Questions and Answers on Vaccination

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Questions on Immunization and Vaccination and Short Answers

Bağışıklama ve Aşı ile İlgili Sorular ve Kısa Cevaplar

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Question 1: When was smallpox eradicated worldwide?

Following the last known and reported natural smallpox case in Somalia in 1977, the Global Verification Commission on Smallpox Eradication declared that smallpox had been eradicated worldwide in December 1979. In 1980, smallpox eradication was confirmed by the World Health Assembly.

Smallpox remains the only human disease that has ever been eradicated. In addition to the absence of a defined animal reservoir, the absence of chronic carriage, the availability of a heat-stable and highly effective vaccine and a simple and effective vaccination technique, mass vaccination activities, intensified surveillance and contact vaccination activities carried out within the scope of the "Smallpox Eradication Program" initiated by the World Health Organization (WHO) at the 11th World Health Assembly in 1958 and the "Intensified Eradication Program", which was subsequently switched in 1967, were also effective in achieving this success.

Eradicated variola virus collections are stored for research and development purposes at the Centers for Disease Control in the United States of America, one of the WHO's high-security cooperation centers, and at the Federal Budgetary Research Institution-State Research Center for Virology and Biotechnology of the Russian Federation.

Although it has been 47 years since the last reported case of smallpox in the world, smallpox and smallpox vaccines have remained a hot topic due to outbreaks of zoonotic orthopoxviruses, the emergence of new orthopoxviruses and concerns about the use of poxviruses such as variola for bioterrorism.

Question 2: When was the last case of smallpox reported in Türkiye?

Following the last endemic case reported in 1952, no smallpox case was reported in Türkiye between 1952 and 1956, thanks to the compulsory smallpox vaccination, systematic and intensive vaccination efforts, public education and other preventive measures during a period dating back to the Ottoman Empire. After the last outbreak caused by imported cases in 1957, no more smallpox cases were reported in Türkiye.

Question 3: What are the types of smallpox vaccines used in the world and in Türkiye throughout history?

In the variolation practice, which is known to have been widely used in Asia (Iran, India, China, Afghanistan, Baluchistan), some parts of Africa, and by Circassian and Georgian communities, and which takes its name from "variola" meaning "smallpox", a piece of pus was taken from the pustule of a child who had a mild case of the disease, another child who

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had not developed smallpox was scratched on the arm and this pus was applied to the cut (inoculation); the vaccinated person was made to have a milder disease. There are records that inoculation was used in a similar way in Türkiye in the mid-17th century (1679).

It is accepted that variolation in the form of inoculation was introduced to Europe in 1721 when Lady Mary Wortley Montagu announced this practice, which she observed during her stay in the Ottoman Empire due to her husband's appointment as ambassador to Türkiye, through her famous letters to England.

Upon the introduction of variolation in England, Dr. Edward Jenner, who was one of the people involved in this practice and who had himself been vaccinated with variolation at the age of eight, inoculated a healthy child with the liquid material taken from a cowpox wound on May 14, 1796, using a method based on the same principles as variolation, but using a viral source such as cowpox virus; and then in 1798, he published a study on a larger scale and proved the efficacy and effectiveness of the vaccine. Following this study, in 1801, more than 100.000 people were vaccinated in England.

After this, the vaccine quickly spread to other continents and was continued in the first few decades of the 19th century by arm-to-arm inoculation. This resulted not only in the rapid spread of diseases such as syphilis and tuberculosis, but also in the gradual weakening of the strains as they attenuated too much through arm-to-arm passages. This prompted scientists to look for another method of vaccination and a stable supply of vaccine, and the method of passaging, i.e. transferring the immunizing agent from one human or animal to another (e.g. transferring the "lymph-" fluid contained in vesicles to calves) was developed. In the late 19th century, the use of glycerinized calf-derived lymph became standard practice. During the Ottoman Empire, smallpox vaccine was introduced in İstanbul in 1801, soon after Jenner developed cowpox vaccine. It is understood that until the late 19th century, the need for smallpox vaccine was met through both local production and vaccines imported from Europe by the Ottoman Vaccine Administration.

Following the establishment of the first official smallpox vaccine production center of the Ottoman Empire, Telkihhane-i Şahane on July 27, 1892, large-scale production of smallpox vaccine from calves began. Telkihhane continued to produce smallpox vaccine during the First World War, between 1914-1919 and during the War of Independence.Until 1934, smallpox vaccine was produced at the Telkihhane in İstanbul, and after the transfer of the Telkihhane to the Refik Saydam Central Institute of Hygiene in 1934, smallpox vaccine production was continued here through calf passaging (with the addition of donkey passages).

Since 1961, the Refik Saydam Central Institute of Hygiene has improved the existing vaccine qualitatively and quantitatively by making some important changes (the number and preparation of animals inoculated weekly, the method used for the preparation and homogenization of the yeast, titration of the vaccine, the antibacterial agent used and the controls of the vaccine, the incubation period required for the elimination of bacteria, etc.) in the glycerin smallpox vaccine production technique using calf lymph, in line with the production technique used by the Lister Institute.

In the world, since the 1950s, with the further development of existing vaccine production techniques, freeze-dried/lyophilized smallpox vaccines, which are heat-stable/thermostable so that they can be stored without the need for refrigeration, have started to be produced. In the light of these developments, following the establishment of the (lyophilized) smallpox vaccine National Production Laboratory at the Refik Saydam Central Institute of Hygiene in 1964, the first lyophilized smallpox vaccine was produced in 1965. The lyophilized vaccine was tested by the Dutch National Institute of Public Health [Rijksinstituut voor Volksgezondheid (now known as RIVM)] on the recommendation and with the assistance of the WHO and found to comply with the international standards for biological products required by the WHO.

Glycerinated and lyophilized smallpox vaccine production in Türkiye continued until the declaration of global eradication in 1980.

Although smallpox vaccine production from egg and cell culture was attempted in the world in the 1960s and 1970s, due to the difficulties in obtaining a thermostable lyophilized product and the fact that the smallpox eradication program was nearing its end, this method of vaccine production was not pursued further.

With the cessation of routine smallpox vaccination following the declaration of eradication, the vaccine stocks held by countries continued to be used for the vaccination of laboratory workers and military personnel for some time.

However, the growing concern regarding the use of smallpox virus as a biological weapon, which emerged especially in 2001, mobilized many countries, especially the United States of America, to develop and produce second and third generation smallpox vaccines, and investments in smallpox vaccine production accelerated following the law on measures against chemical, biological, radiological and nuclear agents, also known as the "Project Bioshield Act", signed in 2004.

Currently, in addition to first-generation smallpox vaccines, there are also second, third and even fourth-generation vaccines in the world. All of these vaccines are live or attenuated vaccines.

First generation smallpox vaccines: Vaccines produced between the 1950s and 1970s during the Smallpox Eradication Program are called first generation smallpox vaccines. The most commonly used vaccine strains in this group include New York City Board of Health (NYCBH), Lister, Tiantan (Temple of Heaven) and EM63. These vaccine strains have been propagated in the skin of live animals (calf, sheep, buffalo), calf lymph or embryonated chicken eggs. The current evidence supporting the use of smallpox vaccine for the prevention of M-Pox comes from data on the Dryvax vaccine (containing the NYCBH strain), which was used during efforts to eradicate smallpox. The Dryvax vaccine is a first-generation smallpox vaccine developed by Wyeth laboratories and its routine use was discontinued in the United States by 1972.

Second generation smallpox vaccines: These are vaccines in which the vaccinia virus strains used in the production of first-generation vaccines are used. However, the difference from the first-generation vaccines is that production is carried out in tissue cell cultures prepared from isolated virus plaques. The ACAM2000 vaccine, which is still in production, is an example of this group of vaccines. First and second-generation smallpox vaccines are replication-competent.

Third generation smallpox vaccines: These are vaccines using more attenuated vaccine strains developed in cell culture or by advanced passages in animals. These vaccines were developed in the period when eradication was approaching or after eradication. Among the vaccines in this group; LC16m8 strain, which was developed in Japan from the Lister strain with B5R gene mutation and has the lowest replication ability, and vaccines prepared from the vaccinia strain known as MVA-BN, which has no replication ability and 30kb has been removed from the viral genome.

Fourth generation smallpox vaccines: A fourth-generation vaccine known as VacΔ6 or OrthopoxVac has also been developed. The production principle is based on modifying the smallpox virus by deleting the genetic material responsible for encoding virulence proteins in its genome.

In addition to these vaccines, several other vaccines are currently under development, such as lipid-encapsulated mRNA-based vaccines.

Question 4: How is M-Pox (MPox) virus (MPXV) related to smallpox virus? What is the significance of the outbreak being declared a "Public Health Emergency of International Concern" by the WHO?

The M-Pox virus (named "monkeypox" in 1957 but renamed "M-Pox" from 2024 onwards), like the variola virus that causes smallpox, is classified in the family *Poxviridae* and genus *Orthopoxvirus*. Although the reservoir of variola virus is exclusively human, M-Pox is a zoonosis. Efforts to identify the animal reservoir of M-Pox virus have been inconclusive, although there is some suggestion that small forest-dwelling rodents may be carriers. Humans, squirrels, primates, black-tailed prairie marmot, African brush-tailed porcupines, rats and mongooses have been identified as natural hosts.

M-Pox virus is a DNA virus consisting of two clades, I and II. Clade II, previously known as the West African clade, is divided into two sub-clades, IIa and IIb. Clade I, previously known as the Congo Basin clade, had a new sub-clade, Ib, identified in Africa in 2024. Clade I is known to be more virulent.

In fact, since 1970, cases of M-Pox have been reported in some countries in the African region where the disease is endemic. In the past, there have been occasional exportations from these countries to other regions of the world.

In May 2022, several countries where the disease is not endemic started to report cases of smallpox that did not appear to be epidemiologically related to endemic regions and became an epidemic; this situation was declared as a Public Health Emergency of International Concern (PHEIC) by the WHO on July 23, 2022. After the outbreak subsided; the emergency was lifted on May 10, 2023. In 2024, with the emergence of a new variant called clade Ib, following the increase in cases in the African Region and the start of exports to countries outside the African region (Sweden, Thailand) in August, a PHEIC was declared again on August 14, 2024.

Question 5: What are the vaccines currently available for M-Pox in the world?

All of the currently available smallpox and M-Pox vaccines are based on the live smallpox vaccine virus.

On 13 September 2024, The World Health Organization (WHO) has announced the MVA-BN vaccine as the first vaccine against mpox to be added to its prequalification list. Other vaccine candidates are still under review. These vaccines are as follows:

MVA-BN: It is a non-replicated attenuated vaccine produced by Bavarian Nordic and developed using the modified Ankara strain. In 2013, it was approved in Canada and by the European Union to protect against smallpox in people aged 18 years and older. In 2019, it was approved in the United States for the prevention of smallpox and M-Pox in adults. In the same year (2019), Canada expanded the indication for the vaccine to include M-Pox. In 2022, the European Union added the indication for M-Pox. The MVA-BN vaccine is not licensed for use in people under 18 years of age. It has been only approved for emergency use for children under 18 years of age in the United States in 2022.

LC16m8: This vaccine, which has the lowest replication ability, was approved for use in Japan in 1975 for smallpox prevention. The indication for use was expanded in 2022 with the addition of M-Pox.

ACAM2000: This replication-competent vaccine, already approved for smallpox, was approved for emergency use for smallpox in the United States. It has been approved for smallpox immunization by the United States Food and Drug Administration and made available under the "Expanded Access Protocol for Unapproved New Drug" for smallpox. The vaccines currently in the preclinical phase are as follows:

BNT166a and BNT166c: Developed as next-generation mRNA vaccines, these vaccines aim to provide a wide range of protection against both MPX virus and other orthopoxviruses. In preclinical studies, promising results have been shown in terms of strong immune response and full protection in challenge studies.

Question 6: What are the administration schemes, routes of administration and target groups for vaccines against the M-Pox virus?

MVA-BN: One dose is 0.5 ml according to the manufacturer. It is administered subcutaneously (SC) in two doses four weeks apart. In the global M-Pox outbreak, it was also administered intradermally (ID) at a dose of 0.1 ml by various authorities. However, with this application, a decrease in serologic antibody titer was observed at the end of six months. The vaccine should be stored frozen. Various storage temperatures have been defined; it should be stored frozen at (-15) - (-25) °C, (-45) - (-55) °C or (-75) - (-85) °C. Shelf life varies depending on the storage temperature. The vaccine should be used immediately after thawing. If previously stored at (-15) - (-25) °C, it can be stored for up to four weeks in the dark at (2) - (8)°C before use.

The vaccine cannot be refrozen after thawing. JYNNEOS® is produced under the name Imvamune®, Imvanex®.

In the United States, under emergency use approval, JYNNEOS® is administered SC as two doses four weeks apart under 18 years of age and ID as two doses four weeks apart at 18 years of age and older.

LC16m8: It is administered as a single dose using the scarification method with a bifurcated needle. It is a lyophilized vaccine. It is in the form of multi-dose vials. It can be stored for a long time between (-35) - (-20) °C. It can be stored at 5 °C for two years and at 37 °C for up to four weeks. Since the vaccine is rapidly inactivated by sunlight, it must be protected from sunlight. Before vaccination, the lyophilized vaccine in the vial should be dissolved with 0.5 ml of diluent. Thus, approximately 250 doses of vaccine solution is obtained in each vial. After preparation, the vaccine can be stored at (2) - (8) °C for one month and at room temperature (23 - 27 °C) for 24 hours.

ACAM2000: It is administered as a single dose using the scarification method with a bifurcated needle. It should be stored in the freezer at a temperature between (-5) - (-25) °C. After the vaccine vial is brought to room temperature, the lyophilized vaccine in the vial is prepared by adding 0.3 ml of diluent. Thus, approximately 100 doses of vaccine solution is obtained in each vial. After the vaccine is prepared, it can be administered within 6 - 8 hours provided that it is stored at room temperature. After preparation, the unused vaccine can be stored in the refrigerator at (2) - (8) °C for up to 30 days. After this time, it should be should be discarded as biohazardous material as it is a live vaccine.

Some Important Considerations on Vaccine Administration

A three-three phased vaccination strategy is currently recommended by the WHO. The first phase aims to vaccinate contacts of cases up to 2-4 weeks old and healthworkers and other frontline personnel working in areas where active cases have been detected, in order to interrupt the chain of transmission and stop outbreaks.

The second phase aims to further spread the virus in the communities in the affected areas. In this phase, in line with the epidemiological characteristics of the affected areas, groups at high risk of severe disease are targeted. This phase also aims for a vaccine coverage of more than 90%, requiring higher vaccine doses, resources and logistical capacity.

In the third phase, in case of an expanding outbreak or for future outbreaks, in line with the recommendations set for all countries by the Strategic Advisory Group of Experts on Immunization of the WHO, a herd-immunity that can be achieved with a vaccine coverage of at least 90% and above is targeted.

It is anticipated that the activities to be carried out in the first six months after the declaration of a "State of Emergency" by the WHO will focus on first-stage vaccination strategies aimed at stopping outbreaks.

Pre- and post-exposure vaccination: Although a mass vaccination program has not yet been recommended by the WHO, pre-exposure vaccination is recommended for people considered to be at high risk of exposure, especially in the current global M-Pox outbreak (men who have sexual intercourse with gay, bisexual or polyamorous men, all individuals with multiple sexual partners, sex workers, healthcare workers at risk of repeated exposure, laboratory personnel working with orthopoxviruses, healthcare workers and clinical laboratory personnel performing diagnostic tests for M-Pox virus, and personnel involved in outbreak response studies. Since the risk level of exposure may vary from group to group, it is left to countries to prioritize risk levels, especially in the case of limited vaccine supply. Post-exposure vaccine prophylaxis is recommended by the WHO, preferably within the first four days after contact with the case (and up to the 14th day after contact if symptoms have not started).

Pregnancy and vaccination: Data on the use of MVA-BN vaccine in pregnancy are insufficient. There are no studies on the use of LC16m8 and ACAM2000 vaccines in pregnancy.

Continuation of the vaccination schedule with another smallpox/mpox vaccine: There are no studies on this issue.

Concurrent administration of smallpox/mpox vaccines with other vaccines in the schedule: There are no studies on this issue.

Vaccination of people who have previously had M-Pox: There is no need to vaccinate people who have had mpox.

Question 7: Is there any level of protection against M-Pox for people who were vaccinated against smallpox until 1980?

After smallpox vaccination, it is known that protection lasts up to five years, partially persists up to 10 years, and decreases to negligible levels after the 20th year.

Travel vaccination was discontinued by the WHO in 1980 and has not been considered necessary by any country since 1982. People who have been vaccinated against smallpox in the past may have partial immunity to other orthopoxviruses.

The increase in the incidence of M-Pox in recent years has been temporally correlated with the decline in population immunity to orthopoxviruses following the worldwide cessation of vaccination.

Surveillance data from the Democratic Republic of Congo showed that among people born before 1980, those who had received first-generation vaccinia virus-based smallpox vaccine had a 5.2-fold lower risk of contracting M-Pox than those who had not received the vaccine (0.78 per 10.000 vs. 4.05 per 10.000), indicating a pre-exposure vaccine efficacy against M-Pox of 80.7% (95% CI= 68.2 - 88.4%).

Another surveillance study in the Democratic Republic of Congo with 338 participants showed that Dryvax, a first-generation smallpox vaccine based on vaccinia virus, was 85% effective against M-Pox.

Although these studies are still small in number and limited to small groups, they provide the first and early evidence that smallpox vaccination provides cross-protection against M-Pox.

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