

Smallpox vaccination: Complications and present role

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Introduction:

EVER SINCE JENNERIAN vaccination was widely adopted in the control of smallpox in many endemic countries, attention had been focussed on its complications. With the virtual eradication of smallpox in many Western countries, these complications have raised major controversies about the very usefulness of vaccination in controlling outbreaks of smallpox. We have now sufficient knowledge of smallpox from many epidemiological studies to justify a proper assessment of the exact place of vaccination.

Malaysia has been free from smallpox since the last outbreak in Kedah in 1946-47 when 599 cases were reported with 293 deaths. In the middle of September 1971, a suspected case of smallpox seen in the University Hospital, Petaling Jaya, aroused the fear of imported smallpox in Klang, followed by a mass vaccination campaign. This paper presents the results of a study of the complications seen following the mass vaccination, and reviews the present role of vaccination.

Materials and Methods

Between 15th and 19th September 1971, 186,329 people of all ages were vaccinated in Klang. All doctors in the hospital and in private practice were asked to look for complications and to refer patients to the hospital for this study. Forty cases were studied in detail. Where necessary, patients were treated as in-patients.

Results

The following complications were seen during the study.

1. Generalised vaccinia	12
2. Toxic erythema	12
3. Auto-inoculation	4
4. Erythema exudativum	2
5. Local necrosis	1
6. Miliary eruption	1
7. Herpes zoster	1
8. Angio-neurotic edema	1
9. Steven-Johnson syndrome	1

10. Eczema vaccinatum	1
11. Encephalomyelitis	3
12. Vaccinia in newborn	1

Discussion

Complications of smallpox vaccination may be broadly classified into three types:

1. Cutaneous complications
2. Neurological complications
3. Miscellaneous complications.

Cutaneous Complications:

1. *Secondary Bacterial Infections:* These are quite common, especially in children. Being a minor complication, few were referred to the hospital. Local application of an antibiotic cream, such as achromycine, usually heals most lesions.

2. *Local Necrosis:* This can occur as a result of severe secondary bacterial infection or severe pustulation itself. In the case seen in this study, severe necrosis in a Malay male, aged 27, was accompanied by brawny edema of the whole upper limb.

3. *Auto-inoculation:* This follows scratching and transfer of the vaccine material to other parts of the body or to another person in close contact with the vaccinated person. This usually occurs during the first 9 days after vaccination.

Case 1. A 38-year-old Chinese female developed typical vesicles over the upper and lower eyelid with edema of the surrounding area, on the fifth day after vaccination. Recovery was uneventful.

Case 2. A recently vaccinated mother brought her 8-month-old child with typical vesicles over the back of the child's neck, due to auto-inoculation while carrying the child on her left arm.

4. *Toxic Eruptions:* These were the commonest cutaneous complication seen, accounting for 15 cases.

(a) *Miliarial eruptions:* One patient presented with miliarial eruptions along the lymph channels leading from the site of vesiculation.

(b) *Erythema Multiforme:* This is a very common complication, occurring usually 7 to 10 days after vaccination, sometimes up to the 14th day. The eruptions may be localised or generalised, cause little constitutional disturbance and clear in 3-5 days. Sarkany and Caron (1962) described toxic erythema, erythema nodosum, pityriasis rosea, eczema and granuloma annulare after vaccination. Of these, toxic erythema was the commonest type seen in the present study.

(c) *Erythema exudativum:* This is a more severe form of toxic erythema with generalised bullous

formation, fever and protracted course, often described in dermatological literature. Three of our patients had this complication.

Case 1: A Malay female, aged 60, had localised bullous eruptions over the deltoid with echymotic areas.

Case 2: A 9-year-old Malay girl was admitted to the hospital, 8 days after vaccination, with high fever and vomiting. She had developed generalised erythematous eruptions, affecting the whole body, including the soles and palms, with multiple bullae all over, which left large raw areas, on rupture. Healing was satisfactory at the end of 2 weeks. She was very ill on admission, and the fever subsided after 7 days. Treatment included Prednisolone, Marboran 3 GM b.d. for a day, and oral achromycine. These toxic eruptions are probably due to some form of allergy to the vaccine.

4. *Allergic Reactions:* A case of angino-neurotic edema with urticarial eruptions over the trunk was seen. The edema affected the right eyelid and both lips. Another patient had mild Steven-Johnson syndrome.

5. *Eczema Vaccinatum:* This has been reported often since Kaposi originally described the 'varicelliform' eruption named after him. This description is now known to be a misnomer, as the lesion is not caused by varicella at all, and is usually vacciniform or varioliform. Kaposi's eruptions are pox exanthems on a previously damaged skin, usually by chronic eczema. Both vaccinia, herpes simplex and other agents may produce acute pock rash in these cases. Copeman and Wallace (1964) reported 185 cases of eczema vaccinatum during the smallpox outbreak in England and Wales, with 11 deaths. During the outbreak, 3½ million people were given primary vaccination and an equal number re-vaccinated.

Eczema vaccinatum usually occurs 5-14 days after vaccination in an individual with eczema or accidental inoculation by contact with a vaccinated person. Severe forms are marked by toxicity and high fever. The lesions are always more localised to the areas of eczema, and asymmetrical. It generalised, the lesions may closely simulate smallpox. The palms and soles are spared.

Case 1: A 7-year-old Chinese boy was refused vaccination during the campaign, on account of flexural eczema of 3-4 years duration. However, he was in close contact with 9 other recently vaccinated persons at home. He was admitted with extensive eczema vaccinatum on 15.10.71, with a temperature of 103° F. He had developed profuse confluent eruptions over the areas of eczema over

SMALL POX VACCINATION

Table 1

	Generalised Vaccinia	Smallpox	Chicken-pox
1. Prodromal Period	None. More likely with skin disease	Constant even in benign cases Uniform composition and period	None.
2. Distribution of Lesions	No constant pattern	Centrifugal	Centripetal.
3. Lesions on palms, soles	None	Present except in scanty lesions	Absent.
4. Restriction to some areas	Common	Widespread even in scanty lesions	Widespread.
5. Lesions with skin disease	Restricted to diseased skin	Also numerous over diseased skin but distribution elsewhere unaltered	
6. Symmetrical distribution	May be asymmetrical	Always symmetrically bilateral	
7. Confluence of pocks	Unilateral	Bilateral	Bilateral.

the neck, axillae and flexural areas over the trunk, 10 days prior to the date of admission. The general practitioner who saw this boy sent him as a suspected case of smallpox. The fever subsided after 7 days in the hospital. Oral achromycine and Prednisolone 5 mg. t.d.s. for a week enabled a complete recovery.

Winston Turner et al (1962) found Marboran effective in treating eczema vaccinatum, though gamma-globulin was ineffective.

6. *Generalised Vaccinia*: Brown (1965) doubts the existence of this type of lesions and is of the opinion that varicella or other causes are responsible for the lesions. However, most authors with wide experience of smallpox agree that these lesions have distinct characteristics. Jubb (1943) has best pointed out these features:

- (a) Auto-inoculation is to be excluded.
- (b) The eruptions do not appear earlier than the 4th day and seldom earlier than the 9th day after vaccination.
- (c) The eruptions are away from the site of vaccination.
- (d) Vesicular stage must be present.

Jubb estimated the incidence of these eruptions as 1 in 100,000 vaccinations. Lawrence et al (1952) found them in 1 in 25,000 vaccinations in children

in the first year of life.

The distinguishing features of generalised vaccinia, smallpox and chicken-pox are summarised in the following table.

During the mass vaccination campaign, many cases of chicken-pox were seen. However, it was not difficult to diagnose the 12 cases of generalised vaccinia seen. Of these, 2 had fever for two days before they were vaccinated. Three others, including a child who had primary vaccination, had fever with the eruptions. One child had boils on the scalp, while an adult had chronic acne. A labourer who works under the sun daily had the generalised vaccinia localised to the areas exposed to the sun.

Marboran was given for most of these cases with satisfactory results.

7. *Vaccinia in the newborn*: It is now widely accepted that smallpox vaccination is contra-indicated in pregnancy. Both variola and vaccinia can cause abortion and intra-uterine death of the foetus. Abortion can occur even when exposed after the ninth week of pregnancy (S. M. Tucker and D. E. Sibson, 1962). The foetus is at risk even at mid-term (Entwistle et al, 1962). The foetus can develop generalised vaccinia. Pre-natal vaccinia can occur even when the mother is unvaccinated, probably due to airborne vaccinia infection, as report-

ed by Wielenga et al (1961). Eighteen fatal cases of generalised vaccinia in the foetus have been reported so far in the literature. MacArthur reported 10 abortions in 34 women vaccinated in the second and third months of pregnancy. In Poland, the abortion rate in women vaccinated before the 16th week of pregnancy was found to be three times that among controls.

In South Wales in 1962, 2 foetal vaccinia cases were seen among 242 cutaneous complications. One of them survived.

In our study, an Indian boy born on 2.11.71, about a month after the mother had been vaccinated, was found at birth to have generalised vaccinia, of an abortive type, with little vesiculation.

8. *Herpes Zoster Intercostalis*: This may arise in a recently vaccinated person, presumably due to re-activation. One of our patients had this complication. A similar case was reported before from Singapore (1964).

9. *Progressive Generalised Vaccinia*: Here the initial vaccinal lesion fails to heal and spreads to the adjacent skin with necrosis. Metastatic lesions develop in skin, bones and viscera. This rare and fatal complication is associated with hypo- or a-gammaglobulinaemia.

II. Neurological Complications

These have become important as one of the major complications of vaccination in many countries, notably Holland and Britain. In South Wales in 1962, 39 neurological complications were seen after 800,000 vaccinations, out of which 30 involved the C.N.S., with 11 cases of encephalomyelitis. Spillane and Wells have reviewed these complications.

(a) *Post-vaccinal Encephalomyelitis*: This occurs only after the vaccination of the non-immune (primary or re-vaccination), usually after an incubation period of 8-15 days. Fever, headache, vomiting, meningitic signs, paralyses, drowsiness and coma or convulsions are the main clinical features. The C.S.F. shows an increase in cells, mainly lymphocytes, and in protein. E.E.G. shows high voltage slow waves. This complication occurs usually in older children and adults and does not occur in children below 2 years. Recovery is complete.

In the acute stage, mutism, dysarthria and involuntary movements are common. Sometimes the spinal cord is involved with the sequelae of spastic weakness of the lower limbs. Amnesia for the illness is permanent though recovery is complete.

C.S.F. shows an increase in cells, mainly lym-

phocytes, and in protein. E.E.G. shows high voltage slow waves.

Encephalomyelitis does not occur below the age of 2 years, and is usually seen in adults and older children.

In Spillane's series, steroids produced dramatic improvement in 3 cases.

Case 1.: A 13-year-old Chinese schoolgirl (K.K.E.) was admitted on 27.9.71 with history of inability to walk, a week after vaccination. She had a well-formed vesicle. She walked with an unsteady gait, looked dazed and withdrawn and exhibited mutism and marked slowness in executing voluntary movements. The cranial nerves were normal. There was slight neck rigidity and spasticity of the left leg. Reflexes were brisk. Plantar was extensor on the right side. Fundi were normal. On admission she had a fever of 101.4°F.

Lumbar puncture was unsuccessful. She was treated with Marboran 3 GM b.d. for a day, and Prednisolone 20 mg. t.d.s. for five days, the dose being tapered off. Penbritin 250 gm. every 6 hours was also given. Her temperature touched normal after three days and she made a slow recovery, regaining her speech. Amnesia for her recent illness was noted. She was discharged on 4.10.71.

Case 2.: A 39-year-old Chinese male (C.C.W.) was re-vaccinated on 18.9.71. He complained of headache for a week after the vaccination and was admitted on 26.9.71 with inability to walk for two days, with difficulties in speech. He had a temp. of 102°F. He was aphasic and had marked spasticity of all limbs, with opisthotonus. Reflexes were brisk, with bilateral extensor plantar response. B.P. was 150/100.

Lumbar puncture showed C.S.F. under pressure, with 71 cells mostly polymorphs, with sugar 28 mg. %, chlorides 606 mg. %, protein 108 mg. %, and globulin. He was treated with Marboran, A.C.T.H., and antibiotics. His condition did not improve and he died on 1.10.71.

In this case, post-vaccinal encephalomyelitis is the most probable cause of the illness.

Case 3.: A 13-year-old Malay girl (R.b.O.) was vaccinated on 18.9.71. A week after the vaccination, she developed fever and an unsteady gait, and some eruptions on her trunk and lower extremities. On admission on 6.10.71, she was very ill and occasionally delirious. Temp. was 101°F. There was neck rigidity. She was anaemic and also dehydrated. She had lesions of erythema exudativum on her sacrum, and left knee. C.S.F. was turbid, with sugar 216 mg. %, chlorides 704 mg. %, protein 21 mg. %, globulin negative.

SMALL POX VACCINATION

Table 2.
Neurological Complications of Vaccination

	Encephalo- myelitis	Encephalo- pathy
1. Age group of victims	More than 2 yrs.	Infancy and childhood.
2. Incubation period	8-15 days	20 to 18 days.
3. Clinical features	Fever, vomiting, headache, drowsiness, coma, convulsions, mutism, paralyses	Abrupt fever Convulsions Hemiplegia Aphasia
4. C.S.F.	Protein raised Cells raised	Protein may be raised or normal Cells normal
5. E.E.G.	High voltage slow waves	Slow asymmetrical focal activity
6. Pathology	Peri-venous microglial proliferation	Cerebral edema and vascular lesions
7. Involvement of spinal cord	Present	Absent
8. Recovery	Complete Amnesia common	CNS signs may persist No amnesia

In spite of treatment with parenteral fluids, Penbritin and Prednisolone, her temperature did not touch normal except for a day. She developed jaundice and died of septicaemia on 11.10.71.

The clinical picture and the close relationship in time of the illness in the above two cases, to recent vaccination, strongly suggested that these two patients were suffering from post-vaccinal encephalomyelitis.

(b) Encephalopathy: Here, after an incubation period of 2-18 days, usually 8 days, abrupt onset of high fever is followed by convulsions, aphasia and hemiplegia. The spinal cord is not involved. C.S.F. is normal, with some increase in protein in some cases. E.E.G. shows asymmetrical, slow focal activity. Amnesia is uncommon. In some, residual C.N.S. signs may persist. Encephalopathy usually affects children below 2 years.

Table 2 summarises the clinical features of encephalomyelitis and encephalopathy after vaccination.

Meningism, polyneuritis and facial palsy have been reported after vaccination but are rare.

Wynne Griffith has reviewed the neurological complications of vaccination in the United Kingdom since 1896. He found the incidence of encephalitis highest in the first year of life, 15.8 per million (mortality 8.7 per million). It was lowest in those between 1-4 years, 2.1 per million with no deaths. After the age of 15 years, the incidence was 28.7 per million with 2.9 deaths per million.

III. Miscellaneous Complications: Thrombocytopenic purpura (8 cases in literature), osteomyelitis, hyperostosis of bones and cardiac complications, such as angina with E.C.G. changes, pericarditis, arrhythmias and acute focal myocarditis have been reported as complications of vaccination.

Present role of Vaccination:

The present study has focussed attention on the complications of vaccination. There is no doubt the 40 cases seen were a small proportion of the actual number affected, as many patients are unwilling to go to hospital unless the complications are very severe. There is a large amount of morbidity following vaccination, causing a lot of personal inconvenience and suffering, with consequent absence from work. It may be relevant therefore in this context to review the current thinking on the value and place of vaccination.

Dixon has pointed out the limitations of vaccination. According to him, universal infant vaccination will produce immune infants, partially immune older children and generally susceptible adults. Prof. Dick has emphasised that mass vaccination in response to public demand has little effect in controlling the spread of infection. Recent studies by the W.H.O. in African countries has shown that smallpox is not a disease that can spread like wildfire, and contrary to lay opinion, its transmission is slow and limited to the immediate environment of the patient.

Epidemiological control of outbreaks is done on the "ring vaccination" plan (Dixon). The basis of such control is to isolate the case, seek out and vaccinate every contact and keep them under effective surveillance. Thus, vaccination is done "only to protect the right people at the right place at the right time" (Dick). That mass vaccination has seldom any value in the control of a smallpox outbreak has been amply borne out in the outbreak in England and Wales between December 1961 and April 1962. The report by the Ministry of Health

pointed out that indiscriminate mass vaccination did nothing to control the outbreak. Only when the well-tried epidemiological procedures of case-finding, contact tracing and control appear to be failing should vaccination of the whole community be considered, and at first it should be limited to the area where the outbreak exists. (Leader, B.M.J., (1964), II, 1148). "Mass vaccination during a smallpox outbreak is a panic measure and as such is of little preventive value and is to be condemned". (B.M.J. 1964, II, 1348).

Between 1951 and 1970, there were 100 deaths due to vaccination in England and Wales, half of them due to neurological complications. During the same period, 13 imported cases of smallpox gave rise to 103 cases with 37 deaths. (George Dick, 1971) In Canada in the last 20 years, only one fatal case of smallpox occurred compared to 21 deaths due to vaccination. No wonder that countries like the U.S.A. and Great Britain no longer insist, from 1971, on travellers to these countries having valid smallpox vaccination certificates, unless they come from an area where there is a recent outbreak of the disease.

Of course, in many of the African and some of

the Asian and South American countries, where smallpox is still prevalent every year, control measures will be based on an effective programme of infant vaccination and selective re-vaccination of contacts to control outbreaks as and when they occur. The World Health Organisation is carrying out very effective smallpox eradication campaigns in all these countries and the day is not far off when the disease will be eradicated on a global level.

Summary

Forty cases of complications following a mass vaccination campaign to prevent an outbreak of smallpox in Klang are presented. There were two deaths due to encephalomyelitis. Common complications of smallpox vaccination are reviewed. The limited place of vaccination in the effective control of smallpox outbreaks is emphasised. Mass vaccination is rarely indicated.

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