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RESEARCH ON ALTERNATIVE MEASLES VACCINES:
TECHNICAL BACKGROUND AND RECOMMENDED FORMAT FOR REPORTING FIELD TRIALS

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Measles vaccine

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1. INTRODUCTION

1.1. Background

Over the last five years, a large volume of research has been undertaken on the efficacy of various measles strains, potencies and schedules. It has become increasingly clear that comparability of results is a major issue. Because of its unique role in fostering international cooperation in matters relating to public health, the World Health Organization has taken the lead in guiding investigators to produce results which can be compared with each other. This paper attempts to identify the key issues in comparing field trial results of alternative measles vaccines, and recommends to investigators methods of presentation of results which should facilitate these comparisons.

The Global Advisory Group and the EPI Research and Development Group discussed alternative measles vaccine in Abidjan, Cote d'Ivoire, October 1988. Their conclusions and recommendations are included in Appendices 2 and 3.

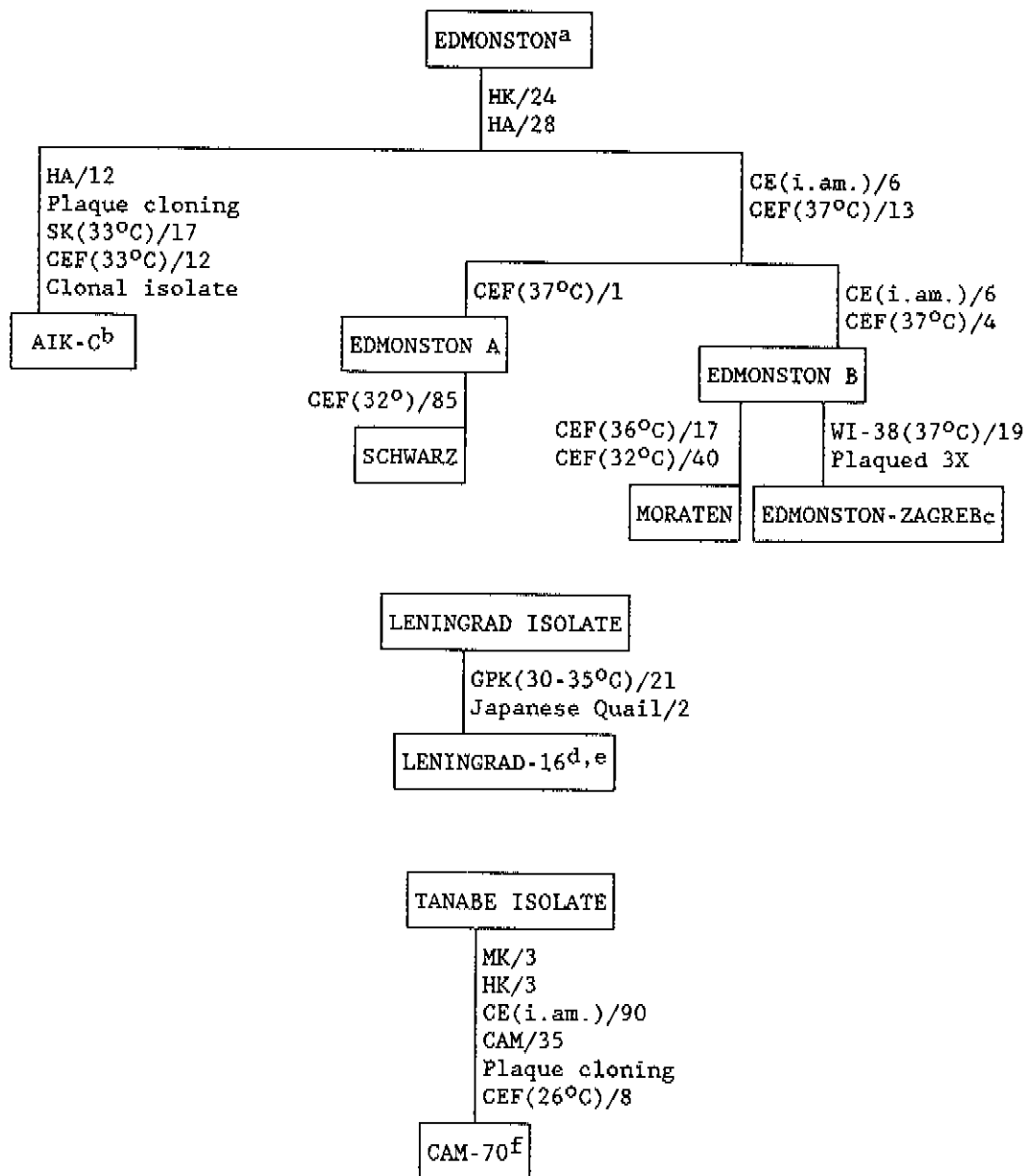
1.2. Measles vaccine strains

A number of measles vaccine strains are presently in use throughout the world for immunizing children. This paper will concentrate on those strains which are presently under consideration for use in children below nine months of age, or which are useful as benchmarks. These include four strains derived from the Edmonston strain, including the Schwarz and Moraten strains in use in much of the Western world, the AIK-C strain from Japan, and the Edmonston-Zagreb (EZ) strains from Yugoslavia. Also considered are the Leningrad-16 strain from the USSR and the CAM-70 strain from Japan, which are separate isolates derived by a number of passages. A schematic history of these passages is given in Table 1, and a summary of the Edmonston attenuations can be found in reference (1).

1.3. Method of Attenuation.

Five of these six strains, Schwarz, Moraten, AIK-C (2), Leningrad-16 (4, 5), and CAM-70 (6), were attenuated by low temperature passages, and three of them were derived from plaqued isolates. The CAM-70 strain was derived from a clone selected by plaque isolation from chick chorio-allantoic membrane at 36°, then passaged eight times in chick embryo fibroblasts at 26°. The EZ strain (3) was plaqued three times, at the ninth, eleventh, and thirteenth passages in

Table 1. Attenuation History of Some Measles Vaccines



Abbreviations: HK=human kidney cell culture; HA=human amnion cell culture; SK=sheep kidney cell culture; CE(i.am.)=chick embryo (intraamniotic cavity); CEF=chick embryo fibroblast cell culture; WI-38=human diploid cell line; GPK=guinea pig kidney cell culture; MK=monkey kidney cell culture; CAM=chick chorioallantoic membrane. /number indicates the number of passages

- a Hirayama (1)
- b Makino (2)
- c Ikic (3)
- d Gordienko (4)
- e Smorodintsnev (5)
- f Okuno (6)

human diploid WI-38 cells, selecting large plaques each time. The AIK-C strain (2) was derived from a plaqued isolate in sheep kidney cells adapted to 33°, and after re-adaptation to chick embryo fibroblasts, a further clonal isolate was used for vaccine production. Only in the development of the EZ strain, however, was the large plaque type specifically selected.

1.4. Plaque Morphology.

The different strains have characteristic plaques. This is reflected in the fact that there is a difference in the plaque size of measles strain isolates grown on Vero cells (7, 8). Schwarz and Moraten strains have small plaques, while EZ forms large granular plaques. The Leningrad-16 strain forms a majority of large syncytial bordered plaques, as does the CAM-70 strain (G. Mann, personal communication, 1988). Thus, three strains, EZ, CAM-70, and Leningrad-16, share the characteristic of large plaque morphology on Vero cells.

Ikic et al. (3) reported that the plaques of the EZ vaccine in HeLa cells were large, with a mean plaque size of 0.61 mm, and uniform in size, while those produced by the Schwarz strain were smaller, with a mean plaque size of 0.49 mm, and of variable size. Thus, in at least two cell types, the EZ vaccine has shown large and uniform plaque size in contrast to the Schwarz strain which has a smaller plaque size.

1.5. Growth in Human Diploid Cells.

The number of passages in human diploid cells required before attainment of optimal titers was studied (9). The Schwarz strain showed increasing titers on passage, attaining a titer of $10^{4.07}$ after five passages, and $10^{6.15}$ after 20 passages. Similarly, the CAM-70 strain showed optimal titer ($10^{6.0}$) only after 20 passages on human diploid cells, while the Leningrad-16 and AIK-C strains attained optimal titers ($10^{6.0}$ and $10^{5.45}$, respectively) after five passages in human diploid cells. The EZ strain, having been already adapted to human cells, attained a titer of $10^{5.65}$ on the first passage. Thus, the ease of adaptability to HDC for these five strains decreases in the order EZ > Leningrad-16 - AIK-C > Schwarz - CAM-70.

* * * *

2. TECHNICAL ISSUES

2.1. Potency Measurements.

The WHO Requirements describe two alternative ways of determining the potency of measles vaccine: by measurement of plaque forming units (PFU) in Vero cells, and by determination of tissue culture infective doses (TCID₅₀), also in Vero cells (10, 11). However, the requirements do not specify in detail the optimal methods of performing these tests. Comparative studies suggest that the potency measurements may vary depending on the method of determination (Table 2).

For example, using equivalent conditions of virus adsorption (adsorption to dilute cell suspension), Mann (7) found that 1 TCID₅₀ was equivalent to 0.60 PFU in tests on the Moraten strain in Vero cells. This relationship was equivalent to that theoretically expected (12). When comparing TCID₅₀ assays in which the virus was adsorbed to dilute cell suspensions to plaque assay on preformed monolayers, Kenny and Schell (13) reported that the plaque assay method was ten times more sensitive. Workers in Mexico (14) found a similar observation for the Edmonston-Zagreb strain using similar assay systems. Albrecht (15), using preformed monolayers for both TCID₅₀ and PFU tests, found that the two methods gave similar values for Edmonston-Zagreb. He also found that the TCID₅₀ method was more sensitive than PFU by about 0.4 log₁₀ for the Schwarz strain. These data are summarized in Table 2.

Based on the Poissonian distribution of virus particles among cells for the TCID₅₀ assay (12), the theoretical relationship between these two assay methods, is 1:0.69. There are many influences on the relationship between these two methods for determination of vaccine potency, including the method of adsorption of virus; cell type and concentration used for the test; effect of overlay and stain in the plaqueing method; design of the test; and influence of tissue culture plates, media, temperature, and humidity. According to Cooper (12), if 70 plaques can be counted per plate, one plaque culture is statistically equivalent to 100 end-dilution hosts (e.g., microtiter wells). Therefore, as the tests are generally performed, the PFU method is statistically more accurate.

The differences and variability in the methods highlight the need for more studies to determine the best way to measure potency. Consideration should be given to expressing potency in terms of an international reference preparation.

TABLE 2. COMPARISON OF DIFFERENT METHODS OF POTENCY DETERMINATION

VACCINE STRAIN	ADSORPTION METHOD* (PFU/TCID ₅₀)	PFU/TCID ₅₀	REFERENCE
NA	THEORETICAL	0.69	12
MORATEN	S/S	0.60	7
SCHWARZ	P/P	2.5	15
SCHWARZ	P/S	10	13
EDMONSTON-ZAGREB	P/P	1.0	15
EDMONSTON-ZAGREB	P/S	17	14

*P - virus adsorbed onto preformed monolayers
 S - virus adsorbed in dilute cell suspension

Moreover, since it is not known how the growth characteristics of the different measles virus vaccine strains differ relative to each other when grown in different host cells, the cells used for assaying potency must be carefully defined. Potency estimates should be related to clinical efficacy. One possible interpretation of the results obtained on dose dependence of seroconversion in infants under 9 months of age is that the potency of the Edmonston-Zagreb vaccine as determined in the typical Vero cell assay system is greatly underestimated.

2.2. Dose dependence of seroconversion and duration of immunity

For the reasons mentioned above, determining the minimal dose required for seroresponse depends on the method used to determine the administered dose. The definition of seroresponse, to be discussed in more detail below, is also an important consideration in determining dose dependence, as well as duration of immunity. With these caveats in mind, some information on the subject is available. Makino (2) has reported that a dose of >100 TCID₅₀ of AIK-C vaccine gave a 100% seroconversion rate in Japanese children eight months to eight years of age. Ten year follow-up (1) shows continuing protection from measles in successfully immunized individuals. One study on the CAM-70 strain (16) showed a minimum dose for 100% seroconversion of 2500 TCID₅₀ in children 9 months to 7 years of age. Follow-up studies (17) showed detectable antibody in all children 12 to 13 years after immunization. Persistence of immunity of the Leningrad-16 strain in the USSR has been demonstrated for 15 years (18) and in Yugoslavia,

the EZ strain has been shown to give persisting immunity for at least 16 years (19). All these studies have been done in children without maternal antibody.

A number of studies on the EZ strain suggest the dose dependence curve of seroresponse is shifted to lower doses relative to the Schwarz strain in young infants. It may be this phenomenon which enables the E-Z vaccine to overcome the barrier of maternal antibody. However, to date no studies have been performed on duration or dose-dependence of long-term immunity in infants with maternal antibody. Such studies will need to be done. Will the protection afforded by immunization of very young infants be as durable as that of older infants and children? What if the vaccine induces a very adequate rate of seroconversion at age 6 months but the geometric mean titers fall away over time? Encouraging reports from the Gambia indicate that excellent titers are maintained for at least two years (20). Other preliminary reports are not so reassuring (M. Just, personal communication 1988).

2.3. Measurement of serological response

There are three serological tests in general use for measuring seroresponse after measles immunization: the haemagglutination inhibition test (HI), the plaque reduction neutralization test (PRN), and the ELISA assay. Each of these tests measures a different aspect of measles immunity, that is, antibody response to measles haemagglutinin, infectivity, and viral components respectively. Not unexpectedly, these tests all have different sensitivities. According to Albrecht (personal communication, 1988), the plaque reduction neutralization test is of such sensitivity that if sera are negative by the test, primary vaccine failure is indicated. This test is 60 times as sensitive as the HI test. A comparison of the use of some of these tests has been published (21).

Under similar conditions, the ELISA test is about as sensitive as the PRN test. However, one characteristic of the ELISA test is that maternal antibody is not well measured by this method. In addition, antibody titer as measured in this way tends to increase over time rather than reaching a plateau or dropping slightly. Perhaps this is because it measures the existence of antibody to viral nucleocapsids and other non-infectious viral components as well as to infectious viral particles.

Because of these differing sensitivities, serological data should be reported in comparison with data derived using the International Standard for human anti-measles serum (Appendix 1). However there will still be variability introduced by the times at which sera are collected.

A second problem in the measurement of serological response is that of the definition of seropositivity. Some investigators have reported results which

defined seroresponse as a change from no detectable antibody at the lowest dilution used (usually 1:4) to detectable antibody in the post-immunization specimen. Other investigators used a two-fold to four-fold rise from pre-immunization levels. Yet others used seropositivity with a cut-off point between 50 and 200 milli-international units (m.I.U.) to indicate protective levels of antibody.

To date, the correlation between antibody titer and protection is not completely clear. Nor has the role of cell-mediated immunity in vaccine-induced protection been adequately explored. Whether different measles vaccine strains differ sufficiently in surface determinants to be distinguishable in terms of their ability to be neutralized by maternal antibody is another question which deserves further study.

* * * *

3. RECOMMENDED FORMAT FOR REPORTING RESULTS OF FIELD TRIALS

As already discussed, comparison is complicated by variations in the potency of the vaccines used, the method of testing for measles antibody, and the criteria used to determine whether an individual had responded successfully to immunization. The technical details of each issue have been raised in preceding paragraphs. Researchers are encouraged to follow the suggested protocol below for reporting of results. Adherence to this protocol will go a long way to overcoming the problems of comparability between studies.

1 Abstract

This should include a brief (200 word) description of the purpose of the study, the study groups and the principal findings. Mention should be made of features unique to this study.

2 Background

2.1 Location

Briefly describe the geographical area, economic conditions and nutritional status prevalent in the community.

2.2 History of measles transmission during the study.

Describe the surveillance system (active, passive), and the number of cases reported from the study area by age. This should include the number of cases of measles per month per study group by age during the study. The following clinical case definition is recommended:

CLINICAL CASE DEFINITION FOR MEASLES

Cases must meet all three of the following criteria:

1. Generalized rash of 3 or more days duration.
2. Fever greater than or equal to 38.3 degrees Centigrade (if measured).
3. Any one of the following:
 - a) Cough
 - b) Coryza
 - c) Conjunctivitis

3 Serological Assays

Determination of serological response should be measured consistently and in relation to the international standard anti-measles serum.

Appendix 1 provides a copy of the package insert from the international standard for anti-measles serum. This gives a description of its contents and instructions for use. It is available from:

Statens Seruminstitut
Department of Biological Standardization
80, Amager Boulevard
DK-2300 Copenhagen S, DENMARK
Telephone: (01) 95 28 17

The ampoule of the International Standard contains 10 IU; thus, if the total contents of the ampoule are reconstituted in 1 ml, the concentration will be 10 IU/ml. When the titer of the reconstituted standard is determined, the number of international units in one ml of the test serum can then be calculated by a simple proportion. For example, in the case of reconstitution in 1 ml, if the titer of the reference is 1:6000 and that of the sample is 1:20,

$$\begin{aligned} \text{IU/ml}_{\text{test sample}} &= 10 \text{ IU/ml}_{\text{reference}} \times 20 / 6000 \\ &= 0.033 \text{ IU} = 33 \text{ mIU} \end{aligned}$$

3.1 Type of Assay.

Indicate whether the serological tests used were haemagglutination inhibition, plaque neutralization or ELISA. Indicate if results from one method were confirmed by, or correlated with, other methods. Each method should be individually correlated with the International Standard Measles Vaccine which is available from the Statens Seruminstitut at the above mentioned address.

3.2 Starting dilution. The recommended starting dilutions for each type of assay are:

<u>Assay</u>	<u>Starting Dilution</u>
Haemagglutination Inhibition	1:2
Plaque Neutralization	1:4
ELISA	1:10

3.3 Definition(s) of seroresponse. Report the definition of seroresponse that was used with each assay method. In use of either the PRN or the ELISA methods, seroresponse should be reported as seroconversion from negative to positive or as a four-fold increase from pre-immunization titers.

If the HI method is used, seroresponse should be reported as seroconversion from less than 100 mIU to greater than 100 mIU or a four-fold increase from pre-immunization titers.

Use of these definitions will allow comparison with existing studies. In all cases, data on serology should be presented in parallel with the use of the International Standard.

4 Report the following for each vaccine studied.

4.1 Vaccine Characteristics

4.1.1 Type: Report the particular strain used, such as Schwarz, Edmonston-Zagreb, Moraten, CAM-70, etc.

4.1.2 Source: Report the name of the producer and whether the vaccine has certification of the national control authority, if applicable. Report whether the vaccine was provided from a manufacturer's production lot and if so, what lot, or was specially prepared by a laboratory or manufacturer for the study.

4.2 Titer: The potency of vaccines used in clinical studies should be determined by a method recommended by WHO (WHO TRS 1966 Rev.1982, 1988; BLG/UNDP/82.1/Rev.1). Until studies are completed to define the behavior of different strains of measles vaccines in the PFU and TCID₅₀ assay systems in different cells, it is recommended that vaccine potency results be presented on the basis of a TCID₅₀ assay with virus adsorbed in dilute cell suspension in addition to any other assay method used.

The WHO measles reference reagent should be titered in parallel by the same method and results obtained for this preparation should be reported as well. Further information on procurement and use of the measles reference reagent can be obtained by writing:

Chief of Biologicals
World Health Organization
CH-1211 Geneva 27, SUISSE
Telephone: (41) 91 38 90

Report potency measurements performed by another laboratory, if applicable. If several potency measurements were performed, report all results and possible explanation for differences.

Do not use terms for titer such as "standard", "medium", or "high" without giving a numerical value of the titer as their definition.

The titer of random samples of the vaccine should be reported for measurements performed at three times during the study

Time 1: After arrival of the vaccine at the study site and prior to the start of the immunization phase of the study.

Time 2: At random times and from random sites during the immunization phase of the study.

Time 3: After completion of the immunization phase of the study.

Measurement of titer should also be performed at anytime there is a suspected break in the cold chain.

VACCINE TITER

		Type of assay	
		log TCID ₅₀	log PFU
Measurements performed by manufacturer	Time 1		
	Time 2		
	Time 3		
Measurements performed by other laboratory	Time 1		
	Time 2		
	Time 3		

4.2 Vaccine Handling

The cold chain should be maintained according to standard WHO protocol including the use of cold chain monitors until the time of immunization. Report any known breaks in the cold chain. Cold chain monitors are available from WHO at the following address:

Expanded Programme on Immunization
World Health Organization
CH-1211 Geneva 27, SUISSE
Telephone: (41) 91 24 89

5. Study Design

5.1 Report the following for each age group studied. The ages of the children studied should be reported as accurately as possible. These ages should be expressed in weeks along with the range. WHO is particularly interested in the ages of 24-28 weeks and 37-41 weeks. When reporting ages younger than 24 weeks, be precise and use as narrow an age range as possible.

STUDY GROUPS

- * Report the number of children studied in each cell
- * Modify this table to include all vaccines and ages tested

NUMBER OF CHILDREN STUDIED IN EACH STUDY GROUP				
VACCINE GROUP	19-23 weeks	24-28 weeks	37-41 weeks	(Other) (weeks)
Vaccine Type ₁ _____ Titer ₁ _____				
Vaccine Type ₂ _____ Titer ₂ _____				
Other Groups				

5.2 Age of child at pre-immunization blood sample and at immunization. Report the age at which the children were actually immunized (rather than the intended age of the study design) as a range and a mean.

5.3 Interval between immunization and first post-immunization blood sample. The recommended interval is 6-8 weeks.

5.4 Interval between immunization and second post-immunization blood sample (if applicable). The recommended interval is 4-6 months.

5.5 Intervals for other post-immunization blood samples (if applicable). Serological follow-up is recommended at two years and five years post immunization.

5.6 Plans for long term follow up. Report the method and time for long term follow up including serological or clinical studies.

6 Serological Results

6.1 Seroresponse. Report seroresponse using the definitions reported in Section 3.3. The response should be shown for the different age groups at various levels of pre-immunization antibody. Report the number tested in each age group with the number responding, the percentage responding and the 95% confidence intervals for that response.

SERORESPONSE BY PRE-IMMUNIZATION MATERNAL ANTIBODY STATUS

PRE-IMMUNIZATION ANTIBODY STATUS	SERORESPONSE BY AGE GROUP					TOTAL
	14-18 weeks	24-28 weeks	37-41 weeks	(Other) (weeks)		
<40 mIU	*No.					
	%					
	95%CI					
40-90 mIU	No.					
	%					
	95%CI					
100-199 mIU	No.					
	%					
	95%CI					
>200 mIU	No.					
	%					
	95%CI					

* Report as: $\frac{\text{Number Responding}}{\text{Total in Each Category}}$

6.2 Seroresponse by presence of maternal antibody. Report seroresponse using the definitions reported in section 3.3 by presence or absence of pre-immunization antibodies. Report the mean and 95% confidence intervals for each group.

SERORESPONSE BY PRE-IMMUNIZATION MATERNAL ANTIBODY STATUS

AGE GROUP

19-23 weeks 24-28 weeks 37-41 weeks (Other) weeks Total

	No.					
Pre-Immunization Seropositives %
Pre-Immunization Seronegatives %
Total %

6.3 GMT. Report the GMT (by mean and 95% confidence interval) for each vaccine by age group and pre-immunization antibody status.

GEOMETRIC MEAN TITERS BY PRE-IMMUNIZATION SERO-STATUS

Age Group _____ Vaccine _____

PRE-IMMUNIZATION ANTIBODY STATUS	BLOOD SAMPLE		
		First Pre-imm	Second Post-imm
<40 mIU	Mean
	95% CI
40-99 mIU	Mean
	95% CI
100-199 mIU	Mean
	95% CI
>200 mIU	Mean
	95% CI

Adverse Events

7.1 Describe the methodology for monitoring adverse reactions. The recommended methodology is active investigation of adverse reactions in all vaccinees 0-30 days post immunization. This should be in addition to long term passive surveillance. State what type of investigation was used and what proportion of vaccinees were actually contacted.

7.2 Reporting of adverse events. Either this table or the following one should be completed for each vaccine studied. The first table allows for reporting of all adverse reactions for a particular study group. The second allows for comparison of common adverse reactions among all study groups.

<u>ADVERSE EVENTS FOLLOWING IMMUNIZATION</u>						
Vaccine Type.....	Vaccine Potency					
Clinical Category	Onset Interval (Days)					Total
	0-1	2-7	8-13	14-20	21-30	
Local Reactions						
Fever(>38° oral or >39° rectal)						
Rash						
Allergic reactions						
Anaphylaxis						
Arthritis and/or arthralgias						
Convulsions- febrile						
Convulsions- non-febrile						
Encephalitis and/or encephalopathy						
Guillain-Barre syndrome						
Other neurologic symptoms						
Sudden Infant Death Syndrome						
Deaths from all other causes*						
Other persons with reactions not listed above						
Total number of persons involved						

*Each death should be investigated and a separate report should be made to include age, time since vaccination and cause of death.

The following adverse events reporting form may be used. It is designed to show comparisons between vaccine groups for possible adverse reactions. When using this type of reporting form, specify the time interval covered by these reports (e.g., within 21 days after immunization) and the source of the reports (mother, nurse, etc.). Adverse events in HIV infected children should be reported separately.

ADVERSE EVENTS FOLLOWING IMMUNIZATION					
VACCINE GROUP	ADVERSE EVENT (% of total studied)				Total No. Studied
	Fever	Diarrhoea	Rash	*Other	
Vaccine ₁ _____ Titer ₁ _____ Age Group ₁ _____					
Vaccine ₂ _____ Titer ₂ _____ Age Group ₂ _____					
Other Groups					

* This should include all deaths or serious events requiring emergency attention. All of these events should be described in detail.

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APPENDIX 1.
INTERNATIONAL STANDARD FOR ANTI-MEASLES SERUM

1. THE STANDARD PREPARATION

The correct name of this preparation today is as written in the heading but the label has not been changed and still read: International Reference Preparation of Anti-Measles Serum.

The standard preparation was established in 1954¹. It was produced from a pool of human convalescent sera collected in Nuuk, Greenland in November 1962, from five female and five male adults, all students at the High School in Nuuk and between 16 and 19 years of age when they experienced measles in June 1962.

2. AMPOULE CONTENTS

Each ampoule contains very near to 94 mg of lyophilized serum (the mean from four ampoules was 93.78 mg). The total contents of each ampoule has been defined to contain 10 International Units of Anti-Measles Serum.

3. USE OF THE STANDARD

After dissolving the total contents of an ampoule the solution will contain 10 IU in the total volume. The solution can now be used in various methods for calibrating other serum preparations in International Units of Anti-Measles Serum (IU) e.g. per ml.

The medium used to dissolve the freeze-dried serum plug will depend on the intended use of the solution. In most cases the diluent used in the test is preferred and it is generally an advantage to dissolve the plug to a concentration near to the strongest concentration used in the test.

When using a very sensitive test, however, it might be preferable to make an intermediate dilution, e.g. containing 1 IU/ml or 0.1 IU/ml and distribute the dilution into smaller containers which are kept in the frozen state. This way the dilution will be stable for a very long time.

A dilution of the standard with 1 IU/ml will in a hemagglutination test typically show a titre of 1:25.

4. GENERAL REMARKS ABOUT INTERNATIONAL REFERENCE MATERIALS

International biological standards and international biological reference reagents provide a means of ensuring uniformity throughout the world in the designation of the potency of preparations used in the prophylaxis, therapy, or diagnosis of disease, where the potency cannot be expressed in terms of physical or chemical quantities. The International Units, however, are still expressions of quantities of "effective constituent"².

The standard is the material as it exists in the ampoules; the "material" thus includes the effective constituents together with all the other constituents that may be present (moisture carrier, buffer, salt etc., according to the form in which the standard is available).

International biological reference materials are intended for use in the calibration of the contents of "effective constituent" in national or working standard preparations and for the expression of these contents in the respective International Units. For the routine use in the laboratory the national or working standards should be used in order to save as much as possible the international reference materials. These are only sent to individual laboratories in very limited amounts. The preparations are sent free of charges but sometimes a small charge might be claimed for the air-freighting.

5. REFERENCES

1. WHO Technical Report Series, 1954, 293, 18
2. N.K. Jerne & E.C. Wood, "The Validity and Meaning of the Results of Biological Assays", Biometrics 5, 273-299 (1949)

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APPENDIX 2.
Recommendations of the Global Advisory Group,
Abidjan, October 1988.

A number of investigators are currently completing large studies comparing different strains and potencies of measles vaccines administered to infants prior to the age of nine months. Preliminary data from these studies were reviewed and discussed by the Research and Development Group at its October 1988 meeting and by the Global Advisory Group.

The results obtained to date from this group of studies were judged very encouraging. They suggest that one or more vaccines will be identified which will be suitable for routine use in infants at high risk of exposure to measles. However, because the studies are still incomplete, several key questions cannot be answered confidently at this time. The GAG made the following recommendation regarding research:

Research should be pursued on the impact of higher than standard potency measles vaccines in some selected urban areas of known high risk. In addition, clinical and laboratory studies of different strains at varying doses should be initiated.

APPENDIX 3.

Recommendations of the EPI Research and Development Group Meeting,
Abidjan, October 1988.

The Research and Development Group reviewed with satisfaction progress on the implementation of studies to measure the effectiveness of alternative strains of measles vaccine administered in high titer at six months of age. While the data available are still preliminary, they strongly suggest that high potency measles vaccines are effective in providing high rates of seroconversion and measles protection. Continuing data analyses and follow up studies will be required to provide sufficient data to formulate new policy recommendations. The potential of this development to significantly enhance global capability to prevent childhood morbidity and mortality is major. Based on discussions during the Research and Development Meeting and in a follow up subgroup meeting chaired by Prof. Kostrzewski, the group makes the following recommendations relevant to research:

Continue studies on alternative measles vaccines

Ongoing studies of alternative measles vaccines administered at or before six months should be completed. Special attention should be paid to follow the duration of vaccine induced antibodies and of vaccine failure rates in children vaccinated at or before 6 months of age. As much as possible methodologies should be standardized to permit comparison of results among studies. EPI Geneva should provide a standardized format to investigators, recommending standard analyses that WHO would like to have.

Promote additional studies in different geographical regions on the use of alternative measles vaccines. Of particular priority are :

- Studies which compare sero-responses after immunization at six months with other vaccine strains (at various titers and in relation to pre-existing levels of maternal antibody) with the Schwarz and E-Z strains.

- Studies which compare sero-response after immunization between the ages of 14 and 24 weeks with different measles vaccines (at various titers and in relation to pre-existing levels of maternal antibody).

Additional studies of high titer vaccines

Studies to evaluate additional high titer vaccine strains at or before 6 months should be encouraged.

Research in Urban Areas

In urban areas where measles transmission rates are high under 12 months of age and control has not been achieved with standard vaccine administered at 9 months of age, studies to measure the effectiveness of high potency vaccines at 6 months should be undertaken. Studies need to be limited to areas that have ongoing systems of surveillance to measure changes in morbidity and to areas for which sufficient supplies of high potency vaccine are assured.

Two-dose measles vaccine schedule

Promote further operational research using standard vaccines from the age of six months to assess the impact of two dose immunization strategies in areas where measles transmission rates remain high despite immunization at the age of nine months. Studies should be limited to those areas which have surveillance systems sufficiently developed to be able to measure changes in measles mortality.

Other Areas of Research

Studies of the safety of high titer vaccines in older non immune children.

A study should be initiated to further evaluate the feasibility and effectiveness of alternative routes of administration of high dose vaccines, particularly intranasally, conjunctivally and intradermally, and at different ages.

Studies should be performed to determine the reason why Edmonston-Zagreb vaccine results in higher response rates than Schwarz vaccine in infants with maternal antibodies.

Studies should be performed to determine the safety and immunogenicity of high dose vaccines in HIV-infected children.

Basic research to characterize the molecular biological characteristics of vaccine strains which appear to be more successful in inducing immunity in the face of maternal antibodies.