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News & views

Medical research

Could the shingles vaccine help to prevent dementia?

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Large-scale analyses of electronic health data suggest that the herpes zoster vaccine could protect against dementia — but it's not yet clear how.

Deaths due to Alzheimer's disease, the most common cause of dementia, have roughly doubled in the past 30 years and are expected to increase with an ageing population[1]. Despite the enormous health and economic impacts of Alzheimer's disease, effective treatments and preventative measures are lacking, partly because there has been a failure to definitively understand what causes the condition[2]. Emerging evidence suggests that viruses in the herpes family that target and affect the nervous system might be involved in the development of Alzheimer's disease[3], raising the possibility that vaccines against these viruses could prevent or delay dementia[4].

Proving this hypothesis is difficult, however, because it requires large, randomized trials of vaccines in individuals without Alzheimer's disease. Such trials are costly and require years of follow-up to establish whether dementia occurs at lower rates in those who are vaccinated than in those who are not. Writing in *Nature*, Eyting *et al.*[5] test this hypothesis in a large-scale 'natural experiment' that takes advantage of a historical happenstance: a policy in Wales that dictated eligibility for a vaccine against shingles, also known as herpes zoster.

The herpes zoster vaccine targets the varicella zoster virus, a herpesvirus that lies dormant in nerve cells after childhood infection but can become reactivated in adulthood, causing a painful, burning rash. Starting from 1 September 2013, people born on or after 2 September 1933 became eligible to receive the vaccine, whereas those born before this date were ineligible. This created a natural experiment in which vaccine uptake was sharply divided between two groups of individuals with nearly identical ages and backgrounds. In other words, assignment to one group or the other was as good as random.

Eyting *et al.* used large-scale electronic health-record data to track dementia diagnoses over a seven-year period, comparing rates of diagnosis between individuals whose 80th birthday fell a few weeks after 1 September 2013 (vaccine eligible) or a few weeks before (vaccine ineligible). The authors found that, in the vaccine-eligible group, rates of herpes zoster vaccination reached 47.2%, compared with 0.01% in the vaccine-ineligible group.

Importantly, the analysis revealed a significant reduction in new dementia diagnoses in those eligible for vaccination. After accounting for the fact that not all who qualified for the vaccine received it, the authors estimated that vaccination led to a 20% relative reduction in dementia risk.

The researchers explored whether other health interventions or confounding variables might explain the observed effect. For example, what if individuals born just after 2 September 1933 were also eligible for other medical care besides the herpes zoster vaccine? If that medical care lowered dementia risk, the authors would incorrectly attribute those benefits to the herpes zoster vaccine. They found no evidence that this was true.

Eyting and colleagues also considered whether their findings might be attributable to increased health-care use among vaccine-ineligible individuals, who were more likely to develop shingles than those who were vaccinated. Shingles is painful, so unvaccinated people might have sought more medical care over the years. Medical providers would have therefore had more opportunities to diagnose dementia in the vaccine-ineligible individuals — an issue known as ascertainment bias. If this were the case, dementia rates would be ascertained to be higher in the vaccine-ineligible group, even though they were not in fact higher. The authors found only minor differences in health-care use between the groups, ruling out this possibility.

How, then, might herpes zoster vaccination reduce the risk of dementia? The

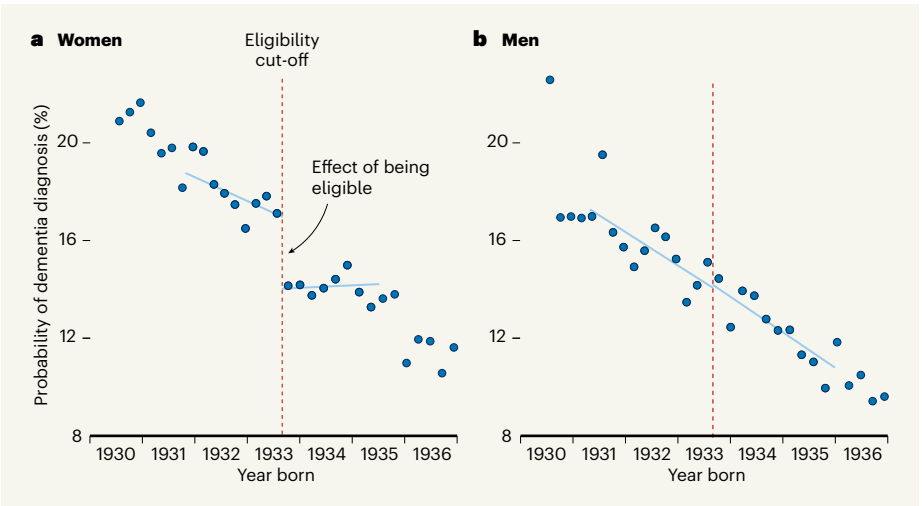

Figure 1 | A link between the shingles vaccine and dementia risk. Viruses in the herpes family have been implicated in the development of Alzheimer's disease, the most common cause of dementia. A policy implemented in Wales in 2013 meant that people who were born on or after 2 September 1933 became eligible for a vaccine against varicella zoster, a herpesvirus that causes shingles (also known as herpes zoster). Using this opportunity as a 'natural experiment', Eyting *et al.*[5] analysed data from thousands of electronic health records over a seven-year follow-up period and found that people born a few weeks after the eligibility cut-off were less likely to be diagnosed with dementia than were those born a few weeks before. This effect was much greater in women (**a**) than in men (**b**). (Adapted from Fig. 5 of ref. 5.)

authors propose three mechanisms. The first is that a shingles episode might be treated with medications that increase the risk of dementia. For example, opioids are sometimes prescribed to relieve pain, and in individuals with considerable opioid use, brain changes related to Alzheimer's disease (namely, deposits of amyloid-β and tau proteins) have been observed[6]. Might the herpes zoster vaccine lower dementia risk by reducing the need for prescription opioids?

Eyting and colleagues explored this possibility by assessing whether those eligible for the herpes zoster vaccine had lower use of any of more than 200 medications, including opioids, that have been associated with an increased risk of dementia. They found no clinically meaningful long-term decreases in any of these medications in those eligible for the vaccine. Therefore, the lower rate of dementia observed among people eligible for the vaccine was not because they used fewer medications that are suspected to increase dementia risk.

Second, the authors propose that reduced reactivation of the dormant varicella zoster virus by the vaccine could lower dementia risk. This might occur if the virus is directly toxic to neurons, or promotes a generalized inflammatory response in the nervous system that is neurotoxic, or both. Reactivation of the virus is thought to cause amyloid-β deposition, tau aggregation and damage to blood vessels – key features of Alzheimer's disease[7]. The authors found suggestive evidence for this mechanism: there were higher rates of dementia in those who had multiple shingles episodes (indicative of repeated viral reactivation), and lower rates of dementia in those who received anti-viral medication (which reduces viral activity) during their shingles episode.

Third, Eyting *et al*. theorize that the shingles vaccine could lower dementia risk independently of any effect it has on varicella zoster virus reactivation. According to this theory, the vaccine lowers dementia risk by creating a generalized immune response that reduces neuroinflammation caused by something other than the varicella zoster virus. This theory is difficult to test, but the authors present several findings that support this effect. For instance, the authors note that pathogen-independent changes to the immune system induced by vaccines are seen more often in women than in men. They found that vaccine eligibility reduced dementia risk much more in women (Fig. 1), consistent with vaccination lowering dementia risk through immune-system modulation.

Eyting and colleagues' work is valuable for several reasons. First, this large-scale study advances scientists' understanding of what causes dementia and lends support to the theory that varicella zoster virus could be one of many factors causally related to the condition. The findings are not conclusive – but they are not expected to be. The clear next steps are detailed hypothesis-testing using laboratory and clinical experiments.

Second, the authors present compelling, effectively randomized evidence that herpes zoster vaccination could reduce the likelihood of dementia. A possible scenario is that vaccine-ineligible people who developed shingles could have received medical interventions other than the ones studied, which could have contributed to dementia. One way to assess this possibility would be to examine all medication use that differed between the vaccine eligible and ineligible in the few years after 1 September 2013.

Relatedly, the authors note that randomized trials that were initially used to test the vaccine focused on its effectiveness at preventing shingles, not Alzheimer's disease. It would be possible, although difficult, to identify participants who underwent randomization in those trials, retrospectively obtain their medical histories, and assess whether dementia risk differed between treatment and control groups. The results of the current study, if replicated by others, are strong enough to warrant that effort.

Third, Eyting and colleagues highlight the power of natural experiments. Although this type of experiment is widely used in economics to study questions of cause and effect, its adoption in medical research has been slow[8]. In most observational studies, researchers retrospectively analyse health outcomes in individuals who received one treatment or another by choice rather than by randomization. Cause and effect cannot be established because those receiving a chosen treatment can differ in unobserved ways that influence the outcomes being studied.

Natural experiments have been used to study important clinical questions, such as the effect of national drug shortages on patient care[9]. A study that addressed a similar question to the one asked by Eyting and colleagues also used a natural experiment: in the United States in 2017, a version of the shingles vaccine containing a live virus was rapidly discontinued, and this sharp cut-off enabled researchers to assess the dementia risk associated with the live vaccine versus a recombinant vaccine containing viral proteins[10]. Although not as comprehensive as the study by Eyting *et al.*, that study suggested that recipients of the recombinant vaccine had lower rates of dementia than those who received the live vaccine.

One of the most compelling aspects of the current study is its methodological rigour. By taking advantage of a well-defined eligibility cut-off dictated by policy, the authors circumvented the usual confounding issues that plague observational studies. Unlike previous studies that have compared vaccinated with unvaccinated individuals – an approach vulnerable to selection bias – the current study's design ensured that the only systematic difference between the groups was the likelihood of vaccination. This strengthens the argument that the observed reduction in dementia risk is attributable to the vaccine itself.

Although it is still unclear precisely how herpes zoster vaccination lowers the risk of dementia, the implications of the study are profound. The vaccine could represent a cost-effective intervention that has public-health benefits strongly 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.

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