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Invited Review

Immunization for midlife women

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Abstract

Objective: Menopause occurs at a critical juncture in life when preventative health care can have a major impact. However, recommendations for immunizations are often neglected, leading to unnecessary morbidity and mortality in aging women. The aim of this review is to highlight the importance of immunization checkpoints at menopause to optimize the quality of care and health maintenance in older women and to provide an overview of the impact of immunizations on women's health.

Methods: This is an opinion article based on the current US and Canadian guidelines. A review of various guidelines from the Centers for Disease Control and Prevention and National Advisory Committee on Immunizations were conducted for each vaccine.

Results and Conclusions: Disease prevention benefits are well established for several diseases, such as hepatitis A, hepatitis B, tetanus, human papillomavirus, streptococcus pneumonia, shingles, and COVID-19. During clinical encounters, a needs assessment regarding vaccinations should be conducted. However, barriers to adult vaccination including lack of patient and provider knowledge about the need for vaccination, lack of priority for preventive services, and concerns regarding costs, insurance coverage, and reimbursement all contribute to the adult immunization gap. Given the importance of immunization and the need to decrease vaccine-preventable diseases, it is the obligation of healthcare practitioners to recommend vaccines and provide education on vaccination guidelines and associated risks. As women often seek medical attention at menopause because of changes in their physiology that require attention, it is the ideal time to discuss the importance of immunization.

Key Words: Immunization – Menopause – Vaccines.

Although menopause is technically that time in a woman's life when there have been no menses for 12 months, it also represents a juncture in life and a time when women may seek medical opinions about preventative health issues. The data from various studies show that cardiac disease, cancers, and osteoporosis have serious impacts on women's health causing death, disability, and poor quality of life.[1] These are known issues and healthcare providers may address risk factors for patients at this time. Immunization, which is another area that addresses prevention, may be overlooked and underused as midlife women address medical concerns. In North America, vaccine-preventable diseases account for high rates of death and disability.[2-5] The menopause visit may be an opportune time to serve as a reminder, providing healthcare providers the opportunity to review all preventative healthcare options and enhance the protection for the women in their practice.

At this particular time, in the midst of a world pandemic, we are also faced with options for vaccination against COVID-19. As women review their general health, as well as the preventions that are advised, it is important to understand the newest COVID-19 immunizations and their impact on women's health.

Currently, national standards for immunizations are set by the Advisory Committee on Immunization Practices in the United States (ACIP) and the National Advisory Committee on Immunizations (NACI) in Canada. In Mexico, the National Immunization Technical Advisory Group sets standards for infants and adolescents but not for adults.

Disease prevention benefits of vaccinations are well established; however, barriers result in a low prevalence of adult immunization.[6] The update to vaccine recommendations by the US National Vaccine Advisory Committee in 2013 cited the following barriers to adult vaccination: lack of patient and provider knowledge about the need for vaccination; lack of priority for preventive services, concerns regarding costs, insurance coverage, and reimbursement; and care by multiple providers, all of which complicate the coordination of care.

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Facilitators of provider recommendation and offer of vaccination during the same visit predict compliance for meeting adult vaccination recommendations.[7]

Providers are advised by the US National Vaccine Advisory Committee to not only educate themselves and their patients about current vaccine recommendations but also include an immunization needs assessment in every clinical encounter. A National Vaccine Plan was developed in 2020 with the purpose of coordinating goals and priorities for immunization. With the advent of the current pandemic and the role of vaccines to prevent COVID-19, it becomes even more important to lay the framework for a robust immunization effort in the general population.[8]

This review focuses on hepatitis A and B, human papillomavirus (HPV), pneumococcal, shingles, tetanus, and COVID-19 vaccines. Several other vaccines are not discussed in this review because they are not offered to the general public and their use is dependent on specific circumstances, such as travel and occupation risk.

METHODS

This is an opinion article based on the current US and Canadian guidelines. A review of various guidelines from the Centers for Disease Control and Prevention (CDC) and NACI was conducted for each vaccine.

Hepatitis A and B vaccines

Hepatitis A virus and hepatitis B virus (HBV) cause infection of the liver with associated morbidity and mortality. Chronic hepatitis, related to HBV, can lead to an increased risk of cirrhosis and hepatoma. Multiple vaccines are available. ACIP recommends routine vaccination of children aged 12 to 23 months and catch-up vaccination for children and adolescents aged 2 to 18 years who have not been previously vaccinated. For unvaccinated adults with risk factors, including illicit-drug users, persons with chronic liver disease, and travelers to countries with intermediate or high rates of hepatitis A, the vaccine is recommended. There is no booster recommended, because immunoglobulin G anti–hepatitis A virus produced after vaccination confers long-term immunity.[9] NACI does not have guidelines for routine immunization of infants and children, although there is guidelines on postexposure prophylaxis.[10]

Hepatitis B vaccination

There has been a universal hepatitis B vaccine for all infants and children since the 1990s in both the United States and Canada. Hepatitis B vaccine is recommended for vaccination of adults at risk for HBV infection, including universal vaccination of adults in settings in which a high proportion has risk factors for HBV infection and vaccination of adults requesting protection from HBV without acknowledgment of a specific risk factor.

This includes adults with more than one sex partner in the previous 6 months, healthcare personnel, patients with end-stage renal disease, and adults seen in sexually transmitted infection and HIV testing and treatment facilities. Furthermore, ACIP recommends testing all pregnant women for hepatitis B surface antigen; administration of hepatitis B vaccine and hepatitis B immune globulin for infants born to HBV-infected women within 12 hours of birth, followed by completion of the vaccine series and postvaccination serologic testing; universal hepatitis B vaccination within 24 hours of birth, followed by completion of the vaccine series; and vaccination of children and adolescents younger than 19 years who have not been vaccinated previously.[11] Currently, there is no evidence for a booster dose in healthy people because immune memory is long lasting.[12]

HPV vaccine

HPV is associated with cervical, vulvar, and vaginal cancer in women; penile cancer in men; and anal and oropharyngeal cancer in men and women. HPV 6 and 11 are also the cause of 90% of genital warts and are included in both the quadrivalent and nonovalent vaccines.[13] Three HPV vaccines are currently approved for routine vaccination: bivalent, quadrivalent, and 9-valent. These vaccines protect against HPV types 16 and 18, the major oncogenic strains of HPV, accounting for 70% of cervical cancers. The quadrivalent vaccine includes 6, 11, 16, and 18. However, the 9-valent now targets five additional strains accounting for an additional 15% of cervical cancers. Vaccination is now recommended for women and men aged up to 26 years, including men who have sex with men and immunocompromised patients. In Canada, NACI recommends HPV vaccination for at-risk women and men older than 26 years, with no upper age limit, although Health Canada has approved the vaccine only up to the age of 45 years.[14]

This is a permissive statement from NACI that suggests focusing on risk, regardless of age past 45 years.

The recommendation is slightly different in the United States because the CDC recommends the vaccine for men and women up to the age of 26 years. For those older than 26 years, the CDC does not recommend catch-up HPV vaccination for all adults but does recommend shared clinical decision-making regarding HPV vaccination for adults aged 27 through 45 years.[15] HPV vaccines are not licensed for use in adults older than 45 years. Clinicians practicing in the United States do encounter unvaccinated women older than 26 years who request immunization, may be deemed to be at risk or high risk, and may choose the protection of being vaccinated. In these cases, it is reasonable to offer the vaccine. However, this then becomes a personal decision for the doctor and patient as it is considered off-label.

HPV immunization has been recommended even if an individual has already been infected or has been given a diagnosis of a cancer or precursor of cancer. The research shows that, by immunizing those women, there is a decreased risk of recurrence of HPV in the original site or another location.[16,17]

The product monograph in the United States for the HPV 9 vaccine includes the indication for prevention of oropharyngeal and other head and neck cancers caused by types 16, 18, 31, 33, 45, 52, and 58 in both men and women. This is significant because oropharyngeal cancers, particularly in men, have been increasing in both Canada and the United States.[18]

HPV type 16 is the type most often linked to cancer of the oropharynx, especially those in the tonsil and base of the tongue. HPV DNA is associated with two of three oropharyngeal cancers. The

number of oropharyngeal cancers linked to HPV has risen greatly for the past few decades. These cancers are becoming more common in younger people who have a history of multiple sex partners (including oral sex) and no history of alcohol abuse or tobacco use, previously a common risk factor for these cancers. The discussion then in menopause can be about risk assessment, the likelihood of new exposure, and the understanding that, with aging, the immune system is less robust. A previous HPV infection that has been dormant or latent may then become more active, leading to recurrent or new disease in a given woman. Indeed, the statistics for cervical cancer, generally a cancer of younger women, reveal there is a second peak of cancers in older women, past the age of menopause. In Canada, incidence peaks among women in their 40s and then again among women 70 years or older.[19]

Pneumococcal vaccines

Streptococcus pneumoniae remains a leading infectious cause of serious illness in adults and is responsible for 500,000 cases of pneumococcal pneumonia annually. There is both an increased risk of hospitalization and of death with age.[20] The 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended by ACIP for all adults older than 65 years and younger immunocompromised and at-risk adults. In 2011, a new 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the US Food and Drug Administration (FDA) for adults 50 years and older. In 2014, ACIP recommended routine vaccination of all adults older than 65 years and adults younger than 65 years at risk for invasive pneumococcal disease. However, in 2019, ACIP stated PCV13 vaccination is no longer *routinely* recommended for all adults 65 years and older. Instead, shared clinical decision-making for PCV13 use is recommended for persons 65 years and older who are not at a high risk. Shared clinical decision-making considerations may include risk for exposure to PCV13 serotypes and the risk for pneumococcal disease as a result of underlying medical conditions.[21]

Most recently, in 2021, two new vaccines were licensed in the United States, PCV15 and PCV20. These vaccines are conjugated and have a greater number of serotypes, which is likely to translate into less disease risk for the patient. In October 2021, the ACIP working group reviewed some considerations with respect to the use of these vaccines. The conclusions were both age based and risk based. What the working group recommended was that, in a patient 65 years and older who had not received a previous pneumococcal vaccine or in whose history was unknown, he/she should receive either PCV20 alone or PCV15 followed by PPSV23. For those 19 years and older with risk factors, comorbid conditions, and immunologic risk, they also should receive PCV20 alone or PCV15 followed by PPSV23.[22]

On an individual basis, vaccine decision should consider general health factors, including pregnancy, comorbidities, occupational risks and consequences of disease, loss of productivity, potential loss of daily living capacities, pain resulting from the vaccine-preventable disease complications, and the protection of others (patients, pupils, family).[23]

The schedule for vaccinating is variable and may depend on age and underlying risk. In a patient 65 years and older or in a younger patient with risk, the ideal option is to immunize with PCV13 first, or now in the United States, PCV15 or PCV20 because it is a conjugate vaccine. Immunogenicity studies evaluating responses to PCV13 and PPSV23 administered in series showed a better immune response when PCV13 was administered first.[24] If PCV13 or PCV15 is used, it is then followed by PPSV23, the polysaccharide vaccine. The Canadian guidelines suggest an 8-week interval is sufficient, whereas ACIP suggests a 1-year interval. If PPSV23 has been administered, guidelines in both countries recommend a year before the administration of PCV13.

Shingles vaccine

Herpes zoster (shingles) increases with age, and the incidence of postherpetic neuralgia, interference with daily activities, and hospitalizations increases as well. To prevent herpes zoster and its complications, the FDA and Health Canada have approved two vaccines for use in people older than 50 years. The live zoster vaccine (LZV or Zostavax) has been on the market since 2011, and the newer recombinant zoster vaccine (RZV or Shingrix) came to market in 2017. ACIP advised that adults older than 50 years should be immunized regardless of shingles history and regardless of whether they were previously immunized with the LZV vaccine.[25] The study of the herpes zoster subunit vaccine (RZV) conducted in older adults revealed excellent efficacy of more than 97% in all age groups. For this reason, this vaccine is now the vaccine of choice. NACI, with the Canadian recommendations, states that although both vaccines remain as options, RZV has longer-lasting efficacy, is more cost-effective, and does not have the same contraindications as LZV, including the use in immunocompromised patients. RZV is becoming the standard of care. LZV may be used if RZV is unavailable or contraindicated.[26]

In both the United States and Canada, the RZV has been approved for adults younger than 50 years if they are immunocompromised. This is a reflection of the increased risk of this disease in that cohort. Although the usual dosing schedule is to have the second dose between 2 and 6 months after the first, the CDC suggests for immunocompromised adults, a shorter interval of 1 to 2 months can be followed if the patient would benefit from completing the series in a shorter period.

Tetanus vaccine and tetanus, diphtheria, pertussis vaccine

A one-time dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) booster (rather than the decennial dose of tetanus and diphtheria toxoids [Td vaccine]) is recommended for adults who have not previously received Tdap. In 2001, the FDA expanded the age indication for Tdap to include those older than 65 years. Tdap may be given regardless of the interval since the last tetanus or diphtheria-toxoid vaccine. A single dose of Tdap is recommended for providers with direct patient care contact who have not received the vaccine as an adult and for persons older than 65 years who have or anticipate close contact with an infant younger than 1 year to reduce transmission of pertussis (eg, adults who have recently become grandparents).[27]

COVID vaccines

Three coronavirus (COVID-19) vaccines are currently authorized for use in the United States. The FDA issued Emergency Use Authorization for the Pfizer-BioNTech COVID-19 vaccine on December 11, 2020, and for the Moderna COVID-19 vaccine on December 18, 2020; each is administered as a two-dose series.[28] ACIP issued interim recommendations for Pfizer-BioNTech and Moderna COVID-19 vaccines on December 12, 2020,[29] and December 19, 2020.[30] Both of these vaccines, known as messenger RNA vaccines, are also approved by Health Canada and are being administered in Canada.[31]

The Johnson & Johnson/Janssen (J&J/Janssen) vaccine, the third vaccine that has been approved in the United States, was on a temporary pause because of concerns of rare blood clots. On April 23, 2021, however, the CDC and FDA have recommended that use of J&J/Janssen COVID-19 vaccine resume in the United States, effective April 23, 2021. However, women younger than 50 years should be aware of the rare risk of blood clots with low platelets after vaccination. These risks are very rare and thought to be related to abnormal reaction of platelets, similar to heparin-induced blood clots. According to the American Society of Hematology (April 23, 2021), the term now being used to describe these rare events is vaccine-induced immune thrombotic thrombocytopenia. The diagnosis is based on four criteria, all of which must be met. These include COVID vaccine (J&J/AstraZeneca *only* to date) 4 to 30 days previously, venous or arterial thrombosis (often cerebral or abdominal), thrombocytopenia, and a positive PF4 "HIT" (heparin-induced thrombocytopenia) ELISA test. The event is described as extremely rare.[32]

The viral vector vaccines, by AstraZeneca and J&J/Janssen, have also been approved for use in Canada but have various limitations based on age and risk. This is partially dependent on each province because there are different implementation guidelines in different parts of the country.

According to Thrombosis Canada, a well-respected national guideline body on thrombosis and uses of anticoagulants, the risk of a significant blood clot with the AstraZeneca vaccine is 4 per 1 million. By comparison, the risk with the use of birth control pills is 900 per 1 million. The average Canadian has a risk of 1,290 per 1 million, and the risk in a hospitalized patient with COVID-19 is 147,000 per 1 million.[33] Thrombosis Canada further concludes that having had a previous blood clot, having factor V Leiden, or having a need for ongoing anticoagulant therapies all are not contraindications to having any of the vaccines.

It must be recognized that, as new data emerge, both NACI and ACIP will review and update guidelines accordingly. VAERS, the Vaccine Adverse Event Reporting System, is an existing national passive surveillance system in the United States that accepts reports from healthcare providers, vaccine manufacturers, and the public. There is a safety monitoring system established by the CDC specifically for the COVID-19 vaccination program. From VAERS reporting, there have been very reassuring data. Both mRNA vaccines have excellent safety profiles.[27] VAERS has not detected patterns in the cause of death that would indicate a safety problem with COVID-19 vaccines.[27]

There are some specific details, however, that impact women. First, it is not uncommon to develop lymphadenopathy in the region where one has received a vaccine, such as in the axilla. This has the potential to be read as abnormal in a subsequent mammogram. Therefore, the Society of Breast Imaging suggests doing routine mammograms before being vaccinated for COVID-19 or waiting 4 to 6 weeks after the second dose before a mammogram.[34] This adverse event of lymphadenopathy was noted at 11.6% for Moderna versus 5% for placebo. Reported numbers were lower for Pfizer; however, unilateral adenopathy, revealed in a mammogram, clearly is a concern and would warrant assessment, if it was other than reactive.

In general, women tend to have more adverse effects from the vaccines than men, although it is not clear whether it is at least partially because of reporting bias. Common adverse effects include headache, fatigue, and dizziness. Anaphylaxis is very rare; however, it was also seen more commonly in women.[35] Biologically, women produce greater numbers of antibodies after flu shots and vaccines for measles, mumps, and rubella, as well as hepatitis A and B. Men and women differ in their immunological responses to foreign antigens and self-antigens and show distinctions in innate and adaptive immune responses. Certain immunological sex differences are present throughout life, whereas others are only apparent after puberty and before reproductive senescence, suggesting that both genes and hormones are involved. These sex-based immunological differences contribute to variations in the incidence of autoimmune diseases and malignancies, susceptibility to infectious diseases, and responses to vaccines in males and females.[36]

Finally, pregnancy has been shown to be a disproportionate risk with respect to COVID-19 infection severity. Severe illness includes illness that results in intensive care admission, mechanical ventilation, or death. In addition, pregnant women with COVID-19 might be at an increased risk of adverse pregnancy outcomes, such as preterm birth, compared with pregnant women without COVID-19.[37] Current advice from the Society of Obstetricians and Gynecologists of Canada, as well as the CDC, has stated that although studies were not completed on pregnant women, given the risk for greater severity of disease and greater risk overall, there is an agreement that immunization is supported. The Society of Obstetricians and Gynecologists of Canada states specifically that use of all COVID-19 vaccines approved in Canada can be administered in any trimester of pregnancy and during breastfeeding.[38]

DISCUSSION

Women often seek medical attention at the time of menopause, recognizing that there are many changes in their physiology that need attention. This is a time to discuss various preventions, including immunization. There is much discussion about barriers and hesitancy in the lay press and among clinicians. In Canada, physicians thought that the number 1 barrier for patients to accept vaccination was cost. This was rated as number 1 by 92% to 95% of physicians. Perceived barriers of cost may limit recommendations for vaccination, particularly among older women or men.[39] For patients, however, the number 1 reported barrier to vaccination

was not having a recommendation from a doctor. Cost was seen as a barrier by only 18% (male) and 20% (female) of participants.[40] Given the importance of immunization and the need to decrease vaccine-preventable diseases, it is our obligation to recommend vaccines, allowing patients to understand the guidelines, the risks not only of the vaccine but also of not being vaccinated for a given disease, and the impact to them personally and to their community. This is the ideal time in a woman's life to embark on healthy preventions as the average woman now lives about one third of her life in menopause. Our aim is to help make that time one of good health, independence, and free of vaccine-preventable illness.

CONCLUSIONS

Although disease prevention benefits are well established for several diseases, there are many barriers to adult vaccination that contribute to the adult immunization gap. As such, it is important for healthcare practitioners to recommend vaccines and help educate the women in their practice regarding vaccination guidelines and associated risks. As women often seek medical attention at menopause because of changes in their physiology that require attention, it is the ideal time to discuss the importance of immunization to protect their future health and independence.

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