

## VACCINE TRIALS

**Safety of an aerosol attenuated measles vaccine in healthy subjects with Omron's nebulizer: Phase I open, non-controlled, sequential by age group, parallel trial**

**Introduction:** The current measles vaccine, which has been available for more than 40 years, is safe, effective and inexpensive. This vaccine is administered parenterally. In some countries the availability of trained personnel to safely administer injections is limited and there is concern over injection practices. These problems are more critical during mass measles immunization campaigns when millions of doses of vaccine are administered. A measles vaccine, which could be inhaled, would avoid potential problems related to the use of needles, their cost, disposal and waste management. Several studies in Mexico and South Africa have reported the safety and immunogenicity of this route of administration. The measles aerosol project is carried out by a partnership: WHO, the American Red Cross and the United States Centre for Disease Control and Prevention. Its goal is to develop and license at least one method (vaccine plus delivery device) for respiratory delivery of currently licensed measles vaccines.

**Objectives:**

1. To determine the safety of aerosol administration of live Edmonston Zagreb attenuated measles vaccine given to healthy volunteers.
2. To measure the serum plaque reduction neutralization titres before and after aerosol administration of live attenuated measles vaccine given to healthy volunteers.

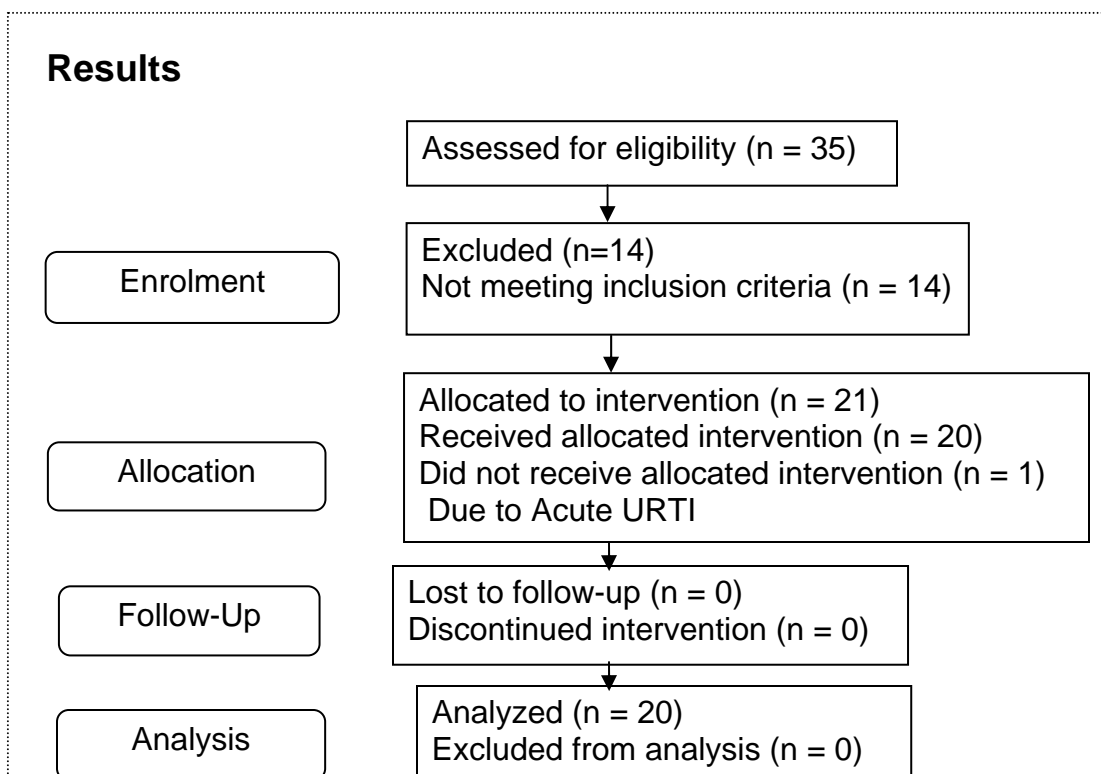
**Study Design:** All study participants in the following sequence of age group, Group 1:18- 35 years, Group 2: 5-17 years, Group 3: 1- 4 years receive the Measles aerosol vaccine. They will be followed upto 365 days after vaccination for assessing the safety of the vaccine. Subjects will be evaluated for initial safety (clinical and laboratory assessment)

at 14 days after vaccination. Immunogenicity of the vaccine will be assessed upto 90 days after vaccination.

**Activities:** WHO consultants and monitors visited Chennai by December first week of 2005 and changed the study site for the second age group 5-17 years as Nandivaram PHC since this PHC is working as a model PHC. The standard operating procedures were prepared to conduct this trial. Based on the revised January-2006 protocol we conducted Good Clinical Practice (GCP) for investigators and device training in first week of April 06.

The recruitment procedure of subjects in the age group of 18 - 35years started in June 2006.

**Methods and highlights:** Twenty healthy male participants were selected and they were been vaccinated with measles aerosol in two batches. The following are the results of our enrolment process.**Error!**



Only a few acute reactogenicity (Adverse events) detected within 14 days of follow-up and none has developed serious adverse events. All the participants recovered within a few days. The details are as follows:

- Six participants developed highly probable mild adverse events within 3 days of vaccination and the symptoms were conjunctivitis, fatigue, head ache, loss of appetite, sore Throat, redness of eyes, coryza. All these persons were not treated but recovered from these symptoms.
- Five participants developed possible / probable mild AE after 3 days of vaccination and the symptoms were cough anorexia, head ache, fatigue, fever, coryza, and runny nose, and sore throat, diarrhoea, vomiting and shivering. Some of these participants were treated symptomatically and all recovered. None of the adverse events were detected as moderate, serious or severe.

The following table shows the relation of acute reactogenicity to vaccination

1. Definitely not Related	0
2. Improbable	0
3. Possibly related	43 (53.8%)
4. Probably related	17 (21.3%)
5.Highly Probable	11 (13.8.7%)

Denominator: Number of Signs reported since Vaccination (within 14 days)

The acute toxicity assessment after 14 days of vaccination for the entire 20 participant resulted that only one participant had the significant abnormality in SGPT (Bio-chemistry) and the same was repeated and found normal on 90<sup>th</sup> day.

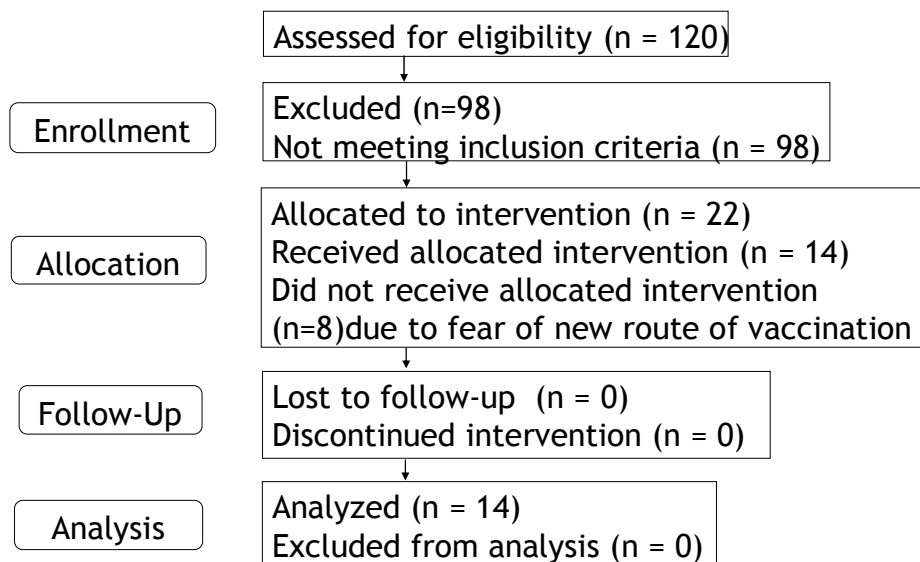
After Visit 9 (day 28) and within 90 days of vaccination one had cervical lymphadenitis and one had a viral conjunctivitis. We followed these cases till

they were asymptomatic. The consultant physician of these two participants declared that these two events were not related to vaccination.

In one of the 3 sites of measles aerosol vaccination in India it was observed that the eosinophil count of their participants was raised after the vaccination. So they did a comparative trial on healthy adults and found that the increase in the eosinophil count is almost equal in both routes (sub-cutaneous and aerosol). To record these changes the parameters IgE and eosinophil count were included for the next two groups.

The screening process for the next age group (5 - 17years) started on 2<sup>nd</sup> July and completed on 18<sup>th</sup> July 2007 at Nadivaram, Tamil Nadu. The following are the results of our enrolment process.

## Results



Following are the list of possible / probable mild Acute Reactogenicity and Adverse Events symptoms occurred in 8 participants of group2:

Muscle Pain, Anorexia, Coryza, Cough, Fever, Reduction of Physical activity, Pain in the Upper lids, Headache, Shortness of breath, Fatigue,

Shivering, Malaise, Sore throat/redness of throat, Irritability, Low Muscle tone, Conjunctivitis, Continuous crying, Redness of eyes, Wheeze in Lungs.

Following table shows the relation of acute reactogenicity to vaccination

1. Not related	44(62.9%)
2. Unlikely	12(17.1%)
3. Possibly related	4(5.7%)
4. Probably related	3(4.3%)

Denominator: Number of Signs reported since Vaccination (within 14 days)

All the signs were mild and moderate. Few of the subjects were required treatment and all the subjects became asymptomatic. None of them required hospitalization, no serious adverse events occurred.

Acute toxicity in group 2 on day 14:

11 subjects out of 14 had mild non significant abnormalities in lab. Parameters on day 14 and the details are as follows:

- Seven subjects had mild increase in Blood Eosinophil, 2 subjects developed mild increase in Blood Platelets, 1 subject had grade 3 increase in Serum potassium, 1 subject had mild increase in Urine WBC, 2 subjects had mild increase in Blood glucose. The subjects with above mentioned non significant abnormal lab parameters were investigated further in 28<sup>th</sup> day, 90<sup>th</sup> day and in 180<sup>th</sup> day visits and the lab parameters became normal except 2 subjects (one subject with mild increase in the blood eosinophils and 1 subject with mild increase in Blood platelets and blood eosinophils).

All the subjects have finished 12 visits of follow up

Group 3 screening started in last week of November 2007 at ICH & HC, Egmore and continued in first week of January 2008. During this period we have screened 74 participants and found only one eligible for PRNT. All other persons were not eligible mainly due to low neutrophils percentage, high eosonophil percentage, high TWBC, high Platelets and low hemoglobin

In reply to revise the criteria for the above parameters, we were asked to re-screen the borderline cases. So in February 2008 we have re-screened 23 participants and screened 14 new participants. Among these borderline participants we found only 2 were eligible for PRNT and for the remaining, the abnormal parameters became normal and some other normal parameters became abnormal. None were eligible from the new participants. In all, out off 111 samples only 3 satisfied the inclusion criteria laid down for the laboratory parameters.

Hence to recruit 20 healthy persons, this centre would have to screen large number of participants due to this high proportion of abnormality (108/111).This also suggests to seek participants from better economic status than the present A meeting was conducted on 14-03-2008 under the head of Dr.Kumaraswamy - NIE Officer-in-charge, Dr.Saradha Suresh-Director from ICH, Dr.Vijaya Sekaran-Clinical monitor, Dr.Oommen John-WHO National consultant.

With the above efforts the field site for screening is being changed and the screening was carried out from 08 April 2008 to 11 April 2008 at Nandivaram PHC and at Nanganallur Hindu Mission Hospital.(better economic status)

During this period we screened 85 Participants from Hindu Mission Hospital, Nanganallur and Nandhivaram PHC (6+79).

Only 3 were found to be eligible out of these 85 participants. In the remaining:

54(64%) of them were having less than the normal in neutrophils percentage. 41 (48%) were having abnormal eosinophils percentage, 41 (48%) were having abnormal platelet counts, 22 (26%) were having abnormal in TWBC and 36 (42%) were low Hb levels. One of the possible reasons for this result of Low Neutrophils percentage may be due to abnormal delay (6 hrs) in transport of specimen to SMF. To rule out the delay the group planned to do only 10 samples per day and carry out the serum separation at SMF so that the samples will be handed over to SMF as early as possible. This has to be tried out as a trial basis from 24-4-08 onwards to find out the changes in the differential counts.

Due to measles vaccination death in Tamil Nadu on 23-4-08 the state government suspended the routine measles immunization program, which forced us to suspend temporarily our screening program also.

In all group 3 - Phase 1 of measles aerosol vaccine trial at Chennai is suspended temporarily due to Tamil Nadu State Government's blanket order of banning all activities related to measles vaccination due to the deaths which occurred after administering measles vaccine at Thiruvallur of Tamil Nadu on 23<sup>rd</sup> April 2008 in their routine programme until further orders. As a consequence we are unable to enter into the field and carry out our MAVT research activities any further.

Due to several technical reasons and problems in the hematological biochemical reference values, group 3 recruitment has not taken place within the envisaged time frame. We have reported this problem to WHO and requested them to permit us for closure of the project as it is difficult to screen and enroll 20 eligible subjects for group 3.