

Review of Vaccines against Herpes Zoster: the Efficacy, Safety and Impact on Quality of Life of Shingrix® and Zostavax®

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ABSTRACT

Herpes Zoster is caused by the reactivation of latent Varicella zoster virus infection on the sensory nerve ganglion, with a significant proportion of patients developing serious complications. Zostavax and Shingrix are the two available vaccines for preventing herpes zoster. Zostavax was introduced in Hong Kong in 2007, which is followed by a newer entity Shingrix being registered in Hong Kong in 2020. This review focuses on the comparison of the efficacy, safety and the impact on quality of life of the herpes zoster vaccines.

Based on the currently available published studies, Shingrix is shown to have a higher vaccine efficacy in the age group of 50 or above while Zostavax has a significantly lower vaccine efficacy in the age group of 70 or above. Greater effectiveness in improving quality of life and durability of protection have also been reported in Shingrix recipients. Regarding safety, Injection reactions were common in both Shingrix and Zostavax but more systemic reactions were identified for Shingrix. Clinical studies, along with the recommendations from foreign public health authorities, suggest that Shingrix is superior to Zostavax. Thus, Shingrix is believed to have great potential in replacing Zostavax for preventing herpes zoster in Hong Kong.

Keywords: Herpes Zoster Vaccine, Zostavax, Shingrix, Adjuvanted recombinant zoster vaccine, Live Zoster Vaccine, Herpes Zoster

Abbreviations

HZ= Herpes Zoster

LZV= Live Zoster Vaccine/ Zostavax

PHN= Postherpetic Neuralgia

QoL= Quality Of Life

RZV= Recombinant Zoster Vaccine/ Shingrix

VE_{HZ}= Vaccine efficacy in reducing the incidence of Herpes Zoster

INTRODUCTION

Herpes Zoster (HZ), commonly known as shingles, refers to the reactivation of latent Varicella zoster virus (VZV) infection on the sensory nerve ganglion, characterized by painful rashes which typically resolve in 2 to 4 weeks.⁽¹⁾ In Hong Kong, the actual prevalence of HZ was not reported, but a survey conducted by the University of Hong Kong estimated the prevalence of HZ in Hong Kong to be 16.8%.⁽²⁾

Studies also suggested that factors such as old age and immunosuppressive diseases were significant risk factors for HZ.⁽³⁾ One of the common but serious complications of HZ is postherpetic neuralgia (PHN), which is defined as a neuropathic pain syndrome associated with HZ rated 3 or more on a scale of 0 to 10 and occurs persistently or appears more than 90 days after the onset of HZ rash.⁽¹⁾ The same study indicated that 29.8% of HZ patients develop such serious complication, and 2% may further develop into fatal complications such as stroke and myocardial infarction.⁽⁴⁾

Current treatment objectives for HZ are mainly to improve quality of life (QoL) of patients and to minimize the severity of pain in patients.⁽⁵⁾ Common treatments include the use of oral antivirals such as acyclovir within 72 hours of onset. In immunosuppressed patients or patients with high risk of serious complications associated with delayed treatment, intravenous antivirals may also be considered.⁽⁵⁾ With the high prevalence of HZ and risk of complications, there is an urgent demand to develop prevention strategies for HZ and its associated complications.

Currently, two types of vaccines indicated for prevention of HZ are available in Hong Kong, namely live attenuated zoster vaccine (LZV, Zostavax®) and recombinant zoster vaccine (RZV, Shingrix®) which was registered in 2007 and 2020 respectively. In this article, the mechanisms, efficacy, safety and impact on QoL of Shingrix and Zostavax will be discussed.

ZOSTAVAX (LZV)⁽⁶⁾

Therapeutic Indication

Zostavax is indicated for the prevention of HZ and HZ-related post-herpetic neuralgia (PHN) in individuals aged 50 years and older.

Mechanism of Action

Primary infection with VZV induces specific memory T-cells production that is sufficient to keep the virus in its latent form. However, general immunosuppressed state or waning immunity associated with aging may reduce T-cells to a level that is unable to inhibit viral replication,

the decline in VZV-specific immunity thereby increases the likelihood of the virus reactivation. Zostavax, which contains a lyophilized preparation of live, attenuated VZV activates specific T-cell production to boost VZV-specific immunity and avoid VZV reactivation.

Dose and Administration

Zostavax is injected subcutaneously, preferably in the deltoid region of the upper arm. It is given in one dose as a shot after reconstitution within 30 minutes.

Clinical studies

The table below (**Table 1**) summarizes the key clinical studies of LZV.

Table 1. Key clinical studies of LZV (Zostavax)					
Trial	Publication year	Objective	Study summary*	Mean follow-up years	Key findings#
1.Shingles Prevention Study (SPS) ⁽⁹⁾	2005	Evaluate the vaccine efficacy in terms of incidence of HZ, burden of illness and incidence and postherpetic neuralgia in older adults with age of 60 or above	- Randomized, placebo-controlled and double blinded clinical trial at 22 sites in the United States - n=38546	3.13 years	i) Efficacy and QoL: - Overall VE_{HZ}: 51.3% - VE_{HZ} of age ≥70: 37.6% - VE_{HZ} of age 60-69: 63.9% - Reduced incidence of PHN by 66.5% - Reduced burden of illness by 61.1% - Protection through 4 years after vaccination ii) Safety: - More adverse events were reported by the participants in the vaccinated group than that of the placebo group - Most common adverse events were injection site reactions like erythema, pain and swelling
2. ZEST ⁽¹⁰⁾	2014	Evaluate the efficacy and effectiveness of Zostavax in adults with age of 50-59	- Randomized, placebo-controlled, double blinded clinical trial conducted in Europe and North America - n=22439	1.30 years	i) Efficacy: - Overall VE_{HZ}: 69.8% ii) Safety: - More participants in the vaccinated group reported adverse events than the placebo group - Most common systemic adverse event was headache
3.Short-Term Persistence Substudy (STPS) ⁽¹¹⁾	2012	Evaluate the persistence of VE for HZ burden of illness, incidence of PHN, and incidence of HZ each year through year 7	- Re-enrolled subjects from SPS with analogous methods 12 of 22 original Shingles Prevention Study sites in the United States - n=1427	0.98 years for placebo recipients and 1.36 years for vaccine recipients	Efficacy: - Vaccine efficacy for each study outcome was lower in the STPS than in the SPS - Evidence of persistence of vaccine efficacy through year 5 post vaccination
4.Long-Term Persistence Substudy (LTPS) ⁽¹¹⁾	2015	Evaluate the persistence of vaccine efficacy for HZ burden of illness, incidence of PHN, and incidence of HZ each year from 7 to 11 years post vaccination	- Re-enrolled subjects from SPS with analogous methods 12 STPS sites - n=6867 (SPS vaccine recipients)	3.74 years	Efficacy: Statistically significant vaccine efficacy for incidence of HZ persisted only through year 8
5. A study on the long-term effectiveness of HZ vaccine conducted at Kaiser Permanente Southern California ⁽¹²⁾	2016	Evaluate the long-term effectiveness of HZ vaccine in terms of overall incidence of HZ and the cumulative risk of HZ in the vaccinated and unvaccinated cohort in adults with age of 60 or above	- Conducted at Kaiser Permanente Southern California - n=704312 (176 078 vaccinated and 528 234 unvaccinated)	8.00 years	Efficacy: - Rapid decline in effectiveness of HZ prevention - Vaccines provide little protection against HZ beyond 8 years

Remark: (*): n refers to the total number of participants in the study, (#): VE refers to vaccine efficacy and VE_{HZ} refers to vaccine efficacy in reducing the incidence of HZ

Table 2. Key clinical studies of RZV (Shingrix)

Trial	Publication year	Objective	Study summary*	Mean follow-up years (Post vaccination)	Key findings#
1. ZOE-50 ⁽¹³⁾	2015	Evaluate the efficacy and safety of the subunit vaccine (Shingrix) in older adults with age of 50 or above	- Randomized, placebo-controlled, phase 3 study in 18 countries in Europe, North America, Latin America, and Asia–Australian - n=15411	3.2-3.5 years	i) Efficacy and QoL: - Overall VE_{HZ}: 97.2% - No significant difference of VE_{HZ} between age groups - significant VE in preventing postherpetic neuralgia (PHN) - Reduced the HZ burden of illness significantly ii) Safety: - More injection site reaction and systemic reaction in the vaccinated group and the symptoms are mild to moderate in intensity - Pain was the most common injection-site reaction while myalgia was the most common systemic reaction
2. ZOE-70 ⁽¹⁴⁾	2016	Evaluate the efficacy and safety of the subunit vaccine (Shingrix) in adults with age of 70 or above	- Same study design to ZOE-50 (randomized, placebo-controlled, phase 3 study in 18 countries in Europe, North America, Latin America, and Asia–Australia) - n=13900 in ZOE-70 - n=17531 in the pooled analysis of participants from ZOE-50 and ZOE-70	3.7-4.0 years	i) Efficacy and QoL: - Overall VE_{HZ}: 89.8% - No significant difference of VE_{HZ} between age groups - Significant VE in preventing postherpetic neuralgia (PHN) - Reduced the HZ burden of illness significantly ii) Safety: - More adverse events were reported in the vaccinated group than the placebo group - The most common injection-site reaction and systemic reaction were pain and fatigue respectively
3. NCT01295320 ⁽¹⁵⁾	2015	Evaluate cell-mediated and humoral immune responses to Shingrix in healthy older adults at 48, 60, and 72 months after the first dose	- Phase II, open-label, multicenter, single-group trial conducted in 4 counties - n=129	Between Month 48 and Month 72 after the first dose	Efficacy: 6 years after vaccination, gE-specific cell-mediated immune responses and anti-gE antibody concentrations remained higher than the pre vaccination values
4. NCT02735915 ⁽¹⁶⁾	2020	Evaluate persistence of humoral and Cell-mediated immune response to Shingrix at months 108 and 120 after the first dose.	- Single-arm, open-label, phase IIIB, long-term follow-up study of the initial phase II trial (NCT00434577) - Conducted in 3 countries (The Czech Republic, Germany, Sweden) - n=70	Between 9 and 10 years after the first dose	Efficacy: Immune responses persist through 20 years
5. NCT02723773 ⁽¹⁷⁾	2012	Evaluate the efficacy of RZV in the prevention of HZ over the total duration of the current Long Term Follow Up (LTFU) study	- Ongoing open-label, phase 3B, LTFU study of the two pivotal phase 3 clinical trials (ZOE-50 & ZOE-70) - Conducted in 18 countries - n=14648	Between 5.1 and 7.1 years post-vaccination	Efficacy: Clinical benefit of Shingrix in older adults is preserved for at least 7 years post-vaccination
6. NCT01610414 ⁽¹⁸⁾	2019	Evaluate the efficacy and adverse event profile of the recombinant zoster vaccine in immunocompromised autologous Haematopoietic Stem Cell Transplant (HSCT) recipients.	- Phase 3, randomized, observer-blinded study conducted in 167 centers in 28 countries among 1846 patients aged 18 years or older who had undergone recent autologous HSCT - n=1846	29 months	i) Efficacy: - Post hoc analysis shows that efficacy for HSCT patients may not exceed 2 years ii) Safety: - Generally well tolerated, symptoms are mild and transient

Remark: (*) n refers to the total number of participants in the study, (#) VE_{HZ} refers to vaccine efficacy in reducing the incidence of HZ

Therapeutic Indication

Shingrix is indicated for the prevention of HZ in adults aged 50 years and older, and in adults aged 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy.

Mechanism of Action

Shingrix is a recombinant vaccine, consisting of a highly specific antigen (i.e. glycoprotein E (gE)) in an adjuvant system (AS01B). Glycoprotein E is the most abundant surface protein of VZV that stimulates robust and persistent VZV-specific antibody and CD4+ T cell responses the specific HZ virus. The adjuvant system enhances activation of the immune system, hence giving a stronger and sustained immune response to VZV.

Therefore, these two components together can assist the body to overcome age-related decline in immunity, which is a presiding driver of HZ.

Dose and Administration

Shingrix is provided as a 2-dose series. A first dose is at month 0, then followed by a second dose given between two to six months later. It is supplied in 2 vials, which must be reconstituted before injection. The powder (i.e. lyophilized VZV glycoprotein E (gE) antigen component) is reconstituted with the accompanying liquid solution (i.e. AS01B adjuvant suspension component). It should be administered intramuscularly and the deltoid region of the upper arm is the preferred site for injection.

Clinical studies

The table below (**Table 2**) summarizes the key clinical studies of RZV.

EFFICACY: PREVENTION OF HERPES ZOSTER(HZ)**Zostavax**

Shingles Prevention Study (SPS) was conducted in 1998 to 2001 and the result was published in 2005.⁽⁹⁾ It is a randomized, placebo-controlled trial. A total of 38546 participants with age of 60 or above were enrolled, in which there were 957 confirmed cases of HZ (315 from the vaccinated group and 642 from the placebo group) after excluding those confirmed cases within 30 days

of vaccination. Hence, the incidence of Shingles was significantly reduced by 51.3% in the vaccine group when compared to the placebo group. However, another key finding is that the vaccine efficacy, measured by the incidence of having HZ (VE_{HZ}) is 37.6% among those with age of 70 or older and 63.9% in younger subjects (i.e. age of 60-69). This has indicated that LZV has a higher efficacy in adults with age of 60-69 than that of 70 or above.

With the basis of SPS, another study called the Zostavax Efficacy and Safety Trial (ZEST) was conducted in participants aged 50-59 and published in 2012.⁽¹⁰⁾ ZEST is a randomized, placebo-controlled trial conducted in Europe and North America. Participants received either placebo or one dose of LZV with a mean follow up of 1.3 years after vaccination. Out of 129 confirmed cases of HZ, 30 cases were from the vaccinated group and 99 cases were from placebo group. From the intention-to-treat analysis, LZV could significantly lower the incidence of HZ with an VE_{HZ} of 69.8%.

In short, SPS and ZEST are the two major studies that evaluate the VE_{HZ} . LZV has shown a VE_{HZ} of 69.8% in older adults aged 50-59 in the ZEST study. Meanwhile, in SPS, it has VE_{HZ} of 63.9% and 37.6% in the age group of 60-69 and 70 or above respectively. Even though LZV can significantly reduce the incidence of HZ, lower efficacy is reported in older adults aged 70 or above.

Shingrix

With reference to the ZOE-50 trial in 2015,⁽¹³⁾ the efficacy and safety of RZV is studied through a randomized, placebo-controlled phase 3 clinical trial in 18 countries. The trial was conducted in adults with age of 50 or above and further stratified into 50-59, 60-69 and 70 or above. A total of around 15400 participants were evaluated, in which they received either the vaccine or placebo in two intramuscular doses two months apart. With a mean follow-up of 3.2 years, there were 216 confirmed cases of Shingles, in which 6 cases belonged to the vaccinated group and 210 cases belonged to the placebo group. As a result, the VE_{HZ} was reported to be 97.2%. Meanwhile, the VE_{HZ} were similar in all the stratified age groups, ranging from 96.6% to 97.9%.

Another trial, ZOE-70 was concurrently conducted at the same sites with an aim to investigate the safety and efficacy of the RZV in adults aged 70 or above.⁽¹⁴⁾ The methodology used in ZOE-70 is similar to that of ZOE-50. A pooled analysis on the safety and efficacy of the vaccine (i.e. reducing the risk of HZ and PHN) was evaluated in adults aged 70 or above from both ZOE-50

and ZOE-70. Out of 16,600 participants in the modified vaccinated cohort, 246 cases of HZ were reported after a mean follow-up of 3.7 years. Out of these 246 cases, 23 were from those who received RZV and 223 were from those receiving placebo. Thus, a VE_{HZ} of 89.8% was reported. No significant difference was shown between the age group of 70-79 and 80 or above.

Therefore, with reference to both ZOE-50 and ZOE-70, the RZV was reported to significantly lower the risk of HZ with a higher VE_{HZ} than placebo controls in adults aged 50 or above. Same result patterns were shown in ZOE-70.

Summary of vaccine efficacy of Zostavax and Shingrix

With reference to *Table 1* and *Table 2*, the four clinical trials (ZOE-50, ZOE-70, SPS and ZEST) have assessed the VE_{HZ} in adults aged 50 or above. Note that RZV has shown no profound difference in VE_{HZ} in different age groups (i.e. older adults aged 50 or above). By contrast, LZV has shown a lower VE_{HZ} in the age group of 70 or above. Therefore, it suggests that RZV is more suitable for patients aged 70 or above due to a higher VE_{HZ} . Moreover, several trials showed that the newly invented RZV had a higher VE_{HZ} in the corresponding age groups than that of LZV.⁽¹⁹⁻²¹⁾

Both the clinical trials of RZV and LZV are funded by their manufacturer, GSK and MSD respectively. Hence, there are slight differences in terms of study design, including the countries of participants and total sample size. Yet, due to a relatively large sample size (> 14000 participants), these trials serve as a strong reference in testing the VE_{HZ} of RZV and LZV.

EFFICACY: PREVENTION OF POSTHERPETIC NEURALGIA(PHN)

Zostavax

In SPS, the incidence of PHN amongst adults aged 60 or above who received LZV zoster vaccine was compared with that in the placebo group. The prespecified criteria for success required a reduction of 62% or more in the incidence of PHN in the vaccine group as compared with that in the placebo group.⁽⁹⁾

With a total of 957 cases of HZ with a median of 3.12 years of surveillance, there were 107 cases of PHN: 27 out of 315 patients in the vaccine group (0.46 case per 1000 person-years) and 80 out of 642 patients

in placebo group (1.38 cases per 1000 person-years). The results met the prespecified criteria for success as the use of the vaccine reduced the incidence of PHN by 66.5%. No difference in the vaccine efficacy with respect to the incidence of PHN was observed when results were stratified according to sex and age.

The long term vaccine effectiveness against PHN was estimated in an ongoing interim analysis of a prospective observational cohort study conducted in the US integrated healthcare system database.⁽²²⁾ At the time of the interim analysis, 1,355,720 individuals aged 50 and above with 392,677 who received LZV were included. From the period of 2007 to 2014, there were 48,616 cases of HZ. Amongst those with incident HZ episode, 3,297 cases developed PHN (322 cases in the vaccinated cohort and 2,975 in the unvaccinated cohort). The overall effectiveness of LZV regarding the prevention of PHN during the period covered in this interim analysis in all age groups was 69%. For individuals aged 60-69, 70-79 and 80 or older at the time of vaccination, the average vaccine effectiveness against PHN over the first five years following vaccination was 72%, 69% and 61% respectively. It was concluded that the effectiveness of vaccines against HZ-induced PHN declined with age of which patients are vaccinated.⁽²³⁾

Shingrix

From the pooled data of ZOE-50 and ZOE-70 (with 16596 participants), RZV vaccination reduced the incidence of PHN by 88.8% in participants of 70 years of age and above when compared with the placebo group. The effective protection could be apparently attributed to the high vaccine efficacy of 91.3% in the pooled analysis in preventing HZ. Among participants of 50 years of age or above, 91.2% of reduction in the incidence of PHN was observed, with 4 of 32 participants (0.1 case per 1000 person-years) who received 2 doses of RZV developed PHN as compared to 46 out of 477 (0.9 case per 1000 person-years) in the placebo group, given 3.8 years of mean follow-up period. This shows the high efficacy of RZV in preventing incidence of PHN.^(13, 14)

Summary of prevention of PHN

From the above studies, it shows that for a period of less than 4 years post-vaccination, RZV is more efficacious in reducing the incidence of PHN than LZV. The former offers 91.2% and 88.8% of reduction in developing PHN in participants of at least 50 and 70 years of age respectively, while the latter reduced the incidence by 66.5% and 69% in individuals aged 60 or above and all age groups respectively.

EFFICACY: DURATION OF PROTECTION

Zostavax

As mentioned, the SPS trial examined the vaccine efficacy in terms of HZ-induced PHN and incidence of HZ through 4 years after vaccination. The result showed that LZV could provide protection through 4 years after vaccination.⁽⁹⁾

Short-Term Persistence Substudy (STPS), which was another study conducted approximately 15 months after SPS, re-enrolled 7320 vaccine and 6950 placebo recipients from the SPS population.⁽¹¹⁾ It assessed the persistence of vaccine efficacy throughout the 3.3–7.8 years after vaccination. Same as SPS, vaccine efficacy for the 3 outcome measures (i.e. HZ burden of illness, incidence of PHN and incidence of HZ) were also assessed in STPS. Compared to the SPS, it is reported that the vaccine efficacy for HZ burden of illness, incidence of PHN, and incidence of HZ, declined by 11.0%, 6.4% and 11.7% respectively. Since STPS is carried out after the completion of SPS, the aforementioned result implies that the efficacy of LZV declines overtime. In addition, when combining the data reported in SPS and STPS, the vaccine efficacy for HZ incidence and the HZ burden of illness were shown to be statistically significant at the year 5 mark. Yet, vaccine efficacy for the aforementioned two outcome measures was no longer statistically significant in year 6 and year 7 as reported in STPS. Therefore, it is concluded that the length of immunity for LZV is around 5 years, and vaccine efficacy beyond this time point is uncertain.

Following STPS, a Long-Term Persistence Substudy (LTPS) was initiated to further investigate the long-term vaccine efficacy of LZV.⁽¹⁾ 6867 SPS vaccine recipients were re-enrolled and were assessed for each year from 7 through 11 years. Although the vaccine efficacy was reported to decline from 46.0% in year 7 to 14.1% in year 10 for the incidence of HZ, the vaccine efficacy for incidence of HZ remained statistically significant through year 8 after vaccination, which is 3 years longer than the result obtained in STPS. Meanwhile, vaccine efficacy for reducing the incidence of PHN varied through year 7 to 11.

In another large observational study conducted in Kaiser Permanente Southern California (KPSC), which included 704,312 aged ≥ 60 years adults.⁽¹²⁾ 176,078 individuals were vaccinated with LZV, while 528,234 were unvaccinated. The vaccine effectiveness in terms of the incidence of HZ by follow-up year after vaccination, which was estimated as 1–adjusted hazard ratios, was recorded over 8 years. Generally consistent with the

results in SPS and STPS, rapid waning of protection from this live, attenuated vaccine was noted, in which the vaccine effectiveness reduced from 69% to 4% during this period. In addition, a revaccination strategy is also proposed in the same study.

From the results of these trials, it can be concluded that the efficacy of LZV in prevention of HZ diminished rapidly, even though the efficacy for prevention of PHN was partly maintained. It is also noted that most evidence supports the persistence of overall vaccine efficacy and protection through year 5 only, meanwhile, all efficacy data for incidence of HZ presented was not statistically significant 8 years after vaccination. Therefore, the evidence for protection 6 years post-vaccination remains uncertain.

Shingrix

In a phase II multicenter trial, 129 individuals who had received two doses of RZV in a pivotal trial (single-blind, randomized, controlled trial, NCT00434577) were followed up.⁽¹⁵⁾ It aimed to evaluate the persistence of immune responses induced by two doses of RZV in two age cohorts (i.e. 60–69 years and ≥ 70 years of age) and at 3 different time points (i.e. 48, 60, and 72 months after the first dose of RZV). Results suggested that at month 72, the median gE-specific cell-mediated immunity response and anti-IgE antibody concentration were still 3.8 and 7.3-fold above the pre vaccination value, suggesting that RZV-induced immune responses persist for up to 6 years in healthy older adults.

Moreover, in a phase IIIB, long-term follow-up study of the initial phase II trial (NCT00434577), 70 adults ≥ 60 years of age who completed a 2-dose RZV vaccination were assessed for the immune responses through 10 years after initial vaccination.⁽¹⁶⁾ Results were in line with the previous study, with additional observation showing that IgE-specific cell-mediated immunity response and anti-IgE antibody concentration remained 3.5 times and 6 times higher than the pre-vaccination levels 10 years after initial vaccination. In the same study, 3 validated models were also used for prediction, and it was proposed that immune responses could persist through 20 years.

Yet, as there is no established information regarding immunological threshold of protection against HZ, the immune response illustrated in these two studies cannot infer the clinical protection.

The other long term follow-up study indeed provided more information regarding the persistence of clinical

benefit of RZV.⁽¹⁷⁾ Out of the 7294 former participants of the ZOE-50/70 pivotal clinical trials, 7 and 169 shingles cases were reported in the vaccine and control group during the period ranging from a mean of approximately 5.1 to 7.1 years post-vaccination, indicating that RZV was 84.0% efficacious in preventing HZ for this period. Therefore, these findings confirmed that RZV provides clinical benefits for not less than 7 years post-vaccination for older adults.

Based on the above trials, it can be concluded that immune responses induced by RZV remain for 10 years, and potentially for 20 years. Meanwhile, clinical efficacy against HZ is confirmed to last for at least 7 years after vaccination.

Summary of protective duration

Based on the present clinical studies, it can be confirmed that the persistence of vaccine efficacy for LZV and RZV is 5 years and at least 7 years respectively. Modeling of RZV immunological results show that immune responses persist even through 20 years. Additionally, RZV's efficacy also plateaued at a very high level (i.e. 84.0%) at 5-7 years post vaccination. On the contrary, LZV not only has lower efficacy, but its effectiveness also wanes rapidly, especially by year 5 after vaccination. Such differences between 2 vaccines may be related to the adjuvant system in RZV, which enhances the immune system's response for a long lasting protection effects.

IMPACT ON QUALITY OF LIFE (QoL)

Zostavax

The impact of zoster vaccination on the HZ-related interference with activity of daily life (ADLs) and health related QoL (HRQL) were assessed in the study population of SPS. ADL and HRQL evaluations were repeated in a span of 182 days. Overall, 957 cases in which 315 belong to the vaccine group and the remaining 642 belong to the placebo group were analyzed.⁽²⁴⁾

Zoster Brief Pain Inventory (ZBPI) was used to quantify pain and discomfort associated with HZ and measure certain activities of daily living (ADLs) and health. Participants were to rate HZ pain and discomfort in four aspects (the worst, least and average during the past 24 hours and now) as well as the interference of HZ pain and discomfort towards seven ADLs: general activity, mood, walking ability, work, relation with others, sleep and enjoyment of life on a scale of 0-10 using the 11-point Likert scale. To deduce the ZBPI ADL burden of interference, the average score of the HZ pain and

discomfort regarding the seven ADLs items were taken. From day 0 to day 182 in the modified intention to treat population, LVZ was able to reduce the ZBPI ADL burden of interference by 66%.

On the other hand, the Medical Outcomes Study 12-item Short Form Survey (SF-12) was used to measure the HRQL where participants self-evaluated their general health, including limitations in daily activity, emotional problem, interference of pain with work, etc. The SF-12 is summarized into mental component summary (MCS) and physical component summary (PCS) scores. For the entire study population, LVZ reduced HZ-related decrements in PCS and MCS by 55% when compared to placebo controls. Overall, LVZ reduced the HZ-related burden of interference with daily activity by two-third and HZ-related effect on HRQL by half in the vaccinated group.

Shingrix

The QoL impact of RZV was determined in 2 trials, ZOE-50 and ZOE-70, with the following assessments: First, for patients who developed HZ after RZV vaccination (8 patients out of 7340 in ZOE-50 and 23 out of 8250 in pooled ZOE-70), the ZBPI instrument was used to assess participants' "burden of illness" and "burden of interference with ADL", as compared with 241 patients out of 7413 receiving placebo in ZOE-50 and 263 out of 8346 receiving placebo in pooled ZOE-70 respectively. Patients self-evaluated pain on 11-point Likert-type scales over a period of time. The "worst pain over the last 24 hours" category was considered clinically significant and most reliably correlated with vaccine efficacy in reducing the "burden of illness" associated with HZ pain. For "burden of interference with ADL", the extent of interference to 7 ADLs was rated based on 11-point Likert-type scales for 182 days starting from HZ rash onset.⁽²⁵⁾

Reduction in burden of illness and burden of interference with ADLs was greater than 90% in both ZOE-50 and pooled ZOE-70. The mean worst pain scores were lower in the RZV group than the placebo group. Also, the median time to resolution of the "worst pain" was 14 days for both ZOE-50 and pooled ZOE-17, versus 17 and 22 days in the placebo groups in the respective studies.

Second, the utility loss of the HZ patients in the RZV and placebo groups in both studies over the first 28 days after rash onset was assessed with the mean EuroQol-5 Dimension (EQ-5D) utility index and compared. Patients were to grade their extent of problems on mobility, self-care, usual activities, pain or discomfort and anxiety or depression. The combination of the grades was

converted to health states then into utility scores. The utility score ranged from less than 0 to 1, from the worst to best possible health state. Reduction in patients' utility loss was approximately 63.7% in ZOE-50 and 21.2% in pooled ZOE-70. In breakthrough HZ cases, estimated differences up to 0.14 in ZOE-50 study on the EQ-5D index of the HZ episode were observed, suggesting less loss of QoL in vaccinated groups.

Third, the 36-Item Short Form Survey (SF-36) was given to all patients to assess QoL with psychometric properties. Higher QoL scores were observed in RZV groups than placebo groups in both studies, but very few comparisons showed statistical significance.

Overall, RZV is shown to reduce HZ burden of illness and interference in daily activity, resulting in shorter duration of pain and increase QoL over the initial 4 weeks following rash onset. Thus, severity of HZ in vaccinated patients would decrease.

Summary of improving QoL

Both studies utilized the ZBPI to assess patients' burden of interference with ADL. The efficacy of RZV in reducing the burden of interference with ADL in patients with HZ (over 90%) appeared to be significantly higher when compared to that of the LZV (60%). However, it should be noted that there was a slight difference in the approach used to analyze the statistics. In the LZV study, the ZBPI ADL interference items were summarized into a single score for further analysis through taking the mean of the seven items, whereas the two consecutive ZBPI worst-pain scores were averaged in the RVZ study.

In terms of patient's QoL, RZV reduced patient's utility loss by approximately 63.7% in the ZOE-50 study whereas a 55% reduction in HZ-related decrements in QoL was observed after the use of LZV. As different health surveys were used (SF-12 MCS and PCS used in the RZV study vs SF-36 and EQ-5D used in the LZV study), this is a limitation for a direct comparison between the 2 vaccine studies.

SAFETY

Adverse events of LZV and RZV can be classified into local or systemic, non-serious or serious.

Zostavax

Zostavax (LZV) is generally well tolerated. In ZEST,

63.9% of the LZV recipients and 14.4% of placebo recipients aged 50 to 59 reported injection site reactions such as pain, erythema and swelling.⁽¹⁰⁾ Common systemic adverse reactions reported include headache (9.4% in LZV group and 8.2% in placebo group) and pain in extremity (1.3% in LZV group and 0.8% in placebo group). On the other hand, 48% of the LZV recipients and around 17% of placebo recipients reported injection site reactions in SPS.⁽⁹⁾ Common systemic adverse reactions ($\geq 1\%$) reported include headache (1.4% in LZV group and 0.8% in placebo group). In ZEST and SPS, the number of participants reported serious adverse events within the post vaccination period of 42 days is similar in the LZV group (0.6% in ZEST and 1.4% in SPS) and placebo group (0.5% in ZEST and 1.4% in SPS). Both trials also demonstrated a similar overall incidence of death between the LZV and placebo group within the post vaccination period of 42 days. In ZEST, the mortality rate (per 1000 person per year) was 1.18 in the LZV group and 1.90 in the placebo group. In SPS, 14 and 16 cases of death were reported in the LZV group and the placebo group respectively, of which the most common cause of death was cardiovascular disease (10 in the LZV group and 8 in the placebo group).

A post-licensure retrospective study analyzed reports from the Vaccine Adverse Event Reporting System in the US and reported consistent findings as the above trials.⁽²⁶⁾ Non-serious common adverse events reported among adults ≥ 50 years with LZV administered included injection site redness (27%), HZ (17%), injection site swelling (17%), and rash (14%). Among the serious reports, HZ (29%), pain (18%), and rash (16%) were the most common symptoms.

Number of zoster-like rashes and varicella-like rashes within the post vaccination period of 42 days was low in the LZV and placebo groups in ZEST and SPS. Less than 0.2% of the participants in the LZV and placebo groups reported zoster-like rashes in both trials.^(9, 10) On the other hand, less than 0.7% of the participants in the LZV and placebo groups reported varicella-like rashes. These rashes were generally mild. Among the rashes tested positive for varicella-zoster virus (VZV), all were associated with the wild type VZV. The Oak/Merck strain which was used in LZV was not detected.

Shingrix

Adults Aged 50 Years and Older

The safety profile of RZV in adults aged 50 or over has been evaluated in two phase III clinical trials (ZOE-50 and ZOE-70). Total of 29,305 participants over the age

of 50 were involved, where 14,645 participants received at least 1 dose of RZV and 14,660 participants received placebo.^(13, 14) It is noted that the mean age of these participants was 69 years old and Asian participants (18%) were included.

Among the 14,645 vaccinated participants, 1 subject reported lymphadenitis and 1 subject reported fever over 39°C. Common adverse events within 7 days after the administration of RZV (both doses combined) included injection site reactions such as pain (78%), erythema (38%), and swelling (26%). Local reactions affecting daily activities such as pain (Grade 3) were reported in 9.4% of them. Systemic adverse reactions such as myalgia (45%), fatigue (45%), headache (38%), shivering (27%), fever (21%), and gastrointestinal symptoms (17%) were reported. Around 10.8% of the vaccine recipients reported systemic reactions affecting daily activities, which was higher than that of the placebo group (2.4%). Grade 3 systemic adverse reactions were reported more frequently in participants after receiving the second dose. Generally, these common adverse events were more prevalent in adults aged between 50 and 69 than that of over 70 years old. Most of these local and systemic adverse reactions lasted for 2 to 3 days. There were no significant differences in the percentage of the participants experiencing serious adverse events between the vaccine and placebo groups. The incidence of death was similar in both RZV and placebo groups.

A post-licensure safety surveillance study reported similar findings like the aforementioned phase III clinical studies.⁽²⁷⁾ A low rate of serious adverse events was observed. Meanwhile, common adverse events like injection site reaction, swelling and pain were reported. It was also reported that adults aged between 50 and 69 had a greater chance to experience systemic reactions, whereas adults aged over 70 were more likely to have local adverse reactions.

Nonetheless, a post-marketing observational study including 849,397 RZV-vaccinated and 1,817,099 LZV-vaccinated participants aged 65 or above showed a possible increased risk of developing Guillain-Barré Syndrome (GBS), defined as an autoimmune disorder which causes nerve damages and thus lead to muscle weakness.⁽²⁷⁾ An increased risk of GBS was observed in adults aged 65 or above within 42 days after vaccination, with an estimation of 3 excess cases of GBS per million doses administered. Meanwhile, 6 excess cases of GBS per million doses administered to adults aged 65 or above within 42 days after receiving the first dose of RZV were estimated in secondary analyses. There was no increased risk observed after receiving the second dose. Some other adverse reactions, including decreased

mobility of the injected arm for one or more weeks and hypersensitivity reactions, were reported during post-approval use of RZV. Yet, no causal relationship could be established between these adverse reactions and RZV due to insufficient evidence.

Immunocompromised Adults Aged 18 Years and Above

The safety profile of RZV in immunocompromised adults aged 18 or above has also been evaluated in 6 placebo-controlled clinical studies including 3116 participants from 5 different groups of immunocompromised populations, namely autologous hematopoietic stem cell transplant (auHSCT) recipients,^(18, 28) renal transplant recipients,⁽²⁹⁾ those with solid tumors receiving chemotherapy⁽³⁰⁾ or hematologic malignancies⁽³¹⁾ and HIV-infected participants.⁽³²⁾ Out of the total participants, 28% of the participants were aged 18 to 49 and the remaining 72% of the participants were aged over 50. Similar to the previous ZOE-50 and ZOE-70 trials, Asian population (17%) was included.

In the auHSCT study, recipients (aged 18 to 49 and ≥50 years of age) reported local adverse reactions such as pain (88% and 83%), erythema (30% and 35%), and swelling (21% and 18%) within 7 days after the administration of RZV (both doses combined).⁽¹⁸⁾ Regarding systemic adverse reactions, fatigue (64% and 54%), myalgia (58% and 52%), headache (44% and 30%), gastrointestinal symptoms (21% and 28%), shivering (31% and 25%), and fever (28% and 18%) were also reported. The local and systemic adverse reactions generally lasted for 1 to 3 days among these participants. Also, within the post vaccination period of 30 days and the post vaccination period of 1 year, there was no notable difference in the percentage of participants experiencing serious adverse events between the RZV (7% and 26%) and placebo (8% and 27%) groups. The incidence of death is similar in the RZV (0.1% and 6%) and placebo (0.5 and 6%) groups. Furthermore, there was no significant difference in the new onset of potential immune-mediated diseases (pIMDs) or exacerbation of current pIMDs between the vaccine (1.3%) and placebo (1.0%) groups up to 1 year after the vaccination of the first administered dose.

Summary of Safety

Injection site reactions including erythema, pain and swelling were common after the administration of both RZV and LZV, yet more common in RZV recipients. Systemic adverse reactions were more prevalent in the RZV recipients. However, these systemic reactions are generally resolved within 2 to 3 days. On the other

hand, increased risk of GBS was reported among RZV recipients.

Regarding the safety of the vaccines in immunocompromised adults, RZV is safe. Local and general adverse reactions reported by these participants were similar to those of the general population. Also, there was no significant difference in the new onset pIMDs or worsening of existing pIMDs between the vaccinated group and the placebo group. LZV contains the live and attenuated VZV, which may induce HZ infection in the immunocompromised adults. Therefore, LZV is contraindicated in this group of people while RZV is recommended for them.

APPLICATION IN HONG KONG

Having reviewed the efficacy, safety and impact on QoL of Zostavax and Shingrix, recommendations specifically for the Hong Kong population taking social context into account are drawn.

Recommendations from foreign authorities

There is a growing popularity of Shingrix worldwide. Several health authorities advise the use of Shingrix over Zostavax. Centers for Disease Control (CDC) in the United States recommends adults aged 50 or above and immunocompromised adults to receive two doses of Shingrix to prevent HZ and the related complications.⁽³³⁾ In addition, those vaccinated with Zostavax in the past can be revaccinated the full dose of Shingrix, supporting the effectiveness of Shingrix. Consistent with the recommendation of CDC, the Australian Technical Advisory Group on Immunization (ATAGI) in Australia also supports that Shingrix is superior over Zostavax for adults aged 50 or above in terms of its efficacy, and has recommended Shingrix as the preferred vaccine.⁽³⁴⁾

Aging population in Hong Kong

Aging is one of the risk factors for HZ.⁽³⁾ According to a report from the Census and Statistics Department, the proportion of elderly (i.e. age 65 or above) increased significantly from 13.5% in 2001 to 20.4% in 2021, and the life expectancy for both genders have generally increased in the past 50 years. Therefore, the public who is older than 70 years of age is recommended to receive Shingrix.

Public consciousness and Cost of vaccination

Although Shingrix is shown to have a higher efficacy in previous studies (i.e. ZOE50 and ZOE70), some hospitals and clinics in Hong Kong may still provide Zostavax as

the only vaccination option for HZ prevention. Having both options available for the public is important as the price of Shingrix is generally higher than Zostavax. The price of Shingrix (both doses combined) is around HKD\$5500, while Zostavax costs around HKD\$1000-1800 in private medical providers. According to a study by HKMJ, less than 30% of respondents refused to be vaccinated due to high cost.⁽³⁵⁾ The same study also showed that up to 70% of respondents revealed interest in knowing more about prevention of HZ and would like to ask their doctors about HZ vaccination. Thus, it is important to promote and educate the public in regard to the advantages of having HZ vaccinations.

Limitations of the study

Several clinical studies were summarized in the current review article. However, the parameters used in the studies are slightly different, thus direct head-to-head comparison is not feasible. This is most notable in the comparison of the vaccines' impact on participants' QoL, which there are different approaches on selecting the data obtained from ZBPI to measure HZ-related interference with ADL in the LZV and RZV studies, as well as different survey designs used to assess the health related QoL measures. In addition, some of the significant studies were funded by pharmaceutical companies that have high financial stakes in the vaccines being evaluated. For instance, the ZOE-50, ZOE-70 trials and the ZEST study received their funding support from the same company that developed the vaccines.^(10, 13, 14) These interests might potentially cause bias.

Although this article covered the safety and efficacy aspects of Zostavax and Shingrix, its efficacy in the long term and the need for revaccination are still unclear, especially for Shingrix which has only been registered in Hong Kong for less than 5 years. Further studies may be needed to determine the need and safety of revaccination.

CONCLUSION

After reviewing the efficacy, safety and impact on QoL of Zostavax and Shingrix, it can be concluded that Shingrix is superior, despite the relatively high cost. With the hope of more public education, it is anticipated that HZ vaccines will receive wide support from the local market and play a dominant role in reducing the incidence rate of HZ as well as PHN in Hong Kong. A clear guideline on the need for revaccination is helpful when discussing the pros and cons with the public or high-risk groups of patients.

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pcccchk.com) to fill in their answers there.)

1. Which of the following statements concerning vaccine administration is the most appropriate?

- a. Zostavax is injected intravenously, preferably in a large vein
- b. Zostavax is injected intramuscularly, preferably in a deltoid region of the upper arm
- c. Shingrix is injected intramuscularly, preferably in a deltoid region of the upper arm
- d. Shingrix is injected intradermally, preferably in the lower arm

2. Postherpetic neuralgia (PHN) is a common adverse event associated with HZ infection. Which precaution is incorrect?

- a. Both HZ vaccines are effective to lower the incidence of PHN
- b. Shingrix can reduce the incidence of PHN by at least 80% in clients aged 50 years old or above who completed 2 doses of vaccine
- c. Zostavax is shown to be effective to protect clients against PHN over 10 years post-vaccination
- d. The efficacy of PHN prevention by Zostavax reduces with age

3. The common side effects associated with Zostavax include:

- a. Bone pain
- b. Angioedema
- c. Increased risk of fungal infections
- d. Herpes Zoster

4. How should an adult patient be advised in proper administration of Shingrix?

- a. It should be given subcutaneously if there is no known allergy
- b. Pre-treatment screening is needed for those patients who have family history of hepatitis B infections
- c. It is administered as a 2-dose series with 2-6 months interval
- d. Annual live attenuated influenza vaccine is not required if clients had Shingrix in the same year

5. A 52-year-old Chinese male client weighs 60 kg and has no known drug allergies, who got HZ infection last year despite one dose of Zostavax 7 years ago. He is worried to have HZ infection again. Which of the following is the most appropriate option?

- a. Have 1 dose of Shingrix, as he had 1 dose of Zostavax previously
- b. Have 2 doses of Shingrix with 2-6 months apart



2 CE Units

Review of Vaccines against Herpes Zoster: the Efficacy, Safety and Impact on Quality of Life of Shingrix® and Zostavax®

- c. Have another dose of Zostavax as a booster
- d. No action is required as he got HZ infection last year

6. Which one of the following situations would recommend the patient to receive HZ vaccine?

- a. COVID-19 PCR positive
- b. Hepatitis B surface antibody positive and low HBV DNA load
- c. Pregnancy test negative
- d. Scheduled renal transplant in 3 months

7. The key findings in ZOE-50 include the following, except:

- a. HZ-induced burden of illness is reduced by HZ vaccine
- b. The risk of HZ-induced PHN is reduced in patients who had HZ vaccine
- c. Reduction of HZ incidence is no different in those who received HZ vaccine between age groups
- d. Rhabdomyolysis is the most common systemic reaction

8. The correct counselling points concerning Shingrix include:

- a. Up to 80% of clients experience headache after vaccination
- b. Shingrix does not cause gastrointestinal symptoms
- c. Symptomatic anaemic patients should avoid Shingrix
- d. The common adverse reactions may last for 1 to 3 days

9. The indications of HZ vaccines do not cover:

- a. Treatment of active HZ infections in adults aged 50 years or above
- b. Prevention of HZ-induced PHN
- c. Minimizing the risk of HZ in immunosuppressed patients aged 18 years or above
- d. Elderly who is worried about own health

10. Which of the following statements concerning the efficacy of Shingrix is incorrect?

- a. The specific anti-IgE antibody is undetectable before 2 doses of vaccines are completed
- b. The efficacy of reducing HZ-induced PHN is shown in adults aged 50 years or above
- c. The duration of protection against HZ infection can last for 10 years
- d. There is no established immunological threshold of protection against HZ

Answers will be released in the next issue of HKPJ.

CE Questions Answer for 311(D&T)

Overview of the Drug Therapy of Psoriatic Arthritis

1. B 2. D 3. D 4. D 5. B 6. A 7. C 8. B 9. B 10. D