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A Randomised Single Blind Trial of a Combined Mumps Measles Rubella Vaccine to Evaluate Serological Response and Reactions in the UK Population

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Four hundred and twenty children were randomly assigned to receive either mumps measles rubella (MMR) vaccine (207) or measles vaccine (213) in a single blind study, to investigate the reactogenicity and serology of the MMR vaccine. There was no significant difference between the number of children developing symptoms after MMR vaccination to those developing symptoms after measles vaccination. Both vaccines are associated with a rash, temperature and restlessness five to thirteen days after vaccination. The serological response to measles vaccine was similar in both groups with 92–6% seroconverting with MMR, and 96–8% with measles. Seroconvertion against mumps and rubella with the MMR vaccine was 88% and 96% respectively. This study confirms the safety and efficacy of the MMR vaccine in a UK population.

Introduction

The mumps measles rubella (MMR) vaccine was introduced into the UK vaccination schedule in October 1988.[1]

It is hoped that this change in immunisation policy will boost vaccination rates against measles towards the 90% uptake target for 1990 suggested by the WHO and lead ultimately to the erradication of measles, mumps and rubella.

The MMR vaccine has been available in America since the 1970s, and Scandinavia since 1982.[2] There are many data from these countries concerning the vaccine. The majority of these studies used vaccines containing Jeryl Lynn (mumps) and Moraten (measles) virus strains.[3,4,5] In the UK we are also using Urabe AM/9 (mumps) Schwarz (measles) combination. This combination has been compared to Jeryl Lynn–Moraten vaccine, and found to be at least equally immunogenic and reactogenic.[6] Some workers have suggested the immunogenicity and reactogenicity of the Urabe AM/9 Schwarz combination to be greater.[7,8]

It is important we define the benefits and the risks of the vaccine in the UK population if we are to counsel parents appropriately and strive to achieve the 90% uptake target.

This is a report of the results of a single blind randomized control trial, evaluating the serological response, and reactogenicity of a MMR vaccine, Trimovax (Schwarz 1000$TCID_{50}$, Urabe AM/9 5000 $TCID_{50}$, rubella RA 27/3 1000 $TCID_{50}$) using a measles vaccine, Rouvax (Schwarz 100 $TCID_{50}$) as control, under routine conditions in the UK.

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Table I Exclusion criteria

1.	Infants aged less than 12 months or over 48 months
2.	Infants with malignant disease
3.	Infants who were immunocomprised
4.	Infants with a history of convulsions*
5.	Infants with a history of anaphylactic reaction to eggs, neomycin or kanomycin
6.	Infants with a history of measles or mumps (not rubella because of the inaccuracy of the diagnosis)

*Infants who had suffered from convulsions were excluded from the study because of the limited licence of the MMR vaccination at the time of the study.

Method

The study was based in two areas of Nottingham (Rushcliffe and Broxtowe) and was carried out over a 12 month period. The names of children who would be eligible for measles vaccination at this time (age 13–15 months) were obtained from health visitors' birth books. Parents were approached by letter. If they expressed an interest in the study they were visited by a doctor (SE), the study was explained in detail and written consent was obtained.

Children who fell into any of the categories in Table I were excluded from the study. Vaccination was deferred in any child who had been in contact with measles, mumps or rubella in the previous three weeks, had a febrile illness, had received gamma globulin in the previous three months or had received a vaccine in the previous month.

The child was randomly assigned to receive MMR vaccine or measles vaccine by a system of sealed number envelopes, the numbers corresponding to the child's study number. Randomization occurred at the time of vaccination in the Child Health Clinic.

The vaccination was given in the upper arm, unless the parents objected in which case it was given in the upper leg. Prior to vaccination 1.5 ml of venous blood was taken into a dry tube. Parents were given a diary and asked to record any symptoms in the child, whether or not they thought them attributable to the vaccination. The diary asked specifically if the child had: anything to see at the injection site, sore arm, pain anywhere, a rash, a fever, or if they had received medication. There was also a space to record if the child was different from usual and in what way. The diary was completed daily for three weeks. The parents were asked to continue to monitor their child for a further three weeks and record any symptoms weekly in the diary. After six weeks the diaries were collected and any symptoms discussed with the parents. A second blood sample was taken at this time for serology. The trial code was broken and the parents informed which vaccine the child had received. If the child had received only measles vaccine they were offered mumps (Immovax) and rubella (Rudivax) vaccinations.

The information from the diaries was categorised into symptom groups:

1. Local symptoms: erythema, induration, pain.
2. General specific symptoms; rash, parotitis, testicular swelling, arthralgia, arthritis, conjunctival inflammation, convulsion.
3. General non-specific symptoms; fever, adenopathy, nasopharyngeal inflammation, digestive disorders, restlessness.

Restlessness is the term we have used to describe a non-specifically unwell child; it covers such terms as irritable, miserable, tearful, clingy, not sleeping, noted by the parents.

The blood for serology was separated and the serum frozen at −20°C. It was transported on dry ice to the laboratories of Institute Merieux, Lyon, France, where analysis was performed.

Measles and rubella antibody levels were determined using Haem-agglutination inhibition; the mumps antibody titres were determined using the neutralisation test.[9]

Immunity to measles and rubella was assumed if the antibody titre was greater than 20, and to mumps if the antibody titre was greater than 120. In cases where there was an insufficient sample for full analysis, titres were estimated in the priority measles, mumps, rubella. The Study was approved by the local ethical committee.

Results

Four hundred and twenty children were enrolled into the study: 213 were assigned to the measles group and 207 to the MMR group. Completed diaries were received for 196 (92%) children in the measles group and for 198 (95.6%) in the MMR group. Completed diaries were unavailable for the remainder, either because the parents did not wish further contact with the study (19), or failed to complete the diary but did attend for follow-up (6), or moved from the area during the study period (1).

Paired blood samples were obtained for 308 (73%) subjects. The mean age of vaccination of children in the measles group was 14.5 months (SD 2.5 months), and in the MMR group 14.7 months (SD 1.5 months).

The symptoms observed are shown in Table II. Only 8 children in the measles group and 11 in the MMR group recorded no symptoms. There was no difference in the frequency of

Table II Percentage of children who developed symptoms

	MMR % ($n=198$)	Measles % ($n=196$)
Local symptoms		
erythema	9.1	8.2*
induration	0.5	0
pain	4.5	7.1*
General symptoms (specific):		
rash	43.9	51.0*
parotitis	2.5	0
conjunctivitis	8.6	10.7*
testicular swelling	0	0
arthralgia	0	0
arthritis	0	0
convulsion	0	0
General symptoms (non-specific):		
fever	38.3	37.8*
adenopathy	1.0	1.5
nasopharyngeal disorders	57.1	58.7*
gastrointestinal disorders	41.9	37.8*
restlesness	62.6	75.0*

* No difference in frequency of symptoms between the two groups, using χ^2 test. $P=>0.05$

asterised symptoms between the two vaccine groups, using the chi-square test ($P > 0.05$). Local symptoms of vaccination were rarely noted and tended to occur within the first two days. Three general symptoms, fever, restlessness and rash, were clustered, and had a peak incidence on days 5 to 13 after vaccination (Figure 1). The incidence of gastro-intestinal disorders, conjunctivitis, and nasopharyngeal inflammation, varied throughout the six weeks in both groups and had no relationship to the vaccination. The rates were 2–6%, 5–15% and 0–3% respectively. Parotitis was observed in five children who had received the

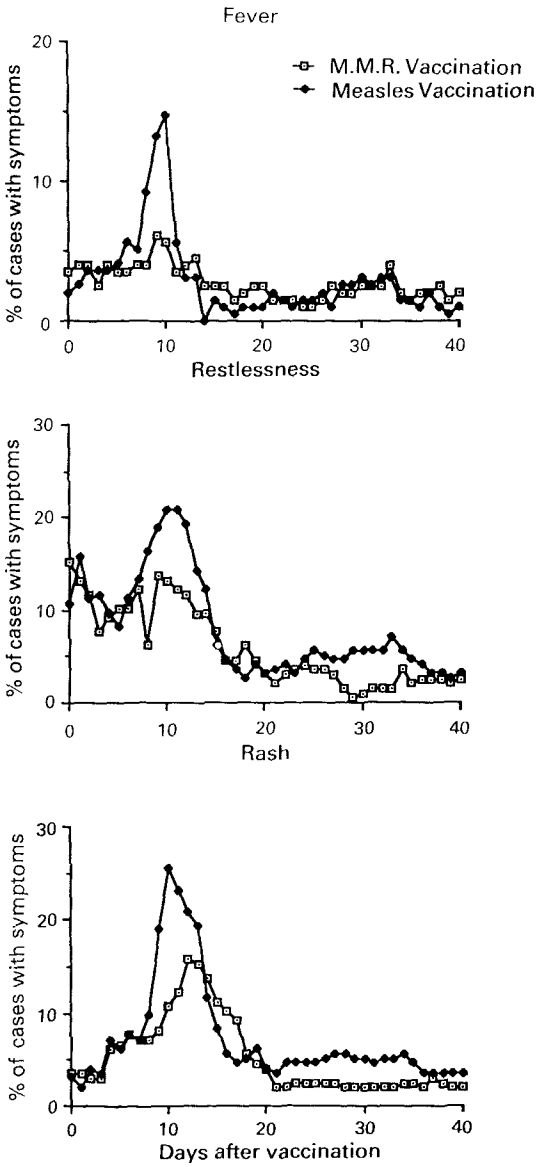

Figure 1 Clustering of symptoms occurring post-vaccination.

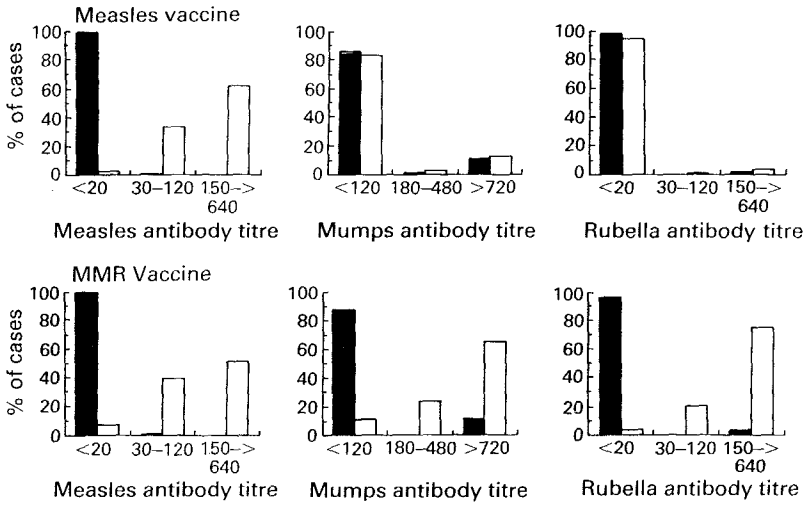

Figure 2 Antibody titres pre- and post-vaccination (■, pre-vaccination; □, post-vaccination).

MMR vaccine. It developed between 21 and 42 days after vaccination and it was present for an average of eight days. Three cases of mumps, confirmed by antibody titres, were noted in school-age siblings of children who had received the MMR vaccine occurring between 20 and 25 days post-vaccination.

The antibody distributions pre- and post-vaccination are shown in Figure 2. The seroconversion rates obtained from paired sera for non-immune children are demonstrated in Table III.

Only one child failed to respond to all the components of the MMR vaccine, two did not develop immunity to both mumps and measles, whilst several did not respond to individual components (measles 8, mumps 12, rubella 4).

We looked more closely at those children who had developed a fever, rash and restlessness between days 5 and 13 after the vaccination. Two hundred and forty three (60%) of the children had one of the symptoms in this time, 41 (10%) had all of the symptoms. We looked for a relationship between antibody response and symptomatology. Of the children who had one sympton in the period, 120 had a measles titre of greater than 150, and 29 of the children who had all three symptoms had a high antibody response to one component of the vaccine. (Measles greater than 150, mumps greater than 720, rubella greater than 150.)

Table III Seroconversion on paired sera from non-immune children pre-vaccination

	Measles vaccine			MMR vaccine		
	Pre-vaccination non-immune children	Post-vaccination immune children	Sero-conversion (%)	Pre-vaccination non-immune children	Post-vaccination immune children	Sero-conversion (%)
Measles	157	152	96.8	149	138	92.6
Mumps	133	4	3.0	122	107	87.7
Rubella	133	4	3.0	125	120	96.0

Discussion

It is essential that when a vaccine is introduced into a community, its effects in that community are defined. Two earlier studies in the UK looked at the serological response to the MMR vaccine, but the open nature of the study made it difficult to interpret reactogenicity.[10,11]

In this study, to minimise bias of symptom reporting, the parents were not informed which vaccine their child had received. Ideally one would use a placebo control group but we felt it unethical to do so in an invasive study, and opted to compare the new vaccine (MMR) with the one it has replaced (measles).

Many parents reported their children to have symptoms. This high illness level occurred throughout the six-week period, and involved nasopharyngeal and gastrointestinal symptoms. There was no temporal relationship to vaccination. This probably represents background illness and is in agreement with the findings of Vesikari *et al.*[6]

A symptom complex of rash, fever and restlessness in the second week of vaccination is a well-recognised reaction to measles vaccination. Sixty per cent of our study were affected by one of these symptoms: this is quite high, but is in accordance with other workers who have shown between 30 and 40% to be affected by fever following measles vaccination.[6,7,10] A more accurate assessment of true adverse reaction is thought to be that of Petola and Heinonen in their study using a placebo group.[3] As far as possible we tried to create the conditions of the routine use of the vaccine. However, although parental anxiety may well be higher in study conditions, it is our impression that most parents will observe their child closely following vaccination. Thus, though the rate of adverse reaction we report may not be the true reaction rate, it is the rate perceived by parents. We have found this rate to be similar for both MMR and measles vaccination. Health workers should be aware that mild and self-limiting reactions are common after most vaccinations so that parents are fully informed and can be adequately reassured. The reactions are similar to those after the measles vaccine alone.

Parotitis associated with mumps vaccination occurred in 2.5% of our study. This is higher than has previously been reported in the majority of other studies using Jeryl Lynn mumps vaccine. The Oxford study[11] (using the same vaccine as this study) reported an incidence of 1%. In view of the low incidence and small numbers of the studies, the differences observed in rates are probably not significant.

It has been suggested that Urabe AM/9, which produces a higher incidence of post-vaccination symptoms than Jeryl Lynn, is also more immunogenic. We have not found evidence to support this claim. The seroconversion rate for mumps was relatively low. The mumps antibody was analysed using the neutralization test, which has been reported to be the most reliable and sensitive method.[12] Most studies use the ELISA method. The comparatively low seroconversion rate may be attributable to the high pre-vaccination mumps immunity (13%) in our sample, a reflection of the prevalence of wild mumps at the time of the study. American researchers found 3% of 18-month olds were seropositive for mumps.[12] If a given percentage of the population are non-responders to either wild mumps or vaccine strains then the proportion of these within the non-immune group will increase with exposure. Thus the greater the exposure to wild mumps the more likely it will be that the vaccination conversion rate is falsely low.

The circulation of wild mumps at the time of the study could also explain the three cases of mumps observed in siblings. Further surveillance of this reaction is required. Mumps virus has been isolated from throat swabs of symptomatic vaccinees—this could have implications when vaccinating selected groups within closed communities, for example residential schools.

Some consider that a marked reaction to a vaccine in an individual would be associated with a high antibody response. This has not been shown in these results. The study supports the safety and efficacy of the MMR vaccine and provides data for informed advice to parents on the reactogenicity of the vaccine.

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