

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE
FOR THE EASTERN MEDITERRANEAN



ORGANISATION MONDIALE DE LA SANTÉ
BUREAU RÉGIONAL
POUR LA MÉDITERRANÉE ORIENTALE

SEMINAR ON SMALLPOX ERADICATION
Dacca, 29 October - 5 November 1969

EM/SEM./SE/13

ENGLISH ONLY

TECHNICAL CONSIDERATION IN SMALLPOX
VACCINATION

by

Dr. Henry M. Gelfand^{*}
WHO Temporary Adviser

*

Epidemiologist, US Public Health Services for Europe, London.

EMRO/69/1107

Immunization against smallpox by means of the inoculation of a living preparation of vaccinia virus particles is based on the almost antigenic identity of variola virus with that contained in the vaccine. The difference between them are minor and subtle, and, for all practical purposes, the immunity resulting from infection with one provides cross-protection against the other. The differences that do exist, however, together with the fact that inoculation into the skin is not the "normal" portal of entry for smallpox, produce immune responses that are quantitatively different, and these influence requirements and recommendations for the use of smallpox vaccine.

It should be emphasized that infection with the smallpox or vaccinia virus is subject to the same fundamental principles of pathogenesis and immunology as that following other viruses. Among those of practical importance to us may be listed the following:

- (1) The likelihood of inducing infection in the non-immune is related to the dose inoculated and to the successful placement of infectious particles in proximity to susceptible cells (i.e. the technique of vaccination).
- (2) After infection is induced, the continued multiplication of the virus in vivo provides the necessary antigenic mass for a sufficient immune response, but the amount of the original inoculum may influence the rate of multiplication and therefore the speed of the immune response.
- (3) Infection induces the formation of various humoral antibodies, at different rates and persisting for different periods of time, but only neutralizing antibody (NA) is believed to be biologically active in protection from reinfection.

Complement fixing (CF), hemagglutination-inhibiting (HI), and precipitating antibodies probably play no role in the immune mechanism but serve as useful diagnostic indicators.

- (4) Neutralizing antibody usually persists for years following active infection, but it gradually declines, and with this decline immunity gradually diminishes and ultimately may disappear. The rate of loss of protection can be roughly expressed for a population of people, but there is much individual variation among persons.
- (5) The level of protection possessed by a previously vaccinated individual is related both to his immune status and to the dose of virus to which he is later exposed. This applies both to subsequent revaccination and to exposure to smallpox, and influences the dose requirement for revaccination and the relative protection needed by people with high or low potential exposures to smallpox cases.
- (6) Reinfections with vaccinia virus (i.e. revaccination) result in more rapid, heightened, and more lasting antibody responses than those following primary vaccination.
- (7) Different strains of vaccinia virus may have differing antigenicities (i.e. immunity-provoking effects) and reactogenicities (i.e. adverse clinical responses).

1. Immunologic basis of vaccination against smallpox

1.1 Immunity following infection with variola virus

In general, antibody response to smallpox is more rapid, of higher titer, and persists for a longer period of time than that following

vaccination. Neutralizing antibodies are usually present by the sixth day of illness. The vigor of the immune response is presumably related to the large quantity and wide distribution of the virus in the body. In fatal cases, however, the NA titer before or after death is generally low - either because of a deficiency in antibody production (and thus contributing to the fatal outcome) or because antibody is bound by the large quantity of viral antigen.

CF antibodies are usually present by the eighth day after onset of smallpox and usually disappear within six months. HI antibodies are detectable usually in 5 to 7 days after onset and usually disappear within a year. Titers vary greatly from case to case.

NA may persist for life following recovery from smallpox, and this is perhaps related to the expected life-long immunity to the recurrence of disease. Second attacks of smallpox have been documented infrequently, but these have usually occurred many years after the first attack and under conditions of very heavy exposure. It is often possible to obtain a successful vaccination "take" in persons with a past history of smallpox. Since this indicates insufficient immunity to withstand the virus challenge, it also indicates that such people should be vaccinated for complete protection.

1.2 Antibody response following primary vaccination (PV)

Neutralizing antibodies do not appear until 12 -15 days after the first successful vaccination. Titers reach their peak levels only after three to four weeks, and are normally lower than those following smallpox. However, if vaccination is complicated by generalized vaccinia, during which there is systematic dissemination of large amounts of virus, NA titers may reach the same levels as are found after smallpox.

NA antibodies eventually reach about the same peak titers after PV with vaccines of either high or low potency, but a longer period of time is required when the vaccine (or the vaccination technique) was of poor quality. The evolution of the vaccinal lesion is similarly delayed with poor vaccine. This slow response may have great significance when speed is essential, such as when vaccination is performed in persons who have already had known contact with a smallpox case, or in a community under epidemic threat.

CF antibodies may not be detectable at all following primary vaccination, or they may be found in low titer after two weeks and then disappear during the next several months. HI antibodies usually appear after two weeks, and at a titer higher than after revaccination but lower than after smallpox, and then decline to low levels within a year.

1.3 Antibody response after revaccination (RV)

Whether or not neutralizing antibodies persist from previous vaccination, RV results in a rapid rise in titer (within 5 to 8 days) to a level 5 to 10 times higher than after PV. The persistence of a significant titer following RV is likely to be of many years duration.

CF and HI antibodies may or may not reappear after RV, and are usually at about the same level or lower than those after PV.

1.4 Effectiveness and duration of immunity following vaccination

1.4.1 As measured by resistance to subsequent vaccination

Within the first year after PV attempts at vaccination frequently fail, even with the use of highly potent vaccine and excellent technique. During the years following, consistent with the gradual decline in NA, increasing proportions of vaccinees develop major reactions

with fever.

There is a reciprocal relationship between dermal resistance to revaccination and the titer of vaccinia virus required to overcome it. In those vaccinated one to three years previously, the vaccinia virus concentration required is about 50 times as great as that needed for successful PV, after 10 to 20 years a vaccine of only 10-fold greater potency is necessary, and beyond 20 years after PV many revaccinees will show major reactions resembling "primary takes" with vaccine of the same potency as that required for primary vaccinees.

These findings have significance for two practical considerations. First, they indicate the need for revaccination if immunity is to be maintained, since dermal susceptibility to RV is considered to reflect relative susceptibility to smallpox infection. Second, in order to be successful RV requires fully potent vaccine and good technique. If the vaccine used meets minimum WHO standards (10^8 PFU/ml) and the technique of vaccination is of acceptable quality, it should be possible to induce "major reactions" in about 90% of a general population of revaccinees.

1.4.2 As measured by resistance to subsequent disease

It has been extraordinarily difficult to measure precisely the degree and duration of protection afforded by vaccination against natural infection by the smallpox virus. The relationship between antibody level and protection has not been determined directly and can only be inferred on epidemiologic grounds. Prospective epidemiologic studies are almost impossible, and retrospective studies are subject to many biases and variables relating to differences in exposure and to the

intervals since vaccination and revaccination.

Dixon's (1) estimates of the probability of contracting smallpox after primary vaccination, based on an extensive review of a large number of smallpox cases, are widely known but are reproduced below.

| <u>No. of years since PV</u> | <u>Probability of contracting SP</u> | <u>% vaccine effectiveness</u> |
|------------------------------|--------------------------------------|--------------------------------|
| 1 | 1 : 1,000 | 99.9 |
| 3 | 1 : 200 | 99.5 |
| 10 | 1 : 8 | 87.5 |
| 20 | 1 : 2 | 50.0 |
| over 20 | little no protection | - |

There is no doubt that almost complete protection is produced for at least one year, and smallpox cases within three years after successful vaccination are infrequent and generally mild.

In most epidemic studies it has only been possible to express the effect of prior vaccination by comparing the attack rates for unvaccinated persons and those bearing vaccination scars, disregarding the interval since vaccination or the frequency of R.V. An example from here in Dacca District was recently published in the Weekly Epidemiological Record (2) the pertinent effectiveness data are as follows:

| <u>Age (years)</u> | <u>Unvaccinated</u> | | | <u>Vaccinated</u> | | | <u>% vaccine effectiveness</u> |
|--------------------|---------------------|------------------|-----------|-------------------|------------------|-----------|--------------------------------|
| | <u>Number</u> | <u>No. cases</u> | <u>AR</u> | <u>Number</u> | <u>No. cases</u> | <u>AR</u> | |
| 0 - 4 | 688 | 30 | 4.4 | 884 | 1 | 0.1 | 98 |
| 5 - 14 | 217 | 35 | 16.0 | 2386 | 24 | 1.0 | 94 |
| 15 + | 74 | 6 | 9.4 | 3444 | 14 | 0.4 | 96 |

It is unlikely that many vaccinees below 5 years old had been vaccinated more than once, but the interval since vaccination was necessarily just

a few years. The interval since PV was probably much greater among those over 15 years old, but many may have been revaccinated.

In a study of intrafamilial transmissions of smallpox, conducted by Dr. A.R. Rao and associates in Madras (3), somewhat greater precision of estimation was possible, and the effect of revaccination could be examined separately. The following table is based on his data:

| Vac. status | Household contacts | | | % vaccine effectiveness |
|--------------|--------------------|--------------|------|-------------------------|
| | Number | No. SP cases | AR | |
| Unvaccinated | 103 | 38 | 36.9 | - |
| PV only | 904 | 13 | 1.4 | 96 |
| PV + RV | 242 | 1 | 0.4 | 99 |

It should be noted that the contacts included in Rao's study were living under conditions of heavy exposure within infected households. Nevertheless, and despite the long interval since vaccination in many instances, PV alone afforded a very high level of protection and RV enhanced this effect almost to the point of complete insusceptibility.

The significance of these data to recommendations for revaccination will be discussed below (section 3).

2. Age at first vaccination

There appears to be no age-related "natural" resistance to smallpox in man. Unless an infant is born with passively-transmitted maternal antibodies he is susceptible from the moment of birth, and the probability of his becoming infected is determined solely by exposure. Maternally-derived, passive immunity disappears within 5 to 6 months. Therefore, when the probability of exposure is great, vaccination should be performed as early in life as possible.

The two basic considerations in the utilization of any vaccine, safety and effectiveness, apply with greater than usual force in infancy, and especially in the neonatal period. The newborn is traditionally considered to be both a uniquely tender host and relatively incapable of an adequate immune response. Neither concept is entirely correct as regards smallpox vaccination, and any age, from birth onward, may be considered for primary vaccination. The recommendations to be made must be based on a balance between the likelihood of exposure to smallpox, the probability of adverse reactions, and vaccine potency.

2.1 In endemic areas or when exposure to smallpox is threatened in non-endemic areas

Large-scale vaccination in newborn babies has been practiced in Hong Kong for some years, with complete safety and with over 90 per cent take rates ⁽⁴⁾. Neonatal vaccination is also performed routinely, although on a smaller scale, in Madras. There seems little doubt that babies only two to three days old respond adequately to vaccination, if vaccine potency is adequate (see 2.3), and that severe reactions and complications are no more frequent than with older infants. In fact, reactions may be less marked than with older people if the infant has passively-acquired antibodies from a vaccinated mother.

In endemic areas, therefore, or following a smallpox introduction into non-endemic areas, PV should be performed at the earliest age practicable. The peculiar susceptibility of infants to the more severe, fatal types of smallpox, and the accessibility of newborns in hospital or at home under the supervision of a midwife, are excellent reasons for urging vaccination as soon as possible after delivery. Immunity may wane more rapidly following vaccination very early in life, however,

and RV should be performed at about the first birthday.

Although simultaneous immunization with multiple antigens will be discussed separately by another speaker, it may be appropriate to mention BCG vaccination at this time. The latter was performed concurrently with smallpox vaccination in 300 000 newborns in Hong Kong ⁽⁴⁾, and excellent results were obtained with both vaccines.

2.2 Routine vaccination in non-endemic areas

The considerations mentioned above, in favour of neonatal vaccination, apply also to routine practice in non-endemic areas. The neonatal period may be the most practicable time to reach infants in many countries.

In many parts of the world the infant becomes subject, a few weeks after birth, to a variety of immunizing agents such as DPT, poliovaccine, measles vaccine etc. For this reason, smallpox vaccination has often been postponed to about 6 months of age. At this time maternally-derived antibodies have disappeared. There is some evidence, which will be discussed by another speaker, that complications of vaccination are somewhat more frequent during the second half of the first year of life, leading to the recommendation that vaccination be further postponed until after the first birthday. Where the threat of smallpox is minimal, and the facilities for detecting possible importations are good, such postponement may be considered. These considerations must be balanced, however, against the need to ensure that no large body of susceptible children is accumulated until smallpox eradication is achieved.

2.3 Relationship of age to vaccine dose

When PV is performed in the neonatal period, many vaccinees will have some degree of passive immunity from maternally-derived NA. Comparative

studies have shown that this interferes with vaccination to a degree similar to the resistance shown by adults revaccinated 10 - 20 years after PV. A 10-fold greater potency of vaccine is required than with infants five to six months old.

Smallpox vaccines meeting WHO requirements must have 10^8 PFU/ml. This is an adequate titer to surmount the resistance of neonates if the vaccine is properly prepared and handled and if vaccination technique is good, and "take rates" of 95 - 100 % should be obtained.

3. Frequency of revaccination

Although it would be desirable to ensure complete immunity in the entire population, this ideal is difficult to maintain in practice. It is therefore necessary to balance the need for protection against the risk of exposure.

3.1 Routine recommendations in endemic countries

Neonatal PV should be followed by RV at about one year of age. Following PV in later infancy or early childhood, RV should be administered at school-entering age (i.e. 5 to 6 years), again after another ten years (at school leaving or 14 -16 years of age), and again after a further ten years.

Where the disease is heavily endemic, or where area-wide mass vaccination campaigns are the practice, revaccination every three, five, or seven years may be advisable - depending on circumstances.

3.2 Routine recommendations in non-endemic countries

A single revaccination at the time of school entrance (following PV in infancy) should be sufficient if it is performed with potent vaccine and good technique, and if facilities for the prompt detection

of smallpox introductions are adequate. Where the threat of smallpox introduction is great and the possibility exists that introductions may be overlooked for some time, routine revaccination every 5 to 10 years is advisable.

3.3 For persons subject to unusual risk

Medical and hospital personnel, certain field health workers, laboratory personnel, and other persons in endemic countries likely to be intimately exposed to smallpox cases should be revaccinated annually.

The present requirement for RV every three years for international travellers continues to be reasonable. A similar requirement should be adopted for the special categories mentioned in the preceding paragraph, in non-endemic countries, and to selected port and airport personnel everywhere.

3.4 For persons with known or probable exposure in outbreaks

Immediate revaccination of all individuals at reasonable risk should be required regardless of previous vaccination history.

4. Number of vaccine insertions required

4.1 Relationship between immunity and number and size of vaccination scars

There is a general quantitative relationship between antigenic mass and immunological response. There thus exists a theoretical basis for expecting that multiple insertions of smallpox vaccine might result in more effective and more long-lasting immunity. The evidence that this is true in practice is equivocal, however, and it is unlikely that there is any advantage to more than one inoculation in routine modern practice.

The NA titer resulting from successful vaccination with a vaccine of suboptimal potency is ultimately as high as that following use of a fully acceptable one, although delayed. Furthermore, no significant difference in NA titer has been found among individuals with one, two, three or four scars.

On the other hand, studies in Europe early in this century showed that the death rate among smallpox patients with one vaccination scar was several times greater than that of patients with four PV scars, and a more recent study in India showed both lower mortality and milder disease to be associated with multiple PV scarring. These investigations, however, did not rule out the possibility of biases related to the comparability of the groups with regard to interval since vaccination, frequency of RV, etc.

A more likely explanation of these results is related to the quality of the vaccines then in use. With low virus titer, and traumatic vaccination technique and heavy bacterial contamination, many "vaccination" scars probably resulted from bacterial infection rather than vaccinia virus multiplication. Furthermore, with active bacterial and viral infections concurrent in the same lesion, interference may have inhibited full expression of the viral antigenic stimulus.

Modern experience has repeatedly demonstrated the efficacy of a single insertion of vaccine (meeting WHO standards, which prescribe minimum potency and maximum bacterial contamination) and a small vaccination scar.

4.2 Probability of take

Where vaccine potency is low, technique uncertain, or resistance to reinfection high (in revaccination), multiple insertion improves the

likelihood of successful vaccination purely on the basis of chance. For example, if the probability of "take" is 50% for one insertion, it will be 75% that at least one will "take" if two are administered. At the 90% level of chance for one insertion, the probability for two is raised to 99%.

4.3 Risk of vaccine complications

General systemic reactions with fever are often more severe following PV at multiple sites. Severe reactions of this sort serve to increase the reluctance of the general public to submit to vaccination and make good public relations difficult. Furthermore, there is some evidence that multiple insertions in PV increase the frequency of the more serious complications.

4.4 Recommendations

On the assumption that fully potent vaccine and good vaccination technique are used, a single insertion only should be used for primary vaccination in routine practice. In epidemic situations, and particularly when exposure has already taken place, two PV insertions should be given.

For routine revaccination, particularly in endemic areas, two insertions are advisable; in urgent situations, three RV insertions can be given.

5. Immunogenicity and reactogenicity of vaccine virus strains

Immunogenicity and reactogenicity are separate but apparently associated qualities of vaccinia strains. It has long been recognized that some vaccine preparations produce larger and more ulcerating lesions than others, with more local pain and tenderness and higher

fevers and greater general malaise. Only within the last several years has this been studied in detail, with laboratory control.

The virus population comprising a vaccine is heterogeneous, and contains a variable proportion of at least two kinds of virus particles, with different growth characteristics in chick embryos or on tissue culture and differing antigenicity and reactogenicity in man. By selection it is possible to produce a "pure" vaccine of one or another genetic type, or various mixtures of the two. Unfortunately, a vaccine producing the minimum of undesirable local and systematic effects may have an unacceptably low "take" rate, despite high titer, and one which induces an exceptionally good antibody response and a high "take" rate may produce systemic effects too severe to be acceptable.

Further research will undoubtedly continue in the search for a strain with maximum immunogenicity and minimum reactogenicity. In the meanwhile, it is only possible to strike an acceptable balance between the two, and a "moderate" degree of dermal reaction and fever appears to be desirable and unavoidable.

REFERENCES

1. Dixon, C.W. "Smallpox", London, J. & A. Churchill Ltd., 1962.
2. World Health Organization. Wkly. Epid. Rec. 44 : 418, 20 June 1969.
3. Rao, A.R. et al. Indian J. Med. Res. 56 : 1826, 1968.
4. Moodie, A.S. and Cheng, G.K.K. Tubercle (Edinb). 40 : 155, 1962.