been conducted that include elderly patients across the U.S. and that span over multiple influenza seasons where the vaccine effectiveness at reducing mortality is consistently higher among females than males (81, 83).

Unlike the influenza vaccines, sex differences in vaccine efficacy in the elderly have only been measured in a modest number of studies for the herpes zoster and pneumococcal vaccines, and not at all for the Td/Tdap vaccines. In a retrospective study examining the hospitalization rate among vaccinated individuals between 2005 and 2009 in Germany, the proportion of hospitalizations due to herpes zoster infection was higher in males compared with females (55). Another large study examined all deaths registered on U.S. death certificates reporting any pneumococcal infection from 1968 to 2006. Data obtained from this study indicated that, following the introduction of the 23-valent pneumococcal vaccine in 1983, there was a significant reduction in mortality, especially in white females over the age of 65 (102). Another study examined the effectiveness of the 23-valent pneumococcal vaccine at preventing Streptococcus pneumoniae community-acquired pneumonia (SpCAP) in the elderly and showed that there were significantly fewer females who were hospitalized with confirmed cases of SpCAP than males (data extracted from both the U.S. and Europe) (114). Overall, vaccine efficacy tends to be higher in elderly females than in males (Table 1), although the measurement of efficacy and effectiveness for each vaccine can be different. Increased analysis and reporting of sex differences in vaccine efficacy as well as defining the absolute correlates of protection and determining whether these measures of protection differ between the sexes is required for future studies.

**Biological Mechanisms Mediating Sex Differences in Vaccine Efficacy in the Elderly**

**Sex Steroids**

The prevailing hypothesis for immunological differences between the sexes is that sex steroids, particularly testosterone, estradiol, and progesterone, influence the functioning of immune cells. Sex steroids alter the functioning of immune cells by binding to specific receptors, which are expressed in various lymphoid tissue cells as well as in circulating lymphocytes, macrophages, and DCs (68). The binding of sex steroids to their respective steroid receptors directly influences cell signaling pathways, including NF-κB, c-Jun, and IRF1, resulting in differential production of cytokines and chemokines (75, 88).

With age, the hormonal milieu dramatically changes as ovarian function in females and testicular production of sex steroids in males decline (Figure 1) (5, 80, 87). The hormonal changes associated with menopause in females are dramatic and relatively abrupt, since ovarian production of estradiol declines and progesterone production is reduced to that which is synthesized by the adrenal glands. In males, the reduction in testosterone production is more gradual. The reduction in sex steroid concentrations and sex steroid receptor signaling with age likely contributes to age-associated dysregulation of immune function (Figure 1) (45). This has been directly studied in females pre- and postmenopausal, with menopause (either naturally occurring or surgically induced) resulting in lower numbers of B and T cells and greater concentrations of proinflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) (46, 61, 69). Use of hormone replacement therapy in postmenopausal females affects immune function by increasing circulating numbers of B cells and reducing baseline concentrations of proinflammatory cytokines compared with postmenopausal females not on hormone replacement therapy (28, 61). Whether testosterone replacement therapy affects immune responses in aged males has not been determined. Also, whether treatment with hormone replacement therapies affects the outcome of vaccines in either females or males has not been reported.

**Genetic and Epigenetic Regulation**

In addition to hormonal influences, genetic and epigenetic factors contribute to sex-based differences in an immune response to vaccination (67). Sex-based differences in responses to vaccines are

[FIGURE 1]
observed before puberty, during reproductive years, and after reproductive senescence, suggesting a role for factors other than sex steroids. A large number of immune-related genes encoding proteins are located on the X chromosome (38). A number of critical transcriptional and translational control effectors that function downstream of activated cytokine receptors are also encoded on the X chromosome. Given that males are XY and females are XX, any damaging mutations or polymorphisms to X-linked genes are more likely to have an immune consequence in males compared with females (1). The combined effects of hormones influencing the epigenetic regulation of gene expression, and gene composition on the X chromosome potentially differing between XX females and XY males, might determine an immune response to vaccination (67).

The expression of X-linked genes may be affected by X-linked micro-RNAs (miRNAs), which are small noncoding RNAs that regulate gene expression at a posttranscriptional level and play a role in maintaining immunological homeostasis (89). There are disproportionately more miRNAs located on the X chromosome than on any autosomal chromosome (89). The X chromosome contains 10% of the ~800 miRNAs in the genome, whereas the Y chromosome contains only 2 miRNAs (43). Lastly, polymorphisms in sex chromosome and autosomal genes that encode for immunological proteins can contribute to sex differences in immune responses (93) and antibody responses to vaccination (48).

**Microbiome**

The human microbiota is composed of microbial communities in different habitats, including skin, gut, oral cavity, and genitals, which can vary according to sex and age. For example, age-related vaginal changes that occur pre- and postmenopause can affect the vaginal microbiome (13). Bacteria can metabolize inactive sex hormones into their bioactive state, mediated by hydroxysteroid dehydrogenase enzymes (41). Antibiotic use can deplete bacterial populations, impairing this bacteria-regulated hormone metabolism and decreasing the availability of active, circulating sex hormones and, thus, alter the immune response to vaccines. Accumulating evidence indicates that hormonal status can shape gut microbiome composition such that the onset of puberty and concomitant hormone-specific changes result in sex-specific microbiome profiles (116). Recent studies utilizing prepubertal and young adult mice illustrate that immune function and spontaneous development of autoimmune diseases, including Type 1 diabetes, is mediated by sex-specific composition of the gut microbiome and the hormonal milieu (73, 117).

Consequently, microbiome composition can directly influence immune function in a sex-specific manner, but how this changes with age requires consideration.

**Chronic Infection**

There is growing interest in how latent infections impact the outcome of vaccination. Cytomegalovirus (CMV), in particular, is a β-herpes virus that infects most of the population in childhood and remains in a latent, primarily quiescent state for our lifetime. In healthy individuals, CMV latency only causes a chronic, asymptomatic infection with low levels of intermittent virus shedding. In young adults (humans and mice), CMV infection is associated with elevated antibody responses to influenza vaccines (40). In aged individuals, CMV seropositivity is associated with chronic inflammation (6) and lower antibody responses to influenza vaccines (30, 31). Whether the impact of CMV on immunocompetence in aged individuals is sex-dependent has not been reported. Incidence of CMV infection (based on seropositivity) is reportedly higher in young females than in males (50), suggesting that, in aged individuals, the impact of CMV on immunological aging and responses to vaccination may be greater for females than for males.

**Conclusions and Future Directions**

Males and females are biologically and in some cases socially and culturally different, which can impact acceptance of and responses to vaccines in aged individuals. The social or culture differences between males and females appear to impact knowledge about the value of vaccines as well as receipt of vaccines in the elderly. The biological differences, spanning hormones and genes to the microbiome and past exposures to infections, may differentially influence immune responses to vaccines in males and females. As a result of the biological differences between males and females, “precision vaccines” should be developed that consider how sex influences the outcome of vaccination. For example, increasing the breadth and magnitude of the immune response to vaccines in aged males might be a productive mechanism for increasing vaccine efficacy in males. In contrast, vaccination strategies for aged females should be focused on reducing inflammation and adverse reactions while retaining elevated antibody responses and vaccine efficacy. The concept of sex-specific dosage recommendations has been more readily applied to drugs than to biologics, such as vaccines. This review highlights a need to better consider how vaccine efficacy and acceptance
could be improved by considering sex as a variable in vaccine trials in aged populations.

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