IMMUNOGENICITY AND SAFETY OF A VARICELLA VACCINE, OKAVAX™, AND A TRIVALENT MEASLES, MUMPS AND RUBELLA VACCINE, MMR-II™, ADMINISTERED CONCOMITANTLY IN HEALTHY FILIPINO CHILDREN AGED 12-24 MONTHS

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Abstract. This trial was conducted to assess the immunogenicity and safety of the varicella vaccine, Okavax™, when administered concomitantly with the measles, mumps and rubella vaccine, MMR-II, to children aged 12-24 months. A total of 299 children were randomized into three groups, those receiving Okavax only, MMR-II only, or both vaccines concomitantly. Antibody titers were determined by ELISA in blood samples taken immediately before, and 6 weeks after, vaccination. Parents recorded local and systemic reactions. Okavax elicited similar varicella seroconversion rates (≥ 93.9%) and high GMTs when given alone or with MMR-II (99.6 and 95.7 mIU/ml, respectively). The seroconversion rates (measles and rubella 100%, mumps ≥75.0%) and high GMTs elicited by MMR-II were not affected by concomitant administration of Okavax. The incidence of adverse events was similar whether MMR-II and Okavax were administered concomitantly or separately, and the majority of local reactions were mild and transient, with fever the most frequent systemic event in all groups. In conclusion, these results show that the immune response and the reactogenicity profile of Okavax and MMR-II were similar when given together or alone. Concomitant administration of these vaccines can therefore be recommended for children in their second year of life.

INTRODUCTION

Vaccines against measles, mumps and rubella have been distributed worldwide for many years and their use in routine immunization programs, especially as combined measles, mumps, rubella (MMR) vaccines, has resulted in significant control of these diseases as well as a reduction in their incidence in many countries (Carter and Cambell, 1993; Watson *et al*, 1998). Indeed, vaccination programs using these vaccines have already resulted in the elimination of measles, mumps and rubella in some countries (Peltola *et al*, 1994; 2000). Furthermore, these diseases have now been targeted for eradication through vaccination (WHO, 1995; Watson *et al*, 1998). Varicella vaccines, which have been available since the 1970s, were initially only used for general vaccination in Japan and Korea, however, more recently they have been included in mass vaccination programs in several other countries, including the United States, and have been shown to be safe and effective (White *et al*, 1991; Meurice *et al*, 1996; Breuer, 2001; Takahashi, 2001). In the United States, routine vaccination has dramatically decreased the number of cases of measles, mumps, rubella and congenital rubella syndrome occurring each year, and has reduced the amount of serious varicella disease (Watson *et al*, 1998; Arvin, 2001). The World Health Organization's Expanded Programme of Immunization (EPI) has helped significantly to reduce global morbidity and mortality from measles in both the developed and developing world (Cutts *et al*, 1991).

In spite of these advances, the measles, mumps, rubella and varicella viruses are still circulating so that there is always a risk of outbreaks

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occurring. Measles still causes significant disease problems, especially in developing countries where it results in a high number of deaths each year (Redd *et al*, 1999). Complications and deaths due to varicella, mumps and rubella are much rarer, but these diseases still have socio-economic costs for society (WHO, 1998; Galazka, 1999; Plotkin, 2001).

Unless vaccine coverage remains high, the achievements made in controlling these diseases will be difficult to maintain. Indeed, there are already signs that there is a resurgence of cases in some countries (CDC, 1989; Arguedas *et al*, 1991; CDC, 1991; National Vaccine Advisory Committee, 1991; WHO, 1999). Good vaccine compliance is needed to maintain vaccine coverage in today's complex immunization programs and it is generally agreed that a reduction in the total number of injections to be administered would help this compliance. This can be achieved by the use of both concomitant vaccinations (*ie* two or more vaccines administered at different sites at the same visit) and combined vaccines (*ie* several immunogens physically combined in a single preparation and administered in a single injection). Since varicella vaccine and combined measles, mumps, and rubella vaccine are both given to children in their second year of life it is logical that they be administered at the same visit. Indeed, this method of administration is already recommended in the United States (CDC, 1996). Millions of doses of both MMR-II™, a combined measles, mumps and rubella virus vaccine, and Okavax™, a varicella vaccine derived from the Oka strain varicella-zoster virus (VZV), have been safely administered to children worldwide and have been shown to be effective. The aim of this study was to assess the immunogenicity and safety of MMR-II and Okavax administered concomitantly in children aged 12-24 months.

MATERIALS AND METHODS

Subjects and study design

This open, randomized study was conducted in Manila, Philippines, from January 31, 2000 to October 10, 2000 after approval of the protocol by the Institutional and Ethic Review Board of the Research Institute for Tropical Medicine, Manila. The study was conducted according to the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

Healthy children of both sexes, aged from 12 to 24 months, were included in the study after written informed consent was obtained from their parents or guardians. Children with any of the following were excluded from the study: history of clinical varicella, measles, mumps or rubella infection or contact with these diseases in the preceding 4 weeks, previous varicella, measles, mumps or rubella vaccination; allergy to any component of the vaccines, including egg proteins or gelatine, or any condition related to contraindications to the vaccines; chronic and severe illness, congenital or acquired immunodeficiency; vaccine administration or use of blood, blood derivatives, immunoglobulins, immunosuppressor, immunomodulators within a period of 90 days prior to vaccination (30 days for vaccines) to 42 days after vaccination; treatment with aspirin or steroids at doses sufficient, in the investigator's opinion, to significantly alter systemic immunity; acute or febrile illness (axillary temperature > 37.5°C) within 72 hours before vaccination; simultaneous or planned participation in another clinical study.

Children enrolled into the study were randomly assigned into one of three equal groups at the first study visit and, after a physical examination and collection of a pre-vaccination blood sample, the vaccine(s) were administered. A second blood sample for evaluation of immune response was collected on day 42 (± 5 days) after vaccination.

Vaccines

Subjects assigned to treatment group A received the live attenuated Oka strain varicella-zoster virus vaccine, Okavax™ (The Research Foundation for Microbial Diseases of Osaka University, Japan), by subcutaneous injection in the thigh. The potency of the Okavax vaccine after reconstitution with the diluent is not less than 1,000 plaque-forming units per 0.5 ml dose. Treatment group B received the combined live attenuated measles, mumps, rubella virus vaccine, MMR-II™ (Merck, Sharp & Dohme, Westpoint, PA, USA), by intramuscular injection in the thigh.

Each dose of the lyophilized MMR-II vaccine reconstituted in 0.5ml diluent (water for injection) contains 1,000 50% tissue culture infectious dose ($TCID_{50}$) of Edmonston 749D strain measles virus, 20,000 $TCID_{50}$ of Jeryl Lynn strain mumps virus and 1,000 $TCID_{50}$ of Wistar RA 27/3M strain rubella virus. Treatment group C received concomitant injections of Okavax (subcutaneously) and MMR-II (intramuscularly) in separate thighs. Commercial batches of each vaccine were used in the study.

Laboratory assays (Serological assays/Serology)

Separate pre- and post-vaccination serum samples, kept at -17°C to -25ºC, were sent to Aventis Pasteur Clinical Immunology Platform, Val de Reuil, France where the serological assays were performed in a blinded manner. Antibody levels to measles, mumps and rubella were measured by enzyme-linked immunosorbent assays (ELISA) using commercial kits (Behring's Enzygnost® Anti-Measles virus/IgG, Enzygnost® Anti-Parotitis virus /IgG for mumps, Enzygnost® Anti-Rubella virus/IgG). IgG antibodies to VZV were measured in paired serum samples at an initial dilution of 1:100 using a glycoprotein (gp) ELISA; the reference serum (NIBSC British Standard for varicella-zoster antibody, 90/690) and quality control samples were tested in parallel. VZV antibody concentrations were determined by reference to the calibration curve of the reference serum and expressed in mIU/ml.

Safety

All subjects were monitored at the study center for immediate reactions during the first 30 minutes post-vaccination. Each subject's family was supplied with a transparent bangle for local reaction measurement and a diary card to record any local and systemic adverse events throughout the following 42-day period, with particular attention being made to events occurring during the first 3 days after vaccination. Specific adverse events solicited on the card were local pain, redness, induration and swelling, as well as systemic events: fever (axillary temperature ≥36.6°C), rash, pruritus, purpura and parotid gland swelling.

Statistical methods

This was a descriptive study. However, sample size calculations showed that with a seroconversion rate of at least 94%, 75 subjects per group would provide a satisfactory level of precision for the 95% confidence interval (lower limit ≥87%).

Seroconversion was defined as the presence of an antibody level higher than the respective assay cut-off (varicella: 12 mIU/ml, measles: 300 mIU/ml, mumps: 500 U/ml, rubella: 8 IU/ml) in an initially seronegative subject (*ie* a subject who presented with an antibody level lower than the cut-off before vaccination). Seroconversion rates and geometric mean titers (GMT) for varicella, measles, mumps and rubella antibodies, each with their 95% CI, were calculated at day 42 post-vaccination in initially seronegative subjects.

The numbers and percentages of subjects with at least one immediate reaction (occurring within 30 minutes of vaccination), one delayed local reaction or one delayed systemic event (each occurring within 42 days following vaccination), as well as the frequencies of each different type of event, were calculated for all treatment groups.

RESULTS

Immunogenicity

A total of 299 subjects, mean age 17.6 months (range 12.0-24.9 months), were enrolled (Table 1). All but one subject received their respective vaccines according to the randomization; the exception was randomized into the Okavax group but received MMR-II and consequently was included in the MMR-II group for the analyses. Reactogenicity data were not available for ten subjects who did not return for the second visit. Blood samples were not obtained from a further 35 subjects at the second visit, 6 due to parental refusal of the blood draw and 29 because the subjects reported more than 105 days after vaccination. Only one subject violated the exclusion criteria; this subject, in the Okavax group, received a rabies vaccine during the study period and was excluded from immunogenicity analysis. The different numbers of subjects in the immunogenicity analyses for the different antigens reflect those subjects who were excluded from these analyses because they were seropositive before vaccination.

Table 1
Age of subjects and numbers included in the analyses.

	Okavax	Okavax and MMR-II given concomitantly	MMR-II
Numbers of subjects enrolled: all included in immediate safety analysis	99	99	101
Mean age, months	18.2	17.4	17.3
(Age range)	(12.1 - 24.5)	(12.0 - 24.9)	(12.1 - 24.7)
Numbers of subjects included in delayed safety analysis	92	96	101
Numbers of subjects eligible for inclusion in immunogenicity analysis[a]	86	92	96

[a]For each antigen, initially seropositive subjects were removed from the analysis. This is reflected in the different numbers of subjects in the immunogenicity analyses for the different antigens.

Table 2
Seroconversion rates and GMTs at 6 weeks post-vaccination for initially seronegative vaccinees.

	Okavax		Okavax and MMR-II given concomitantly		MMR-II	
	N	Response	N	Response	N	Response
Varicella	82		86			
SCR (%)		93.9%		97.7%		-
[95%CI]		[86.3-98.0]		[91.9-99.7]		
GMT (mIU/ml)		99.6		95.7		-
[95%CI]		[81.1-122]		[79.0-116]		
Mumps			83		88	
SCR (%)		-		79.5%		75.0%
[95%CI]				[69.2-87.6]		[64.6-83.6]
GMT (U/ml)		-		1,128		1,144
[95%CI]				[905-1,406]		[901-1,452]
Measles			83		86	
SCR (%)		-		100%		100%
[95%CI]				[95.7-100]		[95.8-100]
GMT (mIU/ml)		-		3,673		3,467
[95%CI]				[3,272-4,123]		[3,034-3,961]
Rubella			80		84	
SCR (%)		-		100%		100%
[95%CI]				[95.5-100]		[95.7-100]
GMT (IU/ml)		-		90.6		109
[95%CI]				[77.7-106]		[94.3-127]

N = number of initially seronegative subjects included in the analysis; SCR = seroconversion rate; GMT = geometric mean titer; 95% CI = 95% confidence interval.

For each of the four antigens, the seroconversion rates were similar and post-vaccination GMTs were similar, whether the vaccines were given alone or concomitantly; the 95% CI indicates that there would have been no significant differences for any of these criteria if these had been tested (Table 2).

Seroconversion rates for varicella were 93.9% when Okavax was given alone or 97.7% when given concomitantly with MMR-II. Post-

Table 3
Percentages of subjects with local reactions and systemic adverse events.

	Okavax		Okavax and MMR-II given concomitantly				MMR-II	
			Okavax site		MMR-II site			
	N	%	N	%	N	%	N	%
Subjects with at least one immediate reaction[a]	99	38.4	99	38.4	99	27.3	101	31.7
Induration		5.1		9.1		4.0		5.9
Local pain		7.1		11.1		10.1		6.9
Redness		29.3		32.3		16.2		24.8
Swelling		0		0		1.0		0
Subjects with at least one delayed local reaction[b]	92	7.6	96	10.4	96	6.3	101	10.9
Induration		2.2		4.2		5.2		4.0
Local pain		4.3		7.3		5.2		9.9
Redness		2.2		4.2		3.1		1.0
Swelling		1.1		7.3		3.1		5.0
	N	%		N	%		N	%
Subjects with at least one related systemic event[c]	92	42.4		96	34.4		101	43.6
Fever (axillary T° ≥36.6°C)		41.3			33.3			42.6
Rash		1.1			1.0			1.0
Viral infection		1.1			1.0			1.0
Pain		1.1			0			0
Diarrhea		0			0			1.0

N= Number of subjects included in the analysis. All 299 enrolled were included in the analysis of immediate local reactions for 30 minutes after vaccination. Only the 289 subjects returning for visit 2 were included in the assessment of delayed local reactions and systemic events.

[a]Immediate reactions defined as occurring within 30 minutes of injection.

[b]Delayed reactions defined as occurring 30 minutes to 42 days after injection.

[c]Systemic events occurring within 42 days after injection and considered by the investigator to be possibly, probably or definitely related to the vaccines.

vaccination anti-varicella GMTs were 99.6 mIU/ml when Okavax was given alone and 95.7 mIU/ml when given concomitantly with MMR-II (Table 2).

Seroconversion rates were 100% for measles and rubella and were ≥75.0% for mumps whether MMR-II was given alone or concomitantly with Okavax. Post-vaccination GMTs of antibodies against measles, mumps, and rubella were similar in the groups given MMR-II only or as a concomitant vaccination with the varicella vaccine (Table 2).

Safety

All local reactions in all three treatment groups occurred within 3 days of vaccination. The majority occurred within 30 minutes of injection, lasted for 24 hours or less and were considered to be mild in intensity. As shown in Table 3, redness was the most frequent immediate reaction (≤32.3% at Okavax sites; ≤24.8% at MMR-II sites) while the most frequent delayed reactions were pain (≤7.3%) and swelling (≤7.3%) at the Okavax sites and pain (≤9.9%) and induration ≤5.2%) at the MMR-II sites. The rate of local reactions at the Okavax injection sites tended to be higher when the vaccine was given concomitantly with MMR-II than when it was given alone. However, the reverse was seen for the MMR-II sites where fewer reactions were reported when the

vaccine was given concomitantly with Okavax than when it was given alone. Only three severe local reactions were reported, all at Okavax injection sites; two were cases of redness with a diameter >5 cm which lasted for less than one day following Okavax alone and one was a case of induration with a diameter >5 cm following Okavax given concomitantly, which began on the day of vaccination and lasted for a further 12 days.

Systemic events considered by the investigator to be possibly, probably or definitely related to the vaccines were reported slightly less frequently following concomitant Okavax and MMR-II (34.4%) than Okavax alone (42.4%) or MMR-II alone (43.6%) (Table 3). In all groups, fever was the most frequently reported systemic event (33.3% after concomitant Okavax and MMR-II and ≤42.6% after Okavax or MMR-II alone). This high incidence of fever may, in part, be explained by the wide fever definition used in this study (axillary temperature ≥36.6°C within 42 days after vaccination). Most cases of fever were mild (37.6°C or less), occurred within 3 days of vaccination and lasted 7 days or less. Rashes and other systemic events were reported very infrequently. There were only nine severe systemic events considered to have a relationship to the vaccines; all were cases of severe fever with most lasting for 3 days or less. Most severe fevers were < 40.0°C but three subjects had fever peaks of 40.0°C. Five of these severe fevers occurred after Okavax and four after the concomitant vaccines and none were associated with other symptoms except for two subjects who also had colds and coughs. No serious adverse events in the study subjects were reported.

DISCUSSION

Combination and/or concomitant vaccines form the foundations of routine vaccination programs today, but as the number of recommended vaccines for inclusion in these programs is increasing annually, the development of more combinations and the more frequent use of concomitant administrations is required (Decker and Edwards, 1999). However, it is acknowledged that the efficacy or immunogenicity and safety of vaccines should not be compromised by such means of administration.

In the present study, the immunogenicity of MMR-II, in terms of seroconversion rates and GMTs for measles, mumps and rubella, was similar when it was administered alone or concomitantly with Okavax. However, although all the subjects vaccinated with MMR-II seroconverted for measles and rubella, fewer than 80% of subjects seroconverted for mumps when MMR-II was given alone or with Okavax. Interestingly, a study of the MMR vaccine, Trimovax™ (Aventis Pasteur, Lyon, France), which contains the Urabe rather than the Jeryl Lynn mumps strain used in MMR-II, was performed in the same population, at the same center and at the same time as the present study. The results of this other study, in which Trimovax was also given alone or concomitantly with Okavax, showed similar seroconversion rates for measles and rubella but a much higher rate for mumps antibodies (≥94.6%) than those seen in the present study (Gatchalian and Desauziers, 2002). These differences are consistent with published data showing that the immune response to the mumps component of MMR vaccines, especially in terms of the immediate post-vaccination mumps seroconversion rate, is consistently lower for vaccines containing the Jeryl Lynn strain than for those containing the Urabe strain (Nokes and Anderson, 1991; Plotkin and Warton, 1999). Since protective efficacy data for these vaccines are lacking, the clinical significance of this difference is not entirely clear. However, a study in the UK of children vaccinated with different MMR vaccines containing the Jeryl Lynn or Urabe mumps virus strains has shown that significant proportions of the children, regardless of which vaccine they had received, had no detectable mumps neutralizing antibodies 4 years after vaccination, suggesting the probable need for a second dose of vaccine for all children if elimination of mumps is to be achieved (Miller *et al*, 1995).

Varicella seroconversion rates were similar when Okavax was administered alone or concomitantly with MMR-II and were similar to those already published for Okavax given separately (Osaki *et al*, 2000; Takahashi, 2001). This is in contrast to previous findings, which have shown that the immunogenicity of varicella vaccines is reduced when they are administered concomi-

tantly with MMR vaccines as compared to administration alone (Just *et al*, 1986; Berger and Just, 1988; Vesikari *et al*, 1991; Shinefield *et al*, 1998). Furthermore, studies have shown that the measles, mumps, rubella, varicella (MMRV) combination vaccines including the most recent formulations, elicit even lower varicella antibody responses than when varicella and MMR vaccines are given concomitantly (Watson *et al*, 1996; White *et al*, 1997). Low varicella antibody responses are important, since it has been demonstrated that the likelihood of developing a modified varicella-like syndrome increases with lower post-vaccination varicella titers (White *et al*, 1992; Clements, 1996).

In this study, the majority of the subjects vaccinated with concomitant MMR-II and Okavax experienced local reactions or systemic events. However, most of the local reactions were mild and lasted for one day or less. The most commonly reported systemic events were of the type often found in this age group (*ie* mild fever and respiratory diseases) and most were considered to be unrelated to vaccination. This is similar to what has previously been reported for MMR vaccinations, with most adverse events being considered to be temporally rather than causally related to the vaccine (Peltola and Heinonen, 1986). In this study, as already reported for concomitant MMR and varicella vaccines, mild fever was the most frequently reported systemic event; however, skin rashes, which occurred in more than 5% of subjects in other studies (White *et al*, 1997; Shinefield *et al*, 1998), occurred very infrequently in this study. The incidences of adverse events following the separate administration of MMR-II and Okavax in this study are similar, except for the lower incidence of rash, to those already reported in the literature for these vaccines (Usonis, 1999; Osaki, 2000; Takahashi, 2001).

Furthermore, in this study, the incidence of both systemic adverse events and local adverse events at the MMR-II injection site tended to be lower when MMR-II and Okavax were given concomitantly than when they were given alone. This is in contrast to what has been reported in the literature, where modest, but sometimes significant, increases in adverse events have been reported following the concomitant administration of vaccines, including MMR and varicella vaccines, as compared to their separate administration (Shinefield *et al*, 1998; Decker *et al*, 1999).

The practical advantages to be gained by administering MMR and varicella vaccines at the same visit are already recognized, and when neither the immunogenicity of the vaccines nor the comfort of the vaccinees are jeopardized, as shown in this study, this method of administration becomes even more desirable. The results of this study suggest that the use of concomitant MMR-II and Okavax in routine vaccination programs could really help to improve parental compliance and overall vaccine coverage. However, the efficacy and long-term protection provided by MMR and varicella vaccines, especially those administered concomitantly, has not been completely clarified and this must be considered when planning routine immunization programs (Decker and Edwards, 1999). Additional doses of vaccine may be required to maintain protective antibody levels, even during childhood. In fact, a second dose of MMR vaccine is recommended to be given at the time children enter school in some countries (AAP, 1998). The situation is less clear for varicella, as it is not yet known whether vaccine-induced immunity will wane with time (Johnson *et al*, 1997; Zerboni *et al*, 1998). At present, varicella antibody titers are boosted naturally by exposure to circulating wild-type virus, but booster doses may be needed once annual chickenpox epidemics no longer occur (Arvin, 2001). Changes in the epidemiology of diseases caused in part by vaccination mean that the long-term protection provided by vaccines, including those given concomitantly, should be monitored regularly.

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REFERENCES

American Academy of Pediatrics (AAP): Committee on Infectious Diseases. Age for routine administration of the second dose of measles-mumps-rubella vaccine. *Pediatrics* 1998; 101: 129-33.

Arguedas AG, Deveikis AA, Marks MI. Measles. *Am J Infect Control* 1991; 19: 290-8.

Arvin AM. Varicella vaccine-the first six years. *N Engl J Med* 2001; 344: 1007-9.

Berger R, Just M. Interference between strains in live virus vaccines. II: Combined vaccination with varicella and measles-mumps-rubella vaccines. *J Biol Stand* 1988; 16: 275-9.

Breuer J. Vaccination to prevent varicella and shingles. *J Clin Pathol* 2001; 54: 743-7.

Carter H, Campbell H. Rational use of measles, mumps and rubella (MMR) vaccine. *Drugs* 1993; 45: 677-83.

Centers for Disease Control and Prevention (CDC). Mumps – United States, 1985-1988. *Morb Mortal Wkly Rep* 1989; 38: 101-5.

Centers for Disease Control and Prevention (CDC). Increase in rubella and congenital rubella syndrome – United States, 1988-1990. *Morb Mortal Wkly Rep* 1991; 40: 93-9.

Centers for Disease Control and Prevention. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mortal Wkly Rep* 1996; 45: 1-36.

Clements DA. Modified varicella-like syndrome. *Infect Dis Clin North Am* 1996; 10: 617-29.

Cutts FT, Henderson RH, Clements CJ, Chen RT, Patriarca PA. Principles of measles control. *Bull WHO* 1991; 69: 1-7.

Decker MD, Edwards KM. Combination vaccines. In: Plotkin SA, Orenstein WA, eds. Vaccines. 3rd ed. Philadelphia: WB Saunders, 1999: 508-18.

Gatchalian S, Desauziers E. Immunogenicity and safety of MMR Trimovax™ and Varicella Okavax™ vaccines given concomitantly in children 1-2 years old. Santiago, Chile: 3rd World Congress of Pediatric Infectious Diseases (WSPID). Nov 19-23, 2002.

Galazka AM, Robertson SE, Kraigher A. Mumps and mumps vaccine: a global review. *Bull WHO* 1999; 77: 3-14.

Johnson CE, Stancin T, Fattlar D, Rome LP, Kumar ML. A long-term prospective study of varicella vaccine in healthy children. *Pediatrics* 1997; 100: 761-6.

Just M, Berger R, Just V. Evaluation of a combined measles-mumps-rubella-chickenpox vaccine. *Dev Biol Stand* 1986; 65: 85-8.

Meurice F, De Bouver J-L, Vandevoorde D, Woods S, Bogaerts H. Immunogenicity and safety of a live attenuated varicella vaccine (Oka/SB Bio) in healthy children. *J Infect Dis* 1996; 174 (suppl 3): S324-S9.

Miller E, Hill A, Morgan-Capner P, Forsey T, Rush M. Antibodies to measles, mumps and rubella in UK children 4 years after vaccination with different MMR vaccines. *Vaccine* 1995; 13:799-802.

National Vaccine Advisory Committee. The measles epidemic. The problems, barriers and recommendations. *JAMA* 1991; 266: 1547-52.

Nokes, DJ, Anderson RM. Vaccine safety versus vaccine efficacy in mass immunisation programmes. *Lancet* 1991; 338: 1309-12.

Osaki T, Nishimura N, Kajita Y. Experience with live attenuated varicella vaccine (Oka strain) in healthy Japanese subjects; 10-year survey at pediatric clinic. *Vaccine* 2000; 18: 2375-80.

Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine. *Lancet* 1986; i: 939-42.

Peltola H, Heinonen OP, Valle M, *et al*. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. *N Engl J Med* 1994; 331: 1397-402.

Peltola H, Davidkin I, Paunio M, Valle M, Leinikki P, Heinonen OP. Mumps and rubella eliminated from Finland. *JAMA* 2000; 284: 2643-7.

Plotkin SA, Warton M. Mumps vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. 3rd ed. Philadelphia: WB Saunders; 1999: 267-92.

Plotkin SA. Review. Rubella eradication. *Vaccine* 2001; 19: 3311-9.

Redd S, Markowitz L, Katz S. Measles vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. 3rd ed. Philadelphia: WB Saunders; 1999: 222-50.

Shinefield HR, Black SB, Staehle BO, *et al*. Safety, tolerability and immunogenicity of concomitant injections in separate locations of M-M-R®$_{II}$, VARIVAX® and TETRAMUNE® in healthy children *vs* concomitant injections of M-M-R®$_{II}$ and TETRAMUNE® followed six weeks later by VARIVAX®. *Pediatr Infect Dis J* 1998; 17: 980-5.

Takahashi M. 25 years'experience with the Biken Oka strain varicella vaccine. A clinical overview. *Paediatr Drugs* 2001; 3: 285-92.

Usonis V, Bakasenas V, Kaufhold A, Chitour K, Clemens R. Reactogenicity of a new live attenuated combined measles, mumps, rubella vaccine in healthy children. *Pediatr Infect Dis J* 1999; 18: 42-8.

Vesikari T, Ohrling A, Baer M, Delem A, Bogaerts H,

Andre FE. Evaluation of live attenuated varicella vaccine (OKA-RIT strain) and combined varicella and MMR vaccination in 13-17- month-old children. *Acta Paediatr Scand* 1991; 80: 1051-7.

Watson JC, Hadler SC, Dykewicz CA, Reef S, Phillips L. Measles, mumps, and rubella - vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Recom Rep* 1998; 47: 1-57.

Watson BM, Laufer DS, Kuter BJ, Staehle B, White CJ. Safety and immunogenicity of a combined live attenuated measles, mumps, rubella and varicella vaccine ($MMR_{II}V$) in healthy children. *J Infect Dis* 1996; 173: 731-4.

White CJ, Kuter BJ, Hildebrand CS, *et al*. Varicella vaccine (Varivax) in healthy children and adolescents: results from clinical trails, 1987 to 1989. *Pediatrics* 1991; 87: 604-10.

White CJ, Kuter BJ, Ngai A, *et al*. Modified cases of chickenpox after varicella vaccination: correlation of protection with antibody response. *Pediatr Infect Dis J* 1992; 11: 19-23.

White CJ, Stinson D, Staehle B, *et al*. Measles, mumps, rubella, and varicella combination vaccine: safety and immunogenicity alone and in combination with other vaccines given to children. *Clin Infect Dis* 1997; 24: 925-31.

World Health Organisation (WHO). Expanded Programme of Immunisation. Immunisation schedules in the WHO European region 1995. *Wkly Epidemiol Rec* 1995; 70: 221-7.

World Health Organisation (WHO). Varicella vaccines. WHO position paper. *Wkly Epidemiol Rec* 1998; 32: 241-8.

World Health Organisation (WHO). Measles. Progress towards global control and regional elimination, 1998-1999. *Wkly Epidemiol Rec* 1999; 50: 429-39.

Zerboni L, Nader S, Aoki K, Arvin AM. Analysis of the persistence of humoral and cellular immunity in children and adults immunized with varicella vaccine. *J Infect Dis* 1998; 177: 1701-4.