Review Article

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Prophylactic vaccination strategies for adult patients with diabetes: a narrative review of safety profiles and clinical effectiveness

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This narrative review analyzed roles of several prophylactic vaccinations in adult patients with diabetes, focusing on their safety profiles and clinical effectiveness. Individuals with diabetes mellitus are at increased risk for infections, making vaccination a critical component of their healthcare. The review assessed various vaccines that are particularly relevant for this population, i.e., vaccines for pneumococcus, meningococcus, severe acute respiratory syndrome coronavirus 2, influenza, herpes zoster, human papillomavirus, and dengue. It highlighted the safety profiles and clinical effectiveness of these vaccines in preventing serious infections and improving long-term health outcomes in diabetic patients. Taken together, this review emphasized the importance of prophylactic vaccinations in reducing infection-related morbidity and mortality as well as encouraged fostering greater adoption and advocacy for immunization programs among diabetic adults.

Keywords: Diabetes mellitus; Adults; Vaccination; Safety; Clinical benefits

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose concentrations (i.e., hyperglycemia) due to insufficient secretion of insulin (i.e., type 1 diabetes) and/or tissue resistance to the activity of insulin to transfer glucose into muscle and adipose tissue (i.e., type 2 diabetes) [1,2]. With its rapidly rising incidence, diabetes has emerged as one of the top 10 causes of global mortality [3-5]. This is observed among Indonesians as well, where the number of diabetes cases is projected to increase from 18.7 million in 2020 to 40.7 million cases in 2045. Likewise, the mortality rate is projected to double from 433,752 in 2020 to 944,468 cases in 2045 [6].

The management of diabetes is performed through control of hyperglycemia, by commonly targeting concentrations of hemoglobin A_{1c} at <7% (53 mmol/mol) for

diabetes-confirmed individual or <6.5% (47.5 mmol/mol) for prediabetes-confirmed individual [7,8]. The strategy in controlling hyperglycemia includes promoting healthy behaviors (through medical nutrition therapy, physical activity, weight management, tobacco/substance abuse counseling, life style changes and psychological support) as well as using pharmacological treatments (insulin, metformin, glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter 2 inhibitors, gastric inhibitory polypeptide, dipeptidyl peptidase 4 inhibitors, thiazolidinediones and the 2nd generation of sulfonylurea) [7].

As shown in **Fig. 1**, diabetic patients with poorly controlled hyperglycemia are indeed at higher risks for a range of complications that significantly contribute to the disease's high mortality rate [9]. Notably, those patients have an increased susceptibility to infections caused by bacteria, viruses, or even fungi (**Table 1**), due to impaired immune system regulation [10-12]. Educating diabetic patients to routinely practice public health measurements (e.g., proper hand washing and wound management) will thus reduce the risk of infections. Furthermore, vaccination as the cornerstone of public health policy should be widely used by diabetic patients in preventing infections and/or attenuating related morbidities and mortalities [13]. Indeed, it was estimated that prior to the pandemic of coronavirus disease 2019 (COVID-19), vaccination efforts targeting 10 pathogens across 112 countries will prevent 97 million deaths from 2000 to 2030. Of this total, 50 million deaths were projected to be averted through vaccination activities between 2000 and 2019 [14].

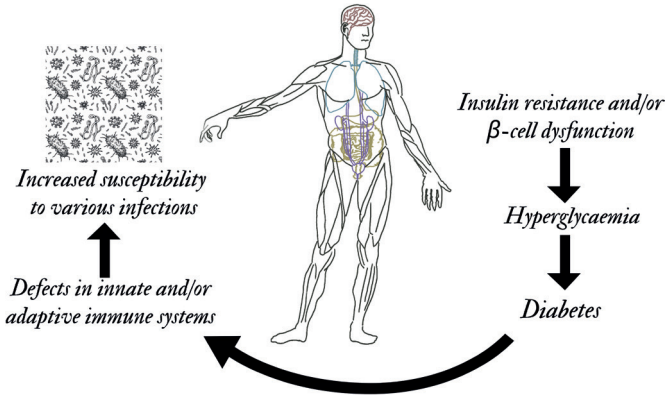

Fig. 1. A schematic drawing on association between diabetes and infection. Diabetes with a hallmark of hyperglycaemia is caused by b-cell dysfunction (i.e., type 1 diabetes) and/or insulin resistance (i.e., type 2 diabetes). Hyperglycaemia negatively influences the immune response, causing defects in innate and/or adaptive immune systems. This results in higher risks to contract infections by various pathogens (including bacteria, viruses or fungi) among diabetic individuals.

A vaccine is a biological product designed to safely stimulate the immune system in providing protection against infection or disease upon subsequent exposure to a pathogen, in which it contains antigen(s) from the pathogen or its synthetic analog, which is able to trigger immune responses that confer protection [13]. Various technology platforms have been used to formulate the relevant antigens used in licensed vaccines thus far, including traditional methods (e.g., live-attenuated, inactivated, subunit, and conjugate vaccines) and novel methods (e.g., viral vector, virus-like particle, and nucleic acid-based vaccines) [13,15].

Briefly, a live-attenuated vaccine is a weakened form of the pathogen, hence unable to cause harmful infection but still can generate a robust immune response. Examples of licensed vaccines using this platform include vaccines for smallpox, measles, mumps, rubella, yellow fever, influenza, polio (oral poliovirus vaccine), Japanese encephalitis, rotavirus, varicella zoster, as well as tuberculosis (bacille Calmette-Guerin vaccine) [13,15]. An inactivated vaccine utilizes a completely non-infectious pathogen, which has been rendered inert by using heat or chemical yet retains its antigenic properties. Examples of it include vaccines for pertussis (whole-cell), polio (inactivated poliovirus vaccine), influenza, Japanese encephalitis, hepatitis A and rabies [13,15]. A subunit vaccine consists of a partial component (recombinant protein or polysaccharide) of the pathogen that can elicit a specific immune response, in which its examples are vaccines for hepatitis B, human papillomavirus (HPV), pertussis (acellular pertussis vaccine), meningococcal B and *Streptococcus pneumococcus* infections [13,15]. Certain vaccines are also based on formaldehyde-inactivated bacterial toxins (toxoid vaccines), including the ones for diphtheria and tetanus [13,15]. In addition, as a polysaccharide-based vaccine does not generate a robust immune response, a polysaccharide is conjugated with a certain inactivated toxin (as a carrier protein) to create a conjugate vaccine as it is more immunogenic. Examples of conjugate vaccine are vaccines for *Haemophilus influenzae* type B, *Streptococcus pneumoniae* and *Neisseria meningitidis* [13, 15].

Next, a viral vector vaccine employs a distinct, harmless virus as the vehicle for expressing the antigenic component of the virus of interest. Examples of its licensed vaccines are vaccines for Ebola and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [13,15]. A virus-like particle vaccine is a type of subunit vaccine based on virus-derived proteins, which are assembled to form a particle. Its examples are vaccines for hepatitis B virus and HPV [13,15]. Finally, a nucleic acid-based vaccine consists of either target antigen-encoding deoxyribonucleic acid (DNA) or

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Table 1. Various infections found in diabetic patients

Pathogen	Disease(s)	Vaccine availability (Yes/No)	Recommended for diabetic patients*
Bacteria			
Bordetella pertussis	Pertussis	Yes, as Diphteria-Tetanus-Pertussis vaccine or Tetanus-Pertussis booster vaccine	Yes
Clostridium tetani	Tetanus		Yes
Corynebacterium diphtheriae	Diphtheria		Yes
Haemophilus influenzae type B	Invasive Hib diseases, including meningitis	Yes	Maybe
Mycobacterium tuberculosis	Tuberculosis	Yes	Yes
Neisseria meningitidis	Invasive meningococcal diseases, including meningitis	Yes	Maybe
Streptococcus pneumoniae	Invasive pneumococcal diseases, including pneumonia and meningitis	Yes	Yes
Viruses			
Dengue virus	Dengue	Yes	No, recommendation yet
Hepatitis virus A	Hepatitis A	Yes	Maybe
Hepatitis virus B	Hepatitis B	Yes	Yes
Hepatitis virus C	Hepatitis C	No	Not available
Human immunodeficiency virus	HIV infection and acquired immunodeficiency syndrome	No	Not available
Human papillomavirus	Epithelial cancers	Yes	Yes
Influenza virus A	Influenza	Yes	Yes
Influenza virus B	Influenza	Yes	Yes
Respiratory syncytial virus	Bronchiolitis	Yes	Yes
Severe acute respiratory syndrome coronavirus 2	Coronavirus disease 2019	Yes	Yes
Varicella-zoster virus	Varicella and herpes soster/Shingles	Yes	Yes, for shingles (maybe for varicella)
Fungi			
Aspergillus species	Aspergillosis	No	Not available
Candida species	Candidiasis	No	Not available
Mucormycetes	Mucormycosis	No	Not available

HIV, human immunodeficiency virus.
*It is constructed based on recommendations from American Diabetes Association (https://diabetes.org/about-diabetes/vaccinations), National Foundation for Infectious Diseases (https://www.nfid.org/immunization/vaccines-and-diabetes/), and Immunize.org (https://www.immunize.org/).

messenger ribonucleic acid (mRNA), which facilitates the induction of specific adaptive immune responses once the encoded antigen(s) is expressed following the uptake of nucleic acid by cells. A current example of it is vaccines for SARS-CoV-2 and respiratory syncytial virus [13,15].

This narrative review was therefore written to describe several vaccines for infectious diseases commonly found among adult patients with diabetes, particularly on bacterial and viral infections (**Table 2**). It assessed technology platforms, safety profiles, as well as clinical efficacies of those vaccines in protecting diabetic patients from certain infectious diseases. Despite diabetic patients are at higher risk to contract fungal infections, fungal infection was not discussed in this review as no vaccine is available thus far. Furthermore, we focused on several bacterial infections (i.e., *S. pneumoniae* as well as *N. meningitidis*) and viral infections (i.e., of SARS-CoV-2, influenza virus, varicella-zoster virus [VZV], HPV, and dengue virus [DENV]) due to the high incidences of the inflicted diseases among diabetic adults as well as the availability of effective, prophylactic vaccines. Of note, certain diseases were excluded (e.g., tetanus, diphtheria, pertussis, and hepatitis B) because the respective prophylactic vaccines are included in the national immunization program for children worldwide.

VACCINES AGAINST BACTERIAL INFECTIONS

Invasive pneumococcal diseases due to *S. pneumoniae* infection

S. pneumoniae (pneumococcus) is a fastidious, facultative anaerobic, encapsulated, Gram-positive bacterium belonging to a family of *Streptococcaceae*, which is a commensal residing in the mucosal surfaces of the human upper respiratory tract [16,17]. Although it is an opportunistic pathogen,

Table 2. Prophylactic vaccines for several pathogens commonly infecting adult diabetic patients

Pathogen	Vaccine platform	Example of licensed vaccine
Streptococcus pneumoniae	Pneumococcal polysaccharide vaccine	PPSV23
	Pneumococcal conjugate vaccine	PCV7, PCV10, PCV13, PCV15, PCV20, PCV21
Neisseria meningitidis	Meningococcal polysaccharide vaccines	MPSV bivalent (*A-C*), MPSV trivalent (*A-C-W-135*), MPSV tetravalent (*A -C-W-135-Y*)
	Meningococcal conjugate vaccine	MenA-TT, MenC-CRM_{197}, MenC-TT, MenACWY-D, MenACWY-CRM_{197}, MenACWY-TT
	Meningococcal protein vaccines for serogroup B	VA-MENGOC-BC, MenBvac, MeNZB, 4CMenB, MenB-FHbp
Severe acute respiratory syndrome Coronavirus 2	Inactivated vaccine	BBIBP-CorV, BBV152, CoronaVac, CoviVac,
	Recombinant protein vaccine	NVX-CoV2373, ZF2001
	Adenovirus-based viral vector vaccine	ChAdOx1, Ad26.COV2.S, Sputnik V, Ad5-nCoV
	mRNA vaccine	BNT162b2, mRNA-1273
Influenza viruses A and B	Live-attenuated vaccine	Trivalent, Tetravalent
	Inactivated vaccine	Embryonated chicken egg-based (trivalent or tetravalent), Recombinant (trivalent)
Varicella-zoster virus	Live-attenuated varicella-zoster vaccine	Zoster vaccine live
	Adjuvanted varicella-zoster glycoprotein E subunit vaccine	Recombinant zoster vaccine
HPV	Virus-like particle vaccine	Bivalent (*HPV16-HPV18*), Quadrivalent (*HPV6-HPV11-HPV16-HPV18*), Nonavalent (*HPV6-HPV11-HPV16-HPV18-HPV31-HPV33-HPV45-HPV52-HPV58*)
Dengue virus	Live-attenuated vaccine	CYD-TDV, TAK-003

mRNA, messenger ribonucleic acid; HPV, human papillomavirus.

S. pneumoniae is the leading bacterial cause of various infections, including otitis media, sepsis, meningitis, as well as community-acquired pneumonia (also known as pneumococcal pneumonia) [17]. The capsular polysaccharide of *S. pneumoniae* is considered the main virulence factor and is utilized to classify the bacterium into more than 100 serotypes thus far [18]. In adults, serotypes 3, 6A, 9N, 11A, 16F, 19A, and 19F are associated with high prevalence of case fatality rate [18]. It is important to note that natural-acquired immunity to pneumococcal capsular polysaccharide develops during childhood, strengthens in young adulthood, but declines in the elderly [18], suggesting that older adults and adults with chronic medical conditions, particularly immunodeficiencies, are at higher risk to be infected with *S. pneumoniae*.

The pneumococcal vaccine was initially developed by using the purified capsular polysaccharide antigens, called pneumococcal polysaccharide vaccine (PPSV) [18]. An example of it is PPSV23 as it uses antigens from 23 serotypes. As polysaccharide is a T cell-independent antigen, however, the PPSV only activates B cells (generating less powerful antibodies) without immunological memory and it is poorly immunogenic in young children [13,18]. The subsequent development of pneumococcal vaccine was by conjugating polysaccharide antigen with carrier protein (i.e., tetanus toxoid, diphtheria toxoid, or diphtheria protein cross-reactive material 197), called pneumococcal conjugate vaccine (PCV), to activate both B and T cells; hence it is highly immunogenic and can create an immunological memory [13]. Several examples of PCV are PCV7, PCV10, PCV13, PCV15, PCV20 and PCV21, based on numbers of serotypes used in the respective vaccines [18,19].

Of note, PPSV23 as well as PCV13, PCV15, PCV20 and PCV21 are licensed for adults [18-20]. While PPSV23 is administered 1–3 doses via intramuscular or subcutaneous, PCV13, PCV15 and PCV20 are administered as a single dose, respectively, via intramuscular [19,20]. A recent meta-analysis in adults living in industrialized countries reported that the pooled PPSV23 effectiveness was 45% against PPSV23-type invasive pneumococcal disease and 18% against PPSV23-type pneumococcal pneumonia, while one randomized clinical trial on PCV13 administration in community-dwelling Dutch adults ≥65 years old reported the vaccine efficacy of 75% against PCV13-type invasive pneumococcal disease and 45% against PCV13-type pneumococcal pneumonia [21,22]. These findings suggested that while vaccine efficacy of PCV13 was relatively higher than PPSV23, both PPSV23 and PCV13 are effective against vaccine type-invasive pneumococcal disease and pneumococcal pneumonia in adults. Nonetheless, as PPSV23 contains more serotypes than PCV13, it is of interest to use both vaccines in broadening the protection. Impacts of sequential vaccination using both PPSV23 and PCV13 had been studied, of which a schedule of initial PCV13 followed by PPSV23 (with an interval of 1 year) was better than a schedule of initial PPSV23 followed by PCV13 in generating

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anti-pneumococcal humoral immunity among pneumococcal vaccine-naïve adults 60–64 years old [23]. In addition, the sequential administration of PCV13-PPSV23 was associated with a lower incidence of cardiovascular disease, as compared to the individual administration of either PCV13 or PPSV23 [24]. Therefore, the Advisory Committee on Immunization Practices (ACIP) initially recommended a sequential administration of a dose of PCV13 followed by 1–3 doses of PPSV23 (with an interval of ≥12 months between PCV13 and PPSV23 vaccination) for persons aged ≥2 years who are at high risk for pneumococcal disease because of underlying medical conditions as well as all adults aged ≥65 years who have not previously received pneumococcal vaccine [20].

Next, as PCV15, PCV20, and PCV21 vaccines were recently introduced, hence their vaccine efficacy data are not yet available although they were reported to be immunogenic [19,20]. Nonetheless, in order to generate a broader pneumococcus-specific immune response, the ACIP recommendations in 2023 specified the administration of either PCV20 alone or PCV15 followed by PPSV23 for all adults aged 65 and older, as well as for adults aged 19–64 with specific underlying medical conditions (e.g., diabetes) or an unknown vaccination history [20]. The ACIP also recommended the administration of either a single dose of PCV20 or ≥1 dose of PPSV23 for adults who began their pneumococcal vaccination with PCV13 but have not completed the recommended PPSV23 doses [20]. In addition, the ACIP recommended PCV21 as an option for adults aged ≥19 years who are currently recommended to receive a dose of PCV [19]. Importantly, post-licensure safety reviews of PPSV23, PCV13, and PCV20, along with safety data from clinical trials on PCV15 and PCV21, revealed no significant new safety issues. The common adverse events included injection site reactions, fatigue and muscle pain, in which the rates of serious adverse events were comparable across the pneumococcal vaccines, with no new or unexpected adverse events been identified [19,20].

Diabetic patients are at an increased risk of contracting pneumonia and often have severe outcomes (i.e., bacteremia, cardiac complications, sepsis, and septic shock) and increased mortality rates [25]. A recent systematic review indeed reported that diabetic patients had higher risks to contract pneumococcal pneumonia (unadjusted odds ratio [OR], 2.98), invasive pneumococcal disease (unadjusted OR, 2.42) and intensive care unit admission for pneumococcal disease (unadjusted OR, 2.09), as compared to healthy individuals [26]. Prophylactic pneumococcal vaccines were therefore highly recommended for diabetic patients [25]. The vaccine efficacy data of PPSV23 and PCV13 are available for diabetic patients, in which a meta-analysis on PPSV23 administration reported that this vaccine's administration was associated with a lower risk of hospitalization or death in adults with diabetes [27], while a post-hoc analysis of the Community-Acquired Pneumonia Immunization Trial in Adults study reported that vaccine efficacy of PCV13 was significantly higher among diabetic elder subjects compared to the ones without diabetes [28]. These findings were confirmed by a meta-analysis on PPSV23 and PCV13 administration in diabetic patients, in which no significant difference was observed between efficacies of PPSV23 and PCV13 [26]. No particular studies assessing safety of pneumococcal vaccination among diabetic elder patients could be found thus far. Nonetheless, its safety profiles were supported by findings in adults aged ≥65 years old in the United States and in in adults with immune-mediated inflammatory diseases in the United Kingdom, reporting no increased rate of adverse events following PPSV23 or PCV13 administration [29,30].

Invasive meningococcal diseases due to *N. meningitidis* infection

N. meningitidis (meningococcus) is a fastidious, aerobic, gram-negative diplococcus belonging to the family of *Neisseriaceae*, which can be found in the nasopharynx-oropharynx of healthy individuals [31,32]. Most clinically important strains of *N. meningitidis* are encapsulated, in which the capsular polysaccharides (i.e., A, B, C, E-29, H, I, K, L, W-135, X, Y, Z, and Z'/29E) are used to classify various *N. meningitidis* into at least 13 serogroups [32]. Thus far, 6 serogroups of *N. meningitidis* have been identified to cause life-threatening disease (i.e., A, B, C, W-135, X, and Y) [32]. The virulence mechanisms of *N. meningitidis* are influenced by the expression of capsular polysaccharides, expression of surface adhesive proteins (i.e., pili, porin proteins PorA and B, as well as adhesion molecules Opa and Opc), mechanism of iron sequestration and presence of lipopolysaccharide [31,32]. *N. meningitidis* spreads via aerosol and temporarily colonizes the upper respiratory tract, from which it can translocate to the lower respiratory tract (causing meningococcal pneumonia) or it can enter the blood stream (causing septicemia) and infect the meninges (causing meningococcal meningitis) and other tissues [31,32].

Similar to pneumococcal vaccine, the meningococcal vaccine was developed by using the purified capsular polysaccharide antigens from serogroup A, C, W-135 or Y, either as bivalent (A and C), trivalent (A, C and W-135) or tetravalent (A, C, W-135, and Y) vaccine [33]. The meningococcal polysaccharide vaccines generated short-term immune protection, however, and could not induce the specific immune memory [34]. Thus, meningococcal conjugate vaccine was

developed against *N. meningitidis* by conjugating the polysaccharide antigen with carrier protein, i.e., tetanus toxoid (TT), diphtheria toxoid (D) or diphtheria protein cross-reactive material 197 (CRM_{197}) [34]. Initially, the monovalent conjugate vaccines were developed against meningococcus serogroup A (e.g., MenA-TT) or C (e.g., MenC-CRM_{197} or MenC-TT) [34]. In order to confer protection towards multiple serogroups, the quadrivalent conjugate vaccines were subsequently developed against meningococcus serogroups A, C, W-135 and Y, including MenACWY-D, MenACWY-$CRM_{197,}$ and MenACWY-TT vaccines [34].

Of note, no polysaccharide vaccine exists for the serogroup B because its polysaccharide is poorly immunogenic and can potentially cause autoimmune reactions due to its similarity to polysialic acid expressed by many cells [35]. The vaccines for *N. meningitidis* serogroup B were developed based on its protein antigens instead, including (i) the outer membrane protein porin A (used in the outer membrane vesicles-based vaccines, e.g., VA-MENGOC-BC, MenBvac, MeNZB); (ii) a mixture of outer membrane protein porin PorA, Neisserial heparin binding antigen, human factor H binding protein and Neisseria adhesin A (used in the 4CMenB vaccine); as well as (iii) the lipidated recombinant human factor H binding protein (used in the MenB-FHbp vaccine) [34]. Importantly, as these meningococcal protein vaccines contain antigens that are also expressed by various serogroups of *N. meningitidis*, these vaccines can plausibly generate a cross-immunity [34].

The Food and Drug Administration (FDA) in the United States currently recommends three types of meningococcal vaccine for adults at risk (e.g., the annual Hajj pilgrims due to the crowded living conditions), including (i) the quadrivalent meningococcal conjugate vaccines for the serogroups A, C, W-135 and Y (i.e., MenACWY-CRM_{197} and MenACWY-TT), (ii) the subunit protein-based meningococcal vaccine for the serogroup B (i.e., 4CMenB and MenB-FHbp), as well as (iii) the pentavalent meningococcal vaccine for the serogroups A, B, C, W-135 and Y (i.e., a combination of MenACWY-TT and MenB-FHbp) [36,37]. While the quadrivalent vaccines were administered as a single dose intramuscularly in adults, the MenB and pentavalent vaccines were at least administered as two doses (with an interval of 6 months) intramuscularly in adults [36]. The MenACWY-CRM_{197} vaccine was reported to be immunogenic upon a single dose administration in healthy adults aged 19–55 years old [38]. Furthermore, administration of a single dose of MenACWY-CRM_{197} among university students aged 18–24 years in the United Kingdom reported a reduction of meningococcal carriage rates during the first 12 months post vaccination [39]. This finding was partly supported by the administration of MenACWY-CRM_{197} among the Republic of Korea Armed Forces, reported that the vaccinated persons had reduced rates of meningococcal disease and related mortality cases, as compared to the unvaccinated persons [40]. A review on various studies assessing immunogenicity of MenACWY-TT reported that the MenACWY-TT was immunogenic across age groups, hence supporting its usage in adults [41]. Next, administration of 2 doses of 4CMenB among university students aged 18–24 years in the United Kingdom was associated with a reduction of meningococcal carriage rates during the first 12 months post vaccination [39]. A study assessing the immunogenicity of MenB-FHbp in adolescents and young adults from the United States, Canada, Denmark, Finland, Poland and Spain reported a ≥4-fold rise in the serum bactericidal antibody assay with human complement against diverse meningococcal B strains after the second and third dose of the vaccine in majority of study participants, supporting its immunogenicity against the serogroup B [42]. Finally, a review on several studies assessing 2 doses of pentavalent meningococcal vaccine (MenACWY-TT/MenB-FHbp), as compared to the control (i.e., 1 dose of MenACWY-CRM and 2 doses of MenB-FHbp), reported that the MenACWY-TT/MenB-FHbp vaccine could generate humoral immunity against serogroups A, B, C, W-135 and Y, relatively better than the control, which was detected after 1 and 48 months upon the vaccination [37]. Of note, the duration of protective humoral immunity generated by quadrivalent and subunit protein meningococcal vaccines were relatively short (i.e., within 5 and 1–2 years, respectively), indicating a necessity to routinely provide booster vaccination to adults at risk [36].

The safety profiles of those meningococcal vaccines have been well documented. The MenACWY-CRM was well tolerated in adults 19 to 55 years old, with the common adverse event was pain at the injection's site [38]. Similarly, the MenACWY-TT was well tolerated in adults as well [41]. No serious adverse events were related to the quadrivalent meningococcal vaccines [38,41]. The subunit protein meningococcal vaccines (4CMenB and MenB-FHbp) also demonstrated a favorable safety profile, in which both vaccines could generate mild local inflammation, fatigue, headache, myalgia and nausea. Notably, while a higher incidence of fever was reported in children who received MenB-FHbp, no severe adverse events were related to the subunit protein meningococcal serogroup B vaccines [34]. Similarly, the administration of pentavalent meningococcal vaccine was not associated with severe adverse events, in which its common adverse events were injection site pain, fatigue and headache [37].

Of note, adults with diabetes had a two-fold higher risk of contracting community-acquired adult bacterial meningitis,

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either caused by *S. pneumoniae*, *Listeria monocytogenes* or *N. meningitidis* [43-45]. Intriguingly, in contrast to *S. pneumoniae* and *Listeria monocytogenes* infections, bacterial meningitis due to *N. meningitidis* infection was less prevalent among diabetic patients [43,44]. Nonetheless, a less prevalence does not mean no incidence, particularly for older adults with diabetes [43-45]. Thus, administering meningococcal vaccines, in addition to pneumococcal vaccines, to diabetic patients would provide a better protection against community-acquired adult bacterial meningitis. However, lack of reports on the effectiveness and safety of these polysaccharide conjugate and protein-based meningococcal vaccines among diabetic patients obstruct the wide-implementation of meningococcal vaccines among this at-risk-group [46]. These concerns could be partially addressed, nonetheless, due to the effectiveness and safety of meningococcal conjugate vaccines among adults [38,47].

VACCINES AGAINST VIRAL INFECTIONS

COVID-19 due to SARS-CoV-2 infection

SARS-CoV-2 virus is an enveloped, positive-sense, single-stranded RNA virus that belongs to the genus of *Betacoronavirus* [48]. The zoonotic emergence of the SARS-CoV-2 virus has triggered a global pandemic of COVID-19 for more than 3 years [48]. Worldwide, 776 million cases have been reported, leading to over 7 million deaths thus far [49]. The virus spreads through respiratory fluid excretion, initially infecting the upper respiratory tract and disseminating to the lungs [48]. In the early phase of COVID-19 (mild COVID-19), the virus mainly infected bronchial epithelial cells, type I and II alveolar pneumocytes, as well as capillary endothelial cells, causing an inflammatory response. The inflammation however could persist into the later phase of COVID-19 (severe COVID-19), resulting in alveolar interstitial thickening, increased vascular permeability, edema, excess myeloid cell recruitment, blood clots and tissue damage [50-52]. The risk factors for developing severe COVID-19 included age, hypertension, obesity, chronic kidney disease and diabetes [48,50,52,53].

It is important to appreciate that without the swift development of various vaccines against SARS-CoV-2 as well as the mass vaccination worldwide, the SARS-CoV-2 infection could cause higher numbers of severe COVID-19 and mortality globally [54,55]. Various SARS-CoV-2 vaccines have been approved by 2023, including platforms of inactivated vaccine (e.g., BBIBP-CorV, BBV152, CoronaVac, and CoviVac), recombinant protein vaccine (e.g., NVX-CoV2373 and ZF2001), adenovirus-based viral vector vaccine (e.g., ChAdOx1, Ad26.COV2.S, Sputnik V, and Ad5-nCoV), as well as mRNA vaccine (e.g., BNT162b2 and mRNA-1273) [56]. Those vaccines were administered via intramuscular injection, with the primary dosage ranged from one to three doses [56]. A recent Cochrane systematic review had reported that, as compared to placebo, several COVID-19 vaccines (i.e., BNT162b2, mRNA-1273, ChAdOx1, Ad26.COV2.S, BBIBP-Cor, and BBV152) had high-certainty evidence in reducing the proportion of participants with confirmed symptomatic COVID-19 [57]. It also reported high-certainty evidence that administration of BNT162b2, mRNA-1273, Ad26.COV2.S, and BBV152 vaccine largely reduced incidences of severe COVID-19 compared to placebo [57]. Importantly, there was probably little or no difference between most COVID-19 vaccines and placebo in causing serious adverse events, although the evidence was uncertain for BNT162b2, CoronaVac, BBIBP-CorV, and NVX-CoV2373 because of the low numbers of reported events [57]. Taken together, it appeared that the mRNA and viral vector-based vaccines would generate strong protection against symptomatic SARS-CoV-2 infection or severe COVID-19.

As diabetes was closely associated with a poorer prognosis upon SARS-CoV-2 infection [48,50,52,53,58], the diabetic patients indeed became one of the prioritized population groups to be vaccinated [59-61]. Importantly, a strong immune response following COVID-19 vaccination was observed in diabetic patients, although their SARS-CoV-2-specific immune responses were reported weaker compared to the ones observed in healthy individuals [62]. It was also reported that vaccine effectiveness was high in diabetic patients, of which the natural declining of vaccine effectiveness could be rescued by an administration of booster vaccine, particular by using mRNA vaccine [63].

The safety profiles of licensed SARS-CoV-2 vaccines were generally established for diabetic individuals, with the incidence of severe adverse events were similar from those in the general population [62]. Of note, no increase in the incidence of severe adverse event was observed for administration of inactivated vaccine (BBIBP-CorV or CoronaVac) [64,65], adenovirus-based viral vector vaccine (ChAdOx1) [66] or mRNA-based vaccine (BNT162b2) [67]. However, another study on the vaccinated population in the United States of America reported that adult patients with type 2 diabetes could experience more severe adverse events, (e.g., cerebral venous sinus thrombosis, encephalitis myelitis encephalomyelitis, Bell's palsy, lymphadenopathy, ischemic stroke, deep vein thrombosis, thrombocytopenia and pulmonary embolism), after receiving either mRNA (mRNA-1273 or BNT162b2) or adenovirus-based viral vector vaccine (JNJ-78436735) than those without diabetes

[60]. This suggested that careful monitoring against severe adverse events might be required among diabetic patients upon receiving mRNA or viral vector COVID-19 vaccine.

Influenza due to infection of influenza A and B viruses

All influenza viruses are enveloped, negative-sense, single-stranded RNA viruses with a segmented genome, which belong to the family of *Orthomyxoviridae* [68]. Two primary influenza viruses in humans are influenza A (genus of *Alphainfluenzavirus*) and influenza B (genus of *Betainfluenzavirus*) viruses, which contain eight RNA segments that encode various proteins, including haemagglutinin and neuraminidase [68]. Influenza caused by influenza A and B viruses is a contagious respiratory infection with significant global morbidity and mortality, characterized by symptoms such as fever, body aches, and cough. Influenza pathogenesis starts with viral infection of epithelial cells in the respiratory tract through droplets and aerosols from an infected person, triggering rapid inflammation and systemic symptoms like fever and myalgia, which can progress to severe complications, e.g., pneumonia and myocarditis [68,69]. This virus has caused numerous pandemics, with the greatest occurring between 1918 to 1919, with a recorded 21 million deaths worldwide [68,69]. Of note, certain risk factors, including age or diabetes as comorbidity, may exacerbate the disease progression, resulting in higher incidences of hospitalization and mortality. Taken together, preventive measurements of influenza, including administration of influenza vaccines, serves a crucial role in reducing risks of morbidity and mortality as well as in improving health outcomes for diabetic individuals [70].

Influenza vaccines are mainly available as inactivated and live-attenuated vaccines, in which they are designed to express haemagglutinin and neuraminidase proteins derived from the prevalence of recent circulating strains of influenza viruses. The strains are identified through surveillance data collected by multiple laboratories participating in the World Health Organization-sponsored influenza monitoring program [68,71]. While the live-attenuated vaccine contains live, temperature-sensitive influenza virus (thus the virus only replicates in the nasal passages) that is administered intranasally, the inactivated vaccine contains chemical-inactivated influenza virus grown in embryonated chicken egg that is administered intramuscularly [72-74]. The currently most used influenza vaccines are inactivated vaccines, utilizing either three (trivalent) or four (quadrivalent) distinct virus strains to elicit broader immunity. These vaccines contain 2 strains of influenza A virus (H1N1 and H3N2) as well as one or two strains of influenza B virus of Yamagata or Victoria lineage (as trivalent or tetravalent vaccine, respectively) [71]. As an alternative to egg-based inactivated influenza vaccines, cell culture-based or recombinant trivalent influenza vaccines are now licensed in certain countries, in which they can be administered intramuscularly for adults 18 years old and above [69]. Of note, the annual seasonal influenza vaccination is recommended because of waning immunity over time and antigenic drift among circulating influenza viruses which necessitates annual updates to the antigens used in the vaccines.

Among inactivated vaccines, quadrivalent influenza vaccine is noted for its enhanced effectiveness in developing immunity and eliciting better immune responses compared to the trivalent influenza vaccine. The adverse events of both quadrivalent and trivalent influenza vaccines are similar and not serious, including local inflammation, fatigue, headache, myalgia and fever in adults, as well as diarrhea, nasopharyngitis, cough and oropharyngeal pain in children [75]. Conversely, the current live-attenuated influenza vaccine could induce robust humoral and cellular immune responses in the upper airways. However, as it contains a live virus, it is not recommended for the vulnerable groups, including children under 2 years old, the elderlies above 55 years old, or the immunocompromised individuals [71].

Pertaining to the diabetic patients, the influenza vaccination significantly reduced pneumonia-associated hospitalization, all-cause mortality and cardiovascular-related death, comparable to the vaccinated healthy individuals [76,77]. Of note, diabetic patients are not recommended to obtain the live attenuated influenza vaccine due to a concern of their immunocompromised situation [76]. The vaccination of diabetic patients with inactivated quadrivalent vaccine did not cause serious adverse events [76,78].

Herpes zoster due to infection of VZV

The VZV is an enveloped, double-stranded DNA genome that only naturally infects humans, which belongs to the genus of *Varicellovirus* [79]. It spreads through direct contact with fluid from blisters, inhalation of respiratory droplets, or via contact with respiratory secretions, targeting T lymphocytes, epithelial cells, and ganglia [79]. The primary infection results in chickenpox, in which VZV remains latent in the sensory nerve ganglia [79]. The VZV can reactivate later in life, causing shingles or herpes zoster, which manifests as a painful, localized rash and could subsequently cause post-herpetic neuralgia [79]. A recent study on 5 selected countries in Southeast Asia (Indonesia, Thailand, Malaysia, Philippines, and Vietnam) calculated that there would be a total of approximately 10 million herpes zoster cases, 2.1 million post-herpetic neuralgia cases as well as 1.4 million non-post-herpetic neuralgia complications in individuals

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aged 50 years and older, suggesting a substantial disease burden among older adults in this region [80]. In addition, it has been reported approximately 10 per year per 1,000 people aged 60 years and older living in the United States would suffer from herpes zoster [81].

Diabetic patients are at higher risks to contract herpes zoster due to the impaired immunity [82]. The severity of herpes zoster also significantly increased among these patients, including post-herpetic neuralgia [82]. Additionally, certain pharmacological treatments for diabetes (e.g., thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors and insulin) had been associated with higher risks to contract herpes zoster [83,84].

Two vaccines are currently available for preventing herpes zoster, i.e., live-attenuated (zoster vaccine live) and recombinant zoster vaccines [85]. The zoster vaccine live contains the Oka strain of VZV, which is administered as a single subcutaneous dose and is recommended for immunocompetent adults aged 50 years and older [85-87]. The recombinant zoster vaccine contains VZV glycoprotein E and the AS01B adjuvant system, which is administered as two intramuscular doses separated by 2 months and is recommended for immunocompetent adults aged 50 years and older as well as immunocompromised adults aged 18 years and older [80,85,88].

It had been reported that the live-attenuated zoster vaccine live was initially effective, but its effectiveness waned substantially after 10 years [87]. Conversely, the administration of recombinant zoster vaccine in immunocompetent older adults was effective against herpes zoster and postherpetic neuralgia, in which the slow waning of this vaccine's efficacy had been described after a median follow-up of 10 years, indicating that the recombinant zoster vaccine was a suitable option [85,88,89]. Next, the safety profiles of both live-attenuated and recombinant zoster vaccines had been generally established. In a 10-year review of phase IV clinical study on the live-attenuated vaccine, most of its adverse events were non serious, including local injection site reactions [86]. However, the second most frequently reported adverse events upon administration of live-attenuated zoster vaccine in the phase IV study was actually herpes zoster or herpes zoster-related rash [86], indicating a potential safety issue in using a weakened virus to prevent herpes zoster in certain population groups [85]. Upon administration of the recombinant zoster vaccine, while the temporary local reactions at the injection sites (i.e., pain, redness and swelling) were observed, its safety profile was favorable in both immunocompetent and immunodeficient adults [88]. Taken together, these findings justified the preferential usage of recombinant zoster vaccine in preventing herpes zoster and related complications [90].

Several systematic reviews had been performed to assess effectiveness and safety of both live-attenuated inactivated and recombinant zoster vaccines in diabetic patients. While the effectiveness of live-attenuated zoster vaccine against incidence of herpes zoster in diabetic patients was approximately 48% as compared to placebo [91,92], the effectiveness of recombinant zoster vaccine was higher, reaching 91% as compared to placebo [91]. Of note, while the safety data on live-attenuated zoster vaccine was not reported, no difference in severe adverse events was observed in the usage of recombinant zoster vaccine as compared to placebo [91].

Epithelial cancers due to HPV infection

HPV is a non-enveloped, double-stranded DNA virus that belongs to the genus of *Papillomaviruses*, which is capable to infect epithelial tissue of human beings [93]. Currently, there are more than 200 genotypes of HPV, which are categorized into phylogenetic genus of alpha, beta, gamma, mu, and nu [93]. While most HPV infections are transient and resolve spontaneously, persistent infection with high-risk HPV types of the Alpha genus (e.g., HPV16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70) can lead to pre-cancerous lesions and, eventually, carcinoma, including cervical, vaginal, vulvar, penile, anal or oropharyngeal cancer [93].

The current technology platform for HPV vaccines is based on virus-like particles expressing the major HPV coat protein L1, of which three HPV VLP prophylactic vaccines have been licensed, i.e., the bivalent vaccine (contains HPV16 and HPV18), the quadrivalent vaccine (contains HPV6, HPV11, HPV16, and HPV18) and the nonavalent vaccine (contains HPV6, HPV11, HPV16, HPV18, HPV31, HPV33, HPV45, HPV52, and HPV58) [93]. Those vaccines are administered via intramuscular injection for both females and males in a two-dose series for individuals aged 9–14 or a three-dose series for those 15 years and older [93-95]. Importantly, those HPV vaccines are very effective in controlling high-risk HPV infections and HPV-related cancers [93,96,97]. Furthermore, the licensed HPV vaccines have excellent safety profiles, in which the most common reported side effects were mild, including pain at injection site [98,99].

There is a strong tendency that diabetic patients had a higher risk to be infected by HPV [100-102]. This might explain the association between high-risk HPV-infected female patients with diabetes and a higher risk to develop cervical cancer [101,103]. No published data on the effectiveness of HPV vaccines in diabetic patients is available thus far. Nonetheless, it had been reported that administration of HPV vaccines did not increase the risk to develop type 1

diabetes [104,105], reinforcing the safety profiles of licensed HPV vaccines.

Dengue illness due to infection by DENVs

DENVs are enveloped, positive-sense, single-stranded RNA viruses belong to the to the genus of *Flavivirus*, which can be classified into 4 serotypes (i.e., DENV1, 2, 3 and 4) [106]. DENVs are transmitted to humans through the bite of infected *Aedes* mosquitoes (primarily *Aedes aegypti* or *Aedes albopictus*). Upon inoculation into the skin, DENVs replicated in Langerhans cells, dendritic cells or macrophages. These infected cells could migrate from the initial site of infection to lymph nodes, resulting in the recruitment of monocytes and macrophages that became subsequent targets of DENV infection [106]. The infection could result in dengue illness, either as dengue without or with warning signs or as severe dengue [106]. Of note, neutralizing antibodies generated during an infection offer long-lasting protection against the homologous serotype but provide only temporary immunity against the other 3 serotypes. Hence, individuals at risk of secondary infections, presumably by other serotypes, are likely to experience severe disease due to the antibody-dependent enhancement phenomenon, which leads to increased viral replication and a higher viral load [106].

Creating an effective prophylactic dengue vaccine is challenging due to the global presence of 4 serotypes of DENVs and to the necessity of creating sufficient immune responses (including titers of neutralizing antibodies) against all serotypes to attenuate the risk of severe dengue. This indicates that a dengue vaccine should contain antigens of 4 serotypes to generate immune responses against all serotypes of DENVs. Currently there are two licensed dengue vaccines, covering DENV1-2-3-4, based on the platform of live-attenuated vaccine, i.e., CYD-TDV vaccine based on a yellow fever backbone that was introduced in 2015 as well as TAK-003 vaccine based on a DENV2 backbone with recombinant strains expressing surface proteins for DENV1, DENV3 and DENV4 that was introduced in 2023 [107-111]. The CYD-TDV vaccine is administered subcutaneously in three doses at 0 months, 6 months, and 12 months [112]. The TAK-003 vaccine is administered subcutaneously in two doses with 3 months [113]. interval During the first 25 months of phase 3 study, CYD-TDV vaccination demonstrated an efficacy rate of 60.3% (95% confidence interval [CI], 55.7 to 64.5), in preventing symptomatic dengue for all participants [108]. However, during the third year of follow-up, the risk of hospitalized dengue patients was higher in the vaccine group among dengue-naïve younger children compared to the placebo group. As per 2024, CYD-TDV vaccine has been approved in 19 countries, including Brazil and the European Union. However, it has not been approved by the US FDA for use in individuals who have not been previously infected with any DENV serotype or whose infection history is unknown [107,108,114]. In contrast, during the phase 3 study of 4.5 years, TAK-003 vaccination demonstrated an efficacy rate of 61·2% (95% CI, 56.0 to 65.8) in preventing virologically-confirmed dengue for all participants [111]. It is of interest to note that among dengue-naïve individuals, TAK-003 vaccine was only effective against DENV-1 and DENV-2 [111], suggesting a plausible risk for the vaccinated individuals to suffer from severe dengue upon subsequent infection by DENV-3 or DENV-4 [115]. Nonetheless, the serious adverse events upon administration of TAK-003 vaccine were not different from the ones upon administration of placebo [111]. As per 2024, TAK-003 vaccine is approved for use in children and adults in Indonesia, Thailand and both private and selected public programs in Argentina and Brazil, as well as in the private market across European countries [107]. Taken together, while the use of CYD-TDV vaccine is highly limited due to a requirement of pre-screening dengue infection prior vaccination, the TAK-003 vaccine is currently prioritized by several endemic countries [107].

Diabetic patients were reported to have a higher risk to be infected by DENVs than non-diabetic individuals [116]. It was also reported that diabetic patients were at higher risk to contract dengue with warning signs or even severe dengue [117,118]. This link was further reinforced by a study, reporting that metformin administration for diabetic patients could reduce the risk of developing severe dengue [119]. Collectively, the contemporary evidence suggested that prevention of DENV infections, such as by administering dengue vaccines, would be beneficial for the diabetic patients. However, there are no data available yet regarding the efficacy and safety of licensed dengue vaccines in diabetic patients, probably be attributed to the relatively recent approval of those vaccines.

CONCLUSION

This review highlights the increased vulnerability of diabetic adults to a range of infections as well as the clinical effectiveness of various prophylactic vaccines in reducing the morbidity and mortality associated with bacterial and viral infections in this population. This review is aimed to increase public awareness of the critical role these vaccines play in protecting adult patients with diabetes, especially given the current global challenge of low vaccination coverage in this group. This important issue is beyond the scope

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of this narrative review, but it is aggravated by the limited financial support for adult immunization programs in many countries that hinders broader access to these preventive measures. By emphasizing the benefits of vaccination, we aim to foster greater adoption and advocacy for immunization programs among diabetic adults.

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