Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 “KMB” Vaccination Procedure Guideline

English Ver. 1.0

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1. Before vaccination

Vaccination Availability
Persons at risk of exposure to Mpox Certain medical personnel who are expected to be in charge of hospitalized patients with Mpox, laboratory personnel who are expected to be involved in testing for Mpox at regional health laboratories, public health workers who are expected to be in contact with patients with Mpox during transport, and during epidemiological surveys. *1) Persons who have been in close contact with a person who has been diagnosed with Mpox within 14 days. *2 1 Refer to https://www.mhlw.go.jp/content/10906000/000971358.pdf for more information on Mpox. 2 According to the guidance issued by the WHO Guidance on Vaccines and Immunization for Mpox recommends that within 4 days of exposure to the Mpox virus (within 14 days if no symptoms are present), an appropriate second or third-generation pox vaccine should be administered.
Precautions when in contact with persons eligible for vaccination
Healthcare workers should be checked for signs and symptoms of suspected Mpox infection when they inoculated dry cell culture varicella vaccine LC16 "KMB" in persons who have been in close contact with those diagnosed with Mpox within 14 days. If the onset of Mpox is suspected, post-exposure prophylaxis should not be administered, and the priority is to diagnose Mpox. In addition, if the person is not adequately evaluated to be diagnosed, treat the person following the same infection control measures of patients with Mpox.
Persons for whom it is not appropriate to receive immunisation
(1) Persons with high fever (2) Persons suffering from a serious acute illness (3) Persons who have a history of anaphylaxis caused by an ingredient of the vaccine (4) Patients who have a disease with clearly abnormal immune function or who are receiving immunosuppressive treatment (e.g., those who are taking adrenocortical steroids or immunosuppressive drugs and those who have received other live vaccines within 27 days). (Refer to the "Interactions" section of the package insert.) (5) Patients who are known to be pregnant (6) Persons suffering from a proliferative skin disease that may be impaired by inoculation with a vaccinia. (7) In addition to those listed above, persons with conditions that make it inappropriate to administer vaccinations.
Drug
・Freeze-dried Smallpox Vaccine Prepared in Cell Culture LC16 “KMB” ・Provided diluent (water for injection with 20 vol% glycerin)

・Sterilized bifurcated needle
・Sterilized syringe (for a total volume of 0.5 mL to dissolve the vaccine)
・Sterilized injection needle (for a total volume of 0.5 mL to dissolve the vaccine)
・ Alcohol swabs
・Sharp Disposal Containers
・Disposal container for medical waste
・Medication tray
・Light-shielding cover for medication
・PPE as needed
・Vaccination of target persons before exposure: follow standard precautions
・Vaccination of target persons post-exposure: gown, face shield, gloves, and N95 mask (for protection against aerosols if necessary)
・Equipment to respond to emergencies (emergency crash cart)

Precautions for vaccination (excerpt from the package insert)

① Persons in whom vaccination requires caution

(Persons in whom caution should be exercised when determining vaccination)

When any of the following apply to the person to be inoculated, careful medical examination and determination of the advisability of vaccination should be performed considering the person's health status and constitution.

Vaccination should be performed after providing a thorough explanation of the importance of preventive vaccination, side effects and usefulness, and obtaining consent reliably.

1) Persons with a history of hypersensitivity, such as shock and anaphylaxis (hives, respiratory distress, lip edema, and laryngeal edema), to foods and drugs containing gelatin.
2) Persons with underlying illnesses such as cardiovascular disease, kidney disease, liver disease, blood disease, and developmental disorders.
3) Persons who have exhibited fever within 2 days of vaccination with a preventive vaccine and those with symptoms suggestive of allergy, such as generalized exanthem.
4) Persons with a history of convulsive
5) Persons with a prior diagnosis of immunodeficiency and those who have a close relative with congenital immunodeficiency
6) Persons who might be allergic to the ingredients used in this drug.

② Important basic precautions

This drug is to be used following the Japanese "Immunization Act" and the "main points for the implementation of routine vaccination."

1) The health status of the person to be vaccinated must be investigated before vaccination by recording the person's medical history and body temperature and performing a medical examination (visual examination and auscultation)
2) This drug contains gelatin derived from a stock solution (≤ 0.15 w/v%). It has been reported that the administration of vaccines containing gelatin can cause hypersensitivity reactions, such as shock and anaphylaxis (hives, respiratory distress, lip edema, and laryngeal edema, among others). Therefore, the person's medical history should be thoroughly recorded and reviewed, and careful observation should be performed after vaccination
3) This drug contains streptomycin as an additive. Therefore, hypersensitivity may occur in persons with sensitivity to streptomycin. After vaccination, the patient should be carefully observed, and if symptoms appear, appropriate treatment

should be administered

4) The person receiving the vaccine and/or their guardian is to be informed in advance to avoid excessive exercise on the day of vaccination, to keep the vaccination site clean, and to pay attention to monitor their health after vaccination, and if abnormal localized reactions or changes to one's condition occur, or if abnormal symptoms manifest such as high fever, convulsive, and serious skin symptoms, they are to consult their physician without delay.

③ Interactions

1) Contraindicated concurrent use (do not use in combination)

Drug name	Clinical symptoms and treatment methods	Mechanism and risk factors
Adrenocorticosteroids such as prednisolone Immunosuppressants Cyclosporin (Sandimmun) Tacrolimus (Prograf) Azathioprine (Imuran)	Administration of this vaccine can cause the appearance of smallpox-like symptoms as a result of the mechanism noted on the right, and thus should not be given.	Administration of this drug in immunosuppressed persons can intensify and cause a continuation of infection by the vaccine virus. Persons who were administered treatment through drugs with an immunosuppressive action, receiving long-term or high-dose treatment, and those who have discontinued treatment within less than 6 months have reduced immune function.

2) Drugs with concurrent use (caution should be exercised with concurrent use)

Reaction with other vaccines: interference from other live vaccines (oral live polio, measles, rubella, mumps vaccine, chickenpox, BCG, and yellow fever) might prevent the virus of this drug from proliferating and prevent immunity from being obtained. Thus, persons receiving other live vaccines should usually be administered after at least 27 days.

Side effects

① Serious side effects

1) Shock, anaphylaxis (both incidences unknown)

Shock and anaphylaxis (hives, respiratory distress, lip edema, and laryngeal edema) can occur. Therefore, the patient should be placed under careful observation after vaccination, and if an abnormality is observed, appropriate treatment should be administered.

2) Convulsions (< 0.1 %):

Febrile convulsions can occur. If an abnormality is observed, appropriate treatment should be administered.

② Other side effects (incidence unknown)

In addition to localized reactions at the inoculation site, systemic reactions that can occur for approximately 10 days after vaccination include fever, rash, and swelling of the axillary lymph nodes. Furthermore, allergic dermatitis and erythema multiforme have been reported.

③ Symptoms observed in clinical trials

Children (data at the time of vaccination of approximately 50,000 children since 1974)

Febrile seizure in 3 cases, eczema vaccinatum in 1 case, autoinoculation (blisters caused by virus inoculation from the inoculation site to another site caused by the hand.) in 9 cases, vaccinia (blisters and abscesses observed near the inoculation area) in 28 cases, and vaccinal eruption (allergic eczema appearing in various forms such as hives and erythema observed from approximately day 7–10 after vaccination) in 8 cases.

Adults (data at the time of vaccination of approximately 268 adults since 2005)

Lymph node edema in 19.4%, vaccination site erythema in 5.2%, fever in 1.5%, malaise in 0.7%, post-vaccine complications (causing satellite lesions/rash other than in the vaccination site) in 0.7%, vaccination site swelling in 0.4 %, and post-vaccination autoinoculation (suspected ectopic inoculation) in 0.4 %.

Adults (refer to data at the time of vaccination of 3,221 adults from 2002 to 2005, JAMA. 2009;301(10):1025-1033)

Among the 3,221, monitoring was performed on 1,066 patients, and adverse events were reported in 148.

Lymph node swelling in 96 patients, fever (> 37.5 °C) in 21, itching and hives in 7, flu-like symptoms in 6, headache in 5, muscular pain of the neck, check, and upper limbs in 4, cervical lymph node swelling in 3, diarrhea in 2, acute neurosensory deafness in 1, dizziness in 1, peri-orbital swelling in 1, and joint pain in 1.

Vaccination of pregnant, parturient, and lactating women

Pregnant women should not be inoculated with this vaccine. Potentially childbearing women are recommended to be inoculated after taking contraception for approximately 1 month. In addition, women should pay attention to prevent pregnancy for approximately 2 months after inoculation. Lactating women decide on continuing or discontinuing breastfeeding after considering the benefits of preventive vaccination and the benefits of breastfeeding.

Important points when handling the vaccine

① Storage

1) Store at a temperature between −35 °C and −20 °C. Avoid storage below −35 °C as it could cause the rubber stopper to deteriorate and become damaged.

2) The vaccine virus is weakened by sunlight and is rapidly inactivated. Thus, exercise caution to keep away from light regardless of before or after dissolving.

3) Freezing the diluent can damage the container.

② Storage method

Store away from the light below −20 °C.

③ Before vaccination

When dissolving, examine the contents well, and do not use if sedimentation, contamination with foreign substances, and other abnormalities are observed.

④ At the time of vaccination

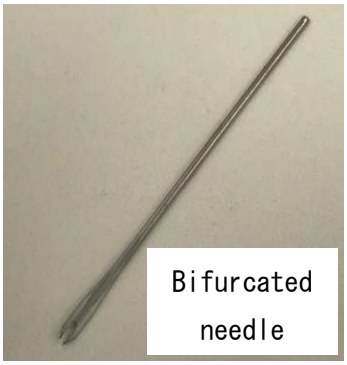
1) Dissolve the vaccine in the diluent immediately before vaccination, and use the vaccine immediately once it has been dissolved

2) The vaccine does not contain thimerosal (preservative) as an additive. Therefore, once the stopper has been removed, the liquid remaining in the vial must be disposed. Avoid storing and using it for the second time.

3) After mixing with the diluent, doses of the vaccine solution for ≥ 50 persons can be collected with the special bifurcated needle.

2. At vaccination

Vaccination equipment



For vaccination, a sterilized bifurcated needle is usually used.
The vaccination needle must be changed for each person to be inoculated.

The flow up to vaccination completion (※refer to the package insert as needed)

1 Preparing vaccine

Dissolve the vaccine in the diluent just before vaccination, and use it immediately once it has dissolved.

1) Remove the plastic cap from the freeze-dried vial and the diluent vial. Disinfect the container stopper and around the stopper using alcohol.
2) Draw 0.5 mL of the diluent using a syringe through the rubber stopper from the diluent vial, and transfer it to the freeze-dried vial.
3) Dissolve well, and after confirming the contents, remove the aluminum cap (with split structure) and the rubber stopper.

2 Drugs of the vaccination site

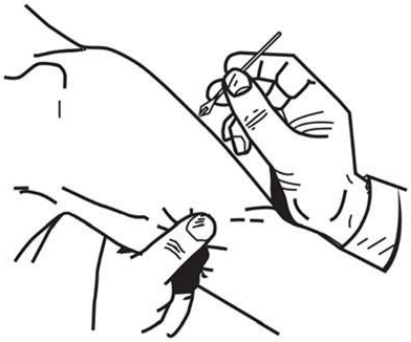
As a rule, the vaccination site is the lateral upper arm at the origin of the triceps brachii muscle, which is disinfected with an alcohol swab that has been firmly wrung and left to dry (to avoid virus inactivation at the time of vaccination).

3 Vaccination

Soak the tip of the bifurcated needle (bifurcated side) in the vial with the dissolved vaccine.

Check that the tip of the bifurcated needle holds the vaccine solution, and administer the vaccine using the multiple puncture technique.

1)The inoculator holds the bifurcated needle in the dominant hand and holds the arm from the back of the inoculation site with the other hand. At this time, the skin at the vaccination site can be slightly stretched. (see image below)



2) The wrist of the hand holding the needle is placed on the skin of the individual being vaccinated, and the needle is held perpendicular to the skin.

3) The bifurcated needle is moved to press lightly on the skin, and vaccination is administered in an area of approximately 5 mm (slight bleeding can occur to the extent of oozing). Aim to press 15 times.

4) The vaccination area extends approximately 5 mm in diameter on the lateral upper arm at the origin of the triceps brachii muscle.

5) When using another bifurcated needle, the puncture should be made paying due care to the precautions for using such bifurcated needles.

6) Residual vaccine solution in the vaccination site is to be wiped away with a firmly wrung alcohol swab after 1 to 3 minutes.

Post-vaccination observation

After vaccination, persons who receive the vaccination need to remain in an appointed area and be observed for 30 minutes.

Management of the vaccination site after returning home (guidance for persons who are vaccinated)
※ refer to the separate document

Persons are instructed to avoid bathing, drinking alcohol, performing strenuous exercise on the day of receiving the vaccination, and avoiding touching the vaccination site until the following day. Instruct persons to avoid touching blisters and scabs if they form at the vaccination site on the day following vaccination and to apply gauze or the like as needed. Instruct persons that if they touch the vaccination site directly with their fingers, they should avoid touching others with that hand and wash their fingers well. Instruct persons to pay due care to avoid touching other persons at the vaccination site.
Inform persons that they should avoid becoming pregnant for 2 months after vaccination and that they cannot donate blood for 2 months after vaccination.

Other precautions

Following vaccination overseas with a live vaccine (injectable drug) using a different vaccinia virus strain to this drug, horizontal transmission of the vaccinated person to a nonvaccinated person has been reported. Avoid directly touching the vaccination site, and if touched, wash the fingers well.

About materials following vaccination

Once the stopper has been removed, any remaining liquid in the vial is not to be stored for use for the next vaccination and should be immediately discarded.
※ For disposal methods, refer to the item regarding disposal methods for materials used at the time of vaccination in Section 4. Other precautions

3. Confirmation of take

What is take?

Take is defined by the appearance of the state indicating that immunity has been obtained that can be traced to the vaccination (a state when it is confirmed that there is a localized inflammatory response at the vaccination site, such as redness, swelling, the sensation of heat, induration, and blisters).

Confirmation method

A physical examination will be performed between 10 and 14 days after inoculation, to confirm take.

4. Other precautions

Disposal for materials used for vaccination

Materials used for vaccination are infectious and should be disposed appropriately.

Separate document: Information sheet for persons being vaccinated (pre-exposure)

To persons receiving the smallpox vaccine,

We would like to inform you of a few important matters about receiving the smallpox vaccine.
Please read and make sure you understand the following.

I. Smallpox vaccine

The smallpox vaccine is a live attenuated vaccine of the same vaccinia virus strain used against Mpox. It has been reported to prevent onset at a rate of at least 85 % by vaccination with the smallpox vaccine before exposure to the Mpox virus. The WHO also recommends that medical workers at risk of exposure receive this preventive vaccination. On 2 August 2022, the freeze-dried smallpox vaccine prepared in cell culture LC16 “KMB” was approved for an additional indication of prevention against Mpox.

II. Persons who are unsuited to receive preventive vaccination

As a rule, the following persons cannot receive the smallpox vaccine. For more details, please consult your physician.

1. Persons who have had anaphylaxis caused by an ingredient of this drug
2. Persons presenting high fever
3. Persons who have suffered a serious acute illness
4. Persons with illness presenting with clear abnormality in immune function and those receiving treatment that can cause immunosuppression
5. Persons who are pregnant or who might be pregnant
6. Persons with contagious skin disease and those who might develop disorders as a result of the preventive vaccine
7. In addition to the individual listed above, those whose condition makes them unsuitable to receive preventive vaccination and women who are presently breastfeeding are to please consult their physician at the time of medical history taking about vaccination.

III. Vaccination method

The vaccine is to be administered using a special needle for smallpox vaccine and pressed lightly 15 times on your skin. Bleeding can occur to the extent of oozing. Disinfect before vaccination using an alcohol cotton swab, and administer the vaccine once it has fully dried (for prevention of the inactivation of the vaccine).
After vaccination, the residual vaccine solution in the vaccination site is to be wiped away with a firmly wrung alcohol swab after 1–3 minutes (for the prevention of autoinoculation and details, refer to side effects below).
The vaccination site does not need to be covered with gauze. However, if changes such as redness, blisters, and scabbing, among others, appear at the vaccination site after vaccination, cover it with gauze, as needed, and take care so as avoid directly touching it.

IV. Precautions following vaccination

Persons should avoid bathing, drinking alcohol, performing strenuous exercise on the day of receiving the vaccination, and touching the vaccination site up to the following day. On the day following vaccination and thereafter, blisters and scabs can appear, and in such instances, please do not touch with the hands, and cover with gauze, as needed. In the event of touching, wash your hands thoroughly.

If the vaccination site is touched directly with the fingers, do not touch other people with that hand. Take care so that the vaccination site does not touch other people directly.
Please do not attempt to conceive or become pregnant for 2 months after vaccination. Furthermore, we ask your comprehension to refuse to donate blood for 2 months after vaccination.
The state indicating that immunity has been obtained that can be traced to the vaccination (a state when it is confirmed that there is a localized inflammatory response at the vaccination site, such as redness, swelling, a sensation of heat, induration, and blisters, among others) is to be verified 10 to 14 days after vaccination.

V. Side effects

Although the onset of serious side effects of the smallpox vaccine is rare, on rare occasions, the following side effects can occur:
Anticipated serious side effects
Shock and anaphylaxis (both incidences unknown), and febrile seizure (< 0.1%)
Other side effects
In addition to inflammatory reaction at the inoculation site, systemic reactions up to 10 days after vaccination, which include fever, swelling of the axillary lymph nodes, malaise, itchiness, hives, headache, muscle-pain-like pain, and autoinoculation (blisters caused by virus inoculation from the inoculation site to another site by the hand, among others), vaccinia (the appearance of blisters and abscess near the vaccination site), and vaccinia (allergic eczema appearing in a hive or erythema-like form seen from approximately 7 to 10 days after vaccination) can occur.

For any queries, please contact us below.

Medical institution name: xxxxx
Contact: xxxx

Separate document: Information sheet for persons being vaccinated (post-exposure)

To persons receiving the smallpox vaccine,

We would like to inform you of a few important points about receiving the smallpox vaccine. Please read and make sure you understand the following.

I. Smallpox vaccine

The smallpox vaccine is a live attenuated vaccine of the same vaccinia virus strain used against Mpox. In the Mpox vaccine and preventive vaccination guidance published by the WHO, vaccination within 4 days of Mpox exposure (within 14 days in the absence of symptoms) with an appropriate second or third-generation smallpox vaccine is recommended. On 2 August 2022, the freeze-dried smallpox vaccine prepared in cell culture LC16 “KMB” was approved for an additional indication of prevention against Mpox.

II. Persons who are unsuited to receive preventive vaccination

As a rule, the following Persons cannot receive the smallpox vaccine. For more details, please consult your physician.

1. Persons who have clearly had anaphylaxis caused by an ingredient of this drug
2. Persons presenting clear fever
3. Persons who have clearly suffered serious acute illness
4. Persons with illness presenting with clear abnormality in immune function and those receiving treatment that can cause immunosuppression
5. Persons who are pregnant or who might be pregnant
6. Persons with contagious skin disease and those who might develop disorders as a result of the preventive vaccine
7. In addition to the individual listed above, those whose condition makes them unsuitable to receive preventive vaccination and women who are presently breastfeeding are to please consult their physician at the time of medical history taking about vaccination.

III. Vaccination method

The vaccine is to be administered using a special needle for smallpox vaccine administration and pressed lightly 15 times on your skin. Bleeding can occur to the extent of oozing. Disinfect before vaccination using an alcohol cotton swab, and administer the vaccine once it has fully dried. After vaccination (to prevent inactivation of the vaccine), residual vaccine solution in the vaccination site is to be wiped away with a firmly wrung alcohol swab after 1–3 minutes (for the prevention of autoinoculation and details, refer to side effects below).

The vaccination site does not need to be covered with gauze. However, if changes such as redness, blister, scabbing, and appear at the vaccination site after vaccination, cover it with gauze, as needed, and take care to avoid directly touching it.

VI. Precautions following vaccination

Persons are to avoid bathing, drinking alcohol, performing strenuous exercise on the day of receiving the vaccination, and not touching the vaccination site up to the following day. On the day following vaccination and thereafter, blisters and scabs can appear, and in such instances, please do not touch the hands, and cover them with gauze, as needed. In the event of touching, wash your hands thoroughly.

If the vaccination site is touched directly with the fingers, do not touch other people with that hand. Take care so that the

vaccination site does not touch other people directly.
Please avoid becoming pregnant for 2 months after vaccination. Furthermore, we ask for your comprehension to refuse to donate blood for 2 months after vaccination.
The state indicating that immunity has been obtained that can be traced to the vaccination (a state when it is confirmed that there is a localized inflammatory response at the vaccination site, such as redness, swelling, a sensation of heat, induration, and blisters) is to be verified 10 to 14 days after vaccination.

V. Side effects

Although the onset of serious side effects of the smallpox vaccine is rare, the following side effects can occur on rare occasions.
Anticipated serious side effects
Shock and anaphylaxis (both incidences unknown), and febrile seizure (< 0.1%)
Other side effects
In addition to inflammatory reaction at the inoculation site, systemic reactions up to 10 days after vaccination, which include fever, swelling of the axillary lymph nodes, malaise, itchiness and hives, headache, muscle-pain-like pain, and autoinoculation (blisters caused by virus inoculation from the inoculation site to another site by the hand), vaccinia (the appearance of blisters and abscess near the vaccination site), and vaccinia (allergic eczema appearing in a hive or erythema-like form seen from approximately 7 to 10 days after vaccination) can occur. For any queries, please contact us below.

Medical institution name: xxxxx
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