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Dr. Vivien Brown is a family physician and author in Toronto. Educated at McGill University, she currently is appointed to the Department of Family & Community Medicine at the University of Toronto, holding the rank of Assistant Professor. An award winner for teaching on many levels, her major interests are in the area of health promotion and prevention for women, and continuing medical education, Adult Immunization and Vaccine Preventable Illness. The College of Family Physicians of Ontario named Dr. Brown "Physician of the Year for the Region of Toronto" in 2012. She is the Past President of the Federation of Medical Women of Canada and is immediate past Vice President for North America for the Medical Women's International Association. In March 2017, she was honored to present HPV initiatives in Canada at the UN meetings for the Commission on the Status of Women. In 2018 she was honored with the Media Award from the North American Menopause Society for her work in Women's Health. She also received the May Cohen Award from the Federation of Medical Women of Canada for her work in Women's Health. Her most recent book, *The New Woman's Guide to Healthy Aging*, was recently published to rave reviews.

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IMMUNIZATION IN MIDLIFE

Introduction

Midlife is often defined as age 50 and above and is a period of life when patients commonly access the healthcare system, having recognized the need for various preventions. The Women's Health Initiative (WHI) identified cardiovascular disease (CVD), cancer and osteoporosis as the most common causes of morbidity, disability, and poor quality of life in post-menopausal women.[1] Healthcare professionals routinely screen patients with risk factors for these diseases and offer prevention and treatment to improve their quality of life. However, recommendations for immunizations are often neglected leading to unnecessary morbidity and mortality in our aging population. In Canada, it is estimated that 20,000 hospitalizations related to influenza occur each year[2] and that 4,000 to 8,000 Canadians die from influenza-related complications alone.[2,3] Vaccines can prevent the debilitating and fatal effects of infectious disease,[4] yet clinical evidence has revealed an adult immunization gap.[5] Midlife screening and intervention should serve as an immunization checkpoint, providing an opportunity for healthcare professionals to optimize quality of care and health maintenance in older patients.

Vaccination Measures and Protocols

Currently, in the midst of a global pandemic, we are also faced with options for vaccination against COVID-19. As patients review their general health and the preventions that are advised by healthcare professionals (HCPs), it is important to understand the newest COVID-19 immunizations that are available and their impact on long-term health.

National immunization standards are established 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 (NITAG) establishes standards for infants and adolescents, but not for adults. Although the disease-prevention benefits of various vaccinations have been well-established, several known barriers result in a low prevalence of adult immunization.[6] The United States National Vaccine Advisory Committee (NVAC) updated their vaccine recommendations in 2013 and cited barriers to adult vaccination including lack of patient and healthcare provider knowledge about the need for vaccination; lack of priority given to preventive services; affordability concerns; healthcare insurance coverage and reimbursement; and care by multiple providers, which complicates the coordination of care. Facilitators of adult vaccination include the provider's recommendation and offer of vaccination during the same visit, which has

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been shown to predict compliance for meeting adult vaccination recommendations.

NVAC advises that healthcare providers not only educate themselves and their patients about current vaccine recommendations but that that they also include an immunization needs assessment in every clinical encounter. In 2020, a National Vaccine Plan was developed to coordinate immunization objectives and priorities . With the advent of the COVID-19 pandemic and the role of vaccines in its prevention, these objectives and strategies have become even more important in outlining the framework for a robust immunization effort in the general population.[7]

Hepatitis A and Hepatitis B vaccination overview

The hepatitis A virus (HAV) and hepatitis B virus (HBV) cause liver infection with associated morbidity and mortality. Chronic HBV can lead to increased risk of cirrhosis and hepatoma. Multiple vaccines are available as immunization against HAV and HBV. The ACIP recommends the routine vaccination of children aged 12-23 months, and catch-up vaccination for children and adolescents aged 2-18 who have not previously been vaccinated. For unvaccinated adults with risk factors, including illicit-drug users, individuals with chronic liver disease (CLD), and travellers to countries with intermediate or high incidence of HAV, vaccination is recommended. Boosters are not recommended, as IgG anti-HAV antibodies produced post-vaccination confer long term immunity.[8] NACI does not provide guidance for the routine immunization of infants and children, although it has published guidance on post-exposure prophylaxis.[9]

Hepatitis B Vaccine

A universal HBV vaccine for infants and children of all ages has been available since the 1990s in both the United States and Canada. The vaccine is recommended for adults at risk for HBV infection; this includes universal vaccination of adults in settings where a high proportion of individuals have risk factors for HBV infection. In addition, it is recommended in adults requesting protection from HBV without acknowledgment of a specific risk factor. The criteria include adults who have had more than one sex partner in the previous six months, healthcare personnel, patients with end-stage renal disease (ESRD), and adults who have consulted sexually transmitted infection (STI) and HIV testing and treatment facilities. Furthermore, the ACIP recommends the following: testing all pregnant women for hepatitis B surface antigen; administration of the HBV vaccine and hepatitis B immune globulin (HBIG) testing in infants born to HBV-infected women within 12 hours of birth, followed by completion of the vaccine series and post-vaccination serologic testing; universal hepatitis B vaccination within 24 hours of birth, followed by completion of the vaccine series; and vaccination of children and adolescents age <19 years who have not previously been vaccinated.[10] Currently, there is no clinical evidence supporting the administration of a booster dose in healthy individuals in light of the fact that immunological memory is long-lasting.[11]

Human Papillomavirus Vaccine

The human papillomavirus virus (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.[12] Currently, three HPV vaccines are approved for routine vaccination: bivalent, quadrivalent and 9-valent. These vaccines protect against HPV types 16 and 18, the major oncogenic strains of HPV which account for 70% of cervical cancers. The quadrivalent vaccine includes 6, 11, 16 and 18. However, the 9-valent now targets five additional strains which account for an additional 15% of cervical cancers. Vaccination is now recommended for women and men up to age 26, including men who have sex with men and immunocompromised individuals. In Canada, NACI recommends HPV vaccination for at-risk women and men > 26 years of age, with no upper age limit. However, Health Canada has approved the vaccine only up to age 45,[13] reflecting a permissive statement from NACI suggesting that practitioners focus on patient risk, regardless of age past 45.

The recommendation is slightly different in the United States as the Centers for Disease Control and Prevention (CDC) recommends vaccination for men and women up to age 26. For those aged older than 26 years, the CDC does not recommend catch-up HPV vaccination for all adults; however, it does recommend shared clinical decision-making regarding HPV vaccination for adults aged 27 through 45 years.[14] HPV vaccines are not licensed for use in adults older than 45 years of age. Clinicians practicing in the United States do encounter unvaccinated women older than 26 years of age who request immunization. They may be deemed to be at risk or high risk and may choose the protection vaccination provides. In these cases, it is reasonable to offer the vaccine. However, this is a decision for the physician and patient to make together as vaccination in this circumstance is considered off-label.

HPV immunization has been recommended even if an individual has already been infected or has been diagnosed with a cancer or precursor of cancer. The research has demonstrated that by immunizing these women, there is a decreased risk of recurrence of HPV in the original site or in a different location.[15,16]

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

men, has been increasing in both the United States and Canada.[17]

HPV type 16 (HPV16) is the type most often linked to cancer of the oropharynx, especially in the tonsil and base of the tongue. HPV DNA is associated with two out of three oropharyngeal cancers. The number of oropharyngeal cancers linked to HPV has risen greatly over the past few decades. These cancers are becoming more common in younger individuals with a history of multiple sex partners (including the practice of oral sex) and no history of alcohol abuse or tobacco use, previously a common risk factor for these cancers. In midlife, the vaccination discussion should be focused on 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 subsequently become more active, leading to recurrent or new disease in a given patient. Indeed, the statistics for cervical cancer, generally a cancer occurring in younger women, reveal there is a second peak of cancers in older, post-menopausal women. In Canada, HPV incidence peaks among women in their 40s, and then again among women ≥ 70 years of age.[18]

Pneumococcal Vaccines

Streptococcus pneumonia remains a leading infectious cause of serious illness in adults and is responsible for 500,000 cases of pneumococcal pneumonia annually. It is associated with both increased risk of hospitalization and mortality with increasing age.[19] The 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended by the ACIP for all adults >65 years of age, and in younger, immunocompromised and at- risk adults. In 2011, a new 13-valent pneumococcal conjugate vaccine (PCV13) was approved by the Food and Drug Administration (FDA) in the United States for adults aged 50 years and older. In 2014, the ACIP recommended routine vaccination of all adults >65 years of age and adults <65 years of age at risk for invasive pneumococcal disease. However, in 2019, the ACIP stated that PCV13 vaccination is no longer *routinely* recommended for all adults aged 65 and older. Instead, shared clinical decision-making for PCV13 use is recommended for individuals aged 65 years and older who are not 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.[20]

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 reduced disease risk for the patient. In October 2021,the ACIP Working Group reviewed several considerations regarding the use of these vaccines. Their conclusions were both age- and risk-based. The Working Group recommended that patients aged 65 and older who had *not* received a previous pneumococcal vaccine or whose history was unknown should receive either PCV20 alone or PCV15 followed by PPSV23. For those age 19 and older with risk factors, comorbid conditions, and immunologic risk, they also should receive PCV20 alone, or PCV15 followed by PPSV23.[21]

On an individual basis, vaccine decision-making should consider general health factors, including pregnancy; co-morbidities; occupational risks and consequences of disease; loss of work-related productivity; potential loss of daily living capacities; pain resulting from the vaccine; preventable disease complications; and the protection of others (patients, pupils, family).[22]

The vaccination schedule is variable and may depend on a patient's age and underlying risk. In a patient aged 65 and older or in a younger patient with risk, the ideal option is to immunize with PCV13 first, or currently in the United States, PCV15 or PCV20 as they are conjugate vaccines. Immunogenicity studies evaluating responses to PCV13 and PPSV23 administered in series showed an improved immune response when PCV13 was administered first.[23] If PCV13 or 15 is used, it is then followed by PPSV23, the polysaccharide vaccine. The Canadian guidelines suggest that an eight-week interval is sufficient, while ACIP suggests a one-year interval. If PPSV23 has been administered, guidelines in both countries recommend waiting one year before the administration of PCV13.

Pneumococcal Vaccines: Canadian Guidelines Recommendations

It is important to understand the level of recommendation that NACI assigns to any given statement. A strong recommendation applies to most populations/individuals and should be adhered to unless a clear and compelling rationale for an alternative approach is present. A discretionary recommendation may be offered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

NACI recommends that the pneumococcal conjugate vaccine, PCV20, be offered to pneumococcal vaccine-naïve adults aged 65 and older, and individuals 50-64 years of age with risk factors that place them at higher risk for contracting pneumococcal disease. As well, individuals 18-49 years of age with immunocompromising conditions should be vaccinated. This was a strong NACI recommendation. NACI had a discretionary recommendation for these same cohorts, offering PCV15 as an alternative to PCV20 if needed, but followed by PPSV23, similar to the ACIP recommendation.

NACI recommends that PCV20 be offered to adults 65 and older if they have previously been immunized with PPSV23 alone or, if they have received the series of PCV13 followed by PPSV23 more than five years prior. Once again, this is a strong recommendation. If adults aged 65 and older have received PCV13 alone, they should be reimmunized with PCV20 as early as within one year. This

is a discretionary recommendation.

NACI supports the continued use of PCV13 and PPSV23 in adults only when PCV15 and/or PCV20 are unavailable or inaccessible.

Currently, there are no public health level recommendations on the use of PCV15 or PCV20 in adults 18-49 years of age with non-immunocompromising risk factors that place them at high risk of IPD, as additional analyses on the cost-effectiveness of conjugate PCV15 and PCV20 in this population are needed. PCV15 or PCV20 may be considered for these adults at the clinician's discretion.[24]

Shingles Vaccine

The incidence of herpes zoster, commonly known as shingles, along with the incidence of postherpetic neuralgia, interference with daily activities and hospitalizations, increases with age. To prevent herpes zoster and its complications, the FDA and Health Canada have approved two vaccines for use in individuals over the age of 50: The live virus vaccine (Zostavax®II [Live Zoster Vaccine, LZV]) which has been on the market since 2011, and the newer recombinant vaccine (RZV or Shingrix®) which came to market in 2017. The ACIP has advised that adults > 50 years of age should be immunized regardless of history of shingles, and regardless of whether or not they were previously immunized with the LZV vaccine.[25] The clinical study of the herpes zoster subunit vaccine (RZV) conducted in older adults revealed excellent efficacy of >97% in all age groups. For this reason, this vaccine is has now become the vaccine of choice for herpes zoster. NACI states that while 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. RSV is becoming the standard of care. LZV may be used if RZV is unavailable or contraindicated.[26]

Tetanus (Td) and Tdap Vaccines

A one-time dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) booster (rather than the decennial dose of Td) is recommended for adults who have not previously received Tdap. In 2001, the FDA expanded the age indication for Tdap to include those >65 years of age. Tdap may be administered regardless of the interval since the last tetanus or diphtheria-toxoid vaccine. A single dose of Tdap is recommended for practitioners with direct patient care contact who have not received the vaccine as an adult, and for persons >65 years of age who have or anticipate close contact with an infant less than 1 year old to reduce the transmission of pertussis (e.g., adults who have recently become grandparents) Booster doses of Td vaccine continue to be recommended every 10 years.[27]

COVID-19 Vaccines

Three coronavirus (COVID-19) vaccines are currently authorized for use in the United States. The FDA issued Emergency Use Authorization (EUA) 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] The Advisory Committee on Immunization Practices issued interim recommendations for the Pfizer-BioNTech and Moderna COVID-19 vaccines on December 12, 2020,[29] and December 19, 2020.[30] Both of these vaccines, known as mRNA vaccines, are approved by Health Canada and are being administered in Canada.[31]

The Johnson & Johnson/Janssen (J&J/Janssen) vaccine, the third vaccine approved in the United States, was temporarily paused due to concerns of rare blood clots. On April 23, 2021, the CDC and FDA recommended that use of the J&J/Janssen COVID-19 vaccine be resumed in the United States. However, women < 50 years of age should be aware of the rare risk of blood clots with low platelets that can occur post-vaccination. However, these occurrences are extremely rare and are thought to be related to an abnormal reaction of platelets, similar to heparin-induced blood clots. According to the American Society of Hematology, the term now being used to describe these rare events is vaccine-induced immune thrombotic thrombocytopenia (VITT). Its diagnosis is based on four criteria, all of which must be met. These include the administration of the COVID-19 vaccine (Johnson & Johnson and AstraZeneca (AZ) 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.[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 as different implementation guidelines exist in various parts of the country.

According to Thrombosis Canada, a well-respected national guidelines body for thrombosis and the use of anticoagulants, the risk of a significant blood clot with the AZ vaccine is four per one million. By comparison, the risk with the use of birth control pills is 900 per one million. The average Canadian has a thrombosis risk of 1,290 per 1 million, and the risk in a patient hospitalized with COVID-19 is 147,000 per one million.[33] Thrombosis Canada further concludes that a history of blood clot, Factor V Leiden, or the need for ongoing anticoagulant therapies are not contraindications to receiving any of the vaccines.

It must be recognized that as new data emerges, both NACI and ACIP review and update their guidance accordingly. The Vaccine Adverse Event Reporting System (VAERS), is a national passive surveillance system in the United States that accepts reports from healthcare providers, vaccine manufacturers and the public. In

NACI Recommendation		
Population by age	**Primary series**	**Booster dose(s) per recommended interval if not already received**
Adults ≥ 65 years	**Should be** offered	• **At least one** booster dose is recommeneded • **Regardless of previous booster** doses a booster since the start of fall 2022 **should be offered**
Adults 18–64 years	**Should be** offered	**High-risk population** • **At least one** booster dose is recommeneded • **Regardless of previous booster** doses a booster since the start of fall 2022 **should be offered** **Not High-risk population** • **At least one** booster dose is recommeneded • **Regardless of previous booster** doses a booster since the start of fall 2022 **may be offered**
Adolecents 12–17 years	**Should be** offered	**High-risk population** • **At least one** booster dose is recommeneded • **Regardless of previous booster** doses a booster since the start of fall 2022 **should be offered** **Not High-risk population** • **A booster** since the start of fall 2022 **may be offered**
Children 5–11 years	**Should be** offered	**High-risk population** • **A booster** since the start of fall 2022 **should be offered** **Not High-risk population** • **A booster** since the start of fall 2022 **may be offered**
Children 6 months to < 5 years	**May be** offered	No authorized product; not recommended

Figure 1: NACI Guidance on COVID-19 Vaccine Booster Doses (Initial Considerations for 2023)

addition, a safety monitoring system has been established by the CDC specifically for the COVID-19 vaccination program. VAERS reporting has shown extremely reassuring data. Both mRNA vaccines have excellent safety profiles.[27] VAERS has not detected patterns in cause of death that would indicate a safety issue relating to the COVID-19 vaccines.[27]

The current guideline for COVID-19 vaccination, focusing on booster doses, appears in **Figure 1**.

Beginning in the spring of 2023, NACI recommends that an additional booster dose may be offered per the recommended interval to the following individuals who are at increased risk of severe illness:

- Adults 80 years of age and older
- Adult residents of long-term care homes and others in congregate senior living settings, or those with complex medical care need
- Adults 18 years of age and older who are moderately to severely immunocompromised (due to an underlying condition or treatment)
- Adults 65 to 79 years of age, particularly if they do not have a known prior history of SARS-CoV-2 infection
- Individuals who have not previously received recommended doses, including a primary series or Fall 2022 booster dose, are now recommended to receive them[34]

Within the above, however, there are specific details that impact women. First, it is common to develop lymphadenopathy in the region where one has received vaccine, such as the axilla. This has the potential to be read as abnormal in a subsequent mammogram. Therefore, the Society of Breast Imaging suggests conducting routine mammograms before being vaccinated for COVID-19 or waiting four-to-six weeks after the second dose prior to having a mammogram.[35] Lymphadenopathy was noted at 11.6% for the Moderna vaccine vs 5% for placebo. Reported numbers were lower for the Pfizer vaccine; however, unilateral adenopathy revealed in a mammogram is clearly a concern and would warrant assessment, if it was other than reactive.

In general, women tend to experience a greater number of side effects from the vaccines than men, though it is not clear if this is at least partially due to reporting bias. Common side effects include headache, fatigue and dizziness. Anaphylaxis is extremely rare but has been seen more commonly in women than in men.[36]. Biologically, women produce a greater number of antibodies following

flu shots, vaccines for measles, mumps and rubella, and hepatitis A and B. Males and females differ in their immunological responses to foreign and self-antigens and show distinctions in innate and adaptive immune responses. Certain immunological sex differences are present throughout life, whereas others become apparent only 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.[37]

Finally, pregnancy has been shown to be associated with a disproportionate risk with respect to COVID-19 infection severity. Severe illness includes illness that results in intensive care admission, mechanical ventilation, or death. Additionally, pregnant women with COVID-19 might be at increased risk of adverse pregnancy outcomes, such as preterm birth, compared with pregnant women without COVID-19.[38] According to the Canadian Society of Obstetricians and Gynecologists (SOGC) and the CDC, while studies have not been completed on pregnant women, given the risk for greater severity of disease and greater risk overall, this cohort of women should be immunized against COVID-19. The SOGC states specifically that all COVID-19 vaccines approved in Canada can be administered in any trimester of pregnancy and during breastfeeding.[39]

Discussion

Patients often seek medical attention in midlife, recognizing that many changes in their physiology that require attention. This is a time to discuss various disease prevention strategies, including immunization. There is significant discussion about barriers to vaccination, as well as hesitancy in the lay press and among clinicians. In Canada, physicians consider financial expense as the chief barrier for patient acceptance of vaccination; it has been rated as the primary concern by 92%-95% of physicians. Perceived barriers of cost may limit recommendations for vaccination, particularly among older women and men.[40] For patients however, the number one reported barrier to vaccination was not having a recommendation from a physician. Cost was seen as a barrier by only 18% (male) and 20% (female) of study participants.[41] Given the importance of immunization and the need to decrease the prevalence of vaccine-preventable diseases, it is our obligation to recommend vaccines, ensuring that patients understand the guidelines and risks, not only of the vaccine but of not being vaccinated for a given disease, and the impact to them personally and to their community. In light of our aging population, this is the ideal time in a patient's life to employ healthy, preventive measures. Our objective is to help make this time of life one of good health, independence, and freedom from vaccine-preventable illness.

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