SYNTHESIS

# Shingles vaccination recommendations and the role of the Shingrix vaccine

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## Introduction

Herpes Zoster is a virus exclusive to humans and is the cause of two clinical manifestations: chicken-pox and shingles. Shingles is a common viral skin infection, caused by the reactivation of the varicella zoster virus (VZV), principally affecting adults. Complications, such as bacterial superinfections, neurological signs, meningitis, encephalitis, and particularly post-herpetic neuralgia (PHN), affect individuals aged 50 years and older.

In 2013, the French High Council for Public Health (HCSP) recommended the administration of the Zostavax vaccine in France to adults from 65 to 74 years inclusive, according to a single-dose schedule for the prevention of shingles and post-herpetic neuralgia (PHN).

In response to a referral by the French Ministry of Health (DGS) and with a view to making the Shingrix vaccine available in France, the French National Authority for Health (HAS) reviewed the data in respect of this vaccine to evaluate its place in the current shingles vaccination strategy.

### Epidemiology

In Europe, among those aged under 40 years, annual incidence is less than 2 cases per 1,000. It then increases to 7 to 8 cases per 1,000 in individuals aged 50 years and older, and to almost 10 cases per 1,000 from the age of 80 years. In Metropolitan France, according to the Sentinelles network, in 2022, the annual incidence rate of shingles in the general population was 346 new shingles cases per 100,000 inhabitants (95% CI 324; 368) versus 418 in 2021. The median age of shingles onset is 65 years, with 69% of cases aged from 50 to 89 years.

In 2023, a study conducted by Santé Publique France estimated the burden of shingles in France using the databases of the Programme for Clinical Information Systems (PMSI). The study extracted 135,016 hospital stays from the PMSI database between 2008 and 2021. The hospitalised case incidence rate for shingles varied between 4.18 in 2008 and 5.14 per 100,000 inhabitants in 2018. For PHN, the hospitalised case incidence rate varied between 0.31 and 0.47 per 100,000 in 2018. Of the 36,200 hospital stays for shingles or PHN selected over the 14 years, 554 deaths were reported during hospital stays, all causes of death combined. This represents 1.5% of hospital stays for shingles. Of the hospital stays analysed, 27% (n = 9,716) concerned immunosuppressed patients. In terms of hospital deaths, 41% concerned immunosuppressed patients: this proportion varied from 27%, in 2021, to 54%, in 2012. In-hospital lethality among immunosuppressed patients was higher than that among immunocompetent patients (2.3 vs 1.2 respectively).

# International recommendations

Internationally, shingles vaccination is currently recommended and covered by national insurance in several countries. The recommended Shingles vaccines are Zostavax (a live attenuated vaccine) and Shingrix (a recombinant vaccine). The majority of countries have included Shingrix in their recommendations. By way of example, Germany, Austria, Belgium, and the Netherlands only recommend Shingrix. Other countries, such as Australia, Canada, and Ireland, include both vaccines (Shingrix and Zostavax) in their vaccination program. No countries have suspended the implementation of shingles vaccination recommendations (regardless of the vaccine).

# Methodology

The HAS public health assessment and vaccine assessment department (SESPEV) and documentation department reviewed the literature. The literature search strategy concerned literature published from 2012 to June 2023.

The assessment of the methodological quality of the publications and the presentation of the data analysis were performed in accordance with the WHO guidance for the development of evidence-based vaccination-related recommendations. A working group with experts in clinical practice, epidemiology and the context (users) was set up to discuss the results obtained from the literature review.

# Results

## Immunogenicity

Vaccine responses were greater in subjects vaccinated with Shingrix than in those vaccinated with Zostavax.

It should be noted that no immunological correlate of protection against shingles was established. Hence, the level of immune response providing this protection is not known.

## Vaccine effectiveness

A systematic review with meta-analysis assessing the real-life effectiveness (VE) of shingles vaccines estimated the protection of the Shingrix vaccine to be 79.3%, whereas the real-life vaccine effectiveness (VE) of Zostavax was 45.9% in immunocompetent adults aged 50 years and older. In the population with comorbidities, the Shingrix vaccine was found to be more effective than Zostavax in preventing shingles (~70% versus ~50%).

The VE against shingles incidence (confirmed cases and suspected cases) is greater with the Shingrix vaccine than with Zostavax (77% vs 63%) including against PHN (Shingrix 87%).

## Safety

The Shingrix vaccine has a good safety profile. When co-administered with other vaccines (PCV13, PPV23, dTpa, seasonal influenza, mRNA-1273 vaccine), a greater proportion of local adverse events and systemic adverse events were reported compared to the control group.

### Post-marketing safety of Shingrix vaccine

Two publications have reported the onset of Guillain-Barré Syndrome (GBS) in adults vaccinated with Shingrix. These reports led the Advisory Committee on Immunization Practices (ACIP) to review the benefit-risk balance for this vaccine. Following this review, the ACIP decided to continue the vaccination of immunocompetent adults with Shingrix after observing a greater benefit relative to the risk of

GBS, as vaccination would help prevent 43,000 to 63,000 cases of shingles and complications per million vaccinated individuals for each age group.

## Economic evaluations

A systematic review with meta-analysis was conducted to determine the incremental net monetary or health benefit (INB) of shingles vaccines (Shingrix and Zostavax). The Shingrix vaccine was cost-effective compared to non-vaccination from a societal viewpoint, mainly in individuals aged 60 years and older. When comparing the two vaccines, Shingrix was also cost-effective compared to Zostavax. An economic evaluation for the French context would help establish the cost-effectiveness ratio of the Shingrix vaccine, by accounting for the characteristics of the French healthcare system, as well as the burden of the disease in the population who might benefit from shingles vaccination.

## Acceptability

A systematic review with meta-analysis estimated the rate of amenability to shingles vaccination among adults aged 50 years and older. The acceptability rate from the grouped analysis was 56%. There was no difference between the transverse surveys conducted in an inpatient context (58%) and in an outpatient context (53.4%). It should be noted that in the context where vaccination was recommended by healthcare professionals, this rate was higher, as 75% of adults accepted to receive a shingles vaccine compared to the cohort who had not received recommendations from a healthcare professional. In 2020, a French survey on immunocompetent adults aged 65 years and older was conducted in Lyon. The proportion of individuals who considered shingles as a severe illness was statistically significant and higher in the group who would accept to be vaccinated against shingles (64.2% versus 52.8%, p= 0.02). Healthcare professional participation would be a key factor in increasing vaccination coverage among adults aged 50 years and older.

## Shingles vaccination recommendations and the role of the Shingrix vaccine

For the purposes of simplifying the vaccination schedule and communication to the general public with a view to improving vaccination coverage, after its assessment, the HAS recommends shingles vaccination for immunocompetent adults aged 65 years and older, preferentially with the Shingrix vaccine.

The HAS also recommends shingles vaccination with the Shingrix vaccine for individuals aged 18 years and older who have immune deficiency, due to congenital (e.g. primary immune deficiency) or acquired (e.g. HIV infection-related immunosuppression) disorders or treatment (e.g. long-term corticosteroid therapy or immunosuppressant treatments). The vaccination of immunosuppressed individuals will be the subject of specific recommendations.

The primary vaccination schedule of Shingrix consists of administration in two doses, with a two-month interval between each dose. If needed, the interval may be between two and six months. It is also not necessary to restart the vaccination schedule if the six-month interval is exceeded.

For the individuals targeted by this recommendation who have previous history of shingles or Zostavax vaccination, the HAS recommends a complete Shingrix vaccine schedule, after an interval of at least one year.

In specific contexts (imminent induction of immunosuppression or recurrent bouts of shingles), the Shingrix vaccine may be administered on recovery from shingles.

The HAS recommends vaccination with the Shingrix vaccine prior to commencing immunosuppressant therapy. It is recommended to administer the vaccine as early as possible, so that vaccination is

complete ideally 14 days prior to commencing treatment. In this context, the interval between the two vaccine doses may be reduced to one month.

The Shingrix vaccine may be administered at the same time as an inactivated, non-adjuvanted seasonal influenza vaccine, pneumococcal vaccine or dTpa (reduced antigen diphtheria-tetanus-acellular pertussis) vaccine, and with an mRNA Covid-19 vaccine. There is no minimum interval required between any of these vaccines and the Shingrix vaccine. The vaccines must be administered at different injection sites.

To date, the need for a booster dose after primary vaccination with Shingrix has not been established.

Due to the lack of clinical data on the safety profile of the Shingrix vaccine in breastfeeding women, its administration should be assessed on a case-by-case basis, and within the framework of a shared medical decision with the care team.

The HAS recommends the development of information materials tailored to different audiences.

Finally, the HAS emphasises that studies on the duration of shingles vaccination protection in immunosuppressed individuals are needed, and that it would also like to see economic evaluations in the French context.

These recommendations may be updated according to changes in scientific knowledge.