Format for Application for *Ad-hoc* Research Projects and Guidelines for Operation of Extramural Projects

Indian Council of Medical Research
V. Ramalingaswami Bhawan, Ansari Nagar, P.Box No. 4911
New Delhi – 110029
### Section A
**GENERAL**

<table>
<thead>
<tr>
<th>Impact of measles rubella (MR) vaccination campaign on population immunity in India [IMRVI study]</th>
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<tbody>
<tr>
<td>2. Name and Designation of</td>
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<tr>
<td>1. Principal Investigator &amp; Email:</td>
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<tr>
<td>Dr Nivedita Gupta, Scientist E, Division of Epidemiology &amp; Communicable Diseases, Indian Council of Medical Research, Ansari Nagar, New Delhi – 110029.</td>
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<tr>
<td>ii) Co-Investigator(s) &amp; Email:</td>
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<tr>
<td>a. Indian co-investigators:</td>
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<tr>
<td>2. Dr Manoj Murhekar, Director, National Institute of Epidemiology, R127, 3rd Avenue, TNHB, Ayapakkam, Chennai- 600077. Email: <a href="mailto:mmurhekar@gmail.com">mmurhekar@gmail.com</a></td>
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<tr>
<td>3. Dr Santosh Kumar, Scientist B, National Institute of Epidemiology, Chennai</td>
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<td>4. Dr Jeromie Wesley Vivian, Scientist B, National Institute of Epidemiology, Chennai</td>
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<td>5. Mr Augustine Duraiswamy, Technical Officer-C, National Institute of Epidemiology, Chennai</td>
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<td>6. Mr Sabarinathan, Scientist C, National Institute of Epidemiology, Chennai</td>
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<tr>
<td>7. Dr. Lucky Sangal, National Professional Officer, VPD, NPSP, WHO-India, R. K. Khanna Tennis Stadium, Safdarjung Enclave, New Delhi – 1100029. Email: <a href="mailto:sangallu@who.int">sangallu@who.int</a></td>
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<td>8. Dr Pauline Harvey, Team Lead, NPSP, WHO-India, R. K. Khanna Tennis Stadium, Safdarjung Enclave, New Delhi.</td>
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<td>9. Dr Gajanan Sapkal, Scientist E, National Institute of Virology, Pune.</td>
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<td>10. Dr Gururaj Rao Deshpande, Scientist C, National Institute of Virology, Pune.</td>
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<tr>
<td>11. Dr Ullas PT, Scientist B, National Institute of Virology, Pune.</td>
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<tr>
<td>12. Dr Sanjay Mehendale, Director Research PD, Hinduja National Hospital &amp; Medical Research Center, SVS Road, Mahim West, Shivaji Park, Mumbai, Maharashtra.</td>
</tr>
</tbody>
</table>
b. Foreign Co-investigators:

13. Dr. William Moss, Professor, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA. Email: wmoss1@jhu.edu
14. Dr. Kyla Hayford, Assistant Scientist, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA. Email: kylahayford@jhu.edu
15. Christine Prosperi, Research Associate, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA. Email: cprospe1@jhu.edu
16. Alvira Z Hasan, India Research Program Coordinator, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA. Email: ahasan7@jhmi.edu
17. Dr. Amy Winter, Postdoctoral Fellow, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.
18. Keya Joshi, Programmer Analyst, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.
19. Dr. Justin Lessler, Associate Professor, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA. Email: justin@jhu.edu
20. Dr. Jessica Metcalf, Assistant Professor, Princeton University, Princeton, USA. Email: cmetcalf@princeton.edu
21. Dr. Mathew Ferrari, Associate Professor, Penn State University, University Park, USA. Email: matthewferrari@icloud.com
22. Andrew Azman, Assistant Scientist, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.
23. Sonia Hegde, Postdoctoral Fellow, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA.

c. MRHRU (site) coordinators:

   a. Ghatampur, UP: Dr Avi Kumar Bansal, Scientist D & Dr Sandeep Sharma, Scientist B, NJIL&OMD, Agra
   b. Dahanu, Maharashtra: Dr SL Chauhan, Scientist G & Dr Ragini Kulkarni, Scientist D, NIRRH, Mumbai
   c. Chabua, Assam: Dr SK Sharma, Scientist F, RMRC Dibrugarh
   d. Khumulwng, Tripura: Dr SK Sharma, Scientist F, RMRC Dibrugarh
   e. Hoshiarpur, Punjab: Dr AK Jain, Scientist F, NIOP, Delhi & Dr Gagandeep Singh Grover, Programme Officer, MRHRU/ DHR Punjab.
   f. Tirunelveli, Tamilnadu: Dr Yuvaraj J, Scientist F, NIE Chennai
   g. Chittoor, Andhra Pradesh: Dr Jaga Jeevan Babu Geddam, Scientist E, NIN Hyderabad.

d. Non-MRHRU sites:

   a. Thiruvananthapuram, Kerala: Dr. Biju Soman, Professor & Associate Dean, Sree Chitra Tirunal Institute for Medical Sciences and Technology,
Trivandrum.
b. Hyderabad, Andhra Pradesh: Dr. Jaga Jeevan Babu Geddam, Scientist E, NIN Hyderabad.

e. Project Monitoring:
a. Dr. Mohammad Ahmad, NPO – Research, VPD, NPSP, WHO-India, R. K. Khanna Tennis Stadium, Safdarjung Enclave, New Delhi – 1100029. Email: ahmadmoh@who.int
b. Dr Babasaheb V. Tandale, Scientist F, National Institute of Virology, Pune.

3. Duration of Research Project: 3 years [October 2017 to Dec 2020]

4. Amount of grant-in-aid asked for (details are to be furnished in Section B):
None

| i.   | Staff                                      | 1,08,22,188 |
| ii.  | Contingencies                             | 4,03,33,686  |
|      | Recurring                                 | 20,73,000    |
|      | Non-recurring (equipment)                 |             |
| iii. | Trainings, meetings and Travel            | 36,22,961    |
|      |                                           | 0            |
| iv.  | Overhead charges                          | 1,06,77,121  |
|      |                                           | 0            |
| Total*|                                          | 6,75,28,956  |

*Above total reflects the revised total budget. The original budget was Rs 4,32,01,200, an additional budget of Rs 2,43,27,756 is added to the original resulting in a total budget of Rs 6,75,28,956.

Grand Total -

5. Institution responsible for the research project

<table>
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<tr>
<th>Name</th>
<th>Indian Council of Medical Research [ICMR]</th>
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<tr>
<td>Postal address</td>
<td>POB 4911, Ansari Nagar, New Delhi 110029</td>
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<tr>
<td>Telephone</td>
<td>+91-11-26588895</td>
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<td>e-mail</td>
<td><a href="mailto:headquarters@icmr.org.in">headquarters@icmr.org.in</a></td>
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<tr>
<td>Fax No.</td>
<td>+91-11-26588662</td>
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6. Institutional ethical clearance and Project approval (Necessary documents indicating institutional ethical clearance must be enclosed for research involving human subjects as also animal experiments).
7. Is radio tagged material proposed to be used in the project either for clinical trials or experimental purposes? If so, clearance from Nuclear Medicine Committee, Bhabha Atomic Research Centre, Mumbai, indicating should be attached.

No, radio tagged material will not be used.

8. Projects involving recombinant DNA/Genetic engineering work should be examined and certificate by the Institutional Biosafety Committee (IBSC) to be enclosed. Guidelines for constitution of IBSC can be obtained from Secretary, Department of Biotechnology, CGO Complex, Lodhi Road, New Delhi-110003.

The project will not involve recombinant DNA or genetic engineering work.

9. Approval of the institutional ethics committee (IEC) should be enclosed. Guidelines for IEC for animal experiments should follow CPCSEA requirements and for human studies should follow ICMR guidelines.

10. The Institution where the study is being done should ensure that there is no financial conflict of interest by the investigators.
DECLARATION AND ATTESTATION

i. I/We have read the terms and conditions for ICMR Research Grant. All necessary Institutional facilities will be provided if the research project is approved for financial assistance.

ii. I/We agree to submit within one month from the date of termination of the project the final report and a list of articles, both expendable and non-expendable, left on the closure of the project.

iii. I/We agree to submit audited statement of accounts duly audited by the auditors as stipulated by the ICMR.

iv. It is certified that the equipment(s) is/are not available in the Institute/Department or these are available but cannot be spared for the project.

v. It is further certified that the equipment(s) required for the project have not been purchased from the funds provided by ICMR for another project(s) in the Institute.

vi. I/We agree to submit (online) all the raw data (along with descriptions) generated from the project to the ICMR Data Repository within one month from the date of completion /termination of the project.

If any equipment already exists with the Department/Institute, the investigator should justify purchase of the another equipment.

Signature of the:

a) Principal Investigator: Dr Nivedita Gupta

b) Co-Investigator(s): Dr Manoj Murhekar, Dr Santosh Kumar, Dr Jeromie Wesley Vivian, Augustine Duraiswamy, Dr Saravana Kumar, Sabarinathan, Dr Lucky Sangal, Dr Pauline Harvey, Dr Gururaj Rao Deshpande, Dr Ullas PT, Dr Sanjay Mehendale, Dr. William Moss, Dr. Kyla Hayford, Christine Prosperi, Alvira Z Hasan, Dr Amy Winter, Keya Joshi, Dr. Andrew Azman, Dr Sonia Hegde, Dr Jessica Metcalf, Dr Justin Lessler, Dr Matt Ferrari, Dr Mohammad Ahmad and Dr Babasaheb V. Tandale.

Signature of the Head of the Institution with seal

Date:

P.S. ICMR should be reminded if no acknowledgement is received within one month from the date of sending the application.
1. Title of the project:

**Impact of measles rubella (MR) vaccination campaign on population immunity in India [IMRVI study]**

2. Objectives

**Primary Objectives:**

1. Estimate age-specific population immunity to measles and rubella viruses within a specified precision of ±10% within three age strata (children 9 months to less than 60 months and 5 to less than 15 years of age, and women 15 to less than 50 years of age) in India using serological surveys.

2. Compare the accuracy, precision and cost of estimating age-specific measles and rubella population immunity using convenience samples from health care facilities versus community-based serosurveys.

**Secondary objectives:**

3. Validate and calibrate seroprevalence estimates obtained by using dried blood spots (DBS) with results of venous serum samples in a subset of survey samples.

4. Assess the risk profile of measles and rubella/CRS through mathematical modelling by extrapolating the data generated through the study.

5. Estimate the seroprevalence for other vaccine preventable diseases or other diseases of national interest if the residual samples of study subjects permits.

3. **Summary of the proposed research (up to 150 words) indicating overall aims of the research and importance of the research proposal. Application of the work in the context of national priorities of medical research, if any, may also be mentioned**

This study will consist of community-based, cross-sectional serosurveys in different age groups to estimate the population immunity to measles and rubella viruses in districts with MRHRUs and other priority areas. Second, a facility-based serosurvey from participants in a similar population (eg. a representative convenience or easy access sample such as children at the outpatient department) will be compared to the community-based serosurveys. These surveys will help assess the tradeoffs between cost and accuracy of facility-based versus community-based...
based serosurveys. The research will support capacity building to collect, analyze, and visualize results from serological data and could be leveraged for future serosurveys or expansion to other MRHRUs in India. Population immunity to other emerging or endemic infectious diseases, such as viral hepatitis, polioviruses, dengue viruses etc. may be added based on the epidemiological setting and health policy priorities in the selected MRHRUs.

4. **Present knowledge and relevant bibliography including full titles of articles relating to the project:**

   a. **Global priority and country goals and targets:**

   Globally, significant progress has been made in the measles elimination programme wherein over the last 15 years (2000 - 2015), the incidence of measles has declined by 75% bringing the incidence down to 36 per million in 2015 (1). Deaths have decreased by an impressive 79% which has resulted in measles moving down from being the 5th to the 15th leading cause of <5 child mortality (1 and 2). As per the WHO/IVB database, as of 05 September 2016, 161 countries had introduced MCV2 and 149 countries have rubella containing vaccines (3). For rubella containing vaccines, while coverage has been increasing gradually over time, global coverage was only 46% in 2015 (3). The Americas have provided proof of principle that measles and rubella can be eliminated. In 2015, all countries in the American Region were verified as free of rubella and CRS. The challenge now is maintaining elimination in the face of ongoing importations. The 11 countries of South-East Asia Region (SEAR) including India adopted the goal of measles elimination and rubella/CRS control by 2020 during the SEAR Committee meeting in September 2013, New Delhi. A Regional Strategic Plan was prepared for achieving elimination of measles and control of rubella/CRS by 2020 with the key objectives of immunization, surveillance, strengthening laboratory network and improving support & linkages (4). There has been an estimated 66% reduction in mortality due to measles in the Region in 2015 compared to 2000, with 51% reduction in India and 91% reduction in the rest of the Region (5). India still contributes to an estimated 37% of global deaths due to measles (5). Two doses of measles containing vaccine was introduced in routine immunization schedule in all 11 countries of the Region. Rubella containing vaccine was introduced in 9 of the 11 Member States. Laboratory supported surveillance for measles and rubella was established in all SEAR countries and 7 countries have CRS surveillance (4 and 6).

   b. **Measles rubella surveillance in India:**

   India started outbreak-based and laboratory-supported measles and rubella surveillance in 2005, which was scaled up in a phased manner to cover the whole country by 2015. The robust platform for AFP surveillance was used for measles and rubella surveillance. More than 40 000 reporting sites across India started reporting suspected measles cases. Based on
clustering of 5 cases in time and place, a suspected measles outbreak is flagged for house to house investigation. A detailed line list is generated for all measles suspected cases identified in the outbreak area. Serum specimens from five measles suspected cases are collected for laboratory confirmation. WHO India–NPSP provides technical support through its field units by the building capacity of state and district medical officers for implementation in their respective areas. The MR surveillance data generated from outbreak investigations and laboratory confirmation provides key epidemiological evidence on measles and rubella transmission in the country. The information has been very useful in driving programmatic policies and decision making regarding measles elimination and rubella control in the country.

c. Measles and Rubella burden in India:
Direct estimate of measles mortality in India are unavailable. Recent studies have revealed that there were 92,000 measles deaths in children 1-59, months of age in India in 2005, representing a mortality rate of 3.3 (99% CI 2.3-5.0) per 1000 live births and about 6% of all 1-59 month deaths. In children under 15 years of age, there were 107,000, (99% CI 74,000-158,000) measles deaths. The measles mortality rate was nearly 70% greater in girls, than in boys, and 60% of the deaths were in three populous states Uttar Pradesh, Bihar, and Madhya Pradesh in India 5 (7). Measles case fatality rates seem to be decreasing in recent years as evident from a study conducted in Bihar (8). As per the WHO estimates, India has shown ~55% measles mortality reduction by the year 2014, when compared to year 2000 (9).

CRS is known to account for 10-15% of pediatric cataracts and 10-50% of children born with congenital anomalies have laboratory evidence of CRS. 10-30% of adolescent females and 12-30% of women in the reproductive age-group are susceptible to rubella infection in India. (10). Serosurveys conducted in India have also confirmed that 6–47% of women are susceptible to rubella infection (11).

Evidence from NPSP-WHO India supported laboratory-based outbreak measles and rubella surveillance shows that in 2016 measles and rubella outbreaks are widespread across India. A total of 1,427 suspected measles outbreaks were investigated in the country during the year 2016, of which 763 were laboratory confirmed as measles outbreaks, 259 confirmed as rubella outbreaks, and 63 outbreaks showed evidence of both measles and rubella circulation in the community and were classified as mixed (figure 1). Though most of the cases are reported in children less than 10 years of age, 17% are reported in age group of more than 10 years (figure 2). Most of these measles cases received zero doses or are of unknown vaccination status, 12% cases had received > 2 measles vaccine doses (figure3).
The D8 genotype of measles virus is most widely circulated strain, followed by D4 and B3. For rubella virus, genotype 2B was found circulating.

Serologically confirmed measles and rubella outbreaks 2016

![Maps showing measles and rubella outbreaks in India 2016](image)

- Measles outbreaks: 763 outbreaks
- Mixed outbreaks: 63 outbreaks
- Rubella outbreaks: 259 outbreaks

Figure 1: Spot map of serologically confirmed measles and rubella outbreaks detected in India 2016

Age distribution pattern of measles and rubella cases 2016

- Measles
- Rubella

![Age distribution bar charts](image)

MCV status of measles cases

- 0 Dose: 28%
- 1 Dose: 43%
- 2 Dose: 11%
- 2+ Dose: 17%
- Unknown: 3%

Total cases: 16853

Figure 2: Bar chart of age distribution of measles and rubella cases in 2016

Figure 3: Pie chart of measles containing vaccine (MCV) status of measles cases in 2016

d. Measles and rubella mass vaccination campaigns in India:

India introduced MCV-2 in 2010 and by mid-2013 all states and union territories of India provided a second dose of measles containing vaccine through a combination of routine services and SIAs 12 (6).

In pursuit of the national goal of eliminating measles and control of rubella /CRS (congenital rubella syndrome) by the year 2020, India has launched the phased mass MR vaccination campaign in February 2017, targeting a wide age range of children from 9 months to less than 15 years (~410 million) in the country. In the first phase, 5 states/UT (Tamil Nadu, Kerala, Goa, Lakshadweep and Puducherry) conducted MR campaigns. During this first phase, ~36 million eligible children were targeted. The remaining states/UTs will be covered in subsequent phases by the end of 2018. At present two options are proposed to scale up the MR campaigns in phased manner (Figure 4). Based on the availability of MR vaccine and
human resource to conduct the campaigns, one of the two options will be finalised by the Ministry of Health and Family Welfare (MOHFW). It is estimated that this initiative would be the largest ever in any country to introduce a vaccine in communities in campaign mode (5).

Figure 4: Two options proposed to MOHFW for conducting MR campaigns in phase manner

Importance of measles and rubella seroprevalence studies in India:

While MR surveillance in India generates useful information, understanding population immunity against measles and rubella viruses could support strategic decision making and evaluation of the progress of the measles elimination and rubella control program. Apart from coverage evaluations of immunization initiatives and generating surveillance data, well-planned, large scale measles and rubella seroprevalence studies will help to enhance our understanding of population immunity and susceptibility profiles of communities in different risk settings in India. The India Expert Advisory Group (IEAG) on measles in its first meeting in February 2017 recommended measles serosurveys on to guide the program (12).

The current study is proposing estimation of measles and rubella antibody seroprevalence stratified by age groups in various geographic areas.
1. **Coverage of MR campaign and measles and rubella seroprevalence:** The largest ever measles and rubella (MR) vaccine campaign will be conducted throughout India in 2017-2018, administering the combined vaccine to all children 9 months to 15 years of age. Mass vaccination campaigns can be evaluated by validating reported coverage with serological surveys. Whereas coverage surveys provide information about vaccine receipt, serological surveys provide direct estimates of population immunity, information on the impact of the SIA, and remaining immunity gaps related to age as well as other social and cultural factors. In this study, we propose to estimate coverage of MR vaccination and sero-prevalence of measles and rubella antibodies at the district level. These districts will serve as a sentinel sites for serological surveillance for measles, rubella and other vaccine preventable and other emerging infectious diseases in future.

2. **Age group stratification:** The phased mass MR vaccination campaigns of 2017-18 are targeting children in the age group of 9 months to 15 years. This study will include seroprevalence surveys for measles and rubella antibodies in children in two age groups, 9 months to less than 60 months and 5 to less than 15 years of age. To understand the immunity gap in older individuals, specifically susceptibility of women of child bearing age for rubella, a measles and rubella serosurvey will be conducted among women in the age group of 15 to less than 50 years. These serosurveys will be important in understanding age-specific immunity gaps that might help in formulating future vaccine policies.

3. **Community and facility-based serosurveys:** Community-based serological surveys provide the most representative estimates of population immunity but can be expensive and logistically challenging. Samples collected at health care facilities may provide reasonable estimates of immunity but are prone to selection bias. Only in scenarios where patients accessing health care facilities are representative of the catchment population are the estimates based on community and facility-based approaches likely to be similar, as in case of women of child bearing age attending antenatal clinics. However, collecting such facility-based convenience samples can be much easier and less expensive. Few data exist on the trade-offs between cost and accuracy of using facility-based, convenience samples compared to community-based samples in estimating seroprevalence to vaccine-preventable diseases.

4. **Validation and calibration of results obtained from DBS versus serum sample:** Serum is considered the gold standard sample for estimation of antibodies. However, to obtain a serum sample, either capillary blood or venepuncture needs to be performed, thus making it an invasive procedure and more difficult to transport. DBS
also can be obtained by a simple finger prick technique but is much easier to transport and store, and is therefore a preferred sample in large scale field studies. However, the results obtained through DBS showed lower optical density values in some studies for antibody estimation as compared to serum samples, especially for rubella. This study proposes to calibrate the results of DBS with serum samples in a subset of survey samples.

The outcomes of these serosurveys are expected to provide critical inputs on strengthening immunization with respect to age, and the need to adopt community-based approaches as guidance to program managers for policy decisions. Accordingly, appropriate programmatic improvements can be made during future mass immunisation campaigns in India.

References:


5. Preliminary work already done by the Investigator on this problem, e.g. selection of subjects, standardization of methods, with results, if any

Principal Investigator:
Dr. Nivedita Gupta has a medical background with specialization in Molecular Medicine and Immunology. For more than a decade she has been coordinating research on viral infections and vaccine preventable diseases at the ICMR. She has a rich experience of steering public health programmes within the Government machinery. She was instrumental in establishing the network of viral research and diagnostic labs (VRDLs) in India. She is currently working on expanding the laboratory capacities for case based surveillance of Measles and Rubella in India, with NPSP/WHO, using the VRDLs of ICMR/DHR. She also steered the programme of setting up a sentinel surveillance system for detection and reporting of cases of Congenital Rubella Syndrome in India.

Key Indian co-investigators:
Dr MM Murhekar heads the National Institute of Epidemiology, Chennai. He is a trained public health specialist and an epidemiologist. He has been working with the Indian Council of Medical Research for more than 20 years. His research interest includes vaccine preventable diseases, diseases surveillance and outbreak response.
Dr Lucky Sangal is Focal Person for laboratories at WHO-India. By education she is a medical microbiologist with specialization in infectious diseases. Dr Lucky is leading the WHO supported polio, measles, rubella and other vaccine preventable laboratory networks of India. Her areas of expertise are laboratory networking, technology transfer, accreditation and monitoring and evaluation of laboratory systems. She was actively involved in protocol development and implementation of measles, rubella and pertussis sero prevalence study of 2016 that is conducted in two states of India.

Dr. Mehendale has extensive experience in infectious disease epidemiology. He was the Coordinator, Trainer and Monitor for the HIV Sentinel Surveillance in the 8 states of Western India while serving in National AIDS Research Institute [ICMR] in Pune from 2006 to 2010. He also served as the National Coordinator for the National Rotavirus Surveillance Network – Phase II from 2012-2017 which extended to 28 centers in India and generated important data that contributed in roll out of indigenous rotavirus vaccine for the Government of India in 2016. He was the Principal Investigator of the Post-Introduction Review conducted in 4 states where the rotavirus vaccine was rolled out initially. Additionally, Dr. Mehendale was the Principal Investigator and Coordinator of the Ministry of Health and Family Welfare, Govt. of India supported Surveillance for Bacterial Meningitis and Invasive Pneumonia study conducted by National Institute of Epidemiology [NIE], Chennai from 2013-2016] which involved 15 sites across India. Dr. Mehendale was involved in implementing the MRHRU scheme of ICMR at Tirunelveli right from the beginning and he has provided several critical inputs in conceptualizing and operationalizing this network in India. MRHRU at Kallur in Tirunelveli district of Tamil Nadu is presently raising a cohort of 50,000 rural population. After completing mapping of the population, demographic surveys are currently underway. The center is also presently conducting a nutrition assessment study in women and children. A strong collaboration has been established with Tirunelveli Medical College and Directorate of Public Health to implement various research programs under the MRHRU. Similar work arrangement also exists in all the other MRHRUs listed on this project.

**Key Foreign co-investigators:**

Dr. William Moss is a pediatric infectious disease specialist with expertise in serological surveys for VPDs, the epidemiology of measles, and epidemiologic methods. Dr. Moss has led multiple studies in Zambia to evaluate population immunity to measles and rubella. He uses innovative sampling strategies, such as satellite/GIS-based sampling, and mathematical modeling tools to understand temporal and spatial changes in immunity and disease burden. He has worked in India on Hib initiative and the Baseline Assessment for *Streptococcus Pneumonia* of India serotypes (BASIS) studies.
Dr. Kyla Hayford is an epidemiologist with expertise in serological surveys for VPDs and immunization surveillance. She has extensive experience conducting community-based serological surveys in Bangladesh, Kenya, Pakistan and Zambia, and has evaluated methods to standardize specimen’s collection and processing of oral fluid and capillary blood. She currently is working on multiplexed methods to monitor multiple pathogens using small volumes of blood. Results from her ongoing studies to standardize and optimize biomarker testing in the field will guide best practices in the field and lab for this study.

Ms. Christine Prosperi is a Research Associate at the International Vaccine Access Center of the Johns Hopkins Bloomberg School of Public Health. She has extensive experience in survey design and data management systems, in part through her position as Coordinator for the Pneumonia Etiology Research for Child Health (PERCH) Study.

Ms. Alvira Z Hasan is the India Research Program Coordinator for this project based in New Delhi, India. She received her MSPH degree from the Johns Hopkins Bloomberg School of Public Health.

Drs. Justin Lessler, Jessica Metcalf, and Matt Ferrari are epidemiologists and ecologists with expertise in modeling the transmission dynamics and disease burden of measles and rubella.

Study platform: MRHRUs provide an ideal platform for district level serological surveillance for vaccine-preventable, endemic and emerging infectious diseases. The advantages of involving MRHRUs in VPD surveillance would be:

1. MRHRUs are in rural areas within the community outreach centres of State Government Medical Colleges and each centre is mentored by an ICMR Institute and linked to a local medical college.
2. Dedicated space is available for carrying out research activities, including laboratory work
3. Dedicated scientific and technical staff, and monitoring framework by the ICMR institutions are available
4. Most MRHRUs have a Research Advisory Committee (RAC) and the ICMR institutes have Institutional Ethical Committees from which approval can be obtained
5. Availability of all basic equipment required for serological testing: ELISA reader & washer, refrigerated centrifuge, -20 C deep freezer, biosafety cabinet, gel documentation system, water bath, oven, Millipore water filtration unit, autoclave, water bath, computer, printer etc. MRHRUs have the capacity to perform enzyme immunoassays for serologic testing.
6. MRHRUs can provide a platform for repeated cross-sectional, community-based surveys for vaccine-preventable and emerging infectious diseases. Additionally, the relationship of ICMR
institutes with the medical colleges can be leveraged to initiate facility-based convenience sample collection at local health care facilities.

7. Viable links with the State Directorate of Health Services which is also linked to the Integrated Disease Surveillance Project (IDSP) and National Vector Borne Disease Control Programme (NVBDCP).

6. **Links with Other ICMR projects (ad- hoc, task force or collaborative): None**

7. **List of publications of last 5 years of all the investigators in the relevant fields (enclose reprints if available)**


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**8. Detailed Research plan**

8.1 **Research Setting:**

Around 70% of the population of India resides in the rural areas. The rural population is grossly under-served in terms of available health care services, access to new and affordable technologies and much needed diagnostic services for common infectious and non-infectious diseases. To address this issue, the Department of Health Research (DHR) under the aegis of Ministry of Health & Family Welfare formulated a scheme to set up Model Rural Health Research Units (MRHRUs) in 15 geographically diverse rural areas of the country. The Cabinet-
approved scheme was implemented in 2013 and a total of 12 MRHRUs have been approved and sanctioned by the DHR. As of now, 8 MRHRUs have basic infrastructure to initiate scientific studies.

Each MRHRU has been set up near a state health facility and is linked with one of the ICMR institutions/centres for mentoring. The nearby State Medical College is also linked with the MRHRUs for providing local insights into various health problems. These Units have a rich infrastructure in terms of space, all basic scientific equipment and staff. They also have the advantage of being strategically located, good access to local community as well as high quality scientific and clinical expertise. Hence, the Units could serve as a valuable platform for conducting community based as well as cohort studies.

Well-equipped laboratories have been established in all MRHRUs. Availability of basic equipment required for serological testing is available in MRHUs, which includes ELISA reader & washer, refrigerated centrifuge, -20 C deep freezer, biosafety cabinet, gel documentation system, water bath, oven, Millipore water filtration unit, autoclave, water bath, computer, printer, etc.

The seven MRHRUs have been carefully selected in this study based on their geographically diverse locations as well as their functional status, and the possible opportunity to conduct serosurveys at district level pre-or post MR vaccination campaign as per dates proposed by the Ministry of Health & Family Welfare for MR campaigns in various States. For this study, seven MRHRUs have been selected due to following reasons:

1. **MRHRU Ghatampur, Kanpur Nagar Uttar Pradesh:** this is the oldest and best performing of all the MRHRUs. This site has experience in conducting various studies in the past. Its geographical location in UP is also important for the study, as this state is the most populous with weak public health infrastructure.

2. **MRHRU Dahanu, District Palghar, Maharashtra:** this site caters to 70% schedule tribe population, an underserved community. Geographically, it is located near to Mumbai, the biggest metropolitan city of India.

3. **MRHRU Chabua, Assam:** this site is located in the heart of north-eastern states of India. This region comprises of the most remote and less developed 8 states of the country.

4. **MRHRU Khumulwng, Tripura:** Tripura state is the poorest performing state among north eastern states for health indicators. This site is unique because it caters to the most difficult to reach indigenous population of Tripura.
5. MRHRU Bhunga, District Hoshiarpur, Punjab: Punjab is one of the good performing states for routine immunisation. Inclusion of this site will provide data in good performing state for comparison.

6. MRHRU Kallur, District Tirunelveli, Tamil Nadu: there are different views regarding the coverage of recently conducted MR campaign in Tamil Nadu. Generation of serosurvey data in post MR campaign phase will provide solid evidence of immunity gaps in this state. Further, the Kallur MRHRU is a well performing site at which 60% of the households and 30% of the villages have been mapped with the help of GIS coordinates and census enumeration.

7. MRHRU, Chandragiri, District Chittoor, Andhra Pradesh: this site has been selected because Andhra Pradesh is taken up in the second phase of MR campaign to be held in August / September 2017. Secondly, the MRHRU is fully functional and equipped to fast track the study. Results from this site will help us to gain experience and execute the research study more smoothly at other more challenging sites.

Although these MRHRUs are strategically located in rural settings; it is proposed that the survey will be conducted in the entire district so as to arrive at estimates of measles and rubella vaccination coverage and sero-prevalence at the district level. Besides these seven districts, we also propose to conduct surveys in two purposively selected districts in Telangana (Hyderabad) and Kerala (Thiruvananthapuram) where the health seeking behaviour of the community is more towards private sector and rubella vaccine has been used extensively. The Kerala Government has introduced rubella vaccine in the UIP schedule two years ago. The rubella prevalence in these two areas, especially in women of child bearing age group would be of immense importance in understanding rubella immunity gaps. As MRHRUs do not exist in these two areas (Hyderabad and Thiruvananthapuram), it is proposed to conduct the serosurvey in Hyderabad and Thiruvananthapuram through the following institutes:

2. Sree Chitra Tirunal Institute of Medical Sciences, Thiruvananthapuram for Thiruvananthapuram, Kerala.

Figure 5 below shows the geographical spread of these 7 MRHRUs and table 1 shows the linked ICMR institute and state medical college along with the catchment population of MRHRUs. These geographically and demographically diverse sites will serve as sentinel district-level sites for assessing population immunity to measles, rubella and other vaccine preventable and emerging infectious diseases.
8.2 Study Design:

The study has three components:

1. Community based surveys for estimation of (a) population immunity against measles and rubella and (b) coverage of MR vaccine campaign: The study design will consist of cross-sectional serosurveys in the community in 9 sites – 7 districts where MRHRUs are located and 2 purposively selected districts where rubella vaccine has been in use in private sector. In all the study sites, MR vaccine coverage surveys as well as serosurveys will be conducted. In some sites, the MR vaccine campaign would have been completed before the launch of the study, therefore, the MR vaccine coverage survey and post-campaign serosurveys will be conducted. The five sites where only a post campaign survey is possible include: Tirunelveli district in Tamil Nadu, Chittoor district in Andhra Pradesh, Hyderabad district in Telangana, Thiruvananthapuram district in Kerala and West Tripura district in Tripura. At remaining four sites, pre-campaign serosurveys will be conducted. Post-campaign vaccine coverage surveys will be conducted at all nine sites. After completion of Phase I, as recommended earlier by the experts, we plan to have an in-depth review of the results of the first round of serosurvey with the Expert Group and accordingly take a decision on the need to conduct post-campaign serosurveys at the sites where pre-surveys would be done. This will enable us to assess the
impact of the MR vaccination campaign as well as validate vaccine coverage data. Detailed plan has been given in Table 2.

The post-MR campaign vaccine coverage evaluation will be conducted one month after the campaign. The sampling frame for the pre-campaign serosurveys and post-MR campaign coverage surveys would be the same. The sampling frame is the full list of villages and wards in the selected district from the 2011 census. In all the sites, the community-based surveys will cover urban, rural and slum populations and will estimate the coverage and seroprevalence at the district level.

2. Facility based survey: This component of the study would compare the seroprevalence estimated from the community-based serosurveys with the seroprevalence based on the facility-based survey. The facility-based surveys will be conducted in two districts (Palghar district in Maharashtra and Kanpur Nagar district in Uttar Pradesh).

3. Validation of results of IgG serology for measles and rubella obtained from DBS versus serum through venous blood: At two sites (Palghar district, Maharashtra and Kanpur Nagar district, Uttar Pradesh), venous blood and DBS samples collected on HemaSpot HF blood collection devices will be collected to compare the results of IgG serology for measles and rubella. In both sites DBS samples will be collected in the post MR campaign survey from women of reproductive age (15 to less than 50 years).

The original plan is summarised in table 2a (as of August 2018). This is has been revised below in table 2b.

Table 2a: Original survey plan

<table>
<thead>
<tr>
<th>SN</th>
<th>Name of MRHRU/ICMR Institute</th>
<th>Proposed MR campaign</th>
<th>Both community &amp; facility</th>
<th>DBS Vs serum samples</th>
<th>Serosurvey (pre/post-campaign/both)</th>
<th>Coverage evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bhunga, Punjab</td>
<td>Jan-Feb 2018</td>
<td>No</td>
<td>No</td>
<td>Pre-campaign</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Chandragiri, AP</td>
<td>Aug-Sep 2017</td>
<td>No</td>
<td>No</td>
<td>Post-campaign</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>NIN, Hyderabad</td>
<td>Aug-Sep 2017</td>
<td>No</td>
<td>No</td>
<td>Post-campaign</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>NIE Chennai for Thiruvananthapuram</td>
<td>Aug-Sep 2017</td>
<td>No</td>
<td>No</td>
<td>Post-campaign</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Chabua, Assam</td>
<td>Jan-Feb 2018</td>
<td>No</td>
<td>No</td>
<td>Both</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Khumulwng,</td>
<td>Jan-Feb</td>
<td>No</td>
<td>No</td>
<td>Pre-campaign</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Table 2b: The revised plan (as of 1 August 2019)

<table>
<thead>
<tr>
<th>SN</th>
<th>Name of MRHRU/ICMR Institute</th>
<th>MR campaign</th>
<th>Facility survey?</th>
<th>DBS vs serum comparison</th>
<th>Dates of pre-campaign serosurvey</th>
<th>Dates of post-campaign serosurvey*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bhunga, Punjab</td>
<td>Completed (May 1 – July 31 2018)</td>
<td>No</td>
<td>No</td>
<td>Completed: Mar 9 – Apr 16, 2018</td>
<td>August 31st 2019</td>
</tr>
<tr>
<td>2</td>
<td>Chabua, Assam</td>
<td>Completed (Aug 18 – Dec 31 2018)</td>
<td>No</td>
<td>No</td>
<td>Completed: Mar 23 – Apr 14, 2018</td>
<td>Planned</td>
</tr>
<tr>
<td>3</td>
<td>Ghatampur, UP</td>
<td>Completed (Nov 26 2018- Feb 28 2019)</td>
<td>Yes Ongoing</td>
<td>Yes Completed</td>
<td>Completed: May 10 – Aug 10, 2018</td>
<td>In Progress (Start: June 1*)</td>
</tr>
<tr>
<td>5</td>
<td>Khumulwng, Tripura</td>
<td>Completed (Sep 15 2018- Jan 5 2019)</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
<td>Planned</td>
</tr>
<tr>
<td>6</td>
<td>Tirunelveli, TN</td>
<td>Completed (Feb 6- June 10 2017)</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
<td>Planned</td>
</tr>
<tr>
<td>7</td>
<td>Chandragiri, AP</td>
<td>Completed (August 1- Sep 8 2017)</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
<td>Planned</td>
</tr>
<tr>
<td>8</td>
<td>NIN, Hyderabad</td>
<td>Completed (August 2017)</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
<td>Planned</td>
</tr>
<tr>
<td>9</td>
<td>SCTIMST Thiruvananthapuram</td>
<td>Completed (October 3 2017 to March 30 2018)</td>
<td>No</td>
<td>No</td>
<td>N/A</td>
<td>Completed: January 11- May 15, 2019</td>
</tr>
</tbody>
</table>

* Combined with coverage evaluation.

### 8.3 Sample size estimation

The sample size calculations are based on objective 1 aimed at estimating age-specific population immunity to measles and rubella viruses in community-based serosurveys.

I. Primary Objective 1: Estimate age-specific seroprevalence to measles and rubella viruses within a specified precision of ±10% within three age strata (children 9 months to less than 60 months and 5 to less than 15 years of age, and women 15 to less than 50 years of age) in India using serological surveys.
II. Primary Objective 2: Compare the accuracy, precision and cost of estimating age-specific measles and rubella seroprevalence using convenience samples from health care facilities versus community-based serosurveys.

Sample size: In each of the 9 districts, surveys will be conducted in three age groups: (a) children aged 9 months to less than 60 months (b) 5- less than 15 years and (c) women of childbearing age group (15- less than 50 years). Assuming a rubella IgG seroprevalence of 50% among children aged 9 months to less than 60 months as well as those aged 5- less than 50 years, and an absolute precision of +10%, the estimated sample size (ESS) would be 103 for a confidence level of 95%. Assuming a design effect of 2 (ICC=0.166), we will need the sample size of 206 (rounded to 210) per age group from 30 clusters. The surveys will be designed to enrol 7 individuals per age group per cluster but final enrolment number will depend on actual response rates. Sero-surveys conducted among pregnant women in India earlier indicate a seroprevalence of 80%. With an absolute precision of 10% and a design effect of 2, we would need to survey 193 (rounded to 210) women in the childbearing age group per district.

8.4 Study subjects:
Community based surveys:

Inclusion criteria:
- All children of 9 months to less than 15 years of age
- All females between 15- less than 50 years of age (only in post campaign surveys)
- Subject/parents willing to participate in the study and give consent and/or assent

Exclusion criteria:
- Non-fulfillment of any inclusion criteria
- Sick individuals requiring hospitalization or undergoing treatment for major illness

Facility-based surveys:

Inclusion criteria:
- Serum collected within 96 hours, kept at 2-8 °C, and will be discarded by facility
- Minimum 80 uL of serum
- Ages 0 - < 50 years. If it is not possible to select by age, collect all ages.
- Specimen can be linked to data on age and sex of patient, date of specimen collection, and name of facility where blood was collected.

Exclusion criteria:
- Non-fulfillment of any inclusion criteria

8.5 Sampling:
Community based survey (for serosurvey as well as coverage evaluation survey):

In each site, coverage of MR vaccine and seroprevalence of measles and rubella antibodies will be estimated at the district level. A two-stage cluster sample survey will be conducted in each district. The following sampling procedure will be adopted for the selection of PSU and study participants.

A. Selection of clusters: The sampling frame for the survey will include the list of villages (in rural areas) and wards (in urban areas) in the district as per the 2011 census. A total of 30 clusters will be selected from each district by probability proportional to size linear systematic sampling method. From the selected wards, one Census Enumeration Block (CEB) will be selected randomly.

B. Mapping and segmentation: The survey team will create a rough map of the selected villages/CEBs. Selected CEBs having equal to or more than 140 households will be further segmented with each segment having at least 70 households. In some states with low child to house ratio, the minimum number of households in a segment maybe raised to 80 households. The procedure for segmentation will be done either by utilizing natural segments in a village like Mohalla or tolla or by creating segments, which are roughly equal in size of 100 households. One segment will be randomly selected from the available segments. Thus, the CEB from urban areas and segment in rural areas will be the primary sampling units.

C. Selecting eligible persons randomly: All the households in the given segment will be enumerated and the name of the persons along with their age will be enlisted. The list of all persons in each of the three age groups will form the sampling frame for selecting persons by simple random sampling. Assuming about 50% of the selected respondents will not be available for the survey (for reasons such as: locked houses, or person not be present at the time of visit of the field team or parents will refuse the consent, insufficient blood sample, and equivocal lab results), we will need to select 13 persons from each of the three age groups. Based on estimated refusal rate from prior districts, NIE may re-evaluate this and consider reducing the number of persons randomly selected from each age group if acceptance is higher. This adjustment will require adjusting the randomization program in the tablet and can only be done between districts based on discussions with the central team. All the selected individuals will be contacted in their houses and consenting persons will be enrolled in the study. If the person is not available at the time of survey, one additional visit will be made to include the person in the study. Alternative sampling strategies for eligible persons within selected households may be used in some study sites.
D. Surveying the eligible persons: After obtaining written informed consent, the selected persons/parents of the selected children or individual will be interviewed to collect information about socio-demographic details. For children aged 9 months to less than 15 years (based on age at the time of MR campaign for the post-campaign surveys), information about prior measles illness history (added recently in some sites) the receipt of MR vaccine will be collected from the child/mother based on vaccination card issued at the time MR vaccination campaigns. If the child has not received MR vaccine during the campaign, reasons for being vaccinated will also be collected. Parents of such children will be encouraged to get their children vaccinated for MR from the nearest public health facility. For children aged less than 5 years at the time of MR campaign, we will also collect the details of other primary vaccines received by the children from the vaccination card or mother’s history, in case card is not available. For women of reproductive age (15 to less than 50 years) we try to collect information of routine receipt of rubella vaccine (either by card or memory). From each participant, a maximum of 2 ml of blood sample will be collected.

We will use the same sampling frame for the pre-MR campaign serosurvey and the post-MR campaign coverage surveys in all sites where MR campaigns will be conducted in 2018/2019. The sampling frame is the full list of villages and wards in the selected district from the 2011 census.

**Facility-based survey:**

We will collect a representative sample of anonymized serum specimens from patients younger than 50 years of age who had blood collected at selected health facilities for diagnostic purposes and have residual blood available. The residual specimens will be accessed before they are discarded. Residual specimens will be labeled with a unique study ID with no way to link the specimen to the individual. We will collect the study ID, data and time of collection, age and sex. If possible, we will also collect whether patient is admitted in the outpatient or inpatient department, whether patient is an antenatal care (ANC) patient, village/ward name and facility where specimen was collected. Residual specimens and linked variables will not be collected using an informed consent document. Patients will incur no risks in the study.

Out of the 9 sites, the facility-based surveys will be conducted in Palghar district in Maharashtra and Kanpur Nagar district in Uttar Pradesh. Each site will select one or more public and/or private facilities to participate, which best reflect the population in the district. Where possible, residual specimens will be collected before, during and after the MR vaccination campaign. A maximum of 6750 specimens will be collected from each site (n=2250 age <5 years; n=2250 ages 5-<15 years; n=2250 ages 15-<50 years). Final sample size will depend on availability of specimens, duration of the study and the number of participating facilities at each site. At least 750 pediatric specimens will be collected (n=375 age<5 years; n=375 ages 5-<15 years) to detect >10% absolute difference in measles and rubella
seroprevalence between each age group. The maximum number of samples per age group and facility approved by local ethical committees (IECs) in each site are specified in table 3.

Table 3. Maximum sample size of residual serum specimens collected per age group approved by IEC

<table>
<thead>
<tr>
<th></th>
<th>&lt;5 years of age</th>
<th>5 to &lt;15 years of age</th>
<th>15+ years of age</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maharashtra</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahanu Subdistrict Hospital</td>
<td>375</td>
<td>375</td>
<td>375</td>
<td>1125</td>
</tr>
<tr>
<td>Kasa Subdistrict Hospital</td>
<td>375</td>
<td>375</td>
<td>375</td>
<td>1125</td>
</tr>
<tr>
<td>Hind Lab, Dahanu</td>
<td>375</td>
<td>375</td>
<td>375</td>
<td>1125</td>
</tr>
<tr>
<td>Hind Lab, Jawhar</td>
<td>375</td>
<td>375</td>
<td>375</td>
<td>1125</td>
</tr>
<tr>
<td>Metropolis Laboratory (private)</td>
<td>375</td>
<td>375</td>
<td>375</td>
<td>1125</td>
</tr>
<tr>
<td>Suburban Laboratory (private)</td>
<td>375</td>
<td>375</td>
<td>375</td>
<td>1125</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2250</td>
<td>2250</td>
<td>2250</td>
<td>6750</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanpur Medical College</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>1800</td>
</tr>
<tr>
<td>Paliwal Diagnostics</td>
<td>600</td>
<td>600</td>
<td>600</td>
<td>1800</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1200</td>
<td>1200</td>
<td>1200</td>
<td>3600</td>
</tr>
</tbody>
</table>

Note: Represents ethically approved maximum sample collected from each facility. Final sample size will depend on available specimens and duration of study at each site.

Data on the costs, time, and feasibility of community-based surveys will be collected and compared to community-based surveys.

8.6 Data collection and data management:
We will use tablet-based data collection. Using the standardized questionnaire, trained study staff will interview the mother or caretaker of children in the eligible age group, and adult participants, to collect information about socio-demographic details and detailed vaccination history for vaccines administered as a part of routine immunization as well as mass vaccination campaigns. For quality assurance, the study questionnaire will be reviewed by the supervisor and study coordinator.

The data from the tablet based data-collection will be uploaded to the NIE server on a daily-basis. Data will be managed using database management techniques of MS Access or another appropriate database. The results of laboratory tests will be entered by the respective laboratory.
The primary dependent variables will be a binary categorization of seroprotection based on antibody measurement using an enzyme immunoassay for measles and rubella viruses. The data from coverage surveys will be analysed to estimate the coverage of measles and rubella vaccine. We will use descriptive statistics, test of two independent proportions and logistic regression models to evaluate differences in seroprevalence estimate by survey after accounting for hypothesized confounders. Cost and time requirements for each survey method will be analyzed and compared. Spatial analysis may be incorporated into the analysis to evaluate geographic variability in seroprevalence. Mathematical modeling may be used to model the impact of the MR campaign and evaluate measles and rubella risk profile in the MRHRUs.

**Capacity building for mathematical modeling:**
In order to build capacity for mathematical modelling in India, experts from the Johns Hopkins Bloomberg School of Public Health will organize modeling workshops for Indian researchers. We also have plans for building the capacity include training of a scientist from NIE at JHU in mathematical modeling and involving him/her in conducting the risk profile analysis of measles and rubella for India, based on available epidemiological data.

8.7 Specimen collection
Venous blood will be collected using syringe and needle using aseptic techniques. A maximum of 2 ml of blood will be collected. Not more than 3 pricks will be attempted to collect blood by venepuncture. The blood sample will be processed into sera in the laboratory and stored at -20 C until shipment to NIV Pune for testing. In a sub set of study subjects and sites, the blood sample will also be collected using retractable lancets and spotted dried blood spots (DBS) using HemaSpot HF blood collection device. DBS specimens will be stored at room temperature up to 1 month at site and then transported to NIV Pune to be stored at -20C until testing.

8.8 Laboratory testing:
Venous samples will be processed into sera and stored at the MRHRUs at -20 to -80 C. Dried blood spots will be stored at room temperature at MRHRU for the short term (up to 1 month) and then transported to NIV Pune for longer term storage at -20 C until testing. For testing, DBS spots will be eluted and tested using standardized protocols. Commercially available measles and rubella enzyme immunoassays (Euroimmun Anti-Measles Virus IgG and Anti-Rubella-Virus IgG kits) will be used to measure antibodies to measles and rubella viruses. Remaining specimens will be stored for testing for other vaccine-preventable, endemic and emerging infectious diseases. The final list of antigens will be determined by study investigators based on specimen volume, available assays, and budget. Laboratory technicians at MRHRUs may be provided training in IgG ELISA testing at NIV Pune, if project timelines and budget permits.
Samples will be classified as seropositive for measles and rubella according to the manufacturer’s protocol.

**Quality assurance of laboratory testing:**
Quality Assurance (QA)/Quality Control (QC) protocols will be prepared and led by NIV Pune.

**8.9 Enrollment of study subjects: consent**
Approval from Ethics Committees of the respective ICMR institutions will be obtained. Study protocol, data collection tools, Participant Information sheet with informed consent forms in English and local language will be submitted to the Ethics Committee for approval.

**Sharing of results with seronegatives:** The study results from the post campaign surveys will be communicated to participants or their parents as soon as possible if their test for measles or rubella immunity was negative. They will be advised on appropriate vaccination and referred to the nearest vaccination site. The findings of this study will also be shared with state health officials.

**9. Facilities in terms of equipment, etc, available at the sponsoring institution for the proposed investigation**
A detailed list to be obtained from each MRHRU

**10. Outcome of the project:**
1. Estimates of age-specific immunity to measles and rubella will be established. Baseline estimates of rubella can be used to model the disease burden due to rubella and congenital rubella syndrome.

2. Level of immunity to measles and rubella in individuals older than 15 years [particularly in women] who were not eligible for vaccination during the campaign will be estimated.

3. Comparison of accuracy, precision and cost of conducting serosurveillance using facility-based convenience samples versus community-based serosurveys will inform the program managers whether it will be possible to rely on facility based convenience sampling during evaluation of vaccination programs.

4. e-tools for data visualization and timely data capture will be developed that will support timely analysis, interpretation and communication of seroprevalence data, including mapping immunity gaps.

5. Capacity for mathematical modelling will be developed in the country.
11. Timelines:

a. **Finalization and approval of study protocol**: approval of the study protocol requires concurrence of an expert group of ICMR. This can be obtained either by calling a formal meeting or by circulation. Timelines June 2017

b. **Ethical clearance**: each MRHRU needs to take the approval from affiliated ICMR institute ethical committee. To conduct the pre-campaign phase surveys, this process need to be fast tracked and completed by July-15 August 2017

c. **Advocacy with state government, local authorities and site assessment**: August/September 2017

d. **Securing funds**: August/September 2017

e. **Trainings**: August/September 2017 onwards

f. **Field implementation**: September- October 2017 onwards

g. **Sample testing**: within 3 months after collection of samples

h. **Data analysis and report writing**: within 6 months after completion of field implementation.

Roles and responsibilities of the partner organizations:

1. **Indian Council of Medical Research**: ICMR will be responsible for planning, partial funding, implementation of the project and testing of samples. ICMR will also be responsible for overall project coordination, data management and data analysis. **ICMR-National Institute of Epidemiology** will be responsible for the overall data management of the project. This will include creating application for data collection, server configuration, syncing (data transfer between device to server and server to device), pilot testing the application and training of field staff. The data collected by different sites will be checked for completeness. NIE will also be involved in training, implementation and data analysis, in partnership with JHU, NPSP and other ICMR institutes. ICMR-National Institute of Virology, Pune will test all samples collected for the community and facility surveys.

2. **National Polio Surveillance Project, WHO-India**: NPSP will be responsible for project facilitation in terms of training and capacity building of MRHRUs, formulation of SoPs, facilitating sample collection in field and liaison with the State Government for smooth execution of project work.

3. **John Hopkins University, USA**: Johns Hopkins University (JHU) will be involved in formulation of SOPs, training, implementation, data management and data analysis in partnership with NPSP and ICMR. JHU will provide technical support in terms of innovative data collection tools, modelling, conceptualization and planning of project activities and partial funding support.
10. Budget requirements (With detailed break up and justification): attached as separate annexure:

Justification for budget increase

Over all with 20% boosting the total original budget of Rs 4,32,01,200 been increased by an additional amount of Rs 2,43,27,756. Hence the total amount of the project now is Rs 6,75,28,956 owing to additional survey activities not accounted for in the previous budget. Additional activities included

1) post campaign community serosurveys in Uttar Pradesh and Punjab (staff, recurring contingency, non recurring contingency, training and travel)

2) For NIV Pune: additional staff hired to support site training and testing activities, supplies, courier and testing costs for additional community survey, facility surveys and DBS (recurring contingency), CDC Luminex training at Atlanta, USA and onsite trainings and travel (trainings and travel)

3) For NIE: additional staff hired to support site training and monitoring, additional charges related study analysis (recurring contingency), longer duration of stay at site trainings and travel.

4) Other: Include budget for portable centrifuges for all survey sites to use in field (non recurring contingency), 2 in person investigators meetings with key Indian and Foreign co-investigators and a modeling workshop.

<table>
<thead>
<tr>
<th>Item</th>
<th>Original cost</th>
<th>Additional cost (boosted by 20%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Staff</td>
<td>INR 63,27,000</td>
<td>INR 44,95,188</td>
<td>INR 1,08,22,188</td>
</tr>
<tr>
<td>2a. Contingencies: Recurring</td>
<td>INR 3,02,46,700</td>
<td>INR 1,00,86,986</td>
<td>INR 4,03,33,686</td>
</tr>
<tr>
<td>2b. Contingencies: Non Recurring</td>
<td>INR 6,75,000</td>
<td>INR 13,98,000</td>
<td>INR 20,73,000</td>
</tr>
<tr>
<td>3. Trainings and meetings</td>
<td>INR 8,02,500</td>
<td>INR 28,20,461</td>
<td>INR 36,22,961</td>
</tr>
<tr>
<td>4. Travel</td>
<td>INR 51,50,000</td>
<td>INR 55,27,121</td>
<td>INR 1,06,77,121</td>
</tr>
<tr>
<td>5. Overhead charges</td>
<td>INR 0</td>
<td>INR 0</td>
<td>INR 0</td>
</tr>
<tr>
<td>Total (INR)</td>
<td>INR 4,32,01,200</td>
<td>INR 2,43,27,756</td>
<td>INR 6,75,28,956</td>
</tr>
</tbody>
</table>

The detailed budget added in “Any other documents”.

Add Justification for duration increase

The original duration of the project was proposed for 2 years (October 2017 to July 2019). However, we will need to extend the duration of the project to December 2020 owing to additional survey activities like 2 additional post campaign surveys, laboratory testing of
samples from facility and DBS substudies along with modeling and rigorous data analysis after field implementation.