The Shingles Vaccine and Dementia: The Evidence Just Got Stronger

7 MIN READ

JAN. 23, 2026

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Two new studies deepen the case for a causal link to lower dementia risk.

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Last April I wrote a Ground Truths article entitled "**The Shingles Vaccine and Reduction of Dementia."** At the time, many were unaware of this unanticipated relationship based on 2 large natural experiments. Two new studies this week have advanced our understanding about the potential biological impact of the Shingles vaccine independent of its effects for preventing Shingles or direct action vs. herpes zoster virus and reinforced its protection from dementia, ~80% of which is attributable to Alzheimer's disease.

TL;DR

- The case for the Shingles vaccine linked to reduced dementia, which is mostly less Alzheimer's disease, has been strengthened with a 4th natural experiment (real-world conditions that allow stronger cause-and-effect inference) that not only corroborates the previous ones, but also, via data triangulation, helps support a cause-and-effect.
- The evidence comes from large, real-world studies across multiple countries, where vaccine eligibility was determined by policy and timing rather than individual choice, helping minimize bias and strengthen confidence in the results

In this post I won't get into the details of what I previously wrote (please **link** back for more perspective), but instead devote the text to the new findings. I'll come back to this summary Figure below shortly.

A Fourth Natural Experiment: Canada

Recently in *Lancet Neurology*, another Shingles vaccine natural experiment was reported that had unique features to help establish cause-and-effect for the vaccine (Zostavax, the live attenuated virus vaccine) and reduction of dementia. To be clear, a natural experiment is an observational study that is based on a naturally occurring situation or policy, such as a country's policy for vaccine eligibility by birthdate. In many ways, these experiments can be considered better than randomized trials because there are no or minimal selection criteria, they are typically orders of magnitude larger with respect to number of individuals assessed, and they are real world rather than in context of a clinical trial which is subject to the "Hawthorne effect'" – just being part of a study can have an impact.

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In the new study of Canadians, the focus was on over 464,000 people aged 70 years and older who were enrolled in a primary care network; and the more than 250,000 from that group who were born in Ontario. The vaccine eligibility cutoff of birthdate before and after Jan 1, 1946 broke the groups from Ontario into two, for either being or not being vaccinated. With 5.5 years of follow-up, there was an absolute 2.0 per cent point reduction of dementia. Using a second date-of-birth eligibility (Jan 1, 1945)

in Ontario, the findings were replicated. Using the same birth cohorts for Ontario compared with the other Canadian provinces that did not implement a Shingles vaccine program, as shown below, the differences for dementia reduction irons were pronounced, increasing over the length of follow-up. This ability to triangulate by birthdates and to other parts of the country without a vaccine program is unique among the 4 natural experiments and helps to further support a cause-and-effect relationship.

Context With All Four Natural Experiments

Previously, there were natural experiments published for the country of **Wales** by Eyting et al (N=280,000), **Australia** by Pomirchy and colleagues (N-101,219), and a **US comparison of the live attenuated vs recombinant (Shingrix)** vaccine by Taquet et al (N=103,615). The numbers in parentheses refer to the number of people assessed, each analysis enabled by birthdate cutoffs. The reports from Wales, Australia and Canada all used the Zostavax (old) Shingles vaccine whereas the US study assessed the difference between recombinant Shingrix vs Zostavax with the main finding of a 17% increase in dementia-free time. All 4 of the reports included an in-depth analysis of potential confounders, showing, as you would expect, minimal differences between groups vaccinated or unvaccinated.

In the simplified Figure below, I've highlighted the consistent reduction in new dementia diagnosis during extended follow-up, along with the differences by sex with 3 of the 4 studies showing significantly greater impact in women. Notably, 3 of these publications were spearheaded by Pascal Geldsetzer at Stanford University.

A recent paper in *Cell* added another feature about the Shingles vaccine (Zostavax) drawn for the natural experiments. The vaccine not only helped prevent or delay mild

cognitive impairment but also slowed the disease course among those with dementia, and reduced deaths attributable to dementia.

Shingles Vaccine and Slowing of Biological Aging

In the *Journal of Gerontology,* Jung Ki Kim and colleagues from the University of Southern California, published a novel study of 3,884 participants, part of the US Health and Retirement study cohort, age 70+ (in 2016) for 7 domains of biology. Half (49.6%) had a Shingles vaccine. The 7 domains were: 1. *Adaptive immunity* (biomarkers of B and T cells and their subtypes); 2. *Innate immunity* (natural killer cells, other white blood cells besides lymphocytes); 3. *Inflammation* (IL-6, C-reactive protein, and 7 other blood inflammation markers); 4. *Epigenetic aging* (PhenoAge, GrimAge, DundedinPACE); 5. *Transcriptomic aging* (transcriptomic mortality-risk age); 6. *Neurodegeneration* biomarkers (p-tau181, GFAP, NFL, and A?42/40 Ratio; and 7. *Simple cardiovascular metrics* (blood pressure, heart rate). A composite score was also derived for all domains except adaptive immunity. Not all participants had all the domains assessed but the minimum number for an assay domain was about 1,500 participants.

As you can see below, the regression coefficients with 95% confidence intervals (the correlation) for having the shingles vaccine were associated with significantly more inflammation and slower epigenetic aging. Also a higher level of adaptive immunity was linked with the vaccine.

In the Figure below, the *relationship of the Shingles vaccine to the domain over time* is plotted. The association of slowing of aging, both by epigenetic clocks and the transcriptomics clock, was somewhat more pronounced (not statistically significant) in the first 3 years of time, but was durable beyond 4 years after vaccination. Innate immunity and inflammation were only observed to be significantly reduced beyond 4+

years after vaccination. Notably, there were no effects on the neurodegenerative blood biomarkers markers of p-tau181, GFAP, NfL, and A?42/40 ratio) even though there are 4 natural experiments showing a reduction of dementia tied to the vaccine.

All of the above data were adjusted for demographic, socioeconomic, and health-related factors.

One Other Thing

The South Korea Study and Cardiovascular Protection
In May 2025, there was **a nationwide report of over 1.6 million South Koreans** who either did or did not receive the Zostavax vaccine. While not a natural experiment, using matching and propensity analysis, and adjustment of known confounding factors, an impressive improvement of cardiovascular outcomes across the board was seen, as summarized in the graph below (MACE-major adverse cardiovascular event), especially in men and age 60+. These results replicate other studies of the Shingles vaccine for cardiovascular protection, at a large scale, although not established via natural experiments.

The Bottom Line

The case for the Shingles vaccine linked to reduced dementia, which is mostly less Alzheimer's disease, has been strengthened with a 4th natural experiment that not only corroborates the previous ones, but also, via data triangulation, helps support a cause-and-effect.

The concern with interpreting these studies has been whether people who get the Shingles vaccine are selecting out a special group, a biased sample, if you will. Beyond the inherent strengths of a natural experiment at scale, comparing data to the

rest of the country without a vaccination program adds another dimension towards certainty of the effect.

But there are uncertainties. Why do women have more benefit in 3 of the 4 studies, and in the largest (Wales) there was no benefit seen for men? We know that Alzheimer's disease is more frequent in women, but that doesn't explain the disproportionate benefit. We now have some data to go from via the mechanistic, biological aging study, with 3 observations, as seen the Figure above: (1) the slowing of epigenetic and transcriptomic age was greater in women; (2) there were significant differences for the vaccine correlation with reduced levels of innate and adaptive immunity, compared with men; and (3) the change in neurodegenerative markers were linked with women, not men. These at least provide some hints for why women are deriving more benefit.

Still unknown is whether the vaccine has a direct effect on the herpes zoster virus or is working indirectly to reduce inflammation and modulate the immune system. We now have evidence for the latter, but that doesn't rule out some connection with the virus.

We also do not know whether people getting the vaccine below age 50 (current US policy is 50+) derive more or any benefit, and whether the association holds for people who have had Shingles.

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As reviewed in the prior *Ground Truths*, **the protection against dementia was predominantly vs Alzheimer's disease** in the studies that got into subtypes of dementia. If this vaccine was a drug and reduced Alzheimer's by 20%, it would be considered a major breakthrough for helping to prevent the disease! But as a vaccine it hasn't reached any sense of being a blockbuster; this indication was never envisioned

when the vaccines were developed and we only “backed into it” from these large and highly consistent natural experiments.

The study in the US is the only one that factored in the new recombinant Shingrix vaccine compared to the old live-attenuated virus version. It is much more effective than Zostavax for preventing Shingles (~50% vs >90% protection) and the **Taquet report also showed** it linked to 17% more freedom from dementia-diagnosis time. That would suggest we *may be underestimating* the reduction of Alzheimer’s from the 3 natural experiments that used an outdated vaccine.

If you are 50+ and have not gotten Shingrix vaccinated, you may want to consider that. You get protection vs Shingles (which can be dreadful), slowing of your biological aging (by methylation and RNA metrics), and ~20% reduction of dementia, predominantly related to Alzheimer’s disease. All of this benefit is magnified in women compared with men, but 3 of the studies showed slowing of dementia in men. As a tradeoff, men appear to derive more cardiovascular benefit, but that evidence is not as compelling as protection from dementia from natural experiments.

Finally, we always want to have independent replication for studies; that’s especially vital when an important finding was not hypothesized or anticipated. Now we have 3 replications and an extension from the original natural experiment. That’s pretty convincing. Beyond that, in correspondence with Prof Pascal Geldsetzer of Stanford (if you check the publication links, he’s senior author on many of them), I learned there are at least 3 more country natural experiment replications on the way for the Shingles vaccine and reduction of dementia. We need more mechanistic studies for how the benefit is achieved, but the new one this week is a good start! If we can nail down the mechanism, it may have an impact on developing other preventive strategies.

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