Review Article

Assessing Vaccine Protection for Older Adults with Diabetes: A Systematic Review

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Abstract

Immunosenescence and comorbidities increase the susceptibility of older adults with diabetes mellitus (DM) to vaccine-preventable diseases, hospitalization, disability, or death. This systematic review synthesizes research on protecting older adults with DM during pandemics, exploring vaccine safety, tolerance, and vaccination uptake by older adults in anticipation of seasonal influenza outbreaks during the current COVID-19 threat. Addressed were: (a) age-related factors influencing the effectiveness of vaccines against infectious disease in older adults; (b) vaccine safety, tolerance, effectiveness for older persons with DM; and (c) issues affecting older adults accepting immunization recommendations. Medline and CINAHL databases yielded 214 studies with 43 meeting inclusion criteria (32 descriptive and 11 controlled trials). Findings show altered glycemic control stimulates proinflammatory mediators, increasing infection risk, vaccines, and annual revaccinations safely reduce hospitalization rates, mortality outcomes, without affecting glycemic control. However, vaccines fail to evoke optimal antibody responses in older adults. Unawareness, fear of side effects, tend to lower vaccination participation.

Keywords

immunization, vaccination, immunosenescence, aging. diabetes, glycemic control

Vaccination rates for adults over age 65 are below the targeted 70% rate recommended by the Healthy People 2020 program and the Center of Disease Control and Prevention (Freedman et al., 2020). These rates raise particular concern for older adults or persons with chronic disease and comorbidities. For example, older adults with diabetes mellitus (DM) are at risk for higher morbidity and mortality from complications of common infectious diseases like influenza than younger persons or those without DM (Jimenez-Garcia et al., 2017). In reports of pandemic influenza, the likelihood of dying from flu complications was tripled for patients with DM (Athamneh & Sansgiry, 2014). For the past generation, there have been serious barriers to the immunization of older adults. Even as people live longer and travel more, many are not immunized and others will not mount a protective immune response to some vaccines, even with immunization (Lang & Aspinalli, 2014). The urgency of protecting older adults from influenza in the face of the current COVID-19 pandemic is apparent as authorities predict the impact on mortality and available hospitalization (Gostin & Salmon, 2020). DM is associated with increased severity and mortality from COVID-19 (Huang et al., 2020). Finding ways to provide vaccine protection to older adults with DM requires an understanding of how diabetes and immunosenescence affect older adults and those with DM. In addition, the sociobehavioral factors that influence access and acceptance of vaccination must be addressed to assure maximum coverage.

Glycemic Control and Immunosenescence affecting Immune Responses of Persons with DM

Diabetes is a major chronic disease affecting many older adults as they age (Kirkman et al., 2012). For persons with DM, maintaining metabolic control of their blood glucose depends on their ability to balance diet, exercise, and pharmacological agents. Elevated levels of blood glucose and glycosylated hemoglobin (A1C) are clinical indicators of altered glucose metabolism that produces oxidative stress, affecting cellular and humoral immunity, and increasing proinflammatory cytokines (Joshi et al., 2009). Oxidative damage from other inflammatory "cytokine storms" throughout

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life also damages aging immune cells, so cellular *immunosenescence* further heightens the risk for all older adults (Ventura et al., 2017). For those with DM, this exacerbates their age-related susceptibility to infectious diseases (Pera et al., 2015). Aging also reduces innate responsiveness to vaccine antigens needed to impart immunity for all older adults (Ventura et al., 2017). To overcome this condition, adjuvant immune response enhancers have been added to vaccines to improve their potency and durability of immunoprotection (Joshi et al., 2009). Beyond initial immunization, annual revaccination is recommended and social distancing is a logical approach during outbreaks (Yang et al., 2017). These approaches require the need to include and engage education family and caretakers in protection plans for older adults with DM.

Purpose

A systematic review was selected as an effective preliminary method to examine the research evidence available to inform prevention plans. The purpose of this review was to assess evidence on vaccine safety and effectiveness for aging adults, immunization issues related to DM, and factors influencing vaccination uptake rates in this population. Of particular concern were questions of risk and tolerance of the vaccine itself by older adults with DM, as well as the vaccine's ability to prevent incidence or severity of the targeted infection. Findings from earlier influenza pandemics were explored to provide information on how healthcare coped with previous outbreaks (Colquhoun et al., 1997; Pozzilli et al., 1986; Selvais et al., 1997). In addition to providing areas of need for their own future research, the authors were mindful of how findings inform education and practice approaches to address prevention and low immunization rates. To achieve the review's purpose, the following questions were posed:

1. What age-related factors influence the effectiveness of vaccines in promoting immunity against infectious disease in older adults?
2. What evidence of vaccine protection, safety, and tolerance, has been established for older persons with DM?
3. What issues affect acceptance of immunization recommendations for older adults?

Method

Design

This systematic review was conducted using guidelines from PRISMA, the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* (Stewart et al., 2015). A meta-analysis was not conducted due to the methodological diversity and heterogeneity of retrieved literature.

Study Eligibility

Inclusion criteria included human subjects, all publication years, all research designs, both type 1 and type 2 DM, and all vaccines recommended to adults with DM over age 65 (e.g. influenza, pneumococcal, hepatitis B, and herpes zoster). Both authors discussed and agreed on inclusion and classification of reviewed articles. Government reports and systematic reviews were used for background information, but were not included in the analysis of the research reviews.

Search Strategy and Results

The authors performed a comprehensive search of relevant research articles published in English, using Medline and CINAHL databases. Key search terms were immunization, vaccination, immunosenescence, older adults, elderly, aged, diabetes, diabetes mellitus, effectiveness, safety, perception, attitudes, and factors, A PRISMA flowchart mapping selection of articles appears in Figure 1. Initial retrieval of 214 articles was scanned, and 40 duplicates or non-relevant topics were removed. The remaining 174 abstracts were reviewed for relevance. Of these, 87 were not applicable to the review focus and the remaining 87 were further reviewed for eligibility. A total of 38 articles met inclusion criteria, while reference lists from retrieved articles provided an additional five articles and raised the total to 43. Of these, 32 articles were descriptive non-experimental studies or retrospective comparisons of vaccine outcomes, and 11 were controlled trials.

Methodological Quality and Data Extraction

Relevant data from reviewed articles were independently extracted and evaluated for quality by the authors. Of specific interest, were study design, purpose, sampling frame and participant characteristics, dependent and independent variables, tables and figures, and measurement methods. Results were analyzed and synthesized in the review.

Level of Evidence

Levels were established for each article using the American Association of Critical Care Nurses (AACN) scale, revised in 2012, grading studies according to methodological rigor and type of design (Peterson et al., 2014). The six grading levels range from the highest, A (meta-analyses and meta syntheses of controlled studies), followed by B (well-designed controlled studies with randomized or nonrandomized samples), C (non-experimental descriptive and varied research designs), D (expert panels or organizational standards), and E (theory based expert opinion or multiple case reports). Based on AACN levels of strength of the study design and level of studies most applicable to review purpose (Peterson et al., 2014), selected studies were limited to levels A to C.

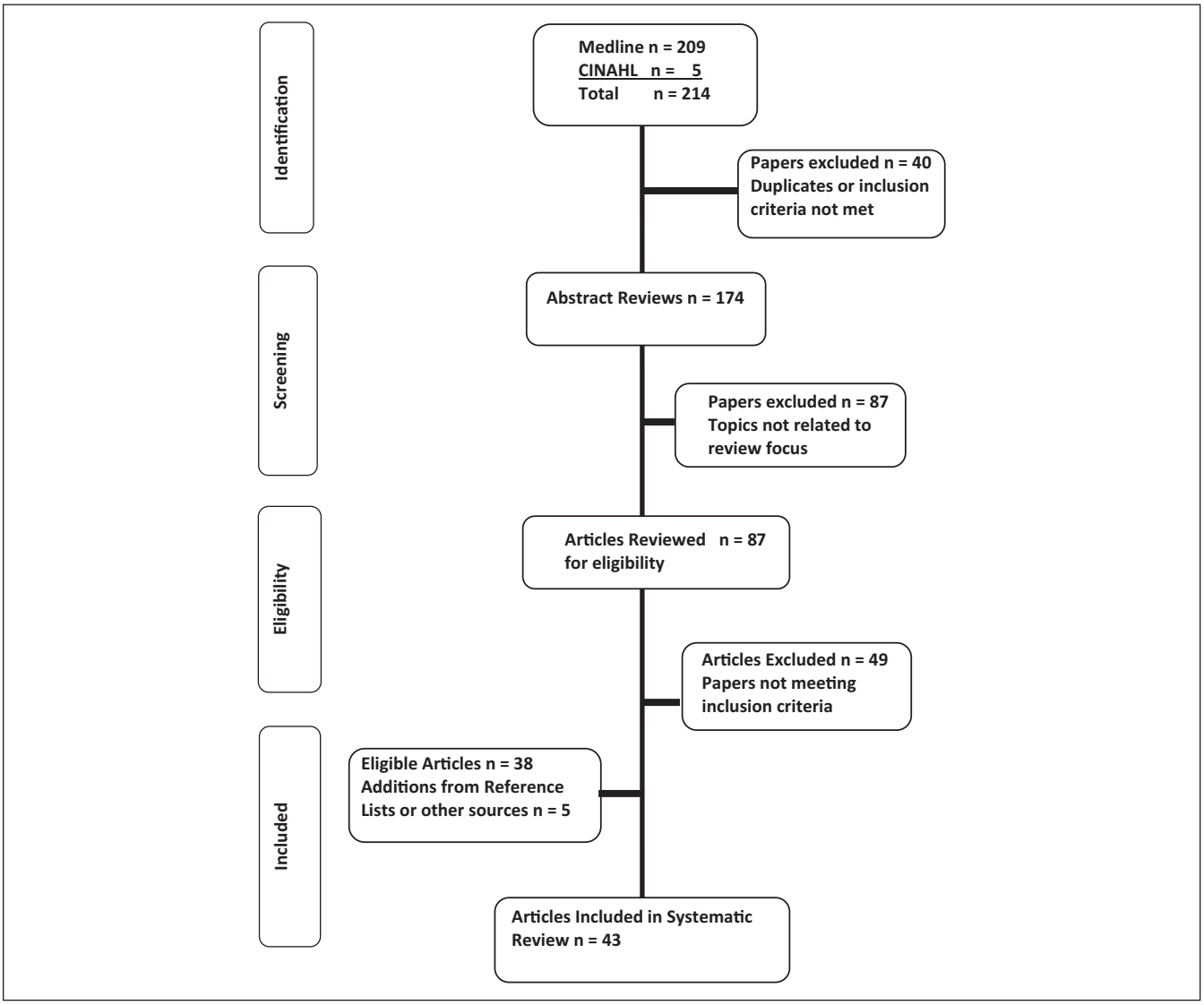

Figure 1. PRISMA Flow Chart.

Quality Appraisal

A PRISMA-guided Checklist (see Table 1) was used to assess methodological rigor of individual studies (Stewart et al., 2015). Each study was read and appraised for selection criteria, sample adequacy, measurable objectives of the study, signs of potential study bias, and appropriate statistical analyses. Only 16 articles mentioned strategies used to address potential study bias.

Defining Efficacy, Effectiveness, and Coverage in Immunization Outcomes

The literature describes how vaccine development influences both the "effect" and "efficacy" of the product and the "coverage" of immunization programs in certain areas. Vaccine science has different meanings for these terms and precise definitions exist to mathematically and explicitly represent functionally important differences (Shim & Galvani, 2012). These terms can cause confusion by being used interchangeably in the literature so, for this review, they are defined broadly and somewhat simplistically. Vaccine efficacy refers to statistical population effects, comparing reduction in disease incidence between vaccinated and unvaccinated groups under controlled conditions and is usually measured in proportions or percent. Several studies of vaccine efficacy are reported in this review showing vaccine-related reductions in overall hospitalization admission rates (Looijmans-Van den Akker et al., 2006), ICU admission and mortality rates (Wang et al., 2013). influenza rates (Vamos et al., 2016), pneumonia rates (Colquhoun et al., 1997; Wang et al., 2013), and secondary death rates from cardiovascular complications (Vamos et al., 2016). A related term used to describe uptake and population acceptance is vaccine coverage, which refers

Table 1. PRISMA Checklist for Quality Assessment of Study Methodology.

Study	Clear Inclusion Criteria Defined	Sample and Settings Described	Relevant Variables Defined	Valid, Reliable Measures Defined	Potential Biases Identified	Strategies to Address Bias Used	Appropriate Statistical Analysis
Achtymichuk et al. (2015)	√	√	√	√	√	√	√
Akmatov et al. (2019)	√	√	√	√	√	√	√
Byeon et al. (2018)	√	√	√	√	√		√
Colquhoun et al. (1997)	√	√	√	√	√		√
Davis et al. (2017)	√	√	√	√	√		√
Diepersloot et al. (1987)	√	√	√	√			√
Dorrell et al. (1997)	√	√	√	√	√		√
Dower et al. (2011)	√	√	√	√	√		√
Egawa et al. (2014)	√	√	√	√	√		√
Egede and Zheng (2003a)	√	√	√	√	√	√	√
Egede and Zheng (2003b)	√	√	√	√	√		√
Feery et al. (1983)	√	√	√	√			√
Frasca et al. (2013)	√	√	√	√			√
Gorska-Ciebiada et al. (2015)	√	√	√	√			√
Haq et al. (2017)	√	√	√	√	√		√
Hoerger et al. (2013)	√	√	√	√	√		√
Jimenez-Garcia et al. (2017)	√	√	√	√	√		√
Jimenez-Trujillo et al. (2015)	√	√	√	√	√	√	√
Jimenez-Trujillo et al. (2013)	√	√	√	√	√		√
Lederman et al. (1981)	√	√	√	√	√		√
Lewis-Parmar and McCann (2002)	√	√	√	√	√	√	√
Looijmans-Van den Akker et al. (2006)	√	√	√	√	√	√	√
Machado et al. (2018)	√	√	√	√	√	√	√
McElhaney et al. (1996)	√	√	√	√	√	√	√
Nam et al. (2011)	√	√	√	√	√		√
Pillsbury et al. (2020)	√	√	√	√	√	√	√
Pozzilli et al. (1986)	√	√	√	√	√		√
Santaularia et al. (2016)	√	√	√	√	√		√
Satman et al. (2013)	√	√	√	√	√	√	√
Selvais et al. (1997)	√	√	√	√			√
Seo et al. (2015)	√	√	√	√	√	√	√
Sheridan et al. (2015)	√	√	√	√	√		√
Shin et al. (2018)	√	√	√	√	√	√	√
Vamos et al. (2016)	√	√	√	√	√	√	√
Van Der Meeren et al. (2016)	√	√	√	√	√		√
Verger et al. (2015)	√	√	√	√	√	√	√
Vila-Córcoles et al. (2006)	√	√	√	√			√
Vila-Córcoles et al. (2007)	√	√	√	√	√	√	√
Voordouw et al. (2004)	√	√	√	√	√	√	√
Wahid et al. (2001)	√	√	√	√			√
Wang et al. (2013)	√	√	√	√	√		√
Yang (2017)	√	√	√	√	√		√
Yu et al. (2014)	√	√	√	√	√		√

to the estimated percentage of individuals who have received specific vaccines (Centers for Disease Control and Prevention [CDC], 2016b). By contrast, vaccine effectiveness is tested in "real world" primary care or clinical settings with an eye to assessing the characteristics of adverse effects and application to clinical relevance. Research and data-collection conditions are often not well-controlled across clinical settings and differences in effectiveness may be influenced by

Table 2. Vaccine Effectiveness to Reduce Incidence and Severity of Infections in Older Adults.

Author(s)/Year	Key Findings
Colquhoun et al. (1997)	• Influenza vaccine effectively lowered hospitalizations among older adults with DM during influenza seasons • Lowered hospitalization rates for pneumonia, bronchitis, and influenza • Effectiveness independent of age, sex, type of DM, year of epidemic, and number of general practitioners' visits
Looijmans-Van den Akker et al. (2006)	• Health complications in unvaccinated adults ages 18–64 years were twice as frequent as those vaccinated • Vaccination in adults over age 65 was associated with 56% fewer older adults' deaths, hospitalization reduced by 14% • No difference in first time and repeat vaccination reducing all-cause mortality risk
Vamos et al. (2016)	• Older adults with DM and comorbidities, on prescribed medications, more likely to be vaccinated • Vaccine reduced hospitalizations for MI, Pneumonia, Stroke, heart failure and death during influenza season
Wang et al. (2013)	• Fewer patients in group over age 75 were vaccinated • Adults with cardiac disease, hypertension, hyperlipidemia, chronic hepatitis more likely to be vaccinated than healthy adults • Patients and physicians have misconceptions about vaccine effectiveness and fear effects • Vaccinated cohort had fewer cases of pneumonia, influenza, respiratory failure, hospitalizations, ICU admission, and mortality.

the way vaccines are scheduled and made available, how well target groups are immunized, and stability of the vaccine itself. These variations could limit some meaningful comparisons between study outcomes of the same vaccine in different settings.

Results

Reviewed literature for this report updates research on immune responsiveness of older adults and describes advances in vaccine science to enhance it. The risks and benefits of immunization experienced by persons with DM are assessed in the context of aging and immunosenescence. In addition, sociobehavioral factors affecting older adults' acceptance of immunization were tracked from earlier pandemics to those currently emerging and assessed for factors applicable to research and practice. Synthesis of the literature was guided and is presented by addressing the three questions underpinning the systematic review. Details addressing each of the three major study purposes are addressed in Tables 2, 3, and 4. Supplementary material is available online with fuller description of each reviewed study. The countries represented by each article in the table collectively represent: USA (eight reports), United Kingdom (five reports), Canada (three reports), Australia (four reports), Netherlands (three reports), Korea (four reports), Taiwan (two reports), Spain (five reports) and one report each from Poland, Turkey, Italy, Japan, Hong Kong, France, Belgium, Germany, and Portugal. One multi-site study included 21 centers from Australia, New Zealand, Canada and USA (Van Der Meeren et al., 2016).

Age-related Factors Influencing Vaccines Effectiveness Against Infectious Disease

The underlying scientific premise of immunosenescence attributes the decline in older adults' antigenic immune vaccine response to aging cells. Research findings confirm that aging decreases the serological response and vaccine effectiveness of several vaccines in older adults with or without diabetes (Frasca et al., 2013; Sheridan et al., 2015) and despite use of adjuvanted inactivated trivalent vaccines (Akmatov et al., 2019). Reviewed reports included global responses, immunization rates, and effectiveness of specific vaccines during serious pandemics (see Table 2). While the effects of revaccination were not found to reduce mortality in the general population, 56% fewer deaths occurred in older vaccinated adults (Looijmans-Van den Akker et al., 2006). There were fewer hospitalizations for pneumonia, bronchitis, and influenza among older adults with DM during influenza season (Colquhoun et al., 1997; Looijmans-Van den Akker et al., 2006; Vamos et al., 2016; Wang et al., 2013). The predominance of studies related to influenza vaccine reflects the emerging nature of changing viral strains and the need to readjust the vaccine to mutations each season. Outcomes of vaccine immunoprotective effectiveness were therefore dependent on the influenza virus strain and its adjuvants or enhancers. Cellular senescence in DM has earlier been advanced as an explanation for the early onset of several other age-related disorders in persons with DM (Shakeri et al., 2018). The potential for higher immunogenic effect is inherent in the suggestion that persons with DM get immunized for hepatitis B as soon as DM

Table 3. Vaccine Protection, Safety, and Tolerance for Older Adults with DM.

Author(s)/Year	Key Findings
1. Akmatov et al. (2019)	• Non-response rates increased by 8% with age and only 36% older adults had adequate vaccine response to all vaccine antigens • DM and history of herpes zoster strongest predictors of weak humoral response to H1N1 strain • Adults with herpes zoster infection had a three-fold higher risk of H3N2 nonresponse
2. Diepersloot et al. (1987)	• Adults with type 1 and diet-managed type 2 DM had lower antibody response than controls, but not statistically significant • Protection rate for H3N2 90% in control group and 85% in those with DM • Delayed type hypersensitivity after vaccination in persons with DM suggests cytotoxic effects on T-cells
3. Dorrel et al. (1997)	• Antibody titer rose to a protective level in 44.8 % of patients with DM versus 58.8% level healthy younger adults • Only 33.3% of older adults, 35.7% with COPD, and 26.5% with HIV met protective levels • Vaccine tolerated well in all groups. Negligible effects in glycemic control following vaccination
4. Egawa et al. (2014)	• Older participants had low antibody response and seroprotection • Lower BMI and physical conditions associated with lower sero-response • Higher A1C associated with lower significant seroprotection • Single dose A(H1N1)pdm09 vaccine sufficiently protected most adults with DM, but not older adults with lower BMI, higher A1C levels
5. Feery et al. (1983)	• Regular vaccines among controls had higher initial and final titers compared to first time vaccine recipients • Patients with DM had lower initial and final titers than controls and no impairment of glycemic control • No titer differences between adults on insulin and oral therapy, but poorly controlled DM diminishes vaccine response • No association between antibody response, insulin dose, duration of DM, or A1C levels
6. Frasca et al. (2013)	• Young and older adults with Type 2 DM have higher TNF-α levels than controls, indicating B-cell-intrinsic inflammation • Despite loss of B-cell function in DM, unexpectedly vaccine responses were not diminished. Other mechanisms suggested • Hyperactive immune response may moderate other molecular mechanisms and counteract negative TNF−α responses, producing normal B cell activity
7. Haq et al. (2017)	• Adults with well-controlled type 2 DM had no reduced vaccine effectiveness no lack of T-cell responsiveness • Cytomegalovirus (CMV) serostatus caused low Granzyme B response to influenza. May be a common predictor of low vaccine response because CMV is prevalent in older adults • No differences found in cytokine responses to vaccine challenge in peripheral blood mononuclear cell between older adults with type 2 DM and healthy older adults
8. Hoerger et al. (2013)	• Declining immunogenicity with aging after age 40, affecting cost-effectiveness of vaccines. Earlier immunization advised • Given growing incidence of hepatitis B in persons with DM, vaccination advised for all between ages 20 and 59 years • Highest risk group for transmission of HIV in adults with both DM and HIV, were those using assisted monitoring of blood glucose, sharing needles
9. Lederman et al. (1981)	• Overall antibody response to pneumococcal vaccine for adults with DM equivalent to controls. Specific antibody types were slightly higher with DM • Height of antibody response with DM not correlated with age, sex, duration of DM, insulin dosage, A1C, or DM control
10. McElhaney et al. (1996)	• Cell-mediated immunity from influenza vaccine in older adults with type 2 DM similar to healthy adults without DM • Having DM did not affect IL-2 or granzyme B responses • Those in both groups vaccinated one year previously had suppressed IL-2 response to vaccine • New vaccine developments may be needed if added protection needed for older recipients with DM
11. Nam et al. (2011)	• A quarter of older adults acquired positive antibodies after vaccinations • Preliminary results showed older adults with DM or with longer DM duration had lower seroconversion rate • Suggests need for second dose or post-vaccine titer check

(continued)

Table 3. (continued)

Author(s)/Year	Key Findings
12. Pillsbury et al. (2020)	• Common adverse events: injection site pain, swelling, redness, tiredness, headache • Severe events less common: vomiting, diarrhea, seizure, altered consciousness • From total sample: 7.4% reported adverse effects. More prevalent in women than men • More adverse effects among 65−69-year-olds than older adults • High-dose trivalent inactivated influenza HD-IIIv3 had more adverse effects than trivalent inactivated influenza aIIIv3 or quadrivalent inactivated influenza QIIV • More adverse effect if participants received QIIV.PPSV23 with aIIIV3 and HD-IIIV3 • Adverse effects higher in adults receiving concomitant pneumococcus vaccine
13. Pozzilli et al. (1986)	• Overall immune response to influenza vaccine similar between age-matched controls and well-controlled adults with DM and persisted to 6 weeks • Significant reduction of interleukin 2 lymphocytes in those with type 2 DM 72h after vaccination, but nondeveloped influenza later on • Significant increase in antibody titer in patients with type 1 DM for the A/Chile (H1N1) strain, but not for A/H3N2 and type B, suggests genetic predisposition to hyperimmune response seen in other studies
14. Seo et al. (2015)	• Vaccine well tolerated; mild-to-moderate adverse reactions • Similar immunogenicity profiles for both groups at one month with declining long-term protection in older adults • Seroprotection for A/H1N1 strain lower in older adults with DM than controls
15. Sheridan et al. (2015)	• Age negatively correlated with antibody response • Obese adults were more likely to have DM. Higher BMI associated with higher antibody production • No antibody response difference between adults with or without DM. No comparison examined whether vaccine was equally protective against influenza in those with or without DM • A1C had small but significant positive association of seroprotection against A/Brisbane/10/2007 (H1N1) strain in Year 1 group, but not with other strains
16. Van Der Meeren et al. (2016)	• Vaccine seroprotective rates decreased with age and high BMI in adults with and without DM • Hepatitis B vaccination less immunogenic in adults with DM but induced protective levels at 75.4% • Recommendation to vaccinate adults with DM while younger with higher immunogenic potential
17. Vila-Córcoles et al. (2007)	• Annual influenza vaccine associated with low risk of all-cause winter mortality from 2002 to 2005 • Mortality rate was associated with age and being male • Influenza vaccine significantly reduced mortality risk during influenza season • The highest vaccine effectiveness rate was at age 65 and decreased with increasing age
18. Voordouw et al. (2004)	• Any influenza vaccination associated with 22% lower risk of all-cause mortality • First vaccination associated with 10% reduction in all-cause mortality • Revaccination associated with 24% reduction in all-cause mortality • All-cause mortality not reduced by revaccination in adults ages 65−69, but significantly reduced all-cause mortality rate in those >70 years old

is diagnosed (Van Der Meeren et al., 2016). Additional details of these studies are available in Online Supplementary Materials, Table 1 *Vaccine effectiveness to reduce incidence and severity of infections in older adults.*

Protection, Safety, and Tolerance of Vaccines in DM

Immune system responses testing effective protection provided by vaccines to older adults with DM were reported in 18 articles (see Table 3). Among these studies, specific contributory factors of the disease are reported linking lower vaccine response to altered metabolic control. Having well-controlled type 2 diabetes (A1C $= 6.33 \pm 0.14$) appeared to protect patients from age-related decline in vaccine immune responses (Haq et al., 2017). Obesity is recognized as a pro-inflammatory state in DM, and a constant contributor to insulin resistance and threat to metabolic control. Its relationship to immunity was found to be an independent risk factor for influenza-related morbidity and mortality during the H1N1 pandemic of 2009 (Sheridan et al., 2012).

Because different influenza vaccines contain specific antigens for specific influenza virus strains, their effectiveness varied somewhat across the reviewed literature. In most comparative studies, individuals with and without type 2 DM had similar levels of immune response to influenza or pneumococcal vaccines, but underlying infection can affect B cell activity (Frasca et al., 2013; Haq et al., 2017; Lederman et al., 1981; McElhaney et al., 1996; Seo et al., 2015; Sheridan et al., 2015). For example, one infection, cytomegalovirus (CMV) is a common chronic infection in older adults that suppresses the antibody response to influenza virus and causes poor T-cell response to the antigen (Haq et al., 2017). Investigators also have reported herpes zoster

Table 4. Factors and Perceptions Influencing Older Adults' Tendencies to Seek Vaccinations.

Author(s)/Year	Key Findings
Achtymichuk et al. (2015)	• Vaccination rates higher in adults with DM over age 65, with healthy behaviors, receiving more medical visits and drugs • Vaccination rate (63%) higher than anticipated • Comorbidities and prescribed medications in older, but not younger adults predictive of seeking immunization
Byeon et al. (2018)	• Highest rates for men 80−84, women 75−79 • High coverage among adults over 50 with chronic disease, including DM • National program offering free vaccination helped improve coverage to 80% for ages ≥65 • Coverage rates lower in healthy 50−54-year-old group regardless of gender
Davis et al. (2017)	• Vaccination rate increased with patients' age and previous pneumonia hospitalization • Self-reported frailty, disability promotes vaccination • Higher rates of self-reported vaccination with active medical comorbidity management • Pneumococcal coverage was suboptimal for persons in this type 2 DM community
Dower et al. (2011)	• Poor self-reported health predicts pneumococcal vaccination for adults with asthma, DM, or cardiovascular disease • Poor self-reported health was predictor for influenza vaccination for adults with DM • Age was strongest predictor of having both pneumococcal and influenza vaccinations • Perceptions of risk or need for vaccination are low and need wider emphasis among all
Egede (2003)	• Repeated physician visits and access to care only modestly increased vaccination rates • More than 10 physician visits in 12 months required to significantly influence vaccination rate • Vaccination rates increase with age of patients • White, unemployed participants had higher influenza vaccination rates
Egede and Zheng (2003a)	• After adjusting for covariates, race/ethnicity predicted receipt of both influenza and pneumococcal vaccines, independent of age, health care access, health coverage, and SES • Immunization rates higher for White than African Americans or Hispanic persons • White patients with two or more high risk conditions were more likely to receive influenza vaccine than Black patients with same conditions
Egede and Zheng (2003b)	• Highest vaccination rates for White adults with DM ≥ 65, household income ≤ $20,000, employed, US born, with health care coverage and access, or comorbid condition • Vaccination rates higher for White adults with DM, chronic heart disorders, and cancer, than for Black adults with same conditions • Rates independent of gender, marital status, education, general health
Gorska-Ciebiada et al. (2015)	• Vaccination rates low for adults with DM (26.48%) • Lifetime uptake rate of influenza vaccination was 31.1%, for pneumococcal vaccine 9.1% • Physician advice increased vaccination rates • Lack of information, low perceived benefits of vaccine, feeling healthy, not recognizing need, low vaccination rates
Jiménez-Garcia et al. (2017)	• Higher uptake rates with adults with comorbid conditions (neuropathy, amputations, heart disease), previous vaccination • Vaccine uptake influenced by being married, older, less education, healthy behavior, and more physician visits • Vaccination deterrents were low perceptions of disease risk and vaccine effectiveness, and fears that vaccine causes influenza or adverse reactions
Jimenez-Trujillo et al. (2015)	• Adherence to repeat influenza vaccination in previous year was only 44.4% among adults with DM, and below 30% coverage for those below age 60 • Gender not associated with vaccine uptake • Vaccine adherence increases with age, healthcare visits, university education, and number of chronic conditions • Findings show urgency for strategies to improve coverage
Jimenez-Trujillo et al. (2013)	• Coverage rates for adults with DM (65%) were higher than for adults without DM (41.2%) • Likelihood of adults with DM age 60−69 being vaccinated: More than 3 times higher than those age 30−39, 6 times higher than those over age 70 • Predictors for vaccination: Being male, poor health, or other chronic diseases, recent physician visit
Lewis-Parmar and McCann (2002)	• Uptake increased from 53.9% in 1997−1998 to 67.6% in 1999−2000, Factors influencing older adults with DM vaccine update: previous vaccination, health care recommendations, or believing vaccines protect against influenza • Health professionals played key role in improving uptake giving reliable information about vaccine effectiveness/safety, encourage healthy behaviors and engage in efforts to provide vaccine access

(continued)

Table 4. (continued)

Author(s)/Year	Key Findings
Machado et al. (2018)	• Overall uptake of influenza vaccine was low in all four seasons. Only 26% reported repeated uptake. Over half of adults with chronic conditions had never been vaccinated • Adults with DM or renal conditions had higher vaccination rates than those with other chronic conditions • Reminders and recalls effective in promoting vaccination, especially if done by a nurse, pharmacist, or medical student
Santaularia et al. (2016)	• Overall state influenza vaccination rate (42.4%) was below Healthy People 2000 target (80%). Findings emphasize need to improve state vaccination rates • Adults with DM and cardiopulmonary comorbidities had higher vaccination rates than adults without DM
Selvais et al. (1997)	• Age was most definitive attribute for influenza vaccination. Insufficient incentives exist for all needed vaccination for adults with DM • Adults with type 2 DM were older, and had higher rates for vaccination than adults with type 1 DM • Poor vaccination coverage for pneumococcal and hepatitis B • MD advice increased vaccination rates in older subjects for influenza, but not for other diseases • Regular medical visits or media coverage did not enhance vaccination rates
Shin et al. (2018)	• Vaccination rates were insufficient in DM group. Higher in older adults with DM than younger adults with DM • Older women have higher influenza vaccination rates than men • Low alcohol-related risk, obesity, higher income, and recent health visits predicted vaccine use among adults with DM
Verger et al. (2015)	• Older adults with DM had higher influenza vaccination rates than younger adults with DM • Vaccination rates increased with DM severity, duration, and comorbidities • No association found between DM severity and physician or nurses visits • Tailored communication strategies advised to better inform younger adults with DM of risks and benefits of vaccination
Vila-Córcoles et al. (2006)	• Free or discounted pneumococcal vaccination quickly improved rates in first year. Slower and more stable in second year • Vaccination rates were lower (46.7%) among 65−74 years than among those 75 or older (60.9%) • Highest coverage among adults with chronic conditions. Those with DM had highest rate of pneumococcal vaccine coverage (65.9%)
Wahid et al. (2001)	• MD recommendations and comorbid chronic pulmonary diseases or heart disease increased rates of influenza and pneumococcal vaccinations rates. However, a large number of non-vaccines were unaware of need, especially for pneumococcal vaccines (91%). Side effects not commonly considered reasons for refusing vaccine • Low vaccination rates unsatisfactory for patients with DM. Health care consultations advised to include topic • Adults with type 2 DM more likely to get influenza and pneumococcal vaccines than those with type 1 DM
Yang et al. (2017)	• Socioeconomic status, smoking habits, chronic conditions, A1C or glycemic levels and vaccination status did not influence vaccination rates • Caregivers, adult children, partners of patients, previously vaccinated adults, more likely to seek vaccination • Perceived effectiveness and safety of vaccine, previous year's vaccination, physician advice, were influential • Barriers: Low perceived risk or severity of influenza infection, fears about vaccines effectiveness and safety
Yu et al. (2014)	• Influenza vaccination rates for adults with DM were low (31%−35%) • Most vaccinated were female, older, with comorbidities, positive perceptions of benefits, and lower perceived barriers • Low knowledge of perceived benefits and barriers decreased vaccination rates • Health beliefs were supported by informational interventions while simultaneous vaccinations reduced risks

as a potentially modifiable risk factor leading to poor B antigen response for adults with DM, but emphasized the need for broader research to explain those findings (Akmatov et al., 2019). Despite screening more than a dozen epidemiological and population-based studies confirming the incidence of herpes zoster in adults with DM, the search found no specific immune factor responsible. The second most studied infection for this review was pneumococcal disease. Although its occurrence may be no higher in people with DM, pneumonia is considered a major cause of mortality in this population (Colquhoun et al., 1997; Lederman et al., 1981). Pneumococcal disease can lead to bacterial pneumonia, bacteremia, and bacterial meningitis in older adults (Lederman et al., 1981). The need to establish higher vaccine effectiveness against these infections remains critical.

The beneficial effect of repeated vaccination was reported in several studies and encouraged in persons with DM, even if the effect is lower than in younger persons or those without DM. Evidence of changes in mortality risk from influenza among 26,071 older adults showed annual revaccination

reduced mortality risk for those with or without comorbidities, including DM (Vila-Córcoles et al., 2007). Persons with DM who had annual or repeated vaccinations had higher initial and final antibody titers immune responses for all of the influenza strains compared to persons without previous vaccination history (Feery et al., 1983). Also, this effect was seen on H1N1 influenza A strain (Egawa et al., 2014; Sheridan et al., 2015). While repeated vaccination of influenza vaccine did not reduce all-cause deaths in a community population of young and older adults (Looijmans-Van den Akker et al., 2006), a study of revaccination in older adults showed a 24% reduction in all-cause mortality (Voordouw et al., 2004). Protective effects of vaccination, and the supportive boost from annual revaccination for adults with DM, wane over time more quickly than for adults without DM (Feery et al., 1983). Levels of antibody responses for A/H1N1 were higher than pre-vaccination levels, at 1 month in adults with DM and control groups, and seroprotective levels 6 months after vaccination were higher than pre-vaccination levels for both groups, but significantly lower among older adults with DM than controls (Seo et al., 2015). Acknowledging these less-than-optimal effects does not obviate the need for revaccination to boost this protection even though it may not reach the levels of persons without DM.

Two factors were of primary interest in reviewing safety and tolerance of vaccines for persons with DM. The first factor was the extent to which immunization protects the older adult with DM. Most studies found that, while persons with DM have lower antibody responses and seroprotection than healthy persons without DM, vaccination provides some protection. This protection is more diminished as adults age (Egawa et al., 2014; Feery et al., 1983; Sheridan et al., 2015; Van Der Meeren et al., 2016). Some studies reported that older adults with DM reached protective levels of antibody titer for H1N1 and H3N2 influenza strains (Dorrell et al., 1997) and confirmed that vaccines are effective in this population (Colquhoun et al., 1997; Nam et al., 2011). An explanation may lie in histological studies indicating B-cell instrinsic inflammation in young and older adults with DM and higher TNF-α than controls. These responses indicate they may have hyperactive immune response that uses other molecular mechanisms to produce a response (Frasca et al., 2013)

The other factor related to safety was whether the immune response is influenced by the person's glycemic status and stability of their DM management. General safety of influenza vaccines is addressed in the research evidence as well as several reports made available to the public by CDC (2016a). Each of the studies and reports examining adverse effects of vaccines on older adults, with or without DM, affirm its safety. In a comparative study of vaccines adverse effects in community populations, these effects are low (7%) and include local redness or irritation of injection site, or side-effects of malaise, fatigue, or headache (Pillsbury et al., 2020). In this study, the younger group of older adults (65−69 years old) had more adverse symptoms than older adults. Less common were vomiting, diarrhea, seizures, or altered consciousness. These severe symptoms were not reported specifically in other reports as adults with DM. Malaise and skin irritations were considered minor in light of the potential for protection. Likewise, there were no indications that vaccines disrupted the older adult with DM's glycemic control or medication management (Dorrell et al., 1997).

Vaccines appear to have no adverse effect on glycemic control (Dorrell et al., 1997) and produce no difference in antibody levels between persons receiving insulin or oral diabetic medication (Feery et al., 1983). However, the reverse association shows difference in antibody responses to vaccination when glycemic control and A1C levels are poorly controlled. In comparisons of adults with type 1 DM with type 2 DM for reactivity to vaccines, there was significantly higher antibody response for H1N1 influenza vaccine in those with type 1 and in adults without DM, than those with type 2 DM (Pozzilli et al., 1986). These investigators raise the possibility that patients with poor metabolic control may have influenced immune responses. They found no differences between the two DM types or those without DM in antibody responses to influenza vaccine strain H3N2 and strain B (Pozzilli et al., 1986). Higher A1C levels resulted in low serological response to the pandemic-targeted influenza A (H1N1) pdm09 vaccine (Egawa et al., 2014). Humoral antibody response and the delayed type hypersensitivity reaction (DTHR) skin test for cellular immunity after trivalent influenza vaccine were lower in adults with DM who had high A1C, than in controls (Diepersloot et al., 1987). The particular strain of influenza virus may play a part in association between A1C level and sero-protection levels so that for other influenza vaccines, there was a marginally significant positive correlation in response to A/Perth/16/2009 (Sheridan et al., 2015). A few studies found no associations between serological response and age, sex, diabetes type, A1C (Colquhoun et al., 1997; Lederman et al., 1981) duration of diabetes (Nam et al., 2011).

Fewer studies were found that discussed safety or effectiveness of hepatitis B vaccine in older adults. This may be a reflection of the misconception that Hepatitis B is a disease of younger adults (Hoerger et al., 2013). However, there is emerging evidence that the incidence of hepatitis B infection may be higher than estimated because symptoms often go unrecognized as the disease progresses. If not treated, the condition presents clinically as an older adult with advanced liver disease. There is a rising incidence in older adults that has been linked, in part, to injection-drug use and multiple sex partners among aging populations (Schillie et al., 2020). For the person with DM, the risk is higher, with a 60% higher prevalence of past or present hepatitis B and double the likelihood of developing acute hepatitis B infection. At the same time, older adults with type 2 DM had lower immune responses to hepatitis B vaccine than those without DM

(Van Der Meeren et al., 2016), which suggests the possible need to vaccinate the person with DM in their youth. Threats of newer cases of hepatitis B are currently seen among older adults with DM who acquire the virus from contaminated or shared assisted blood glucose monitoring equipment in long term care settings (CDC, 2011; Seña et al., 2013). Additional details about these studies are available in Online Supplementary Material, Table 2 *Vaccine Protection, Safety, and Tolerance for Older Adults with DM*,

Issues Affecting Acceptance of Recommended Immunization for Older Adults

This review included 21 studies assessing factors that influenced the uptake, efficacy, or tendency to become vaccinated by studying the strength of these factors as correlates in multifactorial studies, strategies (see Table 4). Resources that addressed or tested strategies to improve uptake for older adults were limited but offered areas for intervention. Older reports from influenza pandemics in the 1980s and 1990s revealed factors of fear and lack of information that have relevance for today. Studies of effectiveness were reviewed to assess characteristics, responses, perceptions, and beliefs that hold clues to accepting immunization (Selvais et al., 1997). Wide agreement across pandemics and time reveals an ongoing need for incentives that persists today (Egede, 2003; Lewis-Parmar & McCann, 2002; Satman et al., 2013; Selvais et al., 1997; Verger et al., 2015; Wahid et al., 2001; Yu et al., 2014). Older adults were more likely to get vaccinated than younger adults and generally this was on advice from physicians. But physician visits did not guarantee increased awareness or education to the patient. Combined with feedback from surveys, most visits did not include vaccination recommendations. Neither number of visits to the physicians, nor DM severity was associated with increasing vaccination rates (Dower et al., 2011; Selvais et al., 1997).

Combined covariates often explained variations across studies in influential factors promoting vaccination. Most often variations were attributed to age (Achtymichuk et al., 2015; Davis et al., 2017; Dower et al., 2011; Egede, 2003; Jimenez-Garcia et al., 2017; Jimenez-Trujillo et al., 2015; Satman et al., 2013; Selvais et al., 1997; Shin et al., 2018; Wahid et al., 2001). Another common covariate that was logically related to frequency of medical oversight was having a chronic condition, such as DM (Byeon et al., 2018; Egede & Zheng, 2003a, 2003b; Machado et al., 2018; Jimenez-Trujillo et al., 2013; Santaularia et al., 2016; Satman et al., 2013; Vamos et al., 2016).

Marital status could have been a predictor related to age of older adults being vaccinated, given that women have a longer life expectancy and were widows (Achtymichuk et al., 2015; Jimenez-Garcia et al., 2017). However, the same could be expected of gender explaining tendency to be vaccinated, since culture and ethnicity can control behavioral differences between men and women regarding healthcare. Depending on age, independence, and accessibility, either men or women may hold different perceptions about immunizations. Behavioral vaccination decisions in one study showed women fearing adverse effects of vaccine and men not perceiving infection risk or need for protection (Jimenez-Garcia et al., 2017). No effect of gender was seen on vaccination rates in some studies (Egede & Zheng, 2003b; Satman et al., 2013), while another reported that males had higher vaccination rates (Jimenez-Trujillo et al., 2013) and another found higher rates in females (Shin et al., 2018; Yu et al., 2014). Finally, gender-related cultural and ethnic influences may have influenced self-reported data and hold some reporting bias (Dodd-McCue & Tartaglia, 2010).

An interesting difference in DM type was found in two studies where older adults with type 2 DM were more likely to accept vaccination than those with type 1 DM (Selvais et al., 1997; Wahid et al., 2001). One factor blamed for this in an older study was the misconception of benefits for vaccinating persons with DM at any age (Selvais et al., 1997). This attitude concerning need for vaccination with DM is seen in the second study that found that older adults with DM had higher vaccination rates because of other comorbidities, not DM (Wahid et al., 2001). Each of these studies contains covariates that suggest possible factors for the variation.

Income or financial barriers were not seen as single factors causing reluctance to be immunized. In fact, in one large study, the national health insurance fund provided influenza vaccinations at no cost, but found attitudinal barriers played an important role in participation (Verger et al., 2015). One study found higher vaccination rates among men with low income, those that were unemployed and married (Byeon et al., 2018). Other studies found their immunized majority were older, married, with lower educational level, but using generally healthy behaviors (Jimenez-Trujillo et al., 2015; Jimenez-Garcia et al., 2017). Those with multiple prescribed medications (Davis, Kauhanen, & Davis, 2017), and age (Gorska-Ciebiada et al., 2015; Lewis-Parmar & McCann, 2002; Satman et al., 2013). Another study found adults with 10−12 or more visits to the physician had increased vaccination rates (Egede, 2003). Other factors identified as increasing vaccination rates included recommendations from family and friends, having previous vaccinations, and having no concerns about vaccine side effects (Lewis-Parmar & McCann, 2002; Yang et al., 2017).

The following deterrents to vaccination were cited: Lack of accurate information about vaccination, low perceived benefits of vaccine (Gorska-Ciebiada et al., 2015; Wahid et al., 2001; Yu et al., 2014), feeling healthy already, wishing to stay home (Davis et al., 2017), and fear of vaccine related complications (Gorska-Ciebiada et al., 2015; Jimenez-Garcia et al., 2017; Wang et al., 2013; Yang et al., 2017). Recommendations encouraged by research investigators included physician encouragement and comprehensive community efforts, such as vaccine campaigns (Selvais et al., 1997; Vila-Córcoles et al., 2006; Wahid et al., 2001; Yang

et al., 2017). It would logically follow that vaccination rates could also be improved by encouragement from physicians, particularly if patients with DM are seen regularly for glycemic management (Villarroel & Vahratian, 2016). Recommendations from care providers are effective, when given, yet some patients report that their physicians have never recommended vaccination to them. Findings related to higher vaccination rates for those with healthy lifestyles, emphasize importance of adherence to recommendations when they receive them from a trusted source (Achtymichuk et al., 2015; Byeon et al., 2018; Lewis-Parmar & McCann, 2002; Wahid et al., 2001; Yang et al., 2017). Additional details about these studies are available in Online Supplementary Material, Table 3 *Factors and Perceptions Influencing Older Adults' Tendencies to Seek Vaccinations.*

Discussion

Aware of the constantly developing composition and technological advancement of vaccines, the authors recognize the transitory nature of the research findings presented here. The field of vaccine science is always moving, acutely defined by the ongoing quest for effective protection, driven by ever-changing characteristics of offending infections. Reviewing some pandemics from the 1980s and 1990s was informative to assess progress and continuing challenges in protecting vulnerable populations.

The nature of the selected studies was diverse, adding interest but creating complexity for comparative assessment. An early decision to not conduct a meta-analysis was appropriate, even though most studies provided some quantitative data. Lack of comparable measurements across studies and the diversity of sample characteristics made meaningful comparisons between studies impossible and did not lend itself to statistical comparisons and generalizability to other populations. (DeShea & Toothaker, 2015). Studies to examine effectiveness of existing vaccine programs were primarily descriptive as were the majority of reports. Outcomes of effectiveness included retrospective assessments of infection-related hospitalizations or deaths to determine effectiveness of vaccination efforts. Still other comparisons were done of the same populations showing the durability or persistence of immune factors over time. Effectiveness, including durability of effect, remains a problem for specific strains of influenza, and the need for annual repeat vaccinations each year is recommended to boost this response. The lack of consistencies in vaccination rates across studies may provide a bias by omitting or failing to adjust for factors that influence behavior, such as culture, work and family obligations, or disabilities. There may be significant differences in healthcare policies, regulations, insurance, and cost reflected in the several international studies reported here. The review possibly missed important reports not published in English, or if the search strategy failed to capture them. Some inconsistencies across study findings regarding uptake, health behaviors, and coverage may reflect the variety of data collection methods used, including self-reports, postal questionnaires (Lewis-Parmar & McCann, 2002), Practice Research Datalink (Vamos et al., 2016), and the Behavioral Risk Factor Surveillance System (BRFSS) (Santaularia et al., 2016). Some studies with focus on coverage or participation did not provide specifics on type or number of survey items. However, the issues of vaccine safety and effectiveness for prevention of three main infectious diseases affecting the aging adult was confirmed by research and CDC reports for older adults with DM.

For health care, the need, supply, and demand for vaccines is challenged by the barriers to participation from the public to become vaccinated. Findings of this systematic review reaffirmed the evidence that aging negatively affects immune responses of older adults and explained approaches to develop vaccines with immune enhancers. These studies report that aging adults with DM experience even lower antibody responsivity to vaccine antigens than aging adults without DM. Yet DM status played a less significant role in seropositivity than age if the person maintained metabolic control and blood glucose management. Regular vaccinations against influenza are found to help the older adult boost seropositive responses to each subsequent vaccination. Vaccines potentially help to maintain the older adults with DM's quality of life by decreasing hospitalizations and ICU admissions, with the need for adjuvant enhancers and repeated annual immunization for the aging population at large. These findings raise both the need for older adults to be immunized and awareness that age-related lower seroprotection makes it necessary to revaccinate. It also points out a reality that, in the light of diminished protection, vaccine-protected older adults will still need to reduce exposure when possible.

The potential bias of healthy-user participants in vaccination studies was confirmed in several studies in the review. Participation of healthy younger adults and older adults with DM with comorbidities was higher than that of younger adults with poor health. This leads experts to predict that higher functional status and health awareness are major determinants of vaccine receipt. Healthy users, with and without DM, may also be more likely to participate in surveys.

The review reveals a definite need for further research on barriers and facilitators surrounding vaccination practices among older adults. Influencing factors and strategies for improvement are likely to differ between older adults who control vaccination decisions for themselves and those who are cared for by others. In clinical practice, this suggests an urgent need to raise awareness among caretakers and responsible family members about necessary vaccine protection of older adults. A nearly unanimous theme from studies concerned with vaccination participation was to promote more encouragement to patients from physicians and primary care providers. Fear of vaccine side effects was an often-reported

reason why persons refuse immunizations and suggests a lack of information about vaccines and their sequelae. CDC recommendations, government sponsored projects, and their websites remain reliable sources of information for patients, families, and caregivers with answers to questions and dispel myths about vaccination. Missing are easily found links to acquaint the general public with these resources.

While repeated annual vaccinations may boost immunity in subsequent seasons, a vaccine-protected community offers even more protection. Campaigns or other efforts to improve protection for older adults are incomplete unless they also encourage steps to reduce factors in the surrounding healthy population that make them vectors to vulnerable members of the entire population.

Findings of this review raise concern for older adults during the winter months of influenza outbreaks and in the context of the current COVID-19 pandemic. A confluence of both diseases will understandably stretch treatment resources. Questions about immune responses and durability of protection run high and challenge the world's health as older adults face the current pandemic. The media images of government officials, celebrities, and trusted national leaders in receiving immunizations have helped to demystify and reduce some fear among the public. But despite development of an effective immunization to prevent COVID-19 infection, the older adult will likely encounter many of the same challenges they face achieving effective influenza immunization.

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Supplemental Material

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