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The recombinant shingles vaccine is associated with lower risk of dementia

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Editor summary:

A natural experiment of over 200,000 people who received a shingles vaccine revealed that the recombinant vaccine is associated with lower risk of dementia than the live vaccine, within 6 years of vaccination

Editor recognition statement:

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1. Extended Data

Figure or Table # Please group Extended Data items by type, in sequential order. Total number of items (Figs. + Tables) must not exceed 10.	Figure/Table title One sentence only	Filename Whole original file name including extension. i.e.: Smith_ED_Fig1.jpg	Figure/Table Legend If you are citing a reference for the first time in these legends, please include all new references in the main text Methods References section, and carry on the numbering from the main References section of the paper. If your paper does not have a Methods section, include all new references at the end of the main Reference list.
Extended Data Fig. 1	Kaplan-Meier curves for secondary outcomes in the 3 months-6 years after shingles vaccination in the primary analysis.	Taquet_ED_Fig1.jpg	The curves represent the Kaplan-Meier estimates of the cumulative incidence of death (A) and the composite outcome of death or dementia (B). Shaded areas around curves represent 95% confidence intervals. n=103,837 in each cohort. P-values were obtained using the z-test defined in the SurvRM2 package in R, two-sided and not corrected for multiple comparisons. The exact p-values for (B) is 3.8×10^{-7}.
Extended Data Fig. 2	Results for the negative control outcome.	Taquet_ED_Fig2.jpg	(A) Curves representing the Kaplan-Meier estimates of the cumulative incidence of the negative control outcome in the 3 months-6 years after shingles vaccination. n=103,837 in each cohort. The p-value was obtained using the z-test defined in the SurvRM2 package in R, two-sided and not corrected for multiple comparisons. (B) Curve representing the time-varying hazard ratio for the negative control outcome (n=103,837 in each cohort). Shaded areas in A and B represent 95% confidence intervals.

Extended Data Fig. 3	Kaplan-Meier curves showing the cumulative incidence of outcomes in the 3 months-6 years after shingles vaccination.	Taquet_ED_Fig3.jpg	(A-H) Results for dementia in the different robustness analyses. In (A), the results correspond to the coarsened exact matching with pairwise alignment of follow-up horizons. (I) Results for the incidence of herpes zoster infection. The ratio of restricted mean time lost (RMTL), the p-value for the association, and the additional time lived diagnosis-free among affected people are reported above each figure. Curves in all panels represent the Kaplan-Meier estimates of the cumulative incidence of the corresponding outcome. Shaded areas in all panels represent 95% confidence intervals. See Supplementary Tables 5-9 for baseline characteristics. The number of individuals in each cohort was respectively (A) 82102, (B) 100532, (C) 110062, (D) 66998, (E) 82102, (F) 20243, (G) 54846, (H) 43990, (I) 103837. P-values were obtained using the z-test defined in the SurvRM2 package in R (except for (A) where it was obtained using bootstrap with 1000 repetitions and is reported as <0.001 because all bootstrap replicates of the ratio of RMTL were below 1), two-sided and not corrected for multiple comparisons. The exact p-values are (B) 7.5×10^{-16}, (C) 1.4×10^{-14}, (D) 1.5×10^{-17}, (E) 1.6×10^{-11}, (G) 2.3×10^{-15}, and (I) 4.3×10^{-41}.
Extended Data Fig. 4	Kaplan-Meier curves for the comparisons between shingles vaccines and two other vaccines: influenza and Tdap.	Taquet_ED_Fig4.jpg	(A-B) Comparison with the recombinant shingles vaccine. (C-D) Comparison with live shingles vaccine. The ratio of restricted mean time lost (RMTL), the number of patients in each cohort, the bootstrap p-value for the association, and the additional time lived diagnosis-free among people affected are reported above each figure. Curves in all panels represent the Kaplan-Meier estimates of the cumulative incidence of the corresponding outcome. Shaded areas in all panels represent 95% confidence intervals. Baseline characteristics for these comparisons are provided in Supplementary Tables 11-14. The number of individuals in each cohort was respectively (A) 209031, (B) 98353, (C) 41466, and (D) 64035. P-values were obtained using the z-test defined in the SurvRM2 package in R, two-sided and not corrected for multiple comparisons. The exact p-values are (A) 1.4×10^{-67}, (B) 2.6×10^{-53}, (C) 1.2×10^{-6}, and (D) 2.1×10^{-9}.
Extended Data Fig. 5	Time-varying hazard ratios (HR).	Taquet_ED_Fig5.jpg	Each curve represents the value of the HR from 3 months to 6 years post-vaccination. In (A), the results correspond to the coarsened exact matching with pairwise alignment of

			follow-up horizons. A HR < 1 indicates the risk is lower in those vaccinated predominantly with the recombinant vaccine. The shaded areas around the curves represent 95% CI. The number of individuals in each cohort was respectively (A) 82102, (B) 100532, (C) 110062, (D) 66998, (E) 82102, (F) 20243, (G) 54846, (H) 43990, (I) 103837.

2. Supplementary Information:

A. PDF Files

Item	Present?	Filename Whole original file name including extension. i.e.: Smith_SI.pdf. The extension must be .pdf	A brief, numerical description of file contents. i.e.: *Supplementary Figures 1-4, Supplementary Discussion, and Supplementary Tables 1-4.*
Supplementary Information	Yes	Taquet_NatMed_ShinglesVaccine_Dementia_Supplement.pdf	Supplementary Notes 1-3, Supplementary Tables 1-14
Reporting Summary	Yes	Taquet_nr-reporting-summary.pdf	
Peer Review Information	No	*OFFICE USE ONLY*	

The recombinant shingles vaccine is associated with lower risk of dementia

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Abstract

There is emerging evidence that the live herpes zoster (shingles) vaccine might protect against dementia. However, the existing data are limited, and only refer to the live vaccine now discontinued in the USA and many other countries in favour of a recombinant vaccine. Whether the recombinant shingles vaccine protects against dementia remains unknown. Here we used a natural experiment opportunity created by the rapid transition from the use of live to the use of recombinant vaccines to compare the risk of dementia between vaccines. We show that the recombinant vaccine is associated with a significantly lower risk of dementia in the 6 years post-vaccination. Specifically, receiving the recombinant vaccine is associated with a 17% increase in diagnosis-free time, translating into 164 additional days lived without a diagnosis of dementia in those subsequently affected. The recombinant shingles vaccine was also associated with lower risks of dementia compared to two other vaccines commonly used in older people: influenza and tetanus/diphtheria/pertussis vaccines. The effect was robust across multiple secondary analyses, and present in both men and women but greater in women. These findings should stimulate studies investigating the mechanisms underpinning the protection and could facilitate the design of a large-scale randomised control trial to confirm the possible additional benefit of the recombinant shingles vaccine.

Main

Varicella-zoster virus is a herpes virus that causes chickenpox (varicella) and shingles (herpes zoster). Given the risk of deleterious consequences of shingles,[1] vaccination is now recommended for older adults in many countries. Recent studies have generated substantial interest in the potential protective effect of shingles vaccination against dementia.[2–7] However, most of these studies have compared vaccinated with unvaccinated cohorts, a design prone to selection bias including healthy vaccinee bias.[8] The only exception is a recent natural experiment which compared people just above and just below the eligibility age cut-off, and which found evidence that live shingles vaccination may protect against dementia.[3] That study only showed an effect in women and was limited to the live vaccine, now discontinued in the USA and being withdrawn in many other countries in favour of a recombinant vaccine. Whether the latter provides protection against dementia remains unknown.[7]

Here, we used electronic health records (EHR) and leveraged a USA-based natural experiment opportunity created by the rapid uptake of the recombinant vaccine and the concurrent disuse of the live vaccine after October 2017 (Fig. 1A). By comparing those who received a shingles vaccine just after versus just before this step change, we were able to accurately estimate the association between exposure to the recombinant vaccine and subsequent incidence of dementia diagnosis. We used propensity-score matching to further control for drifts in the characteristics of the vaccinated population.

A total of 103,837 individuals who received a first dose of shingles vaccine between November 2017 and October 2020 (95% received the recombinant vaccine; median [IQR] follow-up of 4.15 years [3.16–4.99]) were propensity-score matched to 103,837 individuals

who received their first dose between October 2014 and September 2017 (98% received the live vaccine; median [IQR] follow up of 6.0 [5.2–6.0] years; see Supplementary Table 1 for baseline characteristics, Supplementary Table 2 for person-year of follow-up and number of dementia cases and Supplementary Table 3 for the distribution of vaccinations per year). Compared to those who predominantly received the live vaccine, those who predominantly received the recombinant vaccine were at a lower risk of dementia in the next 6 years (restricted mean time lost [RMTL] ratio: 0.83, 95% confidence interval [CI] 0.80-0.87, $P<0.0001$), translating into 17% more time lived diagnosis-free, or 164 (95% CI 124–202) additional diagnosis-free days among those affected (Fig. 1B and Table 1).

The association was consistently found across dementia subcategories except for frontotemporal and Lewy body dementia (Supplementary Table 4). Those vaccinated after October 2017 were also less likely to have a herpes zoster infection in the 6 years post-vaccination (RMTL ratio: 0.65, 95% CI 0.61-0.69, $P<0.0001$). There was no difference in negative control outcomes nor in all-cause mortality, and results remained significant for the composite of dementia or death (Table 1 and Extended Data Figures 1 and 2).

Similar results were found when restricting cohorts to those who received the predominant vaccine; when restricting exposure windows to 6 months either side of the step change; when excluding individuals who received both vaccines; and when adjusting for socioeconomic deprivation (Table 1 and Extended Data Figure 3). Similar differences in risk were observed when the follow-up was entirely contained before the COVID-19 pandemic (HR 0.74, 95% CI 0.62–0.90, log-rank p=0.0019; no evidence of violation of the proportional hazard assumption p=0.56). Results were also replicated when using coarsened exact matching for a core set of covariates (age, sex, race, and neurological comorbidities) and this was the case

with both parametric or bootstrap estimates of the variance (Table 1 and Extended Data Figure 3). Aligning the follow-up horizons at the cohort level (in the primary analysis) and at the level of matched pair of individuals (in the coarsened exact matching analysis) did not affect the results (Table 1). See Supplementary Tables 5-9 for baseline characteristics of secondary analyses.

The association between the recombinant shingles vaccine and dementia was found among both women and men (Fig. 1) and there was moderation by sex, with a greater effect in women than men (22% versus 13% more time lived diagnosis-free, permutation test: P=0.017). The association with herpes zoster infection was also found in both women and men but without moderation by sex (36% vs. 35% more time lived diagnosis-free, permutation test: P=0.87, Table 1).

Both shingles vaccines were associated with lower risk of dementia compared to influenza and tetanus/diphtheria/pertussis (Tdap) vaccines (RMTL ratios 0.73-0.86, all P<0.0001; Extended Data Figure 4 and Supplementary Table 10).

The time-varying hazard ratios (HRs) became significantly lower than 1 within the first year of follow-up and then progressively approached (and, in some but not all robustness analyses, exceeded) 1 towards the end the 6-year follow-up (Figure 1 and Extended Data Figure 5), with differences in the shape of the curve apparent between men and women (Extended Data Figure 5). The time-varying HR for the risk of herpes zoster infection followed a similar pattern (Extended Data Figure 5).

Discussion

Compared to the live vaccine, receiving the recombinant shingles vaccine is associated with a lower risk of dementia within the next 6 years. An increase by 17% in time lived without a dementia diagnosis (or 164 additional days among those later affected) is clinically meaningful and a particularly large effect size given that the live shingles vaccine is itself associated with a lower risk of dementia,[3] as replicated here. The consistency of the association in both sexes is important from a public health point of view and for the credibility of findings. No association between the live shingles vaccine and dementia was found in males in the natural experiment in Wales,[3] which called its causal interpretation into question.[7] Equally, the present study did show a 9% greater protective effect in women than men, which cannot be explained by better protection against shingles in women than men — a finding that merits further investigation.

This study is observational and causality cannot be demonstrated. However, the rapid transition from live to recombinant vaccine offered a window of opportunity to estimate associations with dementia free of the main sources of selection bias.[8] The observation that all-cause mortality was highly similar between cohorts, the lack of association with a composite negative control outcome, and the robustness of findings across several secondary analyses, support the absence of obvious residual confounding. These findings provide rationale for a randomised control trial aiming to confirm them and inform future cost-effectiveness analysis of the recombinant vaccine.[1]

The mechanisms by which the shingles vaccines might protect against dementia remain unclear. One explanation is that it protects against herpes infection which itself causes dementia.[9,10] A link between herpes infections and dementia has been hypothesised for decades.[11,12] While this hypothesis remains debated,[13] it would explain why both shingles

vaccines are associated with lower risks of dementia, why the recombinant vaccine offers greater protection (since it better protects against shingles[1] as replicated in this study), and why the protective effect against dementia appears to wane towards later years of follow-up (as did the protective effect against herpes zoster infections). Additionally, the recombinant vaccine contains immunostimulants[14] and these could contribute to the effect on dementia risk. The observation that the time-varying HR became greater than 1 towards the end of the follow-up might imply that the vaccine delays rather than prevents dementia onset. However, this was not robustly observed across analyses (Extended Data Figure 5) and therefore requires replication.

This study has several limitations besides those inherent to studies based on EHR data (such as no validation of diagnoses, and sparse information on socioeconomic and lifestyle factors, see Supplementary Note 1). First, being diagnosis-free does not imply being disease-free as there can be delays in diagnosis. However, assuming diagnostic delays are similar between cohorts, then differences in disease-free time will follow differences in diagnosis-free time. Second, we did not investigate the impact of multiple vaccine doses. Third, the number of people who received a shingles vaccine increased between before and after the introduction of the recombinant vaccine justifying the need for additional control of covariates (as achieved here using matching). However, the fact that the association was maintained when the exposure window was reduced to 6 months on either side of the step change in recombinant vaccine uptake argues strongly against the possibility that drifts in the population characteristics could explain the main findings. Fourth, the paired nature of the data was not accounted for in the estimation of confidence intervals within the primary analysis, an approach which is recommended by some authors[15] but not others.[16] In any

event, when accounting for it in the secondary analysis based on coarsened exact matching, little difference was observed in the estimated confidence intervals.

Acknowledgements

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Author Contributions Statement

MT and PJH had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept: PJH and JAT

Study design: MT with input from PJH and JAT

Data analysis: MT and QD

Data interpretation: MT, JAT, and PJH

Drafting of the manuscript: MT

Critical revision of the manuscript for important intellectual content: MT, QD, JAT, and PJH

Statistical analysis: MT and QD

Supervision: JAT and PJH

Competing Interests Statement

JAT is a consultant for GSK and Co-Director of the Oxford-GSK Institute for Molecular and Computational Medicine. GSK had no involvement of any kind in this study and were not aware of it until after the manuscript was accepted. The other authors report no conflict of interest.

Table 1 – Summary of results for all analyses.

	N	RMTL ratio (95% CI)	p-value	Additional time lived diagnosis-free among affected people, days (95% CI)
Propensity-score matched cohort studies				
Primary analysis	103837	0.83 (0.79-0.87)	2.9×10^{-15}	164 (124-205)
Aligned follow-up horizons (cohort-wise)	103837	0.83 (0.79-0.87)	4.3×10^{-15}	165 (121-209)
Predominant vaccine	100532	0.82 (0.79-0.86)	7.5×10^{-16}	173 (131-214)
Adjusted for social deprivation	110062	0.84 (0.80–0.88)	1.4×10^{-14}	157 (117–196)
Excluding those who received both vaccines	66998	0.79 (0.74-0.83)	1.5×10^{-17}	214 (165-263)
Restricted exposure window (6-months)	20243	0.83 (0.76-0.92)	0.00025	160 (74-246)
Females	54846	0.78 (0.73-0.83)	2.3×10^{-15}	222 (168-276)
Males	43990	0.87 (0.81-0.94)	0.00028	122 (56-187)
Other outcomes				
Mortality	103837	0.98 (0.95-1.01)	0.22	18 (-11 - 47)
Composite endpoint of dementia or mortality	103837	0.93 (0.91-0.96)	3.8×10^{-7}	64 (39-89)
Negative control outcome	103837	0.97 (0.91-1.03)	0.29	32 (-27 - 90)
Herpes zoster infection	103837	0.65 (0.61-0.69)	4.3×10^{-41}	381 (326-435)
Herpes zoster infection (females)	54846	0.64 (0.59-0.69)	1.4×10^{-26}	393 (322-463)
Herpes zoster infection (males)	43990	0.65 (0.58-0.72)	4.8×10^{-15}	387 (293-482)
Coarsened exact matched cohort studies				
Parametric estimates of variance	82102	0.82 (0.77–0.87)	1.6×10^{-11}	192 (137-248)
Bootstrap estimates of variance	82102	0.82 (0.79–0.86)	<0.001	192 (151-235)
Aligned follow-up horizons (pairwise)	82102	0.85 (0.81–0.89)	<0.001	157 (111-203)

N = number of individuals in each cohort. RMTL=Restricted mean time lost. The sample size for the analysis adjusted for social deprivation was slightly higher because it was conducted at a later point and TriNetX is a live network with data continuously accruing. The p-values correspond to the z-test defined in the SurvRM2 package in R except for the last two rows where a bootstrap test with 1000 repetitions was used. All p-values are two-sided and not corrected for multiple comparisons.

Figure legend

Fig. 1 – **Association between recombinant shingles vaccine and risk of dementia within 6 years of vaccination.** (A) Proportion (in %) of each vaccine being received showing the step change that occurred in October 2017. The exposure windows used in the primary analysis are shown in grey, with the restricted exposure windows used in a robustness analysis in dark grey. (B) Curves representing the Kaplan-Meier estimates of the cumulative incidence of dementia diagnosis in the 3 months-6 years after shingles vaccination in the primary analysis (n=103,837 in each cohort). (C) Curve representing the time-varying hazard ratio (HR) for the risk of dementia in the primary analysis (HR < 1 indicates a lower risk of dementia in those who received their vaccine after October 2017), n=103,837 in each cohort. (D) Curves representing the Kaplan-Meier estimates of the cumulative incidence for herpes zoster infection (n=103,837 in each cohort). (E-F) Curves representing the Kaplan-Meier estimates of the cumulative incidence of dementia among females and males respectively (n=54,846 in each cohort for females, and n=43990 for males). The ratio of restricted mean time lost (RMTL), the p-value (obtained using the z-test defined in the SurvRM2 package in R, two-sided and not corrected for multiple comparisons) for the association, and the additional time lived diagnosis-free among affected people are reported above each figure. The exact p-values are (B) 2.9×10^{-15}, (D) 4.3×10^{-41}, (E) 2.3×10^{-15}. Shaded areas in (B-F) represent 95% confidence intervals of the cumulative incidences (B, D-F) and time-varying HR (C).

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Methods

Study design and data source

We used EHR data from the TriNetX US Collaborative Network covering 62 healthcare organisations (hospitals, primary care, and specialist providers) and >100 million patients (Supplementary Note 1).[17] Available data include demographics, diagnoses, and medications. Data de-identification formally meets standards of the Health Insurance Portability and Accountability Act Privacy Rule §164.514(b)(1). This study follows STROBE guidelines.

TriNetX is a platform that de-identifies and aggregates EHR data from contributing healthcare organizations (HCOs). There is no recruitment that takes place. All patients who are seen at these HCOs have their data de-identified and incorporated into TriNetX. A typical organization will have a complex enterprise architecture where the data will flow through several different databases, such as a data warehouse and a research data repository, on its way to TriNetX. TriNetX is a live platform and data are continuously and regularly refreshed as soon as the HCOs themselves refresh their own data. HCOs update their data at various times, with over 80% refreshing in 1, 2, or 4-week frequency intervals. The average lag time for an HCO's source data refresh is one month. TriNetX has been used in many prior studies including a few that investigated dementia as an outcome.[17–19]

Cohorts and exposures

Cohorts included all patients who received a first shingles vaccine dose at the age of 65 or above between November 1, 2017 and October 31, 2020 (primary cohort) and between October 1, 2014 and September 30, 2017 (comparator cohort). Patients were excluded if, before or up to one month after vaccination, they had any of the following diagnoses recorded in their health records:

- Vascular dementia (ICD-10 code F01)
- Dementia in other diseases classified elsewhere (F02)
- Unspecified dementia (F03)
- Parkinson's disease (G20)
- Other degenerative diseases of the nervous system (G30-G32), which include all other dementia not mentioned above (e.g. Alzheimer's disease [ICD-10 code G30]).

Exclusion of those with a neurodegenerative disorder diagnosed within the first month since vaccination limits the impact of reverse causation due to pre-existing (but undiagnosed) illness. Individuals vaccinated in October 2017 were excluded as this marked the transition from live to recombinant vaccine.

Covariates

Cohorts were matched for 60 covariates including sociodemographic factors, comorbidities (capturing major body systems, and those associated with dementia), history of herpes infection, and history of influenza vaccination. All covariates (with ICD-10 codes for comorbidities) are listed in Supplementary Table 1. Covariates were selected as follows.

All available sociodemographic factors were selected. These include age, sex (as recorded in the individual's EHR), ethnicity, race, and marital status. Age is reported as mean and SD but was matched using 2-year bins (65-66, 67-68, …) up to 95 years old and those 95 and over were grouped together. This provides tighter control on age than using age as a continuous variable.

All broad ICD-10 categories of comorbidities were then included to balance comorbidity profiles between cohorts and since indirect link with dementia can be posited for most comorbidity profiles (e.g. respiratory illness increases risk of infection and delirium and thus dementia; diseases of the ear can increase the risk of hearing loss which is a risk factor for dementia).

Some broad ICD-10 categories were further broken down into their most prevalent constituents. This includes 'Neoplasms' (ICD-10 codes C00-D49) which was deemed too heterogeneous (as it includes both benign and malignant neoplasms); cardiovascular diseases (I00-99) and psychiatric disorders (F10-59) given their strong link with dementia; endocrine, nutritional and metabolic disorders (E00-89) which was deemed too heterogeneous and because it contains specific risk factors for dementia such as overweight and obesity, diabetes, thyroid disorders, and vitamin B deficiency. In addition, prior herpes infections (both herpes simplex and herpes zoster) and prior influenza vaccination (to adjust for general attitude towards vaccination) were included as covariates.

Some factors affecting health and healthcare use (ICD-10 codes Z00-Z99) were also included based on whether they differed substantially between unmatched cohorts (SMD > 0.15) with a prevalence of at least 1 in 30 cases in either cohort.

Finally, to capture proxies of vaccine hesitancy, history of influenza vaccination (recommended every year for all adults in the USA) was included.[20]

Outcomes

The primary outcome was a first diagnosis of dementia from 3 months (to exclude delayed diagnosis of pre-existing dementia) to 6 years post-vaccination in a time-to-event analysis. This included any of six ICD-10 codes: vascular dementia (ICD-10 code F01), dementia in other diseases classified elsewhere (F02), Unspecified dementia (F03), Alzheimer's disease (G30), Frontotemporal dementia (G31.0), and Dementia with Lewy bodies (G31.83), as in our previous studies.[17] Secondary outcomes included all-cause mortality (to assess whether vaccines were associated with overall differences in health), the composite of dementia or death (to assess for survivorship bias), each dementia subcategory, herpes zoster infections (ICD-10 code B02), as well as a composite negative control outcome of any acutely painful condition not associated with dementia (see Supplementary Note 2 for details).

Statistical analyses

Propensity score 1:1 matching with a calliper of 0.1 was used to match cohorts on covariates. Characteristics with a standardised mean difference between cohorts <0.1 were considered well matched.[21] In propensity score matching, the propensity score was calculated using a logistic regression (implemented by the function LogisticRegression of the scikit-learn package in Python 3.7) including each of the covariates mentioned above. To eliminate the influence of ordering of records, the order of the records in the covariate matrix were randomised before matching. The matching itself was performed with numpy 1.21.5 in Python 3.7.

Because most individuals vaccinated before October 2017 were matched to individuals vaccinated after October 2017 (but not vice versa), the estimand of the primary analysis is best interpreted as the average treatment effect in the controls.

Incidences of outcomes were calculated with the Kaplan-Meier estimator. The assumption that the hazards were proportional was tested using the generalized Schoenfeld approach implemented in the cox.zph function of the survival package (version 3.2.3) in R. In doing so, the proportionality assumption was found to be violated in the primary analysis (P<0.0001). Consequently, the Cox proportional hazard model was not used and the restricted mean time lost (RMTL) was used instead.[22–24] This was calculated using R package survRM2 version 1.0.4.

The RMTL is the counterpart of the restricted mean survival time (RMST).[25,26] The ratio of RMTL has a meaningful clinical interpretation: it represents how much more time, on average, an individual has lived without the outcome during the follow-up period.[22] Unless otherwise stated, confidence intervals were estimated using a parametric approach as defined in the SurvRM2 package in R.[27] Absolute differences in RMTL were translated into additional days lived without a diagnosis of dementia among those subsequently affected, calculated as the difference in RMTL divided by the cumulative incidence in the comparator cohort.

In addition, time-varying hazard ratios (HR) were estimated using natural cubic splines fitted to the log-cumulative hazard.[28] This was achieved using the generalized survival models of the rstpm2 package (version 1.5.1) in R.[29] Splines with 1, 2, and 3 degrees of freedom were estimated for both the baseline log-cumulative hazard and its cohort dependency and the number of degrees of freedom leading to the lowest Akaike Information Criterion (AIC) was selected.

Moderation by sex was tested using a permutation test with 1000 permutations as follows. The RMTL ratio between those vaccinated after vs. before October 2017 were first calculated independently for men and women and their difference was recorded. In each permutation, individuals were then randomly reallocated to two groups of the same size as the initial 'women' and 'men' groups and the analysis was repeated within these groups, thus leading to the calculation of RMTL ratios in these two random groups. The difference in absolute value between these RMTL ratios was recorded for each permutation, generating a distribution of 10,000 differences in RMTL ratios under the null hypothesis. The p-value for the permutation test was calculated as:

$$P = \frac{1 + N_{>}}{1 + N},$$

where N=1000 is the number of permutations and $N_{>}$ is the number of permutations for which the difference in RMTL ratios was greater (in absolute value) than that observed in the non-permuted dataset.

Because we used EHR with coded health events, if an event was not present, it was considered absent. Missing data for sex, race and ethnicity were assigned their own category and that category was included in the propensity score matching, so that the matched cohorts had approximately equal numbers of patients with unknown sex/race/ethnicity.

Significance for all tests was set at two-sided $P<0.05$. Analyses were conducted in R 4.2.1.

Secondary analysis

Analyses were repeated after: (1) stratification by sex, given the report that protective effects of the live vaccine were limited to women;[2] (2) restricting cohorts to those known to have received the predominant vaccine during each exposure window, (3) limiting exposure

windows to 6 months either side of October 2017 to further decrease influences of drifts in population characteristics, (4) restricting, within the latter cohorts, the follow-up to 18 months so that it occurred entirely before the COVID-19 pandemic and is not subject to any effect that the pandemic might have had on diagnostic trends, (5) excluding those who received both vaccines, and (6) adjusting for socioeconomic deprivation (ICD-10 code Z59 'Problems related to housing and economic circumstances').

Using a restricted set of key covariates (age, sex, race, and neurological comorbidities), we were then able to repeat the analysis using coarsened exact matching (to control for non-linear effects and interactions in these confounding factors),[30] and comparing both parametric and bootstrap (with 1000 resampling of pairs of matched individuals) estimates of variance (to assess the effect of respecting the paired nature of the data on variance estimates).[16,31]

In addition, to assess whether observed associations were an artefact of the differences in follow-up times between cohorts, analyses were repeated after aligning follow-up times (at the cohort level in the primary analysis, and at the level of pairs of individuals in the analysis based on coarsened exact matching).

Both shingles vaccines were also compared to tetanus, diphtheria, and pertussis (Tdap) and influenza vaccines to control for non-specific effects of vaccination, given in the same exposure windows as the primary cohorts (e.g. when comparing the recombinant vaccine to influenza vaccine, the cohort receiving the influenza vaccine received it between November 1, 2017 and October 31, 2020). In these comparisons with other vaccines, the estimands are best interpreted as conditional average treatment effects (conditional on being in the

subpopulation for which covariates overlap between cohorts) since only subgroups within each cohort were successfully matched to each other.

See Supplementary Note 3 for details on secondary analyses.

Data availability

The TriNetX system returned the results of these analyses as csv files, which we downloaded and archived. Aggregate data, as presented in this article, can be freely accessed at https://osf.io/9frxm/. The data used for this article were acquired from TriNetX. This study had no special privileges. Inclusion criteria specified in the Methods would allow other researchers to identify similar cohorts of patients as we used here for these analyses; however, TriNetX is a live platform with new data being added daily so exact counts will vary. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs might be incurred, and a data sharing agreement would be necessary.

Code availability

The code used to generate the results of this analysis can be freely accessed at https://osf.io/9frxm/.

Methods only references

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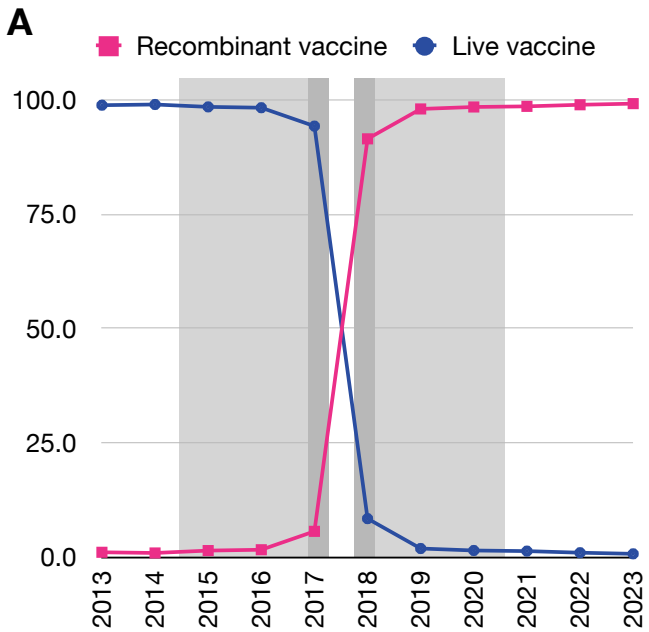
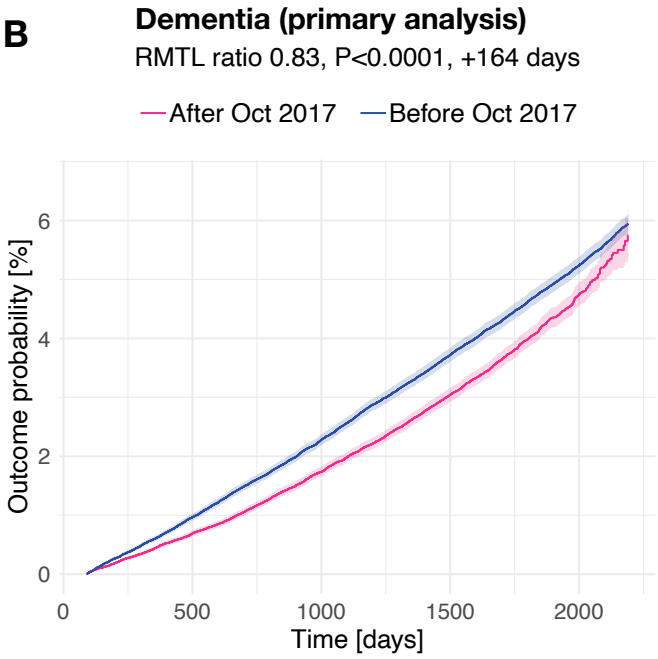
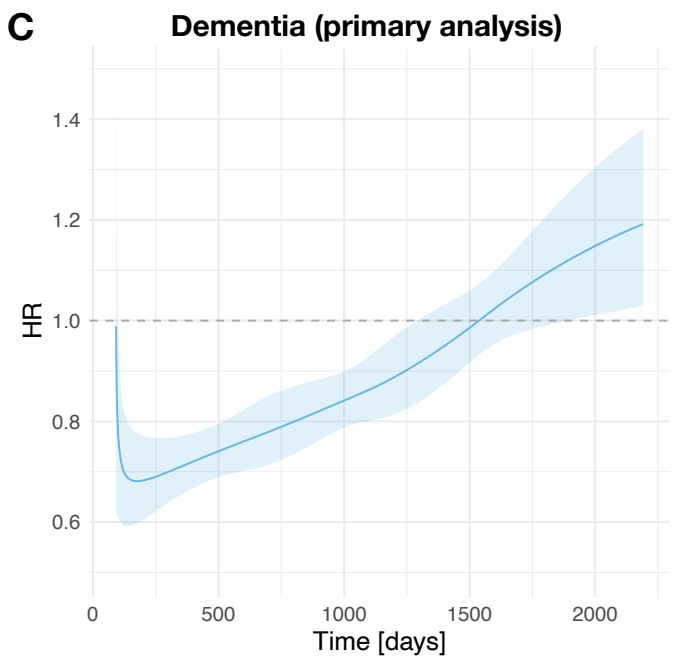
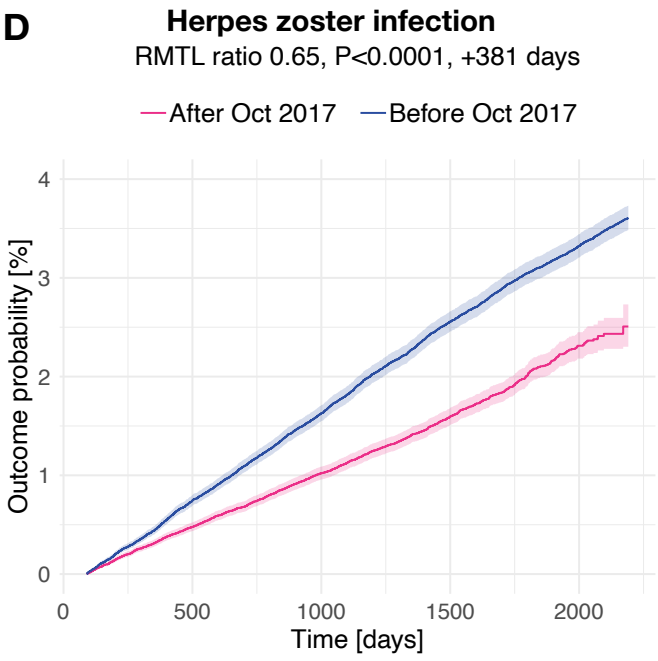
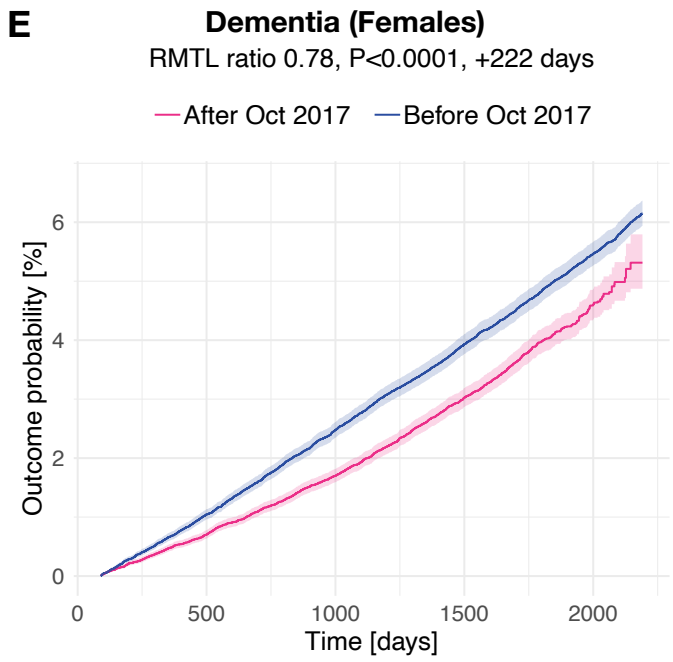
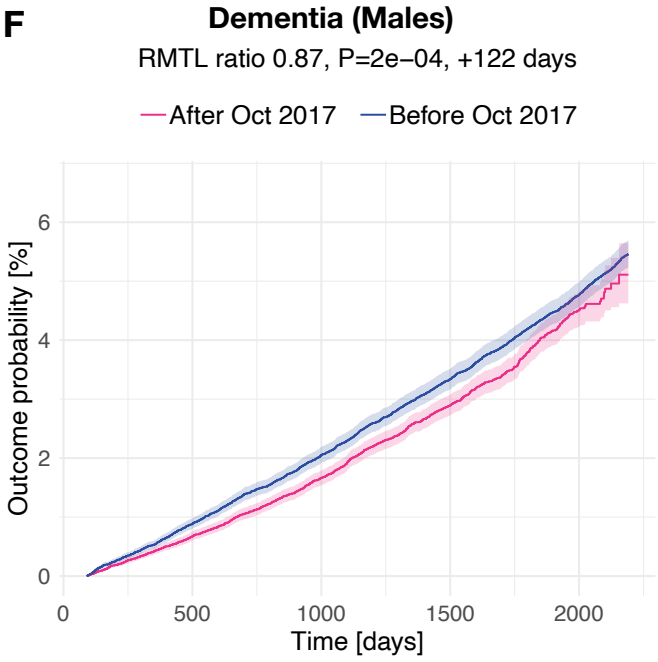

A
Recombinant vaccine
Live vaccine
100.0
75.0
50.0
25.0
0.0
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023

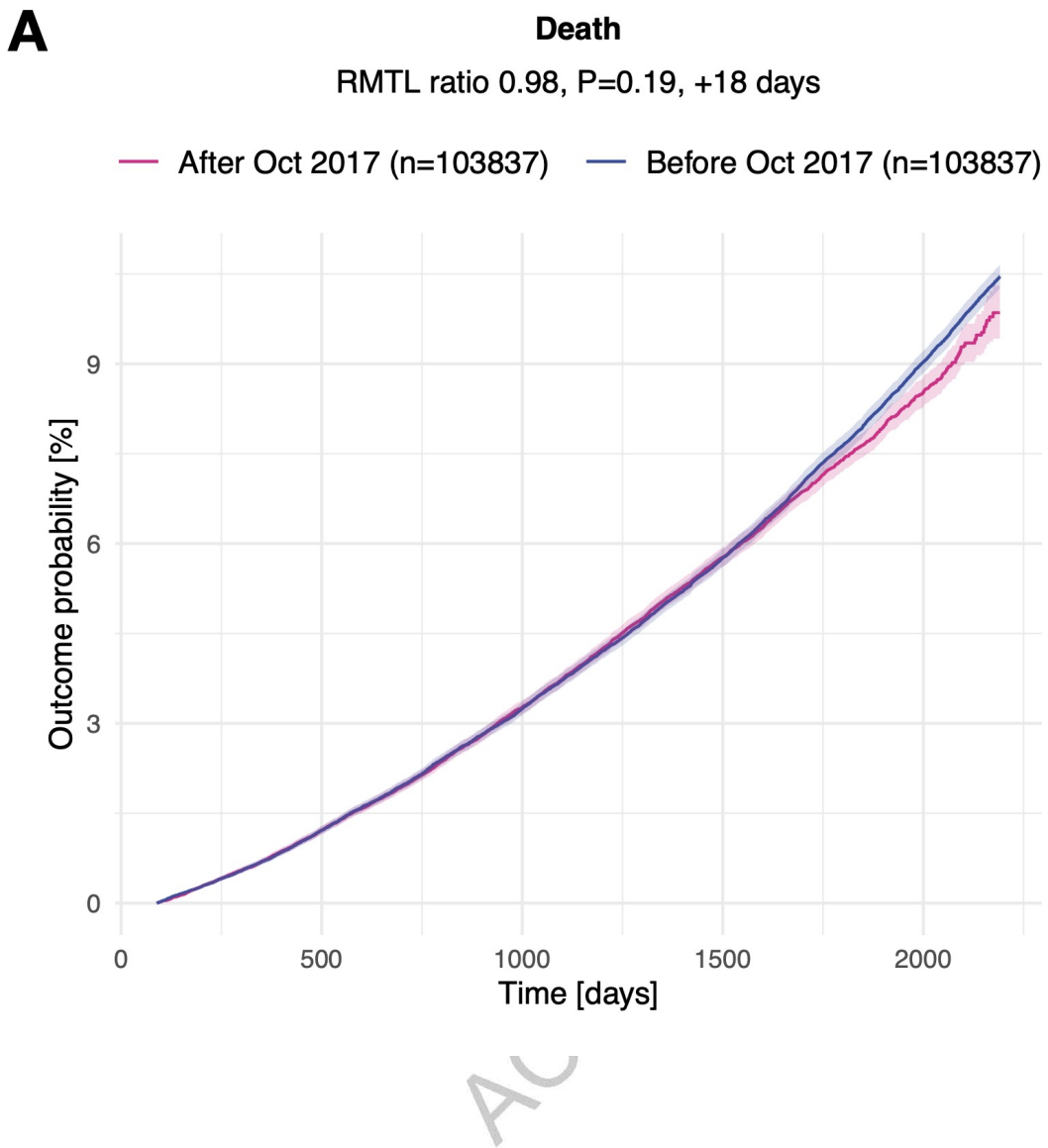

B
Dementia (primary analysis)
RMTL ratio 0.83, P<0.0001, +164 days
After Oct 2017
Before Oct 2017
Outcome probability [%]
Time [days]

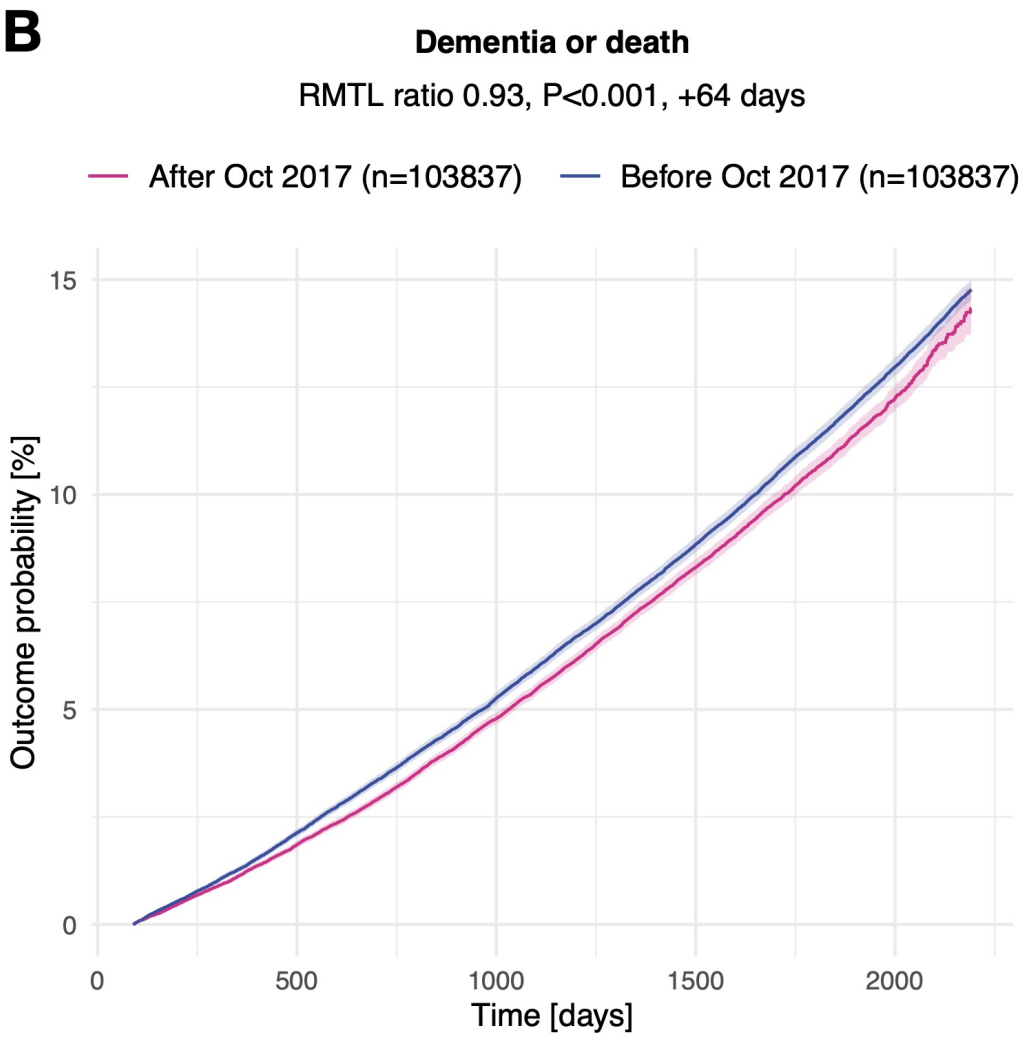

C
Dementia (primary analysis)
HR
Time [days]

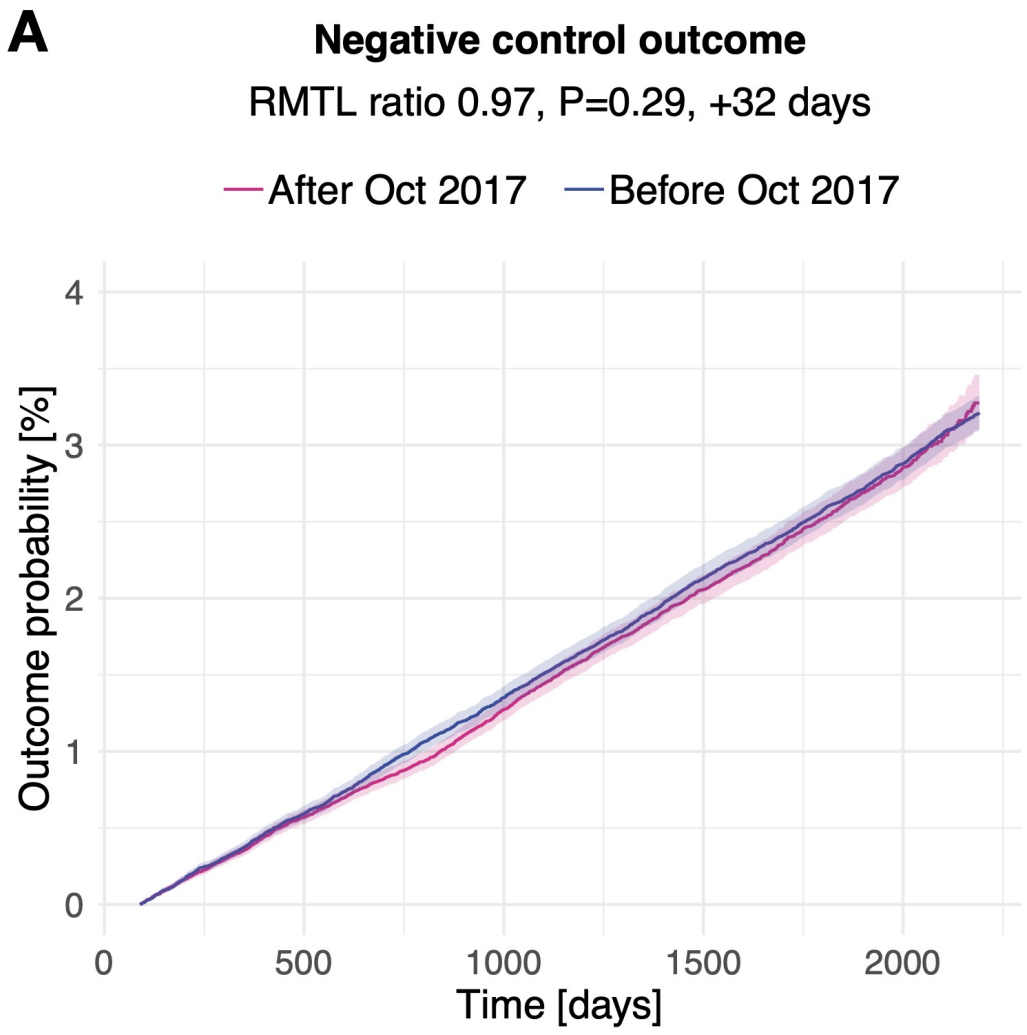

D
Herpes zoster infection
RMTL ratio 0.65, P<0.0001, +381 days
After Oct 2017
Before Oct 2017
Outcome probability [%]
Time [days]

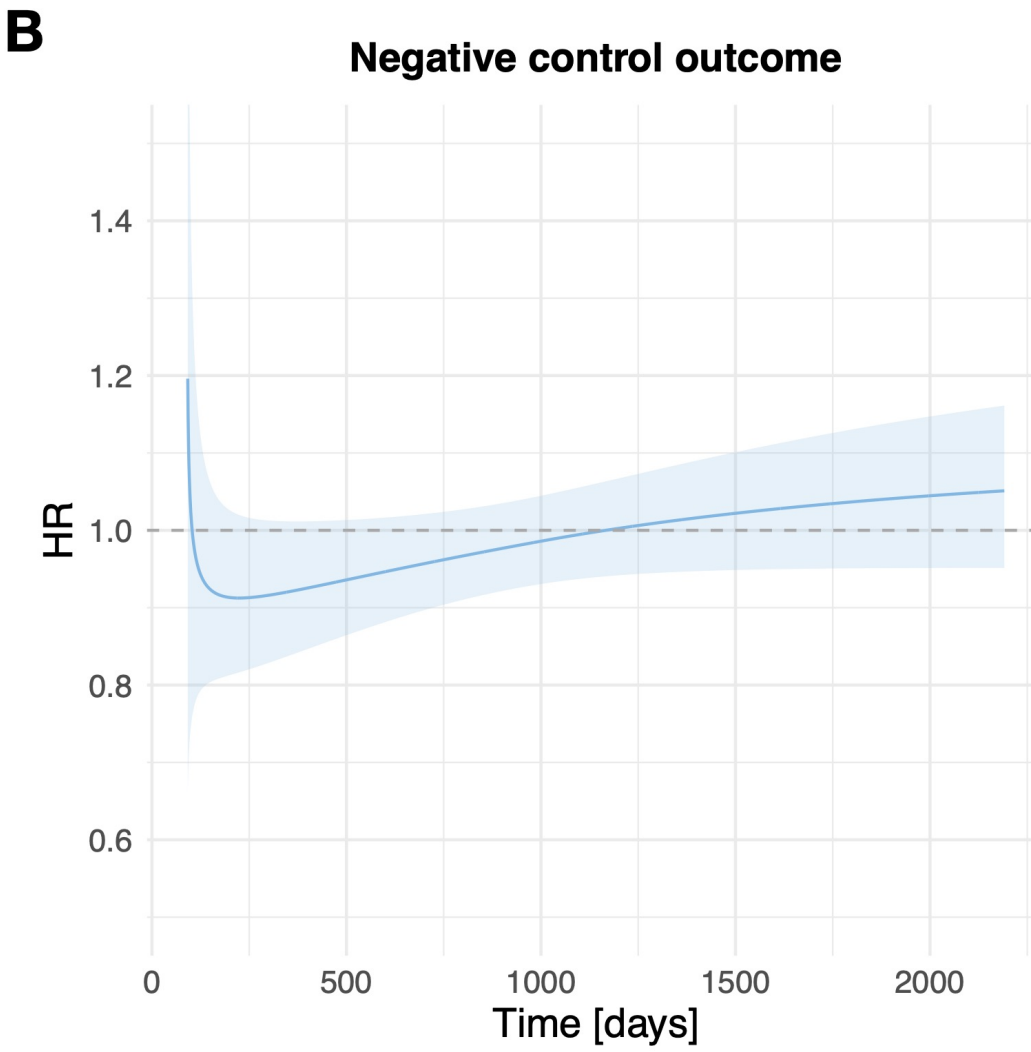

E
Dementia (Females)
RMTL ratio 0.78, P<0.0001, +222 days
After Oct 2017
Before Oct 2017
Outcome probability [%]
Time [days]

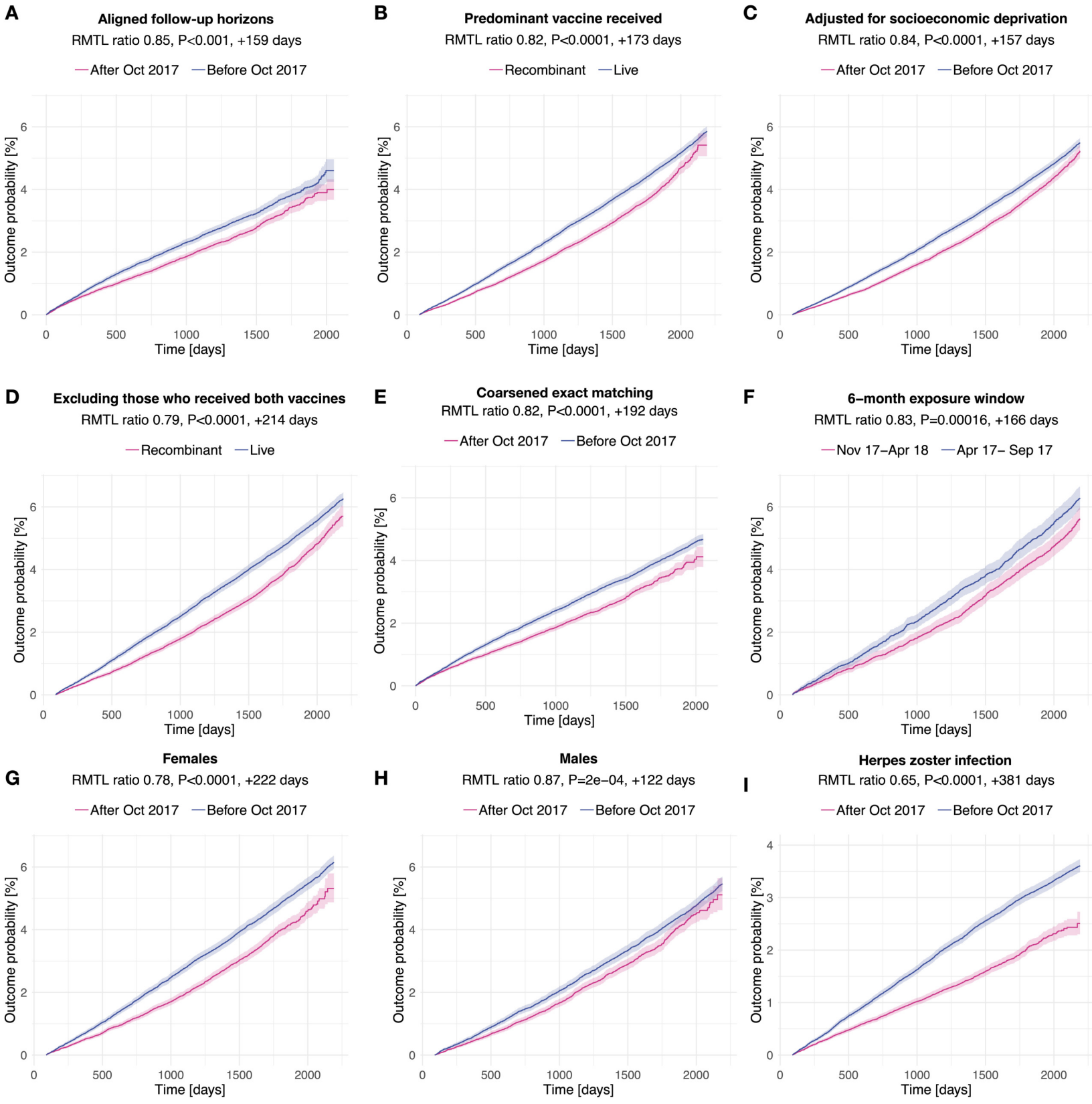

F
Dementia (Males)
RMTL ratio 0.87, P=2e−04, +122 days
After Oct 2017
Before Oct 2017
Outcome probability [%]
Time [days]

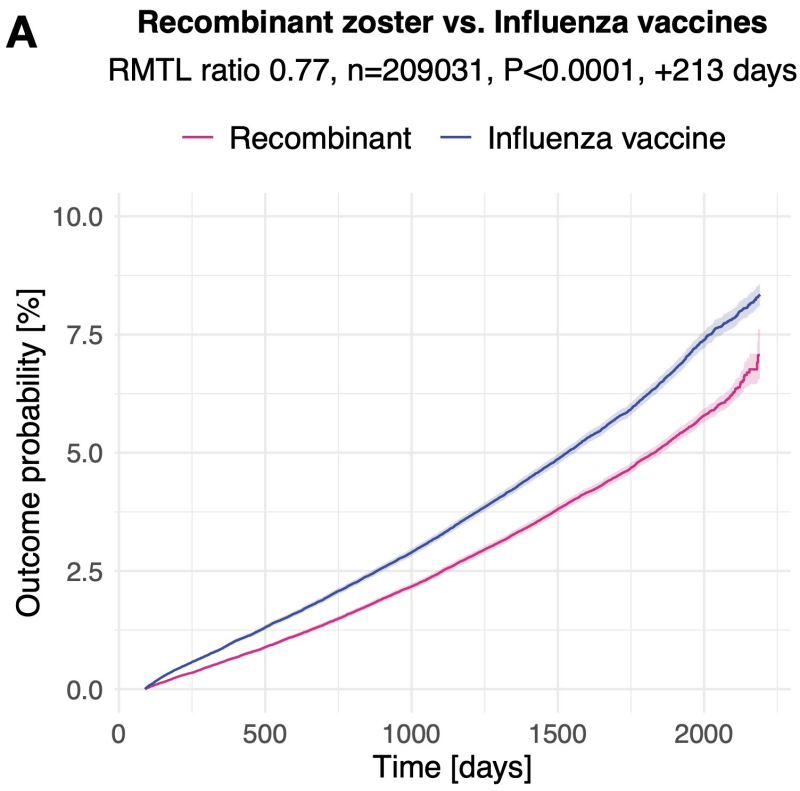

A
Death
RMTL ratio 0.98, P=0.19, +18 days
After Oct 2017 (n=103837)
Before Oct 2017 (n=103837)
Outcome probability [%]
0
3
6
9
0
500
1000
1500
2000
Time [days]

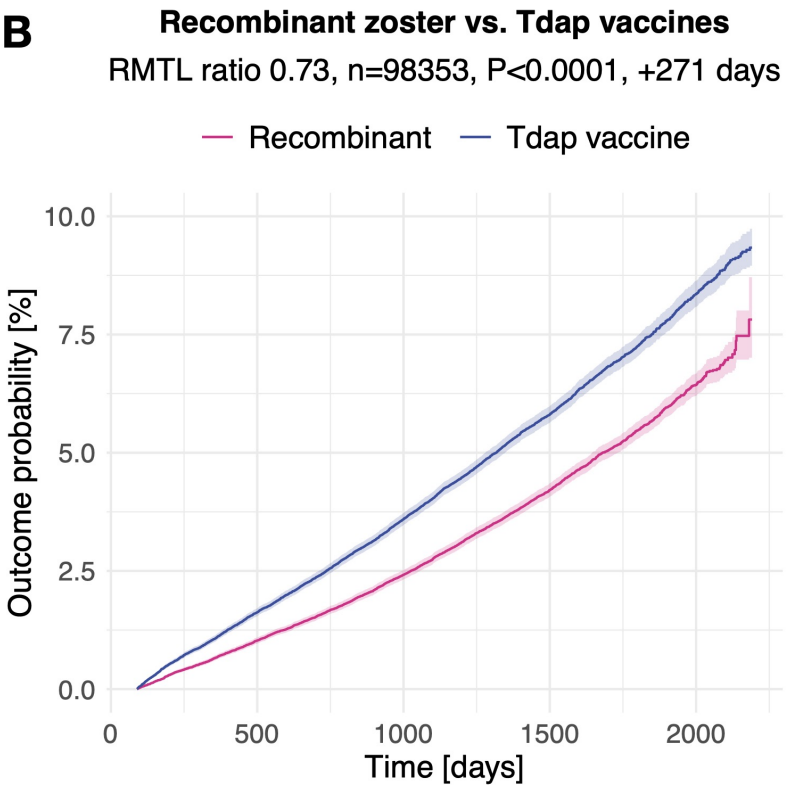

B
Dementia or death
RMTL ratio 0.93, P<0.001, +64 days
After Oct 2017 (n=103837)
Before Oct 2017 (n=103837)
Outcome probability [%]
0
5
10
15
0
500
1000
1500
2000
Time [days]

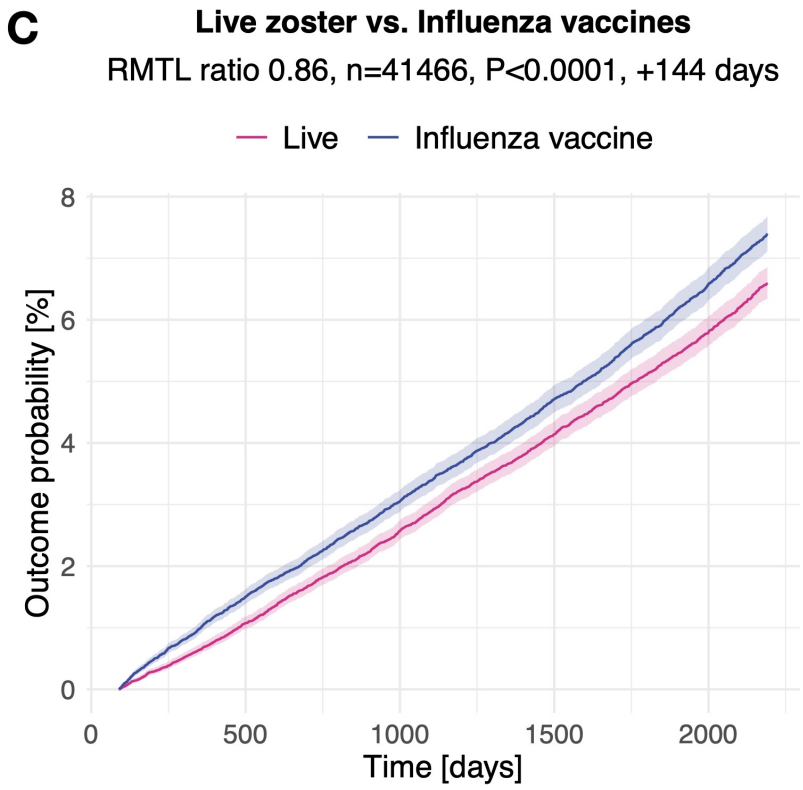

A
Negative control outcome
RMTL ratio 0.97, P=0.29, +32 days
After Oct 2017
Before Oct 2017
Outcome probability [%]
0
1
2
3
4
0
500
1000
1500
2000
Time [days]

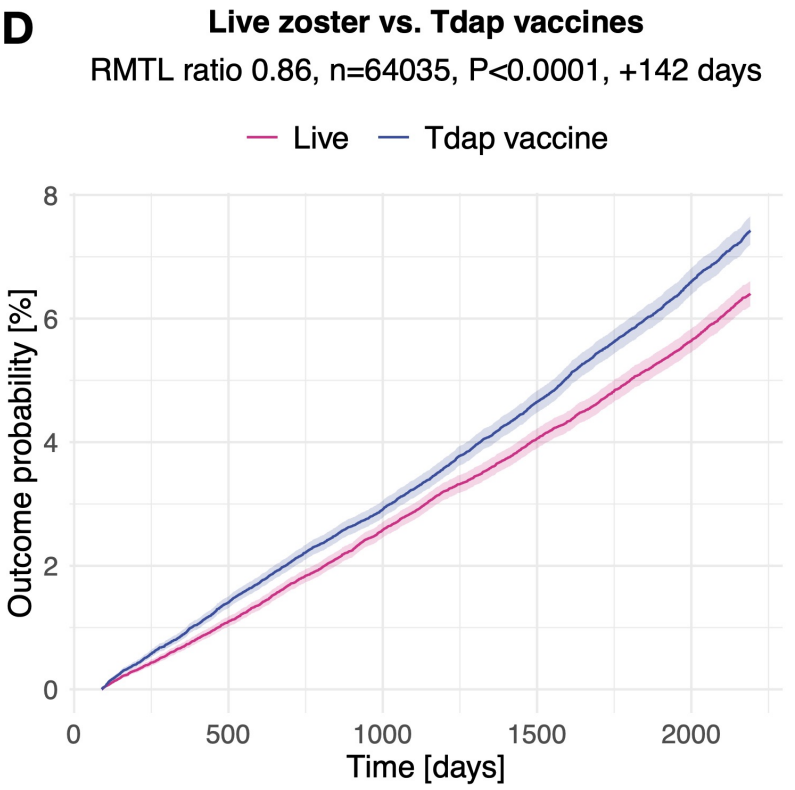

B
Negative control outcome
HR
0.6
0.8
1.0
1.2
1.4
0
500
1000
1500
2000
Time [days]

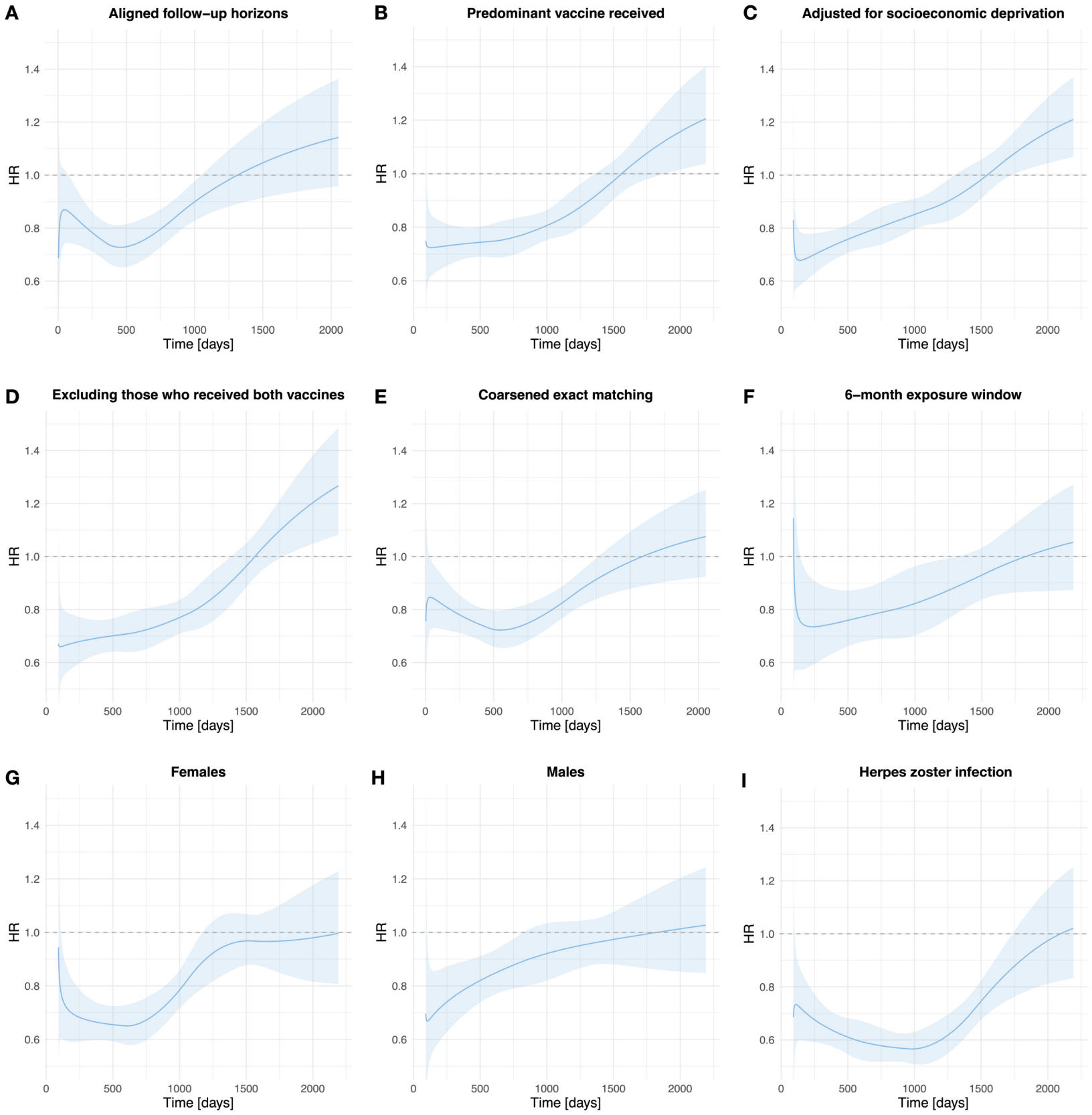

A
Aligned follow-up horizons
RMTL ratio 0.85, P<0.001, +159 days
After Oct 2017
Before Oct 2017
B
Predominant vaccine received
RMTL ratio 0.82, P<0.0001, +173 days
Recombinant
Live
C
Adjusted for socioeconomic deprivation
RMTL ratio 0.84, P<0.0001, +157 days
After Oct 2017
Before Oct 2017
D
Excluding those who received both vaccines
RMTL ratio 0.79, P<0.0001, +214 days
Recombinant
Live
E
Coarsened exact matching
RMTL ratio 0.82, P<0.0001, +192 days
After Oct 2017
Before Oct 2017
F
6–month exposure window
RMTL ratio 0.83, P=0.00016, +166 days
Nov 17–Apr 18
Apr 17– Sep 17
G
Females
RMTL ratio 0.78, P<0.0001, +222 days
After Oct 2017
Before Oct 2017
H
Males
RMTL ratio 0.87, P=2e−04, +122 days
After Oct 2017
Before Oct 2017
I
Herpes zoster infection
RMTL ratio 0.65, P<0.0001, +381 days
After Oct 2017
Before Oct 2017
Outcome probability [%]
Time [days]


A
Recombinant zoster vs. Influenza vaccines
RMTL ratio 0.77, n=209031, P<0.0001, +213 days
Recombinant
Influenza vaccine
Outcome probability [%]
10.0
7.5
5.0
2.5
0.0
0
500
1000
1500
2000
Time [days]


B
Recombinant zoster vs. Tdap vaccines
RMTL ratio 0.73, n=98353, P<0.0001, +271 days
Recombinant
Tdap vaccine
Outcome probability [%]
10.0
7.5
5.0
2.5
0.0
0
500
1000
1500
2000
Time [days]


C
Live zoster vs. Influenza vaccines
RMTL ratio 0.86, n=41466, P<0.0001, +144 days
Live
Influenza vaccine
Outcome probability [%]
8
6
4
2
0
0
500
1000
1500
2000
Time [days]


D
Live zoster vs. Tdap vaccines
RMTL ratio 0.86, n=64035, P<0.0001, +142 days
Live
Tdap vaccine
Outcome probability [%]
8
6
4
2
0
0
500
1000
1500
2000
Time [days]


A
Aligned follow–up horizons
B
Predominant vaccine received
C
Adjusted for socioeconomic deprivation
D
Excluding those who received both vaccines
E
Coarsened exact matching
F
6–month exposure window
G
Females
H
Males
I
Herpes zoster infection
HR
1.4
1.2
1.0
0.8
0.6
0
500
1000
1500
2000
Time [days]

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Last updated by author(s): 2024/03/13

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☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data collection is performed using TriNetX user interface. Demographics are coded to HL7 version 3 administrative standards, diagnoses are represented by ICD-10-CM codes, procedures are coded in ICD-10-PCS or CPT, and measurements are coded to LOINC.
Data analysis	Propensity-score matching was achieved within TriNetX by calculating the propensity score with the scikit-learn package in Python 3.7 and using a nearest neighbour search with numpy 1.21.5 in Python 3.7. Data analysis includes all the processing of data from the life tables of matched cohorts and include Kaplan-Meier estimation, restricted mean time lost estimates, bootstrapping, permutation test and generation of figures. All these steps were conducted in R version 4.2.1. The assumption that the hazards were proportional was tested using the generalized Schoenfeld approach implemented in the cox.zph function of the survival package (version 3.2.3). The restricted mean time lost was calculated using R package survRM2 version 1.0.4. Bootstrapping and permutation tests were conducted using in-house R code that is publicly available. Time-varying hazard ratios were calculated using the generalized survival models of the rstpm2 package (version 1.5.1) in R. All in-house R code is available via the following link: https://osf.io/9frxm/

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Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The TriNetX system returned the results of these analyses as csv files, which we downloaded and archived. Aggregate data, as presented in this article, can be freely accessed at https://osf.io/9frxm/. The data used for this article were acquired from TriNetX. This study had no special privileges. Inclusion criteria specified in the Methods would allow other researchers to identify similar cohorts of patients as we used here for these analyses; however, TriNetX is a live platform with new data being added daily so exact counts will vary. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs might be incurred, and a data sharing agreement would be necessary.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Analysis stratified by sex was performed. The sex was as recorded in the individual's electronic health record.
Reporting on race, ethnicity, or other socially relevant groupings	Self-reported race and ethnicity in TriNetX come from the individual's electronic health record. TriNetX maps race to the following categories: Asian, American Indian or Alaskan Native, Black or African American, Native Hawaiian or Other, White, Unknown race. It maps ethnicity to the following categories: Hispanic or Latino, Not hispanic or latino, Unknown ethnicity.
Population characteristics	All these characteristics are reported in full in Table 1 and Supplementary Tables 2-9.
Recruitment	There was no recruitment as this was a real-world analysis based on electronic health records data. All individuals with a recorded shingles vaccine at the age of 65 or over, between October 2014 and October 2020 and who did not have a diagnosis of a neurodegenerative condition before their vaccine were included.
Ethics oversight	De-identification data are formally attested as per Section §164.514(b)(1) of the HIPAA Privacy Rule, superseding TriNetX's waiver from the Western Institutional Review Board; no further ethical approval was thus needed.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	This is a real-world data analysis which includes all individuals who received a shingles vaccine between October 2014 and October 2020. No sample size calculation was therefore performed.
Data exclusions	Pre-established exclusion criteria included any pre-existing neurodegenerative condition before shingles vaccination. These include dementia (since individuals could not have the outcome before the exposure) and other neurodegenerative conditions (such as Parkinson's disease) since these might indicate that a disease process that might lead to to dementia has already started.
Replication	Findings were replicated in 9 scenarios: (i) when restricting cohorts to those who received the predominant vaccine; (ii) when restricting exposure windows to 6 months either side of the step change; (iii) using coarsened exact matching; after aligning follow-up times (iv) at the cohort level and (v) the individual level; (vi) after adjusting for socioeconomic deprivation; (vii) among women and (viii) men; and (ix) after limiting follow-up so that it is fully contained before the COVID-19 pandemic. All attempts at replication were successful.
Randomization	The influence of covariates was strongly limited by the use of a natural experiment created by the rapid transition from the use of live shingles vaccine to the use of recombinant shingles vaccine. Remaining covariates imbalance (e.g. due to drift in characteristics of the population being vaccinated) were further controlled for by propensity-score matching (in the primary analysis) and by coarsened exact matching (in a robustness analysis).
Blinding	Cohorts were created based on predefined inclusion and exclusion criteria. The outcome was ascertained based on routine electronic health records data and not by any investigator of this study. As a result, blinding was not necessary.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A