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COMMITTEE ON SAFETY OF MEDICINES

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

JOINT SUB-COMMITTEE ON ADVERSE REACTIONS TO VACCINES AND IMMUNOLOGICAL PRODUCTS

Measles Vaccine - "Early Onset" Adverse Reactions

1. Introduction

In the Summer of 1983 the Committee on the Safety of Medicines (CSM) received a small flurry of reports of anaphylactic and similar reactions occurring immediately after measles vaccination. These appeared to be associated with a particular batch (M88 M44) of the newly marketed Rimevax (Schwarz strain) vaccine. Extensive laboratory testing carried out at the National Institute of Biological Standards and Control in the Summer and Autumn of 1983 did not reveal any untoward findings (Appendix 1). In particular, the vaccine in this batch did not have a raised protein content, no bacterial contamination was detected and the only antibiotic found was neomycin, in trace amounts as expected. High pressure liquid chromatography tracings were similar to other batches of the same product. Similar adverse reactions were subsequently noted also to occur infrequently with other batches of this vaccine. These adverse reactions were initially reported to ARVI in October 1983. Since then similar reports have been sparse until this Summer when a further four reports were received. Two recent reports occurred among three children vaccinated in one session with vials of batch No. M93Q 44A. Rabbit pyrogen tests on samples of the vaccine and the diluent of this batch were negative. However, the limulus amoebocyte lysate test was positive. Further tests are being carried out on samples of this batch.

Similar adverse reactions which have occurred in Australia, mostly in association with Rimevax, have been termed "early onset reactions" to measles vaccine. This paper further considers these adverse reactions and similar reports from other countries in an attempt to establish whether these recent reports constitute a new phenomena

and whether a particular period of observation following measles immunisation is necessary as advised in Australia.

2. Australian Reports

In 1981 Van Asperen et al described three Australian children who had experienced reactions which had begun within 30 minutes of vaccination with Rimevax. Initial symptoms included vomiting (three children) and cyanosis (two children). All three children later developed other symptoms such as fever and rash which resolved in a few hours. Prior knowledge of this paper (Appendix 2) prompted the Australian Adverse Drug Reactions Advisory Committee (ADRAC) to review the reports it had received during the preceding 18 months. It found six similar episodes which were mentioned in an article accompanying the paper of Van Asperen et al (Appendix 3). Subsequently a further nine similar cases were reported to ADRAC making a total of 15 submitted between February 1980 and March 1982, excluding the three cases published by Van Asperen. An account of these reactions which occurred within 30 minutes of vaccination was published in the Medical Journal of Australia in November 1983 (Appendix 4) and were termed "early onset reactions".

In the ADRAC cases the most commonly reported feature was an acute change in skin colour, usually described as cyanosis, which occurred in 10 of the 15 cases. Coughing (in seven children) was the next reported symptom; vomiting, signs of impaired central nervous function (drowsiness, hypotonia and lethargy) and hypersensitivity symptoms (coryza, lacrimation, urticaria and skin oedema) were each reported five times. Respiratory difficulty occurred in three children. Only two of the 15 children developed additional symptoms more than one hour after the onset of the early reaction in contrast to all of the three children reported by Van Asperen.

The time of onset ranged from 3 to 30 minutes after the vaccination. On at least six occasions the children had been taken away from the vaccine centre before the onset of the reaction. In five of the children, symptoms commenced more than 15 minutes after vaccination.

Fourteen of the 15 reports were associated with the Rimevax vaccine, the only measles vaccine which is used in the Public Health Sector in Australia. These adverse reactions were associated with at least four different batches of the vaccine. In none of these reports was there a documented history of sensitivity to egg, chicken or neomycin.

3. Norwegian Reports

In 1980 Aukrust et al published details of a clinical and immunological investigation of "severe hypersentivity or intolerance reactions" which had occurred in six Norwegian children immediately after the use of a live attenuated measles vaccine (Mevilin). These reactions were considered to be immediate hypersensitivity reactions most probably due to allergy, although investigations did not reveal the cause (Appendix 5). None of the Norwegian patients had evidence of hypersensitivity to egg yolk or white, cows milk or calf serum. Whilst trace amounts of calf serum proteins were demonstrated in the measles vaccine, egg antigens were not detected by crossed immunoelectrophoresis. Approximately 60,000 children were vaccinated during the 18 months the six cases occurred.

4. Reports from other countries

The licence holder for Rimevax has supplied a world-wide list of "early onset" reactions which have been reported following the administration of Rimevax. Apart from reports originating from Australia and the United Kingdom, reports of two such adverse reactions have been received from Botswana and three from Belgium.

5. Reports received by the CSM

5.1 An analysis has been carried out of the suspected adverse reactions associated with measles vaccine which have been reported to the CSM. Those reports with similar symptoms to those described in the ADRAC cases and occurring on the day of immunisation have been identified and classified according to the brand of the vaccine. Three brands of measles vaccines are currently available in the UK. Mevilin (Schwarz strain) became available in May 1968 for routine measles vaccination of children. Between March 1969 and July 1981

Mevilin was the only available measles vaccine. In July 1981 Attenuvax (Moraten strain) was introduced to the UK. In October 1981 Rimevax, another vaccine of the Schwarz strain, was marketed. The numbers of the initial batches and total doses of Rimevax distributed from each batch are given in Table 1. The clinical features of the cases under analysis associated with Rimevax have been tabulated in Table 2. This type of reaction has not yet been reported in association with Attenuvax. The clinical features of the cases associated with Mevilin have been tabulated in Table 3. It is probable that a further analysis of adverse reactions with other symptoms reported to the CSM prior to 1981 will reveal additional reports associated with Mevilin which could be classified under the heading of "early onset" adverse reactions. Further, there are a number of reports where the brand of the vaccine is not stated but the time of administration is such that the brand was almost certainly Mevilin. However, in view of the recent marketing of Rimevax, most if not all of the adverse reactions associated with Rimevax which were compatible with this "early onset" reaction have been identified.

5.2 Suspected "early onset" adverse reactions associated with Rimevax

Clinical symptoms and signs

Fifteen reports have been received which are compatible with the cases reported in Australia (Table 2). As in Australia an acute skin colour change is the most frequently reported (nine cases), usually either as cyanosis or mottling of the skin. In six of the reports anaphylaxis or an anaphylactoid reaction was either reported or judged by the assessing doctor to be present, often with hypotonia, and in a further two reports the child was noted to be markedly hypotonic. Drowsiness or lethargy was not reported. Dyspnoea was reported in seven children which was accompanied by coughing in two, and there was one report of coughing without dyspnoea. A tachycardia was reported in five children and vomiting in four. Facial swelling, urticaria and/or rashes were reported in four patients. There were no reports of coryza, lachrimation, agitation or irritability.

Time of onset

The time of onset varied from 2 minutes to 30 minutes after vaccination. The adverse reactions occurred within ten minutes in nine of the 15 children and in only two cases was the time interval between vaccination and onset greater than 15 minutes. One was a case of an anaphylactic reaction with cyanosis and tachycardia and the other a case of cyanosis and dyspnoea. The first responded to anti-histamine and the second to adrenaline.

Predisposition

None of the reports mentioned a history of hypersensitivity to eggs or an allergy.

Treatment

Treatment was considered necessary in 11 cases: five children were treated with adrenaline, two with hydro-cortisone and four with an anti-histamine. All the children recovered.

5.3 Suspected "early onset" adverse reactions associated with Mevilin

Clinical symptoms and signs

Thirty-five reports have been identified which are compatible with the cases reported in Australia (Table 3). Eighteen of these reports have either been reported as, or judged by the assessing doctor to be, a case of anaphylactoid reaction or anaphylactoid shock. In a number of these reports the child was hypotonic and in one further case hypotonia was also present. The symptoms associated with these 18 reports of anaphylactic reaction or shock did not appear to differ significantly from the remaining cases except perhaps that they were more severe. There were 18 reports of facial swelling, urticaria or skin reactions. There were no reports of lachrimation nor of coryza. In 11 cases pallor was reported and in 9 an acute skin colour change, usually cyanosis. Respiratory difficulties were reported in six children: two children with coughing and dyspnoea, three with dyspnoea alone and one with coughing alone. Vomiting occurred in four children and drowsiness in three. Tachycardia was not specifically mentioned in any report.

Time of onset

The time interval between the administration of the vaccine and onset of symptoms was recorded in 32 of the 35 cases and varied from "immediate" to three hours. Half the cases occurred within ten minutes. In 11 children the time interval exceeded 15 minutes (Table 4 below) and a further child was brought back to the surgery after vaccination. However, the last nine cases all occurred within 15 minutes of vaccination (Table 3).

Table 4

"Early onset" reactions: Mevilin

Time interval Vaccination/Onset (minutes)	No. of Reports
Up to 5	11
6-10	5
11-15	5
16-20	1
21-30	5
30-60	2
120	2
180	1
Total	32

Predisposition

Only the first report mentioned a history of hypersensitivity to eggs.

Treatment

Treatment was considered necessary in 21 children: the child who was hypersensitive to eggs was treated with antihistamine, adrenaline and hydrocortisone; nine children were treated with antihistamine, nine with adrenaline and two with hydrocortisone. All the children recovered.

6. Comment by the Australian Drug Evaluation Committee (ADEC)

ADEC in its initial comment on these reactions described them as "immediate". However, in the subsequent report the term "early onset" was considered preferable since it more adequately conveyed to practitioners that the onset had occurred up to 30 minutes after vaccination. In 1981 ADEC recommended that patients should be observed for at least 20 minutes following measles vaccination.

The causes and mechanisms of these reactions remain unknown. ADEC noted that although features of a hypersensitivity reaction (rash, urticaria) were noted in some reports the clinical details did not clearly fit the description of acute anaphylaxis (Appendix 3).

7. Some comments on the CSM cases

7.1 Analysis of the CSM cases with features similar to those recently reported in Australia does not appear to produce a clear symptom complex which could be easily distinguished from those adverse reactions that traditionally are reported by physicians in this country as anaphylaxis, anaphylactoid reaction or anaphylactic shock.

7.2 The CSM has received reports, compatible with the "early onset" reactions reported in Australia, associated with both Rimevax and Mevilin. These types of adverse reactions following the administration of measles vaccines derived from the Schwarz strain have occurred over the years since the beginning of the measles immunisation programme. However, the last reported "early onset" type of reaction associated with Mevilin occurred in August 1981. So far no reports have been received associated with Attenuvax (Moraten strain).

7.3 Time of onset

The time interval between immunisation and onset of the reaction in the CSM cases tends to be shorter in the Rimevax cases than that reported for the Australian cases. Eight of the 15 CSM reports associated with Rimevax occurred within five minutes, and 13 of 15

in the first fifteen minutes. In contrast only five of the 15 Australian cases occurred within five minutes of vaccination, and in five cases the time interval exceeded fifteen minutes.

On the basis of the CSM data on "early onset" adverse reactions associated with Rimevax, it is questionable whether the publication of a recommendation similar to the ADEC recommendation, i.e. that children should be observed for at least 20 minutes following measles vaccination, would be advantageous.

8. Action being taken by licence holder of Rimevax

The licence holder of Rimevax intends to insert the following statement in the adverse reactions section of the data sheet (Appendix 6):

"Allergic type reactions have been reported rarely."

The licence holder is also in the process of reformulating Rimevax to reduce the molecular weight of the Dextran which is included as a stabiliser since theoretically this could cause an occasional problem.

For ease of reference the current data sheets for Mevilin and Attenuvax are also annexed at Appendices 7 and 8 .

TABLE 1

TOTAL BATCHES 'RIMEVAX' DESPATCHED OR USED FOR QC SAMPLES

Batch No.	Start	Finish	Total Doses	
M81 L44	1.10.81	27.7.82	103,650	
M81 L44A	13.4.82	7.10.82	34,950	163,600
M81 L44B	20.5.82	28.7.82	25,000	
M88 M44	2.8.82	31.1.83	95,950	
M88 M44A	4.1.83	23.1.83	15,450	111,400
M93 I44	4.1.83	28.9.83	43,811	
M93 Q44A	15.3.83	28.9.83	92,700	
			411,511	

Table 2

"EARLY ONSET REACTIONS" ASSOCIATED WITH RIMEVAX

Yellow Card Number	Age (mnths)	Sex	Time of onset (mins)	Duration (mins)	Acute skin colour change including Cyanosis	Erythema or Flushing	Pallor	Coughing	Dyspnoea	Vomiting	AR AS or Hypotonia	Facial swelling urticaria or skin rashes	Fever or Rigor	Tachycardia	Other	Treatment	Batch No.
119502		M	4-5	10			✓			✓					Malaise		
121512	20	F	5	45		✓						✓					M81L44
122304	60	F	<15								AR						M93Q44A
123245		F	5	30	✓				✓		AS			✓		Anti-histamine	
124505		F	2	30	✓				✓		A		✓			Adrenaline	M88M44
127183	22	M	15	Few			✓	✓			AR	✓				Adrenaline	
123016	16	F	30		✓						AR			✓		Adrenaline	M88M44
124504	13	F	2	30	✓				✓		AS					Adrenaline	M88M44
127883	19	F	5-7	60	✓	✓		✓	✓			✓				Anti-histamine	
132773	22	F	<15	10	✓											Anti-histamine	M93Q44A
137577	15	M	30	120	✓				✓			✓	✓		Twitching No Convulsions	Anti-histamine	
SC	13	M	5	10			✓			✓				✓	Malaise		M88M44
SG	17	M	2		✓					✓	✓			✓		Hydrocortisone	M93Q44A
AP	17	M	2		✓					✓	✓			✓		Hydrocortisone	M93Q44A
TOTAL 15					9	2	3	2	5	4	8	4	2	5			

KEY AR = Anaphylaxis or Anaphylactoid Reaction
AS = Anaphylactic shock
A = Anaphylaxis

Table 3 (page 1)

"EARLY-ONSET REACTIONS" ASSOCIATED WITH MEVILIN

Yellow Card Number	Age	Sex	Time of onset (mins)	Duration (mins) (hrs)	Acute skin colour change including Cyanosis	Erythema or Flushing	Pallor	Coughing	Dyspnoea	Vomiting	Drowsiness	AR AS Hypotoria or Collapse	Facial swelling or urticaria skin rashes	Fever or Rigor	Other	Treatment
19709	22	F	5		✓		✓					AR			Hypersensitive to eggs	Antihistamine Adrenaline Hydrocortisone
21581	2 yrs	M	5-10	15 mins								AR				
27828	16	F	Immed.	60 mins	✓							AS				
31916	13	M	10	60 mins								AR		✓	Sweating	
41293	20	M										A				
44454	14	M	120	120 mins									✓	✓		Antihistamine
45137	16	M	<15				✓			✓	✓	AR			Pulse and respiration slow	Antihistamine
45411	21	F	30	24 hrs									✓			
45714	17	M	10	20 mins								AS	✓			Antihistamine
45987	15	M	120	24 hrs				✓	✓							
46824	15	F	<30										✓			
47282	13	F	5	90 mins			✓			✓		AR	✓		Sweating	Antihistamine
47283	15	F	10				✓					AR	✓		Sweating	Antihistamine

Table 3 (page 2)

"EARLY-ONSET REACTIONS" ASSOCIATED WITH MEVILIN

Yellow Card Number	Age	Sex	Time of onset (mins)	Duration (mins) (hrs)	Acute skin colour change including Cyanosis	Erythema or Flushing	Pallor	Coughing	Dyspnoea	Vomiting	Drowsiness	AR AS Hypotoria or Collapse	Facial swelling or urticaria skin rashes	Fever or Rigor	Other	Treatment
50396	18	M	< 30	48 hrs					✓				✓		-	
51823			15	Same day			✓					✓	✓			
53431	20	M	5	10 mins			✓		✓						"Wandering eyes"	Adrenaline
53623	16	F	20		✓										"Staring eyes, kicking"	
55111	19	M	3 hrs	3 hrs	✓	✓						AR	✓		Tremor	Anti-histamine
58977	14	M	5	1 hr		✓	✓					AR			Sweating	Adrenaline
59125	21	M	1hr	15-20		✓						AR				Adrenaline
60446	22	F	3 mins	5 min	✓				✓			AR				Adrenaline
69467	17	F										AR				
69931	14	M	30	45 mins									✓			Hydrocortisone
74997	18	F	*										✓		Crying	Adrenaline
79439	17	F	45										✓			
79454	15	M	15	45 mins								AR	✓			Adrenaline
80985	14	M	<30	Few hrs						✓			✓		Bradycardia	Anti-histamine

Table 3 (page 3)

"EARLY-ONSET REACTIONS" ASSOCIATED WITH MEVILIN

Yellow Card Number	Age	Sex	Time of onset (mins)	Duration (mins) (hrs)	Acute skin colour change including Cyanosis	Erythema or Flushing	Pallor	Coughing	Dyspnoea	Vomiting	Drowsiness	AR AS Hypotoria or Collapse	Facial swelling or urticaria skin rashes	Fever or Rigor	Other	Treat
82152	18	F	10				✓					AR				Anti-histamine
82733	15	F	2				✓			✓	✓				Sweating	
83028	14		Few mins												Allergic reaction	
85390	14		Few mins				✓				✓		✓			
92912	15	M	Few mins	5 mins	✓			✓				AR				Adrenaline
94501	14	M	15 mins	24 hrs									✓			Hydro-cortisone
109587	16	M	4	1 hr	✓								✓			Anti-histamine
111719	22	M	15	Settled rapidly	✓		✓									Anti-histamine
112981	14	F	5		✓			✓	✓				✓ (1 hr later)			Adrenaline
TOTAL 35					9	3	11	3	5	4	3	18	18	2		

AR = ANAPHYLACTIC REACTION
AS = ANAPHYLACTIC SHOCK
A = ANAPHYLAXIS

* Very shortly after leaving clinic.

Appendix I

NATIONAL BIOLOGICAL STANDARDS BOARD

DIVISION OF VIRAL PRODUCTS
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WORLD HEALTH ORGANIZATION
COLLABORATING CENTRE FOR
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17 September 1984

Dr D Zuttshi
DHSS
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Dear Derek

SKF Measles vaccines (Rimevax)
Batch M88 M44

A number of laboratory tests have been carried out by Dr Mairin Clarke on the above final vaccine as summarized below. The results did not reveal any defect.

1. Protein of chick origin, less than 1 µg/ml.
2. Bovine serum albumin, less than 1µg/ml.
3. Bacterial sterility - no contamination detected.
4. Antibiotic - only neomycin detected in trace amounts as expected.
5. High pressure liquid chromatography - tracings not significantly different from other batches of the same product.
6. Measles virus infectivity content $10^{3.8}$pfu per dose - ie. satisfactory potency.

We intend to perform comparative pyrogenicity and endotoxin assays on this and a number of other batches of measles vaccine.

I hope this information will be of interest to you.

Yours sincerely

G C Schild

19/86
LTAAMJ

Appendix 2

The recommended treatment of chlamydial respiratory infection is erythromycin (50 mg per kilogram per day) or sulfisoxazole (150 mg per kilogram per day) for two to three weeks.[8] Beem *et al* found that in 24 of 29 infants nasopharyngeal shedding of chlamydiae ceased and clinical improvement occurred after a week's treatment, compared with persistent shedding and unimproved symptoms for an average of 43 days in 11 untreated infants.[8] A high index of suspicion for chlamydial respiratory infection will lead to its increasing recognition and treatment in Australian infants.

Acknowledgements

We gratefully acknowledge the advice of Dr Craig Mellis and Professor Thomas Stapleton of the Royal Alexandra Hospital for Children. We would also like to thank Mr K. M. Ng and the Institute of Clinical Pathology and Medical Research, Westmead Hospital for doing the chlamydial serological investigations, and Dr N. Kappagoda of the Royal Prince Alfred Hospital for the chlamydial isolation in Patient 11.

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Immediate reactions following live attenuated measles vaccine

P. P. Van Asperen, J. McEniery and A. S. Kemp

ABSTRACT: Three children had an immediate reaction following live attenuated measles vaccine (Rimevax). This reaction consisted of vomiting, fever and a rash, and in two cases cyanosis. In each case the reaction commenced within 30 minutes of vaccination. Parents should be warned of the possibility of an immediate reaction after measles vaccination, and asked to notify their doctor if any occurs.

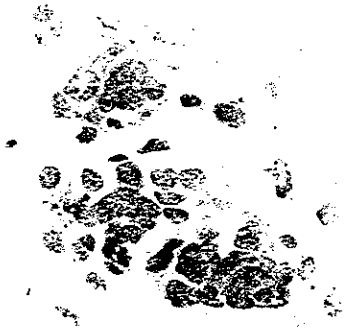
THE SCHWARZ STRAIN of live attenuated virus has been used for measles vaccination in Australia since 1970. This has been supplied as Lirugen and, since July, 1979, as Rimevax. Delayed reactions following vaccination are well documented, and are believed to be due to infection with the live attenuated virus.[1,2] About half of 442 children studied after being given Rimevax had delayed reactions consisting of fever, cough and sometimes rash, generally appearing between six and 12 days after vaccination.[2] We now report in three children immediate reactions to Rimevax, occurring within 30 minutes of injection.

Case 1

A 12-month-old girl received her measles vaccination in the afternoon. Within 30 minutes she began vomiting, and by 60 minutes she developed an apparent high fever with rigors, which was treated with paracetamol. The following morning a rash was noted, which was described by her doctor as an erythematous confluent maculopapular rash, typically morbilliform. It lasted only four to six hours, and all symptoms disappeared within 24 hours of the vaccination. About ten days after the vaccination she had another febrile illness associated with cervical lymphadenopathy and an erythematous macular rash, more typical of the usually reported illness following measles immunization. Paired measles antibody titres 17 and 31 days after vaccination were 1/32 and 1/64 respectively, consistent with immunization rather than "wild" measles infection. The child is now well.

Case 2

A 12-month-old girl started vomiting and coughing, and was described as going blue, within 15 minutes of vaccination. She was immediately returned to the surgery where she vomited several times but was discharged after 30 minutes' observation. Within two hours of the immunization she developed a rash and high fever with rigors and again was returned to her doctor. The rash was described as an erythematous papular rash, not typically morbilliform, and lasted about one hour. Over the next 24 hours she developed a bronchitic illness which lasted about ten days, from which she recovered completely.



Nasal smear from a child with measles showing the characteristic mutinucleated giant cells.

Case 3

A 12-month-old girl became hot and erythematous and then centrally and peripherally cyanosed within a minute of vaccination. She subsequently became pale and a petechial rash developed over her face and upper chest. She also vomited once, and because her doctor thought she was in a pre-convulsive state, she was given diazepam intramuscularly. Within 15 minutes of the vaccination she was transferred to hospital and on arrival was found to be normotensive, but pale and irritable with a petechial rash. The platelet count was normal. She was considered to have had a possible anaphylactic reaction to the vaccine and was given hydrocortisone intravenously. Over the next two to three hours she

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developed a generalized urticarial rash but otherwise improved. Within 24 hours this rash faded and she was perfectly well again. There have been no further problems.

Discussion

These three cases illustrate immediate reactions occurring within 30 minutes of receiving measles vaccine, and consisting of vomiting, fever and rash, with cyanosis in two cases and a shock-like state in one. In none of these three children were there any contraindications to measles vaccination. The reactions are quite different from the delayed reaction previously described, which usually occurs between six and twelve days after measles vaccine.[2] We are unaware of any reports in the literature of similar immediate reactions.

The mechanism of the reaction remains unclear. It may be due to an immediate hypersensitivity to one of the vaccine components, though which one must be a matter of conjecture. The vaccine is said by the manufacturers to be contraindicated in egg-allergic patients, but there was no history of egg sensitivity in our cases. However, it would seem that the chick fibroblast on which the vaccine is cultured is antigenically different from egg protein, as even egg-sensitive individuals can tolerate measles vaccine.[3] It is possible that this immediate reaction is due to IgE antibodies to the virus itself, perhaps formed during infection with wild measles virus while the infant was protected by maternal antibodies. However, previous studies on the use of live attenuated virus vaccines, in subjects who already had measles antibodies, revealed no local or immediate reactions, although delayed reactions did occur.[1]

Although we were unable to ascertain the exact batch number, this reaction could be a batch-related phenomenon. However, Case 3 occurred in May, 1980, well before the other two cases which occurred in March, 1981. It would be interesting to know if similar immediate reactions have been noted recently. Another possibility is that symptoms were due to a concomitant viral infection, although the fact that all children were perfectly well immediately before receiving the vaccine, and the short time between vaccination and onset of symptoms, makes this unlikely. For the same reason it would not seem possible that this reaction is due to replication of live attenuated virus itself.

We conclude that immediate reactions to live attenuated measles vaccine can occur. We feel that parents should be informed of the possibility of an immediate reaction and instructed to notify their doctor if any symptoms develop. In view of the severe reaction encountered in Case 3 it would be wise to observe children for a few minutes after giving them measles vaccine.

Acknowledgements

The writers would like to thank Dr G. Kewley, Dr J. White and Dr D. Yap for help in supplying clinical details, Dr M. Burgess and Dr C. M. Mellis for reviewing the manuscript, and Ms A. Georgiou for secretarial assistance.

Added in Proof: Since submission of this paper another report of immediate reactions to live attenuated measles vaccine has been brought to our attention: Akrust L, Almeland TL, Retsum D, Aas K. Severe hypersensitivity or intolerance reactions to measles vaccine in six children. *Allergy* 1980; 35: 581.

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Balloon dilatation in the treatment of early intermittent claudication

William S. C. Hare, Kenneth R. Thomson, Peter L. Field and Donald B. Robertson

ABSTRACT: Balloon dilatation of atherosclerotic arteries is an established procedure with a high success rate and low morbidity. In the past 18 months, 71 patients underwent balloon dilatation at the Royal Melbourne Hospital, with a success rate of 90%. This technique is most successful in short stenoses or occlusions, and earlier investigation of selected patients with intermittent claudication is recommended.

DILATATION of diseased arteries was first used in 1964 as a last resort in patients in whom surgery was considered inadvisable due to age, diabetes, myocardial ischaemia or other disability.[1] The angioplasty was often successful in these cases, but far better results were obtained in short stenoses or occlusions.

Recently, an improved balloon-dilatation catheter which offered easier dilatation to larger diameters than the previous systems was developed,[2] and is now in use at the Royal Melbourne Hospital. The balloons impart a pressure of up to 700 kPa to a predetermined diameter, and have a safe "failure mode"—they leak rather than burst when they fail (Figure 1).

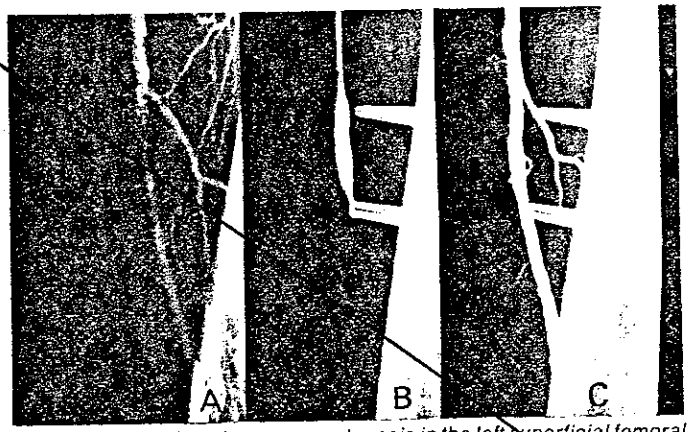

FIGURE 1: A.—A 2 cm long severe stenosis in the left superficial femoral artery with good run-off into the popliteal artery. B.—Two artery forceps placed on the skin to localise the stenosis, while the balloon catheter is positioned and inflated with contrast medium. C.—Immediately after dilatation—the stenosis section has been obliterated.

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Appendix 3

of a new opponent. Mr Fraser is tough and not exhausted at this point of time (mid 1975) by continuing direct confrontation since 1972."

These comments remain true, even though one cannot attest to the fall of Whitlam purely in terms of exhaustion terms. However, the genesis of the loans affair and its aftermath may be translated into the politics of exhaustion.

The survival of the new Prime Minister (Mr Fraser) may now be aided by the survival of a Leader of the Opposition who appears to remain exhausted (Mr Whitlam). An Opposition must be able to counter exhaustion, and there are only certain ways in which this "brave new real politick" can do it. First, the Opposition must be aware of the power of political exhaustion. Second, it should prepare to counter the consequences. The Leader of the Opposition should be buffered against it. The organisation of his office should enable the advisers and the administrators to be discrete entities. There should be teams of each able to be moved in and out at regular intervals. Nobody has the luxury in Opposition of being able to divorce himself from the life and workstyle of the Leader—neither should anybody be so close to the Leader that he has no private life of his own.

There are always signs that a person is in need of pasture. One of these I call the "conference syndrome". The spoken voice says: "It would really help if I went to a conference in Melbourne". The unseen voice is literally yelling at you: ". . . or Thredbo or anywhere—just let me get out of Canberra".

Boredom is, paradoxically, another contributor to exhaustion. The rituals of politics are not solely the rituals of Parliament. However, there are a number of these not the least, it would appear, the process of cooping up many people in a confined space for long periods of time. Due to the dictates of the Division, and activity of the Whips, there is no alternative but to sit around and wait. Parliament House becomes a fortress from the time Parliament sits to the time it rises. One is confined and even if one wanted to go out and see what the weather is like, there is no opportunity. There are the lunch breaks and the dinner breaks, but because of the unfailing nature of these, it is rather like the ritual exercise-time in the prison yard.

The isolated nature of Parliament House means that leaving the House at the intervals is in itself difficult.

Whether one admits to boredom is one thing; but at certain times to assert an independence, and to believe one has to get away from rituals, is to counteract the sameness of the existence.

Staff do not have the problem of the Division, but they do have the ritual of being servants. Because of their dependence on the leader or the deputy leader or the Minister, they are required to "stand and wait" a large amount of time. They have to do this on all occasions, and it demands a high threshold to boredom to withstand the discomfiture of sitting through a luncheon or waiting for something to happen.

In the case of political party advisers, they should shuttle between the leader's office and the Federal organisational wing. This allows for a different pace, and these changes should ensure more co-operation between organisation and Parliamentary party. I believe it is inappropriate to have a political organisation based solely on a business corporation model. It needs flexibility, it needs commitment, and it needs a moving target. In exposing everybody to some of the "heat" generated by the Leader of the Opposition, everyone can avoid sleep deprivation and exhaustion.

"Adviser" is a euphemistic term for a member of the intelligent, thinking cadres. Again they should be movable. They can work in the depersonalised existence close to the Leader for a period, and then be "pastured". I believe the best pasturing for the adviser is to get him into the community, to allow him to travel, to meet, to broaden the contacts of the Opposition. After Canberra it is important that advisers go out in the community and see what people are actually thinking and doing. They can act as advance men for the Leader of the Opposition and his senior colleagues. They can find out what is occurring at the grassroots of the Party, and they can recuperate.

The Leader of the Opposition must realise that he is the target for a process of exhaustion. If he tries to go the pace he must have fresh forces, who for instance, enable him to leave his office relatively early when Parliament is sitting, or who will say to the enthusiastic Party branch that the Leader needs sleep more than a late night supper. Everybody wants to say, "I spoke to the Leader and I told him straight . . .". But it is not feasible. The Leader should be able to excuse himself and leave the talk and the requests to his aides.

This is a rule which needs more prominence. The end result of trying to please everybody is exhaustion and finally self-destruction.

Immediate reactions to measles vaccine

Comment by ADEC—and a request for information

MEASLES VACCINATION is so frequently followed after five to 12 days by a febrile illness that this reaction must be anticipated and adequate warning given to parents. Immediate reactions have rarely been reported, but include a cluster of six cases in Norway.[1]

In this issue, three episodes in Australian children are described by Van Asperen *et al* (MJA, Oct 3, 330). In addition to these three cases, the Adverse Drug Reactions Advisory Committee (ADRAC) holds at least six apparently similar reports of immediate reactions which have occurred in Australia in the past 18 months. The infants' ages ranged from 11 to 20 months.

Elements common to many of the reports include choking or coughing, vomiting, respiratory difficulty and cyanosis occurring within half-an-hour of vaccination. Some infants later had transient rash and high fever, within 24 hours of vaccination. A theme common to several reports was for the infant to have been taken from the vaccination centre, and returned in distress about 15 minutes later.

Although features of an hypersensitivity reaction (rash, urticaria) were noted in some reports, the clinical details do not clearly fit the description of "acute anaphylaxis". Some infants received treatment, including adrenaline, and all recovered. The reactions cannot be attributed to any one batch of vaccine; in the Norwegian cases, a different brand of vaccine was involved.

No mechanism has been established to explain either the Norwegian or Australian experiences.

In view of the Australian Drug Evaluation Committee:

(i) These reactions appear to be uncommon, and do not bring into question the general safety of measles vaccination.

(ii) The occurrence of the reaction does not appear to be predictable on the basis of an atopic history either in the infant or the family.

(iii) As with the use of any vaccine, prudent medical management when performing measles vaccination should include: observation of the patient for an adequate period following vaccination (on the basis of the Australian reports, at least 20 minutes observation is suggested), and adequate warning to the parents; and ready availability of appropriate equipment, medication and personnel to manage any acute reaction.

(iv) **Much more information is needed on the frequency and nature of these reactions.** All practitioners are requested to report any such events they may encounter to: Adverse Drug Reactions Advisory Committee, P.O. Box 100, Woden, ACT 2606.

S. J. M. GOULSTON,
Chairman,
Australian Drug Evaluation Committee.

1. Aukrust L, Almeland TL, Refsum D, Aas K. *Allergy* 1980; 35: 581-587.

Appendix 4 p.1.

Aaverse Drug Reactions Advisory Committee

Early-onset reaction after measles vaccination

Further Australian reports

John McEwen

ABSTRACT: Fifteen reports of reactions occurring within 30 minutes of vaccination with live attenuated measles virus have been received by the Adverse Drug Reactions Advisory Committee (ADRAC) up to March 30, 1982. These reactions were similar to those in three episodes reported recently. An acute change in skin colour, described as cyanosis, slight cyanosis, or mottling was the most commonly reported symptom. All the children recovered. The causes and mechanisms of these reactions remain unknown.

(Med J Aust 1983, 2:503-505)

UNTIL 1980, reactions to live attenuated measles vaccine occurring shortly after vaccination had not been documented, and advice was issued in the United States,[1] and in Australia,[2] that no severe hypersensitivity reactions to the live attenuated measles, mumps or rubella vaccines prepared from viruses grown in cell cultures had been reported. However, in 1980, Aukrust *et al.* published details of an investigation of severe hypersensitivity or intolerance reactions occurring in six Norwegian children immediately after the use of a live attenuated measles vaccine.[3] These reactions happened during an 18-month period in which approximately 60 000 children were vaccinated, and were associated with the use of a vaccine which was manufactured in the United Kingdom and not available in Australia. Dyspnoea (five children), angioedema (four children), cyanosis (four children), urticaria (four children), erythema (three children) and stridor (three children) were the most commonly reported symptoms. In October, 1981, Van Asperen *et al.*, in a report published in this Journal, described three Australian children who had experienced reactions which began within 30 minutes of vaccination with the Rimevax brand of live attenuated measles vaccine.[4] Initial symptoms included vomiting (three children) and cyanosis (two children). All three children later developed other symptoms, such as fever and rash, which resolved within a few hours.

Notification of this report to the Adverse Drug Reactions Advisory Committee (ADRAC) before its publication prompted a review of Australian reports which uncovered at least six similar episodes which had occurred in the preceding 18 months. These were mentioned in the leading article which accompanied the paper of Van Asperen *et al.*[5] Reporting of similar suspected reactions has continued, and the registry now contains 15 reports (in addition to those published by Van Asperen *et al.*), submitted between February, 1980, and March, 1982.

Adverse Drug Reactions Advisory Committee, PO Box 100, Woden, ACT 2606.
John McEwen, MB, BS, MSc, MPS, Secretary.
Reprints: The Secretary.

Analysis of reports

Clinical symptoms and signs

Details of the symptoms in the 15 reported reactions are shown in Table 1. An acute change in skin colour, described as cyanosis, slight cyanosis, peripheral cyanosis, peripheral mottling, or peripheral and central purplish mottling, was reported in 10 of the 15 children. Coughing (seven children) was the next most reported symptom. Vomiting, signs of impaired central nervous function (drowsiness, hypotonia or lethargy), and common hypersensitivity symptoms (coryza, lacrimation, urticaria and skin oedema) were each reported five times. Respiratory difficulty was reported in three children. The reactions occured in 11 boys and four girls; their ages ranged from 12 to 22 months, except for one boy who was aged four years. It is interesting that similar reactions occurred in twin boys, aged 15 months, who were vaccinated on the same day (Reports 12 and 13). They were thought to be identical twins, but ADRAC has not been able to establish this with certainty. Only one girl (Report 8) was reported to have had other vaccinations together with the measles vaccine on the same day. She had received a separate injection of diphtheria and tetanus (CDT) vaccine. Previous exposure to triple-antigen and Sabin vaccines had had no adverse effects.

Time of onset

The time of onset of the reactions ranged between three and 30 minutes after the injection. On at least six occasions, the children had been taken away from the vaccination centre before the onset of the reaction and were subsequently

TABLE 1: Summary of symptoms described in 15 Australian reports of early-onset reactions after measles vaccination

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total
Age (months) and sex	16M	19M	20M	15M	14M	12F	14F	19F	15M	12F	22M	15M	15M	48M	14M	
Time of onset (minutes)*	15	3-5	30	15-30	5-10	*	*	10	30	30	15	5	5	20	10	
Acute skin-colour change†	PC		SC	C		C		SC	PM		PC	PCM	PCM		C	10
Coughing					1	1	1	1				1	1		1	7
Pallor			1	1			1				1				1	5
Vomiting	1	1					1			1				1		5
Drowsiness or lethargy	1		1									1	1		1	5
Disturbed breathing‡				W			D								IB	3
Erythema or flushing					1			1		1						3
Hypotonia or collapse	1			1											1	3
Coryza or lacrimation												1	1	1		3
Urticaria and skin oedema		1									1					2
Fever or rigors								1								1
Agitation or irritability		1														1

*Onset was described as "after a few minutes" in Report 6, and as "shortly after vaccination" in Report 7.
† C = "cyanosis"; PC = "peripheral cyanosis"; SC = "slight cyanosis"; PM = "peripheral mottling"; PCM = "peripheral and central purplish mottling".
‡ D = "dyspnoea"; W = "wheeze"; IB = "irregular breathing".
M = male; F = female.

returned to the centre. One episode of cyanosis occurred in a supermarket and another in a car being driven by the child's mother. Two children developed additional symptoms which occurred after the initial events, but within 24 hours of vaccination. Between one and three hours after vaccination, a 16-month-old boy (Report 1) developed a mild fever (38°C) and a transient pink rash and purpuric spots, and a 15-month-old boy (Report 9), who initially had fever, rigors, and peripheral mottling, developed a transient rash within 90 minutes of the onset of the reaction.

Predisposition

A 22-month-old boy was noted to have small patches of eczema on the face, and a four-year-old boy had a history of mild eczema until 18 months of age, but neither child had any other history of allergy. None of the other reports described a history of atopy.

Treatment

Ten of the children were simply observed. Treatment of the other children included administration of adrenaline and hydrocortisone injections, oxygen therapy and injection of adrenaline, promethazine injection, oral administration of pheniramine and terbutaline syrups, and pheniramine syrup, respectively.

Brand and batches of vaccine

From the details of brand or batch number reported, and from follow-up by ADRAC, the vaccine involved in 14 of the 15 reports has been identified as Rimevax vaccine. At least four different batches of Rimevax vaccine have been associated with these reactions. With the exception of the twin boys, the only suggestion of a clustering of the reactions involves Reports 5, 6, and 7. These three reactions were encountered by one practitioner within a period of four weeks, but at least two different batches of Rimevax vaccine were involved. Each of the remaining 10 reactions was reported by a different practitioner in New South Wales, Queensland, Victoria, and the Australian Capital Territory.

Discussion

Vaccination against measles is an important public health measure and public acceptance will be enhanced if questions about possible risks can be answered with confidence.

A febrile illness occurring between five and 12 days after measles vaccination is common and well documented. The continued reporting of the early reactions detailed in this paper suggests that these, too, must be accepted as a risk of measles vaccination, although they are much less common than the delayed reactions. Such reactions were apparently not recorded in a recently reported surveillance study of 10 035 children in the City of Oxford, United Kingdom, who were vaccinated with live attenuated measles vaccine (Mevilin, Glaxo Laboratories) from June, 1970, to March, 1980.[6] However the occurrence of these reactions is not exclusively an Australian phenomenon, since, in addition to the Norwegian reports, enquiries by ADRAC have disclosed that small numbers of similar reports are held by national drug monitoring centres in several other countries.

Although these reactions have been described in previous reports[3,4] as immediate, it is considered that the term "early onset" more adequately conveys to practitioners that onset has occurred up to 30 minutes after vaccination.

The most common symptoms in the 15 episodes were acute changes in skin colour and coughing. Twelve of the 15 reports included these symptoms or described disturbances of breathing. The same symptoms were prominent in the descriptions given by Aukrust *et al.* and Van Asperen *et al.*[3,4]

The mechanism of these reactions remains unknown. Although the vaccines used in Norway and Australia were of different manufacture, both were produced from virus cultured in chicken-embryo fibroblasts and are unlikely to contain egg proteins. The product information for Rimevax vaccine states that its use is contraindicated in patients with known hypersensitivity to eggs, chicken and chicken feathers. The justification for this warning has been challenged,[7,8] and Aukrust *et al.* were unable to demonstrate contaminants from eggs in the vaccine used in Norway. Rimevax vaccine contains neomycin (not more than 25 μg of neomycin B sulphate per dose) and known hypersensitivity to neomycin is also stated as a contraindication to its use. It has been argued that neomycin is an unlikely cause of severe anaphylactoid reactions to vaccines,[9] and, furthermore, the vaccine implicated in the Norwegian reactions contained

streptomycin and not neomycin. None of the Australian children described in this paper had a documented sensitivity to [illegible]s, chickens, or neomycin, but, in the absence of formal testing, this is not conclusive evidence of the relevance or otherwise of an allergic history. The possible roles of other constituents of the vaccine, including small quantities of dextran, must be considered.

The accumulated evidence is not consistent with faults peculiar to a particular brand or batch of vaccine. The reactions in Norway, and some of the apparently similar reactions reported to national centres in other countries, followed the use of brands of vaccine other than Rimevax. Since February, 1979, Rimevax has been the only brand of measles vaccine provided for free immunization in Australia. ADRAC has not received any reports associating other brands with similar symptoms, but this may represent relative usage or a failure to report reactions rather than a real difference.

All three children reported by Van Asperen *et al.* developed additional symptoms more than one hour after the onset of the early reaction. No adequate explanation can be offered why similar later events were reported in only two of the 15 children described in this paper.

In the majority of the children reported to ADRAC, the symptoms resolved without active treatment, and the part played by therapy in the recovery of the other children cannot be assessed. While the self-limiting nature of these reactions is reassuring, experience to date is small. Cyanosis and disturbances of respiration are important symptoms, and medical attendants should be in a position to take active measures if prompt spontaneous resolution does not occur.

Conclusion

The Australian experience suggests that early-onset reactions may follow the use of live attenuated measles vaccine. They are probably uncommon, but ADRAC does not have access to adequate data to permit an assessment of their incidence. The Australian Drug Evaluation Committee (ADEC) has previously recommended that patients should be observed for a sufficient time after vaccination (at least 20 minutes was suggested), that adequate warning should be given to the parents, and that appropriate equipment, medication and personnel to manage any acute reactions should be readily available.[5] ADRAC has received representations arguing that the suggested period of observation causes inconvenience to parents and increases anxiety about the safety of vaccination. However, ADRAC believes that it must continue to give this advice until such reactions are better understood. Practitioners are urged to continue to report all adverse reactions to vaccination that they encounter.

Acknowledgements

I thank Dr Gwyn Howells, Director-General of Health, for permission to publish this article, and the Chairman and members of the Adverse Drug Reactions Advisory Committee for their assistance in its preparation. Dr David Howes and Mr John Withell of the National Biological Standards Laboratory provided helpful comment. The contributions of the doctors who reported these reactions, and of the company which markets Rimevax vaccine in Australia, are gratefully acknowledged.

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Notice Board

Dilantin hypersensitivity study

Studies aimed at developing an in-vitro diagnostic test for Dilantin hypersensitivity are being carried out in the Department of Medicine, Westmead Centre, Sydney. The studies require 40 mL of venous blood from persons who are, or have been, hypersensitive to Dilantin. Blood samples can either be transported to the study centre or be collected by an investigator. Persons who are willing to participate in the study should contact Dr Geoff Farrell, Department of Medicine, Westmead Centre, Westmead, NSW 2145. Phone: (02) 633 6033.

Cancer research fellowships

The World Health Organisation's International Agency for Research on Cancer, based in Lyon, France, offers each year a number of fellowships to enable junior scientists to receive training in the fields of epidemiology, biostatistics and environmental carcinogenesis.

Fellowships, which are awarded for one year, are tenable at the Agency or in another suitable institution abroad. Applicants should be engaged in research in medical or allied sciences and should intend to pursue a career in cancer research. They should have some post-doctoral research experience related to cancer in medicine or the natural sciences, and an adequate knowledge, both spoken and written, of the language of the country in which their fellowship will be tenable.

Applications for 1984-1985 fellowships must reach the Agency before *December 31, 1983*.

More information and application forms are available from The Chairman, Fellowships Selection Committee, International Agency for Research on Cancer, 150 Cours Albert-Thomas, 69372 Lyon Cedex 08, France.

Ethics in research

The Medical Research Ethics Committee of the National Health and Medical Research Council is inviting comment on the topic of ethics in epidemiological research.

Comments should be addressed to the Secretary, National Health and Medical Research Council, PO Box 100, Woden, ACT 2606.

— ELIZABETH KEENAN, Co-ordinator.

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Allergy 1980, 35, 581–587

Severe Hypersensitivity or Intolerance Reactions to Measles Vaccine in Six Children

Clinical and Immunological studies

L. Aukrust, T. L. Almeland, D. Refsum and K. Aas

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Pediatric Research Institute, Rikshospitalet, University of Oslo, Oslo, Norway

Six reported cases of anaphylactic reactions due to measles vaccinations of children were investigated. The reactions appeared to be immediate hypersensitivity reactions most probably due to allergy. Trace amounts of calf serum proteins were demonstrated in the measles vaccine by means of crossed immunoelectrophoresis whereas egg antigens could not be detected by this method. The reason for the untoward reactions was not identified. Atopic traits were not reported in any of the patients but were found in first degree family members of three of them. Skin prick testing with measles vaccine was positive in one of the patients only, whereas skin prick testing with egg yolk, egg white, cow's milk and calf serum were negative in all cases. RAST was performed with allergosorbents containing different material used during the vaccine production, but was negative in all cases.

The results with control individuals were in accord with previous reports that patients with allergy to hen's egg tolerate the injection of measles vaccine. Immediate hypersensitivity reactions to measles vaccine may occur independent of allergy to egg and even in children without any known allergy or atopic heredity.

Key words: calf serum; crossed immunoelectrophoresis; hypersensitivity; measles; radioallergosorbent test; vaccine.

Accepted for publication 25 March 1980

In Norway, as in several other countries, measles vaccine is given to all children at the age of 1–3 years routinely as a single shot. During an 18-month period height instances of immediate reactions, suggesting severe allergy or anaphylaxis following measles vaccinations in children, were reported to the health authorities in Norway. Approximately 60,000 children were vaccinated during the period in question. Two of the reactions reported were shown to be of minor degree. This paper reports the results of clinical and immunological investigations carried out in six patients with severe reactions, and immunological studies of the measles vaccine.

PATIENTS AND CONTROL INDIVIDUALS

The parents of all eight children, as well as the physicians or nurses who had given the vaccine, were contacted. Six of the incidences reported were of an anaphylactic type and raised suspicion of immediate hypersensitivity mediated by immunoglobulin E (IgE), or intolerance with anaphylactoid symptoms. Two incidences reported were found to be rather faint and atypical ones and were not investigated in this study. All eight cases were reported by different physicians from different areas in Norway.

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As control individuals six atopic children were selected matching the patients with respect to age, and who had received measles vaccine without any untoward reaction. Four of the control individuals were selected because they were known to be clinically allergic to hen's egg with positive radioallergosorbent test (RAST) to egg white, and skin prick test (SPT) reactions (1) to egg white and egg yolk, whereas two were not allergic to egg. Serum was collected 4–8 months after the measles vaccine injection.

MATERIAL

All patients had been injected with measles vaccine produced by the manufacturer who provided the measles vaccine material used in the present study (Evans Biologicals Ltd., Speke). In four of the severe cases the particular vaccine bottles were submitted by the physicians—all from one lot of vaccine. The amounts of vaccine left in the bottles were too small for laboratory analysis, but sufficient for skin prick testing. It was not possible, however, to get further samples of this particular lot of measles vaccine reported to cause the hypersensitivity reactions in question. The manufacturer provided lyophilized, live attenuated measles vaccine delivered in glass ampoules. They also provided the following other variants of measles vaccines and single components of the vaccine: measles vaccine containing streptomycin, measles vaccine without streptomycin, attenuated measles harvest + streptomycin, cell growth medium, calf serum antigen, anti-calf antiserum prepared in rabbits, sheep antiserum to measles virus and anti-calf antiserum diluted 1/15.

Measles virus produced in monkey kidney cells, in phosphate-buffered saline were a gift from Dr B. Vandvik. The following antigens and rabbit antisera were purchased from Behringwerke AG (Marburg/Lahn, Germany): lyophilized bovine albumin, bovine immunoglobulins, anti-cattle serum (different batches), anti-bovine albumin, anti-chicken serum, anti-chicken ovalbumin and anti-bovine casein.

Normal allantoic fluid, anti-allantoic fluid, allantoic membrane preparations and anti-allantoic membrane serum from rabbit were gifts from Dr G. Hoddevik, Virus Department of the State Institute for Health, Oslo. Phadebas® RAST egg white allergen allergosorbents were purchased from Pharmacia, Uppsala, Sweden. Antigenic material and patient sera were stored without additives at −20°C until analysed. The antisera contained 0.1% sodium-azide and were stored at +4°C.

METHODS

The parents and the physician or nurse who had observed the untoward reaction in question, were asked to describe the reaction as detailed as possible. Data with respect to allergies or allergic-like symptoms in the child and in parents and siblings were recorded. Skin prick testing (SPT) was performed according to routine procedures and were read and recorded following the Scandinavian Allergy Reference System (1).

Radioallergosorbent test (RAST)

Paper disc allergosorbents were prepared and RAST assays were performed as described by Yman et al. (9). The following allergosorbents were prepared and used.

- Measles vaccine + streptomycin (pH 7.3)
- Measles vaccine — streptomycin (pH 7.6)
- Measles harvest + streptomycin (pH 7.7)
- Cell growth medium (pH 7.7)
- Calf serum, 1 mg/ml
- Normal allantoic fluid, undiluted
- Phadebas® egg white allergen discs (as purchased from Pharmacia, Uppsala, Sweden).

Calf serum was coupled to the sorbent in a protein concentration of 1 mg/ml according to preliminary dose-response experiments. The other antigens were coupled in their original concentrations. The pH during coupling was between 7.3 and 7.7 in all cases. The results were expressed as percent uptake of ^{125}I-anti-IgE of the total amount applied.

Radioimmunosorbent test (RIST)

Total serum IgE were determined by means of Phadebas® RIST kits (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions.

Gel precipitation techniques

Gel precipitation experiments were performed in a 1% agarose (HSB, Litex, Glostrup, Denmark) using a buffer containing 0.073 mol/l Tris, 0.024 mol/l barbital, 0.006 mol/l calcium lactate and 0.003 mol/l sodium azide (pH 8.6, 25°C). Double immunodiffusion, crossed immunoelectrophoresis (CIE) and crossed line immunoelectrophoresis were performed as described by Krøll, Ouchterlony and Weeke, (4, 5, 7, 8).

EXPERIMENTS AND RESULTS

The clinical and serological information about the patients of relevance for this study is summarized in Table 1. Atopic traits were not found in any of the patients but were reported in first degree family members of three of them. None of the patients had a history suggesting allergy to hen's egg, calf serum or cow's milk or any other substance.

In one patient SPT with undiluted measles vaccine elicited a positive whealing (+++/++++) reaction slightly more pronounced than the reaction elicited by the positive histamine (5.43 mol/l) reference, with an appearance similar to immunologically specific IgE-mediated skin reactions. All the other patients showed negative reactions to SPT with the vaccine, and all patients were negative to SPT with egg yolk, egg white, cow's milk and calf serum used in concentrations known to discriminate specific from non-specific skin reactions in atopic individuals.

Three of the patients were also negative in skin prick test with vaccine from the particular bottle that 6–18 months previously had provoked their severe reaction.

RAST was performed with all the listed allergosorbents in six patients. All results were negative. No IgE antibodies were found in any of the patients' sera against the components in the measles vaccine or any of the media used for preparation of the vaccine as listed. Except for positive reactions to egg white in the egg white-allergic control individuals, no reactions whatsoever were obtained with the tests performed in the control individuals.

INVESTIGATIONS OF ANTIGENS IN THE MEASLES VACCINE

Sensitivity of the test systems

With the calf serum antigen–antiserum system used, we found the maximum sensitivity of the double diffusion techniques to correspond to a 1/5120 dilution of the calf serum (10 μl of diluted calf serum and 10 μl of anti-calf serum in the wells). The maximum sensitivity of the CIE, however, was found to correspond to a 1/40,000 dilution of calf serum. This demonstrated that the sensitivity of the CIE was superior to that of the gel-diffusion technique used, and it was decided to use CIE for further work.

Crossed immunoelectrophoresis analysis

All experiments were performed with the measles vaccine material as found in the ampoules available for vaccination. We prepared the vaccine in a concentration five times higher than that prescribed for injection. Higher concentrations were not possible to apply, however, due to the high salt concentrations, and dialysis was not performed due to the risk of losing important components. The lack of more concentrated measles vaccine material limited the experiments in the study of non-measles virus antigens in the vaccine.

Direct evidence for the presence of calf serum components in the vaccine was obtained when CIE was performed using 15 μl five times

Table 1
Clinical data from patients with hypersensitivity reactions following measles vaccination

Patient No.	Sex	Age at time of reaction (months)	Type of reaction	Effect of adren.*	Atopy in Patient	Atopy in 1° Family	Serum IgE (U/ml)	Vaccine	SPT to Calf serum	Egg white	RAST Egg white
1	F	12	cyanosis cough dyspnoea	+	—	—	6	—	—	—	0
2	M	14	shock angioedema urticaria stridor dyspnoea	+	—	—	450	—	—	—	0
3	M	15	shock cyanosis angioedema urticaria stridor dyspnoea	+	—	+	25	—	—	—	0
4	F	18	sopor cyanosis angioedema urticaria erythema	+	—	+	10	+++(+)	—	—	0
5	M	16	sopor. cyanosis urticaria erythema dyspnoea	+	—	—	ND	—	—	—	0
6	F	14	angioedema erythema stridor dyspnoea vomiting	+	—	—	10	—	—	—	0

* Adren. = adrenaline/epinephrine (injection)

(1/100 and 500 μl anti-measles virus. These preparations gave rise to one sharp precipitate differing from the albumin precipitate both in appearance and in its relative position.

Further evidence for the presence of calf serum components in the vaccine was obtained when CIE experiments were performed with five times concentrated vaccine and anti-bovine serum from Behringwerke. One batch from Behringwerke was particularly potent in this respect. Using this antiserum the measles vaccine was shown to contain seven precipitates, one of them due to albumin (Fig. 1). It was not possible to reproduce the results with the other antisera, however. Several other batches were tried and all gave rise to one precipitate corresponding to albumin, but did not give rise to other precipitates.

The patients' sera were analysed for presence of precipitating antibodies against the vaccine. CIE was performed, using either 15 μl five times concentrated vaccine or 15 μl calf serum (1/10) against 300 μl patient serum. In no case were precipitates observed. Thus, none of the patient sera contained precipitating antibodies against components in the vaccine detectable in CIE.

Fig. 1. Crossed immunoelectrophoresis of 15 μl (five times concentrated) measles vaccine and 200 μl anti-bovine serum from Behringwerke AG (OTPF 04/03 batch 2528V). The albumin precipitate is indicated by an arrow. The electrophoresis was run 30 min at 10 V/cm for the first dimension and 15 h at 2 V/cm for the second dimension.

Egg antigens in the measles vaccine

CIE was performed using 15μl allantoic fluid and 200 μl antiserum to allantoic fluid. Eight precipitates could be demonstrated. One of them was particularly dense as compared to the others. In parallel CIE experiments using 15 μl allantoic membrane extract and 200 μl antiserum to allantoic membrane, only three faint precipitates could be demonstrated. It appeared that the quality of the antiserum was not optimal. CIE experiments were performed using 30 μl of five times concentrated measles vaccine and 200 μl antiserum to allantoic fluid or 200 μl antiserum to allantoic membrane, respectively. No precipitates were formed. It was thus not possible to detect allantoic fluid or membrane antigens in the measles vaccine using CIE with the available antisera.

concentrated measles vaccine and 200 μl anti-calf serum. Such preparations gave rise to one precipitate in a reproducible manner. The corresponding antigen was identified as serum-albumin. Crossed line immunoelectrophoresis was performed with bovine serum albumin in an intermediate gel. The albumin line precipitate thus obtained fused with the albumin-like precipitate from the vaccine, demonstrating immunological identity.

Indirect evidence was obtained for the presence of one additional but unidentified component from calf serum in the measles vaccine. Anti-measles virus from sheep had been prepared by Evans by immunization with their measles virus propagated in dog kidney cells. This antiserum contained antibodies to a component in calf serum as demonstrated by CIE using 15 μl calf serum

DISCUSSION

The reactions reported appear to be immediate hypersensitivity reactions most probably due to allergy. At present, however, there is no direct evidence of immunological mechanisms being involved, perhaps with the exception of the one case showing immediate reactions to SPT with the vaccine. Anaphylaxis due to complement activation cannot be excluded. The reactions might possibly be caused by some non-immunological intolerance, the mechanisms of which are more difficult to explain.

Egg allergy has been considered a contraindication to the use of vaccines with virus grown on egg embryo cultures (2, 6). Measles virus for the vaccine in question, however, is grown on fibroblasts from chicken embryo, and it is not likely that the vaccine contains any hen's egg protein at all. Our experiments indicate that contaminants from egg were at least not present in concentrations detectable with CIE using available antisera. Only highly sensitive allergic individuals would be expected to react to the above or lower concentrations of such allergens, if present. The four control individuals having moderate egg-white allergy, had been injected with measles vaccine without any untoward reactions. This is in accord with previous reports that patients with allergy to hen's egg tolerate the injection of measles vaccine (3). The six patients investigated in the present study show that immediate hypersensitivity reactions to measles vaccine may occur independent of allergy to egg and even in children without any known allergy or atopic heredity*.

Sensitization to calf serum proteins is a possible cause of allergic reactions following vaccination. The measles vaccine used was declared by the manufacturer not to contain calf serum contaminants detectable by the double diffusion in gel techniques employed by the manufacturer and by the control authorities. CIE was found to be a more sensitive method in this respect since calf serum antigens were found to be present in sufficient concentrations to give distinct and specific CIE precipitates. Seven different antigenic components were demonstrated, one of them was albumin. This would be more than sufficient to elicit allergic reactions in susceptible individuals or to act as carrier proteins for haptenic material.

The vaccine is produced in a quite complicated manner, and there are many trace components which may be considered candidates for allergenicity, including antibiotics used to combat growth of micro-organisms. Some of these agents may act as complete allergens only after being conjugated to e.g. serum components in the recipient or present in the vaccine. Since appropriate ways of conjugation to make such agents allergenic are not known, analogous conjugates cannot be imitated with certainty in the laboratory for the production of test materials. Allergies to such conjugates may therefore not be detected by skin testing or RAST.

Skin testing with the measles vaccine might be useful to predict allergy in some individuals, but only for a minority of those at risk according to our material. The lack of reactions to prick testing with the test material in use may have several different explanations. The untoward reactions to the vaccine may not be caused by IgE-mediated allergy at all. The skin reactivity in this low age group may be too low. The vaccine used for skin testing may lack complete allergenic components, or it may differ in composition from that which gave the anaphylactic reactions, with respect to the eliciting component.

The fact that severe hypersensitivity reactions have occurred in Norway with an incidence of 1:15,000–1:20,000 during a certain period, contrasts the reported incidence of only 1–2 severe reactions per million doses in other countries using the same vaccine from the same manufacturer. It is not likely that the differences in incidence are related to genetic differences as regards immune responsiveness in the populations in question. It rather suggests a particular batch or lot problem with the vaccine used in this country during the actual period, unless extreme differences should exist with respect to the practice of reporting untoward reactions to vaccines in the different countries.

The production of the measles vaccine in question satisfied all the requirements set by the health authorities and the British Pharmacopaeia. Such requirements do not, however, sufficiently take into consideration the risks for allergic reactions which may be caused by otherwise unmeasurable concentrations of potential allergens. For allergic individuals certain production lots may become antigenically dangerous through unidentifiable contaminations arising during certain procedures. Such contamination may, for instance, occur during lyophilization of the material if the lyophilization outfit has been used also for other (allergenic) material. This adds another difficulty to identifying causes of allergy-like intolerance reactions to injectable drugs and vaccines.

In conclusion, the reason (or reasons) for the untoward reactions reported following measles vaccination in Norway has not been identified. In one case the risk for the patient could have been detected in advance by SPT with undiluted vaccine, but not in the other cases. We conclude that highly sensitive atopic patients should be skin prick tested with the vaccine prior to injection. The failure of skin testing or atopic history to predict severe reactions, speaks for a high degree of alertness when the injections are given and throughout a period of at least 20 min following the injection. Appropriate anti-anaphylactic measures should always be readily available when vaccination is carried out, also in children without any known allergy.

* On contact by correspondence, the parents of five of the patients reply and report that no other signs or symptoms of allergy have been observed during 2 years of observation following the hypersensitivity reaction to the measles vaccine.

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Appendix 5 p4.

P[illegible]EVAX®
[illegible]ies vaccine, live BP
(Schwarz strain)

Presentation Rimevax Measles Vaccine, prepared in chicken embryo fibroblasts, is presented as a pink freeze-dried pellet in a glass vial with a separate ampoule of clear, colourless, sterile diluent. Each 0.5 ml dose of reconstituted vaccine contains not less than 1,000 $TCID_{50}$ of the highly attenuated live Schwarz strain measles virus and not more than 25 μg (17 i.u.) of neomycin sulphate.

Uses Rimevax is indicated for active immunisation against measles (rubeola).

If given to contacts within three days of exposure to measles, the full clinical disease may be suppressed.

Dosage and administration *Adults and children:* 0.5 ml of the reconstituted vaccine subcutaneously or intramuscularly. The vaccine should be reconstituted using the sterile diluent provided.

The vaccine is quickly inactivated by ether, alcohol and detergents and care should be taken to avoid contact with these substances when cleaning skin prior to vaccination. Syringes need to be dry sterilised.

Contra-indications, warnings, etc
Contra-indications: Do not use Rimevax in the presence of acute illness, whether active or expected following exposure to infection other than measles. This applies particularly to active tuberculosis and respiratory tract infection. It is also contra-indicated in states of altered immunity including those which may accompany conditions such as leukaemia, lymphoma, generalised malignancy or treatment with corticosteroids, cytotoxic drugs or irradiation.

Rimevax may contain traces of chick embryo protein, but this does not normally contra-indicate its use except in cases of severe hypersensitivity to eggs. Rimevax should not be given to those known to be hypersensitive to neomycin. A solution of 1:1000 adrenaline should be available for injection in rare cases of anaphylactic reaction.

Do not use during pregnancy.

Cautions: Measles vaccine should only be given to children with a history of convulsions with the simultaneous administration of human normal immunoglobulin [recommended dosage 1.3 mg protein/kg (0.6 mg protein/lb) body weight]. In such children or those with a family history of convulsions, consideration should be given to delaying immunisation until after the second birthday.

Because of the possibility of interference from passive antibodies, measles vaccine should not normally be given to infants below the age of one year, or to subjects who have received blood or human plasma transfusions or human immunoglobulin within the previous three months. If the vaccine is given in these circumstances, serum antibodies should be checked at a later date.

Tuberculin testing should be delayed for about eight weeks after measles vaccination since false-negative results may be obtained during this period.

It is not usually recommended that live vaccines be given within three weeks of each other.

Adverse reactions: These are usually mild and are more likely around the eighth day after vaccination. They may include rash, malaise, cough, pharyngitis, coryza, pyrexia and headache. In a very few subjects convulsions may accompany the fever. Very rarely encephalitis has been reported in association with measles vaccination.

Pharmaceutical precautions Protect from light. Rimevax Measles Vaccine should be stored between 2°C and 8°C and should not be frozen (lower temperatures will not harm the vaccine but may damage the diluent ampoule). At room temperature (20°–25°C) Rimevax is stable for up to four weeks.

The vaccine should be reconstituted using the sterile diluent provided. Once reconstituted Rimevax should be used immediately and certainly within one hour.

Legal category POM.

Package quantities Single-dose vials, each with a separate ampoule containing sterile diluent, singly and in packs of 50.

Further information Current policy recommends routine vaccination against measles for children between 1 and 2 years of age. Rimevax may also be used for older children and adults known to be susceptible to measles.

The following groups of children at special risk may in particular benefit from vaccination: children from the age of one year upwards in residential care; those entering nursery school or other establishments accepting children for day care; those with chronic conditions affecting physical development such as cystic fibrosis or congenital heart disease; and those with a history of convulsions provided the appropriate cautions (see *Cautions* above) are observed.

Maximum periods of stability of freeze-dried Rimevax:

2°–8°C	2 years
20°–25°C	4 weeks
37°C	14 days
41°C	7 days

It is recommended that the vaccine is stored at 2°–8°C (see *Pharmaceutical precautions*).

Product licence number 0002/0088.

MEVILIN*-L
Measles Vaccine (Live Attenuated) BP (Schwarz strain) Meas/Vac (Live)

Presentation Mevilin-L is a freeze-dried preparation of living attenuated virus of the Schwarz strain. It must be reconstituted with Water for Injections BP immediately prior to injection; the reconstituted vaccine may vary in colour from pale straw to pink – this variation is not indicative of deterioration.

Uses General prophylaxis against measles and within 3 days of exposure to measles.

Dosage and administration One dose by intramuscular or subcutaneous injection (contains not less than 1,000 $TCID_{50}$ of measles virus). Mevilin-L should be administered to infants at about 12 months of age. There is no upper age limit for measles vaccination.

To reconstitute Mevilin-L inject the required amount of Water for Injections BP (0.5 ml for the single-dose vial) into the vial containing the freeze-dried vaccine, allow to stand for about a minute then mix the suspension by withdrawing it into the syringe and expelling it back into the vial. The use of a 2 ml disposable syringe is recommended. The dose of the reconstituted vaccine is 0.5 ml.

Contra-indications, warnings, etc
Contra-indications: Mevilin-L should not be given to children below the age of one year unless at special risk. If this is the case, a second dose should be given at a later date as interference from maternally derived antibody may cause a failure to respond.

Any active or suspected infection is reason for delaying vaccination.

Mevilin-L should not be given to children suffering from leukaemia, Hodgkin's disease or other malignant conditions or hypogammaglobulinaemia. Also those with impaired immune responsiveness, whether occurring naturally or as a result of treatment with steroids, radiotherapy, cytotoxic drugs or other agents.

Pregnancy is a contra-indication. Also hypersensitivity to hen's egg, neomycin and polymyxin.

Children with the following conditions should not be given measles vaccine, unless with the simultaneous administration of normal immunoglobulin (0.6 mg/lb (1.3 mg/kg) body weight)† with a specific content of measles antibody:

1. History of convulsions.
2. Parental history of epilepsy (non traumatic).
3. Chronic disease of the heart or lungs.
4. Seriously underdeveloped.

† Human Normal Immunoglobulin for use with Measles Vaccine is issued in ampoules, each containing 4–8 i.u. measles antibody in 15 mg protein in 0.5 ml solution. (See CMO letter CMO 5/68, CMO 18/71 and CMO (77) 3.) Supplies are available from Area Health Authorities in England and from Blood Transfusion Centres in Scotland.

If there is a history of convulsions or a history or family history of epilepsy, consideration should be given to delaying immunisation until after the second birthday.

Human Normal Immunoglobulin with a specific content of measles antibody is used to reduce the potential for adverse reactions where constitutional disturbance may be avoided in administering measles vaccine. A separate syringe should be used for injecting the immunoglobulin into the contralateral arm. It is important not to exceed the dose as overdosage can prevent the development of immunity.

Precautions: Attenuated measles vaccine is quickly killed by ether, alcohol and detergents: these agents should not be used for sterilising syringes prior to immunisation. Liquids used for cleansing the skin prior to injection should be allowed to dry before the vaccine is given.

Warnings: A sterile syringe and Adrenaline Injection BP should be ready for use, in case the need arises for emergency treatment of an allergic reaction.

Mevilin-L must not be given intravenously and should not normally be given within 3 months of a transfusion of blood or human plasma or treatment with Human Immunoglobulin except as previously specified. If any of these substances have been used near to the time of vaccination a test for the presence of measles antibody should be made at a later date.

The vaccine should not normally be given less than 3 weeks before or after immunisation with other live virus vaccines.

Measles vaccine may depress tuberculin skin sensitivity for 4 weeks or longer.

Adverse effects: When adverse reactions occur they usually appear about the eighth day. The symptoms are usually mild and may include malaise, cough, coryza, rash, pharyngitis, pyrexia and headache. Convulsions may accompany the fever.

Severe reactions are uncommon, but encephalitis has been reported – the incidence is considered to be approximately 1 in 1,000,000 vaccinees.

Pharmaceutical precautions Mevilin-L should be protected from light and stored in a refrigerator at between 2°C and 8°C (36°F to 46°F). Do not freeze.

The reconstituted vaccine should be used as soon as possible and certainly within one hour.

Neomycin and polymyxin are used in the tissue culture medium employed during manufacture and traces of these antibiotics may be present in the final vaccine.

Legal category POM.

Package quantities Single dose vial with 0.5 ml ampoule of Water for Injections BP.

Further information It is important to recognise that children in residential or day care over the age of one year are at special risk.

Product licence number 0021/0059.

Thomas Morson Pharmaceuticals
Division of Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU

ATTENUVAX® ▼

Presentation Lyophilised powder for injection. When reconstituted, each dose of Attenuvax Injection contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of measles virus vaccine expressed in terms of the assigned titre of the FDA Reference Measles Virus. Attenuvax is a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain.

Uses For general immunisation against measles.

Children: The Department of Health recommends that children 12 months of age or older be vaccinated against measles. (Please refer to *'Contra-indications'*.)

Attenuvax given immediately after exposure to natural measles may provide some protection. If, however, the vaccine is given a few days before exposure, substantial protection may be provided.

Dosage and administration After suitably cleansing the injection site, the total volume of reconstituted vaccine should be injected subcutaneously, preferably into the outer aspect of the arm. Attenuvax must not be given intravenously.

The dose of vaccine is the same for all patients.

Warning: A sterile syringe and Adrenaline Injection BP (1:1,000) should be ready for immediate use should an anaphylactoid reaction occur.

Contra-indications, warnings, etc *Contra-indications:* Infants below 15 months of age may fail to respond to the vaccine due to the presence of residual measles antibody of maternal origin; the younger the infant, the lower the chance of seroconversion. Children below the age of 12 months should not normally be given Attenuvax unless they are at special risk. Where immunisation below the age of 12 months is deemed necessary, a second dose should be given after the child has reached 15 months of age.

Any active or suspected infection is reason for delaying vaccination. Active untreated tuberculosis. Malignant disease.

Attenuvax should not be given to those with impaired immunoresponsiveness occurring naturally, or as a result of treatment with steroids, radiotherapy, cytotoxic drugs or other agents. This contra-indication does not apply to patients receiving corticosteroids for replacement therapy, e.g. Addison's disease.

Hypersensitivity to neomycin (each dose of reconstituted vaccine contains approximately 25 mcg of neomycin).

Hypersensitivity to eggs, chicken or chicken feathers: Attenuvax is essentially devoid of potentially allergenic substances derived from host tissues (chick embryo). However, since this vaccine is propagated in cell cultures of chick embryos, the benefits of its use in patients hypersensitive to eggs, chicken or chicken feathers must be weighed against the potential risks of hypersensitivity reactions. Significantly, children with known allergies experienced no reactions other than those already seen in non-allergic children.

Pregnancy: Do not give Attenuvax to pregnant women, because the possible effects of the vaccine on foetal development are unknown at this time. It is recommended that pregnancy at the time of vaccination be ruled out, and that the possibility of pregnancy occurring in the three months following vaccination must be prevented by medically acceptable methods.

Warnings and adverse effects: Attenuvax is for subcutaneous injection only; *it must not be given intravenously.*

Attenuvax may be given simultaneously with monovalent or trivalent poliovirus vaccine, live, oral, with Meruvax® II (Rubella Virus Vaccine, Live) and/or Mumpsvax® (Mumps Virus Vaccine, Live). Attenuvax should not be given less than one month before or after immunisation with other live virus vaccines.

Children with a history of convulsions, or with parental history of epilepsy (non-traumatic) are considered to be at greater risk of convulsions.

In these cases, it is recognised that the simultaneous administration of normal immune globulin (0.6 mg/lb [1.3 mg/kg] bodyweight) could be beneficial, although it should be recognised that the administration of immunoglobulin might increase the proportion of failures to immune.

It may therefore be necessary to undertake a serological test to determine whether immunisation has been successful.

Attenuvax should not normally be given within three months of a transfusion with blood, or human plasma, or treatment with human immunoglobulin. If any of these substances have been used near to the time of vaccination, a test for the presence of measles antibody should be made at a later date.

It has been reported that live attenuated measles virus vaccine may result in a temporary depression of tuberculin skin sensitivity. If a tuberculin test is to be done, it should be administered either before or with Attenuvax.

Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunised with live measles virus vaccine, and no studies have been reported on the effect of measles virus vaccines on untreated tuberculous children.

The occurrence of thrombocytopenia and purpura associated with live virus measles vaccines has been extremely rare.

Because the vaccine is slightly acidic (pH 6.2–6.6), patients may complain of burning and/or stinging at the injection site for a short time.

Moderate fever and rash may occur during the month after vaccination. Rarely, high fever or local reaction may occur. Children developing fever may, on rare occasions, exhibit febrile convulsions.

There have been isolated reports of ocular palsies and Guillain-Barre syndrome occurring after immunisation with vaccines containing live attenuated measles virus. The ocular palsies have occurred approximately 3–24 days following vaccination. No definite causal relationship has been established between either of these events and vaccination.

There have been reports of subacute sclerosing panencephalitis (SSPE) in children who did not have a history of natural measles but did receive measles vaccine. Some of these cases may have resulted from unrecognised measles in the first year of life or possibly from the measles vaccination. Based on estimated nationwide measles vaccine distribution in the USA, the association of SSPE cases to measles vaccination is about one case per million vaccine doses distributed. This is far less than the association with natural measles: 5–10 cases of SSPE per million cases of measles.

Local reactions characterised by marked swelling, redness and vesiculation at the injection site of attenuated live virus measles vaccines have occurred in children who have previously received killed measles vaccine. Allergic reactions such as wheal and flare at the injection site have been reported.

Treatment of overdosage: Not applicable.

Pharmaceutical precautions Prior to reconstitution, the vaccine should be shipped and stored between 2°–8°C. *Protect from light.*

Studies have shown that the vaccine contains a minimum of 1,000 $TCID_{50}$ per dose after storage at any one of the following temperatures for the stated time period:

Dried Vaccine Storage Temperature	*Retention of Potency 1,000 $TCID_{50}$ per dose*
2°–8°C	2 years
20°–25°C	4 months
37°C	2 weeks
45°C	6 days

The vaccine should be reconstituted using only the diluent provided, and used immediately after reconstitution.

Colour: The vaccine when reconstituted is yellow. It is acceptable for use only when clear.

Legal category POM.

Package quantities A single-dose vial of lyophilised vaccine, packed with an ampoule containing diluent.

Further information Experience from more than 80 million doses of all live measles vaccines given in the USA through 1975 indicates that significant central nervous system reactions such as encephalitis and encephalopathy, occurring within 30 days after vaccination, have been temporally associated with measles vaccine approximately once for every million doses. In no case has it been shown that reactions were actually caused by vaccine. The risk of such serious neurological disorders following live measles virus vaccine administration remains far less than that for encephalitis and encephalopathy caused by natural measles (one per thousand reported cases).

A study suggests that the overall effect of measles vaccine has been to protect against SSPE by preventing measles with its inherent higher risk of SSPE.

Product licence number 0025/0070.