

Measles vaccine in egg allergic children: poor immunogenicity of the Edmoston-Zagreb strain

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Despite the fact that a number of recent studies have shown that measles/mumps/rubella vaccine is safe for egg allergic children, many pediatricians are still concerned about immunization in egg allergic children. In Europe, a measles vaccine with the Edmoston-Zagreb strain (EZMV) grown in human fibroblast culture has been developed and recommended for children with egg allergy. However, some doubt arises on the efficacy of this strain due to its weak immunogenicity. The aim of this study was to investigate the immunogenicity of the EZMV in comparison to the measles vaccine with the Schwarz strain (SWMV) grown in a chick embryo fibroblast culture.

Thirty-nine children affected by severe immediate manifestations due to IgE mediated egg allergy were enrolled. The children received at random the SWMV (Morupar, Sclavo) or the EZMV (Triviraten, Berna) in one 0.5 ml subcutaneous injection, and were checked for any immediate allergic reactions in the following 4 hours. Blood samples were taken for the detection of specific antibody response 5 months after the immunization. In SWMV seroconverted children (18/19) the geometric mean antibody titer was 3 times higher than that observed in EZMV seroconverted children (17/20) ($p < 0.01$). No allergic reactions occurred following the immunization with the two different vaccines. This data confirms the safety of SWMV in egg allergic children. In addition, the present study provides further data on the lower immunogenicity of the EZMV in comparison to the SWMV.

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The safety of measles vaccination in children with allergic reactions to egg, using the Schwarz (SW) strain, (grown in chicken fibroblast), has been proved by several studies performed in different countries (1–3). At present more than 1,326 recognized egg allergic children received this vaccine without reaction (2,3).

Although the American Academy of Pediatrics has recently reviewed the previous guidelines (4) and currently recommends that skin tests with the vaccine must be performed before administration only in individuals with a history of systemic anaphylaxis after egg ingestion (5), there are still some concerns about measles immunization in egg allergic children.

In several European countries, including Italy, besides the measles vaccine with the Schwarz strain

(SWMV), another measles vaccine containing the Edmoston-Zagreb strain (EZMV) (grown in human diploid cells) is also available on the market. The lower incidence of fever (6), associated with the Edmoston-Zagreb (EZ) strain and the warning about the use of the SW strain in egg allergic children encourages pediatricians to use EZ strain in egg allergic children. On the other hand, it is well known that the SW strain is more efficient than EZ strain (7–9).

In addition, no data has been reported on both the immunogenicity and side effects of the EZ strain in comparison to the SW strain in children with egg allergy.

The aim of this study was to investigate the immunogenicity of both the EZ and the SW strains in children with egg allergy.

Table 1. Clinical features of the studied children

	Measles vaccine		P
	SCHWARZ STRAIN	EDMOSTON-ZAGREB STRAIN	
	No. children (%)	No. children (%)	
Males	10 (53)	14 (70)	NS
Females	9 (47)	6 (30)	NS
Median age (months)	24.5 (15–72)	24.5 (15–72)	NS
Positive skin test to egg	19 (100)	20 (100)	NS
Positive RAST to egg	15 (79)	17 (85)	NS
Positive challenge test to egg	19 (100)	20 (100)	NS
Symptoms induced by egg			
Angioedema and/or urticaria	4 (21)	6 (30)	NS
Asthma and oculorhinitis	6 (31)	4 (20)	NS
Atopic dermatitis	9 (48)	10 (50)	NS

Material and methods

Thirty-nine children (24 males, 15 females) aged 15 to 72 months (median 24.5 months), attending the Department of Pediatric Allergy and Immunology from 1991 to 1994 and who were affected by severe IgE mediated egg allergy, were enrolled into the present study. The children had no history of measles and of measles vaccination.

The clinical features of the enrolled children are reported in Table 1. There was no significant difference in the two groups in sex, age, positive skin test to egg, positive RAST to egg, positive challenge test to egg and allergic symptoms induced by egg ingestion.

The main symptoms reported, following egg ingestion, included angioedema and urticaria, atopic dermatitis, asthma and oculorhinitis. Ten of the thirty-nine (26%) had a history of severe anaphylactic reactions after egg ingestion, twenty-nine of the group (74%) had severe atopic dermatitis or asthma and oculorhinitis.

The children's history of egg allergy was confirmed by a positive challenge test and a positive skin test and/or RAST to egg. Prick tests to ovalbumin (Sarm, Roma), were positive in 39 (100%) children after 20 minutes. Specific IgE antibodies (Phadebas RAST) to egg (judged positive if higher than 0.35 UI/ml) were present in 31 (79%). To confirm egg allergy, an open challenge test was done under observation and with emergency equipment to hand as previously reported (10). Reactions were considered positive when there were objective cutaneous, respiratory, or gastrointestinal symptoms within two hours following the last food challenge. The main symptoms induced by the challenge tests were: angioedema and/or urticaria, asthma and oculorhinitis, atopic dermatitis. All the 39 children (100%) had positive challenge test: 10/39 (26%) had anaphylactic reaction, 19/39 (48%) had immediate

and severe appearance of atopic skin lesions, 10/39 (26%) had immediate and severe asthma and oculorhinitis.

The children randomly received the SWMV (Morupar, Biocine Sclavo) or the EZMV (Triviraten, Berna) containing the vaccine in one 0.5 ml subcutaneous injection, and were checked for any immediate allergic reactions during the following 4 hours. In addition, the parents recorded other usual reactions such as fever and/or rash at home (all of them were interviewed for side effects one month after the vaccination).

At least 5 months after the immunization, blood samples were taken from all the 39 children. After clotting, serum samples were kept frozen at -20°C until the test was carried out. Antimeasles antibodies were detected by an ELISA technique, using the Behring Enzygnost Anti-Masemvirus/IgG Kit.

With this kit the antibody activity is calculated in terms of mIU/ml from the results in optical density and with a single dilution point of 1/231.

The "translation" for IU is based on "the international standard for antimeasles serum (1st International Standard Preparation)" of the World Health Organization.

After manual distribution of samples onto the sensitized microplates, the ELISA test and the reading of results was performed with an automated Behring ELISA processor II (BEP II).

Statistical analysis

The statistical analysis of seroconversion percentages was evaluated by the Fisher exact test and that of the geometric mean titer (GMT) values by means of *t* student test for independent samples. X2 test was used to compare the percentages of reactions (fever and/or rash) following immunization in the two groups.

Results

The antibody response according to the type of strain is reported in Table 2: 18/19 and 17/20 children immunized respectively with SW and EZ strain seroconverted ($p=0.32$).

The GMT resulted 3 times higher in the children immunized with the SW strain compared to those immunized with the EZ strain ($p<0.01$).

No allergic reactions occurred following the immunization with the two different vaccines.

No significant differences were reported in the usual reactions following the immunization according to the type of strain (Table 3). In the children immunized with the SW strain the usual reactions, including fever and attenuated rash occurred seven days later, were recorded in 7/19 children (37%); namely fever in 4, attenuated rash in 2, both in 1. In

Table 2. Serological results

	Vaccine strain		p
	Schwarz	Edmonston-Zagreb	
No. children	19	20	
Positive	18	17	
% (95% C.L.*)	94.7(74.0–99.9)	85.0(62.1–96.2)	0.32 ¹
Median	2700	770	
GMT** (95% C.L.*)	2444.4 (2197.7–2718.8)	786.8 (507.5–1220.0)	<0.01 ²
GMT** ratio (95% C.L.*)	3.1	1.7–5.7	

*C.L.: confidence limits.

**GMT: Geometric mean titer calculated on positive sera.

¹Fischer exact test²t student test

the children immunized with the EZ strain the usual reactions were recorded in 5/20 children (25%): fever in 4, attenuated rash in 1.

Discussion

The results of the present study show that the immunogenicity of the SW strain evaluated by the specific antibody titer is significantly higher compared to the EZ strain ($p < 0.01$). In addition, seroconversion has been observed in 95% of the SW immunized children and in 85% of the EZ ones.

This data agrees with previous studies (7–9) where the EZ strain was mainly used at high, medium and standard doses at an earlier age (4 to 9 months).

However, the evaluation of seroconversion is strongly conditioned by the distance between vaccination and bleeding and by the exposition to the residual circulation of the infection. This may explain the fluctuation of seroconversion results (11–15). The absence of detectable antibodies does not mean absence of protection. In fact, in a study (14) the attack rate of measles in children exposed to infection was lower among EZ vaccinated children with no detectable antibodies than among unvaccinated susceptible children (4/12 against 18/22, $p = 0.008$).

There were, however, concerns raised in using high titre of the EZ strain at 6 months of age be-

cause this was associated with unexpected and unexplained higher mortality rates within two years of life. This procedure has now been discontinued (16).

This study also shows that immunization was well tolerated and no allergic reactions occurred with the SW strain as well as, with the EZ, thus providing further data on the safety of SWMV even in children with severe egg allergy. Up to now, it has been reported that a total number of 1,326 egg allergic children who received the SWMV suffered no allergic reactions, whereas 43 non egg allergic children showed immediate reactions after the immunization.

This data indicates that SWMV is safe in egg allergic children and the reported immediate reactions following the vaccine may be non specific (irritability, vomiting, etc.) or due to other vaccine constituents, such as neomycin, kanamycin, sorbitol and gelatin (2, 17–20).

We have reported (21) a systemic reaction (severe dyspnea, rhinoconjunctivitis and lip cyanosis) which occurred in a 2-year-old boy suffering from cow's milk and egg induced atopic dermatitis. Following the measles immunization with the EZMV which contains lactose, this may trigger allergic symptoms in children with cow's milk allergy, due to contamination with cow's milk protein.

The usual reactions following measles vaccination, including fever and attenuated rash, were not significantly different according to the type of vaccine in the present study. This data does not agree with a previous study (8) which showed that the reactivity to the SWMV was significantly higher than that observed after EZMV. This difference might be explained by the different method of recording side effects. The reported incidence of side effects is higher if it is recorded fifteen days after vaccination, whereas the reported incidences were lower when side effects were recorded after one month.

In conclusion, the present study provides further data on the lower immunogenicity of EZ strain.

In addition, the results confirm the safety of SWMV in egg allergic children.

The lower rate of trivial side effects should not promote the use of vaccines with poor immunogenicity. Such use may be dangerous in inducing a more severe course of the disease contracted at adult age.

Table 3. Usual reactions following immunization according to vaccine strain

	VACCINE STRAIN		p
	SCHWARZ	EDMONSTON-ZAGREB	
	No. children (%)	No. children (%)	
Fever	4/19 (21)	4/20 (20)	NS
Attenuated rash	2/19 (11)	1/20 (5)	NS
Fever + Attenuated rash	1/19 (5)	0/20 (0)	NS
Total	7/19 (37)	5/20 (25)	NS

References

- BUSINCO L, GRANDOLFO M, BRUNO G. Safety of measles immunization in egg-allergic children. *Pediatr Allergy – Immunol* 1991; 4: 195–8.
- BUSINCO L. Measles, mumps, rubella immunization in egg-allergic children: a long-lasting debate. *Ann Allergy* 1994; 72: 1–3.

3. JAMES JM, BURKS AW, ROBERSON PK, SAMPSON HA. Safe administration of the measles vaccine to children allergic to egg. *New Eng J Med* 1995; 332: 1262-6.
4. Report of Committee on Infectious Disease. American Academy of Pediatrics. Peter G, Lepow ML, McCracken GH Jr, Phillips CF eds. 22nd edn Red Book, Elk Grove, IL: Red Book, 1991: 28-30.
5. Report of Committee on Infectious Disease. American Academy of Pediatrics. Peter G, Halsey NA, Marcuse EK, Pickering LK eds. 23rd edn Red Book, Elk Grove, IL: Red Book, 1994: 36-7.
6. CONTARDI I, LUSARDI C, CATTANEO GG. Studio comparativo su tre differenti tipi di vaccino trivalente anti morbillo-parotite-rosolia. *Pediatr Med Chir* 1992; 14: 421-4.
7. ZOTTI C, CORTESE MG, FUOCO F, et al. Vaccino trivalente antimorbillo-rosolia-parotite: immunogenicità a breve termine di differenti preparati commerciali. Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica 36° Congresso Nazionale-Sassari/Alghero, 28 settembre-1 ottobre 1994: 25.
8. ZOTTI C, CORTESE MG, DALL'ACQUA M, et al. Vaccinazione antimorbillo- reattogenicità ed immunogenicità di vaccini di ceppo Schwarz e di ceppo Edmonston-Zagreb. Società Italiana di Igiene, Medicina Preventiva e Sanità Pubblica 36° Congresso Nazionale-Sassari/Alghero, 28 settembre-1 ottobre 1994: 25.
9. GRILLI G, CIMINI D, VACCA F, GERACE R, ANDREOZZI S, GRANDOLFO ME. Effetti collaterali e sieroconversione dopo la vaccinazione contro il morbillo effettuata con ceppi vaccinali Edmonston-Zagreb e Schwarz. *Notiziario ISS* 1994; 7: 1-6.
10. BRUNO G, GIAMPIETRO PG, GRANDOLFO ME, MILITA O, BUSINCO L. Safety of measles immunization in children with IgE-mediated egg allergy. *Lancet* 1990; 1: 739.
11. BOLOTOUSKI VM, GRABOWSKY M, CLEMENUS CJ, et al. Immunization of 6 and 9 months old infants with AIK-C, Edmonston-Zagreb, Leningrad-16 and Schwarz measles vaccine. *Int J Epidemiol* 1994; 23: 1069-77.
12. MARKOWITZ LE, SEPULVEDA J, DIAZ-ORTEGA JL, et al. Immunization of six-months old infants with different doses of Edmonston-Zagreb and Schwarz strain measles vaccines. *New Engl J Med* 1990; 322: 580-7.
13. WHITTLE HC, CAMPBELL H, RAHMAN S, ARMSTRONG JRM. Antibody persistence in Gambian children after high dose Edmonston-Zagreb measles vaccine. *Lancet* 1990; 336: 1046-8.
14. SAMB B, AABY P, WHITTLE H, COLL-SECK AM, SIMONDON F. Protective efficacy of higher-titre measles vaccines administered from the age of five months: a community study in rural Senegal. *Trans R Soc Trop Med Hyg* 1993; 87: 697-701.
15. CUTTS FT, OTHEPA O, VERNON AA, et al. Measles control in Kushasa, Zaire improved with higher coverage and use of medium titre Edmonston-Zagreb vaccine at age 6 months. *Int J Epidemiol* 1994; 23: 624-31.
16. Expanded Programme on Immunization (EPI). Safety of higher titre measles vaccines. *Weekly Epidemiological Rec* 1992; 67, n.48: 357-61.
17. PUVVADA L, SILVERMAN B, BASSET C, CHIAROMONTE L. Systemic reactions to measles-mumps-rubella vaccine skin testing. *Pediatrics* 1993; 91: 835-6.
18. TROTTER AC, STONE BD, LASZLO DJ, GEORGITIS JW. Measles, mumps, rubella vaccine administration in egg-sensitive children: systemic reactions during vaccine desensitization. *Ann Allergy* 1994; 72: 25-8.
19. LAVI S, ZIMMERMAN B. Administration of measles, mumps and rubella virus vaccine (live) to egg allergic children. *JAMA* 1990; 263: 269-71.
20. KELSO JM, JONES RT, YUNGINGER JW. Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin. *J Allergy Clin Immunol* 1993; 91: 867-72.
21. GIAMPIETRO PG, BRUNO G, GRANDOLFO M, BUSINCO L. Adverse reaction to measles immunization. *Eur J Pediatr* 1993; 152: 8.