Journal of Alzheimer's Disease xx (20xx) x–xx
DOI 10.3233/JAD-221231
IOS Press

The Impact of Routine Vaccinations on Alzheimer's Disease Risk in Persons 65 Years and Older: A Claims-Based Cohort Study using Propensity Score Matching

Kristofer Harris[a,1], Yaobin Ling[b,1], Avram S. Bukhbinder[a,c,1], Luyao Chen[b], Kamal N. Phelps[a], Gabriela Cruz[a], Jenna Thomas[a], Yejin Kim[b], Xiaoqian Jiang[b] and Paul E. Schulz[a,*]
[a]*Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA*
[b]*School of Biomedical Informatics, University of Texas Health Science Center at Houston, Houston, TX, USA*
[c]*Division of Pediatric Neurology, Massachusetts General Hospital, Boston, MA, USA*

Accepted 5 July 2023
Pre-press 7 August 2023

Abstract.
Background: Accumulating evidence suggests that adult vaccinations can reduce the risk of developing Alzheimer's disease (AD) and Alzheimer's disease related dementias.
Objective: To compare the risk for developing AD between adults with and without prior vaccination against tetanus and diphtheria, with or without pertussis (Tdap/Td); herpes zoster (HZ); or pneumococcus.
Methods: A retrospective cohort study was performed using Optum's de-identified Clinformatics® Data Mart Database. Included patients were free of dementia during a 2-year look-back period and were ≥ 65 years old by the start of the 8-year follow-up period. We compared two similar cohorts identified using propensity score matching (PSM), one vaccinated and another unvaccinated, with Tdap/Td, HZ, or pneumococcal vaccines. We calculated the relative risk (RR) and absolute risk reduction (ARR) for developing AD.
Results: For the Tdap/Td vaccine, 7.2% ($n = 8{,}370$) vaccinated patients and 10.2% ($n = 11{,}857$) unvaccinated patients developed AD during follow-up; the RR was 0.70 (95% CI, 0.68–0.72) and ARR was 0.03 (95% CI, 0.02–0.03). For the HZ vaccine, 8.1% ($n = 16{,}106$) vaccinated patients and 10.7% ($n = 21{,}273$) unvaccinated patients developed AD during follow-up; the RR was 0.75 (95% CI, 0.73–0.76) and ARR was 0.02 (95% CI, 0.02–0.02). For the pneumococcal vaccine, 7.92% ($n = 20{,}583$) vaccinated patients and 10.9% ($n = 28{,}558$) unvaccinated patients developed AD during follow-up; the RR was 0.73 (95% CI, 0.71–0.74) and ARR was 0.02 (95% CI, 0.02–0.03).
Conclusion: Several vaccinations, including Tdap/Td, HZ, and pneumococcal, are associated with a reduced risk for developing AD.

Keywords: Alzheimer's disease, cohort, dementia, diphtheria, epidemiology, herpes zoster, pertussis, pneumococcus, tetanus, vaccine

[1]These authors contributed equally to this work.

*Correspondence to: Paul Schulz, MD, Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston, 1941 East Rd, Houston, TX 77054, USA. Tel.: +1 713 486 0500; E-mail: Paul.E.Schulz@uth.tmc.edu.

INTRODUCTION

There are multiple theories as to the etiology of Alzheimer's disease (AD). One hypothesis is that infection may play a causative role in the development of AD and Alzheimer's disease related dementias (ADRDs) [1–4]. Viral, bacterial, and fungal infections may increase neuroinflammation, thereby causing or exacerbating neurodegeneration, and subsequently dementia [1, 3]. Vaccines may reduce the risk for developing infections, or limit their severity, reducing an individual's neuroinflammatory burden, decreasing the immune mechanisms that may contribute to the development of AD/ADRD [5]. Alternately, vaccines may activate alternative pathways of the immune system that may alter the risk for AD/ADRD [5, 6].

Three vaccines recommended by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) for older adults are against tetanus, diphtheria, with and without pertussis; herpes zoster; and pneumococcus [7].

Tetanus, diphtheria, and pertussis are bacterial infections that can lead to severe complications including hospitalization and death, especially in patients 65 and older. These infections are caused by *Clostridium tetani* through wounds [8], and *Corynebacterium diphtheria* and *Bordetella pertussis* through respiratory droplets [9, 10]. Pertussis has been of interest for researchers studying AD. One hypothesis postulates that pertussis colonization in the nasopharynx and potential accrual in the central nervous system through the olfactory nerve leads to or exacerbates amyloid-beta and tau tangle accumulation in the brain [11]. Vaccines for these three diseases are available to adults as either a combined tetanus, diphtheria, and acellular pertussis vaccine (Tdap), and tetanus and diphtheria (Td) [12]. Tetanus toxoid (TT) has been utilized in patients with a tetanus-prone wound; however, it is not recommended over Tdap and Td [13]. There are multiple brands of the Tdap (Adacel, Boostrix) and Td (TENIVAC, TDVAX) vaccines available in the United States [12]. A single dose of Tdap is given to patients who have never received Tdap previously [7]. A booster of Tdap or Td can then be given every ten years. Tdap or Td are recommended for a tetanus-prone wound if a patient has not received such a vaccine in the past five years [12, 14].

Herpes zoster (HZ) is caused by reactivation of latent varicella zoster virus [15]. Estimates of lifetime HZ incidence show that nearly one-third of the world's population will develop HZ [16, 17]. Patients with a history of HZ have an increased risk for developing dementia [18–20]. The herpes zoster vaccine currently recommended in the US, Shingrix, has been available since 2017 to patients 50 years and older and immunocompromised patients 19 years and older [21]. Shingrix is a recombinant vaccine containing varicella-zoster glycoprotein E antigen and an adjuvant which is given as a two-dose series. It has been demonstrated to be 91% effective at preventing HZ [21]. From 2008 to 2020, the live-attenuated varicella vaccine, Zostavax, was recommended in the US for the prevention of herpes zoster among those 60 and older [22, 23]. The Zostavax vaccine reduces the risk of HZ by 51% [22, 24].

Pneumococcal infection is caused by *Streptococcus pneumoniae* (i.e., pneumococcus) [25]. Patients 65 and older are at higher risk for severe disease [26]. There are two types of pneumococcal vaccines for adults: the pneumococcal polysaccharide vaccine (PPSV-23) and the pneumococcal conjugate vaccine (PCV13, PCV15, or PCV20) [25]. The PPSV-23 vaccine contains the purified capsular polysaccharide for twenty-three different serotypes of *Streptococcus pneumoniae*; whereas the PCV-13 vaccine only contains thirteen serotypes, but also contains a modified diphtheria toxin protein as a conjugant [25]. PPSV-23 was first approved for use in 1983, and until 2021, the CDC recommended that all adults 65 and older receive a dose of PPSV-23 [25, 27]. Between 2014–2019, it was recommended that adults aged 65 years and older receive a dose of PCV-13 prior to the PPSV-23. Since June 2019, however, PCV-13 is no longer routinely recommended for immunocompetent adults 65 or older. Instead, it is given after "shared clinical decision-making" [28]. PCV-13 is 75% effective at preventing invasive serotype-specific pneumococcal disease, while PPSV-23 is 60–70% effective [29].

Previous studies on the effect of vaccinations on dementia risk have proven promising. Recent publications utilizing a retrospective design have demonstrated a decreased risk of dementia among patients who received an HZ vaccine [30–33], Tdap vaccine [30, 34], or pneumococcal vaccine [35, 36]. However, there are gaps within the literature that this study addresses, including differences in the effects of various types of vaccines (i.e., recombinant versus live attenuated, conjugated versus unconjugated) on the risk of AD. There are two purposes for this study: 1) To evaluate the relationship between exposure to either the HZ, Tdap/Td, or pneumococcal

vaccines and the risk of AD; and, 2) to investigate whether the effects of HZ or pneumococcal vaccines on the risk of AD, if present, vary by the type of vaccine (i.e., recombinant versus live attenuated for HZ vaccination, conjugated versus unconjugated for pneumococcal vaccination). Differences in immunogenicity among the vaccine types, such as the involvement of CD4+ T-cells and production of long-lasting humoral immunity induced by the conjugated pneumococcal vaccines (e.g., PCV13) but not by polysaccharide-only vaccines (e.g., PPSV23) [37], may result in differential effects on AD risk among the differing vaccine types. Alternatively, the efficacy of protection against infectious burden among vaccines targeting the same pathogen (e.g., Shingrix versus Zostavax against Herpes Zoster) may modulate the magnitude of an effect between these vaccines and AD risk. In light of the above, we hypothesize that routine adult vaccinations decrease the risk of AD in patients 65 years and older. We also hypothesize that that recombinant (when compared with live attenuated) and conjugated (when compared with unconjugated) vaccinations are associated with a greater decrease in AD risk due to the greater protection against infectious disease from Shingrix (compared to Zostavax) and the more robust adaptive immune response induced by conjugated vaccines.

METHODS

Data source and study period

The study cohort was obtained from Optum's de-identified Clinformatics® Data Mart Database (CDM). The claims database records information from different sources in the United States, such as medical, pharmaceutical, and administrative claims, as well as laboratory test results. The database includes patients who have both medical and prescription drug coverage through private insurance or Medicare Advantage with Part D. Mortality information from hospital discharge claims and the Social Security Administration Death Master file is also available in the CDM. All data are verified, adjudicated, adjusted, and de-identified before inclusion in the CDM.

The CDM for our study includes the years 2009 through 2019. With the exception of three sub-analyses (as discussed in the Analysis Overview section below), all analyses were performed using a look-back period of September 1, 2009 to August 31, 2011 and a follow-up period of September 1, 2011 to August 31, 2019.

Cohort selection

With the definition of the look-back period and the follow-up period, we implemented inclusion and exclusion criteria to build a cohort for analyzing the effects of the targeted vaccines (Fig. 1).

We included patients who were at least 65 years old at the start of the follow-up period. Patients were included if they had at least one record in the look-back period and had at least two records during the follow-up. If patients had 1) a recorded diagnosis of dementia, mild cognitive impairment, or encephalopathy, or 2) were prescribed any medication primarily indicated for AD (i.e., donepezil, galantamine, rivastigmine, or memantine) during the look-back period, they were excluded from the cohort.

Exposure measurement

Vaccinations were counted if they were received on or after the index date (i.e., the first day of the follow-up period) but before the following occurred: 1) AD onset, 2) death, or 3) the end of the follow-up period. We investigated three kinds of vaccination in this study: Tdap/Td, herpes zoster, and pneumococcal vaccines. To identify vaccinations, we queried the database for their brand names and generic names as found in Supplementary Table 1. For the Tdap/Td vaccine sample, we excluded vaccines not indicated for patients 65 years and older (i.e., DTaP). For the HZ vaccines, only the two brands of vaccines approved by the FDA for use in the U.S. were included: Zostavax and Shingrix. And for the pneumococcal vaccines, we included PCV13 and PPSV23, while excluding Pneumococcal 7-val vaccines as they are only used for pediatric patients [26].

Outcome measurement

The procedure and rationale for outcome measurement is the same as what was used in our recent study of incident AD risk following influenza vaccination [38]. We identified patients as having AD if they met any of the following three criteria in any 12-month window during the follow-up period: 1) two or more diagnoses of AD in their records, 2) one or more diagnoses of AD and one or more prescription records for AD-related medications, or 3) two

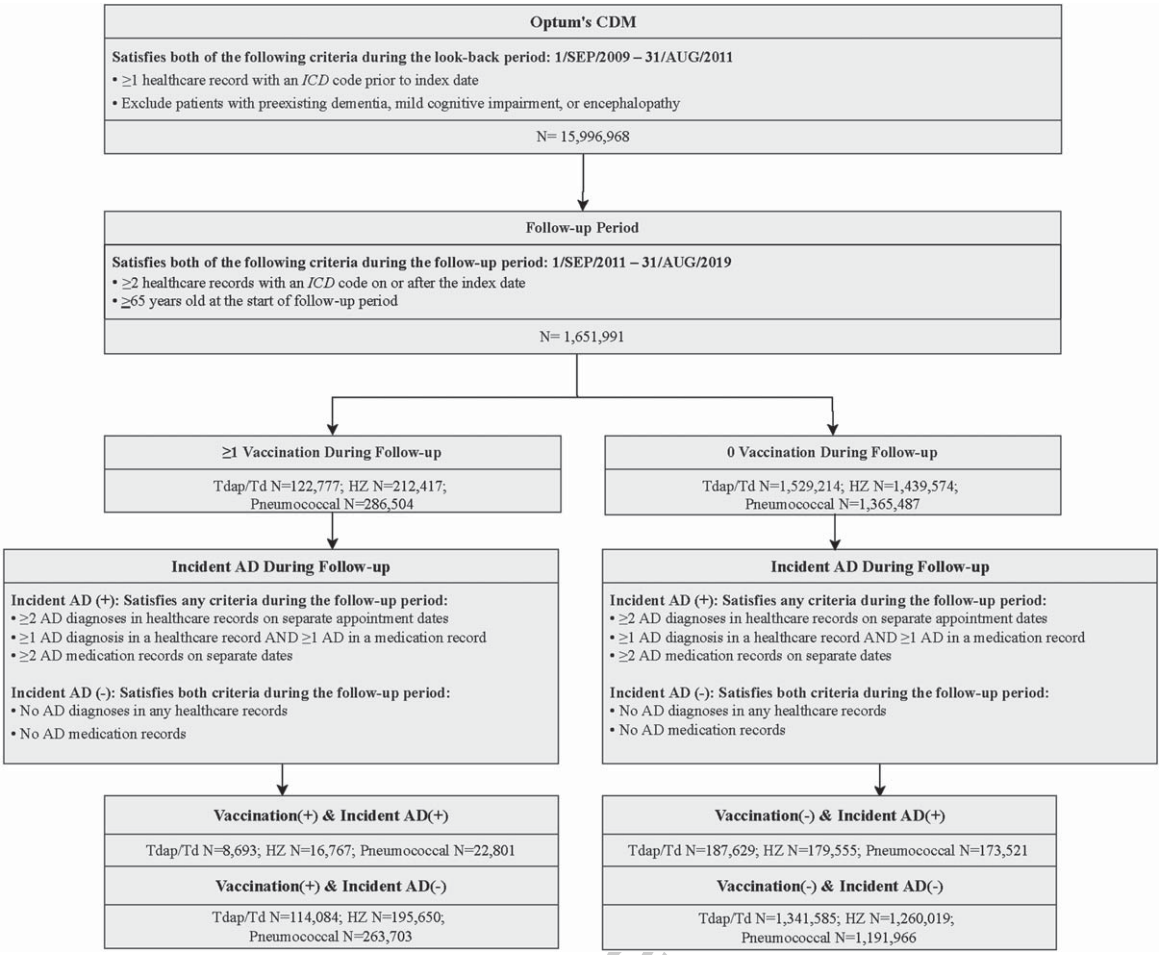

Fig. 1. Flowchart of Sampling Methodology. The three main analyses using Tdap/Td, HZ, and pneumococcal vaccinations are shown. AD, Alzheimer's disease; CDM, Optum's de-identified Clinformatics® Data Mart Database; HZ, Herpes zoster; ICD, International Classification of Diseases; Tdap/Td, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis/Tetanus toxoid, and reduced diphtheria toxoid. Figure adapted from Bukhbinder et al. [38]. Reprinted from *Journal of Alzheimer's Disease*, vol. 88, no. 3, Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE, Risk of Alzheimer's disease following influenza vaccination: a claims-based cohort study using propensity score matching, pp. 1061-1074, 2022, with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-220361.

or more prescription records for AD-related medications. Patients who only have one record of an AD diagnosis or AD-related prescription were removed from the cohort. The *ICD* codes and medications used for identifying AD are located in Supplementary Table 1. A systematic review of validation studies for AD and ADRD in administrative datasets provide support for our inclusion and exclusion criteria for the outcome measurement [39]. The authors found that the positive predictive value (PPV) of a patient having dementia increased from 68% to 94% if two or more diagnosis codes were utilized instead of just one. Further, they found that the PPV is 97% when using AD medication codes to identify patients with AD. Lastly, we elected to make use of nonspecific dementia codes, as well as AD specific codes, in identifying AD patients. This is because, although 60–70% of dementia cases among older adults are secondary to AD, nonspecific dementia codes (e.g., senile dementia) are significantly more common than codes for specific dementia subtypes (e.g., AD, vascular dementia) in administrative claims data [40, 41]. For example, a study of Medicare beneficiaries found that 46.1% of patients only had a code for dementia not otherwise specified, 4.5% of patients only had a code for AD, and 29% of patients had codes for both dementia not otherwise specified and for AD [40].

Covariate measurement

Similar to our previous research on influenza vaccination and AD risk [38], and to another study on influenza vaccination and dementia in a Veterans Affairs cohort [42], we included covariates for patient demographics, comorbidities, medication use, and the number of healthcare encounters and routine "well visit" examinations (as proxies for healthcare utilization rate). For this analysis, we also included information pertaining to receipt of routine vaccinations, including those against tetanus, diphtheria, with or without pertussis; herpes zoster; pneumococcus; and influenza. Importantly, the vaccine(s) used in the exposure definition (see "Analysis Overview" below) for a given analysis was not included as a covariate in that analysis; for example, in the analysis comparing persons who received either Tdap or Td with those who received neither during follow-up, Tdap and Td vaccinations during the look-back period were not included as a covariate in the propensity score model. A detailed list of the covariates and their definitions is provided in Supplementary Table 1. For all covariates except age, the last measurement recorded in the look-back period was used as the baseline covariate value.

Estimating ATT using propensity score matching

We estimate the average treatment effect on the treated (ATT) of the three vaccination groups on AD risk using propensity score matched (PSM) (Fig. 2). We utilized PSM to minimize selection bias from unbalanced confounders between the vaccinated and unvaccinated groups. The propensity scores were estimated by fitting a logistic regression model with all the baseline characteristics measured during the look-back period to predict the probability of vaccination. For non-static variables (e.g., BMI), the last measurement in the look-back period (i.e., the one closest to the start of follow-up) was used. We assumed that receiving one kind of vaccine would lead to a higher probability of receiving other kinds of adult vaccines, and therefore, we included other routine vaccines as covariates (see "Covariate Measurement" above). Patients with unknown sex, geographic region, or race were excluded from this analysis. Once we estimated the propensity scores using logistic regression, a one-to-one nearest neighbor matching with a caliper width of 0.2 standard deviations of the logit of the propensity score and without replacement was used to match each patient that met target vaccine group criterion with a patient in the unvaccinated group [43]. To evaluate the balance between vaccinated and unvaccinated groups after matching, we calculated the standardized mean difference (SMD) for each covariate before and after matching. An adequate balance between the groups was defined as an SMD ≤ 0.10 [44].

Analysis overview

We performed three main analyses and then separate sub-analyses for each of the vaccines recommended by the CDC. In these analyses, we created vaccinated and unvaccinated balanced cohorts by PSM and estimated ATT in order to evaluate for heterogeneity in the effect size among the vaccines targeting the same pathogenic species. Each analysis performed had a different unvaccinated cohort. There were thirteen analyses performed in total.

In the Tdap/Td vaccine group, the main analysis was performed on patients who were vaccinated with either Tdap and Td as the exposed group and unvaccinated patients in an unexposed cohort. We included four other analyses: patients who received 1) at least one Tdap, Td, or TT vaccine; 2) at least one Tdap vaccine; 3) at least one Td vaccine; and, 4) at least one TT vaccine.

With regard to HZ vaccines, the main analysis included patients who received at least one Zostavax or at least one Shingrix vaccine. The sub-analyses included patients who 1) were fully vaccinated using the Shingrix vaccine (completed two doses of the vaccine); 2) received at least one Zostavax vaccine and were fully vaccinated using the Shingrix vaccine; 3) received at least one Shingrix vaccine but no Zostavax vaccine; and, 4) received at least one Zostavax vaccine but no Shingrix vaccine.

For the pneumococcal vaccines, the main analysis included patients who received at least one PCV-13 vaccine or PPSV-23 vaccine. The two sub-analyses were for patients who received 1) at least one PCV-13 vaccine, but no PPSV-23 vaccine; and 2) at least one PPSV-23 vaccine, but no PCV-13 vaccine.

The look-back and follow-up periods were 2009–2011 and 2011–2019 for most of the analyses, with three exceptions necessary to account for the year in which two of the vaccines (Shingrix and PCV-13) were added to the CDC's routine immunization schedule for older adults. As discussed earlier, Shingrix was first approved and recommended for use in 2017 [15, 21]. Hence, for the sub-analysis of patients who received at least one Shingrix vaccination but

Table 1
Baseline characteristics of patients with and without Tdap/Td during the follow-up period before and after PSM

	Panel 1: Before propensity score matching			Panel 2: After propensity score matching		
	No Tdap vaccinations during follow-up (n = 1,529,214)	≥1 Tdap vaccinations during follow-up (n = 122,777)	SMD	No Tdap vaccinations during follow-up (n = 116,400)	≥1 Tdap vaccinations during follow-up (n = 116,400)	SMD
Age, y, mean (SD)	73.1 (5.7)	71.9 (5.0)	0.2101	72.0 (5.2)	72.0 (5.0)	–0.0072
Sex						
Unknown	214 (0.01%)	11 (0.01%)	0.0047	NA	NA	
Female	854,745 (55.89%)	70,836 (57.69%)	–0.0364	67,025 (57.58%)	67,114 (57.66%)	–0.0015
Male	674,256 (44.09%)	51,930 (42.3%)	0.0121	49,375 (42.42%)	49,286 (42.34%)	0.0015
Race						
Unknown	114,104 (7.46%)	6,315 (5.14%)	0.0955	NA	NA	
Asian	43,079 (2.82%)	3,554 (2.89%)	–0.0047	3,035 (2.61%)	3,553 (3.05%)	–0.0268
Black	135,762 (8.88%)	11,087 (9.03%)	–0.0053	10,152 (8.72%)	11,085 (9.52%)	–0.0278
Hispanic	134,543 (8.8%)	8,636 (7.03%)	0.0669	9,367 (8.04%)	8,627 (7.41%)	0.0238
White	1,101,727 (72.05%)	93,185 (75.9%)	–0.0879	93,846 (80.62%)	93135 (80.01%)	0.0154
Geographic region						
Unknown	1,048 (0.07%)	56 (0.05%)	0.0096	NA	NA	
Northeast	138,212 (9.04%)	11,409 (9.29%)	–0.0088	10,788 (9.27%)	10,821 (9.3%)	–0.001
North central	344,302 (22.51%)	29,280 (23.85%)	–0.0316	27,113 (23.29%)	28,037 (24.09%)	–0.0187
South	566,337 (37.03%)	42,670 (34.75%)	0.0476	43,156 (37.08%)	41,018 (35.24%)	0.0382
West	479,316 (31.34%)	39,362 (32.06%)	–0.0154	35,343 (30.36%)	36,524 (31.38%)	–0.022
No. of health care encounters[a], mean (SD)	24.9 (26.1)	22.9 (21.7)	0.0828	22.1 (22.2)	23.1 (21.8)	–0.0454
No. of routine annual check-ups ("well visits")	0.6 (1.0)	0.7 (1.0)	–0.1418	0.7 (1.1)	0.7 (1.0)	–0.0149
Comorbidities						
Asthma	119,583 (7.82%)	9,276 (7.56%)	0.0099	7,898 (6.79%)	8,863 (7.61%)	–0.0321
Atrial fibrillation or flutter	152,609 (9.98%)	8,831 (7.19%)	0.0996	7,819 (6.72%)	8,452 (7.26%)	–0.0213
B12 deficiency	53,072 (3.47%)	3,559 (2.9%)	0.0326	3,151 (2.71%)	3,406 (2.93%)	–0.0132
Congestive heart failure	139,821 (9.14%)	6,144 (5%)	0.1594	5,353 (4.6%)	5,901 (5.07%)	–0.022

COPD	221,648 (14.49%)	12,163 (9.91%)	0.1405	10,907 (9.37%)	11,663 (10.02%)	–0.022
Hyperlipidemia	1,069,831 (69.96%)	88,677 (72.23%)	–0.05	83,731 (71.93%)	84,339 (72.46%)	–0.0117
Hypertension	1,096,354 (71.69%)	84,550 (68.86%)	0.0619	79,900 (68.64%)	80,535 (69.19%)	–0.0118
Ischemic heart disease	353,523 (23.12%)	22,514 (18.34%)	0.1181	20,766 (17.84%)	21,516 (18.48%)	–0.0167
Obesity	116,184 (7.6%)	9,060 (7.4%)	0.0083	7966 (6.84%)	8,676 (7.45%)	–0.0236
Traumatic brain injury	6,961 (0.46%)	417 (0.34%)	0.0183	399 (0.34%)	401 (0.34%)	–0.0003
Type II diabetes	388,303 (25.39%)	27,155 (22.12%)	0.077	24,722 (21.24%)	25,955 (22.3%)	–0.0257
Stroke	52,951 (3.46%)	2,780 (2.26%)	0.0719	2,366 (2.03%)	2,656 (2.28%)	–0.0171
Alcohol use disorder	14,171 (0.93%)	767 (0.62%)	0.0344	690 (0.59%)	733 (0.63%)	–0.008
Anxiety disorder[b]	162,626 (10.63%)	11,050 (9%)	0.055	9667 (8.3%)	10,561 (9.07%)	–0.0273
Depression	109,197 (7.14%)	6,920 (5.64%)	0.0616	5987 (5.14%)	6,627 (5.69%)	–0.0243
Substance use disorder[c]	11,311 (0.74%)	640 (0.52%)	0.0276	591 (0.51%)	611 (0.52%)	–0.0023
Tobacco use	145,973 (9.55%)	10,088 (8.22%)	0.0467	8,870 (7.62%)	9,626 (8.27%)	–0.024
Medications (sustained use)[d]						
Anticholinergics	86,220 (5.64%)	5,464 (4.45%)	0.0543	5,056 (4.34%)	5,285 (4.54%)	–0.0095
Antihypertensives	41,071 (2.69%)	2,452 (2%)	0.0456	2,146 (1.84%)	2,362 (2.03%)	–0.0135
Antivirals	21,062 (1.38%)	1,996 (1.63%)	–0.0204	1,726 (1.48%)	1,925 (1.65%)	–0.0138
Glucocorticoids	133,544 (8.73%)	10,471 (8.53%)	0.0073	9,056 (7.78%)	10,095 (8.67%)	–0.0325
Metformin	162,350 (10.62%)	13,222 (10.77%)	–0.0049	11,886 (10.21%)	12,661 (10.88%)	–0.0217
NSAIDs	196,438 (12.85%)	17,278 (14.07%)	–0.036	15,247 (13.1%)	16,569 (14.23%)	–0.0331
Statins	623,884 (40.8%)	54,745 (44.59%)	–0.0767	51,308 (44.08%)	52,218 (44.86%)	–0.0157
Sulfonylureas	121,153 (7.92%)	8,336 (6.79%)	0.0434	7,542 (6.48%)	8,008 (6.88%)	–0.016
Vaccination						
Influenza vaccination	86,511 (5.66%)	10,418 (8.49%)	–0.1105	8,980 (7.71%)	10,003 (8.59%)	–0.0321
HZ vaccination	19,716 (1.29%)	2,928 (2.38%)	–0.0816	2,412 (2.07%)	2,752 (2.36%)	–0.0198
Pneumococcal vaccination	10,189 (0.67%)	1,404 (1.14%)	–0.0504	1,155 (0.99%)	1,335 (1.15%)	–0.015

Variable definitions are provided in Supplementary Table 1. Categorical variables are reported as frequency and percentage, and continuous variables as mean and standard deviation. Because patients with unknown geographic region, race, and sex are excluded prior to performing the propensity score matching (PSM), those rows after PSM are labelled as NA. [a]Number of outpatient or inpatient healthcare encounters during the look-back period. [b]"Anxiety disorder" is a composite variable of post-traumatic stress disorder, panic disorder, anxiety disorder not otherwise specified, obsessive compulsive disorder, social phobia, and generalized anxiety disorder. [c]"Substance use disorder" is a composite variable of substance use disorders involving any of the following: opioids; cannabis; sedatives, hypnotics, or anxiolytics; cocaine; amphetamines or other stimulants; hallucinogens; inhalants; and/or other psychoactive substances, including polysubstance use. [d]"Sustained use" is defined as ≥ 2 prescription claims in any 6-month period during the look-back period. COPD, chronic obstructive pulmonary disease; HZ, Herpes zoster; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SMD, standardized mean difference; Tdap, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td, Tetanus toxoid and reduced diphtheria toxoid. Table adapted from Bukhbinder et al. [38]. Reprinted from *Journal of Alzheimer's Disease*, vol. 88, no. 3, Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE, Risk of Alzheimer's disease following influenza vaccination: a claims-based cohort study using propensity score matching, pp. 1061-1074, 2022, with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-220361.

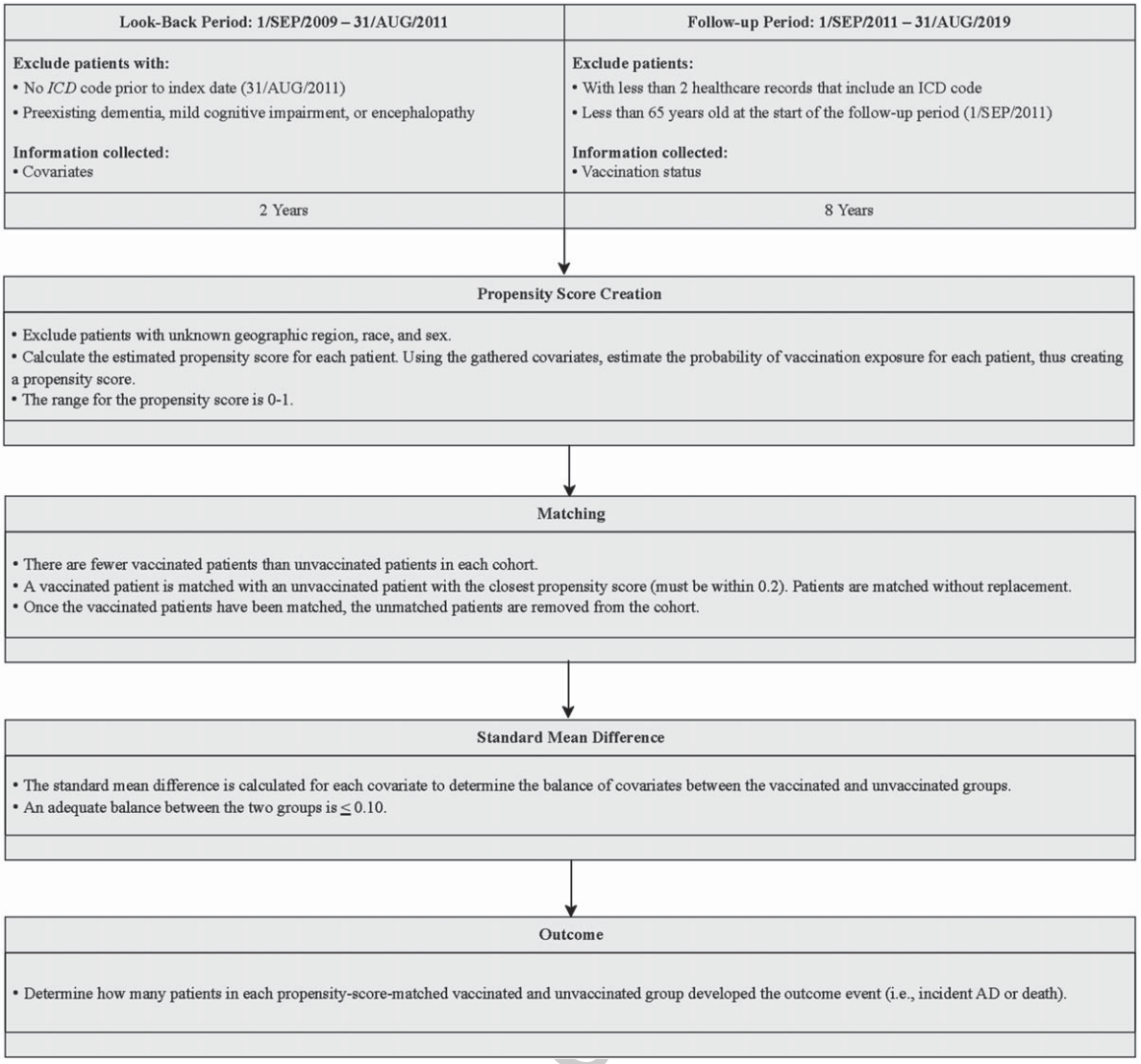

Fig. 2. Overview of Cohort Selection and Propensity Score Matching. AD, Alzheimer's disease; ICD, International Classification of Diseases. Figure adapted from Bukhbinder et al. [38]. Reprinted from *Journal of Alzheimer's Disease*, vol. 88, no. 3, Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE, Risk of Alzheimer's disease following influenza vaccination: a claims-based cohort study using propensity score matching, pp. 1061-1074, 2022, with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-220361.

no Zostavax vaccination, and for the patients who received the full Shingrix series (two doses) during follow-up but no Zostavax vaccines, we set the look-back period to 2009–2017 and the follow-up period to 2017–2019. Similarly, because the PCV-13 vaccine was first recommended for older adults in 2014, the sub-analysis of patients who received at least one PCV-13 vaccination but no PPSV-23 used a look-back period spanning 2009–2014 and a follow-up period spanning 2014–2019 [25, 27, 28].

For all of the analyses, we computed relative risk (RR), absolute risk reduction (ARR), and the corresponding 95% confidence intervals (CIs). When constructing the 95% CI for the point estimators, given that the study cohort is propensity-score-matched cohort, we used a method that accounts for the pairwise dependence between matched samples [45, 46]. E-values for point estimates were calculated to assess how strongly an unmeasured confounder would need to be associated with both the probability of vaccination and the probability of AD, while controlling for the covariates in our analyses, in order to render the results statistically insignificant. For example, if the E-value for the RR of an analysis is 4,

then an unmeasured confounder would need to have a RR of ≥ 4 (while controlling for the same covariates) with both the exposure (vaccination) and with the outcome (incident AD) for the result to become statistically insignificant. PSM was conducted with Python 3.7.7 and CausalML package v0.11.1 [47].

Sensitivity analysis

To investigate the influence of healthy adherer bias, we applied the eligibility criteria described above but then selected a subset of patients who filled at least one statin (i.e., HMG-CoA reductase inhibitor) prescription in the first half of the look-back period (2009–2010) and whose proportion of days covered (PDC) for statin therapy during the second half of the look-back period (2010–2011) was $\geq 80\%$. The remainder of the primary analysis (i.e., ATT estimation using propensity-score matching) was repeated using this subset of statin adherers.

Ethics approval

This study was reviewed by the UTHealth Institutional Review Board, the Committee for the Protection of Human Subjects (CPHS), which deemed this study "non-human subjects research" because the study uses de-identified retrospective claims data. Therefore, the study was approved with a waiver of the HIPAA authorization and waiver of informed consent.

RESULTS

Baseline characteristics

In total, 1,651,991 patients were identified after applying inclusion and exclusion criteria (Fig. 1). Prior to matching, 122,777 patients received vaccinations against tetanus and diphtheria, with and without pertussis; 212,417 received vaccinations against herpes zoster; and 286,504 received vaccines against pneumococcus. Summary of baseline characteristics before and after PSM for Tdap/Td is shown in Table 1, and for HZ and pneumococcal is shown in Supplementary Table 2A and 2B. Vaccinated patients were matched with unvaccinated patients using the nearest propensity score based on covariates such as age, sex, race, geographic region, comorbidities, medications, and vaccinations. The SMDs were all less than 0.1 after PSM, which indicates that the cohorts are balanced.

ATT estimation

The frequency of AD among patients who were vaccinated and unvaccinated after PSM for our main analyses and sub-analysis are shown in Table 2. In the main analyses, for the Tdap/Td vaccine, 7.2% ($n = 8{,}370$) of the vaccinated patients and 10.2% ($n = 11{,}857$) of the unvaccinated patients developed AD during the 8-year follow-up period. For the HZ vaccine, 8.1% ($n = 16{,}106$) of the vaccinated patients and 10.7% ($n = 21{,}273$) of the unvaccinated patients developed AD during the 8-year follow-up period. And for the pneumococcal vaccine, 7.92% ($n = 20{,}583$) of the vaccinated patients and 10.9% ($n = 28{,}558$) of the unvaccinated patients developed AD during the 8-year follow-up period. The estimated RR, ARR, and the number needed to treat (NNT) for the thirteen different analyses are shown in Table 3. All three main analyses showed statistically significant results: Tdap/Td vaccination (RR: 0.70; 95% CI: 0.68–0.72), HZ vaccination (RR: 0.75; 95% CI: 0.73–0.76), and pneumococcal vaccination (RR: 0.73; 95% CI: 0.71–0.74). There were also statistically significant results in several sub-analyses including: 1) at least one dose of Shingrix (excluding any Zostavax vaccinations) (RR: 0.27; 95% CI: 0.25–0.29), 2) those vaccinated with Zostavax (excluding any Shingrix vaccinations) (RR: 0.92; 95% CI: 0.90–0.94), 3) those vaccinated with PCV-13 (excluding any PPSV-23 vaccinations) (RR: 0.73; 95% CI: 0.71–0.74), and 4) those vaccinated with PPSV-23 (excluding any PCV-13 vaccinations) (RR: 0.71; 95% CI: 0.69–0.73) when compared to unvaccinated groups. The median follow-up distributions to AD onset, death, or censoring for each of the analyses are shown in Supplementary Table 3. For the vaccinated groups, the follow-up time begins when the first target vaccine was received during the follow-up period.

Sensitivity analysis

After excluding patients with missing demographics, 1,530,385 patients were identified for the sensitivity analysis cohort. For the first half of the look back period (2009–2010), 544,228 patients had statin records. Of those patients, 281,554 patients had a PDC $\geq 80\%$ during the second half of the look-back period (2010–2011). Statistically significant results were found for the sensitivity analysis: Tdap/Td vaccination (RR: 0.67; 95% CI: 0.64–0.71), HZ vaccination (RR: 0.71; 95% CI: 0.68–0.73),

Table 2
Frequency of AD in vaccinated and unvaccinated patients per analysis after PSM

Exposure Definition	Vaccinated		Unvaccinated	
	AD (+)	AD (–)	AD (+)	AD (–)
Tdap, Td, and/or TT Vaccination versus Unvaccinated				
≥ 1 Tdap or Td without TT*	8,370	108,030	11,857	104,543
≥ 1 Tdap or Td or TT	8,785	110,822	12,317	107,470
≥ 1 Tdap without Td and TT	6,844	90,445	9,922	87,367
≥ 1 Td without Tdap and TT	1,435	16,253	1,785	15,903
≥ 1 TT without Tdap and Td	339	2,229	323	2,245
HZ Vaccination versus Unvaccinated				
≥ 1 Zostavax or Shingrix*	16,106	182,741	21,417	177,430
Completed Shingrix (2 doses) without Zostavax[a]	358	30,798	1,532	29,624
≥ 1 Zostavax with 2 doses Shingrix	92	7,608	646	7,054
≥ 1 Shingrix without Zostavax[a]	789	53,091	2,863	51,017
≥ 1 Zostavax without Shingrix	15,298	128,967	16,148	128,117
Pneumococcal Vaccination versus Unvaccinated				
≥ 1 PCV-13 or PPSV-23*	20,583	239,454	28,558	231,479
≥ 1 PCV-13 without PPSV-23[b]	13,425	149,606	18,342	144,689
≥ 1 PPSV-23 without PCV-13	8,072	101,854	11,325	98,601

The look back period was defined as 2009–2011 and the follow up period as 2011–2019, with the exceptions noted below. Each analysis performed includes a unique unvaccinated cohort. The unvaccinated cohort refers to patients who are not vaccinated with the specified vaccine for that analysis; patients may have still received other vaccinations that were not the exposure variable. For example, for the Zostavax or Shingrix vaccine analysis, the unvaccinated group would be those who did not receive a at least one dose of Zostavax or Shingrix; however, this group could have received a Tdap/Td/TT or pneumococcal vaccine. *Denotes a main analysis. [a]The analysis was performed using a look back period of 2009–2017 and the follow up period of 2017–2019. [b]The analysis was performed using a look back period of 2009–2014 and the follow up period of 2014–2019. AD (+), Alzheimer's disease during the follow-up; AD (–), did not develop incident AD during follow-up; PCV-13, pneumococcal conjugate vaccine 13; HZ, Herpes zoster; ICD, International Classification of Diseases; PPSV, Pneumococcal polysaccharide vaccine 23; PSM, Propensity score matching; Tdap, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td, Tetanus toxoid and reduced diphtheria toxoid; TT, Tetanus toxoid. Table adapted from Bukhbinder et al. [38]. Reprinted from *Journal of Alzheimer's Disease*, vol. 88, no. 3, Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE, Risk of Alzheimer's disease following influenza vaccination: a claims-based cohort study using propensity score matching, pp. 1061-1074, 2022, with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/10.3233/JAD-220361.

and pneumococcal vaccination (RR: 0.73; 95% CI: 0.70–0.75). A comparison between the sensitivity analysis results and the main results are displayed in Table 4.

DISCUSSION

Using a retrospective cohort study, we found that there were significant decreases in AD for patients 65 and older who received a Tdap/Td vaccination (30%), an HZ vaccination (25%), or a pneumococcal vaccination (27%) versus separate unvaccinated groups over an 8-year period. Our main analysis results are consistent with other studies of these three vaccines suggesting a possible preventative effect on dementia [48]. For our secondary objective (i.e., if various types of HZ or pneumococcal vaccines affect the risk of AD differently), we also found decreases in AD in people who received at least one dose of the live-attenuated HZ vaccine (Zostavax) (8% over an 8-year period), at least one dose of the recombinant HZ vaccine (Shingrix) (73% over a 2-year period), the conjugated pneumococcal vaccine (i.e., PCV-13) (27% over a 5-year period), and the polysaccharide pneumococcal vaccine (i.e., PPSV-23) (29% over an 8-year period) when compared to unvaccinated groups.

Mechanisms and vaccine types

The mechanisms that underlie the reduced incidence of AD through vaccinations in our cohort need to be explored further. There may be mitigation of disease-specific mechanisms through the prevention of the disease (e.g., herpes zoster) or the reduction in the severity of the disease that have a diminishing effect on the risk of AD. However, because the results from our previous study with influenza vaccination [38] and now the results from this study demonstrate that multiple vaccinations are associated with a reduced incidence of AD, it may be that there are

Table 3
ATT Estimation for Vaccination During the Follow-up Period

Exposure Definition	Risk ratio (95% CI)	ARR (95% CI)	NNT	E-value
Tdap, Td, and/or TT Vaccination versus Unvaccinated				
≥ 1 Tdap or Td without TT *	0.7059 (0.6876–0.7247)	0.0300 (0.0277–0.0322)	33	2.1848
≥ 1 Tdap or Td or TT	0.7238 (0.7055–0.7427)	0.0302 (0.0280–0.0324)	33	2.1076
≥ 1 Tdap without Td and TT	0.6804 (0.6612–0.7003)	0.0330 (0.0306–0.0355)	30	2.3004
≥ 1 Td without Tdap and TT	0.8039 (0.7533–0.8579)	0.0198 (0.0139–0.0257)	51	1.7947
≥ 1 TT without Tdap and Td	1.0495 (0.9107–1.2096)	0.0062 (–0.0121–0.0245)	–	–
HZ Vaccination versus Unvaccinated				
≥ 1 Zostavax or Shingrix*	0.7520 (0.7378–0.7666)	0.0267 (0.0249–0.0285)	37	1.9919
Completed Shingrix (2 doses) without Zostavax[a]	0.2337 (0.2085–0.2619)	0.0377 (0.0350–0.0404)	26	5.8925
≥ 1 Zostavax with 2 doses Shingrix	0.1424 (0.1148–0.1766)	0.0719 (0.0653–0.0786)	14	13.5243
≥ 1 Shingrix without Zostavax[a]	0.2756 (0.2550–0.2979)	0.0385 (0.0363–0.0406)	26	4.3841
≥ 1 Zostavax without Shingrix	0.9274 (0.9087–0.9466)	0.0083 (0.0060–0.0105)	120	1.3687
Pneumococcal Vaccination versus Unvaccinated				
≥ 1 PCV-13 or PPSV-23*	0.7304 (0.7186–0.7424)	0.0297 (0.0282–0.0312)	34	2.0799
≥ 1 PCV-13 without PPSV-23[b]	0.7319 (0.7167–0.7475)	0.0302 (0.0281–0.0322)	33	2.0736
≥ 1 PPSV-23 without PCV-13	0.7127 (0.6940–0.7320)	0.0295 (0.0273–0.0319)	34	2.1549

The look back period was defined as 2009–2011 and the follow up period as 2011–2019, with the exceptions discussed below. Each analysis performed included a unique and different unvaccinated cohort. The unvaccinated cohort refers to patients who are not vaccinated with the specified vaccine for that analysis; patients may have still received other vaccinations that were not the exposure variable. For example, for the Zostavax or Shingrix vaccine analysis, the unvaccinated group would be those who did not receive a at least one dose of Zostavax or Shingrix; however, this group could have received a Tdap/Td/TT or pneumococcal vaccine. *Denotes a main analysis. [a]Distinguishes that the analysis was performed using a look back period of 2009–2017 and the follow up period of 2017–2019. [b]Characterizes that the analysis was performed using a look back period of 2009–2014 and the follow up period of 2014–2019. AD, Alzheimer's disease; ARR, Absolute risk reduction; CI, Confidence Interval; HZ, Herpes zoster; ICD, International Classification of Diseases; NNT, Number needed to treat; PCV-13, pneumococcal conjugate vaccine 13; PPSV, Pneumococcal polysaccharide vaccine 23; Tdap, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td, Tetanus toxoid and reduced diphtheria toxoid; TT, Tetanus toxoid.

Table 4
Effect size estimates comparing the sensitivity and main analysis results

Exposure Definition	Risk ratio (95% CI) Main Analysis	Risk ratio (95% CI) Sensitivity Analysis
≥ 1 Tdap or Td without TT	0.7059 (0.6876–0.7247)	0.6783 (0.6427–0.7161)
≥ 1 Zostavax or Shingrix	0.7520 (0.7378–0.7666)	0.7122 (0.6860–0.7395)
≥ 1 PCV-13 or PPSV-23	0.7304 (0.7186–0.7424)	0.7316 (0.7069–0.7572)

For both groups of analyses, we compared two cohorts (vaccinated and unvaccinated) identified using propensity score matching (PSM). For the main analysis (the same analysis presented in Table 3), the look back period was defined as 2009–2011 and the follow up period as 2011–2019. The sensitivity analysis look back period was split into two halves: 2009–2010 for identification of patients who take statin medications, and 2010–2011 for determining which of those patients had at least 80% proportion of days covered by statin therapy. The follow up period spanned from 2011–2019. CI, Confidence Interval; PCV-13, pneumococcal conjugate vaccine 13; PPSV-23, Pneumococcal polysaccharide vaccine 23; Tdap, Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; Td, Tetanus toxoid and reduced diphtheria toxoid; TT, Tetanus toxoid.

other, more general mechanisms. These other mechanisms could include innate immune system training and lymphocyte-mediated cross-reactivity, descriptions of which are both expanded upon in our previous influenza vaccination manuscript [38].

Another factor that should be considered is the age of patients when they receive their vaccines against tetanus and diphtheria, with and without pertussis; herpes zoster; and, pneumococcus. The immunogenicity of vaccines is reduced in patients as they age, therefore there is a decrease in vaccine efficacy [49]. Analyses in Supplementary Figure 1A-C) illustrates that the incidence of AD increases with age; however, the risk of developing AD is still diminished in association with the use of Tdap/Td (Supplementary Figure 1A), HZ (Supplementary Figure 1B), and pneumococcal (Supplementary Figure 1 C) vaccinations. As a result, it appears to be advantageous for people 65 years and older to receive these vaccinations to prevent disease and to reduce the risk of AD. Vaccines have been created and have been shown to provide a more robust immune response in patients

65 years and older, including recombinant and conjugated vaccines.

Herpes Zoster: Live-attenuated versus recombinant

Two HZ vaccines have been approved for use in the United States. Zostavax was recommended from 2009–2020. Like the vaccines against varicella recommended in children for protection against primary varicella infection, Zostavax contains a live-attenuated form, but at a much higher titer than currently approved pediatric varicella vaccines [50]. Shingrix, on the other hand, is a recombinant vaccine against HZ that contains both the varicella-zoster glycoprotein E (gE) antigen and the $AS01_B$ adjuvant system [51]. The vaccine utilizes gE as an antigen since it is the glycoprotein that varicella-zoster exhibits most frequently; this glycoprotein is also the target for varicella-zoster CD4+ T cell response [51]. Both Zostavax and Shingrix are capable of eliciting T-cell-independent and T-cell-dependent responses; however, the efficacy of protection provided by these two vaccines differs significantly. The efficacy of Zostavax in HZ risk reduction was only slightly over 50% in patients 60 years and over with previous varicella zoster infection, and the HZ protection provided by this live vaccine reduced after approximately five years [52]. An advantage to Zostavax was that it was given as a one-time dose. Shingrix, in contrast, has an efficacy of 97.2% in reducing HZ risk and, unlike Zostavax, can be safely administered to immunocompromised patients [15, 52]. Shingrix is administered over two doses, with protection lasting approximately seven years [21]. It is now recommended by the CDC that those who previously received Zostavax also receive Shingrix [7].

Pneumococcal: Polysaccharide versus conjugated

For the unconjugated polysaccharide vaccine (i.e., PPSV), the antigenic component consists of polysaccharides from the capsule of pneumococcus [25]. These vaccines can only produce a limited immune response because the polysaccharides are unable to be loaded into the major histocompatibility complex (MHC) cavity; therefore, although they elicit production of IgM antibodies by B cells, polysaccharide vaccines cannot induce T-cell-dependent responses and thus lack several effects of peptide-containing vaccines, including the production of memory B cells, antibody class switching, or affinity maturation [37]. In contrast, conjugated vaccines incorporate capsular polysaccharides covalently bound to a carrier protein in order to elicit a more robust immune response [25]. For PCV13, the carrier is a genetically detoxified form of the diphtheria toxin protein [53]. The conjugate allows both the polysaccharide and the carrier protein to be loaded into the MHC-II cavity, thus allowing for activation of helper T cells [37]. This T-cell-dependent pathway enables the production of memory B cells and non-IgM antibodies (e.g., IgG, IgE). Therefore, the PCV is thought to have a more sustained immune response, overall, when compared with PPSV. The current recommendations have expanded the use of PCV vaccinations. PCV15 and PCV20 were approved by the FDA in 2021. It is now recommended that patients 65 years and older receive either a dose of PCV20, or a dose of PCV15 followed by a dose of PPSV23 one year later.

Public health and an addition to a clinician's toolkit

This study suggests that it is important for patients to have ready access to routine adult vaccinations. Over the past 15 years there has been an incremental increase in vaccine coverage every year for vaccines preventing tetanus and diphtheria, with and without pertussis; herpes zoster; and pneumococcus for patients 19 years and older in the United States [54]. For example, from 2008 to 2018, the rate of patients who received an HZ vaccine increased significantly from 6.7% to 34.8% [55]. Also, it is estimated that 58.9% of adults 65 and older were exposed to a tetanus-containing vaccine between 2008 and 2018 [54]. The increase continued until the COVID-19 pandemic and subsequent shutdowns. During this period, there were reductions in the administration of adult vaccines, with the HZ vaccination rates dropping by 89% and Tdap/Td rates by 70% [56]. Despite the shutdowns and physical isolation, elderly patients are still at risk for developing HZ because the disease is caused by a reactivation of varicella-zoster, as opposed to a new microbial exposure [57]. This reactivation is also associated with an increase in dementia risk [18]. It is estimated that 3.9 million HZ vaccinations were missed in 2020 due to COVID-19 shutdowns, accounting for an estimated 31,945 cases over two years [57]. It is not yet known whether the decrease in vaccination coverage and an increase in vaccine preventable diseases will affect dementia rates.

The clinician-patient relationship, as well as the understanding and knowledge of vaccinations are important parts of a patient's decision to refuse or accept a vaccine [58]. The value of vaccination, as we have demonstrated, goes beyond preventing infection or severe disease from that infection. In fact, there are multiple non-specific potential benefits of vaccination such as improving asthma severity [59], AD prevention [38, 48], and use as an adjuvant cancer therapy (even though it is administered through a non-traditional route) [60, 61], among others. Nicholls et al. [62] found that by emphasizing disease susceptibility and vaccine efficacy/benefits, patients may be more willing to receive vaccinations in the future. By discussing these added non-specific advantages of vaccination with patients, clinicians may be able to convince hesitant patients that the benefits of vaccination with one of the routine adult vaccinations outweighs the risks.

Sensitivity analysis

In order to assess the extent to which healthy adherer bias influenced our results, we performed a similar sensitivity analysis to Wiemkem et al. [30] in which we only included patients who were adherent to statin medications. Because the results from the sensitivity analysis were similar to those results within the original main analysis, we concluded that our study findings showing the association between exposure to adulthood vaccinations and a decreased incidence of AD were not influenced by healthy adherer bias.

Limitations

There are several limitations to our study. 1) Optum's CDM only includes patients with both medical and prescription coverage. Therefore, those with medical insurance but no prescription coverage and vice versa were not included in this study, limiting the generalizability of our findings. The CDM may also lack vaccine exposures for patients who pay out of pocket for their vaccinations; however, if patients were to use their insurance card for vaccinations, then their vaccination would be recorded. 2) Because our study is retrospective in nature, and the main objective for data collection was not adult vaccinations and AD diagnosis, there is risk for misclassification bias. 3) For the outcome variables, we attempted to control for misclassification by including patients that had no AD-related diagnoses or medications or that had at least two healthcare records with some combination of AD-related diagnoses or medications; patients with only one AD-related diagnosis or medication record were excluded to minimize misclassification due to clerical errors. Furthermore, we included patients with the diagnosis code of "senile" or unspecified dementia as patients with AD. Therefore, even though it is known that 60–70% of patients diagnosed with dementia have AD [41], we are unsure of how many patients actually have AD in the CDM. 4) Another consideration and potential limitation of this study was the decision to count vaccinations as valid exposures as long as they occurred at least one day before the initial AD diagnosis. 5) The risk of immortal time bias is another important consideration in this study. To provide a measurement of the time at-risk among vaccinated patients that does not include the period of "immortality" they experience between the start of the follow-up period and the date of vaccination, the distribution of follow-up duration (Supplementary Table 3) for vaccinated patients was defined as the time from vaccine receipt (rather than the start of the follow-up period) to date of incident AD, death, or censoring (i.e., the patient's last record before the end of the follow-up period). As shown in Supplementary Table 3, the median at-risk period for the vaccinated group was greater than that of the unvaccinated group in most of the analyses, a disparity that should be considered when interpreting the results of this study. 6) Although the SMD for each of the post-PSM covariates was < 0.10, which meets the conventional definition for adequate covariate balance between the vaccinated and unvaccinated groups [44], the presence of higher disease burden within the vaccinated groups is noted. If there is a bias present from this difference in comorbidity distributions, it would predispose our analysis against finding a protective effect. 7) While our study did control for some sociodemographic and comorbid conditions, we could not control for other behaviors and characteristics that may influence vaccination acceptance or refusal, such as marital status, educational level, and income status [58, 62]. We reported E-values for each of the point estimates to provide an estimate of how strongly an unmeasured confounder would need to be associated with both the exposure and outcome (adjusting for the same covariates as this analysis) in order to render the point estimate statistically insignificant. 8) Moreover, some vaccines were approved and recommended for use in the general population during our study period. Shingrix is an example: it was introduced in 2017, two years

before the end of our study period. While we were able to move the follow-up period to start in 2017, this did result in a limited period of follow-up (2 years) for patients to receive Shingrix and to study its impact on AD incidence. 9) Finally, exposure to diseases such as HZ and influenza have been associated with an increased incidence of AD; however, we did not control for this in our models because of the difficulty in obtaining an accurate diagnosis for infections, such as influenza, which may lead to misclassification. Relatedly, we cannot be certain whether our observations relate to reduced infection rates versus vaccine-related effects on the immune system.

CONCLUSIONS

Our study demonstrated a statistically significant association between the reduction of AD after exposure to several routinely administered adult vaccinations, including Tdap/Td (30%), HZ (25%), and pneumococcal (27%), for patients 65 and older with an 8-year follow-up. We also demonstrated that there are differences in the association of AD risk between live-attenuated (8%) and recombinant (73%) vaccinations for HZ; however, the AD risk is similar for the pneumococcal conjugate (27%) and polysaccharide (29%) vaccine types. More work is needed to confirm these findings, including a prospective study to specifically measure the impact of vaccines on AD; due to ethical concerns about withholding an important method of preventing infection, a randomized controlled trial to assign people to placebo or immunization groups would not be feasible. Our previous study's finding that the influenza vaccination is associated with a significant reduction in AD risk, and now finding three other sets of vaccines that are also associated with a reduced incidence of AD suggests that vaccines work through another, more general mechanism. Further work, perhaps in animal models, is needed to understand how the risk of AD is being decreased by the influenza vaccine and several routine adult vaccinations.

ACKNOWLEDGMENTS

The authors would like to thank Christine M. Farrell, PhD for her review of the manuscript.

FUNDING

The authors have no funding to report.

CONFLICT OF INTEREST

Paul E. Schulz is funded by the McCord Family Professorship in Neurology, the Umphrey Family Professorship in Neurodegenerative Disorders, multiple NIH grants, several foundation grants, and contracts with multiple pharmaceutical companies related to the performance of clinical trials. He serves as a consultant and speaker for Eli Lilly, Biogen, and Acadia Pharmaceuticals. Xiaoqian Jiang is funded by Christopher Sarofim Family Professorship, the CPRIT RR180012 award, UT Stars award, and NIH grants R01GM114612 and U01TR002062. Avram S. Bukhbinder is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review. All other authors have no conflict of interest to report.

DATA AVAILABILITY

The authors cannot make data and study materials available to other investigators due to licensing restriction; however, interested parties can license the CDM by contacting Optum.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-221231.

REFERENCES

[1] Ashraf GM, Tarasov VV, Makhmutova A, Chubarev VN, Avila-Rodriguez M, Bachurin SO, Aliev G (2019) the possibility of an infectious etiology of Alzheimer disease. *Mol Neurobiol* **56**, 4479-4491.

[2] Maheshwari P, Eslick GD (2015) Bacterial infection and Alzheimer's disease: A meta-analysis. *J Alzheimers Dis* **43**, 957-966.

[3] Sochocka M, Zwolińska K, Leszek J (2017) The infectious etiology of Alzheimer's disease. *Curr Neuropharmacol* **15**, 996-1009.

[4] Barichello T, Giridharan VV, Comim CM, Morales R (2022) What is the role of microbial infection in Alzheimer's disease? *Braz J Psychiatry* **44**, 245-247.

[5] Jorfi M, Maaser-Hecker A, Tanzi RE (2023) The neuroimmune axis of Alzheimer's disease. *Genome Med* **15**, 6.

[6] Yang Y, He Z, Xing Z, Zuo Z, Yuan L, Wu Y, Jiang M, Qi F, Yao Z (2020) Influenza vaccination in early Alzheimer's dis-

ease rescues amyloidosis and ameliorates cognitive deficits in APP/PS1 mice by inhibiting regulatory T cells. *J Neuroinflamm* **17**, 65.

[7] Centers for Disease Control and Prevention (2022) Adult Immunization Schedule, https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html. Posted February 17, 2022, Accessed October 7, 2022.

[8] Centers for Disease Control and Prevention (2022) Tetanus, https://www.cdc.gov/tetanus/clinicians.html. Posted August 29, 2022, Accessed October 8, 2022.

[9] Centers for Disease Control and Prevention (2022) Diphtheria, https://www.cdc.gov/diphtheria/clinicians.html. Posted September 9, 2022, Accessed October 7, 2022.

[10] Centers for Disease Control and Prevention (2022) Pertussis (Whooping Cough), https://www.cdc.gov/pertussis/clinical/features.html. Posted August 4, 2022, Accessed October 8, 2022.

[11] Rubin K, Glazer S (2016) The pertussis hypothesis: Bordetella pertussis colonization in the pathogenesis of Alzheimer's disease. *Immunobiology* **222**, 228-240.

[12] Centers for Disease Control and Prevention (2022) About Diphtheria, Tetanus, and Pertussis Vaccines, https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/about-vaccine.html. Posted September 6, 2022.

[13] Rabadi T, Brady MF (2022) *Tetanus Toxoid*, StatPearls Publishing, Treasure Island, FL.

[14] Havers FP, Moro PL, Hunter P, Hariri S, Bernstein H (2020) Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: Updated recommendations of the Advisory Committee on Immunization Practices - United States, 2019. *MMWR* **69**, 77-83.

[15] Center for Disease Control and Prevention (2020) Shingles (Herpes Zoster), https://www.cdc.gov/shingles/hcp/clinical-overview.html. Posted October 5, 2020, Accessed October 9, 2022.

[16] Kawai K, Gebremeskel BG, Acosta CJ (2014) Systematic review of incidence and complications of herpes zoster: Towards a global perspective. *BMJ Open* **4**, e004833.

[17] Curran D, Callegaro A, Fahrbach K, Neupane B, Vroling H, van Oorschot D, Yawn BP (2022) Meta-regression of herpes zoster incidence worldwide. *Infect Dis Ther* **11**, 389-403.

[18] Chen VC, Wu S, Huang K, Yang Y, Kuo T, Liang H, Huang K, Gossop M (2018) Herpes zoster and dementia: A nationwide population-based cohort study. *J Clin Psychiatry* **79**, 16.

[19] Bae S, Yun S, Kim M, Yoon W, Lim JS, Lee S, Choi S, Kim YS, Woo JH, Kim SY, Kim S (2021) Association of herpes zoster with dementia and effect of antiviral therapy on dementia: A population-based cohort study. *Eur Arch Psychiatry Clin Neurosci* **271**, 987-997.

[20] Tsai M, Cheng W, Sheu J, Huang C, Shia B, Kao L, Lin H (2017) Increased risk of dementia following herpes zoster ophthalmicus. *PLoS One* **12**, e0188490.

[21] Centers for Disease Control and Prevention (2022) Shingles Vaccination, https://www.cdc.gov/vaccines/vpd/shingles/public/shingrix/index.html. Posted May 24, 2022, Accessed October 8, 2022.

[22] Centers for Disease Control and Prevention (2020) What Everyone Should Know about Zostavax, https://www.cdc.gov/vaccines/vpd/shingles/public/zostavax/index.html. Posted October 5, 2020, Accessed October 8, 2022.

[23] Harpaz R, Ortega-Sanchez I, Seward JF (2008) Prevention of herpes zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* **57**, 1-30.

[24] Gabutti G, Valente N, Sulcaj N, Stefanati A (2014) Evaluation of efficacy and effectiveness of live attenuated zoster vaccine. *J Prev Med Hyg* **55**, 130-136.

[25] Musher DM, Rodriguez-Barradas MC (2022) Pneumococcal vaccination in adults, https://www.uptodate.com/contents/pneumococcal-vaccination-in-adults/print. Posted Aug 31, 2022, Accessed October 9, 2022.

[26] Centers for Disease Control and Prevention (2022) Pneumococcal Disease, https://www.cdc.gov/pneumococcal/clinicians/index.html. Posted January 27, 2022, Accessed October 9, 2022.

[27] Kobayashi M, Farrar JL, Gierke R, Britton A, Childs L, Leidner AJ, Campos-Outcalt D, Morgan RL, Long SS, Talbot HK, Poehling KA, Pilishvili T (2022) Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. Adults: Updated recommendation of the Advisory Committee on Immunization Practices - United States, 2022. *MMWR* **71**, 109-117.

[28] Matanock A, Lee G, Gierke R, Kobayashi M, Leidner A, Pilishvili T (2019) Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged≥65 years: Updated recommendations of the Advisory Committee on Immunization Practices. *MMWR* **68**, 1069-1075.

[29] Centers for Disease Control and Prevention (2022) About pneumococcal vaccines, https://www.cdc.gov/vaccines/vpd/pneumo/hcp/about-vaccine.html. Posted January 24 2022.

[30] Wiemken TL, Salas J, Morley JE, Hoft DF, Jacobs C, Scherrer JF (2022) Comparison of rates of dementia among older adult recipients of two, one, or no vaccinations. *J Am Geriatr Soc* **70**, 1157-1168.

[31] Scherrer JF, Salas J, Wiemken TL, Hoft DF, Jacobs C, Morley JE (2021) Impact of herpes zoster vaccination on incident dementia: A retrospective study in two patient cohorts. *PLoS One* **16**, e0257405.

[32] Lophatananon A, Mekli K, Cant R, Burns A, Dobson C, Itzhaki R, Muir K (2021) Shingles, Zostavax vaccination and risk of developing dementia: A nested case–control study—results from the UK Biobank cohort. *BMJ Open* **11**, e045871.

[33] Schnier C, Janbek J, Lathe R, Haas J (2022) Reduced dementia incidence after varicella zoster vaccination in Wales 2013-2020. *Alzheimers Dement (N Y)* **8**, e12293.

[34] Scherrer JF, Salas J, Wiemken TL, Jacobs C, Morley JE, Hoft DF (2021) Lower risk for dementia following adult tetanus, diphtheria, and pertussis (Tdap) vaccination. *J Gerontol* **76**, 1436-1443.

[35] Ukraintseva S, Yashkin A, Duan M, Akushevich I, Arbeev K, Wu D, Stallard E, Tropsha A, Yashin A (2020) Repurposing of existing vaccines for personalized prevention of Alzheimer's disease: Vaccination against pneumonia may reduce AD risk depending on genotype: Genetics/genetic factors of Alzheimer's disease. *Alzheimers Dement* **16**(Suppl 3), e046751.

[36] Ukraintseva S, Akushevich I, Yashkin A, MattDuan, Arbeev K, Wu D, Cohen T, Tropsha A, Yashin A (2019) Vaccination against pneumonia in the elderly may reduce Alzheimer's risk. *Alzheimers Dement* **15**, P1469-P1470.

[37] Rappuoli R, De Gregorio E, Costantino P (2019) On the mechanisms of conjugate vaccines. *Proc Natl Acad Sci U S A* **116**, 14-16.

[38] Bukhbinder AS, Ling Y, Hasan O, Jiang X, Kim Y, Phelps KN, Schmandt RE, Amran A, Coburn R, Ramesh S, Xiao Q, Schulz PE (2022) Risk of Alzheimer's disease following influenza vaccination: A claims-based cohort study using propensity score matching. *J Alzheimers Dis* **88**, 1061-1074.

[39] Wilkinson T, Ly A, Schnier C, Rannikmäe K, Bush K, Brayne C, Quinn TJ, Sudlow CLM (2018) Identifying dementia cases with routinely collected health data: A systematic review. *Alzheimers Dement* **14**, 1038-1051.

[40] Goodman RA, Lochner KA, Thambisetty M, Wingo TS, Posner SF, Ling SM (2016) Prevalence of dementia subtypes in U.S. Medicare fee-for-service beneficiaries, 2011–2013. *Alzheimers Dement* **13**, 28-37.

[41] World Health Organization (2022) Dementia, https://www.who.int/news-room/fact-sheets/detail/dementia. Posted 20 September 2022, Accessed October 15, 2022.

[42] Wiemken TL, Salas J, Hoft DF, Jacobs C, Morley JE, Scherrer JF (2021) Dementia risk following influenza vaccination in a large veteran cohort. *Vaccine* **39**, 5524-5531.

[43] Austin PC (2011) Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* **10**, 150-161.

[44] Ross RD, Shi X, Caram MEV, Tsao PA, Lin P, Bohnert A, Zhang M, Mukherjee B (2021) Veridical causal inference using propensity score methods for comparative effectiveness research with medical claims. *Health Serv Outcomes Res Method* **21**, 206-228.

[45] Austin PC (2010) The performance of different propensity-score methods for estimating differences in proportions (risk differences or absolute risk reductions) in observational studies. *Stat Med* **29**, 2137-2148.

[46] Austin PC (2009) Type I error rates, coverage of confidence intervals, and variance estimation in propensity-score matched analyses. *J Biostat* **5**, Article 13.

[47] Chen H, Harinen T, Jeong-Yoon L, Yung M, Zhao Z (2020) CausalML: Python Package for Causal Machine Learning. *arXiv.org*, https://doi.org/10.48550/arXiv.2002.11631.

[48] Wu X, Yang H, He S, Xia T, Chen D, Zhou Y, Liu J, Liu M, Sun Z (2022) Adult vaccination as a protective factor for dementia: A meta-analysis and systematic review of population-based observational studies. *Front Immunol* **13**, 872542.

[49] Weinberger B (2018) Vaccines for the elderly: Current use and future challenges. *Immun Ageing* **15**, 3.

[50] Gagliardi AMZ, Andriolo BNG, Torloni MR, Soares BGO, de Oliveira Gomes J, Andriolo RB, Canteiro Cruz E, Gagliardi AMZ (2019) Vaccines for preventing herpes zoster in older adults. *Cochrane Database Syst Rev* **2019**, CD008858.

[51] Cunningham AL, Heineman TC, Lal H, Godeaux O, Chlibek R, Hwang S, McElhaney JE, Vesikari T, Andrews C, Choi WS, Esen M, Ikematsu H, Choma MK, Pauksens K, Ravault S, Salaun B, Schwarz TF, Smetana J, Abeele CV, Van den Steen P, Vastiau I, Weckx LY, Levin MJ (2018) Immune responses to a recombinant glycoprotein E herpes zoster vaccine in adults aged 50 years or older. *J Infect Dis* **217**, 1750-1760.

[52] Singh G, Song S, Choi E, Lee P, Nahm FS (2020) Recombinant zoster vaccine (Shingrix (R)): A new option for the prevention of herpes zoster and postherpetic neuralgia. *Korean J Pain* **33**, 201-207.

[53] Park C, Kwon E, Choi S, Cho S, Byun J, Park JY, Lee D, Kang JH, Shin J, Kim H (2017) Comparative evaluation of a newly developed 13-valent pneumococcal conjugate vaccine in a mouse model. *Hum Vaccin Immunother* **13**, 1169-1176.

[54] Lu P, Hung M, Srivastav A, Grohskopf LA, Kobayashi M, Harris AM, Dooling KL, Markowitz LE, Rodriguez-Lainz A, Williams WW (2021) Surveillance of vaccination coverage among adult populations -United States, 2018. *MMWR* **70**, 1-26.

[55] Terlizzi EP, Black LI (2020) Shingles vaccination among adults aged 60 and over: United States, 2018. *NCHS Data Brief*, pp. 1-8.

[56] Hong K, Zhou F, Tsai Y, Jatlaoui TC, Acosta AM, Dooling KL, Kobayashi M, Lindley MC (2021) Decline in receipt of vaccines by medicare beneficiaries during the COVID-19 pandemic - United States, 2020. *MMWR* **70**, 245-249.

[57] Curran D, La EM, Salem A, Singer D, Lecrenier N, Poston S (2022) Modeled impact of the COVID-19 pandemic and associated reduction in adult vaccinations on herpes zoster in the United States. *Hum Vaccin Immunother* **18**, 2027196.

[58] Kumar D, Chandra R, Mathur M, Samdariya S, Kapoor N (2016) Vaccine hesitancy: Understanding better to address better. *Isr J Health Policy Res* **5**, 2.

[59] El-Zein M, Parent M, Benedetti A, Rousseau M (2010) Does BCG vaccination protect against the development of childhood asthma? A systematic review and meta-analysis of epidemiological studies. *Int J Epidemiol* **39**, 469-486.

[60] Benitez MLR, Bender CB, Oliveira TL, Schachtschneider KM, Collares T, Seixas FK (2019) Mycobacterium bovis BCG in metastatic melanoma therapy. *Appl Microbiol Biotechnol* **103**, 7903-7916.

[61] Sfakianos JP, Salome B, Daza J, Farkas A, Bhardwaj N, Horowitz A (2021) Bacillus Calmette-Guerin (BCG): Its fight against pathogens and cancer. *Urol Oncol* **39**, 121-129.

[62] Nicholls LAB, Gallant AJ, Cogan N, Rasmussen S, Young D, Williams L (2021) Older adults' vaccine hesitancy: Psychosocial factors associated with influenza, pneumococcal, and shingles vaccine uptake. *Vaccine* **39**, 3520-3527.