
- Introduction to herpesviruses
- Herpes simplex viruses 1 and 2
- Types of viruses
- Herpesvirus virion
- Hsv-1 genome organization
- Transcription and translation
- Genome Replication
- Assembly and exit of virions from the cell
- HSV-1 replication cycle
- Latent herpesvirus infection
INTRODUCTION TO HERPESVIRUSES

• **Herpesviruses** - name from Greek word *herpein* – to creep.
• More than 100 **herpesviruses** have been isolated from a range of hosts that includes mammals, birds, cold-blooded animals.
• Eight of these viruses are **human viruses**.
• **Characteristics**: when they infected a host, they often remain as persistent infections for the lifetime of the host.
HERPES SIMPLEX VIRUSES 1 AND 2

- (HSV-1 and HSV-2) infect epithelial cells of the oral or genital mucosa, the skin or the cornea.
- The virus may enter neurons and may be transported to their nuclei, where they may establish latent infections.
- HSV-1 commonly infects via lips or nose between the ages of 6 and 18 months.
- HSV-2 is the usual causative agent of genital herpes, which is a sexually transmitted disease.
- In newborn babies infection can result in serious disease, with a mortality rate of about 54%
Varicella Zoster Virus
- occurs in childhood and causes varicella (chickenpox), when the virus spreads through the blood to the skin, causing a rash.
- It may also spread to nerve cells, where it may establish a latent infection.

Epstein-Barr virus (EBV)
- transmitted in saliva.
First infected are Epithelial cells and then it spreads to B cells, which are the main host cell type for this virus.
- More than 90 % of people become infected with EBV, usually during the first years of life, when infection results in few or no symptoms.

Human cytomegalovirus
- symptoms are either absent or they are mild.
In a pregnant woman virus can infect the placenta and then the fetus
Human herpesvirus 6
There are two types of human herpesvirus 6: HHV-6A and HHV-6B. Infection of a child with the latter can cause a fever and the sudden appearance of a rash.

Human herpesvirus 7
was first isolated from a culture of CD4 T cells that developed a cytopathic effect. The virus has been associated with some cases of rash also.

Kaposi’s sarcoma-associated herpesvirus
- was discovered in 1994 and is named after the tumor with which the virus is associated.
THE HERPESVIRUS VIRION

Virions composed of a large number of protein species organized into three distinct structures: capsid, tegument and envelope.

Genome is linear dsDNA molecule.

The DNA is housed in the capsid, and the capsid is surrounded by the tegument.

The HSV-1 tegument contains 15 protein species and some virus mRNA molecules.

Envelope contains a large number of spikes.
- The capsid is constructed from **162 capsomeres**, 12 of which are **pentons** and the remainder of which are **hexons**.

- In HSV-1 the capsomeres are constructed from VP5: a penton is made from five molecules of VP5 and a hexon from six molecules.
HSV-1 GENOME ORGANIZATION

- The genome consists of two unique sequences each flanked by repeat sequences. Not of equal length: the longer is designated UL and the shorter is designated US. The HSV-1 genome encodes at least 74 proteins plus some RNAs that are not translated.
- Both strands of the DNA are used for coding. Replication cycle of this virus has been studied in cell cultures from a number of species, including humans, monkeys, mice and dogs.

![Diagram of HSV-1 genome organization]

Key:
- U: unique sequence
- R: repeat sequence
- L: long
- S: short
- T: terminal
- I: inverted
Herpesvirus genes are expressed in three phases: immediate early (IE), early (E) and late (L)

IE genes are activated by VP16 (major tegument protein)

VP16 binds to complex of cell proteins including Oct-1

Oct-1 binds to specific promoter sequence
VP16 acts as a transcription factor to recruit the host RNA pol II

There are five IE proteins (transcription factors) involved in switching on E and L genes

E proteins have roles in virus DNA replication

Most of the L proteins are virus structural proteins
GENOME REPLICATION

Virus DNA is replicated by E proteins

Origin-binding protein binds to the replication initiation site of virus DNA

Origin-binding proteins have helicase activity
Double helix is prevented from re-forming by binding of copies of ssDNA-binding protein

After primer addition by primase, DNA pol starts to synthesize the leading and lagging strands of DNA
Assembly and exit of virions from the cell

1. Budding through inner membrane, giving the nucleocapsid temporary envelope
2. Fusion of temporary envelope with outer membrane, releasing the nucleocapsid into cytoplasm
3. Acquisition of VP16 and other components of tegument
4. Acquisition of virion envelope by budding into a vesicle
5. Fusion of vesicle membrane with plasma membrane, releasing the virion from the cell
HSV-1 replication cycle

- Attachment
- Entry
- Transcription
- Translation
- Genome replication
- Assembly
- Exit
Latent herpesvirus infection

- Genome is switched off, but few regions are transcribed and few RNAs are synthesized.

- No virus proteins are required to maintain latency.

- Synthesized virus RNAs are known as latency-associated transcripts (LATs).

- LATs are important for ensuring the survival of neurone with HSV-1 infection by inhibiting the apoptosis.
RESEARCH ARTICLE

Safety of live attenuated varicella-zoster vaccine in patients with underlying illnesses compared with healthy adults: a prospective cohort study
Content
Research article: “Safety of live attenuated varicella-zoster vaccine in patients with underlying illnesses compared with healthy adults: a prospective cohort study”

- Introductions (Abbreviations & Keywords)
- Background
- Methods
- Vaccination
- Safety assessment
- Statistical Analysis
- Results: Study Population
# Introduction

## Abbreviations
- **AE**: Adverse event
- **CI**: Confidence interval
- **HZ**: Herpes zoster
- **OR**: Odds ratio
- **PHN**: Post-herpetic neuralgia
- **SAE**: Severe adverse event
- **SD**: Standard deviation
- **VZV**: Varicella-zoster virus

## Keywords:
- Autoimmune diseases
- Diabetes Mellitus
- Herpes Zoster
- Malignancy
- Reactogenicity
- Renal diseases
- Safety
- Varicella-zoster vaccine
Background

**Herpes Zoster** or **Shingles** is one of the important diseases that can decrease quality of life.

- Caused by reactivation of varicella-zoster virus characterized as radicular pain and rash.
- Complication of disease is post-herpetic neuralgia PHN described as intolerable pain.
- Research is done because of increasing occurrence of HZ in Japan.
- Every **10.2/1000 persons**
- Study is focused on adults aged 50 and more years old with particular underlying illnesses which are reported to be high risk conditions for HZ.
Methods
Setting and study subjects

Study included healthy adults and patients with malignancy, diabetes mellitus, autoimmune diseases or chronic renal diseases.

1500 subjects (300 patients and 1200 healthy adults) were examined.

Study was run between November 2016 and November 2017.

Patients were Japanese adults older than 50.
Patients with **malignancy** included those with malignant solid tumor

Excluded patients:

Those who received chemotherapy within preceding 6 months

Those with acute lymphocytic leukemia

Those with a negative result on the delayed skin hypersensitivity test
Inclusion criteria for diabetes mellitus patients were:

Those diagnosed with diabetes mellitus

Those without diabetic neuropathy, retinopathy or nephropathy

Those whose diabetes was not caused by side effects of immunosuppressants

Those who didn’t receive cortical hormones
Patients with **autoimmune diseases** included those rheumatoid arthritis, collagen diseases etc.

Excluded patients were those who received cortical hormones, immunosuppressants or biologic agents within the preceding 6 months.
Patients with **chronic renal diseases** were regarded as those with findings compatible with renal disease on urine-alysis

Patients receiving cortical hormones or immunosuppressant were excluded
Vaccination

Injection of 0.5 mL of live attenuated varicella virus vaccine

Manufactured by The Research Foundation for Microbial Diseases of Osaka University

This vaccine is called varicella-zoster vaccine
Safety assessment

All subjects were carefully observed for signs of any reactions for 30 min after vaccination.

They maintained a daily log of body temperature, symptoms related to the injection-site, systemic symptoms, any medications and hospitalization during the 28 days after vaccination.
Statistical analysis

Safety measures included proportions of subjects with any adverse events (AEs), severe AEs (SAEs) and vaccine-related AEs.

Frequencies and 95% confidence intervals (CIs) of AEs were calculated.

Stratified groups were formed.
Results

In Figure 1 is shown that during this study 1201 healthy adults and 300 patients with underlying illnesses were enrolled.

(49 malignancies, 180 diabetes mellitus, 10 autoimmune diseases, 61 renal diseases)

- 1 healthy adult refuse to participate, so in the end they have 1200 healthy patients and 300 with underlying illnesses.
Results

- half of healthy adults were **males**
- age was approx. around 62 years; older patients were with underlying illnesses
- patients with malignancy had higher rate of HZ history and VZV vaccination than healthy adults

**Table 1** Baseline characteristics of the study subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy adults (N = 1200)</th>
<th>Patients with underlying illnesses (N = 300)</th>
<th>Patients with malignancy (N = 49)</th>
<th>Patients with diabetes mellitus (N = 180)</th>
<th>Patients with autoimmune diseases (N = 10)</th>
<th>Patients with chronic renal diseases (N = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 607 (51%)</td>
<td>188 (63%)*</td>
<td>26 (53%)</td>
<td>120 (67%)*</td>
<td>2 (20%)**</td>
<td>40 (66%)*</td>
</tr>
<tr>
<td>Age (y)</td>
<td>Mean ± SD 62.0 ± 8.0</td>
<td>66.0 ± 8.0</td>
<td>71.0 ± 9.0*</td>
<td>65.0 ± 8.0*</td>
<td>61.0 ± 7.0</td>
<td>69.0 ± 8.0*</td>
</tr>
<tr>
<td>50–59</td>
<td>530 (44%)</td>
<td>63 (21%)*</td>
<td>3 (6%)*</td>
<td>46 (26%)*</td>
<td>4 (40%)</td>
<td>10 (16%)*</td>
</tr>
<tr>
<td>60–69</td>
<td>425 (35%)</td>
<td>129 (43%)</td>
<td>21 (43%)</td>
<td>80 (44%)</td>
<td>4 (40%)</td>
<td>24 (39%)</td>
</tr>
<tr>
<td>70+</td>
<td>245 (20%)</td>
<td>108 (36%)</td>
<td>25 (51%)</td>
<td>54 (30%)</td>
<td>2 (20%)</td>
<td>27 (44%)</td>
</tr>
<tr>
<td>History of HZ</td>
<td>Present 155 (13%)</td>
<td>49 (16%)</td>
<td>11 (22%)*</td>
<td>28 (16%)</td>
<td>1 (10%)</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Previous vaccination</td>
<td>Present 3 (0.3%)</td>
<td>3 (1%)*</td>
<td>2 (4%)*</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>White blood cells (µL)</td>
<td>Mean ± SD 6289 ± 1685</td>
<td>5386 ± 1223</td>
<td>7.0 ± 1.0</td>
<td>6100 ± 520</td>
<td>5980 ± 1430</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>Mean ± SD</td>
<td>–</td>
<td>–</td>
<td>8.0 ± 7.0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes mellitus (y)</td>
<td>Mean ± SD</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>Mean ± SD</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.99 ± 0.15</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>Mean ± SD</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>53 ± 4</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Present</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) unless otherwise indicated

HZ: Herpes zoster, SD: Standard deviation

*P < 0.05, **P < 0.1 (compared with the proportion of subjects among healthy adults)
<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Healthy adults (N=1200)</th>
<th>Patients with underlying illnesses (N=300)</th>
<th>Patients with malignancy (N=65)</th>
<th>Patients with diabetes mellitus (N=180)</th>
<th>Patients with autoimmune diseases (N=10)</th>
<th>Patients with chronic renal diseases (N=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of events</td>
<td>No. of subjects (%) (95% CI)</td>
<td>No. of events</td>
<td>No. of subjects (%) (95% CI)</td>
<td>No. of events</td>
<td>No. of subjects (%) (95% CI)</td>
</tr>
<tr>
<td>Any AEs</td>
<td>1623</td>
<td>603 (50%) (47-53%)</td>
<td>395</td>
<td>146 (49%) (43-54%)</td>
<td>54</td>
<td>25 (51%) (36-56%)</td>
</tr>
<tr>
<td>SAEs</td>
<td>2</td>
<td>2 (0.2%) (0-1%)</td>
<td></td>
<td></td>
<td>0</td>
<td>0 (0%) (0-3%)</td>
</tr>
<tr>
<td>Vaccine-related AEs</td>
<td>1362</td>
<td>509 (42%) (40-45%)</td>
<td>328</td>
<td>125 (42%) (36-47%)</td>
<td>44</td>
<td>20 (41%) (27-56%)</td>
</tr>
<tr>
<td>Injection-site AEs</td>
<td>1306</td>
<td>491 (41%) (38-44%)</td>
<td>314</td>
<td>118 (39%) (34-45%)</td>
<td>41</td>
<td>18 (37%) (23-52%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>405</td>
<td>405 (34%) (26-37%)</td>
<td>94</td>
<td>94 (31%) (26-37%)</td>
<td>14</td>
<td>14 (29%) (17-43%)</td>
</tr>
<tr>
<td>Itching</td>
<td>244</td>
<td>243 (20%) (18-23%)</td>
<td>60</td>
<td>59 (20%) (15-25%)</td>
<td>8</td>
<td>8 (16%) (7-30%)</td>
</tr>
<tr>
<td>Swelling</td>
<td>179</td>
<td>179 (15%) (13-17%)</td>
<td>47</td>
<td>47 (16%) (12-20%)</td>
<td>9</td>
<td>9 (18%) (9-32%)</td>
</tr>
<tr>
<td>Pain</td>
<td>183</td>
<td>182 (15%) (12-17%)</td>
<td>41</td>
<td>41 (14%) (10-18%)</td>
<td>3</td>
<td>3 (6%) (1-17%)**</td>
</tr>
<tr>
<td>Warmth</td>
<td>170</td>
<td>170 (14%) (12-16%)</td>
<td>36</td>
<td>36 (12%) (9-16%)</td>
<td>5</td>
<td>5 (10%) (3-22%)</td>
</tr>
<tr>
<td>Induration</td>
<td>124</td>
<td>124 (10%) (9-12%)</td>
<td>36</td>
<td>36 (12%) (9-16%)</td>
<td>2</td>
<td>2 (4%) (0.5-14%)**</td>
</tr>
<tr>
<td>Eruption</td>
<td>1</td>
<td>1 (0.1%) (0-0.5%)</td>
<td>0</td>
<td>0 (0%) (0-0%)</td>
<td>0</td>
<td>0 (0%) (0-0%)</td>
</tr>
<tr>
<td>Systemic AEs</td>
<td>56</td>
<td>46 (4%) (3-5%)</td>
<td>14</td>
<td>11 (4%) (2-6%)</td>
<td>3</td>
<td>2 (4%) (0.5-14%)**</td>
</tr>
<tr>
<td>Fever</td>
<td>6</td>
<td>5 (0.4%) (0.1-1.0%)</td>
<td>5</td>
<td>5 (2%) (0.5-4)%</td>
<td>2</td>
<td>2 (4%) (0.5-14%)*</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>8 (0.7%) (0.3-1.0%)</td>
<td>2</td>
<td>2 (0.7%) (0.1-2.0%)</td>
<td>0</td>
<td>0 (0%) (0-0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>5 (0.4%) (0.1-1.0%)</td>
<td>3</td>
<td>3 (1%) (0.2-3.0%)</td>
<td>1</td>
<td>1 (2%) (0.1-11%)</td>
</tr>
<tr>
<td>Rash</td>
<td>18</td>
<td>17 (1%) (0.8-2.0%)</td>
<td>1</td>
<td>1 (0.3%) (0.008-2.08)</td>
<td>0</td>
<td>0 (0%) (0-0%)</td>
</tr>
<tr>
<td>Others</td>
<td>19</td>
<td>17 (1%) (0.8-3%)</td>
<td>3</td>
<td>3 (1%) (0.2-3%)</td>
<td>0</td>
<td>0 (0%) (0-0%)</td>
</tr>
</tbody>
</table>

AE: Adverse event, CI: Confidence interval, SAE: Severe adverse event

*P < 0.05, **P < 0.1 (compared with the proportion of subjects among healthy adults)
Safety assesment according to history of HZ

- Among healthy adults those with reported history with HZ had injection-site AEs compared to patients without history of HZ (53% vs 39%)

- only erythema was significantly more common in those who got HZ history than those without it (43% vs 32%)

- no significant differences were observed among healthy patients and those with underlying illnesses
Discussion

No vaccine-related SAEs were observed

Most AEs were similar between healthy adults and patients with underlying illnesses

Fever was significantly higher in patients than in healthy adults

Patients with diabetes are considered to have a high risk for herpes zoster (HZ)

Benefit of receiving a live attenuated varicella-zoster vaccine to prevent HZ exceeds the safety concerns among diabetes patients
Patients with chronic renal diseases are also considered to have a high risk for HZ injection-site adverse events (AEs) were reported more often from patients with lower creatinine levels (mild disease).
Conclusion

Vaccination is highly valuable for patients with underlying illnesses

Study confirmed the safety of freeze-dried live attenuated varicella-zoster vaccine

Results of this study will be useful when providing vaccines to patients