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Important New Evidence Service

In partnership with The Centre for Medicines Optimisation at Keele University

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Dementia: Herpes Zoster vaccination may be protective against dementia

This observational study was able to compare dementia incidence in vaccinated versus unvaccinated older patients in Wales as a result of the way in which the vaccination programme was rolled out. All people whose 80th birthday fell after 1 September 2013 were eligible for vaccination whereas those turning 80 before 1 September 2013 were not. This created two groups with very similar characteristics apart from receipt of the herpes zoster vaccination.

The study found a significantly lower probability of dementia diagnosis in the vaccine eligible group compared with those who were not eligible. The study also found a significantly lower probability of having a shingles diagnosis, consistent with trial data from vaccine development.

Reference: Eyting M, Xie M, Michalik F *et al*. A natural experiment on the effect of herpes zoster vaccination on dementia. *Nature* volume 641, 438 to 446 (2025).

What do we know already?

- Herpes zoster, commonly known as shingles, is a viral infection caused by the reactivation of the varicella-zoster virus, the same virus responsible for chickenpox (varicella).
- The relationship between herpes zoster and dementia is still controversial. Johannesdottir Schmidt et al., (2022) suggest that the likely pathophysiology of dementia could be due to a process of neuroinflammation, involving the formation of misfolded oligomers, amyloid plaque accumulation, and hyperphosphorylated Tau protein containing neurofibrillary tangles. Herpes zoster immunization may have neuroprotective benefits that lessen central nervous system inflammation and/or prevent viruses from infecting the brain compared to no herpes zoster vaccination.
- Systematic review evidence from five studies found a reduced risk of dementia in those given the herpes zoster vaccination with a pooled odds ratio of 0.91 (95% confidence interval [95% CI]: 0.47 to 1.75), but the study had limitations. These included the heterogeneity of methods in the studies included, varying diagnosis standards for dementia, and short study durations.
- The Herpes Zoster vaccination scheme started in Wales in 2013, initially for people aged 70 to 79. The scheme was extended in 2023 to include all immunocompromised individuals aged 50 and over. For immunocompetent individuals, the eligible age was lowered from 70 to 60 years, with a phased implementation over 10 years.

What does this evidence add?

- The study found that there was a significant reduction in the rate of new dementia diagnoses in the vaccine-eligible group compared with the vaccine ineligible group. The authors estimated that vaccination led to a 20% reduction in the relative risk of dementia.
- The authors suggest that the vaccine could represent a cost-effective intervention that has public-health benefits exceeding its intended purpose. Given the substantial economic and social burden of dementia, policymakers and health-care providers might need to reassess the value of widespread herpes zoster vaccination, particularly in older adults.
- Limitations of the study included that the nature of the study meant that there was probable under-detection of dementia cases, both in whether dementia was detected or in how timely a fashion – but this was applicable to both vaccine eligible and ineligible cohorts. Similarly changes to clinical practice or health system incentives to detect and record dementia and the likely disruption to usual practice caused by the COVID-19 pandemic. The study was also heavily weighted to one particular age group (those aged 79 to 80) so estimates may not be more widely applicable. Finally, the estimates apply only to the use of the live -attenuated Zostavax® vaccine which is no longer in use in the UK. It has been replaced by the Shingrix® herpes zoster vaccination.

Study details

- Using linked data records from the Secure Anonymised Information Linkage (SAIL) Databank, which contains detailed electronic health record data on primary care visits from approximately 80% of primary care providers in Wales, linked to secondary care records and the country's death register data.
- Population: adults born between 1 September 1925 and 1 September 1942 who were registered with a primary care provider, resident in Wales and did not have a diagnosis of dementia at the time of the start of the zoster vaccine program in Wales (on 1 September 2013). The study focused on the live-attenuated herpes zoster vaccine (Zostavax®; hereafter, zoster vaccine), because the newer recombinant subunit zoster vaccine (Shingrix®) became available in the UK only after the end of the follow-up period.
- The primary outcome was the incidence of new diagnoses of dementia of any type or cause, recorded in primary, secondary or tertiary care, or mention of dementia as a primary or contributory cause of death. Analyses were carried out using a regression discontinuity design and a series of sensitivity analyses to test robustness of the approach and potential biases.

Results

- The study population consisted of 296,603 individuals born between 1 September 1925 and 1 September 1942 who were registered with a primary care provider in Wales on the start date of the zoster vaccine program rollout (1 September 2013). 13,783 people with a diagnosis of dementia before 1 September 2013 were excluded from the analyses with new diagnoses of dementia as outcome.
- In the vaccine-eligible group, rates of herpes zoster vaccination reached 47.2%, compared with 0.01% in the vaccine-ineligible group.
- Individuals were followed from 1 September 2013 to 31 August 2021,which allowed for a maximum follow-up period of 8 years. During the study 23,049 (8.2%) were lost to follow up through emigrating from Wales, or moving to one of the 20% of practices that did not contribute data to SAIL; 92,629 (37.8%) of adults in the primary analysis cohort died during the follow-up period.
- In the group of people eligible to receive the vaccine the absolute reduction in the probability of a new dementia diagnosis was 1.3% (95% CI 0.2 to 2.7; p = 0.022) with a relative reduction of 8.5% (95% CI = 1.9 to 15.1) over 7 years. In people actually receiving the vaccine, the probability of a new dementia diagnosis was reduced by 3.5% (95% CI, 0.6 to 7.1; p = 0.019). This corresponded to a relative reduction of 20.0% (95% CI 6.5 to 33.4).
- During the seven-year follow up period, a total of 14,465/296,324 adults in the cohort had at least one diagnosis of shingles. Those who were eligible for the vaccine had a reduced probability of having at least one shingles diagnosis by 1.0% (95% CI 0.2 to 1.7; p = 0.010), corresponding to a relative reduction of 18.8% (95% CI 8.8 to 28.9).
- Amongst people who actually received the zoster vaccine, there was a reduction in the probability of having at least one shingles diagnosis of 2.3% (95% CI 0.5 to 3.9; p = 0.011) over the seven-year follow-up period; an effect (37.2% (95% CI 19.7 to 54.7) in relative terms) that is similar in size to that observed in clinical trials of the live-attenuated zoster vaccine (Zostavax).
- The herpes zoster vaccine did not affect the occurrence of any other common causes of mortality or morbidity other than shingles and dementia, and did not lead to increased uptake of other vaccinations or preventive health measures.

Level of Evidence: Level 2 according to the SORT criteria.

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