Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Shingles (Herpes Zoster) Vaccine

Evidence Summary

Observational evidence repeatedly links shingles vaccine to reduced incidence of dementia. The effect may not be pathogen specific. Shingrix is very effective at preventing shingles and shingles complications.

Neuroprotective Benefit: Observational studies have consistently found significantly lower dementia incidence in individuals who receive shingles (or other) vaccines. The association may not be pathogen specific.

Aging and related health concerns: Shingrix vaccination effectively reduces risk of shingles and shingles complications for at least 10 years. Shingles vaccination may be associated with fewer cardiovascular events such as stroke.

Safety: Shingrix reactions like pain and flu-like symptoms are not uncommon. Observational data indicates rare but potential associations between Shingrix and Guillain-Barré syndrome. Studies have not found increases in death or other serious adverse events.

Availability: Rx	**Dose**: Shingrix vaccine schedule involves two doses administered at least 2 months apart for non-immunocompromised individuals.
Half-life: Immunity from Shingrix lasts for at least 10 years; studies are still ongoing.	**BBB**: N/A
Clinical trials: The largest clinical trials of Shingrix included 29,311 participants.	**Observational studies**: Largest observational study of Zostavax had over 1.6 million participants; largest observational study of Shingrix had over 800,000 participants.

What is it?

As reviewed by the CDC, Gilden 2012, and Ayoade & Kumar, 2022, the varicella-zoster virus (VZV), is a herpesvirus that causes chickenpox and shingles. When a VZV-naïve person is infected, the virus typically causes chickenpox, a common childhood illness involving a characteristic rash, fever, and fatigue. While usually mild, especially in children, chickenpox can have serious complications such as pneumonia, brain inflammation, and skin infections. VZV is not eradicated at the end of the disease course. Instead, VZV genomic material persists in the hosts, a phenomenon known as viral latency. VZV is latent, or dormant, in the peripheral nervous system. The immune system – specifically, VZV-specific T-cell immunity – usually maintains this state of affairs: the virus is present in certain neurons, but not replicating. However, reactivation can occur. If or when VZV begins replicating again, it results in shingles, also called herpes zoster (HZ): a painful rash, usually on only one side of the body. Complications of shingles can vary depending on what group(s) of neurons the virus reactivates in, though some complications such as postherpetic neuralgia (PNH) can occur with reactivation of the VZV in any nerve. PNH is sometimes excruciating and the debilitating pain can persist for more than 90 days after the rash appears. Other complications can include but are not limited to vision problems, meningitis, or hearing loss. Shingles is not contagious per say; an individual cannot pass shingles to another. However, if someone who is VZV-naïve is exposed to someone with shingles, that VZV-naïve person can acquire the virus and develop chickenpox.

Up to one third of adults will develop shingles. The risk for shingles, as well as for serious complications, increases with increasing age. Vaccination against HZ can decrease risk of and severity of shingles as well as complications. Currently, a recombinant HZ vaccine called Shingrix is available in the US to adults 50 and older, and it is more than 90% effective at preventing shingles and PNH (CDC). Shingrix replaces Zostavax, a shingles vaccine containing live attenuated virus that was recommended for immunocompetent adults over 60 (CHOP Vaccine Education Center, CDC).

Pathogens have been associated with health conditions other than the disease(s) they cause. A number of observational studies have found lower incidence of health conditions such as dementia after vaccination with shingles vaccines or other vaccines including diphtheria, tetanus, influenza, and BCG. (Schnier et al., 2022). A 2022 meta-analysis of observational studies also found lower incidence of dementia after adult vaccinations; every vaccine they analyzed was associated with a trend towards lower dementia incidence, and seven of those vaccines had significant associations with lower incidence of dementia, including that of the shingles vaccine (Wu et al., 2022).

Neuroprotective Benefit: Observational studies have consistently found significantly lower dementia incidence in individuals who receive shingles (or other) vaccines. The association appears to not be pathogen specific.

Types of evidence:

- 1 meta-analysis and systematic review
- 1 meta-analysis
- 18 observational studies
- 2 commentaries on observational studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No purposeful randomized controlled trials have investigated whether inoculation against HZ can prevent dementia or cognitive decline. Observational studies have found associations between shingles vaccination and incidence of dementia.

A 2022 meta-analysis from Wu and colleagues analyzed observational studies that compared incidence of dementia in vaccinated and unvaccinated cohorts over time. The meta-analysis included 17 total

studies and 1,857,134 participants; 3 of those studies focused on HZ vaccines. The authors reported that along with 6 other vaccines, HZ vaccine was associated with lower incidence of dementia (HR=0.69, 95% CI 0.67 to 0.72, P<0.00). The meta-analysis included the following studies:

- Scherrer et al., 2021b, who report a 31% lower incidence of dementia in participants 50 years and older who received a shingles vaccine (VHA HR=0.69; 95% CI 0.67 to 0.72; MarketScan HR=0.65; 95% CI 0.57 to 0.74). Scherrer and colleagues utilized data from the Veterans Health Administration (VHA) and MarketScan, comprising over 200,000 subjects in total.

- Wiemken et al. 2022 also analyzed data from VHA and MarketScan records using data from different years and slightly different inclusion criteria. They investigated whether vaccination with HZ and Tdap was associated with lower incidence of dementia compared to just HZ or Tdap vaccine, or no vaccine in 209,270 participants 65 years or older. Compared to unvaccinated individuals, those who received both HZ and Tdap vaccines had a lower incidence of dementia diagnosis (VHA HR=0.50; 95% CI 0.43 to 0.59; MarketScan HR=0.58; 95% CI 0.38 to 0.89). When compared to no vaccine, vaccination against HZ alone also was associated with lower incidence of dementia (VHA HR=0.75; 95% CI 0.71 to 0.79; MarketScan HR=0.67; 95% CI 0.57 to 0.80). The authors accounted for potential confounders including healthy adherer bias, preventative healthcare, and socioeconomic status.

- Lophatananon et al., 2021, reported on the incidence of dementia in subjects who received a Zostavax as opposed to those who did not in the UK Biobank. The study included 228,223 participants. The authors found that Zostavax was associated with lowerodds of dementia diagnosis (OR=0.808; 95% CI 0.657 to 0.993)

Multiple groups have analyzed incidence of dementia in health records from Wales, as Wales had an interesting shingles vaccine rollout strategy. Starting on September 1, 2013, Wales began offering the Zostavax herpes zoster vaccine only to specific age groups. Anyone who was born on or earlier than September 1, 1933 and was 80 years or older on September 1, 2013 would never be eligible to receive the vaccine; anyone born on or after September 2, 1933 was or would be eligible at a certain age. Researchers have looked at whether there is a difference in dementia incidence in people who did or didn't get the vaccine – or were or were not able to get the vaccine. Two studies looked at overlapping but different portions of the population with different analytical methods. Both found that dementia incidence was lower in groups that received the shingles vaccine, but the groups had different interpretations.

One study of 336,341 people in Wales who had their 70th birthday between 2013 and 2020 found that individuals who received the shingles vaccine had a lower incidence of dementia diagnosis (aHR=0.72; 95% CI 0.69 to 0.75). The authors examined whether the incidence of dementia diagnosis in vaccinated people varied based on the subtype of dementia. They found that the incidence of vascular dementia (aHR=0.66; 95% CI 0.61 to 0.71) was lower than that of AD (aHR=0.81; 95% CI 0.77 to 0.86). However, the authors were suspicious of selection bias- that is, that the individuals who got the shingles vaccine had a higher life expectancy to start with- because the hazard ratios were very similar in all subgroups who received the vaccine regardless of whether or not they actually developed shingles, and because vaccinated individuals had a lower incidence of several other health events such as myocardial infarction, stroke, and hip fracture, as well as all-cause mortality (Schnier et al., 2022).

Another, not-yet peer reviewed study, compared incidence of dementia in 282,541 Welsh individuals born September 1, 1925 – September 1, 1933 (and thus ineligible for the vaccine) and those born September 2, 1933 – September 1, 1942 (and thus eligible for the vaccine) over the course of 7-8 years after vaccine rollout. The authors argue that the vaccine rollout design created a sort of randomized trial. Using a regression discontinuity design and scaling for vaccine uptake, the authors found that being eligible for the vaccine was associated with 8.5% relative reduction of dementia diagnosis compared to those who were ineligible (1.3 percentage points; 95% CI: 0.2 to 2.7; p=0.02). When they scaled their analysis to account not just for eligibility but actual vaccine uptake, they report that receiving the vaccine was associated with a 19.9% relative reduction in dementia diagnosis (3.5 percentage points; 95% CI 0.6 to 7.1; p=0.019). The association was particularly strong in women; in fact, there was no statistically significant benefit of vaccination in men, and this was a main criticism of the paper. The vaccine was equally effective at preventing shingles and PNH diagnosis in both women and men. The authors found no difference in pre-vaccine health profiles, health measure uptake, or health events between those who were and were not eligible, an indication that those born on or before September 1, 1933 were not health-wise different than those born after. The authors concluded that it was the shingles vaccine itself that was responsible for the protection from dementia (Eyting et al., 2023, not yet peer reviewed).

While Eyting et al., 2023 is not yet peer-reviewed, it does address in part some of the potential confounding factors of other observational studies such as that individuals who receive vaccines may also receive other preventative health care.

Harris et al., 2023 report on the incidence of dementia in individuals who received a shingles, Tdap/Td, or pneumococcal vaccine. The authors used the Optum Clinformatics® Data Mart Database and propensity-score matching to create two retrospective cohorts 65 years and older who had not been diagnosed with dementia: one who received a vaccine of interest, and one that did not. For the shingles vaccine, the authors included both Zostavax and Shingrix vaccines, and included records from 212,415 individuals who did receive a shingles vaccine and 1,439,574 individuals who did not receive a shingles vaccine. In their analysis of the shingles vaccine, they found that 8.1% (n = 16,106) of the vaccinated participants and 10.7% (n = 21,273) unvaccinated participants were diagnosed with AD during the 8 year follow up (RR=0.75; 95% CI 0.73 to 0.76; ARR=0.02; 95% CI 0.02 to 0.02). Interestingly, they also were able to examine those who received only Zostavax and those who received only Shingrix. They found that compared to the unvaccinated group, one dose of Shingrix (excluding any Zostavax vaccinations) was associated with an RR of 0.27 (95% CI: 0.25 to 0.29), whereas vaccination with Zostavax (excluding any Shingrix vaccinations) was associated with an RR of 0.92 (95% CI: 0.90 to 0.94). The authors ran a sensitivity analysis to try to control for healthy adherer bias; the sensitivity analysis still found a reduced incidence of dementia in individuals who received the VZV vaccine. Some caveats to this paper are that the database uses medical and pharmacy insurance claims rather than medical records, and that the follow-up time was longer for most of the unvaccinated groups than the vaccinated groups. Receiving Tdap/Td (RR=0.70; 95% CI 0.68 to 0.72) or pneumococcal vaccines (RR=0.73; 95% CI 0.71 to 0.74) was also associated with reduced incidence of dementia.

Epidemiological evidence also suggests a potential link between HZ and dementia. Some studies have found increased incidence of dementia in individuals who have had shingles; subsequent antiviral treatment of shingles was associated with reduced incidence of dementia in individuals 50+ or with a particular subtype of shingles known as herpes zoster ophthalmicus (Tsai et al., 2017; Chen et al., 2018; Bae et al., 2021, Lindman et al., 2021). However, there is conflicting data; some studies have found no association between shingles diagnosis and dementia (Choi et al., 2021; Warren-Gash et al., 2022; Schmidt et al., 2022).

Human research to suggest benefits to patients with dementia:

No published studies were found that investigated the effects of HZ vaccination in patients with MCI or dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

There are multiple potential mechanisms for how the shingles vaccine might provide neuroprotection. Shingles is a reactivation of latent viral infection in the nervous system; it is possible that the vaccine-induced prevention of HZ viral activity may limit nervous system inflammation and subsequent neuronal damage that can cause or exacerbate neurodegeneration (Scherrer et al., 2021, Harris et al., 2023).

It is also possible that the associations observed between vaccines and lower incidence of dementia is not necessarily specific to the kind of vaccine, but rather reflects a general change in the immune system conferred by vaccines. Vaccines may, for instance, modulate the immune system and reduce overall inflammation and oxidative stress (Scherrer et al., 2021a, Scherrer et al., 2021b). This non-pathogen-specific immune training may act through the innate immune system such as by altering cytokine levels that can affect the efficiency of microglial clearance of aggregates or lowering overall inflammaging, and/or through the adaptive immune system (Bukhbinder et al., 2022).

APOE4 interactions:

No studies have examined differences in effect of HZ vaccines based on APOE status. Whether APOE4 status affects shingles prevalence or severity is also not known; the two studies that looked for any association between APOE allele and herpes zoster had conflicting results and were based on approximately 100 people apiece (Pirttila et al., 2000; Wozniak et al., 2007).

Aging and related health concerns: Shingrix vaccination effectively reduces risk of shingles and shingles complications for at least 10 years. Shingles vaccination may be associated with fewer cardiovascular events such as stroke.

Types of evidence:

- 1 systematic review and meta-analysis
- 2 meta-analyses
- 1 systematic review
- 2 randomized controlled trials
- 2 long-term follow up studies of randomized controlled trials
- 3 observational studies

The risk of shingles, as well as shingles complications, increases with age. Other age-related diseases such as diabetes, cardiovascular disease, and rheumatoid arthritis are also associated with increased risk

of shingles (Marra et al., 2020). As the shingles vaccine helps prevent shingles, HZ vaccination can mitigate some of the risks of these diseases.

Shingles and Shingles Complications such as PNH: BENEFIT

The incidence of shingles and complications from shingles including PNH increases with age. Shingles vaccines, particularly the Shingrix recombinant vaccine, are effective at preventing shingles and complications from shingles. A Cochrane review and meta-analysis published in 2019 found that over the course of an approximately 3 year follow-up period, vaccination with Zostavax decreased incidence of shingles compared to no-vaccination (RR=0.49; 95% CI 0.43 to 0.56, n= 38,546), as did vaccination with Shingrix (RR=0.08; 95% CI 0.03 to 0.23, n= 22,022) (Gagliardi et al., 2019).

The prelicensure RCTs for Shingrix found that Shingrix was over 97% effective in 15,411 adults 50 and older, and over 90% effective in 13,900 adults 70 years and older, over the course of approximately 3 – 3.5 years (Lal et al., 2015; Cunningham et al., 2016). The study of 70+ year old adults also found that the vaccine was 88.8% effective against PNH. In 2022, the results of a long-term follow-up study of 7,277 participants from the prelicensure RCT studies found that the vaccine was 90.9% effective 8 years after the completion of the vaccine series.

Mortality and Lifespan: POTENTIAL BENEFIT

Some observational studies have found lower risk of all-cause mortality in individuals who were vaccinated against VZV. One study of health care record data from 336,341 people in Wales found that individuals who received the shingles vaccine had a significantly reduced rate of all-cause mortality (aHR: 0.58; 95% CI 0.57 to 0.60) (Schnier et al., 2022).

It is unclear whether this finding is a true vaccine benefit or a confounding factor, such as the fact that individuals who receive preventative vaccines may be more likely to take other proactive health measures.

Cardiovascular Health and Stroke: LIKELY BENEFIT

VZV reactivation can occur in large and small blood vessels, including cerebral arteries – a unique feature among viruses, based on current research. Shingles is associated with increased short-term and

long-term risk of both heart attack and stroke, along with other vasculopathies such as aneurysm (Gilden et al., 2009; Wu et al., 2019; Curhan et al., 2022).

Curhan and colleagues detail an analysis of over 205,000 participants from the Nurse's Health Study, Nurse's Health Study II, and Health Professionals Follow-Up Study. This study of well-characterized prospective cohorts was able to control for a number of factors and found that HZ infection was associated with an almost 30% increase in risk of major cardiovascular event. They were not able to investigate the effects of HZ vaccines, given the timing of vaccine recommendations and the data collection for their studies.

Other studies have found that receiving a shingles vaccine reduces incidence of stroke. A 2023 systemic review and meta-analysis on observational studies looked at the association between cardiovascular events in vaccinated vs. unvaccinated HZ patients. They included a total of six studies on HZ vaccines comprising over 1.6 million participants. Vaccination was associated with a lower incidence of stroke compared to no vaccination in participants who had shingles (OR=0.78; 95% CI 0.68 to 0.9; P = 0.001) (Jia et al., 2023).

Parameswaren et al., 2023 is included in the above meta-analysis, and they analyzed the effects of the two shingles vaccines separately and together. Parameswaren and colleagues assessed a population of 2,165,505 patients in the VA healthcare system, 71,911 of them who had shingles. They found that the incidence of stroke was increased in the 30 days following infection (OR=1.93; 95% CI 1.57 to 2.4; P < .0001). A lower incidence of stroke was seen in patients who had received Shingrix (OR=0.57; 95% CI 0.46 to 0.72; P < .0001) or Zostavax (OR=0.77; 95% CI 0.65 to 0.91; P = 0.002).

Safety: Shingrix reactions like pain and flu-like symptoms are not uncommon. Observational data indicates rare but potential associations between Shingrix and Guillain-Barré syndrome. Studies have not found increases in death or other serious adverse events.

Types of evidence:

- 1 Cochrane meta-analysis and review
- 4 resource pages from the CDC, NCBI, and Children's Hospital of Philadelphia
- 2 randomized controlled trials
- 2 long-term follow up studies of randomized controlled trials
- 2 postlicensure surveillance studies
- 1 observational study

A Cochrane review and meta-analysis of RCTs of shingles vaccines by Gagliardi et al., 2019 found that there are no differences between vaccinated group and placebo group in terms of death or serious adverse event for either Zostavax or Shingrix (see table below).

	n	Serious Adverse Event	Death
Zostavax	6,980	RR=1.08; 95% CI 0.95 to 1.21	RR=1.01; 95% CI 0.92 to 1.11
Shingrix	29,311	RR=0.97; 95% CI 0.91 to 1.03	RR=0.94; 95% CI 0.84 to 1.04

For both the live-virus vaccine and the recombinant vaccine, there were higher incidences of adverse events. In the Zostavax trials, the vaccinated group had a higher incidence of one or more adverse events (RR=1.71; 95% CI 1.38 to 2.11) and injection site adverse events of mild to moderate intensity (RR=3.73, 95% CI 1.93 to 7.21) as compared to the placebo group. In the Shingrix trials, vaccinated participants had a higher incidence of adverse events with any systemic symptom (RR=2.23; 95% CI 2.12 to 2.34) and any local symptoms (RR=6.89; 95% CI 6.37 to 7.45). While most participants reported mild or moderate intensity adverse events, there were more dropouts from the vaccine group than the placebo group in the recombinant vaccine trials, as measured by the risk of participants not returning for their second dose 2 months after the first dose (RR=1.25; 95% CI 1.13 to 1.39)

For Shingrix, the vaccinated participants had a higher incidence of systemic adverse events including fever, headache, shivering, fatigue, muscle pain, and GI symptoms, as well as local events such as redness, pain, and swelling (Gagliardi et al., 2019). These adverse events could be severe enough to limit or prevent individuals from doing regular activities, and typically self-resolve in 2-3 days (CDC).

Long-term follow up studies of 7,413 of the participants enrolled in the prelicensure RCTs of Shingrix found no deaths or other serious adverse events that were considered to be causally related to vaccination. In the approximately 10 years of follow-up, 5 participants have reported shingles complications, including PNH (Boutry et al., 2022; Strezova et al., 2022).

Guillain-Barré syndrome (GBS) is a rare immune-mediated neuropathy. The CDC conducted postlicensure surveillance of Shingrix, using the Vaccine Safety Datalink to monitor pre-specified adverse events including GBS. A statistical safety signal appeared for GBS, with a reported rare but statistically significant increase in cases over what would be expected based on the GBS incidence after Zostavax administration. In response, the FDA has attached a black-box warning to the Shingrix vaccine, stating that the data 'show an association' but 'not a confirmed causal relationship' (FDA). Two studies thus far

have further explored this potential connection, including medical record review where possible to adjudicate the potential GBS cases.

Using Medicare claims data of more than 849,000 adults 65 years and older in the US, the CDC, CMS, and FDA jointly conducted a retrospective cohort analysis comparing GBS incidence after Shingrix or Zostavax vaccination. They also performed self-controlled case analyses post-Shingrix vaccine, an analysis in which each individual acts as their own control by comparing events in different time frames- in this instance, comparing GBS diagnoses in the 'risk window' of 6 weeks following vaccination to GBS diagnoses in the 'control window' from 6 weeks to approximately 26 weeks post-vaccination. In their cohort analysis, Shingrix vaccination was associated with higher incidence of GBS as compared to Zostavax based on claims data (rate ratio=2.34; 95% CI 1.01 to 5.41; P = .047; 15 cases in Shingrix group, 9 cases in Zostavax). For the self-controlled case analyses, the authors identified and confirmed via medical record review 7 cases in the risk period and 4 cases in the control period (RR=4.96; 95% CI 1.43 to 17.27; P = .01). Based on their analyses, the authors estimated that there may be approximately 3 excess cases of GBS per million vaccinations (Goud et al., 2021)

Nelson et al., 2023 performed a prospective postlicensure active surveillance study of 403,522 patients aged 50 years of age and older in certain healthcare systems that contribute data to the Vaccine Safety Datalink system. The authors found no statistically significant increase in 10 pre-specified health outcomes such as stroke, anaphylaxis, GBS, or Bell's palsy in individuals who received Shingrix as compared to those who received Zostavax or individuals who received a non-HZ vaccine and had a well-visit during the surveillance study. They did observe an initial safety signal for GBS in Shingrix as compared to Zostavax, but by the end of the study period and after manual medical record review, the signal attenuated, with 3 confirmed cases in the Shingrix group and 2 in the Zostavax group, with 1 other Zostavax case not available for chart review. Shingrix vaccine recipients did not have a significantly different rate of GBS when compared to those who received Zostavax (RR=1.56; 95% CI 0.18 to 18.62) or to a no-HZ vaccine comparator group (RR=0.92; 95% CI 0.34 to 2.52). However, given the small number of GBS cases in this study, the authors caution that it is difficult to draw firm conclusions.

As with any treatment or prevention measure, the potential risks of treatment must be balanced against the potential risks of the condition itself. Higher incidence of GBS have also been reported after shingles, which is in part why Shingrix is still recommended by the Advisory Committee on Immunization Practices (ACIP) (Anderson et al., 2021; Janusz et al., 2022).

Drug interactions:

Shingles vaccines are not recommended for those with active shingles infection or people who are pregnant. While not contraindicated for immunocompromised populations, immunosuppressive drugs may affect the efficacy of the vaccine (CDC, WebMD).

Research underway:

There are approximately 60 ongoing studies involving the shingles vaccine that are registered on ClinicalTrials.Gov. Most of them are investigating the immune response in certain populations after vaccination.

One study, NCT05894954, is investigating whether a precision medicine approach can mitigate the decline of cognitive function in patients with mild cognitive impairment or early dementia. The 9-month long study aims to enroll 72 patients who will be randomized to standard of care or to the personalized medicine approach. The personalized medicine approach will involve a battery of testing to create a personalized treatment plan including diet, sleep habits, stress management, and mental and physical exercise. One of the many potential treatments in the intervention group is a shingles vaccine, if applicable. The study is scheduled to start recruitment in the near future.

Search terms:
Pubmed, Google: shingles, herpes zoster, varicella, varicella zoster, Shingrix, Zostavax

- Dementia, Alzheimer's, strok

Websites visited for shingles vaccine:

- Clinicaltrials.gov
- Drugs.com (Shingrix)
- WebMD.com (Shingrix)
- PubChem (Shingles vaccine)
- DrugBank.ca (Shingrix)
- Cafepharma (Shingrix)

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