IMMUNISATION COALITION

A/Prof Michael Woodward

Head of Aged Care Research, Austin Health, Heidelberg & member of the Influenza Specialist Group

Additional benefits of vaccination (Dementia, Depression etc)

11:25am

Additional benefits of vaccination

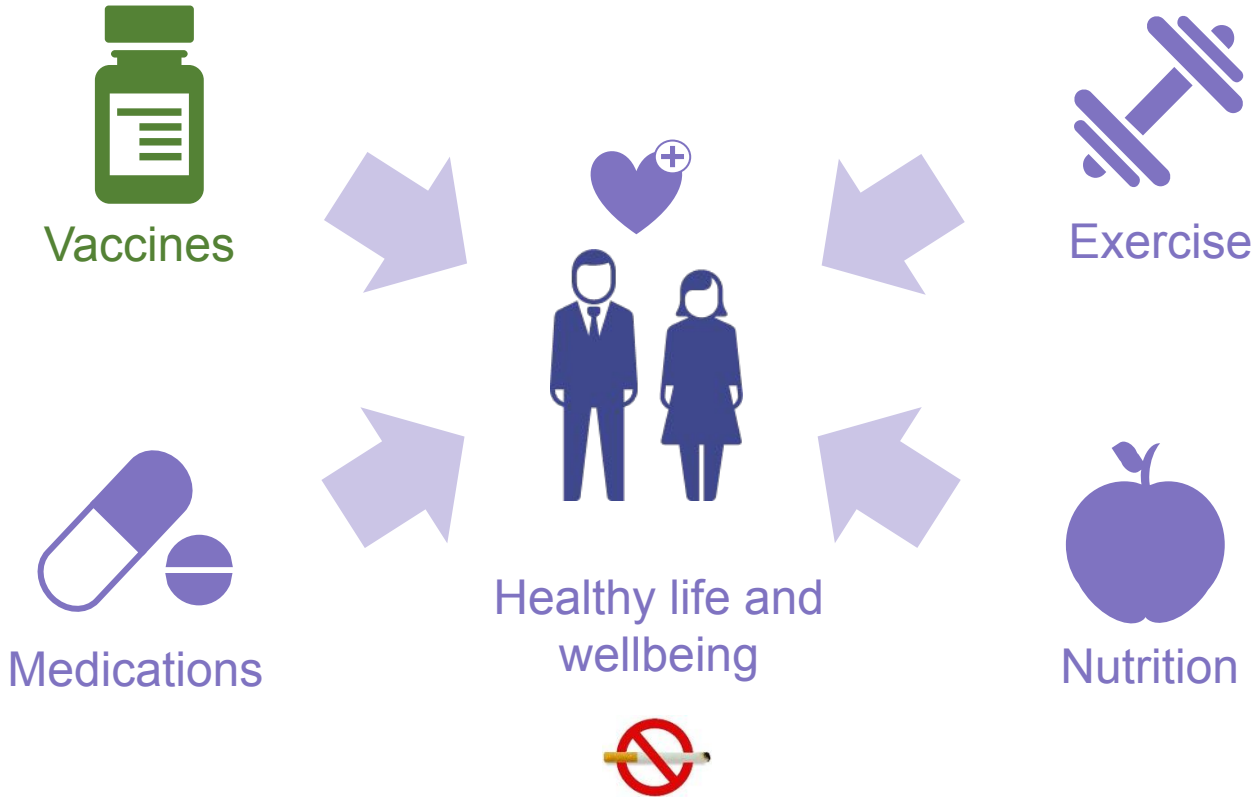
Associate Professor Michael Woodward AM

Immunization Coalition ASM

February 2024

Why is life-course immunisation important?
To increase healthy lives and wellbeing in the population

Life-course immunisation, along with appropriate lifestyle and healthcare interventions, provides an opportunity to live and age in good health[1,2]



WHO, World Health Organization

1. Global Coalition on Aging, 2013. Life-course immunization: a driver of healthy aging. http://www.globalcoalitiononaging.com/v2/data/uploads/documents/life-course-immunization_gcoa-for-web.pdf (accessed November 2016);
2. WHO, 1999. A life course perspective of maintaining independence in older age. whqlibdoc.who.int/hq/1999/WHO_HSC_AHE_99.2_life.pdf (accessed December 2016)

THE VALUE OF VACCINES

Only Clean Drinking Water Rivals Vaccination in Its Ability to Save Lives[1]

4.4 m²

deaths prevented every year by vaccination

$150bn³

the benefit of vaccines to low and middle-income countries over the next 10 years

750,000²

children saved from disability every year

x44⁴

is the estimated return on Investment of the cost of immunization

Healthcare professionnals play a central role in public education and communication of vaccine information[5]

Sources: 1. WHO, UNICEF, World Bank. State of the world's vaccines and immunization, 3rd ed. Geneva, World Health Organization, 2009., p.12; 2. Ehreth J, "The global value of vaccination" in Vaccine 2003 Jan 30; 21 (7-8):596-600. 3. GAVI Alliance Partners' Forum, December 2012 reported by JHB School of Public Health.4. Ozawa S. et al, "Return on investment from childhood immunisation in low- and Middle-Income countries, 2011-20", in Health Affairs, 35, 2 (2016): 199-207 5. Based on data generated by: Hofstetter AM, et al. Vaccine 2017;35:2709–15

CHANGES IN IMMUNE SYSTEM WITH AGE: T-CELLS

Naïve T-cells
Memory T-cells
Ageing T-cells

In older adults:

- **Naïve T-cell numbers decrease[1,3]**
- **T-cells recognise a smaller range of antigens[2]**
- **Ageing T-cell numbers increase[1]**
- **Memory T-cell responses are impaired[3]**

Figure based on concepts derived from Maggi S, et al.

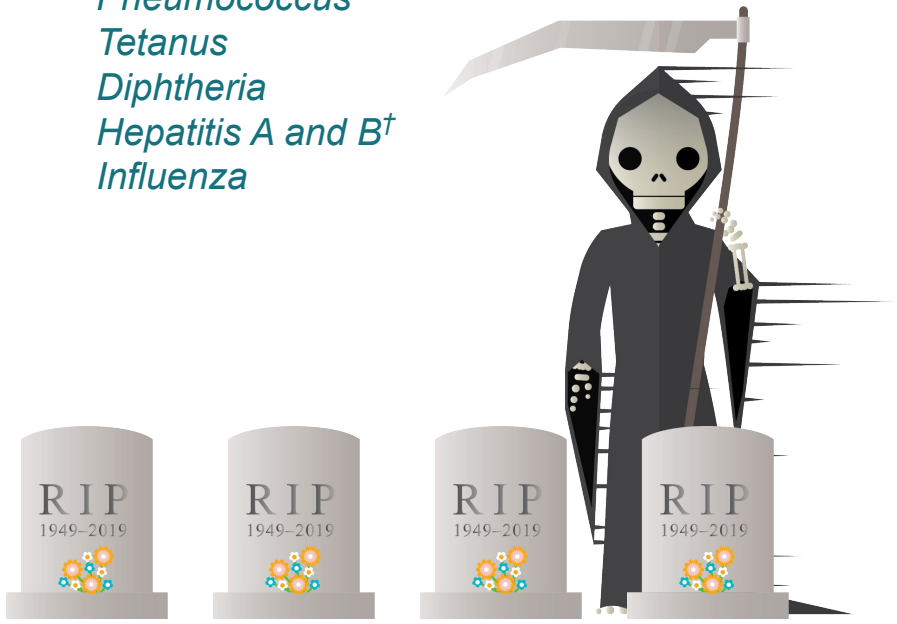
1. Maggi S, et al. Expert Rev Vaccines 2010; 9(3 Suppl.):3-6; 2. Naylor K et al. J Immunal 2005; 174:7446-7452; 3. Kumar R, et al. Expert Rev Vaccines 2008; 7:467-479

In older adults, vaccines can help prevent infectious diseases and improve quality of life[1]

A number of vaccines are currently recommended for older adults to promote healthy ageing[1,2]*

Some vaccines are recommended primarily to **reduce the risk of mortality**

Pneumococcus
Tetanus
Diphtheria
Hepatitis A and B†
Influenza



Some vaccines are recommended primarily to **improve quality of life**

Pertussis
Shingles

*The vaccines listed on this slide are recommended for older adults in a number of European countries and the USA. Specific vaccine recommendations may vary among countries; †Hepatitis B vaccine is recommended for older adults at risk for infection

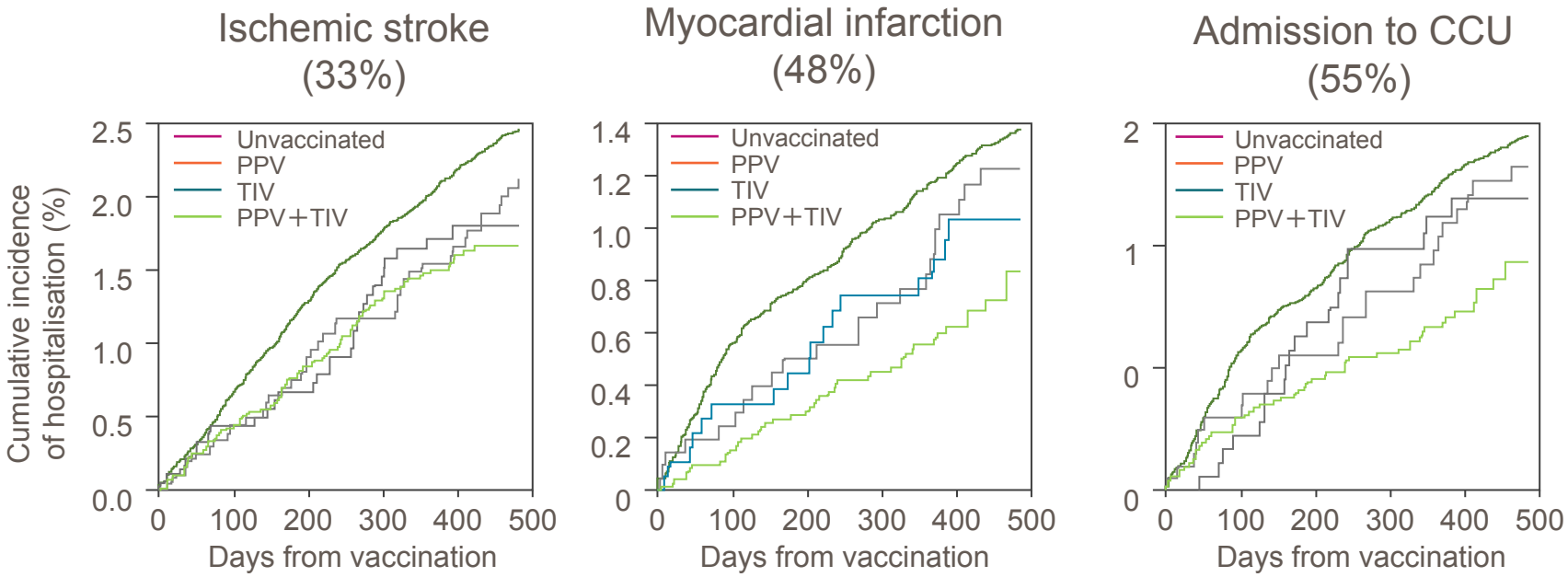
1. Lang PO, Aspinall R. *Drugs Ageing* 2014;31:581–599;
2. Carrion AF, Martin P. *Am J Gastroenterol* 2012;107:691–697

But are there other benefits of vaccination?

beyond disease prevention and improved quality of life

Vaccination in older adults can reduce disease-associated complications, reducing healthcare burden and mortality[1]

Pneumococcal and influenza vaccination protects against vascular events, reducing overall healthcare burden



Complications

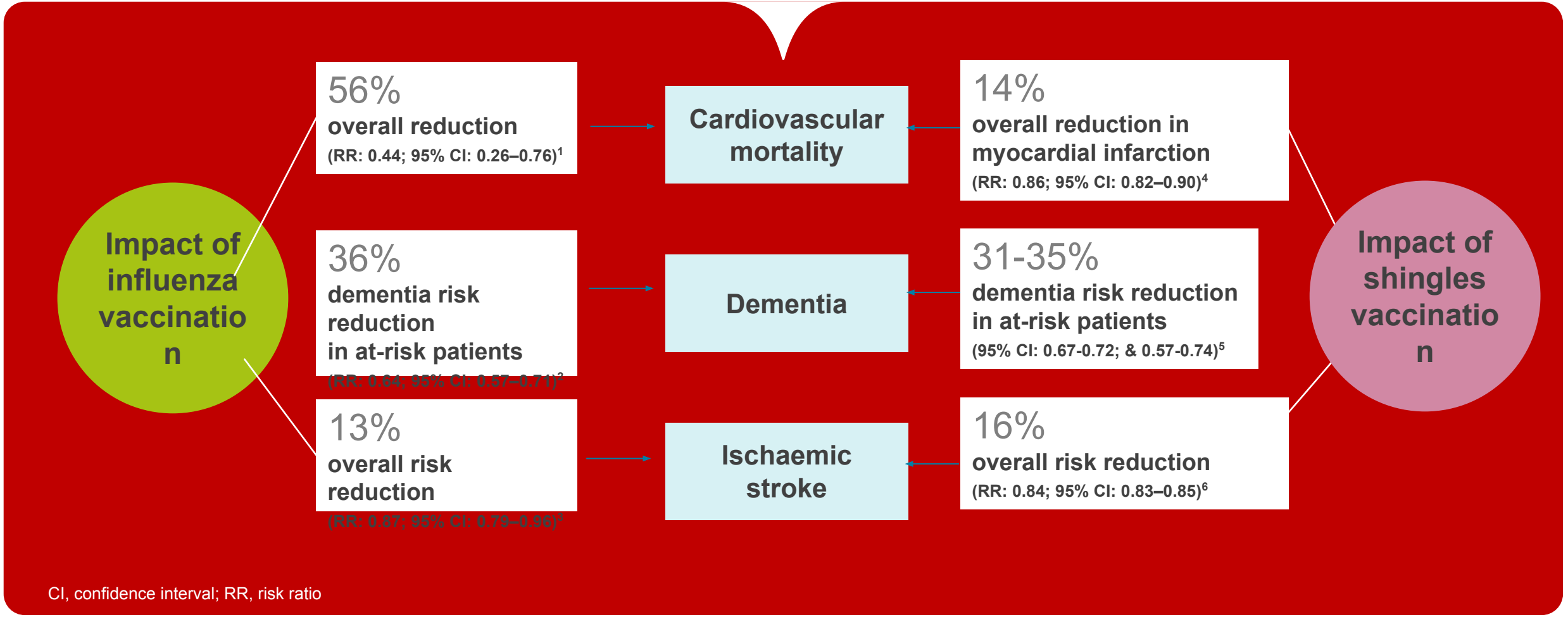
Cardiac/coronary care unit admissions

A prospective cohort study of outpatients aged ≥65 years with chronic illness in Hong Kong, China who participated in a PPV and TIV vaccination programme. Study was conducted from Dec 2007–Jun 2008, with all patients followed until Mar 2009. Of 36,636 subjects recruited, 7292 received both PPV and TIV, 2076 received TIV vaccine alone, 1875 received PPV alone, and 25,393 were unvaccinated. The primary outcome was the rate of death due to the following: pneumonia, COPD, asthma, influenza-like illness, ischaemic stroke, AMI and cardiac failure at Week 64. Compared with the unvaccinated group, PPV + TIV vaccinees had: (a) a 33% reduction in ischaemic stroke (HR: 0.67; 95% CI: 0.54–0.83; *P*<0.001); (b) a 48% reduction in AMI (HR: 0.52; 95% CI: 0.38–0.71; *P*<0.001); (c) a 41% reduction in the rate of coronary care unit admission (HR: 0.59; 95% CI: 0.44–0.79; *P*<0.001)

AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; PPV, pneumococcal polysaccharide vaccine; TIV, trivalent influenza vaccine

Figures adapted from Hung IFN *et al*. *Clin Infect Dis* 2010;51:1007–1016, with permission from Oxford University Press

By helping prevent acute infection, immunization can also help reduce longer-term health complications



CI, confidence interval; RR, risk ratio

1. Clar C et al. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD005050. 2. Liu J et al. Medicine 2016;95:e2868; 3. Tsivgoulis G et al. J Neurol Sci 2018;386:12–18; 4. Schnier C et al., MedRxiv 2021.07.22.21260981; 5. Scherrer JF, et al. PLoS One. 2021 Nov 17;16(11):e0257405; 6. Yang et al. Stroke 2021;52:1712–1721

Could this be a direct “off target”effect of vaccination?

- Known for many years that BCG vaccination for bladder cancer reduced risk of dementia
- But hard to believe that vaccination against a specific microorganism could reduce such disparate diseases
- This presentation will concentrate on dementia risk reduction
  - But also suggestions of reduction of risk for other illnesses
    - Including depression

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Translational Research & Clinical Interventions

RESEARCH ARTICLE

Reduced dementia incidence after varicella zoster vaccination in Wales 2013–2020

Christian Schnier[1] | Janet Janbek[2] | Richard Lathe[1] | Jürgen Haas[1]

Methodology

- Zoster vaccination made available in Wales to those aged 70
  - very little leakage into “private” market
- 56% of those aged 70 were vaccinated over study period
- Followed up for up to 7 years
- Incident dementia was classified as either Alzheimer’s or vascular
- Compared vaccinated with unvaccinated

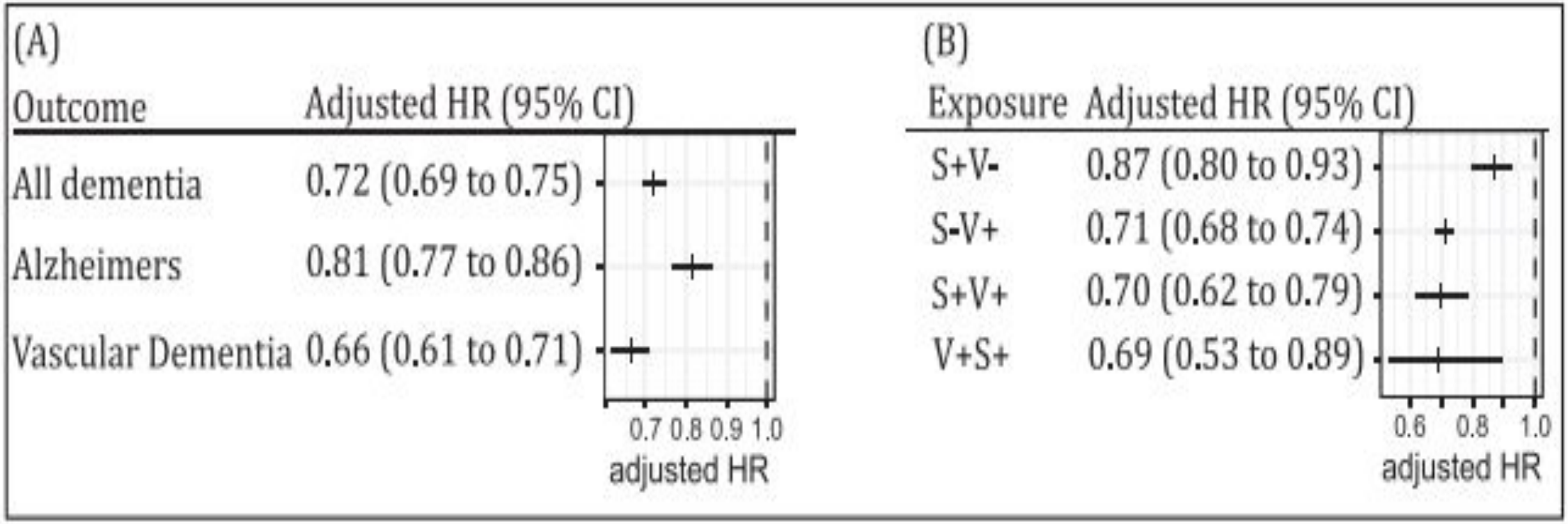


FIGURE 1 Results (adjusted hazard ratio [HR] and 95% confidence interval [CI]) from the multivariable Cox proportional hazard model of the association between exposure to shingles vaccination and dementia. A, Classified by type of dementia (Alzheimer's disease; and vascular

TABLE 1 Association of risk factors with exposure to shingles vaccine

Variable	Level	Total *N*	Vaccinated *N* (%)	Hazard ratio (95% CI)[a]
Sex	Female	174,317	81,064 (47%)	0.95 (0.95 to 0.96)
Born after 1943	Yes	161,476	90,012 (56%)	26.63 (25.99 to 27.29)
WIMD[b]	1	54,950	22,576 (41%)	1.00 (ref)
	2	65,067	27,855 (43%)	1.04 (1.02 to 1.06)
	3	70,425	31,499 (45%)	1.08 (1.07 to 1.1)
	4	67,269	33,150 (49%)	1.22 (1.2 to 1.24)
	5	78,748	40,947 (52%)	1.28 (1.26 to 1.3)
Frailty	Fit	255,118	119,192 (47%)	1.00 (ref)
	Mild	69,379	32,234 (46%)	1.08 (1.07 to 1.09)
	Moderate	10,942	4291 (39%)	0.99 (0.96 to 1.02)
	Severe	1020	310 (30%)	0.85 (0.76 to 0.95)
Care home	Yes	432	89 (21%)	0.57 (0.46 to 0.7)
Prior vaccination	Yes	264,454	141,164 (53%)	3.01 (2.96 to 3.06)
Diabetes	Yes	47,411	22,232 (47%)	1.13 (1.11 to 1.14)
Cancer	Yes	23,987	11,085 (46%)	1.07 (1.05 to 1.1)
Cerebrovascular disease	Yes	10,690	4228 (40%)	0.87 (0.84 to 0.9)
Chronic obstructive pulmonary disease	Yes	37,902	18,449 (49%)	1.13 (1.11 to 1.14)
Chronic heart disease	Yes	4858	1815 (37%)	0.89 (0.85 to 0.94)
Chronic liver disease	Yes	1000	370 (37%)	0.95 (0.85 to 1.05)
Myocardial infarction	Yes	5514	2231 (40%)	0.83 (0.79 to 0.86)
Peptic ulcer	Yes	2085	813 (39%)	0.77 (0.72 to 0.82)
Perivascular disease	Yes	5695	2075 (36%)	0.84 (0.81 to 0.88)
Renal disease	Yes	20,694	9165 (44%)	0.95 (0.93 to 0.97)
Rheumatic disease	Yes	6444	2411 (37%)	0.77 (0.74 to 0.8)

Outcome	Adjusted HR (95% CI)
Shingles	0.43 (0.41 to 0.45)
Mortality	0.58 (0.57 to 0.60)
Stroke	0.86 (0.82 to 0.91)
MI	0.86 (0.82 to 0.90)
Hip fracture	0.55 (0.54 to 0.57)
Cancer	0.98 (0.95 to 1.01)

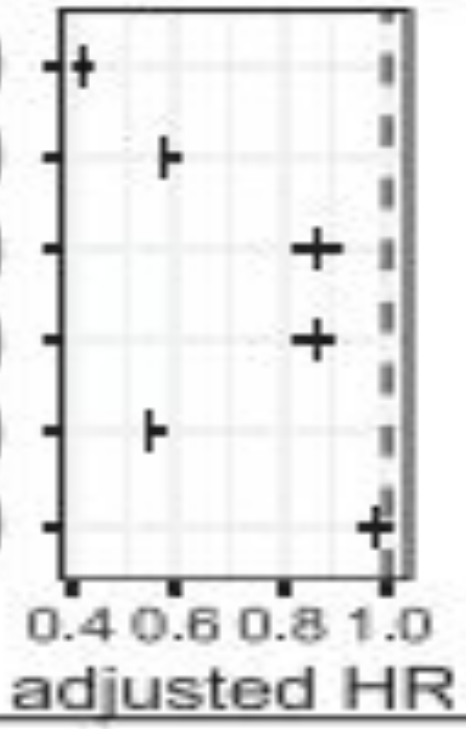


FIGURE 2 Results (adjusted hazard ratio [HR]; and 95% confidence interval [CI]) from the multivariable Cox proportional hazard models of the association between exposure to shingles vaccination and shingles, all-cause mortality, stroke, myocardial infarction, hip fracture, and cancer. The comparison group (HR = 1.0) was not vaccinated. MI, myocardial infarction

Conclusions

- Zoster vaccination (live, attenuated) reduced risk of incident dementia
- Not mediated by reduced incidence of shingles
- Likely mediated by improved cardiovascular health

Causal evidence that herpes zoster vaccination prevents a proportion of dementia cases [1]

Markus Eyting,[1,2,3,†] Min Xie,[1,2,†] Simon Heß,[4] and Pascal Geldsetzer[1,5,6,*]

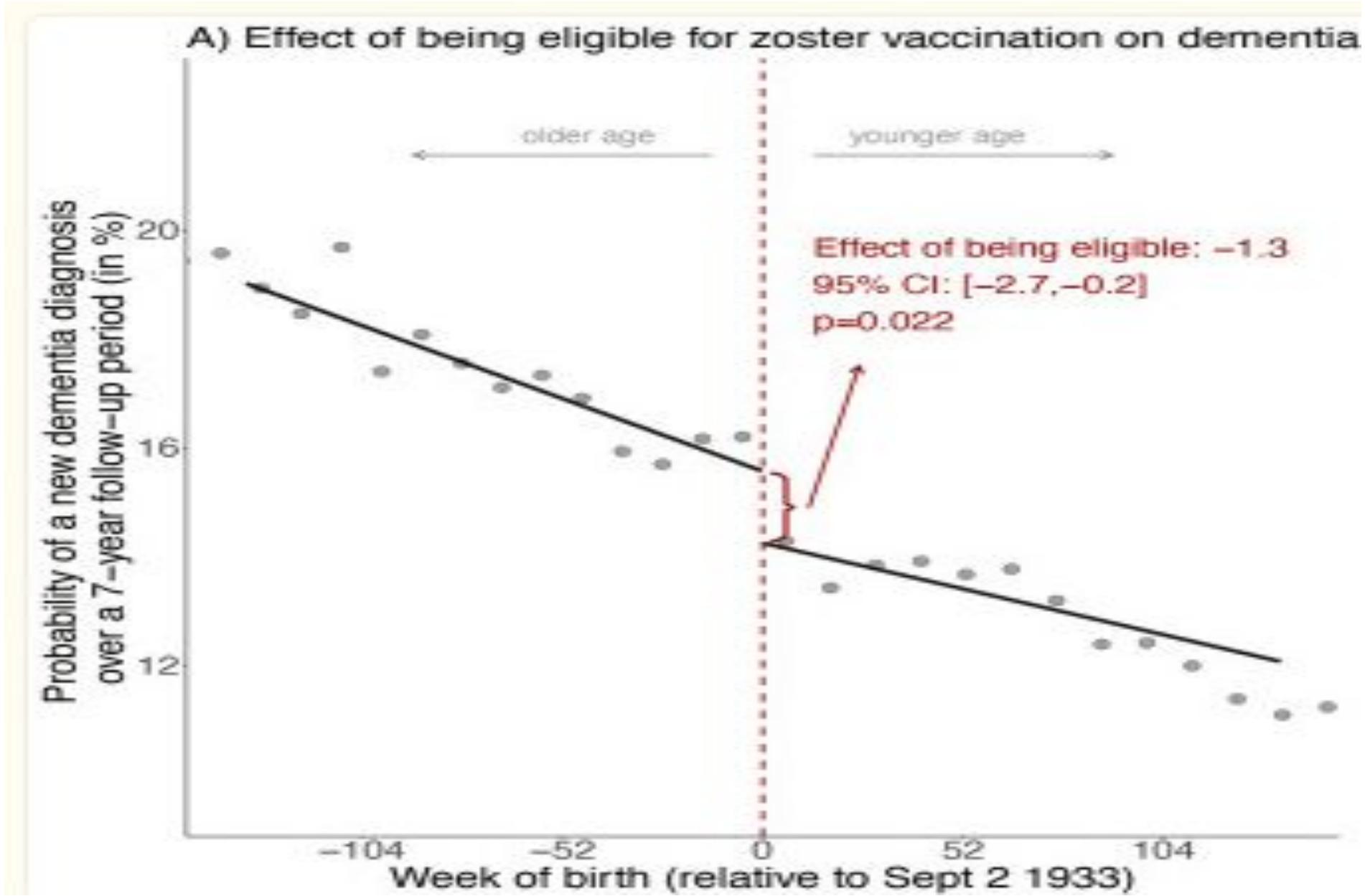
1. Pre-print 2023

In Wales eligibility for the herpes zoster vaccine (Zostavax) for shingles prevention was determined based on an individual's exact date of birth. Those born before September 2 1933 were ineligible and remained ineligible for life, while those born on or after September 2 1933 were eligible to receive the vaccine.

By using country-wide data on all vaccinations received, primary and secondary care encounters, death certificates, and patients' date of birth in weeks, we first show that the percentage of adults who received the vaccine increased from 0.01% among patients who were merely one week too old to be eligible, to 47.2% among those who were just one week younger. Apart from this large difference in the probability of ever receiving the herpes zoster vaccine, there is no plausible reason why those born just one week prior to September 2 1933 should differ systematically from those born one week later.

We demonstrate this empirically by showing that there were no systematic differences (e.g., in pre-existing conditions or uptake of other preventive interventions) between adults across the date-of-birth eligibility cutoff, and that there were no other interventions that used the exact same date-of-birth eligibility cutoff as was used for the herpes zoster vaccine program. This unique natural randomization, thus, allows for robust causal, rather than correlational, effect estimation..

We show that receiving the herpes zoster vaccine reduced the **probability of a new dementia diagnosis over a follow-up period of seven years by 3.5 percentage points (95% CI: 0.6 – 7.1, p=0.019), corresponding to a 19.9% relative reduction in the occurrence of dementia.**


A) Effect of being eligible for zoster vaccination on dementia
older age
younger age
Effect of being eligible: −1.3
95% CI: [−2.7,−0.2]
p=0.022
Probability of a new dementia diagnosis over a 7−year follow−up period (in %)
20
16
12
−104
−52
0
52
104
Week of birth (relative to Sept 2 1933)

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*

Methods

- Optum’s deidentified Clinformatics® Data Mart Database
- Over age 64
- Free of dementia for 2 years prior to start
- 8 year follow-up for incident dementia
- Looked at Td/Tdap, both Shingles vaccines and PCV/PPS.

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

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

Conclusions

- All 3 vaccination types reduced dementia due to Alzheiemr’s risk over subsequent 8 years
  - From about 11% to 8%
  - Around a 25-30% lower risk ratio for vaccinated versus unvaccinated
- Possibly having more than one type of vaccination in a class, or additional doses, is more protective.

Vaccination Against Pneumonia May Provide Genotype-Specific Protection Against Alzheimer's Disease

Svetlana Ukraintseva[a,*], Matt Duan[a], Amanda M. Simanek[b], Rachel Holmes[a], Olivia Bagley[a], Aravind L. Rajendrakumar[a], Arseniy P. Yashkin[a], Igor Akushevich[a], Alexander Tropsha[c], Heather Whitson[d], Anatoliy Yashin[a] and Konstantin Arbeev[a]

A retrospective cohort study among a subset of individuals who survived without AD as of age 75 in the Cardiovascular Health Study (CHS), to estimate associations of vaccinations against pneumonia and influenza (flu) received between ages 65 and 75 with AD onset at age ≥75 years

Looked at the effect of having a specific allele associated with increased AD risk

-linked to ApoE gene

Table 2

Effects of vaccinations against pneumonia and influenza received between ages 65–75 on AD onset at age ≥75 years in CHS data. Unstratified and stratified by *carrier* versus *non-carrier* status of rs6859 A allele. Significance is based on *p*-value <0.05 and 95% confidence intervals

Predictor	Outcome	Beta	*p*	OR (95% CI)	*N*
A) Total sample, without stratification by genotype.					
Pneumonia vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.256	0.126	0.774 (0.558, 1.075)	3,370
Influenza vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.099	0.581	0.906 (0.637, 1.287)	3,385
Number of flu shots	AD onset at age ≥75 (yes/no)	–0.068	0.068	0.934 (0.868, 1.005)	3,385
Total number of pneumonia and flu shots	AD onset at age ≥75 (yes/no)	–0.058	**0.049**	**0.944*** (0.891, 0.999)	3,385
B) Carriers of rs6859 A allele.					
Pneumonia vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.400	**0.0496**	**0.671*** (0.450, 0.999)	2,064
Influenza vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.106	0.629	0.900 (0.586, 1.381)	2,072
Number of flu shots	AD onset at age ≥75 (yes/no)	–0.073	0.101	0.930 (0.852, 1.015)	2,072
Total number of pneumonia and flu shots	AD onset at age ≥75 (yes/no)	–0.070	**0.048**	**0.932*** (0.870, 0.999)	2,072
C) Non-carriers of rs6859 A allele.					
Pneumonia vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.065	0.845	0.937 (0.489, 1.796)	1,143
Influenza vaccine (1 – yes, 0 – no)	AD onset at age ≥75 (yes/no)	–0.236	0.501	0.790 (0.398, 1.568)	1,149
Number of flu shots	AD onset at age ≥75 (yes/no)	–0.060	0.411	0.942 (0.817, 1.086)	1,149
Total number of pneumonia and flu shots	AD onset at age ≥75 (yes/no)	–0.042	0.472	0.959 (0.856, 1.075)	1,149

frontiers | Frontiers in Immunology

SYSTEMATIC REVIEW
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Adult Vaccination as a Protective Factor for Dementia: A Meta-Analysis and Systematic Review of Population-Based Observational Studies

Xinhui Wu[1], *Haixia Yang*[2], *Sixian He*[2], *Ting Xia*[3], *Diang Chen*[4], *Yexin Zhou*[5], *Jin Liu*[6], *MengSi Liu*[7] *and Zhen Sun*[7*]

Details

- 17 studies
- 1.8 million participants
- Numerous vaccines included
  - influenza, herpes zoster, Tdap, hepatitis A, hepatitis B, typhoid, BCG and rabies
- Follow-up 3-20 years

The overall pooled results showed that vaccinations were associated with a 35% lower dementia risk (HR=0.65, 95% CI: 0.60-0.71)

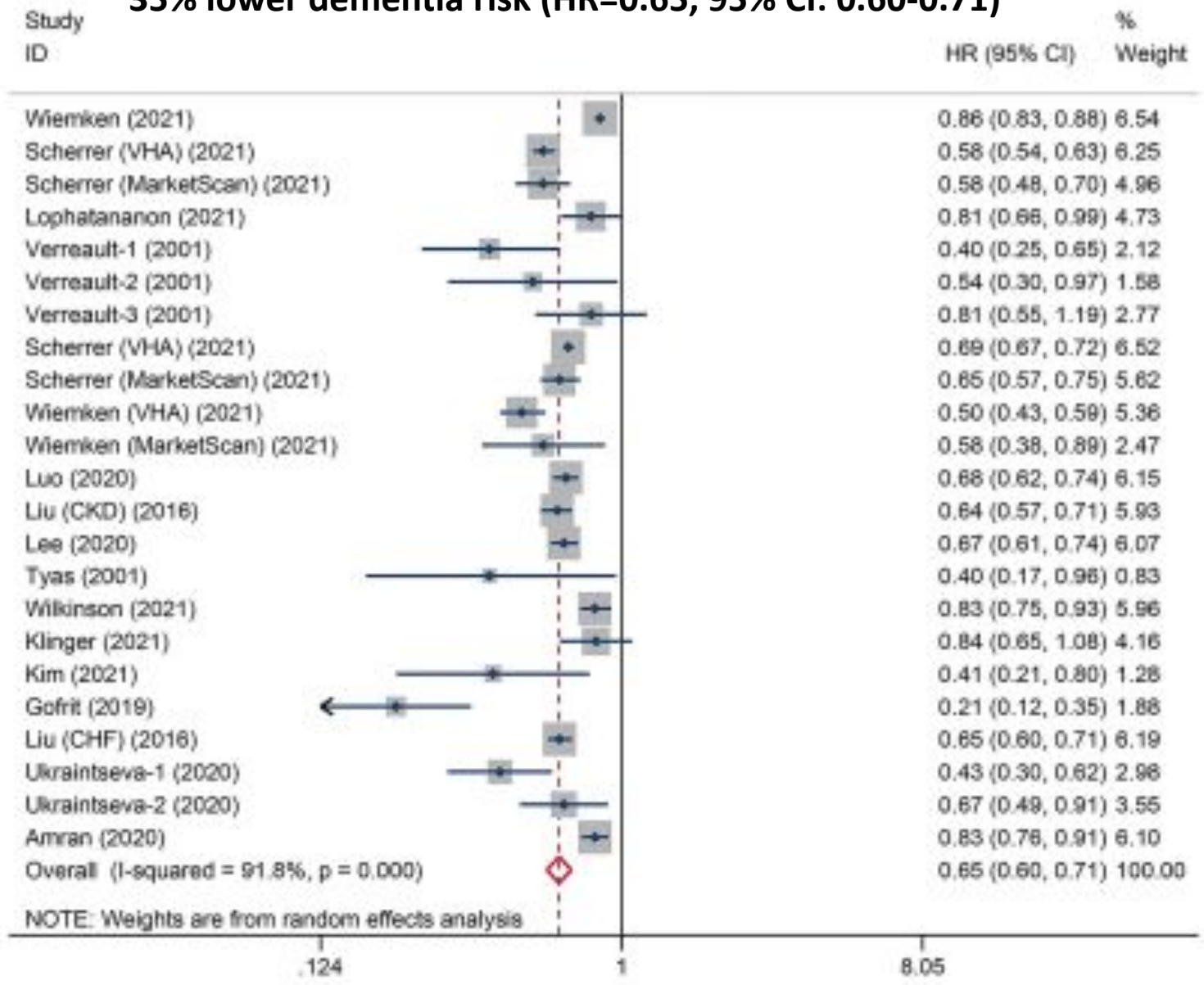

FIGURE 2 | Overall association between adult vaccinations and subsequent dementia risk.

Significance of this effect

- As protective against dementia as reversing recognized factors such as smoking or sedentary lifestyle
- Need to consider this approach as anti-amyloid therapies (which also act on the innate immune system) are expensive and have a range of toxicities
  - Lecanemab, donanemab, aducanumab

How can this protective effect be explained?

- Anti-inflammatory effect?
  - Or reduce the inflammatory response by reducing severity of infection
- Inciting immune response against unwanted proteins?
  - Amyloid
  - Tau
  - ie acting as an “adjuvant”
  - previous studies have also shown that influenza and BCG vaccines in animal models can enhance and maintain microglia activation, restore brain immune homeostasis and reduce Aβ burden, ultimately improving cognitive impairment
- Microbes may induce AD pathology
  - Especially Herpes viruses
  - Gut microbiome increasingly recognized as a risk factor for AD and other dementias
  - Amyloid has antimicrobial effects and may be a response to infection
- Other off-target effects of vaccination
  - Heterologous lymphocyte responses
  - Trained innate immunity
  - Stabilization of the Blood Brain Barrier