often wuoted to show mmr has low reactions

negative pressure is directly proportional to nasal resistance (for a given respiratory effort), any reduction in nasal resistance upon clearance of retained secretions will reduce the inspiratory suction pressure and the risk of oropharyngeal closure. This change may partly explain why children who were severely obstructed before starting on CIP had only mild obstruction with low pressure-time indices when it was interrupted (fig 4). Perhaps CIP also acts to increase muscle tone through stimulation of airway mechanoreceptors, as has been proposed for some patients with nasal CPAP[23] but too little is known of these receptors to permit speculation on the matter.[25]

CIP only relieves the symptoms in airway obstruction, so it is important to guard against a false sense of security and ensure that CIP is not inadvertently discontinued. On its withdrawal, the patient should be carefully observed during sleep to ensure that the OPO has resolved.

The method is deceptively simple. Scrupulous attention must be paid to the tube's position and selection of the appropriate flow rate. The gas needs to be humidified and warmed to render the patient comfortable and to prevent inspissation of secretions, which could raise nasal airway resistance and aggravate the degree of obstruction. Coughing and spluttering with rhinorrhoea is common at the start of therapy and should not deter one. Abdominal distension, gagging, and persistent cough occur when the catheter has been advanced too far or when gas flow rates are too high. CIP may be ineffective when the oropharynx is occluded by a mass.

The simplicity of CIP and the fact that it can be applied with equipment readily available in any large hospital renders it ideal for prompt relief of severe OPO. Subsequent definitive therapy depends on the underlying disorder. When this can be corrected surgically or is expected to resolve within a reasonable period, CIP can be the sole form of airway relief. Otherwise an elective tracheostomy is recommended.

CIP may also help in diagnosis. When snoring cannot be easily distinguished from laryngeal stridor in infants, a response to CIP implicates the oropharynx. We believe that CIP may be of value in adults and in domiciliary care but this has yet to be established.

Preliminary results of this study were presented at the University of California, San Francisco, during the 25th Anniversary celebration of the Cardiovascular Research Institute (C.V.R.I.) in October 1983.

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FREQUENCY OF TRUE ADVERSE REACTIONS TO MEASLES-MUMPS-RUBELLA VACCINE

A Double-blind Placebo-controlled Trial in Twins

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Summary The vast majority of adverse reactions following immunisation of children with live measles-mumps-rubella (MMR) vaccine were shown in a double-blind, placebo-controlled, cross-over study in 581 twin pairs to be only temporally but not causally related to the vaccination. The true frequency of side-effects caused by MMR vaccine, estimated from the discordance rates of individual signs and symptoms between MMR vaccinees and their placebo-injected twins, was between 0·5 and 4·0%. Moreover, respiratory symptoms, nausea, and vomiting were observed more frequently in the placebo-injected group than in the MMR vaccinated group.

Introduction

A VACCINATION programme to eliminate measles, mumps, and rubella (MMR) from Finland began in 1982.[1] The live combined vaccine ('Virivac', Merck Sharp & Dohme)[2–5] is administered in two doses, the first at age 14–18 months and the second at 6 years. In the early stages of the programme, however, children between these age limits are also being immunised.

One of the major concerns in any large-scale vaccination programme is the occurrence of adverse reactions. The measles component[6–9] and, to a lesser extent, the rubella antigen[10,11] are known to be reactogenic, whereas the mumps component is thought to be almost harmless.[12–15] Few studies[3,15,16] have compared common symptoms and signs occurring in vaccinees and controls. In particular, little attention has been paid to reactions caused by the combined MMR vaccine.

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We now report the results of a double-blind, placebo-controlled, crossover study on the reactogenicity of MMR vaccine. The study was carried out in twins to maximise the reliability of the results.

Subjects and Methods

The study population consisted of pairs of twins who were to be MMR vaccinated between Nov 1, 1982, and Oct 31, 1983. 686 twin pairs (aged 14 months to 6 years) were entered into the study. For 104 pairs, however, only the first follow-up forms were completed, and the nurse helped the parents of 1 other pair to fill in their forms; these 105 pairs were excluded. Thus, data on 581 twin pairs were included in the analysis.

When the twins were brought to the child health centre[1] the public-health nurse described the study to the parents and invited them to take part. If the parents were not willing, the children were vaccinated according to the normal procedure. If they agreed to participate and there were no contraindications for MMR vaccination,[1] each pair of twins was allocated a colour-coded vaccination package (one orange, one green), consisting of two doses of vaccine (one active, one placebo) and a questionnaire.

Vaccination

The vaccines were administered blind, but one twin of each pair first received active vaccine then, 3 weeks later, placebo; whereas the other twin was first given placebo and then, after 3 weeks, active vaccine. The injections consisted of 0·5 ml of vaccine[2–5] or placebo (the same product including neomycin and phenol-red indicator but without the viral antigens) and were administered subcutaneously by the nurse to the left deltoid or gluteal region.

Reporting of Reactions

Each twin was given a colour-coded questionnaire to be filled in daily by the parents for 21 days after each injection. Findings were to be marked positive, negative, or "point not checked" for 15 items (table I). The parents were given a thermometer to guarantee daily temperature recording.

If either twin had respiratory or other relevant symptoms at the time of the second injection, vaccination of both children was postponed for 2 weeks.

Analysis of Data

The codes were broken only after all questionnaires had been returned. The discordance rate was calculated by subtracting the frequency of each symptom or sign reported in the placebo-injected twins from that observed in the MMR vaccinated twins. This difference was regarded as the true adverse-reaction rate attributable to the MMR vaccine. Confidence intervals were computed from the poisson distribution of the frequencies of the symptom or sign in the placebo-injected and the MMR vaccinated twins.

TABLE I—SYMPTOMS AND SIGNS CAUSED BY MMR VACCINATION AND DAY OF PEAK OCCURRENCE

Symptom or sign	Maximum difference in rate* (%)	$CI_{95\%}$	Peak frequency (days after vaccination)
Local erythema (>2 cm)	0·8	0·1–1·4	2
Other local reaction	0·4	0–1·4	2
Mild fever (≤38·5°C rectal)	2·7	0–6·1	10
Moderate fever (38·6–39·5°C)	2·9	1·6–4·3	9
High fever (≥39·5°C)	1·4	0·7–2·1	10
Irritability	4·1	2·1–6·1	10
Drowsiness	2·5	1·4–3·6	11
Willingness to stay in bed	1·4	0·5–2·3	11
Generalised rash	1·6	0–3·0	11
Conjunctivitis	2·1	0·9–3·2	10
Arthropathy	0·8	0·2–1·3	7–9
Peripheral tremor	0·4	0–0·9	9
Cough and/or coryza	−1·5†	−4·6–1·6	9
Nausea and/or vomiting	−0·8†	−1·6–0	7–8
Diarrhoea	0·7	0–1·7	11

*Between MMR group and placebo group.
†More in placebo-injected children.

TABLE II—FEVER AFTER MMR VACCINATION OR PLACEBO INJECTION IN 581 TWIN PAIRS: MEAN NO OF CHILDREN AFFECTED PER DAY AND MEAN RATE PER 1000

	Days after injection									
	1–6		7–8		9–10		11–12		13–21	
—	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate
Mild fever (≤38·5°C rectal):										
MMR	190	163	196	168	222	191	206	177	180	155
Placebo	187	162	194	166	196	169	193	166	181	156
Difference	3	1	2	2	26	22	13	11	−1	−1
Moderate fever (38·6–39·5°C rectal):										
MMR	9	8	34	29	42	36	21	18	7	6
Placebo	9	7	13	11	10	9	10	9	9	8
Difference	0	1	21	18	32	27	11	9	−2	−2
High fever (>39·5°C rectal):										
MMR	1	1	7	6	15	13	5	4	2	1
Placebo	1	1	3	3	1	1	1	0	1	1
Difference	0	0	4	3	14	12	4	4	1	0

Results

The order in which the injections had been given seemed to have no major effect on the reaction rates. Therefore the results are presented only according to the type of injection (MMR vaccine or placebo). Table I shows, for each sign and symptom, the maximum discordance rate between the MMR and placebo groups and the day of peak frequency. The most common adverse reaction was irritability; its maximum discordance rate was 4·1% on day 10. On the other hand, respiratory symptoms, nausea, and vomiting were less common in the MMR vaccinees than in the placebo-injected children. The only true rates which may have exceeded a maximum of 6% were those for mild fever and irritability (table I). Tables II–V show that many of the symptoms and signs observed in the vaccinated children were also common in the placebo group.

Fever (Table II)

The vast majority of mild fever (up to 38·5°C) episodes were not due to the MMR vaccine, but high fever (above 39·5°C) was seldom caused by factors other than the MMR vaccine. A fever due to MMR vaccination usually occurred during days 7–12, and high fever was most likely on days 9–10. In the period of peak occurrence 88% of mild fever, 24% of moderate fever, and 7% of high fever episodes were not caused by the MMR vaccine.

Unusual Behaviour (Table III)

Excessive irritability, drowsiness, or willingness to stay in bed had similar time sequences. Virtually no differences were observed between twins during the first 6 days, except that irritability and drowsiness were slightly more common in the placebo-injected controls than in the MMR vaccinees. On days 9–10, however, these signs were reported more often in the MMR children (excess frequency up to 33 per 1000). The behaviour of the two groups was again similar from day 11 onwards.

Measles Signs (Table IV)

Classical signs of measles (generalised rash and conjunctivitis) affected the MMR group only during the

TABLE III—UNUSUAL BEHAVIOUR AFTER MMR VACCINATION OR PLACEBO INJECTION IN 581 TWIN PAIRS: MEAN NO OF CHILDREN AFFECTED PER DAY AND MEAN RATE PER 1000

	Days after injection									
	1–6		7–8		9–10		11–12		13–21	
—	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate
Irritability:										
MMR	37	32	63	54	85	73	81	70	32	27
Placebo	38	33	51	44	47	40	47	40	22	19
Difference	−1	−1	12	10	38	33	34	30	10	8
Drowsiness:										
MMR	15	13	29	25	41	35	32	27	9	8
Placebo	16	14	13	11	17	14	12	10	8	7
Difference	−1	−1	16	14	24	21	20	17	1	1
Willingness to stay in bed:										
MMR	8	7	16	15	21	18	18	15	6	5
Placebo	7	6	7	6	9	7	6	6	7	6
Difference	1	1	9	9	12	11	12	9	−1	−1

TABLE IV—RASH, CONJUNCTIVITIS, ARTHROPATHY, AND PERIPHERAL TREMOR AFTER MMR VACCINATION OR PLACEBO INJECTION IN 581 TWIN PAIRS: MEAN NO OF CHILDREN AFFECTED PER DAY AND MEAN RATE PER 1000

	Days after injection									
	1–6		7–8		9–10		11–12		13–21	
—	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate
Generalised rash:										
MMR	22	19	28	24	49	43	56	48	27	24
Placebo	23	20	29	25	35	30	39	33	24	20
Difference	−1	−1	−1	−1	14	13	26	15	3	4
Conjunctivitis:										
MMR	9	8	24	21	34	29	23	20	10	8
Placebo	11	10	11	10	14	12	7	7	7	6
Difference	−2	−2	13	11	20	17	16	13	3	2
Arthropathy:										
MMR	3	3	10	8	11	10	12	10	4	3
Placebo	4	3	1	0	4	3	4	3	2	1
Difference	−1	0	9	8	7	7	8	7	2	2
Peripheral tremor:										
MMR	3	2	4	3	7	5	3	2	1	1
Placebo	2	1	2	2	2	1	0	0	0	0
Difference	1	1	2	1	5	4	3	2	1	1

TABLE V—RESPIRATORY AND GASTROINTESTINAL SYMPTOMS OR SIGNS AFTER MMR VACCINATION OR PLACEBO INJECTION IN 581 TWIN PAIRS: MEAN NO OF CHILDREN AFFECTED PER DAY AND MEAN RATE PER 1000

	Days after injection									
	1–6		7–8		9–10		11–12		13–21	
—	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate
Cough and/or coryza:										
MMR	105	91	156	134	166	143	162	139	153	132
Placebo	100	85	154	132	181	155	177	152	155	134
Difference	5	6	2	2	−15	−12	−15	−13	−2	−2
Nausea and/or vomiting:										
MMR	6	5	5	4	8	7	11	10	8	7
Placebo	7	6	14	12	14	12	7	6	6	5
Difference	−1	−1	−9	−8	−6	−5	4	4	2	2
Diarrhoea:										
MMR	14	12	19	16	17	14	20	18	12	10
Placebo	16	14	15	13	14	12	14	12	12	10
Difference	−2	−2	4	3	3	2	6	6	0	0

second week. The frequency of rash and eye irritation attributable to the MMR vaccine was, however, surprisingly small (maximum 17 per 1000). Arthropathy and peripheral tremor were both observed at a rate of less than 10 per 1000.

Respiratory and Gastrointestinal Symptoms (Table V)

The most unexpected findings concerned respiratory symptoms and, to a lesser extent, nausea and vomiting. During the first week cough and running nose were slightly more common in the MMR vaccinees, but from day 9 these were clearly more prevalent (12–13 per 1000) in the placebo-injected controls. The difference was so consistent and large that chance is unlikely. Nausea and vomiting, too, tended to be as common in the placebo-injected children as in the MMR vaccinated children, but the numbers were small.

Discussion

The results of the present study show that adverse reactions to the widely used MMR vaccine are much less common than was previously thought. A temporal association between vaccination and symptoms appearing in the following days or weeks does not necessarily imply a causal relationship,[3,15,16] and the results of the present investigation further emphasise the importance of studying a control group for comparison in estimating the frequencies of adverse reactions caused by vaccines. Little attention has been paid to the true reactogenicity of the MMR vaccine, although in the USA, for instance, it is given routinely to almost every child. We are aware of only one study that compared reactions in an MMR vaccinated group and a placebo group.[3] The results are in accordance with those of our study; respiratory symptoms, for example, were reported in 72% of vaccinees and 74% of controls.

The design of a twin study may reduce differences in behavioural symptoms or signs within pairs. In our study it is likely that irritability or willingness to stay in bed due to MMR vaccination was reflected in the behaviour of the other twin too, especially in the youngest age groups. On the other hand, there are no grounds to suspect that reporting of clearly measurable events, such as fever, or skin, eye, or joint signs, or respiratory or gastrointestinal symptoms, would have been biased.

The study was designed to explore relatively common symptoms and signs occurring after the vaccination. The confidence intervals show that our sample size has the power to detect adverse reactions attributable to the MMR vaccine down to a frequency of 1–3%, depending on the background frequency of that particular symptom or sign. The upper limits of the intervals also show that no symptom or sign affected more than 6% of vaccinees (table I).

Rare reactions due to the MMR vaccine cannot be studied with this small sample. We are, however, collecting data on 500 000 vaccinees, which should reveal all essential complications caused by this live vaccine.

At least two factors may explain the small difference between the vaccinated and placebo groups and the high frequency of various "reactions" attributed to vaccinations in general. Firstly, if a child has been immunised, the parents observe him, intentionally or not, more closely than usual, and will tend to blame the vaccination for any signs or symptoms. Secondly, acute infectious diseases are common in a normal, otherwise healthy child population. An epidemiological survey conducted among 7000 children

under 16 years of age in Helsinki in 1978[17] showed that at any time symptoms of common cold were found in 10% of the children, diarrhoea in 5–9% of the boys and 4–5% of the girls, and otitis media in 5–9% of the boys and 2–3% of the girls. Because most of the "vaccination reactions" are symptoms and signs found also in the common infections—a fever being a classical example—the possibility of concurrent infection is often ignored.

Respiratory symptoms, nausea, and vomiting were more common in the controls than in the vaccinees from the second week onwards, as though the MMR vaccine had had a protective effect. In the early 1950s the combination of vaccinia and yellow-fever vaccines was found to reduce the frequency of yellow-fever seroconversions,[18] and the combination of measles (with or without yellow fever) and smallpox vaccines showed a similar effect.[19] Production of interferon in these circumstances might explain this finding.[3,20] Thus the MMR vaccine might, in fact, give some transient protection against the common cold.

This study examined common reactions attributable to the MMR vaccine, but similar results might be obtained with other vaccines if studied under controlled conditions. Many vaccines may be safer than is at present recognised.

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NOCTURNAL ADRENAL SUPPRESSION IN ASTHMATIC CHILDREN TAKING INHALED BECLOMETHASONE DIPROPIONATE

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Summary Plasma cortisol was measured every 20 min and sleep was monitored in nineteen asthmatic children, twelve of whom were receiving various doses of inhaled beclomethasone dipropionate (BDP). Children receiving inhaled BDP had lower cortisol secretion during the night than those who were not taking inhaled BDP, a delayed rise from the nocturnal nadir, and low early morning levels. Inhaled BDP produces a dose-dependent adrenal suppression.

Introduction

THE introduction in 1972 of inhaled corticosteroids in the treatment of asthma was seen as an important advance,[1] since they had the potential to replace oral corticosteroids of which the side-effects include adrenal suppression and extend in children to permanent stunting of growth.[2,3] Subsequent studies on inhaled corticosteroids have been divided on the occurrence of adrenal suppression, some finding none[4-12] and others that it occurs at high doses.[13-17] Many of these studies used non-physiological measurements of the pituitary/adrenal axis (eg, tetracosactrin or insulin tolerance test) or single plasma cortisol measurements, which are difficult to interpret in the face of a broad normal range.

While studying the causes of growth delay in asthma, we had the opportunity to measure nocturnal plasma cortisol concentrations in small blood samples taken regularly throughout the night under optimum sleep laboratory conditions; we now report our findings using these measurements to assess adrenal function.

Patients and Methods

Nineteen asthmatic children (fourteen male, five female) took part in a study to investigate the pathophysiology of growth delay in asthma. They were aged 10–15 years (mean 13·5; bone age 8·1–14·9 "years", mean 12·3). Twelve were taking inhaled beclomethasone dipropionate (BDP) as part of their anti-asthma therapy, 300–1000 μg daily (mean 530±220 μg) divided into 2–4 doses (mean 2·4±0·7 doses per day); seven were taking no inhaled corticosteroids. No patients were taking oral corticosteroids regularly but three had had one or more short courses (<7 days) for an acute asthmatic attack in the previous year but not within the preceding 3 months. In twelve patients there had been no change in inhaled steroid therapy for at least a year. Of those whose therapy had changed, only two had previously been on a higher dose.

The study took place over 48 h; it included monitoring of sleep, endocrinological profiles, and respiratory function throughout a test (second) night. Care was taken to ensure that administration of drugs, bedtime, meals, and so on, were as near to home conditions as possible. The patients spent one night accustoming themselves to the sleep laboratory and the monitoring procedures. Between 1700 h and 2000 h on the test day an indwelling intravenous cannula was positioned in a forearm or antecubital vein so that venous access could be ensured during the night without disturbing the patient. Blood samples were taken every 20 min from midnight until 0600 h. Sleep was monitored with an electroencephalograph and an electro-oculograph by conventional methods.[18] Three measures of sleep adequacy were used: the sleep efficiency index (the ratio of the time