



## **POST COVID-19 IMMUNIZATION HERPES ZOSTER REACTIVATION IN ASIA : A LITERATURE REVIEW**

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### **ABSTRACT**

**Background:** The COVID-19 vaccine that targets viral mRNA has been created and can be used as an effort to end the COVID-19 pandemic that has hit the world since 2020. The COVID-19 vaccine currently being developed has proven its effectiveness and safety in the general adult population. **Objective:** To identify reactivation of Herpes Zoster virus post COVID-19 vaccine. **Methods:** This article review discusses four case reports of Herpes Zoster following the COVID-19 immunization in Asia which were obtained from various sources such as Pubmed Medline Embase. **Results:** The mRNA-type vaccine is associated with skin manifestations with an increased incidence (14.4%) of Herpes Zoster which was observed around 6-8 days after administration of the first dose of vaccine (BNT162b2 vaccine) and 1.5% after administration of the mRNA- 1273 which occurred in the Asian Oceanian race. COVID-19 vaccine substances such as polyethylene glycol (PEG), the polysorbate present in mRNA vaccines, and polysorbate 80 are suspected causing an allergic reactions. **Conclusion:** Health workers must be careful in administering the COVID-19 vaccine, especially to individuals who have risk factors that can decrease their immune system so it can cause reactivation of Herpes Zoster.

### **INTRODUCTION**

The global community has now entered a new era of coexistence with the COVID-19 virus, one of the viral infections whose cases were first reported from Wuhan, China's Huabei Province in 2019<sup>1</sup>. As an effort to deal with the COVID-19 pandemic, making vaccines is an option to survive and prevent death and morbidity. Currently, 56.1% of the world's population has received a complete dose of vaccine and it continues to increase every day<sup>2</sup>. To supply the needs of the wider community, researchers are trying to be able to make vaccines quickly without causing serious side effects. COVID-19 vaccines such as inactivated virus vaccines (Sinopharm's Covilo, Sinovac's CoronaVac, and Bharat Biotech's Covaxin), messenger RNA (mRNA) vaccines (Moderna's Spikevax mRNA-1273 and Pfizer-BioNTech's Comirnaty BNT162b2), adenovirus vector-based vaccines (AstraZeneca's Vaxzevria and Covishield ChAdOx1 and Johnson & Johnson-Janssen's Ad26.COV2.S), and adjuvanted protein vaccines (Novavax's Nuvaxovid and Covovax NVX-CoV2373) are vaccines that is currently widespread and being continuously developed<sup>3,4</sup>. Several cases were reported after individuals received vaccinations where side effects such as pain at the injection site, fever, weakness, headache, muscle aches, chills and diarrhea<sup>5</sup>. It has been reported that side effects of the COVID-19 vaccine can attack the skin and reactivate

the VZV virus (Varicella Zoster Virus), causing Herpes Zoster, which is a manifestation of Varicella disease<sup>6</sup>. Factors that cause reactivation of this virus include old age, stress, immunodeficiency, malignancy and immunosuppressant patients<sup>7</sup>.

### **METHODS**

This research is conducted using a literature study approach and case reports with search keywords "COVID-19", "Herpes Zoster", "COVID-19 Vaccine", "Reactivation of the Herpes Zoster virus post COVID-19 Vaccine". Articles are obtained from various sources such as Pubmed Medline Embase. The articles limited by using these keywords with the year of publication around 2019-2022, and taking place in Asia with the aim of getting relevant article sources according to current scientific developments. Thus the inclusion criteria in this study are: 1) Reviewing the literature with the keywords "COVID-19", "Herpes Zoster", "COVID-19 Vaccine", "Reactivation of the Herpes Zoster virus post COVID-19 Vaccine"; 2) review the articles that published in 2019-2022; 3) review the articles that are relevant to locations in Asia; 4) articles are available in complete manuscripts (full-text). Each phenomenon is grouped and the main issues are taken according to the aim of this research to focus the discussion until get reliable and comprehensive results.



## RESULTS

### Types of COVID-19 Vaccine

Currently, there are three main types of COVID-19 vaccines being produced and used throughout the world, those are Messenger ribonucleic acid (mRNA) vaccines, Adenoviral Vector Vaccines and Inactivated Whole Virus Vaccines. There are two types of mRNA vaccines, including BNT162b2 (Pfizer- BioNTech, New York, New York) and mRNA-1273 (Moderna, Inc., Cambridge, Massachusetts). There are 4 types of Adenoviral vector vaccines, which are ChAdOx1 nCoV-19 (AstraZeneca-Oxford), Gam-COVID-Vac (Gamaleya National Center of Epidemiology and Microbiology), Ad26.COV2.S (Janssen Pharmaceuticals, Inc.), and Ad5- nCoV (CanSinoBIO). Inactivated whole-virus vaccines have only one variant, namely BBIBP-CorV (Sinofarm) and CoronaVac (Sinovac Life Sciences)<sup>8</sup>.

One of the highlights of the mRNA-type vaccine is associated with skin manifestations with an increased incidence (14.4%) of Herpes Zoster which was observed around 6-8 days after administration of the first dose of vaccine (BNT162b2 vaccine) and 1.5% after administration of the mRNA- 1273 which occurred in the Asian Oceanian race. However, the incidence of Herpes Zoster that occurs post vaccination has mild symptom, there have been no reports of deaths<sup>9</sup>.

### Case Reports of Herpes Zoster Virus Reactivation Due to COVID-19 Vaccine Administration in Asia

The first case was reported a 74-year-old man in South Korea came to the ER with a severe headache and pain in his forehead. He also complained of swelling of the left eyelid and photophobia of the left eye. 5 days ago he was vaccinated with BNT162B2 mRNA COVID-19 in his left arm. On the day of vaccination, the patient experienced mild tenderness at the injection site. 2 days later, the patient complained of itching and tingling on the left side of the face. Day 2 after the vaccine, a vesicular skin rash appeared on the left forehead and then spread to the left side of the head, nose and left upper eyelid. History of chickenpox as a child (+), history of herpes Zoster and vaccination for the herpes Zoster virus was denied. The patient is suffering from hypertension, diabetes mellitus, and left extremity hemiplegia due

to a controlled accident and taking medication regularly.

On eye examination, ODS vision 20/32, slit lamp examination showed chemosis, hyperemesis and pseudodendritis in the peripheral cornea, the anterior chamber was calm and the posterior segment was normal. Skin abnormalities were found on the left side of the face, namely clustered vesicles, erythema and crusts.

On supporting examinations, increase in C-Reactive Protein (18.97 mg/dl) and normal white blood cell count (4,710 cells/ml) with a predominance of lymphocytes (100%), high protein levels (74.5 mg/dl) and glucose blood levels (86 mg/dl). The brain MRI examination showed no significant findings. In a lumbar puncture, Varicella Zoster virus was detected in cerebrospinal fluid by PCR method.

The patient was diagnosed with Herpes Zoster Optalmicus and meningitis. This patient was treated with intravenous acyclovir and acyclovir ointment 4x a day. Eye therapy using levofloxacin 1.5% eyedrops 4x a day. On the 3rd day at the hospital, pseudodendrite and swelling were found on the patient's eyelids, and the headache was reduced. On the 10th day, the patient was discharged from the hospital. In this case, the patient has risk factors that could reactivation of the herpes Zoster virus in addition to factors from administering the COVID-19 vaccine, that is old age, suffering from hypertension and diabetes mellitus<sup>10</sup>.

The second case was reported in Nepal, a 51-year-old man came up with complaints of a rash in the abdominal region (T8-T10) since 5 days ago. The rash is itchy and spreads to the periumbilical region. The patient also complains of a painful sensation over the entire surface of the lesion. History of fever, weakness in the upper extremities and paraesthesia was denied. The history of smoking and drinking alcohol was denied. History of herpes Zoster infection at the age of 3 years (+) without getting treatment. History of hypertension, DM, COVID-19, tuberculosis was denied. The patient received the Sinopharm BBIBP COVID-19 vaccine 5 days before the appearance of the rash.

On physical examination, it found lesions distributed in the T8-T10 dermatome spread on the right hypochondrium, epigastrium and back. The lesions are in the form of a maculopapular, vesicular, pustular rash with crusts, tenderness (+).



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The laboratory tests showed normal total and differential leukocytes, serological tests for HbsAg, HIV 1 and 2 antibodies, anti-HCV, antinuclear antibody (ANA), leptospira, salmonella and typhus were non reactive. The tentative diagnosis was Herpes Zoster confirmed by PCR examination. This patient was treated with Valacyclovir 3x1 tablet a day and mupirocin ointment. After 3-7 days from the first visit the patient has improvement.

In this case the patient did not have a history of hypertension, DM, or other chronic diseases. On serological investigations for HbsAg, HIV 1 and 2 antibodies, anti-HCV, antinuclear antibody (ANA), leptospira, salmonella and typhus had non-reactive results. The patient also did not consume alcohol, it means that causative factors of reactivation of the Herpes Zoster virus can be ruled out<sup>11</sup>.

The third case is a 68-year-old man came to a family doctor in Turkey with complaints of a burning sensation and pain that radiated from the chest to the right side of the back. The patient just got the COVID-19 vaccine about 5 days ago. The patient admitted that this was the first time he had this complaint and did not remember his history of chickenpox as a child. This patient has a history of hypertension, dysrhythmia and anxiety. Currently, the patient regularly takes the drugs rivaroxaban, alprazolam, and tianeptine. Psychological history such as stress, immunodeficiency, malignancy, and use of immunosuppressive drugs in this patient was denied.

On physical examination, the patient's vital signs were temperature 36°C, heart rate 82 x/minute, respiratory rate 18 bpm, blood pressure 130/83 mmHg, and oxygen saturation (SpO<sub>2</sub>) 99%. On the skin, several lesions were found in the form of pinheaded vesicular with a reddish base on the chest and on the right side of the back with dermatomal T3-T5. Around the erupting vesicle of lesions, the skin becomes erythematous and feels tender when it was touched.

The treatment was given 1 gram of valacyclovir, 3 times a day for 1 week, acyclovir cream, and paracetamol to reduce pain. The patient was asked to check up on the fifth day. Patients report the lesions becoming crusted, itching and increasing pain. The patient was advised to continue the current medication and use codeine for pain management. In this case, the patient has risk factors that could

reactivation of the herpes Zoster virus in addition to factors from administering the COVID-19 vaccine, those are old age, suffering from chronic diseases, such as hypertension and dysrhythmias<sup>12</sup>.

The fourth case is a 71-year-old Asian female patient who was admitted to the institutional medical ward of the Regional General Hospital in Northern Sri Lanka, with complaints of blisters and soreness on her left arm since 2 days ago. Antigen test for COVID 19 was negative on admission. The patient was recently vaccinated with the first dose of BNT162b2 mRNA COVID-19 Vaccine (Pfizer) 5 days before the onset of symptoms. The patient disclosed a history of chickenpox in her childhood and had not been vaccinated against VZV before. The patient has been suffering from diabetes and hypertension for the past 30 years with regular control and taking diabetes medications (metformin and sitagliptin). The therapy used for anti-hypertension is losartan. The patient denied any systemic or skin side effects while taking her regular medication. In addition, the patient was also diagnosed with moderate-grade adenocarcinoma of the rectum without metastases for 18 months. The patient received radiotherapy for 38 days before the onset of symptoms while awaiting anterior resection. There is no history of allergies and history of recurrent infections in the family. Further examination showed pustular vesicles with various phases on the posterolateral left arm spreading to the anterior arm, in a multi-dermal manner involving dermatomes C4, C5, C6 and T1.

Stable vital signs and systemic manifestations of varicella zoster were absent. Blood samples were taken for complete blood count (FBC), C-reactive protein (CRP), culture and fasting blood glucose sensitivity, with normal results. Negative retroviral studies. PCR test positive for VZV.

The patient was treated with oral acyclovir 800 mg five times daily for 1 week, antibiotics, topical soframycin cream, and potassium permanganate compression dressing after consulting a dermatologist. The results of the therapy were good and she was sent home for outpatient care. The next control was normal examination of T cells (CD4+, CD8+ and CD 19+) on flow cytometry and immunoglobulin (Ig)A, IgM and IgG levels 1 month after recovery. The next dose of the same vaccine is given 8 weeks after the first dose and does not cause any side effects. In this case, the patient had a history



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of chronic disease, malignancy and received chemotherapy which are risk factors for reactivation of the Herpes Zoster virus. This patient also received the first dose of the COVID-19 vaccine which further increased the reactivation of the virus<sup>13</sup>.

**Table 1.** Case of Herpes Zoster reactivation due to Covid-19 vaccine administration

Patient Identity	Post COVID-19 Vaccine	Type of Herpes Zoster	Type of COVID-19 Vaccine
Male, 74 year, South Korea	Day 5	Herpes zoster Ophthalmicus	BNT162b2 mRNA COVID-19 (Pfizer) Vaccine
Male, 51 year, Nepal	Day 5	Herpes Zoster Thoracalis	COVID-19 Sinopharm BBIBP 5 Vaccine
Male, 68 year, Turki	Day 5	Herpes zoster Thoracalis	Inactivated vaccine covid19
Female, 71 year, Sri Langka	Day 5	Herpes zoster thoracalis	BNT162b2 mRNA COVID-19 (Pfizer) Vaccine

## DISCUSSION

The Varicella Zoster Virus is a DNA virus that causes chickenpox as the main infection. After the primary infection, the virus persists latent in the posterior dorsal ganglia, cranial nerve ganglia, and autonomic nerve ganglia. Until several decades later, reactivation of the latent Varicella Zoster virus can appear and secondary infection can cause Herpes Zoster. On the skin, Herpes Zoster usually presents as a painful, itchy vesicular eruption limited to the ipsilateral dermatome<sup>14</sup>.

Factors that decrease immune systems such as HIV infection, chemotherapy, malignancy, and long-term use of corticosteroids can also increase the risk of developing Herpes Zoster<sup>15</sup>.

According to WHO, there are more than 300 types of COVID-19 vaccines being studied. However, due to very fast research time, post-immunization events (AEFI) include relatively new cases of reactivation of varicella Zoster in the form of Herpes Zoster, as discussed in the case above. However, the safety profile of recently developed vaccines is even greater<sup>16</sup>.

There were skin reactions reported during clinical trials and after general using, such as allergic reactions and urticaria, local reactions including redness or swelling at the injection site, and severe forms of allergies such as anaphylaxis, COVID arms, delayed type hypersensitivity, delayed local reactions i.e. morbilliform exanthem and erythromelalgia. VZV or Varicella Zoster is generally a mild type without causing neurological and ophthalmological side effects<sup>17</sup>. The cause of post-vaccination HZ is not known but may be related to stimulation of toll-like receptors (TLRs) 3 and 7 by mRNA vaccine and weak alloreactivity due to the existence of an inactive vaccine and the condition of Covid-19 can decrease immunity which causes lymphopenia and decrease in CD3+, CD4+, and CD8+ T cells<sup>17,18</sup>.

Another study by Mina et al stated that COVID-19 produces an immunosuppressive condition due to functional impairment and a concomitant decrease the number of T lymphocytes, especially CD4+ T cells, CD8+ T cells, and NK cells, which can also be associated with an increased susceptibility to reactivation of Herpes Zoster in COVID-19 patients<sup>19</sup>.

VZV reactivation is the failure of the T cell compartment to maintain the body's immunity. It can also be influenced by the old age factor. On the other hand, vaccines greatly stimulate the immune system and increase T cell response. In healthy adults, vaccination with BNT162b2 induces humoral and cellular adaptive immunity. Seven days after the booster dose, a strong cellular response with spike-specific CD8+ T cells and type 1 (Th1) CD4+ helper T cells developed with a high fraction of those producing interferon- $\gamma$  (IFN $\gamma$ ), a cytokine responsible for some antiviral responses. The magnitude of S-specific CD4+ T cell response was positively correlated with S1-binding IgG and also with the strength of S-specific CD8+ T-cell response, which is also positively correlated with S1-binding IgG. In addition, the SARS-CoV-2 mRNA-1273 vaccine induce a strong CD4 cytokine response involving type 1 T helper cells among participants older than 55 years<sup>20,21</sup>.

It should be noted that other neurological disorders have been reported after the COVID-19 vaccination injection, such as facial nerve paralysis. The mechanism involving Type I interferon may be related to HZ infection as a trigger for facial paralysis.



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Among the substances present in the COVID-19 vaccine are polyethylene glycol (PEG), the polysorbate present in mRNA vaccines, and polysorbate 80, which is found in the adenoviral vector vaccines ChAdOx1 nCoV-19 (AstraZeneca-Oxford) and Ad26.COV2.S (Janssen Pharmaceutical Companies), are suspected substances causing an allergic reactions<sup>22,23,24</sup>.

Other types of vaccines such as astrazeneca compared to the sputnik vaccine which is derived from adenoviral vector vaccines according to existing studies have been reported to cause focal erythema on the skin, like induration (18.7%), local pain (25.9%), Herpes Zoster (88.0%). It has been reported in the Iranian population that the incidence of Herpes zoster is 0.3% more than sputnik vaccine incidence. While vaccines that are made from weakened viruses, namely Sinofarm, the incidence of focal erythema was 6.9% at the injection site, urticaria (2.5%), angioedema (0.5%), herpes zoster (0.5%) and erythema multiforme like eruption (0.5%). According to Preta, et al it was explained that the incidence of Herpes Zoster in the first dose of vaccination was 14.4% more than the second dose of vaccine which was 8.5% in patients receiving mRNA-type vaccines<sup>24,25</sup>.

## CONCLUSION

Based on the results, the development of COVID-19 vaccine which is declared safe, it turns out that there are side effects, which one is reactivation of the Varicella Zoster Virus that causes Herpes Zoster disease, especially in individuals who have risk factors that decrease the immune system. The various reports regarding skin manifestations due to the COVID 19 vaccine, it is better for health workers to provide more complete education in selecting vaccines for patients, carry out further tests before administering the first or second dose of vaccine, and monitoring after vaccination to minimize side effects.

## ETHICAL APPROVAL

There is no ethical approval.

## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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## AUTHOR CONTRIBUTIONS

The author contributions to this review are as follows : conceptualization, collecting literature and writing draft : Danisa Diandra and Nurul Nisa Ulfa ; supervision, review and editing : Puguh Riyanto.

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