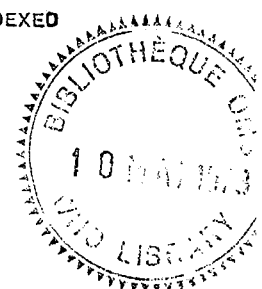




SMALLPOX VACCINATION BEFORE THE AGE OF 3 MONTHS: EVALUATION OF SAFETY¹

by

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Introduction

The most suitable age for primary smallpox vaccination has been the subject of several studies and numerous disputes, especially during the last decade. Traditionally, the serious complications, such as postvaccinal encephalitis, were thought to increase in frequency with age in a continual fashion. This view was modified by findings reported from Great Britain by Conybeare (1964) and from the United States by Neff et al. (1967) and by Lane et al. (1969). These reports concluded that there was a higher risk of serious complications after vaccinations performed before one year of age as compared to vaccination later in life.

In none of these studies, however, was it possible to determine if the complication rates varied within the first year, although from the data of Lane et al. (1969) it appears that the burden falls mainly on the last half of the first year, at least as far as encephalitis is concerned. The failure to distinguish between the various subfractions of the first year is especially unfortunate since no one-year period in life is more variable than the first one with respect to physiological and immunological state, etc. Thus maternal immunity, if at all transferred, is present during the first 3-5 months of life but is mainly absent during the second half-year.

The present study is an attempt to compare the risk of complications after smallpox vaccination in the first trimester of life with the risks in older age-groups.

Take rate, fever and immunity following early vaccination

One of the first studies on vaccination in early infancy was reported by Wolff (1889) who vaccinated newborns and observed a course of reaction that was "almost always completely afebrile". Similar findings were reported later by Donally and Nicholson (1934) and by Malmberg (1935). Another feature of such early vaccination was an apparently higher resistance in the very young infant as reflected by a relatively low take rate. Studies by Kempe and

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Benenson (1953) and by Doorschodt (1955) indicated that antibodies transferred prenatally from the mother were the probable cause of this attenuation of the vaccination reaction. On the other hand, the results of Doorschodt (1955) demonstrated that young infants of unvaccinated mothers were as sensitive as older children, as indicated by take rates.

In several studies in Sweden we have tried to find quantitative estimates of some parameters needed for judging the practicability of early vaccination.

Take rates were compared in infants below 10 weeks of age and in children aged five to 12 months (Espmark and Rabo, 1965a). As shown in Fig. I the pattern of response to the several vaccine doses is similar for both age groups, but the younger group required a vaccine approximately 10 times more concentrated to yield the same take rates as were obtained in the older group. Take rates in the younger age-group were sufficiently high, i.e. 95% or more, provided that vaccine titre was adequate (in excess of 10^8 TCID₅₀ per ml).

Fever reactions, defined as elevation of rectal temperature above 38°C, were almost regularly observed in children aged five months or more although a certain dependence upon the dose of vaccine was noted (Espmark, 1965). This is shown in Fig. II. The two small groups of passively immunized infants, i.e. six 1-2 months old babies of vaccinated mothers and five 5-12 months old children given large doses of vaccinia immune globulin were afebrile or exhibited only a one-day fever response. Also local reactions (pock size) were less marked in the passively immunized groups.

A partial inhibition in the development of immunity, measured as a reduced resistance to revaccination, was noted in infants vaccinated as newborns by Donally and Nicholson (1934). In Swedish experiments, neutralizing antibodies were compared in infants vaccinated at one month of age and at nine to 12 months, respectively (Espmark and Rabo, 1965b). A possible tendency to lower titres in the younger group could not be shown to be significant.

Complications after early vaccination

The findings, in limited trials, of an attenuation of local and febrile reactions in infants with maternal immunity does not necessarily mean that the rate of complications is also low although this would seem likely. The ultimate proof depends on data derived from large numbers of vaccinees. However, there is ample evidence that even a moderate passive immunity, produced by injection of vaccinia immune globulin, will significantly reduce the risk of encephalitis after primary vaccination in adults (Nanning, 1962).

The following data on vaccination policy in Sweden are given as a background for the present study. Vaccination was strictly compulsory in Sweden until 1958 when a certain liberalization was introduced. In spite of this only about 90% of the population was covered by childhood vaccination. There was no recommended revaccination in females until 1966, when voluntary revaccination in the third to fifth grades of the schools (age 10-12 years) was recommended. During the 1963 smallpox outbreak in Stockholm about 5% of the population was revaccinated. Other European outbreaks, as well as international travel, have resulted in further revaccination. It is estimated that 85-90% of the mothers of children covered by this study had received primary vaccination and that less than 10% of them had been revaccinated.

The age of two months was officially recommended as the age of choice for routine smallpox vaccination in 1959 (Kungl. Medicinal-styrelsen, 1959); as an alternative the age of 7-9 months was given. These recommendations were further stressed by official circulars and articles in medical journals in 1965.

In 1972 a questionnaire was sent to vaccine subscribers requesting data on the number of infants vaccinated before three months of age, number of takes and number and types of complications. Through September, about 50% of the 1100 questionnaires had been completed and returned. Of 177 000 vaccinations reported, about 145 000 produced a take. The total reported

corresponds to somewhat less than 15% of the total number of children vaccinated. Evidently this figure is an underestimate. The overall take rate was 82%. The complications reported on the questionnaires were supplemented by data on officially reportable complications available at the Royal Medical Board. No case of serious complication (postvaccinal encephalitis, vaccinia necrosum or eczema vaccinatum) was reported in the 0-3 months age-group. As seen in Table 1 several cases of postvaccinal encephalitis were recorded in older age-groups during the time period of this study. There is no significant difference between the 4-12 months group and the 1-4 years group in so far as the rate of encephalitis is concerned, i.e. about one case per 70 000 vaccines was recorded. With the same rate about two cases would have been expected in the youngest age-group. Clearly, the material is not yet large enough for definitive conclusions to be drawn. However, it does seem justified to state that the risk of serious complications at the age of 0-3 months does not appear to be greater than at any other age.

All the complications reported in the younger age-group were benign, consisting of secondary spread of single or multiple pocks (Table 2).

Summary

Smallpox vaccination in the first trimester of life has been practised on an increasing scale in Sweden for the past 10-15 years. Recently an attempt was made to estimate the rate of complications in this age-group using questionnaires. Among more than 145 000 vaccines with a take, no case of serious complication was noted. This is less than would be expected if rates were the same as in the latter part of the first year; however, the number of observations has to be further increased before definite conclusions can be drawn.

REFERENCES

- Conybeare, E. T. (1964) Illnesses attributed to smallpox vaccination during 1951-1960, Part II: Illnesses reported as affecting the central nervous system, Monthly Bull., Ministry of Health (London) 23, 150-160
- Donally, H. H. & Nicholson, M. M. (1934) A study of vaccination in five hundred new-born infants, J. Amer. Med. Ass., 103, 1269-1275
- Doorschodt, H. J. (1955) Is pockenvaccinatie bij de zeer jonge zuigeling doeltreffend? Thesis, University of Utrecht
- Espmark, J. Å. (1965) Smallpox vaccination studies with serial dilutions of vaccine. IV. Graded local responses and fever reactions following primary vaccination in children, Acta Paediat. Scand., 54, 239-246
- Espmark, J. Å. & Rabo, E. (1965a) Smallpox vaccination studies with serial dilutions of vaccine. III. Comparison of take rates in two age groups of infants (Less than 10 weeks and 5-12 months old respectively) Acta Paediat. Scand., 54, 149-154
- Espmark, J. Å. & Rabo, E. (1965b) The formation of neutralizing antibody following smallpox vaccination in young infants with maternal immunity, Acta Paediat. Scand., 54, 341-347
- Kempe, C. H. & Benenson, A. S. (1953) Vaccinia. Passive immunity in newborn infants. I. Placental transmission of antibodies. II. Response to vaccination, J. Pediat., 42, 525-531
- Kungl. Medicinalstyrelsen (Royal Medical Board): Kungl. Medicinalstyrelsens cirkulär till samtliga läkare med anvisningar angående vaccination jämte föreskrifter om anmälan av komplikationer till dessa; den 8 juni 1959 (MF 43/1959)
- Lane, J. M. et al. (1969) Complications of smallpox vaccination, 1968. National surveillance in the United States, New Engl. J. Med., 281, 1201-1208
- Malmberg, N. (1935) On vaccination for smallpox in the earliest infancy, Acta Paediat. Scand., 17, suppl. I, 293-303
- Nanning, W. (1962) Prophylactic effect of antivaccinia gamma-globulin against post-vaccinal encephalitis, Bull. Wld Hlth Org., 27, 317-324
- Neff, J. M. et al. (1967) Complications of smallpox vaccination. I. National survey in the United States, 1963, New Engl. J. Med., 276, 125-132
- Wolff, M. (1889) Uber Vakzination neugeborener Kinder. Virchows Arch., 117, 357

TABLE 1. REPORTED CASES OF POSTVACCINAL ENCEPHALITIS IN SWEDEN 1961-1971
DISTRIBUTION WITH RESPECT TO AGE

Age-group	Estimated number of primary vaccinees (thousands)*	Number of cases of postvaccinal encephalitis
0-3 months	145+	0
4-12 months	370	5
1-4 years	420	6 (1 death)
5-14 years	215	16 (1 death)
>14 years	110	38 (1 death)
Total	1260	65

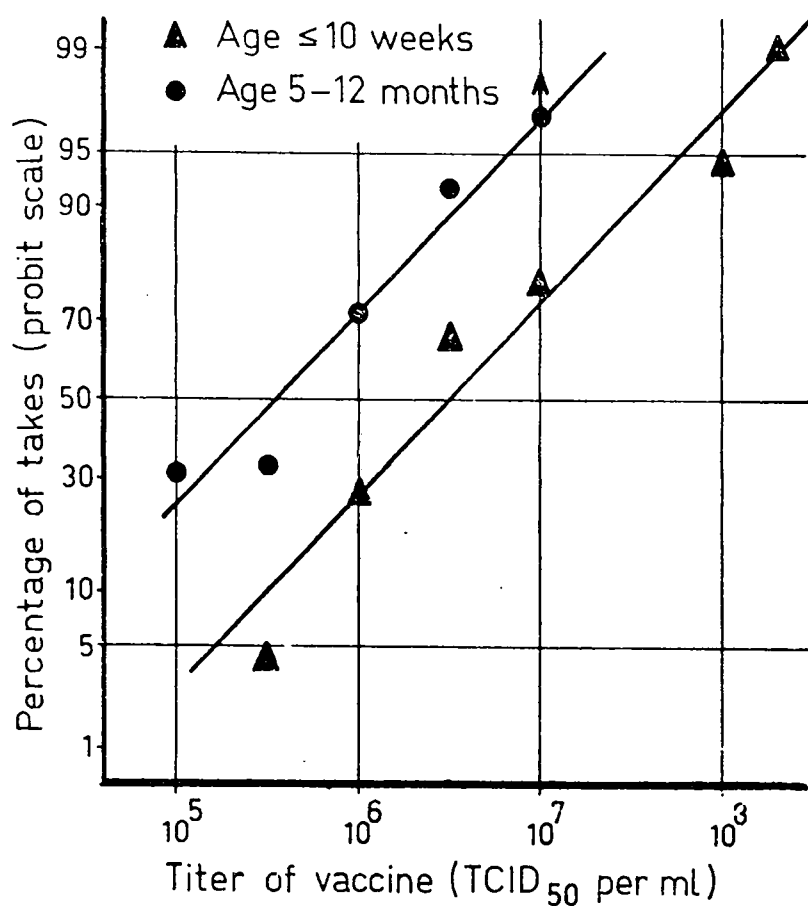
* The first figure is probably much underestimated; remaining figures, based on data from several sources, are very approximate.

TABLE 2. COMPLICATIONS FOLLOWING PRIMARY SMALLPOX VACCINATION OF 145 000 INFANTS BEFORE THE AGE OF THREE MONTHS

Benign generalized vaccinia	2 cases
Multiple secondary pocks	3 cases
Single secondary pocks	6 cases

FIGURE I

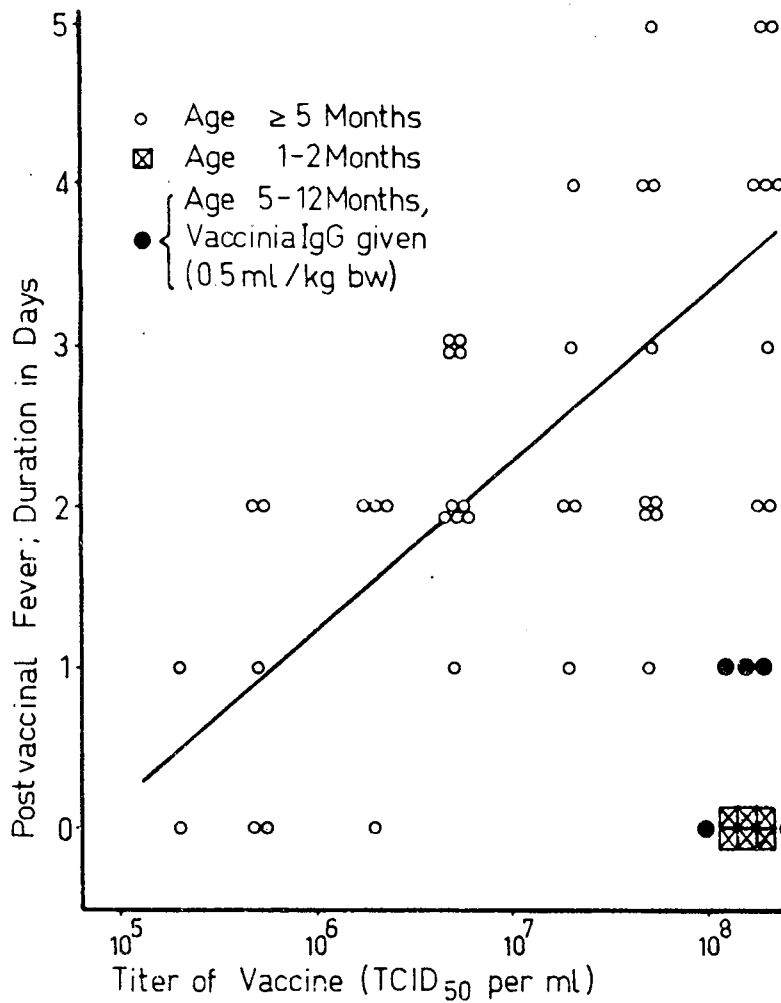
Comparison of take rates in infants aged 10 weeks or less and in children aged 5-12 months after application of a range of dilutions of smallpox vaccine. Success rates, expressed as probits, are plotted against calculated vaccine potencies. The distance between the two parallel curves is almost one \log_{10} .



Data from Table 2 and Figure I of ESPMARK and RABO. 1965a

FIGURE II

The dependence of postvaccinal fever reactions upon the vaccine potency and immunity state. Duration of fever in days is plotted against vaccine potency. Most non-immune children exert fever responses which are partially dose dependent. Note that fever is absent in young infants with maternal immunity and almost absent in older children made passively immune by injection of vaccinia immune globulin.



(Data from ESPMARK, 1965)

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- (1) summaries of some relevant problems of fundamental, epidemiological and operational aspects;
- (2) field project reports and other communications on particular research and eradication aspects which would not normally be published by WHO or elsewhere;
- (3) papers that may eventually appear in print but, on account of their immediate interest or importance, deserve to be made known without delay.

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