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Measles Control in the 1990s: Immunization before 9 months of age

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Contents

1. Introduction

Two international workshops have been convened to discuss the use of measles vaccine in infants less than 9 months of age. The first workshop was held at the Centers for Disease Control in Atlanta, Georgia in November, 1985. At that workshop, data from the first trials of Edmonston-Zagreb (EZ) vaccine in infants were discussed. While data suggested that EZ vaccine was more immunogenic in infants than the commonly used Schwarz vaccine, most of the data presented were from small, non-randomized studies and the workshop participants felt that additional information was needed before a change in policy could be recommended. Subsequently, larger, randomized trials were initiated.

The second workshop was held at the Pan American Health Organization in Washington, D.C. in September 1988. At that time, published trials and other data concerning EZ vaccine were reviewed and preliminary data from unpublished vaccine trials were presented. This information was also presented to the World Health Organization (WHO) Expanded Programme on Immunization (EPI) Research and Development (R&D) Group in October 1988. While these data appeared to confirm that EZ vaccine was more immunogenic in young infants, only preliminary analyses of the larger studies had been completed and some questions remained unanswered. Although only a few of the studies presented at the September 1988 workshop have been published a year later, analyses from most have now been completed.

The purpose of this paper* is to review existing information on EZ vaccine and to determine whether, or how best, to use high dose EZ vaccine in countries with high measles morbidity and mortality in the first year of life.

2. Current Recommendations and Vaccine Requirements

2.1 Current measles immunization policy

Since 1976 the WHO has recommended that measles vaccine be given at 9 months of age in countries where measles in the first year of life is a problem (1). Prior to that time, in many countries measles vaccine was administered to infants as young as 6 months of age because of high morbidity and mortality in that age group. Studies which demonstrated low seroconversion rates in children less than 9 months of age led some countries to institute two dose schedules, with the first dose at 6 months and the second dose at 9 months or older (2,3).

The WHO recommendation for a single dose of measles vaccine at 9 months of age was based on seroconversion data from vaccine trials and epidemiologic data. Age-specific seroconversion rates were obtained from a study conducted in Kenya in 1974 (4). In that study, Schwarz measles vaccine was administered to children 6-9 and 12 months of age.

* This paper was revised subsequent to the 1989 R&D meeting to include some information which was not yet published in October 1989.

These data, combined with age-specific incidence data (5), allowed calculation of the number of cases prevented at different months of age at immunization. It was determined that administration of vaccine at 9 months of age would prevent the maximal number of cases. Subsequently, data from other studies, also using Schwarz vaccine, supported this recommendation (6,7). However, there is no single ideal age for measles immunization in all countries, since age-specific prevalence of maternal antibodies varies in different populations (8), as do age-specific measles incidence rates.

2.2 Biological Requirements for Measles Vaccine

WHO has established requirements for both the potency and stability of freeze-dried measles vaccine. The potency can be assessed by determination of either tissue culture infective doses, 50% ($TICD_{50}$) or plaque forming units (pfu) (9). The potency requirement specifies that measles vaccines contain at least 3.0 $\log_{10}$ pfu or $TCID_{50}$/dose after completion of the stability test (10). There is no maximum potency limit. Since the sensitivities of the methods for potency determination vary, WHO recommends that the International Standard Reference Vaccine be tested in parallel with all vaccines. The reference vaccine is a Schwarz vaccine and, on the basis of a collaborative study, has been assigned a value of 3.7 $\log_{10}$ pfu or $TICD_{50}$ (11). The stability requirement specifies that the potency of the vaccine cannot decrease by more than 1.0 $\log_{10}$ after incubation of the unreconstituted product at 37°C for 1 week.

3. Measles in Infants under 9 Months of Age

3.1 Epidemiology

Measles in infants under 9 months of age has been recognized as a major problem in some parts of the world for many years (12,13). In areas where intense transmission of measles occurs, infants may be exposed to the virus and develop measles as soon as their maternal antibody wanes to non-protective levels. Previously it was thought that increasing coverage in older children would decrease transmission to younger infants. Heymann found a 64% decrease in incidence in infants less than 9 months of age between 1975 and 1979 after a single dose measles immunization schedule at 9 months of age was introduced and coverage rates of 40% were achieved (14). However, recent reports from urban areas in Africa document that a large percentage of cases occurs in infants less than 9 months of age despite coverage as high as 80% in 12-23 month-olds (15,16). This has renewed interest in developing strategies for protection of younger infants.

3.2 Strategies for Increasing Protection of Young Infants

Several strategies have been proposed for addressing the problem of measles in young infants. These include: 1) increasing coverage in the current target age group (9-23 month-olds) to decrease circulation of measles and transmission to younger infants; 2) implementation of a two dose schedule with the first dose at 6 months of age and a second dose at an older age; 3) use of non-parenteral routes of administration of vaccine in infants less than 9 months of age (as a means of overcoming

maternal antibody); and 4) use of different vaccine strains or doses which may be more immunogenic in young infants. Most interest has focused on the use of EZ measles vaccine.

4. Edmonston-Zagreb Measles Vaccine

4.1 History and Attenuation

The EZ vaccine was developed in Yugoslavia in the early 1960s by further attenuation of the Edmonston strain (17). This was accomplished by 19 passages of the vaccine virus in WI-38 human diploid cells (HDC). During the 9th, 11th, and 13th passages, plaquings were performed, at which time large plaques were selected. Most measles vaccines in use world-wide were attenuated in chick embryo fibroblasts (CEF). Some of these strains have been adapted to and produced in HDC (18). While other vaccine strains (AIK-C and CAM-70) have also undergone plaquings during attenuation (19,20), large plaques were not specifically selected. EZ has been found to produce large granular plaques in Hela and Vero cells (17,21). In contrast, the Schwarz and Moraten vaccine strains produce small plaques. Other vaccine strains, including the Leningrad-16 and CAM-70 also produce large plaques. The biologic significance of these <u>in vitro</u> findings is not known. Molecular differences between EZ and other vaccine strains which may account for these characteristics or for the superior immunogenicity of EZ vaccine observed in clinical studies have not been determined.

4.2 Defective Particles

Defective particles were found in EZ vaccine in one study (22). These subgenomic RNAs are of interest and theoretical concern because they may be associated with persistent infection, be related to attenuation, or be responsible for the greater immunogenicity of a given vaccine.

To further investigate this, a collaborative study was undertaken by Swiss investigators and WHO to evaluate the defective particles in several different measles vaccines. Vaccines included in the study were EZ (Conpharma, Smith Kline, Swiss Serum), Schwarz (Merieux, Evans, Sclavo, Connaught), CAM-70 (Biken, Bio Manguinhos) and AIK-C (Merieux, Kitasato). No defective particles were found in the Schwarz vaccines, while they were found in EZ, AIK-C, and CAM-70 vaccines. Varying amounts of defective particles were found in the EZ vaccines produced by different manufacturers. While these results are reassuring since they indicate that other widely used and safe measles vaccines also have defective particles, the possible role of defective particles in the increased immunogenicity of EZ vaccine is not clear. In addition, it is not known whether EZ vaccines from two different manufacturers with different defective particle content would be equally immunogenic or reactogenic.

5. EZ Vaccine Field Trials

5.1 Available Data from published and unpublished studies

Nine immunogenicity studies of EZ vaccine in infants less than 9 months of age have been published (Table 1). In addition, data are available from 6 of 7 unpublished studies (Table 2). Many of the published studies included a small number of subjects and were not randomized; most of the unpublished studies were larger, randomized trials.

The potencies of vaccines used in these studies were determined in different laboratories and have not been reported in reference to the International Standard Reference Vaccine. Therefore, direct comparison of the vaccine dose administered in different studies is not always possible. However, in three of the unpublished studies (33, Haiti, Senegal), several of the same vaccine lots were administered (see below).

Serologic response was measured using different assays which vary in sensitivity, including hemagglutination-inhibition (HI), enzyme-linked immunoassay (ELISA) and plaque reduction neutralization (PRN) or inhibition (PI). While assays in some published and unpublished studies were standardized to the International Reference for anti-measles serum and results expressed in milli international units (mIU) (23), others were not. The different sensitivity of the assays used and timing of specimen collection preclude direct comparison of results from different studies even when results have been standardized to the reference. A variety of definitions of response to vaccine were also used in the studies. Some investigators obtained sera at a time when all maternal antibody would be expected to have waned, and reported seropositivity rates. For this definition, the sensitivity of the antibody assay used will affect the seroresponse rate. Other investigators have required a two-fold or four-fold rise in antibody. This definition will, usually, result in a lower estimate of vaccine response. In this review, "seroresponse" will include either seropositivity or seroconversion.

Both the published and unpublished studies have evaluated a variety of different factors including the effect of strain, dose, route of administration, and level of pre-immunization antibody. Outcome variables include seroconversion or seropositivity rates, geometric mean titers (GMTs), adverse reactions and efficacy.

Table 1

Published Immunogenicity Studies of
Edmonston-Zagreb Measles Vaccine in Infants

Study	Location	Year	Vaccine	Route	Dose* (log10)	Age (mos)
Sabin (24)	Mexico	1983	Schwarz	A	4.1	4-6
			EZ-Mx	A	4.1	4-6
Sabin (28)	Mexico	1984	Schwarz	A	+	4-6
			EZ-Mx	A	+	4-6
			EZ-Mx	SC	3.7	4-6
Whittle (30)	Gambia	1984	EZ-Y	A	3.5	4-6
			EZ-Y	A	3.8	4-6
			EZ-Y	A	3.8	4-6
			EZ-Y	SC	4.6	4-6
			EZ-Y	ID	4.0	4-6
Beck (29)	Yugoslavia	1985	EZ-Y	IN	4.4	6-12
			EZ-Y	SC	4.4	6-12
Fernandez de Castro (26)	Mexico	1986	Schwarz	SC	3.8	6-9
			EZ-Mx	A	NA	6-9
			EZ-Mx	SC	3.3	6-9
Khanum (25)	Bangladesh	1987	Schwarz	A	3.8	4-7
			Schwarz	SC	3.8	4-7
			EZ-Y	A	3.7	4-7
			EZ-Y	SC	3.7	4-7
Whittle (27)	Gambia	1988	Schwarz	SC	4.6	4-6
			EZ-Y	SC	4.6	4-6
			EZ-Y	SC	4.3	4-6
			EZ-Y	SC	4.0	4-6
Whittle (31)	Gambia	1988	Schwarz	SC	3.8	9
			EZ-Y	SC	4.6	4
Tidjani (32)	Togo	1989	EZ-Y	SC	5.0	4-5
			Schwarz	SC	5.0	4-5
			Schwarz	SC	3.9	8-10
			AIK-C	SC	3.7	4-5, 8-10

* pfu or $TCID_{50}$, not corrected for standardization in reference to the International Standard Reference Vaccine

\+ several different doses used

NA =not available, A=Aerosol, SC=Subcutaneous, IN=Intranasal, ID=Intradermal

EZ-Y=EZ vaccine produced by the Institute of Immunology, Zagreb

EZ-Mx=EZ vaccine produced by the National Institute of Virology, Mexico

Table 2

Unpublished Immunogenicity Studies of
Edmonston-Zagreb Measles Vaccine in Infants

Study	Vaccine	Dose*(log10)	Age (mos)
Mexico[1]	EZ-Mx	3.7	6,9
(33)	EZ-Mx	4.6	6
	EZ-Y	4.5	6
	EZ-Y	5.6	6
	Schwarz	3.8	6,9
	Schwarz	4.5	6
	Schwarz	5.3	6
Haiti[1]	EZ-Y	4.5	6,7,8, 9-11
	EZ-Y	5.6	6,7,8, 9-11
	Schwarz	4.5	6,7,8, 9-11
	Schwarz	5.3	6,7,8, 9-11
Senegal[1]	EZ-Y	5.6	5
	Schwarz	5.3	5
	Schwarz	3.8	10
Turkey[2]	EZ-Y	3.8	4-7
	Schwarz	3.8	4-7
Zanzibar[2]	EZ-Y	3.9	5-7
	Schwarz	3.9	5-7
Switzerland[3]	EZ-SS	4.5	6
	Schwarz	5.1	6
Guinea	EZ-Y	4.6	5-7
Bissau	Schwarz	3.8	9

* pfu or $TICD_{50}$, not corrected for standardization in reference to the International Standard Reference Vaccine

EZ-Y=EZ vaccine produced by the Institute of Immunology, Zagreb
EZ-Mx=EZ vaccine produced by the National Institute of Virology, Mexico
EZ-SS=EZ vaccine produced by Swiss Serum
[1]Vaccine dose (pfu) determined by the Food and Drug Administration, USA; [2]Vaccine dose (pfu) determined by Smith Kline Biologics;
[3]Vaccine dose (pfu) determined by Swiss Serum

5.1.1 Serologic Response to Vaccine

Effect of Vaccine Strain

EZ and Schwarz vaccine strains were compared at the same dose and age in five published studies (Table 3). In two studies, vaccine was administered by the aerosol route and in four by the subcutaneous route. Sabin compared EZ and Schwarz by aerosol in 4-6 month-old infants. Of 39 infants who received EZ vaccine, 90% seroconverted compared with only 36% of 39 infants receiving Schwarz vaccine (24). In Bangladesh, Khanum also compared EZ and Schwarz by aerosol; however, there was no difference in seroconversion rates between the two vaccines (25). All four studies which compared EZ and Schwarz by the subcutaneous route found higher seroresponse rates after EZ than Schwarz. However, in one, this difference was not statistically significant (26).

Table 3

Effect of Vaccine Strain on Seroresponse in Infants
Data from Published Studies

Study	Age (mos)	Assay	Dose* (log10)	Definition	Seroresponse Rates EZ No.	EZ %	Schwarz No.	Schwarz %
Aerosol								
Sabin (24)	4-6	PRN	4.1	4-fold rise+	39	90	38	36
Khanum (25)	4-6	HI	3.7	4-fold rise	78	32	59	34
Subcutaneous								
Fernandez de Castro(26)	6-9	HI	3.3	4-fold rise	16	100	32	80
Khanum (25)	4-6	HI	3.7	4-fold rise	42	60	65	37
Whittle (27)	4-6	PI	4.6	seropositive ≥50mIU	39	92	35	46
Tidjani**(32)	4-5	HI	5.0	seropositive ≥200mIU	106	94	137	50

* pfu or $TCID_{50}$, approximately the same dose for both vaccines
\+ above expected based on a 40 day half-life for maternal antibody
** data for infants seronegative at the time of vaccination
HI=hemagglutination-inhibition
PI=plaque inhibition
PRN=plaque reduction neutralization

Six unpublished studies compared EZ and Schwarz vaccine at the same dose and age. In all 6, EZ produced higher seroresponse rates than Schwarz. In 4, this difference was statistically significant (33, Zanzibar, Haiti, Senegal). Results, many of which are still preliminary, are presented below.

Three of the unpublished studies (33, Haiti, Senegal) used the same high dose lots of EZ (produced by the Institute of Immunology, Zagreb) and Schwarz vaccines (Table 4). Using different definitions of seroresponse and timing of specimen collection, the seroresponse rate for EZ vaccine ranged from 83% to 98%.

Table 4

Effect of Vaccine Strain on Seroresponse in Infants,
Data from Unpublished Studies
Using the Same "High Dose" Vaccine Lots
(Preliminary analyses)

Study	Age (mos)	No.*	Assay	Seroresponse Definition (wks post-immunization)	Seroresponse Rates EZ**	Schwarz**
Mexico (33)	6	150	PRN	seropositivity ≥200 mIU (18 weeks)	93%	79%
				seroconversion+ (18 weeks)	94%	86%
				seroconversion+ (8 weeks)	98%	91%
Haiti	6	80-90	PRN	seropositivity ≥200 mIU (8 weeks)	83%	66%
				seropositivity ≥200 mIU (24 weeks)	83%	66%
Senegal	5	120	HI	seropositivity ≥125 mIU (20 weeks)	96%	79%
				seroresponse++ (20 weeks)	88%	67%

* Approximate number of subjects per group

** EZ = 5.6 $\log_{10}$ pfu, Schwarz = 5.3 $\log_{10}$ pfu. Vaccines tested at the FDA where the mean potency obtained for the International Standard Reference Vaccine (assigned value 3.7) was 4.01 $\log_{10}$ pfu.

\+ defined as a four-fold rise above expected titer based on a 6 week antibody half-life.

++ defined as at least same titer if ≥125 mIU or from <125 to ≥125 mIU.

In the Zanzibar study, at 6 weeks post-immunization, the seropositivity rate >50 mIU (by PRN) after EZ vaccine was greater than 95% compared with 84% for Schwarz. In Turkey, the seropositivity rate >78 mIU (by ELISA) was 96% for EZ and 86% for Schwarz. In the Switzerland study, at 4 months post-immunization, the seropositivity rate ≥55 mIU (by PRN) was 76% (39/51) for EZ compared with 56% (9/16) for Schwarz.

GMTs in EZ and Schwarz vaccinees at comparable dose and age were reported in three published studies. Sabin found that although EZ produced higher seroconversion rates, the GMT of those who seroconverted after EZ was lower than the GMT of those who seroconverted after Schwarz vaccine (24). In contrast, Whittle and Tidjani found that EZ produced higher GMTs than Schwarz (27,32). Non-responders were included in the calculation of GMTs in one of the studies (27) which might have resulted in the lower GMT in the Schwarz group.

Data are available on GMTs from three unpublished studies. Two (Zanzibar and Senegal) found that the GMT after EZ vaccine was equal to or greater than that after Schwarz vaccine. The study in Mexico found that GMTs were lower after EZ produced from the Institute of Virology, Mexico (EZ-Mx) compared with either Schwarz vaccine or EZ vaccine produced by the Institute of Immunology, Zagreb (EZ-Y). There were no significant differences in GMTs between EZ-Y and Schwarz vaccinees.

Effect of Dose

Studies published to date have evaluated EZ vaccine at doses ranging from 3.3 to 4.6 $\log_{10}$ pfu or $TCID_{50}$. Since vaccines were tested in different laboratories and were not reported in reference to the International Standard Reference Vaccine, inter-study comparison of responses to different doses of vaccine is not possible.

Only one published study has evaluated the effect of dose on seroconversion rates to subcutaneously administered EZ vaccine (Table 5) (27). In this non-randomized study, EZ was compared at 4.0, 4.3, and 4.6 $\log_{10}$ pfu in 4-6 month-old infants. Increasing seropositivity rates were found with higher doses. The effect of vaccine dose on GMTs was also reported; higher doses produced higher GMTs. The inclusion of non-responders in the calculation may also have influenced these findings.

Table 5

Effect of Dose on Response to
Subcutaneously Administered EZ Vaccine
Whittle, 1988 (27)

Dose (log10)	No.	Seropositive+	GMT* (mIU)
4.0	40	73%	249
4.3	16	94%	442
4.6	21	100%	1541

mIU = milli international units
+defined as ≥50 mIU, $p<0.001$ x^2
*$p<0.001$ t-test

Two unpublished studies evaluated the effect of dose on response to vaccine. In one (33), a dose effect was observed for both Schwarz and EZ vaccines. However, while the difference in seroconversion rates after EZ vaccine at 3.7 $\log_{10}$ pfu and 5.6 $\log_{10}$ pfu was statistically significant, there was no significant difference between EZ at 4.6 $\log_{10}$ pfu and 5.6 $\log_{10}$ pfu. Similarly, in Haiti, while the higher dose produced a higher seroresponse, the difference was not statistically significant (Table 6).

Table 6

Effect of Dose on Response to
Subcutaneously Administered EZ Vaccine
Unpublished Data, Mexico and Haiti

Dose (log10)	Seroresponse Rates	
	Mexico*	Haiti**
4.5	91%	77%
5.6	94%	83%

*seropositivity ≥200 mIU, at 18 weeks
approximately 150 infants/group
**seropositivity ≥200 mIU, at 8 weeks
approximately 80 infants/group

Effect of Route of Administration

Several studies have compared different routes of administration of EZ vaccine. However, some of these studies used different doses by the different routes, making it difficult to separate the effect of dose from that of route.

Three studies provide data on seroresponse rates following administration of measles vaccine by different routes using comparable doses (Table 7). Sabin found equivalent seroconversion rates by aerosol and subcutaneous routes (28). Studies conducted in Yugoslavia found comparable rates after intranasal and subcutaneous administration (29). In Bangladesh, possibly because of technical problems with equipment, significantly lower rates were found by aerosol than by subcutaneous administration (25). All of the unpublished studies have evaluated EZ by the subcutaneous route.

Table 7

Effect of Route of Administration
on Response to EZ Vaccine in Infants

Study	Assay	Route	Dose*(log10)	No.	% Response
Sabin (28)	PRN	SC	3.7	25	64
		A	3.6	78	67
Beck (29)	HI	SC	4.4	36	100
		IN	4.4	34	100
Khanum (25)	HI	SC	3.7	42	60
		A	3.7	78	32

* pfu or $TCID_{50}$
A = Aerosol, SC = Subcutaneous, IN = Intranasal
PRN = Plaque reduction neutralization
HI = Hemagglutination-inhibition

Effect of Pre-immunization Antibody

All studies have included some proportion of vaccinees with maternal antibody at the time of immunization. However, the percentage of infants with maternal antibody and the level of maternal antibody have varied. Use of different serologic assays prevents direct comparison of maternal antibody levels prior to immunization in these studies.

Sabin reported the effect of different levels of pre-immunization antibody on seroconversion rates after either EZ or Schwarz vaccine administered by aerosol (24). EZ was more immunogenic than Schwarz at the same pre-immunization antibody titer: 100% of 18 children with plaque neutralization titers in the range of 25-110 seroconverted after EZ vaccine compared with only 18% of those who received Schwarz. However, at higher titers of maternal antibody, seroconversion rates decreased even for EZ vaccine.

In several studies, a statistically significant negative correlation was found between pre-immunization antibody titer and the height of the titer achieved post-immunization (27,30,31).

Comparison with Schwarz vaccine at 9 months of age

From a programmatic viewpoint, perhaps the most important comparison is between Schwarz at 9 months of age and EZ vaccine at a younger age. Two published studies have reported these data (31,32). In one, EZ at 4.6 log_{10} pfu in 4 month-olds produced a seropositivity rate of 99% (110/111) compared with 95% (100/105) for Schwarz vaccine at 3.8 log_{10} pfu in 9 month-olds. In the other (32), EZ at 5.0 $TCID_{50}$ produced a seropositivity rate of 91% (207/228) in 4-5 month-olds compared with a rate of 73% (47/64) for Schwarz vaccine in 8-10 month-olds. In both, GMTs were higher in the Schwarz group.

Two unpublished studies (33, Guinea Bissau) also compared higher than standard dose EZ (4.6 - 5.6 $\log_{10}$ pfu or $TCID_{50}$) at 4-6 months of age with standard dose Schwarz (3.7 - 3.9 $\log_{10}$ pfu) at 9 months of age. In the Mexico study the seroresponse rate after EZ was equal to or greater than after Schwarz. However, similar to the published data, titers were lower in the 4-6 month-old EZ groups than in the 9 month-old Schwarz groups. However, the difference in GMTs between EZ-Y and Schwarz groups was not statistically significant.

5.1.2 Acute Clinical Adverse Reactions

None of the subjects in the published studies, including the more than 200 who received EZ at a dose of greater than 4.6 $\log_{10}$ pfu, had any severe adverse clinical reactions. However, few of the studies performed careful and close follow-up of vaccinees. Studies which reported adverse reactions (Appendix 1) found no statistically significant differences in common adverse reactions between EZ and Schwarz vaccinees.

Of the unpublished studies, none found any differences in common adverse reactions by vaccine strain or dose. No unusual adverse reactions were reported in the more than 1000 infants in these studies who received EZ vaccine at a dose of 4.6 $\log_{10}$ pfu or greater.

5.1.3 Protective Efficacy

Only two published studies have evaluated efficacy of EZ vaccine in infants less than 9 months of age (31,34) (Table 8). Both included two groups: one received 4.6 $\log_{10}$ pfu EZ vaccine at 4-6 months and the other received 3.8 $\log_{10}$ pfu Schwarz vaccine at 9 months. In Guinea Bissau, infants were followed for two years. No cases occurred among the 243 infants in the EZ group compared with four cases in the 235 infants who received Schwarz vaccine. In The Gambia, two cases occurred in the EZ group and two cases in the Schwarz group.

Of the unpublished studies, only the Senegal study was designed to provide data on efficacy of EZ between 5 and 10 months of age; however, there were too few cases (one in EZ group and three in placebo group) during the study period to calculate a meaningful value.

Table 8

Efficacy of EZ at 5 Months of Age Compared with Schwarz at 9 Months of Age

Study	EZ at 5 months		Schwarz at 9 months	
	No.Vaccinated	Cases*	No.Vaccinated	Cases*
Guinea Bissau (34)	234	0	235	4
Gambia (31)	119	2	109	2

* number of cases after vaccination, e.g. for EZ after 5 months of age and for Schwarz, after 9 months of age.

5.1.4 Persistence of Antibody

One published study has reported data on persistence of antibody at least one year post-immunization (32). In this study, 97% of 34 infants seronegative pre-immunization who responded to EZ vaccine at 4-5 months of age had antibody one year later. However, the percentage of infants who were seropositive pre-immunization who had antibody one year later was lower. Unpublished data are available from Haiti and The Gambia. In Haiti, where sera were tested at both 8 weeks and 6 months post-immunization, there was no decrease in seropositivity rates >200 mIU between these two time periods. Persistence data are also available from a previously published trial in The Gambia in which 4-6 month-old infants received 4.6 $\log_{10}$ pfu EZ vaccine and 9 month-old infants received standard dose Schwarz vaccine (31) (Table 9). Serologic data are available for both groups at 36 months of age (31 months after EZ vaccine and 27 months after Schwarz vaccine). GMTs were higher in both vaccine groups at 36 months of age compared with those 9 months post-immunization. In the EZ group, GMTs were also analyzed by pre-immunization antibody titer (data not shown). Infants with higher titers pre-immunization had lower GMTs at 9 months post-immunization. However, there were no significant differences at 18 or 36 months of age. While these data are encouraging, they suggest that there may have been circulating measles in the population with boosting of antibody titers.

Table 9

Persistence of Antibody Post-Immunization
(Unpublished Data, Whittle)

Vaccine	9 months post vaccination	18 months of age	36 months of age
	GMT in mIU (range)		
EZ* 4 months	650 (529-799) n=111	1392 (1054-1840) n=105	1104 (840-1440) n=94
Schwarz+ 9 months	1660 (1260-2031) n=105	3200 (2406-4257) n=100	2728 (1942-3832) n=89

* 4.6 $\log_{10}$ pfu
\+ 3.8 $\log_{10}$ pfu

5.1.5 Major Findings from Published and Unpublished Studies

- All of the studies that compared EZ and Schwarz vaccines by subcutaneous injection at the same dose and age found that EZ is more immunogenic than Schwarz vaccine in 4-6 month-old infants. This difference was statistically significant in all studies except three (26, Turkey, Switzerland).

- One study (32) found that AIK-C and EZ vaccines are equally immunogenic in young infants.

- The absolute seroresponse rate after higher than standard dose EZ vaccine at 4-6 months of age varied in these studies (range 83% to 100%). This is probably due to the different age groups immunized, different maternal antibody profiles in the populations, different doses of vaccine administered, and different serologic tests and definitions used to measure response.

- Two studies found that higher response rates can be achieved by increasing the dose of EZ vaccine.

- The GMT after EZ-Y is similar to that after Schwarz vaccine; however, the GMT after EZ-Mx vaccine is lower than that produced by Schwarz.

- Subcutaneous administration of EZ vaccine is as effective, or more effective, than non-parenteral routes. Because of technical difficulties, most investigators are not pursuing non-parenteral routes of administration.

- EZ vaccine, even at a high dose, is not associated with an increased risk of common acute adverse reactions compared with Schwarz vaccine.

- Three studies (31-33) which compared higher than standard dose EZ (4.6 - 5.6 $\log_{10}$ pfu or $TCID_{50}$) at 4-6 months with standard dose Schwarz vaccine (3.7 - 3.9 $\log_{10}$ pfu or $TCID_{50}$) at 9 months found the seroresponse rate after EZ equal to or greater than that after Schwarz vaccine. The GMT was lower in infants immunized at 4-6 months with high dose EZ vaccine compared to those immunized at 9 months with standard dose Schwarz.

5.2 Ongoing or planned studies of EZ vaccine

5.2.1 Randomized Trials

Several randomized trials of EZ are being initiated. All will evaluate subcutaneous administration of EZ vaccine. The vaccine groups in these studies and the projected completion dates are presented in Table 10. Additional information provided by these studies will include: 1) comparison of EZ vaccine with five other strains: AIK-C, Moraten, CAM-70, Leningrad-16 and Connaught; 2) information on acute adverse reactions; 3) comparison of EZ vaccines from different manufacturers; 4) efficacy data; 5) comparison of seroresponse after EZ vaccine at 4 and 6 months of age.

5.2.2 Follow-up of previous studies

Follow-up of vaccinees will continue in several studies which have been published or completed. These studies will provide data on persistence of antibody post-immunization: Mexico (2 years), Senegal (4 years), The Gambia and Guinea Bissau (indefinite).

5.2.3 Demonstration projects

An EZ demonstration project has been planned in Kinshasa, Zaire where almost 30% of reported measles cases occur in infants less than 9 months of age (15). In this demonstration project, EZ vaccine will be administered to all infants at 6 months of age. Evaluation will include determination of coverage, overall reported incidence and mortality, and vaccine efficacy.

5.2.4 Other

Several other EZ studies have been initiated or are being planned. These include:

- Immunogenicity and safety of EZ in HIV-infected infants (Rwanda and Zaire)
- Response to a booster dose of EZ vaccine (Gambia)
- Alternative routes of EZ administration (Mexico)

Table 10

Ongoing or Planned Comparative Immunogenicity Studies of Edmonston-Zagreb Vaccine

Study	Vaccines	Dose* (log10)	Age (mos)	Study Dates+
Peru	EZ-Y	3.7	6,9	3/89-2/90
	EZ-Y	5.0	6	
	Biken-CAM	3.7	6,9	
	Biken-CAM	5.0	6	
	Schwarz	5.0	6	
	Schwarz	3.7	9	
Sudan**	EZ-Y	4.8	5	6/89-9/90
	Connaught	4.8	5	
	Schwarz	3.8	9	
Philippines**	EZ		6	9/89-9/91
	Schwarz		9	
USA	EZ-Y	5.0	6,9	1/90-1/91
	Moraten	3.5	9,12,15	
Zaire	EZ-Y	4.0	4,6	4/90-11/90
	EZ-Y	5.0	4	
Turkey	EZ-SK	3.9	9	9/89-9/90
	EZ-SK	3.17	9	
	EZ-Y	3.0	9	
Turkey	EZ-SK	4.9	4-6	9/89-9/90
	EZ-Y	5.0	4-6	
Soviet Union	EZ-Y	4.0	6,9	9/89-9/90
	EZ-Y	5.0	6,9	
	L-16	4.0	6,9	
	L-16	5.0	6,9	
	AIK-C	4.0	6,9	
	AIK-C	5.0	6,9	
	Schwarz	4.0	6,9	
	Schwarz	5.0	6,9	

* pfu or $TCID_{50}$
+ data expected to be available 1 year after completion date
** these studies will also evaluate efficacy
EZ-Y = EZ vaccine from the Institute of Immunology, Zagreb
EZ-SK = EZ vaccine from Smith-Kline, Belgium
L-16 = Leningrad-16

6. Remaining Issues

6.1 Criteria for "Adequate" Seroresponse

Since a protective level of measles antibody has not been established, there are no absolute criteria for determining an "adequate" response to immunization. Data are available from some investigations in the United States evaluating the antibody titer required for protection at the time of exposure to measles (35). However, this value may not necessarily indicate the titer needed immediately post-immunization for "successful immunization". The criteria used for seroresponse will affect the absolute seroresponse rate obtained and, therefore, affect decisions concerning whether the age at vaccination or the vaccine strain should be changed.

6.2 Persistence of Antibody

Previous studies with other vaccine strains have found that young infants who respond to vaccine develop lower titers post-immunization than do children immunized at an older age (36-38). Since 4-6 month-old EZ vaccine recipients have lower titers than older infants who receive Schwarz vaccine (31-33), concerns have been raised about the persistence of antibody post-immunization with EZ vaccine at a young age. While available published and unpublished data are reassuring, the question of persistence of antibody has not been answered definitively. However, it is reasonable to assume that in areas where EZ vaccine at a younger age may be used, there would be circulating measles virus with resultant boosting of antibody titers.

6.3 Efficacy

There are currently few data on protective efficacy of EZ vaccine in infants less than 9 months of age. However, long term efficacy data will be collected from the Senegal, The Gambia, and Guinea Bissau studies. Follow-up in The Gambia and Guinea Bissau will be continued for an indefinite period of time. In Senegal, follow-up is planned until all subjects in the study reach 5 years of age. Efficacy data will also be available from the previously published study in Bangladesh (25).

Of the studies which are ongoing or planned, those in Sudan and the Philippines will evaluate efficacy through 18 months of age (1 year post-immunization for the EZ group). In addition, efficacy data may be available from the demonstration project in Zaire.

6.4 Optimal Dose for EZ vaccine

Several randomized trials have now documented the superior immunogenicity of EZ vaccine; however, the optimal dose for subcutaneous administration of EZ vaccine has not been determined. Dose has been evaluated in only two randomized trials (Haiti, 33) and one non-randomized trial (27).

Increasing the dose of measles vaccine has not previously been found to result in higher seroconversion rates (39-41). However, these studies were performed in older children without maternal antibody. The effect of dose in young infants with maternal antibody may be different. Data from Whittle suggest that even a 2-fold difference in the dose administered will affect response rates (27). However, data from Mexico and Haiti suggest that the differences in seroconversion rates are minimal after administration of vaccine doses which differ 10-fold. The reason for these differences may be the age groups or maternal antibody levels in the populations studied. In addition, data from Mexico suggest that the dose response may not be a linear function, i.e. the major advantage of increasing dose may be when the vaccine dose is increased from 3.5 $\log_{10}$ to 4.5 $\log_{10}$ pfu; increasing the dose above this (from 4.6 and 5.6 $\log_{10}$ pfu) may result in minor gains in seroresponse rates. However, because seroresponse rates achieved with a given dose may depend on the maternal antibody profile in the population, the optimal dose, as well as the optimal age, is likely to vary in different populations. Since no increase in adverse reactions has been observed at higher doses, a higher dose vaccine may be preferable, assuming that such a preparation has a reasonable cost and that production is feasible.

6.5 Optimal Age for Immunization with High Dose EZ

The optimal age for administration of EZ vaccine depends on age-specific seroconversion rates and age-specific incidence rates (42). Programmatic considerations must also be taken into account. While EZ vaccine appears better able to immunize infants in the presence of maternal antibody than Schwarz vaccine, at high maternal antibody levels the seroresponse to EZ vaccine also decreases. Thus, the optimal seroconversion rate after EZ will be obtained at an age which depends on the maternal antibody profile of the population, but will be shifted to a younger age relative to Schwarz vaccine.

Few data are available on seroresponse to EZ vaccine by individual month of age at immunization. The Haiti study will provide information on seroresponse rates at 6,7, and 8 months of age. Data from Sabin and Khanum provided data on seroresponse rates in different age groups below 6 months of age (25,28). Both of these studies found low rates in infants less than 6 months of age; however, a standard dose of EZ vaccine was administered in these studies. In contrast, Whittle reported seroresponse rates over 95% in 18 week-old infants using a higher dose vaccine (31). Studies may be needed to determine the youngest age at which acceptable seroresponse rates can be achieved with higher dose EZ vaccine.

In countries with high morbidity and mortality in the first year of life, it has been suggested that high dose EZ vaccine be administered beginning at 6 months of age. Six months is already the recommended age for measles immunization with standard vaccines for children at high risk for measles before the age of 9 months (such as hospitalized children and those affected by disasters or in refugee camps). This age promises to gain most acceptance by programme managers at the national level and by health workers actually administering the vaccine.

While few cases of measles have been reported in infants less than 6 months of age, the advantage of administering EZ at a younger age is that it could be combined with other vaccines (e.g. the third DPT vaccine) and that higher coverage may be achieved. However, measles immunization at 4 or 5 months would still require delay of the third DPT from the optimal age of 3.5 months (14 weeks). Particularly at 4 months, concern remains that many children would have maternal antibodies at levels high enough to interfere with effective EZ measles immunization. Until the optimal younger age can be confirmed with additional data, 6 months appears to be a reasonable compromise.

6.6 Immunization of infants infected with human immunodeficiency virus (HIV)

Available data suggest that there is no increased risk of adverse reactions in HIV-infected infants after measles immunization using standard dose vaccines. However, seroconversion rates may be lower (42). While data evaluating high dose EZ vaccine in HIV-infected infants are not yet available, there is no reason to suspect an increased risk of adverse reactions in these infants. Indeed, the concern over severe measles disease in HIV-infected infants has led WHO to recommend that they receive measles immunization with standard dose vaccine at 6 months of age, followed by a second dose at 9 months of age (44). While studies of the safety of high dose EZ vaccine as well as studies of standard dose measles vaccines in HIV-infected infants should be pursued, the known benefits of immunization with these vaccines at an early age appear, at present, to far outweigh the risks.

6.7 Comparability of EZ Vaccine from Different Manufacturers

Only one study compared EZ vaccine from two manufacturers, EZ-Y and EZ-Mx (33). This study found that, although seroconversion rates were comparable for vaccines of similar dose, the GMTs achieved post-immunization were lower after EZ-Mx. The reason for this is not known, although it may be due to the fact that Mexico obtained a working seed, rather than a master seed, from Zagreb, which then underwent one additional passage prior to production. Other manufacturers have obtained a master seed from Zagreb. While it is unlikely that there will be substantial differences in EZ vaccine produced by different manufacturers, new manufacturers of EZ vaccine should perform at least small studies of high dose EZ vaccine in young infants to ensure comparable seroresponse rates with EZ from Zagreb.

7. Availability of EZ Vaccine

Previously, it was not known whether high dose EZ vaccine would be available in the quantities required to supply areas designated at high risk of measles transmission in younger infants. However, several manufacturers now have the capability of producing high dose EZ vaccine.

After consultation with WHO, UNICEF solicited bids for measles vaccine for 1990 and 1991 with different specifications from those used previously. Potency requirements are expressed in reference to the International Standard Reference Vaccine.

"Standard" dose vaccine: This measles vaccine must have a potency of at least 4.0 $\log_{10}$ pfu or $TCID_{50}$/dose before the stability test. This new potency requirement applies to all measles vaccines, not only EZ. The requirements for stability have not changed.

"High" dose EZ vaccine*: This EZ measles vaccine must have a potency of at least 5.0 $\log_{10}$ pfu or $TCID_{50}$/dose before the stability test. The requirements for stability have not changed.

UNICEF has received bids for high dose EZ vaccine from four manufacturers: Institute of Immunology, Zagreb, Swiss Serum, Merieux, and Smith Kline-Belgium. A total of 50 million doses of vaccine is expected to be available for 1990 and 1991 from these four manufacturers. In addition, measles vaccine (Schwarz, EZ, and Connaught) at a titer of 4.0 $\log_{10}$ pfu or $TICD_{50}$ will be available in quantities sufficient to meet the needs of countries not receiving high dose EZ vaccine. The cost of the high titer vaccine will range from about $0.10 to $0.50 per dose compared with $0.10 per dose for the standard vaccine. The cost of the high titer vaccine may decrease with continued use.

UNICEF and WHO require that vaccines not only meet the potency and stability standards outlined in the tender, but also meet requirements set by national control authorities in the countries where the vaccine is produced. While some national control authorities require that vaccine be licensed in their own country in order to export vaccine, others do not. If a country does not require licensure, the manufacturer must supply a certificate to WHO stating that the vaccine is "made in accord" with WHO requirements but is not licensed in their country. Swiss Serum and the Institute of Immunology, Zagreb have licenses for EZ vaccine in their respective countries. Smith-Kline does not, but Belgium does not require licensure for export. The status of Merieux EZ vaccine is unclear at the present time.

Measles vaccines procured outside of UNICEF are only required to meet the previous WHO requirement for stability and potency. In theory, this means that "standard" potency vaccines could be of different potencies: higher potency (at least 4.0 $\log_{10}$ pfu) purchased through UNICEF, and lower potency (3.0 $\log_{10}$ pfu) purchased outside of UNICEF). However, in practice, most measles vaccines in current use have a titer of 4.0 $\log_{10}$ pfu before the stability test; therefore, the practical consequences of this change are expected to be minimal.

*A potency of 5.0 $\log_{10}$ pfu or $TCID_{50}$/dose corresponds approximately to the potency of the high dose vaccine used in the Mexico and Haiti studies when corrected for standardization in reference to the International Standard Reference Vaccine

8. Options for Use of High Dose EZ Vaccine

Since high dose EZ vaccine (5.0 $\log_{10}$ pfu) is likely to become available, and realistically could be used in 1990, there are several policy options that can be considered:

8.1 Provide high dose EZ vaccine selectively to areas of the world with high morbidity and mortality from measles in infants under 9 months of age (predominantly sub-Saharan Africa) and, in those areas, recommend that this vaccine be used beginning at 6 months of age with no recommendation for providing a routine second dose at a later age.

Data supporting this option come from studies indicating that EZ at 4-6 months of age is as immunogenic as Schwarz at 9 months of age. Limited data on persistence of antibody and efficacy also indicate that protection after EZ at this age will be durable. While there are still concerns about duration of protection, if immunity wanes after several years, protection would still have been provided through the high mortality age groups. However, waning immunity may have other implications for an immunization program, such as decreased morale due to vaccine failures, or larger numbers of susceptibles in older age groups. These uncertainties need to be balanced against the opportunities to increase coverage and decrease morbidity and mortality in infants afforded by the use of this vaccine at 6 months of age.

By simply moving the recommended age to 6 months, additional measles cases will be prevented. The effect will be most pronounced in densely populated areas where as many as 30% of total cases may occur before the age of 9 months. It is also expected that additional measles cases will be prevented because higher immunization coverage rates may be attained. Measles case-fatality rates between 1% and 10% are commonly reported, with even higher rates reported in some settings. If one assumes that the vaccine efficacy of EZ at 6 or 9 months of age is 90%, that 10% of total measles cases occur prior to the age of 9 months, and that 10% higher coverage can be achieved by moving the recommended age from 9 to 6 months (an increase from 80% to 90%), the potential exists for increasing the proportion of children protected against measles by 17%:

(10% x 90% x 90%) = 8% = % of cases prevented <9 months
(10% x 90%) = 9% = % of cases prevented ≥9 months

At case-fatality rates of 1% to 10%, between two and 17 measles deaths per thousand children could be averted.

8.2 Provide high dose EZ vaccine selectively to areas of the world with high morbidity and mortality from measles in infants under 9 months of age (predominantly sub-Saharan Africa) and, in those areas, recommend a two dose schedule using high dose EZ vaccine beginning at 6 months of age and a second dose of any measles vaccine at 9 months of age or older.

A two dose schedule has been advocated as a means of protecting those infants who lose maternal antibody at a young age. In theory, the first dose would immunize infants who had already lost protective levels of maternal antibody, while the second dose would immunize those who did not respond to the first dose. While two dose schedules have been

successfully implemented in some developed countries (45,46), their success in developing countries has been limited (47). Two dose strategies using high dose EZ or equivalent vaccines, using standard dose vaccines, or using a combination of the two, may eventually prove to have a place in measles immunization programmes in developing countries. However, because of the risk of high drop-out rates between the first and second doses, two dose strategies should only be introduced as routine policy only after individual programmes have assurances that such strategies will, in fact, prove more effective than a single dose strategy and that the gains in measles control will offset the increased cost of measles vaccine. The fact that high dose EZ vaccine produces a seroresponse rate at 6 months of age which is similar or better than Schwarz vaccine at 9 months diminishes the incentive to explore two-dose strategies in countries using this vaccine, unless measles elimination, rather than control, becomes the objective.

8.3 Provide high dose EZ vaccine selectively to areas of the world with high morbidity and mortality from measles in infants under 9 months of age (predominantly sub-Saharan Africa) and, in those areas, recommend no change in the recommended age of immunization until more data become available on persistence of antibody, efficacy, and other vaccine virus strains.

Based on the projected schedule for ongoing and planned studies, additional data on short term persistence of antibody after EZ immunization of young infants should be available from several studies in 1990. Additional data on short term efficacy may be available in two years; however, long term efficacy will not be known for several years. Waiting for additional data on persistence of antibody may be prudent. However, in developing countries where there will be adequate opportunity for exposure to wild virus with resultant boosting, this should be less of a concern than in countries where measles virus circulation has been interrupted. Although there will be data within the next two years from ongoing studies on the immunogenicity of other vaccine strains, this should not impact on the current decision of how best to use the available high dose EZ vaccine.

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Appendix 1

Adverse Reactions
Results from Published Studies of EZ Vaccine

Sabin (24) Aerosol administration of 4.1 $\log_{10}$ pfu to 4-6 month-old infants. Adverse reactions reported among those who seroconverted.

Vaccine	no.	fever >=38°C (rectal)	cough
Schwarz	19	36%	23%
EZ	39	26%	11%
Controls	16	19%	19%

Sabin (28) Subcutaneous administration of 3.7 $\log_{10}$ pfu to 4-6 month-old infants. Adverse reactions reported among those who seroconverted.

Vaccine	no.	fever >=38°C (rectal)	cough
EZ	28	7%	11%

Khanum (25) Subcutaneous and aerosol administration of 3.7 $\log_{10}$ pfu EZ and Schwarz vaccine to 4-6 month-old infants. Rates of fever reported among all vaccinees.

Vaccine	no.	fever
Schwarz-aerosol	98	24%
EZ-aerosol	109	27%
Schwarz-SC	81	31%
EZ-SC	52	36%

Whittle (31) Subcutaneous administration of EZ, 4.6 $\log_{10}$ pfu to 4 month-old infants.

Vaccine	no.	temp	fever >38oC	rash	cough	diarrhoea
EZ	62	45%	11%	0%	53%	29%
Controls	63	43%	8%	0%	75%	35%

EPILOGUE

This document was produced as a working paper for the Expanded Programme on Immunization's Research and Development Group and subsequently to the Global Advisory Group (GAG) Meeting in Tokyo, Japan, 16-20 October 1989. As a result of the presentation and the discussion which followed, the GAG made recommendations regarding the administration of measles vaccine before nine months of age. They are provided below:

Administration of Edmonston Zagreb measles vaccine.

A working paper reviewed the published and unpublished data on the role of strain, potency and age at immunization in affecting safety, efficacy and immunogenicity of different measles vaccines administered before nine months of age. Anticipating the availability of high titer Edmonston Zagreb (EZ) measles vaccine over the next one to two years, different strategies for use of the vaccines were discussed and the following recommendations were made for consideration by the EPI Global Advisory Group:

1. As supplies become available, priority should be given to countries where measles before nine months is a significant cause of death. In these countries, a single dose of high titer* EZ measles vaccine should be administered routinely to infants at six months of age or as soon as possible thereafter. High titer vaccine should be preferentially offered to countries with the most severe measles problems in young infants.

2. Most studies to date on early measles immunization have used EZ measles vaccine produced by the Institute of Immunology, Zagreb, Yugoslavia. Before EZ strains produced elsewhere are accepted for use at six months of age, they should be shown to be comparable in this age group with respect to reactogenicity and immunogenicity to the strain produced in Zagreb. The location of most studies has been in Africa and the Americas; further studies are encouraged in other areas of the world.

3. The evaluation of impact on overall measles incidence and mortality following introduction of high titer EZ vaccine should receive high priority. Programmes should investigate apparent vaccine failures and adverse reactions following immunization whenever possible.

4. In countries where measles is not a significant problem before nine months of age or in countries where high titer EZ vaccine is not available, currently recommended schedules of immunization should be retained using any strain of measles vaccine meeting WHO requirements. These measles vaccines should have a minimum potency of 4.0 $\log_{10}$ infectious units. This recommendation does not preclude further research on immunization schedules to improve measles control using currently available vaccines.

5. WHO EPI should continue to work with UNICEF to help ensure an adequate supply of high potency EZ vaccine, and should develop recommendations for its phased introduction within national programmes.

6. In countries where high titer EZ vaccine will be used, HIV-infected infants (symptomatic and asymptomatic) should also receive it.

*5.0 $\log_{10}$ infectious units when the titer has been measured in parallel with the WHO International Reference Reagent for Measles Vaccine and corrected appropriately. This is approximately equivalent to the high titer vaccine used in several field trials (eg Mexico, Haiti).

Additional studies of EZ vaccine, as well as other vaccines that may be equally or more effective in young infants, should be conducted. Issues of particular interest include:

- Evaluation of antibody persistence and vaccine efficacy in infants immunized before 9 months of age. Long-term follow-up of vaccinees should be encouraged at sites where this is feasible.

- Comparison of the reactogenicity, immunogenicity and efficacy of EZ vaccine with other measles vaccine strains.

- Investigation of the reactogenicity, immunogenicity and efficacy of these vaccines in HIV infected infants.

- Evaluation of the reactogenicity and immunogenicity of these vaccines in infants younger than 6 months.

- Laboratory investigations of the difference between various EZ preparations and other vaccine strains to better understand the molecular basis of attenuation, reactogenicity and immunogenicity.

- Evaluation of the role of two dose schedules for measles control in developing countries.

- Further evaluation of alternate routes of measles vaccine administration.

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