



SMALLPOX

by

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Smallpox is an acute exanthematous, communicable disease caused by variola virus. The virus is transmitted through droplets or droplet nuclei from infected persons with a rash, to susceptibles in close contact or, indirectly, through contaminated laundry or bed linen. Those who experience a mild or sub-clinical illness without rash do not transmit infection to others. After an incubation period of seven to 17 days, the patient experiences prodromal fever and mild to severe constitutional symptoms which resemble those of influenza, with aching pains in the forehead, back, limbs and abdomen. Between the second and fifth days, a rash begins to develop and the temperature and constitutional symptoms subside. In the usual or "ordinary" type of smallpox, the rash first appears as macules on the face and upper part of the body and, within a day or two, on the lower part of the body and legs. Lesions frequently appear on the palms and soles and occur also on the hard and soft palate as well as on the mucosa of the cheeks and tongue. Over a three to four-day period, the macules develop into papules, then vesicles and finally pustules. The characteristic elevated pearly-white pustules are replaced by crusts beginning about the eighth to tenth day. The crusts gradually fall off during the succeeding one to three weeks. Although the lesions over the face tend to mature somewhat more rapidly than those on the extremities, all lesions on any one area of the body are at the same stage of development.

The characteristic rash is referred to as being centrifugal in distribution, as there is a greater concentration of lesions on the face, arms and legs than on the body. Lesions are also more concentrated over extensor surfaces, bony prominences and areas which have recently been irritated by the sun or by abrasion. In very mild cases only a few lesions may be present, while in severe cases the lesions may be so dense that they are confluent. Both the severity of constitutional symptoms and the probability of transmission are correlated directly with the extent of the rash.

While the "ordinary" type of smallpox, as described above, accounts for 80 to 90 per cent. of cases, three other clinical types are recognized, all of which cause problems in diagnosis (WHO, 1966). These types are referred to as (1) haemorrhagic; (2) flat; (3) modified. In the uniformly fatal haemorrhagic type, the patient experiences a severely prostrating prodromal illness followed by the development of a dusky erythema and eventually petechiae and frank haemorrhages into the skin and mucous membranes. Death normally occurs by the fifth or sixth day after onset. In the frequently fatal "flat" variety, the patient experiences prostrating constitutional symptoms. The lesions develop slowly and are essentially confluent. The skin takes on the appearance of a fine-grained reddish-coloured crepe rubber. Haemorrhages into the skin sometimes occur. If the patient survives, the lesions gradually disappear without forming scabs or, in severe cases, large amounts of epidermis may peel away. In the "modified" variety which sometimes occurs in previously vaccinated persons, the patient experiences few symptoms, the lesions are few in number and mature more rapidly than in the ordinary case. They may not progress beyond a papular stage before resolving. Patients

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experiencing "modified" smallpox less frequently transmit infection to others while those with the haemorrhagic and flat varieties excrete large amounts of virus and are particularly dangerous transmitters of infection.

Differences in the proportion of severe and fatal cases between outbreaks in one area and another led to the differentiation of variola major (classical smallpox) and variola minor (alastrim, amass, Kaffir pox, milkpox, Marsden, 1948). In variola major, which is endemic to the Asian subcontinent, case-fatality ratios of 15 to 40 per cent. are observed. In variola minor, which is endemic in South America and South Africa, case-fatality ratios are somewhat less than one per cent. More recently a form of intermediate severity has been recognized in East Africa and in Indonesia with case-fatality ratios of five to 10 per cent. (Bedson, et al. 1963). In all forms, case-fatality ratios are highest in the very young, in the elderly and in pregnant women.

While there may be subtle clinical differences between variola major, variola minor and the intermediate varieties, the type of smallpox cannot be distinguished on clinical grounds in the individual case. The spectrum of severity of illness among patients in an outbreak of variola minor is simply shifted toward the milder one; a larger proportion have minimal to mild systemic symptoms and a sparser rash. Nevertheless, occasional cases of haemorrhagic smallpox are observed. Distinction between the different forms of variola can only be made on the basis of case-fatality ratios during the course of an outbreak, or by special laboratory studies.

#### Prevalence

Because of the extent to which smallpox has been controlled by vaccination, it is difficult today to appreciate that this disease is, by far, the most serious of the communicable diseases which has been known to man. Once as prevalent as measles, between 20 and 40 per cent. of all those afflicted died. Many who recovered were disfigured for life, left blind, or with some other serious consequence of the disease. In Europe itself, significant population growth did not occur until smallpox was brought under partial control in the last half of the eighteenth century (Razzell, 1969).

Smallpox was introduced into the Western Hemisphere by the Spaniards about 15 years after the discovery of America. In Mexico, within a short period, 3 500 000 persons are said to have died of the disease. Catlin in 1841 stated that of 12 000 000 American Indians; 6 000 000 fell victim to smallpox. In Iceland in 1707, 18 000 perished out of a population of 50 000; that is, smallpox killed 36 per cent. of the total population in one year.

Up to the end of the nineteenth century, variola major was the prevalent type of smallpox in most countries of the world. Gradually, however, variola minor became more and more widely disseminated (Hedrick, 1936) and now variola major is found only in Asia. According to Chapin and Smith (1932) variola minor made its appearance in the United States of America at about the time of the Spanish-American War, presumably being introduced by way of the West Indies from South Africa. During the next 40 years, variola major was virtually replaced by variola minor in the United States of America. Despite the availability of vaccine, effective smallpox control in the United States of America was greatly delayed and as late as 1930 49 000 cases were recorded. During the 1930's however, smallpox incidence declined rapidly, a phenomenon attributed by Leake (1943) to the introduction of the electrical refrigerator and consequent better preservation of the heat-labile liquid vaccine. During the early 1940's continuing transmission was interrupted although outbreaks periodically occurred as a result of importations, particularly from Mexico. With the development of a smallpox eradication programme in Mexico the frequency of importations decreased sharply and no cases in the United States of America have been confirmed since 1949.

By the end of the Second World War most of Europe had become free from smallpox and, in the course of a World Health Organization programme in the Americas during the 1950's, Central America became free of the disease. In 1958 it was unanimously agreed in the

World Health Assembly that a global programme for smallpox eradication should be undertaken. During the following nine years some progress was made, but limited funds handicapped the effort. Finally, the 1966 World Health Assembly voted to intensify the programme and for this purpose made special funds available. During the following four years eradication programmes were developed in all of the endemic countries, and by 1970, despite far more complete reporting of cases, smallpox incidence had declined from 131 000 cases in 1967 to 30 000 cases. In this four-year period 16 of 30 endemic countries became smallpox free, including all of those in western and central Africa as well as many in eastern and southern Africa. In addition, smallpox eradication appeared to be imminent in the Americas and Indonesia. At the end of 1970 the principal problem areas consisted of four countries in Asia - India, Pakistan, Nepal and Afghanistan and two in Africa - Ethiopia and Sudan. Eradication programmes were in progress in all of these countries (WHO, 1971).

### Pathogenesis

Concepts of the pathogenesis of smallpox, as reviewed by Downie in 1951, appear to be as valid today.

The site of entry of the virus is the tissues of the upper respiratory tract. At most only a minimal lesion occurs in the mucous membrane, and the virus quickly passes to lymphatic glands and by the bloodstream to internal organs. During the incubation period, the virus multiplies with progressive infection of cells in these organs. Toward the end of this period or at the onset of illness there is an overflow of virus into the bloodstream (viremia). The viremia leads to wide-spread infection of the skin, mucous membranes and other tissues, although lesions do not become apparent in the skin for a further two to three days. As these lesions break down liberating virus on the surface, the patient becomes infective for others. The immune response with formation of antibodies follows. The rapidity and extent of the antibody formation determines, in part, the severity of the disease. The maturation of the eruption proceeds after the antibodies have appeared and is secondary to the destruction of cells infected in the first few days of illness. Persons who die in the late pustular stage of the eruption may have a high titre of antibody in their sera; in such persons death is due to the late effects of earlier virus activity or to some complicating disability or infection. Antibodies persist at a high level for many years after clinical recovery. In some individuals partially protected by previous vaccination, the mobilization of antibodies is so rapid that they have a very brief illness without eruption, variola sine eruptione. Transplacental infection of a foetus in utero of an expectant mother who develops the disease may occur as a sequel of the viremia.

### Mode of transmission

Smallpox is pre-eminently a contagious disease of man. No animal host is known (Arita & Henderson, 1968). The virus makes its exit from the infected host through the lesions in the mucous membrane of the mouth and pharynx and through the lesions of the skin. The patient is most infectious during the first seven to 10 days of rash although the period of communicability is regarded as lasting from the time of appearance of the first lesions to the complete exfoliation of the scabs. Direct transmission for short distances occurs through projection of droplets or droplet nuclei from the upper respiratory tract of an infected host. Indirect transmission takes place through contamination of bed-clothes and other articles in the patient's surroundings. Ordinarily the range of infectiousness is limited to the vicinity of the infected individual although on two occasions (Wehrle, et al. 1971), infection has been conveyed over a considerable distance within the confines of a hospital building.

Smallpox is occasionally transmitted by inoculation of the abraded skin or mucous membrane of a susceptible individual with infectious material from a patient.

### Variola virus

Five major types of the variola-vaccinia virus group are recognized: (1) variola major; (2) variola minor; (3) vaccinia; (4) cowpox; and (5) monkeypox. The viruses are closely related and have similar physical characteristics and properties but they can be readily distinguished by the nature of infection produced in experimental animals as well as by examination in tissue culture systems.

In suspensions prepared from tissues infected with viruses of the variola-vaccinia group, small granules can be demonstrated known variously as elementary bodies, E.B.'s and Paschen bodies, which have been shown to be aggregates of virus molecules. In 1892 Guarnier described the bodies which now bear his name in the deep epithelial cells of the skin in cowpox and smallpox, as well as in the epithelial cells of the cornea of rabbits. These intracellular inclusion bodies are now accepted as being specific. They can be demonstrated in all types of infection with viruses of the variola-vaccinia group. They are believed to be masses of elementary bodies held together by a matrix.

Variola virus is quite stable, in crusts it may retain its viability for many years. Thus Wolff and Croon (1968) found that desquamated crusts which had been stored for 13 years in an envelope at room temperature contained viable virus. While the virus is preserved for long periods in this state, its ability to induce human infections does not appear to extend over more than a few weeks at most under natural conditions. Experience in the course of the global eradication programme has shown that when direct human-to-human transmission is interrupted, smallpox ceases to occur. Presumably residual scabs, which undoubtedly remain in houses of patients or in hospitals, are too low in virus titre to infect and/or the virus is not readily suspended in sufficiently small particles to be inhaled.

The stability of variola virus facilitates diagnostic studies since material for examination can be shipped without refrigeration. Although the virus is quite resistant to desiccation and cold, it is rapidly destroyed in a humid environment and by exposure to sunlight or ultra-violet rays. It is not so easily killed, as are non-sporing bacteria, by many of the chemical germicides in common use.

### Diagnosis

Prompt diagnosis, isolation of the patient and protection of contacts are the key measures in the control of a smallpox outbreak. Ordinary cases offer no difficulty in diagnosis but 10 to 20 per cent. of cases in an outbreak may be atypical and cause problems. Where the health physicians are thoroughly familiar with Ricketts and Byles (1908), mistakes are rare once the suspicion of smallpox has been raised.

Experience in both endemic and non-endemic countries reveals that smallpox is most frequently confused with moderate to severe cases of chickenpox. As the great majority of smallpox cases which occur following importations are among adults, the attending physician should always be alert to the possibility of the diagnosis of smallpox in any adult with an acute, moderate to severe exanthematous disease resembling chickenpox. This is particularly important when death occurs since death following chickenpox is uncommon. Suspicion is, of course, heightened if the patient has returned from an endemic area within the preceding two weeks. However, as the first and often the second generation of cases are often not detected following importation, the absence of travel abroad does not exclude the possibility of smallpox.

Haemorrhagic and flat cases of smallpox being far more difficult to diagnose, are rarely identified until an outbreak has been recognized. Fortunately such cases account for less than five per cent. of cases of variola major (WHO, 1968) and a far smaller proportion of cases of variola minor. Such cases are a special hazard as they excrete large amounts of virus and are highly infectious. Because of the severity of illness, patients with these

types of smallpox are usually hospitalized but rarely isolated as the signs and symptoms frequently are confused with a number of non-infectious illnesses such as thrombo-cytopenic purpura and acute leukemia.

If smallpox is suspected, the patient should be isolated immediately, the appropriate health authorities notified, and all contacts vaccinated and kept under daily surveillance, with temperature determinations for 17 days after last exposure. Vaccinia immune globulin (0.3 ml per kilogram) should also be administered to contacts who have never had a successful primary vaccination, to contacts who are discovered seven or more days after first exposure, and to contacts whose immunological systems are compromised because of a disease of the reticuloendothelial system, steroids or immuno-suppressive drugs.

Laboratory studies should always be immediately undertaken in all smallpox-free areas and in areas where only a few cases are occurring. Specimens should be processed only in laboratories equipped to handle highly infectious materials and, to assure reliable results, in laboratories routinely examining smallpox specimens (WHO, 1969).

Confirmation of diagnosis is achieved by identification of the virus or its antigens in material derived from cutaneous lesions or the demonstration of specific antibodies in serum obtained late in the disease or during convalescence (Bedson & Dumbell, 1967). Although the virus may also be isolated from blood in the early stages of disease or from throat washings or urine for a longer period, such specimens are not usually examined for routine diagnostic purposes.

For identification of virus, vesicular or pustular fluid may be collected by capillary tube or on a cotton-tipped swab; material from aculopapular lesions is scraped with a Hagedorn needle until the surface is moist and the material rubbed on a slide; crusts are simply prised loose with a needle or scalpel and placed in a sterile container. In each instance, material from at least six lesions should be obtained.

A rapid, presumptive identification of the virus being of the variola-vaccinia group may be obtained by examining the material by electron microscopy or by microscopic examination of a stained smear. Pox virus antigen in the specimen may also be identified within four to 24 hours by use of the precipitation-in-gel technique. Definitive identification of the virus however, requires that it be grown in one of a variety of tissue cell culture systems or on the chorioallantoic membrane of 12 to 14 day old chick embryos. On the chorioallantoic membrane, variola, vaccinia, monkeypox and cowpox viruses produce pocks which are morphologically distinctive for each virus type. Differentiation between variola major, variola minor and intermediate strains of variola virus depends on a determination of the relative ability of the different strains to grow at various temperatures.

Neutralizing antibody usually appears by the sixth day of illness, reaches a high concentration in convalescence and persists for many years (Downie, et al. 1969). Complement fixing, precipitating and haemagglutinin-inhibiting antibodies appear about the sixth to eighth day of illness and reach a higher titre than is found after vaccination. Normally, the complement-fixing and precipitating antibodies do not persist for more than a year while, during this period, haemagglutinin-inhibiting antibodies diminish to low but usually detectable concentrations.

#### Treatment

Little more than supportive treatment can be offered the patient. Antibiotics are of value in treatment of the occasional secondary bacterial infections which do occur. Chemotherapeutic agents have proved to be of no value.

Prevention and control

In the non-endemic countries, smallpox prevention has traditionally emphasized vaccination and revaccination throughout the community and maintenance of a quarantine service to ensure that travellers carry a certificate which asserts that they have been satisfactorily vaccinated within the preceding three years. This approach undoubtedly has served to limit the number of importations of smallpox as well as the extent of spread of the disease after introduction. However, the cost of this approach has been substantial both in economic terms and in human health. In the United States of America, various health economists have estimated the cost for vaccination and quarantine activities to be from \$ 20 to \$ 125 million per year. Complications following vaccination have resulted in six to 12 deaths each year, more than 150 serious complications and over 2000 days of hospitalization (Neff, et al. 1967 and Lane, et al. 1969). Despite the application of such costly measures, 29 importations of smallpox occurred in Europe and North America in the 10-year period 1961-1970 and a total of 392 cases resulted before the outbreaks could be contained.

Recognizing the feasibility of smallpox eradication as well as the continuing problem it posed to all countries, the World Health Assembly in 1966 decided to provide financial assistance for a global programme of smallpox eradication. Supporting the view that eradication was a feasible proposition was the fact that smallpox transmission had been interrupted in a number of countries of Asia, Africa and Central America where health services were limited and transport and communication were difficult. It was stated at that time that of all the infectious diseases, smallpox in its epidemiological behaviour, lends itself uniquely to an eradication effort. A number of favourable factors were cited: (1) smallpox is directly transmitted from person to person and there are no known insect or animal reservoirs; (2) the disease rarely occurs in sub-clinical form and so may be readily detected in an area; (3) the victim of the disease is generally incapable of transmitting the virus for more than two weeks and is rendered essentially permanently immune against a subsequent attack; (4) since smallpox has a two-week incubation period, prompt identification of a case permits the initiation of effective containment measures.

The principal approach in smallpox prevention at present is thus directed at reducing the overall reservoir of disease. From 1967, the year in which the intensified global eradication programme began, to 1970, the number of countries recording smallpox decreased from 42 to 23. During 1969 and 1970 there were only two importations of smallpox into Europe and North America.

The second approach in smallpox prevention is to prevent transmission of the disease from one country to another. This is accomplished by ensuring, to the extent possible, that all travellers from endemic areas have been successfully vaccinated within the preceding three years. Thus, International Certificates of Vaccination are required of all travellers from endemic areas.

Finally, when smallpox is introduced into a community, control of the disease depends on early recognition, reporting, isolation of the cases and vaccination of all contacts. If the immunity of the population is high the possibility of further spread is obviously reduced but it is not eliminated. Transmission over a period of several months has occurred in a number of communities in which more than 90 per cent. have been recently vaccinated. Thus a high level of immunity in the general population cannot itself be relied upon for control. Experience, however, has shown that the control of smallpox outbreaks is more readily accomplished than for most infectious diseases. Even in areas where less than 50 per cent. of the population has previously been vaccinated, effective and prompt outbreak control has been readily achieved. There are several reasons for this. Only those with definite rash appear to be able to transmit infection and thus the chain of transmission of infection from one patient to the next can readily be traced and contacts identified. Most cases acquire infection as a result of face-to-face contact with the infected person in the home or hospital - only a small percentage of cases become infected as a result of contact

in markets, trains, buses, and so forth. Thus, contacts can readily be defined for purposes of vaccination and surveillance. Finally, the infected person transmits infection on the average to no more than two to four other persons and since there is an incubation period of two weeks between generations of disease, outbreaks develop and spread comparatively slowly. Because of these factors experience has shown that in most outbreaks not more than 200 to 500 persons need to be protected to effect control. In the developing countries protection is afforded solely by vaccination, but in the developed countries vaccinia immune globulin, if available, is also administered to individuals exposed more than seven days previously, to all who have never been successfully vaccinated and to those whose immunological competence is in doubt (Kempe, et al. 1961). The chemoprophylactic, methisazone, employed experimentally as a protective agent, appears to afford no greater protection than vaccinia immune globulin and has the disadvantage of inducing severe vomiting in a substantial proportion of recipients. In addition to protecting contacts, the patient is isolated and, in the countries with a more sophisticated health service, all contacts are placed under surveillance and their temperatures are measured each evening for a period of 17 days after last contact. If a contact develops a temperature he is isolated and carefully watched for the possible development of a rash.

In the global eradication programme, major emphasis has been placed on the development of reporting and outbreak control. Where this approach has been effectively implemented, smallpox transmission has been interrupted within four weeks or less in over 90 per cent. of outbreaks and throughout an entire country within a period of 24 months.

The marked decrease in smallpox incidence throughout the world and the recognition that specific control measures may rapidly interrupt smallpox transmission have prompted a number of people in recent years, to query the need for continuing routine vaccination programmes. For the developing countries, where health services are sparse and the detection of smallpox cases is unavoidably often delayed, continuing vaccination programmes are necessary to sustain a high level of immunity in the population. By so doing, smallpox transmission is retarded so that by the time cases are detected the outbreak has not developed beyond manageable proportions. Such considerations do not pertain to countries such as those in Europe and North America, and the merits of routine vaccination are more debatable. However, it is hoped that the present rate of progress of the global eradication programme can be sustained and that the absence of smallpox may fully resolve the issue to everyone's satisfaction.

#### Vaccination and smallpox

##### Historical note

The credit for giving vaccination to the world is due to Jenner (1798), who through logical and scientific methods proved that a person who has had the mild disease cowpox enjoys protection against the serious disease smallpox. This fact had been known previously to some of the farmers and folk of England, but it was Jenner who first put this vague belief upon a scientific basis.

Jenner made his crucial experiment in 1796 when he transferred pustular matter from the hand of a dairy maid who was infected with cowpox, to the arm of a boy. A typical take followed, six weeks later he inoculated the boy with variola virus but no disease followed. He also inoculated smallpox virus into 10 persons who had at some previous time contracted cowpox and found that they too were resistant to smallpox. Jenner's observations were published in 1798 as a book which is a medical classic, "An Inquiry into the Causes and Effects of the Variolae Vaccinae, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of Cowpox". The presently employed vaccinia virus derives from cowpox, although its properties have changed as a result of many passages in humans and animals.

In America the first vaccination was done in 1800 when Benjamin Waterhouse of the Harvard Medical School vaccinated his son and two slaves. They were subsequently challenged by inoculation with smallpox, with negative results. In Boston in 1802 an experiment involving the vaccination and subsequent inoculation of 19 boys took place. This firmly established the effectiveness of vaccination.

Eighty years later Pasteur, recognizing the relation of Jenner's discovery to his own work with attenuated agents of disease, extended the term vaccination (from vacca, a cow) to administration of other agents. The term is now generically used for an active immunization, whether with a living or inactivated antigen. Vaccination against smallpox was the first application of a principle which now includes immunization with a number of attenuated micro-organisms.

## Vaccination

### Definition

Vaccination consists of introducing vaccinia virus into the superficial layers of the skin with the object of inducing a vaccinia infection in order to prevent a smallpox (variola) infection. The vaccination or "take" is regarded as successful only when the infection induced is characteristic of a primary vaccination reaction or, following revaccination, when there is evidence that virus multiplication has taken place as evidenced by the presence of definitive induration or congestion at the inoculation site between the sixth and eighth day.

The earlier practice of inoculation or variolation must be distinguished from vaccination. Variolation antedates vaccination by centuries and is the deliberate infection of man with smallpox virus, by cutaneous inoculation. The disease produced is milder than natural smallpox, but just as contagious and, if transmitted, leads to virulent smallpox. Hence, while variolation affords some protection to the individual, it endangers the community unless everyone is inoculated at the same time. Variolation is rapidly disappearing but is still occasionally practised in some remote areas in Asia and Africa.

### Production of vaccine

Most smallpox vaccine is now produced by inoculating the skin of calves with seed virus and harvesting the vesicular lesions. The vaccine is purified by centrifugation and the bacterial content reduced by the addition of phenol. Vaccine is also produced on the chorio-allantoic membrane of chick embryos and experimental tissue culture vaccines are now being evaluated.

In the United States of America as well as in many countries of the Americas, the strain of vaccinia virus most commonly employed in production is one of the derivatives of the New York Board of Health strain. In other parts of the world, the Lister and Ecuador (or EM-63) strains are most frequently used. These three strains appear to be approximately equivalent in reactogenicity and immunogenicity in the human host and cause less severe cutaneous reactions than other strains with which they have been compared.

More attenuated strains (CV-I, CV-II) are being tested which induce a minimal to nil cutaneous reaction but which serve as a primary stimulus prior to revaccination with the traditional strains.

In the endemic countries all vaccine in routine use is freeze-dried vaccine. All lots of this vaccine are tested to ensure that they will retain satisfactory potency for at least one month when kept at room temperature. Such vaccine, after being reconstituted, is considered to remain potent for that day only and is discarded at the end of the day. Vaccine, before or after reconstitution, must be kept out of direct sunlight, as direct sunlight may destroy the virus within hours. Vaccine is presently packaged in vials of 0.25 ml which is sufficient for 100 vaccinations if the bifurcated needle is employed.



In non-endemic, temperate countries, the vaccinia virus is frequently suspended in glycerine and distributed in single dose capillaries. Such vaccine is far less stable than freeze-dried vaccine and must be kept at freezing temperatures at all times until used. In non-endemic countries where refrigeration is ample, freeze-dried vaccine is considered to be suitable for use for one week following reconstitution provided it is maintained at refrigerator temperatures.

#### First vaccination (primary take)

##### Course of the eruption

The period of incubation is about three days, when a papule appears upon the skin where the vaccine virus was inserted. The papule is small, round, bright red and hard, but superficial. It appears in about 72 hours. On the fifth day the top of the papule becomes vesicular. The development is rapid so that by the sixth day the papule, which continues to grow, has almost changed to a vesicle. On the seventh day, the vesicle is fully developed and characteristic, it is whitish, umbilicated, multilocular and contains clear lymph. Although giving the appearance of having turbid contents characteristically it does not become a pustule as does the smallpox lesion. Around the periphery of the vesicle there appears a reddened inflamed area, known as the areola, which rapidly expands to reach a maximum diameter about nine days after vaccination and rapidly dissipates thereafter. Drying begins at the centre, frequently while the vesicle is still enlarging. A dry black or brownish crust which falls off about three weeks after vaccination is the normal end of the reaction. The scar is at first red and finally turns white, with the pits or foveations so characteristic of the pock mark.

##### Revaccination

When vaccination is performed on persons who possess some immunity as a result of previous vaccination or smallpox, a gradation of different cutaneous responses is observed. At one extreme individuals who have not been vaccinated for several decades may develop what appears to be a primary take. Persons with an intermediate level of immunity develop a papule which progresses to form a vesicle or small pustule, finally drying to form a scab. The course of development of the lesion is more rapid than in primary vaccination and the maximum diameter of erythema is reached between three and seven days. In the highly immune person virus multiplication may not occur. However, in such persons, a cutaneous response is normally observed which is the result of hypersensitivity to vaccinia protein (McKinnon & Defries, 1931). A papule and sometimes a vesicle may form and erythema develops. The reaction reaches its peak in the first 48 hours after vaccination and subsequently subsides. By the sixth day there is no evidence of an inflammatory process. This last type of reaction was formerly termed a "reaction of immunity" or "immediate reaction", implying that the individual was immune to smallpox. However, experiments have shown that vaccine which has been fully inactivated by heat or potent vaccine which has been applied with unsatisfactory technique, may induce a similar response even in individuals who have not been vaccinated for many decades.

To distinguish the hypersensitivity type of reaction from one in which virus multiplication has taken place, the site of inoculation is examined between the sixth and eighth day (WHO, 1968). If there is evidence of induration or congestion, virus multiplication (and a neutralizing antibody response) may be assumed. This response is called a "major reaction". If there is no evidence of induration or congestion, virus multiplication may or may not have taken place and, as no conclusion can be drawn, the response is termed an "equivocal reaction". Repeat vaccination is thus advisable. To revaccinate those with an equivocal reaction errs on the conservative side. Experience has shown that, if potent vaccine and good technique are used, approximately half of those with an equivocal reaction experience a fourfold or greater neutralizing antibody response. This response is believed to be the best index of the degree of protection against smallpox. However, considering the severity of smallpox and the need for solid protection among those exposed, revaccination appears to be the most sensible approach.

## Methods of vaccination

### Age

In non-endemic areas, where the risk of exposure to smallpox is low, vaccination during the second year of life is recommended. Fewer neurological and cutaneous complications are observed than among those vaccinated between three and 12 months, or at an older age. In endemic areas vaccination at birth is recommended as the case-fatality ratio among infants acquiring smallpox is very high, more than four times greater than in older children. Extensive studies have shown that vaccination at birth is a safe procedure, perhaps with fewer attendant complications than vaccination at an older age since the infant normally possesses some maternal antibody and vaccination is thus performed under the partial protection of immune globulin. Vaccination of newborns requires the use of a higher titre of vaccine than is required for vaccination of older children. However, present vaccine standards require commercially available vaccine to have a titre which is sufficiently high for this purpose.

Immunity diminishes with the lapse of time and revaccination is necessary to maintain protection. Since revaccination induces a marked increase in neutralizing antibody, the immunity conferred by vaccination and revaccination is believed to be far more permanent and durable than after primary vaccination alone. Primary vaccination at birth in the endemic countries or during the second year in non-endemic countries, followed by revaccination at the age of school entry should provide substantial, long-lasting protection. Subsequent revaccination at 10-year intervals or at the time of an outbreak should provide adequate protection.

### Site

The outer surface of the left arm at the insertion of the deltoid muscle is best. This area is easily kept cool and dry and the skin here is easily made taut during the process of insertion by grasping the underside of the arm. Inspection of the course of the local reaction and the subsequent vaccination scar is also facilitated. However, any part of the skin or exposed mucous membrane is susceptible to vaccinia infection and a take will follow the accidental insertion of the virus into the conjunctiva or the lip for example.

The leg is sometimes selected to avoid visible disfigurement. With insertions on the arm, as now practised, the resulting scar is small, definite and typically pitted, but not disfiguring. The leg is more exposed than the arm to warmth, moisture and street dust. On account of blood stasis, primary leg vaccinations are often accompanied by purplish discoloration and result in a large, slowly healing ulceration; they usually cause temporary disability. For these reasons this site should be avoided.

The skin at the site of insertion is traditionally cleansed with acetone or ether and allowed to dry. Denatured alcohol or non-volatile germicides should not be used for they are apt to inactivate the virus and prevent successful takes. Various studies have shown that neither these methods nor others, short of a time consuming surgical preparation, do more than remove a modest quantum of superficial dirt. Studies have shown no increase in risk of bacterial complications if no skin preparation is used. Thus, in many countries now no attempt is made to cleanse the site before inoculation.

### Insertion

Vaccination consists of introducing into the basal layers of the epidermis sufficient amounts of vaccinia virus to infect susceptible cells and produce a local lesion. Inoculation is, therefore, intradermal never subcutaneous.

Vaccine may be introduced by a variety of techniques, those which produce the highest proportion of successful vaccination are the multiple pressure, multiple puncture and jet

injection methods. The multiple pressure method has been in longest use but is more difficult to perform correctly than the related multiple puncture technique. The multiple puncture and jet injection techniques came into general use in 1967 and 1968, and in the endemic countries effectively all vaccinations are now performed by these methods. Various other techniques such as the scratch, scarification and rotary lancet methods normally produce a lower proportion of successful takes and are no longer recommended.

The jet injectors are useful for rapid vaccination of large numbers of persons, as many as 10 000 to 12 000 persons may be vaccinated per day. To assemble this many persons, however, it is difficult, but if 1500 to 3000 persons each day can be vaccinated the injectors are usually economically practical. If less than this number are to be vaccinated the bifurcated needles are more functional as a single vaccinator can vaccinate 1000 to 1500 persons per day with this device.

If fully potent vaccine is used a single insertion is preferred. Multiple insertions do not invoke a better neutralizing antibody response unless the vaccine used is of low potency and only one of two or more insertions show a satisfactory take.

#### The multiple pressure method (Leake, 1946)

A drop of vaccine is placed on the site for vaccination, a needle which should be sharp and sterile is held parallel or tangential to the skin surface, with the forefinger and middle finger of the right hand above the needle and the thumb below, the needle pointing to the operator's left. The needle should be crosswise to the arm so that the thumb of the operator is not impeded by hitting the skin. The side of the needle point is then pressed as vigorously as possible into a drop of vaccine about 10 times within five seconds for primary vaccination and 30 times for revaccination, the needle being lifted clear of the skin each time. This rapid up and down motion of lifting the needle and pressing it against the skin should be perpendicular to the skin and needle, and not in the direction of the long axis of the needle. The point is not driven into the skin but at each pressure the elasticity of the skin will pull a fraction of an inch of the epidermis over the point of the needle so that the vaccine is carried into the deeper layers of the epidermis where multiplication of the virus takes place. The insertion should be confined to an area not more than one-quarter inch (6 mm) in its greatest diameter. Immediately after the remaining vaccine is gently wiped off the skin with sterile gauze and the sleeve pulled down.

#### Multi-puncture vaccination (WHO, 1970)

For multi-puncture vaccination the bifurcated needle is used. A sterile bifurcated needle (which must be cool if flamed or dry if boiled) is inserted into the ampoule of reconstituted vaccine. On withdrawal, a droplet of vaccine sufficient for vaccination is contained within the fork of the needle. The needle is held at a 90° angle (perpendicular) to the skin, the wrist of the vaccinator rests against the arm. Fifteen up and down (perpendicular) strokes of the needle are rapidly made in an area of about 6 mm in diameter. The strokes should be sufficiently vigorous so that a trace of blood appears at the vaccination site after 15 to 30 seconds. If a trace of blood does not appear the strokes have not been sufficiently vigorous and the procedure should be repeated. Although it is desirable not to induce frank bleeding the proportion of successful takes is not reduced if bleeding does occur. After vaccination the site may be wiped gently with sterile gauze.

#### Jet injection (Millar, et al. 1969)

A special freeze-dried vaccine is used which is more dilute and somewhat more purified than standard vaccines and has a minimal bacterial content. The jet injector head is placed firmly against the arm. The trigger is activated and 0.1 ml of vaccine, under high pressure, passes through a small orifice into the superficial layers of the skin. The small amount of vaccine which remains on the skin surface is wiped off with sterile gauze. A number of different types of injectors have been commercially produced but only a few have been found to produce satisfactory results.

#### After-care

The vaccinated area should be kept dry, cool and clean. Bathing need not be omitted nor any of the ordinary occupations, but care should be taken not to soften the crust with water or sweat. Vaccine vesicles should not be opened and abrasion by clothing or any other form of irritation should be avoided. No ointments or other drugs should be applied. Ordinarily no dressing of any kind should be fixed to the vaccination site, but if the lesion should ooze a loose, non-occlusive dressing may be used to protect the clothing. Shields and pads of any sort are unsafe because they favour softening and secondary infection of the vesicle. The site should be inspected between six and eight days after vaccination to determine whether or not a major reaction has taken place.

Routine after-inspections of all vaccinees are impracticable in mass vaccination programmes, but a sample of those vaccinated should be inspected to assure that the technique as well as the potency of the vaccine are satisfactory (WHO, 1967). As interpretation of revaccination responses is subject to considerable variation, the proportion of primary takes in pre-schoolchildren is relied upon to assess vaccine potency and technique. Primary take rates of 98 per cent. or greater are normally observed, but take rates of 95 per cent. or more are considered acceptable.

#### Immunity conferred by vaccination

The relative degree of protection afforded by vaccination at different intervals after exposure cannot be stated exactly. Control studies are ethically impossible and, in retrospective studies the exact day of acquisition of infection usually cannot be determined because of continued exposure of the contact and the patient over an extended period. However, as immunity conferred by primary vaccination begins to develop about the eighth day and since the incubation period of smallpox is frequently 12 days or more, a successful vaccination performed no later than 24 to 48 hours after exposure usually will prevent an attack. Vaccination within seven days may attenuate the attack. If vaccination is performed later than this, the smallpox eruption and the vaccinal lesion develop concurrently and independently. Because of the more rapid development of antibody response following revaccination, reasonably complete protection against smallpox is afforded by successful revaccination as late as seven days after exposure and partial protection if as late as the eighth or ninth day.

The duration of immunity following vaccination varies with individuals and wanes gradually. Observations in endemic areas indicate that, following successful primary vaccination, more than 95 per cent. are protected for at least five years against variola major and virtually 100 per cent. against variola minor. The occurrence of a few cases within five years may reflect individual variations in response as well as the degree of intensity of exposure. After successful revaccination, protection is far more substantial and longlasting, almost certainly extending to 20 years or more in respect to variola major and probably for life in regard to variola minor. Protection against a fatal outcome persists much longer than protection against acquisition of smallpox.

For purposes of international travel and among high-risk workers in hospitals, vaccination every three years is recommended. This requirement would appear conservative in view of the above. However, in these instances there is a desire to obtain virtually complete assurance of protection irrespective of cost.

In the past it was assumed that the occurrence of a major reaction following revaccination implied lack of protection to smallpox. This definitely is not the case, if sufficiently high titre vaccine is used, more than 90 per cent. of persons successfully vaccinated only a year before will develop a major reaction, yet cases of smallpox among such persons are virtually unknown. Further, a large proportion of persons who have experienced smallpox only 10 years previously will experience major reactions although it is known that second attacks of smallpox are most unusual.

### Contraindications

Contraindications to vaccination differ for endemic and for non-endemic areas. In endemic areas the risk of death and serious complications due to smallpox is so great that the comparatively minor risks of vaccination are ignored. In such areas, only those who are seriously, acutely ill are not vaccinated on the practical grounds that if such a person were to die as a result of his disease, the death might wrongly be attributed to vaccination.

In non-endemic areas, three groups of persons are not vaccinated: (1) persons with eczema or other forms of chronic dermatitis or in contact with such persons in their household; (2) pregnant women; (3) patients with leukemia, lymphoma and other reticuloendothelial malignancies or dysgammaglobulinemia or those under therapy with immunosuppressive drugs. If vaccination is required for persons in such situations because of potential exposure, vaccinia immune globulin (0.3 ml per kg by the intramuscular route) should be administered simultaneously.

### Dangers and complications

Vaccination is a comparatively safe procedure provided the appropriate contraindications are followed. As with any other drug or biological product, however, complications do occur among a small proportion of those vaccinated. Most occur after primary vaccination or in individuals who have not been vaccinated for several decades.

### Post-vaccinal encephalitis

Encephalitis following vaccination is a rare event and occurs normally between the eighth and fifteenth day. It is believed to represent a hypersensitivity phenomenon rather than a central nervous system infection per se. The disease may be associated with fever, headache, vomiting, drowsiness, and sometimes paralyzes, meningitic signs, coma and convulsions. The cerebrospinal fluid usually shows an increase in cells. Paralysis, when it occurs, is generally spastic in type but later may become flaccid. Recovery may be complete or residual paralysis and other central nervous system symptoms may persist. There is no known satisfactory treatment.

Studies conducted in the United States of America in 1963 and 1968 (Neff, et al. 1967 and Lane, et al. 1969), revealed that among an estimated 11.3 million primary vaccinees, 28 cases occurred of which nine were fatal. No cases occurred among 16.3 million revaccinees. Comparable studies in other parts of the world have not been reported. However, based on available data from countries using the Lister strain vaccinia virus, the frequency of post-vaccinal encephalitis following application of this vaccine would appear to be similar. Following application of vaccine produced with such as the now uncommon Copenhagen and Hamburg strains of vaccinia, a higher incidence of post-vaccinal encephalitis is observed.

In appraising the frequency of this complication it must be noted, however, that the diagnosis of encephalitis as to specific cause is often exceedingly difficult and some cases almost certainly are erroneously attributed to vaccination when, in fact, another agent has been responsible. Among young children particularly, encephalitis or sudden death due to other causes is not uncommon and thus the occurrence of encephalitis following vaccination does not necessarily represent encephalitis caused by vaccination.

### Progressive vaccinia (vaccinia gangrenosa)

Progressive vaccinia is an exceedingly rare but often fatal complication among vaccinated persons who have deficient immunity mechanisms, e.g. hypogammaglobulemia, agammaglobulinemia, disturbance of the normal immunity mechanism consequent to tumours of the reticulo-endothelial system (e.g. leukemia) or to whom immunosuppressant drugs have been given. The initial vaccinal lesion fails to heal and progresses to involve adjacent skin with necrosis of tissue.

Dissemination of virus may result in metastatic vaccinia lesions in other parts of the skin, bones or viscera. In the United States of America studies conducted in 1963 and 1968, 12 cases including two deaths, occurred among 11.3 million primary vaccinees and eight cases, including two deaths, among 16.3 million revaccinees. The low case-fatality ratio undoubtedly reflects the influence of therapy, primarily vaccinia immune globulin and thiosemicarbazone. Essentially all of these cases could have been prevented had the accepted contraindications to vaccination been observed.

#### Eczema vaccinatum

Eczema vaccinatum is sometimes a serious complication which may occur in persons with either active or healed eczema. It occasionally occurs among eczematous subjects who are in contact with recent vaccinees but who have not themselves been vaccinated. The disease tends to localize at sites where eczematous lesions are or have been present. Although occasionally resembling smallpox because of the character of the lesions and their occurrence in a single crop, the distribution of lesions is usually different and, interestingly, the tip of the nose is usually spared. In the United States of America studies referred to above, 112 cases occurred among primary vaccinees, 11 among revaccinees and 114 among contacts. Three of the cases among contacts subsequently proved fatal.

Vaccinia immune globulin and the thiosemicarbazone drugs are of help in therapy.

#### Generalized vaccinia

Generalized vaccinia represents a secondary eruption resulting from blood-borne dissemination of vaccinia virus. Almost all cases occur after primary vaccination. The lesions become evident between six and nine days after vaccination; the number of lesions may range from a few to a generalized involvement of the skin. Although resembling vaccinia lesions, they are usually smaller and more superficial and mature more rapidly as a result of developing immunity in the individual. Although all lesions may appear to be at the same stage of development (as in the instance of smallpox), the distribution of the lesions does not correspond with the usual centrifugal distribution observed with variola nor do they have the same consistency on palpation. Although the development of generalized vaccinia may be alarming to both the physician and the vaccinee, it is almost invariably a self-limited illness and complete recovery occurs without benefit of specific therapy.

#### Foetal vaccinia

Foetal vaccinia results from a blood-borne dissemination of vaccinia virus in the pregnant woman given primary vaccinations. It may occur during any trimester of pregnancy, and frequently results in death of the foetus. Less than 20 cases have been recorded in the world's literature.

#### Miscellaneous complications

A great variety of rashes have been reported to be caused by vaccination. The most commonly reported include erythema multiforme and variously distributed urticarial, maculopapular, blotchy erythematous eruptions. In addition, a great variety of other complications have been noted, many of which appear to represent coincidental events unrelated to vaccination itself.

Secondary infection may sometimes occur at the vaccination site. However, in determining whether secondary infection is present, it is well to recall that following primary vaccination a distinct, sometimes angry-appearing erythema which resembles erysipelas may develop, as well as lymphangitis and axillary lymphadenitis. In most instances, such lesions contain no bacteria and healing occurs uneventfully. However, secondary infections due to staphylococci, streptococci, tetanus bacilli and others sometimes occur. Occlusive dressings or, more commonly in tropical areas, the application of miscellaneous local potions such as cow dung, masticated herbs and so forth, favour the development of such infections.

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