ISRCTN81988253 https://doi.org/10.1186/ISRCTN81988253

# Analysis of patient population vaccinated against shingles in Sweden – A register study investigating the effects of Shingrix on developing dementia

**Submission date**
19/08/2024

**Recruitment status**
No longer recruiting

**Registration date**
19/08/2024

**Overall study status**
Ongoing

**Last Edited**
16/12/2025

**Condition category**
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

## Plain English summary of protocol

Background and study aims
The study aims to evaluate the long-term outcomes of vaccination with Shingrix against shingles in Sweden between 2003 and 2024. It particularly seeks to clarify the ongoing debate about the causality between shingles vaccination and protection against dementia, as well as to evaluate outcomes related to cardiovascular and neurological diseases.

Who can participate?
The study population consists of patients who were part of a previous study and received the Shingrix vaccine. Patients were included based on their consent and the fulfillment of specific criteria such as age, previous VZV infection, and not being immunosuppressed, among others.

What does the study involve?
The study is an observational and non-interventional database study using patient data from Sweden. The study will analyze various health outcomes, healthcare utilization, and patient characteristics from 2003 to 2024.

What are the possible benefits and risks of participating?
The benefits include contributing to knowledge that may improve care for patients at risk of developing shingles and related complications, including dementia and cardiovascular diseases. The risks primarily involve the handling of sensitive personal data, which is minimized through pseudonymization and secure data handling protocols.

Where is the study run from?:
The study is conducted by Blekinge Institute of Technology, with collaboration from Lumell Associates for data analysis (Sweden)

When is the study starting and how long is it expected to run for?
January 2024 to December 2026

Who is funding the study?
GlaxoSmithKline is funding the study that is conducted by Lumell Associates (Sweden)

Who is the main contact?
The main contact for the study is Johan Sanmartin Berglund, the principal investigator, johan.sanmartin.berglund@bth.se

# Contact information

### Type(s)
Public, Scientific, Principal investigator


### Contact name
Prof Johan Sanmartin Berglund

### ORCID ID
https://orcid.org/0000-0003-4312-2246

### Contact details
Valhallavägen 10
Karlskrona
Sweden
371 79
+46 455-385471
johan.sanmartin.berglund@bth.se

### Type(s)
Scientific

### Contact name
Dr Lycke Fureby

### ORCID ID
https://orcid.org/0009-0001-6697-5463

### Contact details
Scheelegatan 19
Stockholm
Sweden
11228
+46 (0)703055283
lycke.fureby@lumell.se


# Additional identifiers

### Protocol serial number
LumellShingrix

# Study information

## Scientific Title
Can vaccination against herpes zoster with Shingrix be associated with reduced risk for developing dementia?

## Acronym
ShringixDementia

## Study objectives
Shingles is a herpes disease caused by varicella-zoster virus (VZV), the same virus that causes chickenpox (Wilson & Wilson, 2021). The disease occurs in people who have had a chickenpox infection earlier in life when the virus, which has been dormant in nerve nodes near the spinal cord since the infection, becomes active again. This reactivation can often be due to a stressful lifestyle, diseases and conditions that weaken the immune system, or simply the natural effect of ageing on the body's defense mechanisms. When the virus is active again, it travels along the nerve pathways and manifests itself as a shingles rash, usually on the upper body or face (Wilson & Wilson, 2021). The rash is characterized by redness, blisters and an intense, burning pain. The virus travels along the nerve pathways that run from the spinal cord to the right or left side of the body, causing pain and blisters along the course of the nerves in the skin. Shingles affect between one in four to one in three people and the disease is most common in people over 50 years old, but anyone who has had chickenpox can be affected (Wilson & Wilson, 2021).

Complications from shingles can be both painful and long-lasting and the most frequent complication is postherpetic neuralgia (PHN) which about 15% of shingles patients who are above the age of 50 years and as many as 20% of shingles patients above the age of 60 years develop (Watson, 2011). PHN leads to pain from the rash that persists even after the blisters have healed and the pain can range from a constant burning sensation to sudden, sharp shocks that last for more than three months (Wilson & Wilson, 2021). Other complications of shingles include internal blisters on the middle ear, sternum, collarbone, and brainstem, among others. Other neurological problems can occur with shingles such as memory problems and in rare cases the virus can lead to an inflammation of the brain which can be life-threatening (Patil et al., 2022). The eyes and ears can also be affected, leading to visual impairment and problems with balance and hearing where these complications can be permanent. People with compromised immune systems are at increased risk of developing shingles and for these people the disease is often more widespread, and the mortality rate is higher (Patil et al., 2022; Wilson & Wilson, 2021). The mean hospitalizations per case of shingles increase with the patient’s age, ranging from 1.4% to 8.1% for patients aged 50-54 years to 80+ years respectively (Lee et al., 2021).

Multiple previous systematic reviews have shown an increase in the incidence of shingles across Europe within older age groups, particularly patients in age groups above 50 years of age (Curran et al., 2022; Kawai et al., 2014; Pinchinat et al., 2013). Even with the clear increase in incidence with age and the significant global health burden shingles accounts for, the clinical management for shingles is primarily focused on relieving the symptoms (Curran et al., 2022). Varying levels of analgesics can be used depending on the level of experienced pain and, in some cases, steroids in combination with antivirals such as aciclovir, valaciclovir, or famciclovir may be used (Wilson & Wilson, 2021). Given the limited treatments of shingles and the burden associated with the disease, prophylactic measurements are attractive alternatives to prevent patients from suffering. Preventing elderly patients from falling ill with shingles and sparing the patients from a potentially very difficult case of illness would reduce a significant burden on the patients. There are currently two vaccines against shingles, one containing live attenuated VZV (Zostavax) and the other containing an antigen (glycoprotein E, gE) found on the surface of the virus and virus-infected cells (Shingrix) (The Public Health Agency of Sweden, 2022). Shingrix has

shown to be 97% effective at preventing shingles (CDC, 2023), compared to 51% efficacy for Zostavax (Wilson & Wilson, 2021) among the population of more than 50 years of age. Only Shingrix is authorized for the prevention of herpes zoster in immunocompromised individuals.

There are growing body of evidence about the association of herpes zoster and increased risk of developing neurodegenerative diseases such as Alzheimer's disease and other dementias (Eyting et al., 2023; Schmidt et al., 2022). While other studies have not found such an association. Previous population studies claim that there is an association between herpes zoster vaccination and a reduced risk of dementia. Thus, it is unclear whether vaccination leads to increased protection against neurodegenerative diseases and there is a need to understand the mechanism of action and get more insight into this. Other areas of interest are cognitive impairment, effects on the central nervous system, and cardiovascular diseases.

In previous studies conducted between 2010 and 2015, the efficacy of Shingrix has been evaluated in Zoster Efficacy research projects in adults 50 and 70 years of age or older respectively, hereafter referred to as ZOE-50 and ZOE-70 respectively or simply ZOE studies (Cunningham et al., 2016; Lal et al., 2015). Recruitment to ZOE-50 and ZOE-70 studies took one year (Aug 2010-Jul 2011) and those patients were vaccinated in 2010 and 2011. Following vaccination, the ZOE study participants were followed up for up to 4 years (ZOE-50 mean follow-up period 3.2 y, ZOE-70 - 3.7y). After finishing participation in ZOE studies, the patients in the placebo group were offered the opportunity to get vaccinated. In these studies, participants have consented and agreed that their coded data can be collected in both ZOE studies as well as be used for future scientific and medical purposes. The ZOE studies were conducted in 18 countries, where Sweden was one of the participating countries. In total, there were 1973 participants in the Swedish portion of the studies. Of the total population, 1013 patients were selected to receive the vaccine, completed the full procedure, and were vaccinated between 2010 and 2011 while the remaining 961 patients received a placebo. The patients were either chosen from a register with eligible patients or the patients contacted the study group themselves after viewing advertisements in the respective local press. There were healthcare personnel at the vaccination site during the full duration of the patients' visits. A portion of the patients that received the placebo were later administered the vaccine in 2015 and 2016 which increased the patient population to about 1800-1900 patients.

This project aims to evaluate long-term secondary outcomes (dementia, cardiovascular disease, central nervous system (CNS) complications, PHN) as well as the healthcare consumption seven years prior to, and at least eight years (but no later than 13 years) following, vaccination with Shingrix in Swedish patients during a 21-year period (2003-2024). For healthcare consumption, the overall healthcare resource utilization (HCRU) of the patients following vaccination with Shingrix for the 21-year period will be calculated. To carry out the project, healthcare and data on both prescribed and administered pharmaceuticals of the patients will be analyzed between 2003 and 2024 at national and regional levels, meaning that the data at the two levels are of the same patients through different datasets. Socioeconomic data such as level of education will be used to characterize patients. This would help to a better understanding of potential risk groups which may need better (specialized/adapted) interventions. Lower levels of education have been associated with greater risk of dementia (Sharp & Gatz, 2011). If level of education is not accessible, a proxy such as annual income will be used as the socioeconomic variable. As there is an ongoing debate regarding the impact of vaccination on the risk of developing neurodegenerative diseases such as Alzheimer's disease and other dementias, this study aims to add to the current body of evidence to either support the association or not between herpes zoster vaccination and the reduced risk of developing dementia. This will be done by analyzing data from the participants of the ZOE studies as well as a synthetic control arm on comorbidities, cognitive assessments, prescribed drugs, cause of death, and potential support or

services provided to the elderly and persons with impairments. Other potential benefits of evaluating health outcomes of Shingrix include reduced disease incidence, economic efficiency, and better vaccination strategies, provided that the side effects do not outweigh the positive effects of the vaccination.

To ensure that patients are proactively protected against shingles in Sweden, the vaccine is aimed to be part of the National Immunization Program (NIP). There are 13 criteria that need to be met for the inclusion of new vaccines in the NIP in Sweden, spanning from burden of disease to cost effectiveness and sustainability based on ethical and humanitarian considerations. To help ensure as many people as possible can benefit from Shingrix vaccination for shingles, it is important to further understand the disease burden of shingles as well as the secondary medical outcomes and non-medical consequences, which can inform public health and clinical decision-making.

The data collection will include description of patients' clinical and sociodemographic characteristics, treatments prior to and following the vaccination, clinical and social outcomes, the patient journey, the number of healthcare visits by type, the length of admissions, associated costs for visits (including treatments during the visits) and admissions, potential comorbidities such as dementia and cognitive impairment, and memory assessment activities.

## Ethics approval required
Ethics approval required

## Ethics approval(s)
Approved 14/06/2024, Etikprövningsmyndigheten (Swedish Ethical Review Authority) (Etikprövningsmyndigheten Box 2110, Uppsala, 750 02, Sweden; +46 10-475 08 00; registrator@etikprovning.se), ref: 2024-02767-01

## Primary study design
Observational

## Study design
Retrospective cohort study

## Study type(s)
Other

## Health condition(s) or problem(s) studied
Prevention of dementia in patients that have been vaccinated with Shingrix

## Interventions
This study is a retrospective cohort study based on secondary use of data for select patients in Sweden who have consented to their data being used for a vaccination study and future studies with scientific and medical purposes. The extracted data will range from 1st January 2003 to 31st December 2024 or the latest available date, which allows for effective observation and collection of real-world data describing the incidence of secondary outcomes, HCRU, drug prescription and other relevant characteristics of patients vaccinated against shingles. Each participant of the vaccination study, both vaccinated and placebo who later were vaccinated, will also be matched with three controls which will be a synthetic control group at both the national and regional level. The data extraction at both national and regional levels allows for extensive data for the individual participants from the vaccination study and the synthetic control arm, as

the data on the national level gives an insight into the overall cost for the patient and the data on the regional level gives a detailed level of information about the same patient.
The total study period will range from 1st January 2003 to 31st December 2024 with an inclusion period from 1st January 2010 to 31st December 2016 where the vaccine was administered, a pre-screening period of 7 years prior to the vaccination, and a follow-up period of at least 8 years (but no later than 13 years). Patients who had the vaccine administered in 2010 and 2011 will have a maximum follow-up of 13 years.

### Intervention Type
Other

### Primary outcome(s)
Measured using patient records at a single time point:
1. Number of healthcare visits for patients who received the Shingrix vaccine compared to the synthetic control arm
2. Length of hospitalization for patients who received the Shingrix vaccine compared to the synthetic control arm
3. Costs of visits for patients who received the Shingrix vaccine compared to the synthetic control arm
4. Costs of treatment for patients who received the Shingrix vaccine compared to the synthetic control arm
5. Total reimbursement for sick leave for patients who received the Shingrix vaccine compared to the synthetic control arm

### Key secondary outcome(s)
Measured using patient records at a single time point:
1. Number of healthcare visits for patients who received the Shingrix vaccine compared to the synthetic control arm
2. Length of hospitalization for patients who received the Shingrix vaccine compared to the synthetic control arm
3. Costs of visits for patients who received the Shingrix vaccine compared to the synthetic control arm
4. Costs of treatment for patients who received the Shingrix vaccine compared to the synthetic control arm
5. Total reimbursement for sick leave for patients who received the Shingrix vaccine compared to the synthetic control arm

### Completion date
31/12/2026

## Eligibility

### Key inclusion criteria
Patients that participated in the previous vaccination studies in Sweden will be included in this study. The date of inclusion will be when the first dose of either Shingrix or placebo was administered. Patients can be included at any point during the inclusion period and the associated prescreening and follow-up period will be associated with the inclusion date. Members of the synthetic control arm will have the same inclusion date as their associated patient from the vaccination study.

### Participant type(s)

Other

**Healthy volunteers allowed**
No

**Age group**
Mixed

**Lower age limit**
50 Years

**Upper age limit**
100 Years

**Sex**
All

**Total final enrolment**
0

**Key exclusion criteria**
Individuals without a Swedish personal identification number will be excluded. Individuals that have a confirmed dementia diagnosis in the pre-screening period will be excluded.

**Date of first enrolment**
19/07/2010

**Date of final enrolment**
28/07/2016

# Locations

**Countries of recruitment**
Sweden

**Study participating centre**
**Lumell Associates**
Scheelegatan 19
Stockholm
Sweden
11228

# Sponsor information

**Organisation**

Lumell Associates

# Funder(s)

**Funder type**
Industry

**Funder Name**
GlaxoSmithKline

**Alternative Name(s)**
GlaxoSmithKline plc., GSK plc., GlaxoSmithKline plc, GSK

**Funding Body Type**
Government organisation

**Funding Body Subtype**
For-profit companies (industry)

**Location**
United Kingdom

# Results and Publications

**Individual participant data (IPD) sharing plan**

**IPD sharing plan summary**
Not expected to be made available