Postgrad. med. J. (May 1969) **45**, 323–326.

Measles vaccination by the intradermal route

W. L. BURLAND
M.B., Ch.B., D.C.H.
Clinical Research Unit,
Glaxo Laboratories, Greenford, Middlesex, Englana

Summary

Live further-attenuated measles vaccines have been given to two groups of children in the United Kingdom by either the intradermal or subcutaneous routes. The responses have been measured by antibody titration and reaction studies. Intradermal vaccination has been shown to be acceptable on both counts.

Introduction

Live further-attenuated measles vaccines were made generally available in the United Kingdom early in 1966 following the Measles Vaccine Committee's Report to the Medical Research Council (1966). Two years later the Ministry of Health (1968, Circular CM 05/68) through its Joint Committee on Vaccination and Immunization recommended that measles vaccination should be offered to all children aged between 12 months and 15 years not previously protected by either vaccination or an attack of the disease.

Mass vaccination campaigns employing the standard technique of individual subcutaneous injections are time-consuming and unpopular with children. A safe and successful method allowing rapid, relatively painless vaccination would be welcome. Symptoms induced by the vaccine in the post-vaccination period and referred to as 'reactions', though generally mild with further-attenuated vaccines have, nevertheless, led to some reluctance on the part of physicians to use them. Any new technique introduced for vaccination against measles should not increase reactions and preferably help to reduce them.

Live measles vaccines have been successfully administered to African children by the intradermal route using a spring-loaded needleless injector, the Dermojet (Cooper *et al.*, 1966). In an initial investigation in 1966, involving a small number of children in the United Kingdom (Sutcliffe *et al.*, 1967) five vaccines of different titres were prepared from the Schwarz strain of further-attenuated measles virus and injected intradermally in children aged between 9 months and 2 years. The results suggested that successful antibody response could be expected in substantially all children following intradermal vaccination, using the accepted standard immunizing dose of virus, approximately 1000 Tissue Culture Doses (TCD_{50}) contained in 0·1 ml. These preliminary studies also suggested that post-vaccination reactions might be reduced using the intradermal route. In a period of 16 months following successful vaccination children exposed to measles have remained fully protected (Sutcliffe, Burland & Hitchens, 1968).

Materials and methods

The investigation was extended and live further-attenuated vaccines of the Schwarz strain were prepared containing 1000 TCD_{50} in 0·1 ml for intradermal injection and 1000 TCD_{50} in 0·5 ml for subcutaneous injection by syringe and needle. They were prepared from a single batch of antigen.

(1) Measles antibody titre was estimated in each of eighty-eight children aged between 4 and 18 years in a hospital for the mentally subnormal. Twenty-five were subsequently vaccinated with one or other of the vaccines. The choice was made at random and children received intradermal vaccination using an Intrajet, an apparatus similar in design to the Dermojet but delivering 0·1 ml consistently. All the children were closely observed during the 2 weeks following vaccination, daily records of symptoms arising in vaccinated and unvaccinated children were kept by the nursing staff. Six weeks after vaccination a second sample of blood was taken from vaccinated children for re-estimation of measles antibody. Antibody titrations were carried out by haemagglutination inhibition (HI) as described by Norrby (1962).

(2) Two groups of normal, healthy children aged between, approximately, 12 and 24 months and attending an infant welfare clinic received the same vaccine using one or other of the two methods of

administration. It was not possible to obtain sufficient blood from these children to measure antibody levels but each child was visited at home twice during the 2nd week following vaccination so that details of any illness in the 2 weeks after vaccination coud be reported. One hundred and ninety children were followed, ninety-six of these received 0·5 ml by subcutaneous injection and ninety-four 0·1 ml by the intradermal route.

Results

(1) The results of the investigation in the hospital population have been described elsewhere (Simpson & Burland, 1969). Thirteen children were vaccinated intradermally and twelve subcutaneously, eight of these children had an antibody level of 1 : 8 and one a level of 1 : 12 before vaccination, the remaining sixteen had titres below 1 : 8 (Table 1). A

TABLE 1. HI antibody response in groups of vaccinated children in hospital

Pre-vaccination HI antibody titre	Vaccination group	Total	Geometric mean post-vaccination HI antibody titres
<1 : 8	Intradermal	11	132
	Subcutaneous	5	115
1 : 8 or >1 : 8	Intradermal	2	88
	Subcutaneous	7	142

satisfactory rise in antibody level occurred in all children vaccinated. Those whose pre-vaccination antibody levels were 1 : 8 or 1 : 12 responded as well as those with levels below 1 : 8 (Fig. 1). The mean antibody levels achieved are shown. Eleven (44%) vaccinated children experienced symptoms after vaccination (Table 2). In the same period twenty-nine (46%) unvaccinated children also showed symptoms. In all but one case symptoms were similar

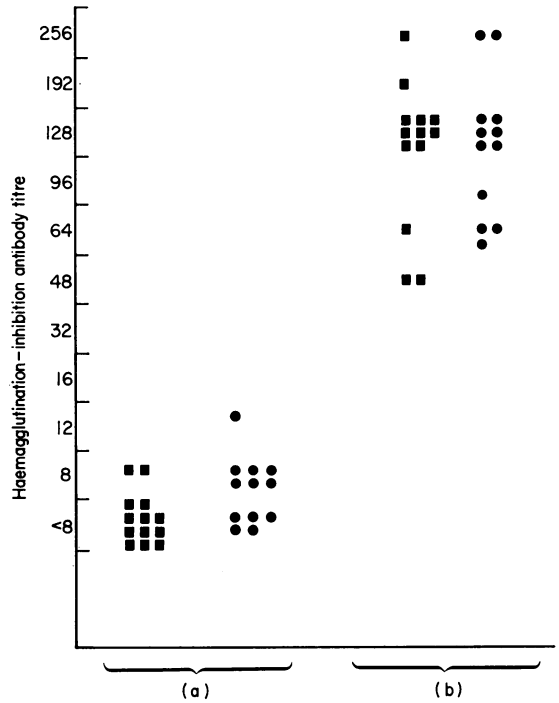

FIG. 1. HI antibody response in vaccinated children in hospital. (a) Before vaccination; (b) 6 weeks after vaccination. ■, Intradermal vaccination; ●, subcutaneous vaccination.

in the two groups. One child developed a mild illness with a morbilliform rash and Koplik's spots after subcutaneous vaccination. Although eleven of the vaccinated children had epilepsy or a history of convulsions, none experienced seizures in the 2 weeks following vaccination.

(2) The symptoms recorded in the young infants are shown in Table 3. There were more children with

TABLE 2. Symptoms in children during the 2 weeks after vaccination in hospital

All symptoms	HA titre <1 : 8		HA titre ⩾1 : 8		Unvaccinated
	Intradermal	Subcutaneous	Intradermal	Subcutaneous	
Fever (T 99·4°F)	1	1	1		5
Rash	1 (localized only)	1			2
Conjunctivitis	1				1
Sore throat			1		2
Coryza	2	2	1	3	27
Cough	2	1	1	1	13
Anorexia					6
Vomiting			1		3
Diarrhoea	2			1	4
Other	3	1	1		7
No. of children with reactions	4	2	1	4	29
Total children in group	11	5	2	7	63

TABLE 3. Symptoms recorded in infants within 2 weeks of vaccination against measles

Method	Patients followed	No. with symptoms within 14 days of vaccination
Needle and syringe	96	44 (45%)
Intrajet	94	34 (36%)

	Syringe	Intrajet
Fever	9 (3 >101·4°F)(38·6°C) (2 >103°F)(39·4°C)	4 (1 >101·4°F)
Rash	4 (1 mild, 2 moderate, 1 severe)	3 (2 mild, 1 moderate)
Conjunctivitis	2	1
Coryza	35	11
Cough	16 (4 'severe')	13 (3 'severe')
Sore throat	1	1
Anorexia	20	9
Vomiting	10 (mild except	2 (mild)
Diarrhoea	8 for 1*)	2
Other e.g.: Irritable, Drowsy, Miserable	16	15
Doctor called	5 (1 admitted to hospital*)	6

* One case of gastroenteritis.

symptoms in the group vaccinated by syringe and needle but the difference is not significant. There were more children with each of the common symptoms such as coryza, cough and anorexia in that group.

Discussion

In the first investigation a dose of live further-attenuated measles vaccine containing 1000 TCD_{50} Schwarz strain of virus produced an adequate rise in antibody level after intradermal injection. There was little difference in symptoms between the two vaccinated groups and between those and the un-vaccinated group. The second investigation shows that although there appeared to be fewer young children with symptoms receiving vaccine by the intradermal route the difference was not significant.

Of the forty-seven children in the hospital thought to have had measles an antibody titre of less than 1 : 8 was found in nine (19%), six of whom had reputedly suffered from measles within the previous 5 years. Krugman, Giles & Friedman (1966) found a mean HI antibody titre approaching 1 : 128 in their group of forty-six institutionalized children 6 years after natural measles infection. Only one child was found to have a titre below 1 : 8. They also showed that children with low titres have a characteristic booster type of response after re-exposure to live measles virus. A second attack of measles is rare and failure to find antibody in young children after an illness supposed to have been measles implies misdiagnosis. Rubella, infectious mononucleosis, roseola infantum and some infections with other viruses, as well as hypersensitivity to drugs such as phenobarbitone, epanutin and antibiotics may be mistaken for measles. It is likely, therefore, that some susceptible children will not be vaccinated. Experience with the hospital population described shows that vaccination of children already immune will simply result in a boost of antibody level without ill-effect and that where there is any reasonable doubt about the previous history of measles, vaccination is indicated.

Acknowledgments

I wish to thank Dr Kenneth Simpson, Consultant Paediatrician and the staff of the Glenfrith Hospital, Leicester, Dr W. Powell Phillips, Medical Officer of Health, City of Cardiff and his staff for their co-operation, and Dr A. J. Beale of Glaxo Laboratories for antibody assays.

References

COOPER, C., MORLEY, D.C., WEEKS, M.C. & BEALE, A.J. (1966) Administration of measles vaccine by Dermojet. *Lancet*, **i**, 1076.

KRUGMAN, S., GILES, J.P. & FRIEDMAN, H. (1966) Studies on immunity to measles. *Proceedings 1st International Conference on Vaccines against Viral and Rickettsial Diseases of Man* (Washington), pp. 353–360.

MEASLES VACCINE COMMITTEE (1966) Report to the Medical Research Council. Vaccination against measles: a clinical trial of live measles vaccine given alone and live vaccine preceded by killed vaccine. *Brit. med. J.*, **1**, 441.

NORRBY, E. (1962) Hemagglutination by measles virus. A simple procedure for production of high potency antigen for hemagglutination-inhibition (HI) tests (27930). *Proc. Soc. exp. Biol. (N.Y.)*, **111**, 814.

SIMPSON, K. & BURLAND, W.L. (1969) Intradermal measles vaccination. *Medical Officer*, **121**, 99.

SUTCLIFFE, W.M., DAVEY, M.F., BURLAND, W.L. & BEALE, A.J. (1967) Effect of different doses of attenuated measles virus by the intradermal route. *Medical Officer*, **117**, 225.

SUTCLIFFE, W.M., BURLAND, W.L. & HITCHENS, R.A.N. (1968) Intradermal measles vaccine. *Medical Officer*, **119**, 180.