IMMUNOGENICITY AND SAFETY OF CONCURRENT ADMINISTRATION OF LIVE, ATTENUATED SA 14-14-2 JAPANESE ENCEPHALITIS VACCINE AND MEASLES-MUMPS-RUBELLA VACCINE IN INFANTS 9-12 MONTHS OF AGE IN THE PHILIPPINES

Protocol Number: JEV06

ClinicalTrials.gov: NCT02880865

Sponsor: PATH

Vaccine Manufacturer: Chengdu Institute of Biological Products

Funding Mechanism: Bill & Melinda Gates Foundation

Investigator: Maria Rosario Capeding, Research Institute for Tropical Medicine

Version Number: 2.0

Date: 18 January 2017

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- The Declaration of Helsinki
- International Ethical Guidelines for Biomedical Research Involving Human Subjects, CIOMS 2002
- International Ethical Guidelines for Epidemiological Studies Involving Human Subjects, 2008
- International Conference on Harmonization (ICH) E6 (Good Clinical Practice)
- The Philippines National Ethical Guidelines for Health Research

All key personnel (all investigators responsible for the design and conduct of this study) will have completed Human Subjects Protection and GCP training prior to interaction with any participants or to having access to their confidential study data.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable ICH guidelines.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
CDIBP	Chengdu Institute of Biological Products
CD-JEV	prequalified live, attenuated SA-14-4-2 Japanese encephalitis vaccine
CRF	case report form
CRO	contract research organization
CRS	congenital rubella syndrome
CSR	Clinical Study Report
DEN	dengue
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EPI	Expanded Programme on Immunization
FDA	Food and Drug Administration
GCP	good clinical practice
GMC	geometric mean concentration
GMT	geometric mean titer
ICH	International Conference on Harmonisation
IEC	Independent or Institutional Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRB	Institutional Review Board
ITT	intent to treat analysis set
JE	Japanese encephalitis
MCV	measles containing vaccine
MMR	measles, mumps, rubella vaccine
MR	measles rubella vaccine
RITM	Research Institute for Tropical Medicine
PHK	primary hamster kidney
PP	per protocol analysis set
PRNT	plaque reduction neutralization test
SAE	serious adverse event
SAGE	WHO Strategic Advisory Group of Experts
SAS	safety analysis set
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
UNICEF	United Nations Children's Fund
US	United States
WIRB	Western Institutional Review Board
WHO	World Health Organization
YF	yellow fever

PROTOCOL SUMMARY

Title:	Immunogenicity and safety of concurrent administration of live, attenuated SA 14-14-2 Japanese encephalitis vaccine and measles-mumps-rubella vaccine in infants 9-12 months of age in the Philippines
Study Code:	JEV06
Phase:	Phase 4, randomized open label
Population:	628 healthy Filipino children aged 9 months at enrollment
Study Site:	Putatan Health Center and Bayanan Health Center located within the study area of the Research Institute for Tropical Medicine, Manila, Philippines
Study Duration:	7 to 8 months, dependent upon enrollment
Participant Duration:	4 months
Agent Description:	JE vaccine (CD-JEV): single 0.5 mL dose of World Health Organization (WHO) prequalified live, attenuated SA 14-14-2 JE vaccine manufactured by Chengdu Institute of Biological Products, Chengdu, China, administered by subcutaneous injection. Measles-mumps-rubella (MMR) vaccine: single 0.5 mL dose of live, attenuated measles-mumps-rubella vaccine (Schwarz measles virus, RIT 4385 mumps strain, and Wistar RA 27/3 rubella virus) manufactured by GlaxoSmithKline, Inc., administered by subcutaneous injection.
Study Rationale:	This non-inferiority study aims to provide evidence that co-administration of MMR and CD-JEV does not adversely affect safety or immunogenicity. With the use of MMR increasing, this study will provide critical data for policy makers considering the use of MMR and/or CD-JEV.
Objectives and Outcome Measures:	<u>Primary Objectives and Outcome Measures:</u> 1. To demonstrate the non-inferiority of MMR vaccination in terms of measles immunogenicity when administered concomitantly to infants 9 months of age with CD-JEV compared to administration alone, as assessed by the rate of seropositivity 56 days after vaccination. Measles immunogenicity will be assessed by the proportion (or percentage) of participants with demonstrated seropositivity for measles at 56 days post-vaccination. Seropositivity will be defined by a concentration of ≥120 mIU/mL of anti-measles neutralizing antibody titer, as measured by the plaque reduction neutralization test (PRNT) (dilution converted to concentration using the 3rd International Standard Reference serum). 2. To demonstrate the non-inferiority of MMR vaccination in terms of rubella immunogenicity when administered to infants 9 months of age concomitantly with CD-JEV compared to administration alone, as assessed by the rate of seropositivity 56 days after vaccination. Rubella immunogenicity will be assessed by the proportion (or percentage) of participants with demonstrated seropositivity for rubella at 56 days post-vaccination Seropositivity will be defined as anti-rubella Immunoglobulin G (IgG) concentration of ≥10 IU/mL (corresponding to an optical density ratio ≥1.10) using a commercial

IgG enzyme-linked immunosorbent assay (ELISA) manufactured by Wampole Laboratories, Princeton, NJ.

Secondary Objectives and Outcome Measures:

1. To demonstrate the non-inferiority of MMR vaccination in terms of mumps immunogenicity when administered to infants 9 months of age concomitantly with CD-JEV compared to administration alone, as assessed by the rate of seropositivity 56 days after vaccination.

   Mumps immunogenicity will be assessed by the proportion (or percentage) of participants with demonstrated seropositivity for mumps at 56 days post-vaccination. Seropositivity will be defined as an optical density ratio ≥1.10 using a commercial ELISA manufactured by Zeus Scientific, Inc., Branchburg, NJ.

2. To evaluate serum anti-measles geometric mean neutralizing antibody concentration (GMC) and anti-rubella IgG GMC at 56 days post-vaccination, comparing when MMR vaccine is co-administered with CD-JEV to when MMR vaccine is given alone.

3. To evaluate anti-measles, anti-mumps, and anti-rubella seroconversion rates 56 days after MMR vaccination, comparing when MMR vaccine is co-administered with CD-JEV to when MMR vaccine is given alone. For participants seronegative at baseline, seroconversion will be defined as a change to seropositive status (as defined above). For those participants seropositive for measles or rubella at baseline, seroconversion will be defined as a four-fold rise in concentration.

4. To compare the anti-JE seropositivity rate 28 days after CD-JEV vaccination administered concurrently with MMR vaccine to CD-JEV administered alone. Anti-JE seropositivity will be defined as an anti-JE serum neutralizing antibody titer of ≥1:10, as measured by JE PRNT-50.

5. To describe anti-JE neutralizing antibody geometric mean titers (GMTs) 28 days after CD-JEV vaccination when MMR vaccine is co-administered, compared to when CD-JEV is administered alone.

6. To describe the safety profiles of CD-JEV and MMR vaccine when given concurrently and separately, as assessed by immediate reactions occurring within 30 minutes, solicited injection site and systemic adverse reactions occurring within 14 days, unsolicited adverse events (AEs) occurring within 28 days, and serious adverse events (SAEs) occurring throughout the study. Outcome measures for safety include:

   a. Frequency counts and percentage of participants reporting immediate reactions occurring within 30 minutes of each vaccination.
   b. Frequency counts and percentage of participants reporting solicited local and systemic AEs occurring within 14 days of each vaccination.
   c. Frequency counts and percentage of participants reporting unsolicited AEs occurring within 28 days of each vaccination.
   d. Frequency counts and percentage of participants reporting SAEs occurring throughout the study.

Exploratory Objective and Outcome Measure:

1. To assess the effect of pre-existing anti-dengue antibody on CD-JEV immunogenicity 28 days following immunization. Pre-existing anti-dengue antibody will be measured first by the presence of anti-dengue IgG in ELISA and secondly by anti-dengue serotype 1-, 2-, 3-, and 4-specific serum neutralizing antibody titer of ≥1:10 as measured by dengue PRNT-50.

Study Design:

This study will be a phase 4 open-label trial in which 628 Philippine infants 9 months of age will be randomized 1:1 to one of two arms:

- Group 1: 314 children receiving one dose of CD-JEV vaccine and one dose of MMR vaccine concurrently at Day 0; Group 1 will also receive a second dose of MMR per the routine immunization schedule at D84 (12 months of age).
- Group 2: 314 children receiving one dose of MMR vaccine at Day 0 and one dose of CD-JEV 56 days later. Group 2 will receive a second dose of MMR per the routine immunization schedule at D84 (12 months of age).

Following receipt of study vaccine(s), infants will be monitored for immediate reactions during the first 30 minutes, solicited injection site and systemic adverse reactions for 14 days, unsolicited adverse events for 28 days, and serious adverse events throughout the duration of the study. All safety events will be identified or observed by study staff and/or reported by a parent. Solicited adverse reactions will be recorded by the parent on diary cards or assessed during clinic visits. Study staff will make a follow-up call to the participant's parent 2(+3) days following vaccination to check on the welfare of the participant and ensure the diary card is being completed. The parent will return with the participant for a clinic visit 14(+3) days following vaccination for the study staff to review the diary card, conduct safety evaluations, and review any adverse events. Information regarding unsolicited AEs will be collected during any scheduled or unscheduled clinic visit. Events will be graded for severity and assessed for relatedness to vaccination by the study clinician.

The study will be open-label; no placebo control will be employed. Due to the unequal number of injections per visit in each study arm, safety assessments will be unblinded.

Blood samples for serologic testing will be collected on Day 0, Day 28(+7), and Day 56(+7) for Group 1; and Day 0, Day 56(+7), and Day 84(+7) for Group 2.

Baseline serologies will test for antibodies to JE, measles, mumps, rubella, and dengue virus. Antibody responses to CD-JEV will be tested 28 days after vaccination, while antibody responses to the first dose of MMR will be tested 56 days after vaccination. All laboratory testing will be conducted in a blinded fashion.

Enrollment:

3 to 4 months

Study Population:

Inclusion Criteria:

Each participant receiving study vaccines must satisfy all of the following inclusion criteria at study entry:

- Age 9 months to <10 months at the time of enrollment.
- Residence in the study area.
- At least one parent or guardian willing to provide written informed consent.

- Generally healthy and free of obvious health problems as established by medical history, physical examination, and clinical judgment.
- A parent or guardian is willing to attend all planned study visits and allow home visits and phone contacts, as required by the protocol.

Exclusion Criteria:

No participant may have any of the following exclusion criteria at study entry:

- Previous receipt of any measles-mumps-rubella containing vaccine.
- Previous receipt of any Japanese encephalitis vaccine.
- History of measles, mumps, rubella, or Japanese encephalitis infection.
- Administration of any other vaccine within 28 days prior to administration of a study vaccine or planned vaccination of any vaccine other than catch-up doses of routine EPI vaccines or oral polio vaccine during the 28 days after study vaccination.
- History of allergic disease or known hypersensitivity to any component of the study vaccines and/or following administration of vaccines included in the local program of immunization.
- Use of any investigational or non-registered drug within 90 days prior to the administration of study vaccines or planned administration during the study period.
- Administration of immunoglobulins and/or any blood products within 90 days prior to the administration of study vaccines or planned administration during the study period.
- Chronic administration (defined as >7 days) of immunosuppressing or other immune-modifying agents within 14 days before or after vaccination (including systemic corticosteroids equivalent to prednisone ≥0.5 mg/kg/day; topical and inhaled steroids are allowed).
- Primary or acquired immunodeficiency, including HIV infection, or a family history of congenital or hereditary immunodeficiency as reported by parent.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by medical history or physical examination, which might interfere with the study objectives.
- Severely malnourished infants as measured by World Health Organization weight-for-height tables (Z-score < -3).
- Any condition or criterion that, in the opinion of the study physician, might compromise the well-being of the participant, compliance with study procedures, or interpretation of the outcomes of the study.
- Acute illness at the time of enrollment defined as the presence of a moderate or severe illness with fever (axillary temperature ≥38.0°C) or without fever (severity determined at the discretion of the study physician).

  Acute illness is a temporary exclusion. Vaccination should be postponed at least 7 days after recovery. A visit for reassessment may be scheduled 7 days or more after temporary exclusion illness is resolved. Eligibility for study participation must be reassessed again at the next visit.

Statistical Analysis: Populations for Analysis

Intent-to-Treat Analysis Set (ITT): all participants who received a study vaccine. Participants in the ITT analysis set who have at least one post-vaccination serology result will be included in the immunogenicity analysis.

Safety Analysis Set (SAS): all participants who received a study vaccine and have at least one safety measure post-vaccination. Participants in SAS will be analyzed based on the actual vaccine received rather than the group to which they have been randomized.

Measles Per-Protocol Analysis Set (measles-PP): all participants who met eligibility criteria; received all study vaccines as planned within the specified time intervals; provided valid pre- and post-vaccination serum specimens for measles within the specified time intervals; did not receive restricted medications within 28 days post vaccination; and did not show seropositivity for measles at baseline.

Mumps Per-Protocol Analysis Set (mumps-PP): all participants who met eligibility criteria; received all study vaccines as planned within the specified time intervals; provided valid pre- and post-vaccination serum specimens for mumps within the specified time intervals; did not receive restricted medications within 28 days post vaccination; and did not show seropositivity for mumps at baseline.

Rubella Per-Protocol Analysis Set (rubella-PP): all participants who met eligibility criteria; received all study vaccines as planned within the specified time intervals; provided valid pre- and post-vaccination serum specimens for rubella within the specified time intervals; did not receive restricted medications within 28 days post vaccination; and did not show seropositivity for rubella at baseline.

JE Per-Protocol Analysis Set (JE-PP): all participants who met eligibility criteria; received all study vaccines as planned within the specified time intervals; provided valid pre- and post-vaccination serum specimens for JE within the specified time intervals; did not receive restricted medications within 28 days post vaccination; and did not show seropositivity for JE at baseline.

Safety analyses will be conducted on the ITT data set. Safety analyses will also be conducted on the SAS in the event participants received vaccine(s) to which they were not randomized. Immunogenicity analyses will be based on the ITT (with at least one post-vaccination serology result), measles-PP, mumps-PP, rubella-PP, and JE-PP.

Primary Analyses:

For each endpoint, non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI in the difference of the seropositivity rates between the two groups (concurrent administration minus separate administration) 56 days after vaccination is >-10%. The 95% CI will be calculated using the Farrington-Manning score method.[1]

Secondary Analyses:

1. Non-inferiority for mumps will be demonstrated if the lower limit of the two-sided 95% CI in the difference of the seropositivity rates between the two groups (concurrent administration minus separate administration) 56 days after vaccination is >-10%. The 95% CI will be calculated using the Farrington-Manning method.

2. The ratio of anti-measles and anti-rubella GMCs between both treatment groups with 95% CI obtained 56 days after vaccination (ratio of concurrent administration to separate administration) will be calculated using parametric models after log transformation of the concentrations and titers, where applicable.
3. The difference with 95% CI between the anti-measles, anti-mumps, and anti-rubella seroconversion rates 56 days after vaccination for the two groups (concurrent administration minus separate administration) will be calculated using the Farrington-Manning method.
4. The difference with 95% CI between the anti-JE seropositivity rates 28 days after vaccination for the two groups (concurrent administration minus separate administration) will be calculated using the Farrington-Manning method.
5. The ratio of anti-JE GMTs between both treatment groups with 95% CI obtained 28 days after vaccination (ratio of concurrent administration to separate administration) will be calculated using parametric models after log transformation of the titers, where applicable.
6. Safety endpoints will be descriptively summarized in terms of frequency counts and percentages by treatment group and severity, where applicable. Frequency counts and percentages will be provided along with 95% CI, where applicable. The 95% CI will be calculated based on the Exact test.

Exploratory Analyses

Post-vaccination serologic responses will be analyzed for any association between the baseline anti-dengue response and anti-JE antibody response 28 days after vaccination with CD-JEV.

Sample Size and Power Estimation

Enrollment size of 628 participants (314 per treatment group) was targeted to achieve an overall power of 90% (approximate individual power of 95% for each co-primary objective). This estimation is based upon a non-inferiority margin of 10%, a one-sided significance level of 2.5%, and assumed (based on historical data) a 95% seropositivity rate for measles vaccine, a 90% seropositivity rate for rubella vaccine, and a 20% non-evaluable rate at 56 days post-vaccination. Individual sample size calculations were based on the Farrington-Manning score test.

Schematic of Study Activities

	Group 1										Group 2											
	On or before D0	D0	D2 (+3)	D14 (+3)	D28 (+7)	D56 (+7)	D84 (+7)	D86 (+3)	D98 (+3)	D112 (+7)	On or before D0	D0	D2 (+3)	D14 (+3)	D28 (+7)	D56 (+7)	D58 (+3)	D70 (+3)	D84 (+7)	D86 (+3)	D98 (+3)	D112 (+7)
Obtain informed consent	X										X											
Collect baseline demographic information		X										X										
Collect/review medical history		X										X										
Perform physical examination		X		X	X	X	X		X	X		X		X	X	X		X	X		X	X
Check/confirm inclusion/exclusion criteria		X										X										
Collect serum for serology testing		X			X	X						X				X			X			
Administer dose of MMR		X					X					X							X			
Administer dose of CD-JEV		X														X						
Observe for immediate reactions for 30 minutes		X					X					X				X			X			
Provide diary card to parent/guardian		X					X					X				X			X			
Call participant to inquire about child's well-being			X					X					X				X			X		
Collect diary card and review reported adverse events				X					X					X				X			X	
Record reported adverse events		X			X	X	X			X		X			X	X			X			X
Record reported serious adverse events		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Exit participant from study										X												X

Schedule of Serum Testing

	Group 1			Group 2		
	D0	D28	D56	D0	D56	D84
Anti-measles PRNT	X		X	X	X	
Anti-rubella ELISA	X		X	X	X	
Anti-mumps ELISA	X		X	X	X	
Anti-JE PRNT	X	X			X	X
Anti-dengue ELISA	X				X	
Anti-dengue PRNT (if indicated)	X				X	

1. KEY ROLES

Institutions:

Sponsor:
PATH
2201 Westlake Avenue, Suite 200
Seattle, WA 98121, USA
[redacted]

Research Institution:
Research Institute for Tropical Medicine
Filinvest Corporate City, Alabang, Muntinlupa City
1781 Metro Manila, Philippines
[redacted]

Vaccine Manufacturer:
Chengdu Institute of Biological Products
Baojiang Bridge
Chengdu, 610023, Sichuan Province, People's Republic of China
[redacted]

GlaxoSmithKline, Inc.
980 Great West Road,
Brentford Middlesex,TW8 9GS, United Kingdom
[redacted]

Monitoring and Pharmacovigilance:
[redacted]

Data Management:
[redacted]

Institutional Review Boards:
Western Institutional Review Board
1019 39th Avenue SE Suite 120
Puyallup, WA 98374-2115
[redacted]

Research Institute for Tropical Medicine
Institutional Review Board
Room 102 RITM Residence Hall
Filinvest Corporate City, Alabang Muntinlupa City
[redacted]

National Ethics Board:
Philippine Health Research Ethics Board
c/o Philippine Council for Health Research and Development
Department of Science and Technology
3/F DOST Administrative Bldg., Gen. Santos Ave., Bicutan, Taguig City

[redacted]

Individuals:

RITM Investigator:

[redacted]

RITM Clinical Operations:

[redacted]

Immunological Laboratory Testing:

[redacted]

PATH Project Director:

[redacted]

PATH Clinical Operations:

[redacted]

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

2.1.1. Measles Virus and Vaccination

Measles virus is an enveloped, single-stranded RNA virus affecting only humans.[2] The virus causes high fever, cough, maculopapular rash, coryza, and conjunctivitis. Complications from the disease include otitis media, laryngo-tracheobronchitis, diarrhea, pneumonia, and in very severe cases, death. Measles is highly infectious through aerosolized respiratory droplets and by direct contact; in the prevaccine period, >90% of individuals were infected by 10 years of age. Before the introduction of measles vaccines, measles virus caused an estimated five to eight million deaths per year.[3] Wide scale introduction of safe and effective measles vaccines has greatly reduced the burden of this disease—from 2000 through 2011, the number of deaths from measles dropped from an estimated 548,000 to 158,000 per year worldwide.[4]

The recommended age for measles immunization in developing countries with ongoing transmission in which the risk of measles mortality among infants remains high is 9 months of age.[5] In countries with low rates of measles transmission, the vaccine is recommended at 12 months of age to take advantage of the higher seroconversion rates achieved at this age. The proportion of children who develop protective antibody levels following measles immunization depends on the presence of inhibitory maternal antibodies and the immunologic maturity of the vaccine recipient. Approximately 85% of children develop protective antibody levels after one dose of measles at 9 months of age; this rate is much lower in children <9 months of age.[3] Thus, routine immunization for measles is not given in children below 9 months.

Since population immunity needs to be >90% in all districts to prevent measles epidemics, high immunization coverage is the cornerstone of effective measles control and the World Health Organization (WHO) now recommends two doses of measles vaccine for all children to ensure adequate immunity.[6] WHO also recommends that countries take the opportunity offered by accelerated measles control and elimination activities to introduce rubella-containing vaccines.[7]

2.1.2. Mumps Virus and Vaccination

Mumps is an enveloped single-stranded RNA virus transmitted by direct contact or through contact with respiratory droplets or saliva.[8] The virus causes respiratory problems with swelling of the salivary glands being the most common symptom. Early symptoms may include joint pain, lack of appetite, general discomfort, low grade fever, and vomiting. Mumps is typically a mild disease in children, but can cause more serious complications such as meningitis, encephalitis, and sensorineural deafness. With peaks every 2 to 5 years, the annual incidence ranges from 100 to 1,000 cases per 100,000 in non-immunized populations.[9] While mumps vaccine is available as monovalent or bivalent product, the trivalent measles, mumps, and rubella (MMR) formulation is the most widely used product.

2.1.3. Rubella Virus and Vaccination

Rubella is an enveloped single-stranded RNA virus.[10] Transmitted by the respiratory route, humans are the sole host of the virus. Rubella disease is a mild, self-limited illness that usually occurs during childhood. It may include a prodromal illness consisting of fever <39.0ºC, malaise, and mild conjunctivitis followed by postauricular, occipital, and posterior cervical lymphadenopathy and a maculopapular, erythematous and often pruritic rash. Post infectious encephalitis occurs in approximately 1/6000 rubella cases. Rubella

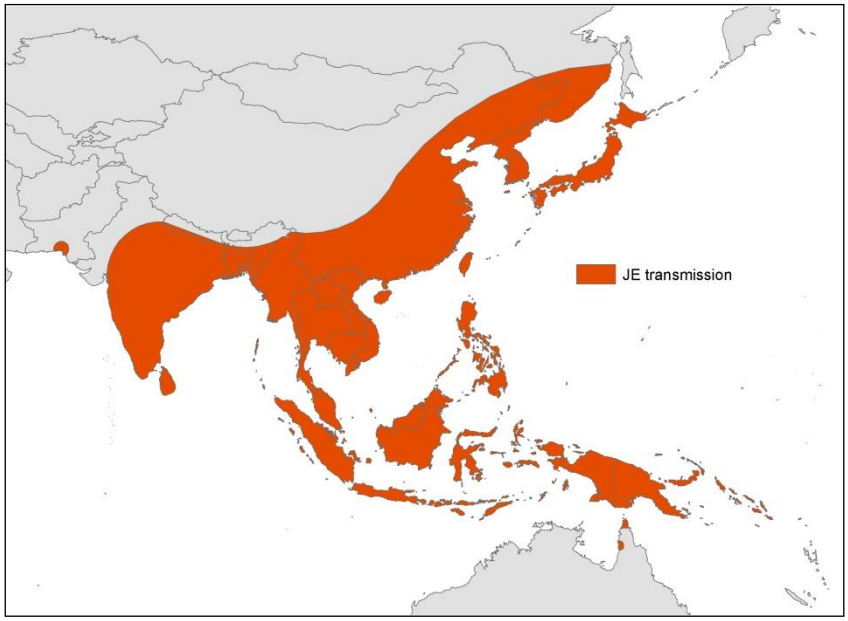
infection occurring just before conception and during early pregnancy may result in miscarriage, fetal death, or congenital defects (including congenital heart disease, cataracts, neurosensory deafness, mental retardation and intrauterine growth retardation) known as congenital rubella syndrome (CRS).[11,12] Rubella usually occurs in a seasonal pattern, with epidemics every 5-9 years.[13] In countries that have not introduced rubella vaccine, the burden of CRS may be high; in 1996 an estimated 46,000 children were born with CRS in South-East Asia.[14] High rubella vaccine coverage has significantly reduced or eliminated rubella and CRS in both developed and developing countries.[15]

Since rubella is not as highly infectious as measles and because the effectiveness of one dose of a rubella containing vaccine is ≥95% when given at 9 months of age, only one dose of rubella vaccine is required to achieve rubella elimination if high coverage is achieved. However, the WHO Strategic Advisory Group of Experts (SAGE) Working Group on Measles and Rubella recently clarified its position through the following recommendation: 1) rubella-containing vaccine should be given in combination with measles-containing vaccine (MCV) as measles-rubella (MR) or MMR and 2) in countries using rubella-containing vaccine in combination with MR or MMR, the same formulation should be used for both doses (either MR or MMR).[7]

2.1.4. Clinical Aspects of Japanese Encephalitis (JE)

With over three billion people living in 24 JE-endemic countries, Japanese encephalitis is the leading cause of viral neurological disease and disability in Asia (Figure 1).[16-19] Children less than 15 years of age are at higher risk of JE than adults in most areas. More than 99 percent of JE infections are subclinical, so in areas with endemic transmission, naturally acquired infection at an early age results in immunity of greater than 80 percent of young adults.[20] However, clinical cases of JE can be very severe; some 70 percent of children with clinical JE either die or have severe, long-term neurologic mental and physical disability. Nearly 70,000 cases are reported annually and cause approximately 10,000 to 15,000 deaths, but because of limited surveillance and complexities in diagnosis, this is probably a substantial underestimate.[21]

Figure 1. Regions reported to have transmission of JE virus



Source: Adapted from Halstead S, Tsai T. Japanese Encephalitis. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th edition. London, UK: W.B. Saunders Company; 2003:919–958.

2.1.5. Epidemiological Profile of JE

JE virus circulates in zoönotic cycles involving mosquitoes and several vertebrate species. Pigs and birds serve as amplifying and reservoir hosts, respectively, and are usually unaffected by infection.[22-24] Pigs develop high viral loads after infection and can be key hosts for outbreaks by rapidly increasing the number of infectious mosquitoes in the environment through viral amplification. However, well-characterized outbreaks in regions without pigs are also recorded in the literature.[25] In such cases, birds are thought to amplify the virus and result in human infections.[26,27] JE virus cannot be transmitted person-to-person nor person-to-mosquito-to-person because the low-level viremia in humans cannot infect mosquitoes or contribute to the transmission cycle.

JE is transmitted to humans by the bite of several mosquito species. The major mosquito vector of JE varies from region to region. *Culex tritaeniorhynchus* is the principal JE vector in Southeast Asia. Other ground pool and rice paddy breeding species, including *C. vishnui*, *C. pseudovisnuri*, *C. gelidus*, *C. fuscocephala*, *C. bitaeniorhynchus*, *C. infula*, *C. whitmorei*, and *C. annulus*, are also important.[23,24]

2.1.6. Live, Attenuated SA 14-14-2 JE Vaccine

Because of its zoönotic cycle, eradicating JE virus from the environment is unrealistic. Therefore, vaccination is the only way to protect children in JE-endemic countries from disease. For widespread use in developing countries, interest is focused on the WHO prequalified live, attenuated SA 14-14-2 JE vaccine (hereafter referred to as CD-JEV), which is manufactured in China by the Chengdu Institute of Biological Products (CDIBP). CD-JEV is safe, effective, and the most affordable vaccine available that could be incorporated into routine immunization programs in endemic countries.

CD-JEV has been used since 1988, with over 400 million doses administered in China and internationally. The vaccine is currently licensed in twelve countries, and, in 2013, vaccine produced at a new Good Manufacturing Practice-compliant production facility was prequalified by WHO. CD-JEV was also selected by UNICEF for use in 2015 Gavi-supported catch-up campaigns in children less than 15 years old.

Like other parenterally administered vaccines, immunization with CD-JEV vaccine may cause local and systematic side effects in some children. These include pain at the injection site for a short while after injection and swelling, redness, and tenderness at the injection site. Fever may occur and, in some cases, a rash may appear in the initial days following the vaccination. Because CD-JEV is a live-attenuated vaccine, there is a theoretical risk that systemic disease including encephalitis could occur if the vaccine strain replicates unchecked or if the vaccine strain reverts to neurovirulence. To date, only one case of encephalitis has been reported related to CD-JEV vaccination.[28] No reports of severe allergic reactions or death have been associated with CD-JEV.

In 2005 and 2006, WHO Global Advisory Committee on Vaccine Safety and the WHO SAGE on Immunization reviewed the safety of CD-JEV and other JE vaccines.[7,29-31] These reviews stated that CD-JEV is well-tolerated across a wide age range and can safely be given to children as young as 8 months of age. No serious adverse events (SAEs) were attributed to CD-JEV in 12 clinical studies conducted from 1992 through 2008 in China, India, the Philippines, South Korea, Sri Lanka, and Thailand.[32-44] In 2013, the WHO Global Advisory Committee on Vaccine Safety reviewed the safety of CD-JEV again and concluded that it had an excellent safety profile.[45]

Seroprotection rates following a single dose of CD-JEV (≥ $10^{5.4}$ plaque-forming units) have been greater than 90% in most clinical trials. Several early Chinese studies have shown a dose-response gradient with 85% to 100% seroconversion after a single dose of CD-JEV vaccine was given to children 1 to 12 years of age.[32,35,36,41-43] In one of the first immunogenicity studies performed outside of China, 95% of participants aged 9 to 15 months were seroprotected within 90 days after CD-JEV vaccination. A Korean study of 68 children 1 to 3 years of age showed high seroconversion rates of 96% four weeks after one dose of CD-JEV.[38] Another long term study in Korea demonstrated that 90% of the study participants had a high level of neutralizing antibody four years after vaccination with a geometric mean titer (GMT) of 133 (range: 11-2991).[46]

PATH, in partnership with CDIBP and others, has conducted Phase IIIb clinical trials evaluating the safety and immunogenicity of CD-JEV when co-administered with measles vaccine in healthy infants in the Philippines.[33,39] These studies demonstrated the long-term immunogenicity and safety of

CD-JEV in infants as young as 8 months, continued seroprotection after three years in more than 80% of participants, and an acceptable safety profile.

Data from this trial showed that in one month following vaccine receipt, levels of neutralizing anti-JE antibody and anti-measles immunoglobulin G (IgG) in infants given CD-JEV and measles vaccine concurrently at 9 months of age were statistically non-inferior to levels in infants given the two vaccines separated by a month (Table 2).[33,39]

Table 2. Seropositivity rates and anti-measles IgG geometric mean concentrations and anti-JE geometric mean titers in Philippine infants vaccinated with JE and measles vaccines.

		Group 1 (CD-JEV then MV) (N=88)		Group 2 (concomitant) (N=219)		Group 3 (MV then CD-JEV) (N=178)	
		% seropositive (95% CI)	GMC/GMT (95% CI)	% seropositive (95% CI)	GMC/GMT (95% CI)	% seropositive (95% CI)	GMC/GMT (95% CI)
Measles vaccine response (anti-measles IgG)	Day 0	1.1 (0.0-6.2)	12.8[a] (10.2-16.2)	0.0 (0.0-1.7)	7.4 (6.3-8.8)	0.0 (0.0-2.1)	7.0 (5.8-8.5)
	Day 28	88.6 (80.1-94.4)	318.9 (273.0-372.6)	91.8 (87.3-95.1)	301.9 (269.0-338.9)	86.5 (80.6-91.2)	262.5 (222.2-310.2)
JE vaccine response (anti-JE neutralizing ant body)	Day 0	3.4 (0.7-9.6)	5.7 (4.9-6.5)	5.4 (2.8-9.3)	5.7 (5.2-6.1)	6.1 (3.1-10.7)	5.9 (5.3-6.6)
	Day 28	92.1 (84.3-96.7)	202.8 (140.5-292.9)	90.5 (85.9-94.1)	155.0 (123.5-194.5)	90.6 (85.3-94.4)	139.4 (109.5-177.5)
	Year 1	90.2 (82.2-95.4)	106.8 (71.5-159.4)	84.0 (78.3-88.6)	80.7 (62.4-104.3)	85.9 (80.5-90.3)	74.9 (59.2-94.9)
	Year 2	81.7 (72.4-89.0)	68.8 (47.3-100.1)	83.0 (77.3-87.8)	61.6 (49.1-77.4)	81.7 (75.8-86.6)	70.1 (54.6-90.1)
	Year 3	79.6 (70.0-87.2)	49.9 (36.5-68.3)	81.9 (75.9-86.8)	45.7 (37.2-56.3)	82.6 (76.8-87.4)	59.3 (47.1-74.8)

CD-JEV: live, attenuated Japanese encephalitis SA 14-14-2 vaccine; MV: measles vaccine; N: number of infants in the per protocol analysis; CI: confidence interval; GMC: milli International Units per milliliter (mIU/mL), seroprotection defined as ≥120 mIU/mL; GMT: geometric mean titer, seroprotection defined as ≥1:10.

[a] Although measles GMC/GMT at baseline were higher in Group 1, the GMC/GMT 28 days after vaccination were not significantly different.

Seroresponse rates to CD-JEV may not be equal in all pediatric populations. A lot-to-lot consistency study conducted in 2012 among 10-month-old Bangladeshi infants in a rural area with a low incidence of JE demonstrated a seropositivity rate of only 82.3% (95% CI 79.0-85.2%) following a single vaccine dose.[47] The reasons for this lower response rate are unclear, but may be related to the high rates of malnutrition found in the population or other population-specific causes. Nevertheless, these findings highlight the value of assessing the performance of the vaccine in other high-risk populations.

In addition to the high seroprotection rates, CD-JEV is the only vaccine other than mouse-brain derived vaccine for which there is vaccine effectiveness data. A post-implementation case-control study from Nepal demonstrated an efficacy of 99.3% (95% CI 94.9–100) following administration of a single dose of live, attenuated SA 14-14-2 JE vaccine given within one week of an outbreak.[48] A follow-up case-control study reported that a protective efficacy rate of 96.2% (95% CI 73.1-99.9) was maintained five years later.[49] CD-JEV vaccine has demonstrated high seroconversion rates after one or two doses in endemic areas of Nepal.[48,50]

2.1.7. JE Disease in the Philippines

While JE virus in the Philippines was isolated in horses in 1943, the first serologically confirmed case was not identified until 1956.[51] In serological surveys that followed, anti-JE neutralization antibodies were found in 3% to 83% of children aged 6 months to 15 years living in three varied Philippine locations—an indication of widespread but variable JE transmission.[52] Subsequent studies on clinical

cases from 1969 to 2006 suggest JE may account for 7% to 40% of all acute encephalitis syndrome (AES) cases.[53]

In 2008, the Philippine Integrated Disease Surveillance and Response system began collecting data on all AES cases and in 2011 added sentinel surveillance for lab-confirmed JE. To understand the public health impact of JE disease, the Philippines Department of Health used the surveillance and response system to identify 1,032 AES cases from January 2011 through March 2013. Of 497 AES cases that underwent laboratory testing, 73 (15%) were positive for JE—of those positive, 55 (75%) were children under 15 years of age.[54]

With AES and laboratory-confirmed JE cases reported from 84% of the provinces, JE disease in the Philippines is likely widespread.[55] Recognizing the public health burden caused by JE, the Philippines Department of Health has planned the introduction of JE vaccination into the national immunization program in 2017.

2.2. Scientific Rationale

When incorporating a new vaccine in the Expanded Programme on Immunization (EPI), it is important to provide evidence that it can be introduced concurrently with other routine pediatric vaccines without significantly impairing the immune response to any vaccine while maximizing coverage and minimizing cost. Based on the youngest age range evaluated in clinical development and to avoid the potential presence of maternal antibodies, the most logical time to administer CD-JEV is 9 to 12 months of age when MCVs are typically given in Asia. An increasing number of JE-endemic countries are introducing, or planning to introduce, MMR vaccine into the EPI. The UNICEF Supply Division expects demand for MMR to continue to increase in the long term. In 2014 demand for MMR reached 12.8 million doses, an increase of 100% above the previous year.[56,57] Currently, measles vaccine is routinely offered at 9 months and MMR at 12 months in the Philippines. Like many countries, however, the Philippines Department of Health is considering moving to a two-dose MMR schedule by immunizing children with MMR at 9 and 12 months.

Although PATH-sponsored studies confirmed CD-JEV and measles vaccine could be administered concomitantly, no data currently exist on the simultaneous administration of CD-JEV and MMR vaccine. There is precedent in the yellow fever (YF) literature that suggests such a study is important. While several studies indicate that YF and measles vaccine can be simultaneously administered without any effects on safety and immunogenicity, a single study of simultaneous administration of YF and MMR vaccines in infants suggests that immunogenicity may be compromised for both YF vaccine and the rubella and mumps components of MMR vaccine.[58] Separating MMR and YF vaccine administration by 30 days mitigated the effect. These findings may have relevance for incorporating JE vaccine into routine immunization, as CD-JEV and YF vaccine are both live, attenuated flavivirus vaccines.

This non-inferiority study aims to compare JE and MMR responses in a population of children in a country where MMR introduction is ongoing or planned. The proposed study design will be similar to that of previous PATH-sponsored co-administration CD-JEV trials.[33,39] In addition, this information will help the Philippines Department of Health evaluate the addition of a second dose of MMR vaccine into routine EPI.

The two-arm study has the advantage of allowing an evaluation of the non-inferiority of co-administration on the immune responses. Serum will be obtained at an optimal time to measure immunogenicity—28 days post-CD-JEV immunization to estimate anti-JE seropositivity rates and GMTs and 56 days post-

MMR vaccination to estimate anti-MMR seropositivity rates and geometric mean concentrations (GMCs).[3,8,59,60] The primary outcome will be the non-inferiority of both measles and rubella seropositivity rates in the group given CD-JEV and MMR together versus that in the group given MMR alone (prior to receipt of CD-JEV). Such a study will require approximately 314 participants per primary comparison arm to provide at least 90 percent power to rule out a difference in seropositivity rates between groups of greater than 10 percent, depending on assumptions of seropositivity and retention rates.

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

Like any vaccine, vaccination with MMR and CD-JEV may cause side effects in some children. The side effects of vaccination may include pain at the injection site for a short while after injection and swelling, redness, and tenderness at the injection site. Fever may occur and in some cases a rash may appear in the initial days following the vaccination. Allergic reactions, febrile convulsions, encephalitis, and death, while rare, may also occur.

The child may experience discomfort and pain from venipuncture for collection of 3-5 mL of blood. Venipuncture is sometimes associated with discomfort during phlebotomy, and rarely, an infection at the site of phlebotomy if improperly conducted. The child may experience discomfort, pain, redness, swelling, and/or local hardness at the injection site.

A study clinician will be on-site during immunizations and will be available for any immediate and/or emergency care that may be needed. Research Institute for Tropical Medicine (RITM) is equipped to handle immediate care that may be needed in the case of an emergency following vaccination.

Should any adverse events occur due to the study procedures, the investigator or a designee will be available to be reached 24 hours a day, via phone, by the participants. The investigator will be responsible for providing any treatment caused by procedures undertaken as part of the research study. If care is needed, parents will be sent to the clinic nearest them for care. If urgent care is needed, participants will be asked to visit RITM which is open 24 hours a day. The study will pay for any costs incurred for any unwanted reaction or other health problem resulting from participation in this clinical study.

Participant personal identifiers, including name, birth date, and contact information (home address, phone number/email address) will be collected and recorded on enrollment logs; as a result, a potential risk for “loss of confidentiality” exists. To reduce this risk, participants will be assigned a unique study participant number that will be used to identify the participant and link an individual to his/her study data. The study participant number will be used on all study forms and in the study computer databases. Individual participants will not be identified in any study related reports, and all study results will be reported in aggregate only.

2.3.2. Known Potential Benefits

Although under consideration by the Philippines Department of Health, two doses of MMR vaccine are not routinely offered as part of the national immunization program. Likewise, JE vaccine has not been introduced into the national immunization program. By participating in this study, participants will benefit by receiving one dose of CD-JEV and two doses of MMR. Receipt of these vaccines may protect the participants against JE, measles, mumps, and rubella. The study clinician will check whether children have received all of their immunizations and counsel the parents on the importance of receiving all EPI

vaccines at the appropriate ages. They will also provide information to the parents on the EPI vaccination schedule.

By participating in this study, the child and consenting parent will contribute greatly needed safety and immunogenicity information regarding the co-administration of these two vaccines. They will be significantly contributing to the advancement of a WHO-prequalified JE vaccine that if proven to be safe and efficacious given in conjunction with MMR vaccine, will be affordable and easily incorporated into routine EPI programs. By participating in this clinical trial they will help build the body of knowledge on CD-JEV and help ministries of health decide the best schedule for introducing CD-JEV to reduce and ultimately eliminate JE disease throughout Asia and the Western Pacific.

3. OBJECTIVES

3.1. Study Objectives

3.1.1. Primary Objectives

1. To demonstrate the non-inferiority of MMR vaccination in terms of measles immunogenicity when administered concomitantly to infants 9 months of age with CD-JEV compared to administered alone, as assessed by the rate of seropositivity 56 days after vaccination.

   Measles vaccine immunogenicity will be evaluated by anti-measles neutralizing antibody titer. Seropositivity will be defined by a concentration of ≥120 mIU/mL, as measured by PRNT (dilution converted to concentration using the 3rd International Standard Reference serum).

2. To demonstrate the non-inferiority of MMR vaccination in terms of rubella immunogenicity when administered to infants 9 months of age concomitantly with CD-JEV compared to administered alone, as assessed by the rate of seropositivity 56 days after vaccination.

   Rubella vaccine immunogenicity will be evaluated by presence of serum anti-rubella IgG antibody. Seropositivity will be defined as a concentration of ≥10 IU/mL corresponding to an optical density (OD) ratio ≥1.10 using a commercial IgG enzyme-linked immunosorbent assay (ELISA) manufactured by Wampole Laboratories, Princeton, NJ.

3.1.2. Secondary Objectives

1. To demonstrate the non-inferiority of MMR vaccination in terms of mumps immunogenicity when administered to infants 9 months of age concomitantly with CD-JEV compared to administered alone, as assessed by the rate of seropositivity 56 days after vaccination.

   Mumps vaccine immunogenicity will be evaluated by the presence of serum anti-mumps IgG antibody. Seropositivity will be defined as an OD ratio ≥1.10 using a commercial ELISA manufactured by Zeus Scientific, Inc., Branchburg, NJ

2. To evaluate serum anti-measles geometric mean neutralizing antibody concentration (GMC) and anti-rubella IgG GMC at 56 days post-vaccination, comparing when MMR vaccine is co-administered with CD-JEV to when MMR vaccine is given alone.

3. To evaluate anti-measles, anti-mumps, and anti-rubella seroconversion rates 56 days after vaccination, comparing when MMR vaccine is co-administered with CD-JEV to when MMR vaccine is given alone. For participants seronegative at baseline, seroconversion will be defined as a change

to seropositive status (as defined above). For participants seropositive for measles or rubella at baseline, seroconversion will be defined as a four-fold rise in concentration.

4. To compare the anti-JE seropositivity rate 28 days after CD-JEV vaccination administered concurrently with MMR vaccine to CD-JEV administered alone. Anti-JE seropositivity will be defined as an anti-JE serum neutralizing antibody titer of ≥1:10, as measured by JE PRNT-50.

5. To describe anti-JE neutralizing antibody GMTs 28 days after CD-JEV vaccination when MMR vaccine is co-administered compared to when CD-JEV is administered alone.

6. To describe the safety profiles of CD-JEV and MMR vaccine when given concurrently and separately, as assessed by immediate reactions occurring within 30 minutes, solicited injection site and systemic adverse reactions occurring within 14 days, unsolicited adverse events (AEs) occurring within 28 days, and SAEs throughout the course of the study.

3.1.3. Exploratory Objectives

1. To assess the effect of pre-existing anti-dengue antibody on CD-JEV immunogenicity. Pre-existing anti-dengue antibody will be measured first by the presence of anti-dengue IgG in ELISA and secondly by anti-dengue serum neutralizing antibody titer of ≥1:10 as measured by dengue PRNT-50.

3.2. Study Outcome Measures

3.2.1. Primary Outcome Measures

1. Measles immunogenicity will be assessed by the proportion (or percentage) of participants with demonstrated seropositivity for MMR at 56 days post-vaccination. Seropositivity will be defined as a post-vaccination concentration of ≥120mIU/mL, as measured by PRNT (using the 3rd International Standard Reference serum to convert dilutions to concentrations).

2. Rubella immunogenicity will be assessed by the proportion (or percentage) of participants with demonstrated seropositivity for rubella at 56 days post-vaccination. Seropositivity will be defined as a post-vaccination concentration of ≥10 IU/mL (corresponding to an OD ratio ≥1.10 using a commercial ELISA manufactured by Wampole Laboratories, Princeton, NJ.

For each endpoint, non-inferiority will be demonstrated if the lower limit of the two-sided 95% CI of the difference of the seropositivity rates between the two groups (concurrent administration and separate administration) 56 days after vaccination is >-10%.

3.2.2. Secondary Outcome Measures

1. Mumps immunogenicity will be assessed by the proportion (or percentage) of participants with demonstrated seropositivity for mumps at 56 days post-vaccination. Seropositivity will be defined as an OD ratio ≥1.10 using a commercial ELISA manufactured by Zeus Scientific, Inc, Branchburg, NJ.
2. Measles and rubella antibody levels will be assessed by the GMC of serum measles neutralizing antibody and the GMC of serum anti-rubella IgG antibody.
3. Measles, mumps, and rubella seroconversion rates will be defined as the proportions of participants with a change in serostatus from negative to positive 56 days after vaccination or a four-fold rise in concentration 56 days after vaccination if seropositive for measles or rubella at baseline.

4. JE immunogenicity will be assessed by the proportion of participants with demonstrated seropositivity for JE at 28 days post vaccination with CD-JEV. Seropositivity will be defined as a JE serum neutralizing antibody titer of ≥1:10 as measured by JE PRNT-50.
5. JE antibody levels will be assessed by the GMT of serum neutralizing antibody to JE virus at 28 days post vaccination with CD-JEV.
6. Study vaccine safety profiles will be assessed by the proportion of participants experiencing specific adverse events categorized into one of the following categories:
    a. Immediate reactions occurring within 30 minutes of each vaccination, measured as observed by study staff or reported by the parent to study staff.
    b. Solicited signs and symptoms occurring within 14 days of each vaccination, measured as observed by parent on diary card or reported to study staff.
    c. All other adverse events occurring within 28 days of each vaccination, measured as observed by study staff or reported by the parent to study staff.
    d. All SAEs occurring throughout the course of the study.

4. STUDY DESIGN

This study will be a phase 4 open-label trial in which 628 Philippine infants 9 months of age will be randomized 1:1 to one of two arms:

- Group 1: 314 children receiving one dose of CD-JEV vaccine and one dose of MMR vaccine concurrently at enrollment; Group 1 will also receive a second dose of MMR per the routine immunization schedule at D84 (12 months of age).

- Group 2: 314 children receiving one dose of MMR vaccine at enrollment and one dose of CD-JEV 56 days later. Group 2 will receive a second dose of MMR per the routine immunization schedule at D84 (12 months of age).

Following receipt of study vaccine, infants will be monitored for immediate reactions during the first 30 minutes, solicited injection site and systemic adverse reactions for 14 days, unsolicited adverse events for 28 days, and serious adverse events throughout the duration of the study. All safety events will be identified or observed by study staff and/or reported by a parent. Solicited adverse reactions will be recorded by the parent on diary cards or assessed during clinic visits. Study staff will make a follow-up call to the participant's parent/guardian 2 days post vaccination (+3 days) to check on the welfare of the participant and ensure the diary card is being completed. The parent will return for a clinic visit 14 days post vaccination (+3 days) for the study staff to review the diary card, conduct safety evaluations, and review any adverse events. Information regarding unsolicited AEs will be collected during any scheduled or unscheduled clinic visit. Events will be graded for severity and assessed for relatedness to vaccination by the study clinician.

The study will be open-label; no placebo control will be employed. Due to the unequal number of injections per visit in each study arm, safety assessments will be unblinded.

Blood samples for serologic testing will be collected on Day 0, Day 28(+7), and Day 56(+7) for Group 1; and Day 0, Day 56(+7), Day 84(+7) for Group 2.

Baseline serologies will test for antibodies to JE, measles, mumps, rubella, and dengue virus. Antibody responses to CD-JEV will be tested 28(+7) days after vaccination, while antibody responses to the first dose of MMR will be tested 56(+7) days after vaccination. All laboratory testing will be conducted in a blinded fashion.

4.1. Study Site

The study will be conducted at RITM, Filinvest Corporate City, Alabang, Muntinlupa City, Philippines. Established to spearhead the planning and implementing of research programs for infectious and/or tropical diseases, RITM's core research facilities are equipped with ample technical support for the conduct of valid and reliable scientific investigations. With a 35-bed research hospital consisting of an intensive care unit, wards, and isolation room, the hospital provides care of patients needing tertiary management of infectious and/or tropical diseases. The research hospital has a clinical and a blood-banking laboratory.

Recruitment of study participants will be conducted at the Putatan Health Center and Bayanan Health Center, two barangay health centers located near RITM. A barangay is the smallest local government unit in the Philippines and is very similar to a village or town. Each barangay health center is headed by a physician and is supported by health workers composed of nurses, midwives, and dentists. RITM will provide medical care in collaboration with the participating clinics or through its medical facility free of cost. All the participants will be encouraged to seek care at the local clinic or RITM for any medical problems, whether minor illness or urgent care. Both health clinics are within 5 kilometers of RITM, which is equipped to handle any care that may be needed in the case of an emergency.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Participant Inclusion Criteria

Each participant receiving study vaccines must satisfy all of the following inclusion criteria at study entry:

- Age 9 months to <10 months at the time of enrollment.
- Residence in the study area.
- At least one parent or guardian willing to provide written informed consent.
- Generally healthy and free of obvious health problems as established by medical history, physical examination, and clinical judgment of the investigator.
- A parent or guardian is willing to attend all planned study visits and allow home visits and phone contacts, as required by the protocol.

5.2. Participant Exclusion Criteria

No participant receiving study vaccines may have any of the following exclusion criteria at study entry:

- Previous receipt of any measles-mumps-rubella containing vaccine.
- Previous receipt of any Japanese encephalitis vaccine.
- History of measles, mumps, rubella, or Japanese encephalitis infection.
- Administration of any other vaccine within 28 days prior to administration of a study vaccine or planned vaccination of any vaccine other than catch-up doses of routine EPI vaccines or oral polio vaccine during the 28 days after study vaccination.
- History of allergic disease or known hypersensitivity to any component of the study vaccines and/or following administration of vaccines included in the local program of immunization.
- Use of any investigational or non-registered drug within 90 days prior to the administration of

study vaccines or planned administration during the study period.

- Administration of immunoglobulins and/or any blood products within 90 days prior to the administration of study vaccines or planned administration during the study period.
- Chronic administration (defined as >7 days) of immunosuppressing or other immune-modifying agents for 14 days before or after vaccination (including systemic corticosteroids equivalent to prednisone ≥0.5 mg/kg/day; topical and inhaled steroids are allowed).
- Primary or acquired immunodeficiency, including HIV infection, or a family history of congenital or hereditary immunodeficiency as reported by parent.
- Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic, or renal functional abnormality, as determined by medical history or physical examination, which in the opinion of the study physician, might interfere with the study objectives.
- Severely malnourished infants as measured by the World Health Organization weight-for-height tables (Z-score < -3).
- Any condition or criterion that, in the opinion of the study physician, might compromise the well-being of the participant, compliance with study procedures, or interpretation of the outcomes of the study.
- Acute illness at the time of enrollment defined as the presence of a moderate or severe illness with fever (axillary temperature ≥38.0°C) or without fever (severity determined at the discretion of the study physician).

  Acute illness is a temporary exclusion. Vaccination should be postponed at least 7 days after recovery. A visit for reassessment may be scheduled 7 days or more after temporary exclusion illness is resolved. Eligibility for study participation must be reassessed again at the next visit

5.3. Treatment Assignment Procedures

5.3.1. Randomization Procedures

This is an unblinded, individually randomized study. Enrolled children will be randomized in a 1:1 ratio to one of two arms:

- Group 1: 314 children receiving one dose of CD-JEV vaccine and one dose of MMR vaccine concurrently at enrollment;
- Group 2: 314 children receiving one dose of MMR vaccine at enrollment and one dose of CD-JEV 56 days later.

A detailed randomization standard operating procedure (SOP) will be developed and executed prior to study initiation to generate the allocation sequence. The study will use a random permuted block design to assure as close to 1:1 group balance is maintained.

PATH will maintain all electronic documents generated as part of the randomization in a secure location not accessible to other study staff involved in the trial.

5.3.2. Allocation and Masking Procedures

A detailed allocation SOP will be developed in cooperation with the investigator. This allocation SOP will specify how enrolled participants must be allocated to study Group 1 (CD-JEV and MMR concurrently) or Group 2 (MMR alone and CD-JEV 56 days later).

Commercial presentations of MMR and CD-JEV will be used in this study. MMR will be procured from the Philippine distributor for MMR vaccine and CD-JEV will be donated by CDIBP. Since this is an open-label trial with licensed vaccines, parents of participants will know whether their child is in the experimental group receiving MMR and CD-JEV concurrently. While study vaccines will not be masked, they will be labeled for clinical trial use per section 6.1.4.

Laboratory staff performing serologic tests will remain masked to individual group assignments during the study period until database lock is performed. Study statisticians will be unmasked to study group identification for the purposes of performing statistical analyses.

5.3.3. Adherence to Randomization

The investigator or designee will document adherence to the allocation SOP. Additionally, specific study vaccines given to each individual participant will be documented.

5.3.4. Reasons for Withdrawal

After enrollment, a participant might be withdrawn from participation for several reasons:

- The investigator requests withdrawal of the participant because the child is not eligible or is no longer eligible, because he/she has developed an AE requiring withdrawal, or because the participant is non-compliant;
- A participant voluntarily withdraws at his/her own request;
- A participant is lost to follow-up;
- The trial is terminated prematurely by the sponsor, institutional or ethical review committees, or the regulatory agency; or
- Death of the participant.

5.3.5. Handling of Withdrawals

In case of premature withdrawal for any reason, the investigator should exert her best effort to:

- Conduct an interview to determine if the participant has had any reaction or AE (serious or non-serious) that has led to the withdrawal during the 28-day period after any study vaccination. Where possible, the investigator should visibly or physically assess any reported adverse reaction or AE.
- Attempt to complete all scheduled procedures and evaluations planned for the next study visit.
- Document the reason for premature withdrawal.
- Complete the end of the study record.

Withdrawal of a participant by the investigator may occur only if the child is identified to have one of the listed exclusion criteria or if continued participation threatens the child's well-being or the integrity of the

study. If the participant develops a reaction to study vaccine which the investigator believes threatens the child's well-being, the withdrawn participant must be treated or transferred to a treatment facility.

If premature withdrawal is initiated by the parent or investigator, PATH must be informed within 48 hours about all instances (excluding lost to follow-up).

5.3.6. Suspension or Termination of Study

The trial might be suspended at any time by PATH or by any ethical review committee overseeing this study for any safety concern. This includes, for example, and without limitation, an SAE resulting in death that is viewed to be related to receipt of study vaccine or an unusually high rate of SAEs. PATH may suspend the study in the event that study conduct is found to be below Good Clinical Practice (GCP) standards.

In the event of the appearance of new data that indicate an increased level of risk to study participants, the clinical trial will be suspended until PATH and all ethical review committees have reviewed relevant data and agreed that the trial may proceed.

6. STUDY VACCINES

6.1. Study Vaccine Descriptions

6.1.1. Live, Attenuated SA 14-14-2 JE Vaccine

The derivation of the live, attenuated Japanese encephalitis virus strain, SA 14-14-2, was through an empirical process of serial passage, principally in PHK cells.[61] The live, attenuated SA 14-14-2 JE virus genome has 57 nucleotide changes from that of wild-type JE virus, resulting in 24 amino acid changes. Eight amino acid changes in the E protein gene, which is strongly associated with neurovirulence, result in attenuation. These eight critical amino acid changes have been shown to be genetically quite stable.

The WHO prequalified live, attenuated SA 14-14-2 JE vaccine manufactured by CDIBP and marketed as CD-JEVAX™ or RS.JEV™ is a preparation of live, attenuated JE virus (strain SA 14-14-2) grown in culture on a monolayer of PHK cells. After cultivation and harvest, an appropriate stabilizer is added in the virus suspension, which is then lyophilized. Live, attenuated JE virus (strain SA 14-14-2), minimum essential medium, and human serum albumin are the major components of the final vaccine.

6.1.2. Measles, Mumps, Rubella Vaccine

The MMR vaccine manufactured by GlaxoSmithKline, Inc., and licensed as Priorix® in the Philippines is a lyophilized vaccine containing live, attenuated Schwarz measles virus produced in chick embryo cells, RIT 4385 mumps (derived from Jeryl Lynn strain) produced in chick embryo cells, and Wistar RA 27/3 rubella virus propagated on human diploid cells. Each single human dose when reconstituted in a volume of 0.5 mL contains not less than 1000 $CCID_{50}$ of measles virus, 5012 $CCID_{50}$ of mumps virus, and 1000 $CCID_{50}$ of rubella virus. The vaccine meets the requirements of WHO Technical Report Series 840 (1994).

6.1.3. Acquisition

RITM will be responsible for vaccine receipt and management of the vaccine. Appropriate vaccine acquisition and handling SOPs will be developed in collaboration with the investigator. Extra doses of both vaccines will be provided and shall be used when the initially allocated dose is broken, damaged, or unusable. For CD-JEV, the manufacturer will donate these vaccines free of charge; whereas, MMR vaccine will be procured. Vaccine accountability practices will be established to ensure receipt, storage, administration, and disposal are documented and monitored. The investigator and their institution will receive no monetary compensation from the manufacturers for their participation in this study.

6.1.4. Packaging and Labeling

Both study vaccines will be provided in their commercial presentation, containing their package insert. The commercial vial labels for these vaccines should remain intact. Study products will be labeled in compliance with any applicable national regulations. At a minimum, an additional label will be affixed to each box and will bear the following information:

- Study number
- Legal information: “For Clinical Trial Use Only”

6.1.5. Product Storage and Stability

CD-JEV and MMR vaccine should be stored in a refrigerator or cold box at a temperature ranging from +2°C to +8°C and protected from light. Storage temperature should be monitored and documented on an appropriate form during the entire trial.

The vaccines should never be frozen. In case of deep freezing or accidental disruption of the cold chain, the vaccine should not be administered and the investigator or the responsible person should contact PATH to receive further instructions.

6.2. Dosage, Preparation, and Administration of Study Vaccines

The vaccines in general should be gently shaken prior to administration to assure homogenous suspension. CD-JEV will be administered subcutaneously into the anterolateral aspect of the right upper thigh. MMR vaccine will be administered subcutaneously into the anterolateral aspect of the left upper thigh.

CD-JEV will be supplied in 5-dose vials as a lyophilized powder that looks like a milky-white crisp cake. After reconstitution, it turns into a transparent orange-red liquid. Each 0.5 mL human dose for subcutaneous injection contains not less than 5.4 log PFU of live JE virus. A single dose of 0.5 mL should be administered by subcutaneous injection with the rest of the vial contents discarded.

Measles-mumps-rubella vaccine appears as a white to slightly pink dry cake. It will be supplied in its monodose commercial presentation. The vaccine should be reconstituted only with the diluent supplied (sterile water for injection). A single dose of 0.5 mL should be administered by subcutaneous injection.

Standard immunization practices will be observed and care will be taken to administer the injections. As with all injectable vaccines, appropriate medical treatment, staff, and supervision will be readily available in case of rare anaphylactic reactions following administration of the study vaccine and epinephrine 1:1000 will be available in case of any anaphylactic reactions.

6.3. Accountability Procedures for the Study Vaccines

Study vaccine must be kept in a secure place. The investigator or the person in charge of vaccine management will maintain records of the vaccine's delivery to the trial site, the inventory at the site, the dose(s) given to each participant, and the return of unused doses to the sponsor. Appropriate vaccine accountability SOPs will be developed in collaboration with the investigator.

If the investigator runs out of vaccine during the trial, she should alert PATH, who will undertake the necessary steps to provide extra doses.

6.4. Concomitant Medications/Treatments

All medications administered must be checked against the inclusion/exclusion criteria. All medications used between enrollment and 28 days post-vaccination, except for topical treatment or vitamins, will be reported, including the following details: international non-proprietary name, dose, frequency, route, duration (start and end date), and indication for the treatment. The parents will be requested not to give the child preemptive analgesic or antipyretic drugs, as they may change the reactogenicity profile of the vaccine.

Injection of immunoglobulin, use of a systemic corticosteroid therapy for more than one week (inhalation will not be considered as systemic treatment) within 14 days before or after vaccination, or administration of any other immunomodulating agent, except the vaccines anticipated in the protocol, during the study period will lead to exclusion of the participant from the per-protocol statistical analysis.

7. STUDY SCHEDULE

7.1. Screening

1. Study staff in charge of recruitment will make sure that the infant will be between 9 months to <10 months of age at the time of enrollment.

7.2. Consent

1. If the child is eligible for the study based on the screening process, the study staff will review the informed consent process with the parent or guardian.

2. The investigator, or a person designated by the investigator, will fully inform the participant's parent(s)/legal guardian(s) of all pertinent aspects of the study, and individual consent will be documented by a signature and/or signature of an impartial literate witness on the consent form.

3. Following confirmation of consent, the child will be given a unique screening number and undergo assessment of eligibility, enrollment, and baseline activities as described below.

7.3. Eligibility/Enrollment/Baseline

For participants in the two groups, the following activities will occur at the time of eligibility assessment (Eligibility Assessment/Enrollment/Allocation/Blood Sample/Vaccine Administration):

1. At the designated location for vaccination, the parent will be interviewed to collect baseline information including demographic (age and gender) and health (known medical conditions and allergies including medications taken) information in order to confirm eligibility.

2. Qualified study staff will perform a physical examination of the child. Results will be reviewed by study staff and with the participant's parents to confirm eligibility prior to conduct of further procedures.

3. Based on collected information, inclusion/exclusion criteria will be verified and eligibility confirmed.

4. If eligible, the participant will be allocated into Group 1 or 2 according to the allocation process and given a unique participant ID number.

5. Prior to administration of the vaccine, a specimen of 3-5 mL of blood will be collected for baseline testing.

6. Study vaccine will be allocated to the participant per the allocation sequence and the child will receive the assigned study vaccination into the anterolateral aspect of the upper thigh.

    a. Group 1 will receive MMR vaccine subcutaneously into the anterolateral aspect of the left upper thigh and CD-JEV subcutaneously into the anterolateral aspect of the right upper thigh.

    b. Group 2 will receive MMR vaccine subcutaneously into the anterolateral aspect of the left upper thigh.

7. The parents will be asked to wait with the child in the clinic for 30 minutes after the vaccination(s), so that the study staff can observe for immediate reactions. If the child experiences an adverse reaction or an SAE during this time period, he/she will be treated or referred as appropriate, and the event will be recorded.

8. The parents will be given a study identification card that indicates that the child has been enrolled in a research study. The card will contain the following information:

    - Name, address, and contact phone numbers of the investigator and local study staff.
    - Child's unique study participant number.
    - Indication that the child is in a vaccine trial and a request that medical personnel who provide care to the child report any suspected adverse events and any abnormal or unusual clinical findings to the investigator.

9. The parents will be given a diary card and trained on how to record solicited and unsolicited adverse events occurring within 14 days post vaccination.

10. Parents will be informed that they will be contacted in 2 days (+3 days) in order to check on the welfare of the participant, answer any questions about the diary card, and assess the occurrence of any local or systemic reactions.

11. An appointment will be made to visit the clinic 14 days after vaccination (+3 days) for a follow-up visit.

12. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the study staff as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7.4. Follow-up Visit 2 Days After Enrollment

7.4.1. Group 1 and Group 2 Visits to Assess Safety (D2+3)

1. The parents will be called to check on the welfare of the child and ensure the diary card is being completed.

2. The parents will be asked if the child experienced any other adverse reaction or SAE and/or sought medical care.

3. The parents will be reminded of their appointment to visit the clinic 14 days after vaccination (+3 days) for a follow-up visit.

4. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the investigator as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7.5. Follow-up Visit 14 Days After Enrollment

7.5.1. Group 1 and Group 2 Visits to Assess Safety (D14+3)

1. The parents will visit the clinic for a follow-up visit in which the diary card will be reviewed and collected. Parents will be asked whether the child experienced any local and systemic reactions during the 14 days after vaccination.

2. The parents will be asked if the child experienced any other adverse reaction or SAE and/or sought medical care.

3. Concomitant therapies since the last visit will be reviewed.

4. Parents will receive an appointment to return to the designated location with their child 28 days after vaccination (+7 days) for a follow-up visit.

5. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the study staff as indicated on the study identification card.

Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7.6. Follow-up Visit 28 Days After Enrollment

7.6.1. Group 1 Visit to Assess Safety and Collect Serum (D28+7)

1. At the designated location for vaccinations/blood draws, the participant's identity will be confirmed.

2. Study staff will review interim medical histories and concomitant medications with the participant since the last visit to the study clinic.

3. Qualified study staff will perform a physical examination of the child. Results will be reviewed by study staff and with the participant's parents.

4. The parents will be asked if the child experienced any adverse reaction or SAE and/or sought medical care since the last visit.

5. A specimen of 3-5 mL of blood will be collected for anti-JE antibody testing.

6. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the study staff as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7. An appointment will be made with the parent to return with the child 56 days (+7 days) after vaccination for a follow-up visit.

7.6.2. Group 2 Visit to Assess Safety (D28+7)

1. At the designated location for vaccinations/blood draws, the participant's identity will be confirmed.

2. Study staff will review interim medical histories and concomitant medications with the participant since the last visit to the study clinic.

3. Qualified study staff will perform a physical examination of the child. Results will be reviewed by study staff and with the participant's parents.

4. The parents will be asked if the child experienced any adverse reaction or SAE and/or sought medical care since the last visit.

5. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the study staff as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

6. An appointment will be made with the parent to return with the child 56 days (+7 days) after vaccination for a follow-up visit.

7.7. Follow-up 56 Days After Enrollment

7.7.1. Group 1 Visit to Collect Serum (D56+7)

1. At the designated location for vaccinations/blood draws, the participant's identity will be confirmed.

2. Study staff will review interim medical histories and concomitant medications with the participant since the last visit to the study clinic.

3. Qualified study staff will perform a physical examination of the child. Results will be reviewed by study staff and with the participant's parents.

4. The parents will be asked if the child experienced any adverse reaction or SAE and/or sought medical care since the last visit.

5. A specimen of 3-5 mL of blood will be collected for anti-measles, anti-mumps, and anti-rubella testing.

6. An appointment will be made with the parent to return with the child 84 days (+7 days) after vaccination for a follow-up visit to receive the second dose of MMR vaccine.

7.7.2. Group 2 Visit to Collect Serum and Provide CD-JEV (D56+7)

1. At the designated location for vaccinations/blood draws, the participant's identity will be confirmed.

2. Study staff will review interim medical histories and concomitant medications with the participant since the last visit to the study clinic.

3. Qualified study staff will perform a physical examination of the child. Results will be reviewed by study staff and with the participant's parents.

4. The parents will be asked if the child experienced any adverse reaction or SAE and/or sought medical care since the last visit.

7. Before administration of vaccine, a specimen of 3-5 mL of blood will be collected for anti-measles, anti-mumps, anti-rubella, anti-JE testing, and anti-dengue.

5. The child will receive CD-JEV into the anterolateral aspect of the right upper thigh.

6. The parents will be asked to wait with the child in the clinic for 30 minutes after the vaccination, so that the physician can observe for immediate reactions. If the child experiences an adverse reaction or an SAE immediately following the vaccination, he/she will be treated or referred as appropriate.

7. Parents will be informed that they will be contacted in 2 days (+3 days) in order to check on the welfare of the participant, answer any questions about the diary card, and assess the occurrence of any local or systemic reactions.

8. The parents will be given a diary card and trained on how to record solicited and unsolicited adverse events occurring within 14 days post vaccination.

9. An appointment will be made to visit the clinic 14 days after vaccination (+3 days) for a follow-up visit.

10. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the investigator as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider

7.8. Follow-up visit 58 Days After Enrollment

7.8.1. Group 2 Visit to Assess Safety 2 Days After CD-JEV (D58+3)

1. The parents will be called to check on the welfare of the child and ensure the diary card is being completed.

2. The parents will be asked if the child experienced any other adverse reaction or SAE and/or sought medical care.

3. The parents will be reminded of their appointment to visit the clinic 14 days after vaccination (+3 days) for a follow-up visit.

4. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the investigator as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7.9. Follow-up Visit 70 days After Enrollment

7.9.1. Group 2 Visit to Assess Safety 14 Days After CD-JEV (D70+3)

1. The parents will visit the clinic for a follow-up visit in which the diary card will be reviewed and collected. Parents will be asked whether the child experienced any local and systemic reactions during the 14 days after vaccination.

2. The parents will be asked if the child experienced any other adverse reaction or SAE and/or sought medical care.

3. Concomitant therapies since the last visit will be reviewed.

4. Parents will receive an appointment to return to the designated location with their child 28 days after receipt of CD-JEV (+7 days) for a follow-up visit to receive the second dose of MMR.

5. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the study staff as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7.10. Follow-up 84 Days After Enrollment

7.10.1. Group 1 Follow-up Visit to Provide MMR (D84+7)

1. At the designated location for vaccinations/blood draws, the participant's identity will be confirmed.

2. Study staff will review interim medical histories and concomitant medications with the participant since the last visit to the study clinic.

3. Qualified study staff will perform a physical examination of the child. Results will be reviewed by study staff and with the participant's parents.

4. The parents will be asked if the child experienced any adverse reaction or SAE and/or sought medical care since the last visit.

5. The child will receive MMR subcutaneously into the anterolateral aspect of the left upper thigh.

6. The parents will be asked to wait with the child in the clinic for 30 minutes after the vaccination, so that the physician can observe for immediate reactions. If the child experiences an adverse reaction or an SAE immediately following the vaccination, he/she will be treated or referred as appropriate.

7. Parents will be informed that they will be contacted in 2 days (+3 days) in order to check on the welfare of the participant, answer any questions about the diary card, and assess the occurrence of any local or systemic reactions.

8. The parents will be given a diary card and trained on how to record solicited and unsolicited adverse events occurring within 14 days post vaccination.

9. An appointment will be made to visit the clinic 14 days after vaccination (+3 days) for a follow-up visit.

10. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the study staff as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7.10.2. Group 2 Follow-up Visit to Assess Safety, Collect Serum, and Provide MMR (D84+7)

1. At the designated location for vaccinations/blood draws, the participant's identity will be confirmed.

2. Study staff will review interim medical histories and concomitant medications with the participant since the last visit to the study clinic.

3. Qualified study staff will perform a physical examination of the child. Results will be reviewed by study staff and with the participant's parents.

4. The parents will be asked if the child experienced any adverse reaction or SAE and/or sought medical care since the last visit.

5. A specimen of 3-5 mL of blood will be collected for anti-JE antibody testing.

6. The child will receive a second dose of MMR vaccine subcutaneously into the anterolateral aspect of the left upper thigh.

7. The parents will be asked to wait with the child in the clinic for 30 minutes after the vaccination, so that the physician can observe for immediate reactions. If the child experiences an adverse reaction or an SAE immediately following the vaccination, he/she will be treated or referred as appropriate.

8. Parents will be informed that they will be contacted in 2 days (+3 days) in order to check on the welfare of the participant, answer any questions about the diary card, and assess the occurrence of any local or systemic reactions.

9. The parents will be given a diary card and trained on how to record solicited and unsolicited adverse events occurring within 14 days post vaccination.

10. An appointment will be made to visit the clinic 14 days after vaccination (+3 days) for a follow-up visit.

11. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the investigator as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7.11. Follow up 86 Days After Enrollment

7.11.1. Group 1 and Group 2 Visits to Assess Safety (D86+3)

1. The parents will be called to check on the welfare of the child and ensure the diary card is being completed.

2. The parents will be asked if the child experienced any other adverse reaction or SAE and/or sought medical care.

3. The parents will be reminded of their appointment to visit the clinic 14 days after vaccination (+3 days) for a follow-up visit.

4. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the investigator as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7.12. Follow-up Visit 98 Days After Enrollment

7.12.1. Group 1 and Group 2 Visits to Assess Safety (D98+3)

1. The parents will visit the clinic for a follow-up visit in which the diary card will be reviewed and collected. Parents will be asked whether the child experienced any local and systemic reactions during the 14 days after vaccination.

2. The parents will be asked if the child experienced any other adverse reaction or SAE and/or sought medical care.

3. Concomitant therapies since the last visit will be reviewed.

4. Parents will receive an appointment to return to the designated location with their child 28 days after vaccination (+7 days) for a follow-up visit.

5. Parents will be reminded to seek medical care as appropriate and inform the study clinician as soon as possible in the event of an adverse reaction or SAE. If the child visits a health care provider, the parents should be sure to inform him/her of the child's participation in the study and present the provider with contact information for the study staff as indicated on the study identification card. Additionally, the parents will be reminded to inform the study clinician that the child has visited a health care provider.

7.13. Final Study Visit 112 Days After Enrollment

7.13.1. Group 1 and Group 2 Final Study Visit to Assess Safety (D112+7)

1. At the designated location for vaccinations/blood draws, the participant's identity will be confirmed.

2. Study staff will review interim medical histories and concomitant medications with the participant since the last visit to the study clinic.

3. Qualified study staff will perform a physical examination of the child. Results will be reviewed by study staff and with the participant's parents.

4. The parents will be asked if the child experienced any adverse reaction or SAE and/or sought medical care since the last visit.

5. The final study record will be completed and participant will be exited from the study.

7.14. Allowable Schedule of Study Visits

For clarity, per-protocol timing of key study visits is provided below. No child should be dropped from the study solely on the basis of a visit falling outside of an allowable time-frame for that visit if there is good faith attempt by study staff and the participant's parent(s)/guardian(s) to adhere to the protocol.

Table 3. Group 1 Allowable Schedule

Study Visit	Should occur	May occur
Visit 0 (screening and consent)	On or before D0	Within 2 weeks of Visit 1
Visit 1 (eligibility, blood draw, MMR/CD-JEV vaccination)	Day 0	on Day 0
Visit 2 (MMR/CD-JEV follow-up)	Day 2	2 to 5 days after MMR/CD-JEV vaccination
Visit 3 (MMR/CD-JEV follow-up)	Day 14	14 to 17 days after MMR/CD-JEV vaccination
Visit 4 (MMR/CD-JEV follow-up, CD-JEV blood draw)	Day 28	28 to 35 days after MMR/CD-JEV vaccination
Visit 5 (MMR blood draw)	Day 56	56 to 63 days after MMR/CD-JEV vaccination
Visit 6 (MMR vaccination)	Day 84	84 to 91 days after MMR/CD-JEV vaccination
Visit 7 (MMR follow-up)	Day 86	2 to 4 days after MMR vaccination
Visit 8 (MMR follow-up)	Day 98	14 to 17 days after MMR vaccination
Visit 9 (final assessment)	Day 112	28 to 35 days after MMR vaccination

Table 4. Group 2 Allowable Schedule

Study Visit	Should occur	May occur
Visit 0 (screening and consent)	On or before D0	Within 2 weeks of visit 1
Visit 1 (eligibility, blood draw, MMR vaccination)	Day 0	on Day 0
Visit 2 (MMR follow-up)	Day 2	2 to 5 days after MMR vaccination
Visit 3 (MMR follow-up)	Day 14	14 to 17 days after MMR vaccination
Visit 4 (MMR follow-up)	Day 28	28 to 35 days after MMR vaccination
Visit 5 (MMR blood draw, CD-JEV vaccination)	Day 56	56 to 63 days after MMR vaccination
Visit 6 (CD-JEV follow-up)	Day 58	2 to 5 day after CD-JEV vaccination
Visit 7 (CD-JEV follow-up)	Day 70	14 to 17 days after CD-JEV vaccination
Visit 8 (CD-JEV blood draw, MMR vaccination)	Day 84	28 to 35 days after CD-JEV vaccination
Visit 9 (MMR follow-up)	Day 86	2 to 5 days after MMR vaccination
Visit 10 (MMR follow-up)	Day 98	14 to 17 days after MMR vaccination
Visit 11 (final assessment)	Day 112	28 to 35 days after MMR vaccination

8. STUDY PROCEDURES/EVALUATIONS

8.1. Clinical Evaluations

A key objective of this study is to describe the safety profile of the study vaccines. AEs and SAEs are defined in Section 9. Included below are brief listings of clinical parameters to be measured and used in evaluation of the general health of the child and in describing safety of study vaccines.

8.1.1. Medical History

At enrollment, medical histories will be reviewed through interview with the participant and his/her parent/legal guardian. The following medical conditions, especially, will be assessed:

- Current or recent febrile illness
- Recent vaccination history
- Hypersensitivity of any kind
- Any chronic disease (cardiac, renal, neurologic, metabolic, or rheumatologic)
- Seizures, including history of febrile seizures, or any other neurologic disorder

8.1.2. Physical Examination

Qualified study staff will collect general information on the participant including:

- Recording of general participant appearance
- Measurement of height and weight
- Measurement of the following vital signs:
    - Body temperature (and body location of measurement)
    - Respiratory rate
    - Pulse rate/heart rate

Qualified study staff will conduct a physical examination of all participants. This physical examination will include the following:

- Physical examination of all organ systems. This includes, without limitation, the following:
    - Chest auscultation
    - Heart auscultation
    - Abdomen palpation

8.1.3. Specific Clinical Signs and Symptoms of Interest

During follow-up, all clinical signs and symptoms must be documented. However, the following signs and symptoms and date of onset/occurrence and resolution will be solicited and recorded for all participants from 30 minutes until 14 days post vaccination per section 9.2.3.1. Signs and symptoms to be solicited will be those commonly reported in the large cumulative experience of CD-JEV and MMR in children.

Local Signs/Symptoms at the Injection Site:

- Ecchymosis (bruising)
- Erythema (redness)
- Edema (swelling)
- Induration (hardness)
- Pain/tenderness

General Signs/Symptoms:

- Fever
- Rash
- Cough
- Runny nose
- Change in eating habits
- Diarrhea
- Sleepiness
- Irritability
- Unusual crying
- Vomiting

In addition, a standardized clinical assessment including history and physical examination will be conducted by all clinicians per routine community practice. Evaluation of the above solicited signs/symptoms and unsolicited adverse events will include assessment of severity per Section 9.2.1.

Reported symptoms and clinical signs will be recorded in a daily diary by parent/guardian. Evaluations will be made by qualified study staff on each day of visit to the study clinic (Group 1: Days 0, 14, 28, 56, 84, 98, 112; Group 2: Days 0, 14, 28, 56, 70, 84, 98, 112) and at any time a participant is seen by a clinician.

Parents will be instructed to complete a daily diary of the above Specific Clinical Signs and Symptoms of Interest to the best of their ability. Parents will be instructed to contact a study clinician in the event of illness that may require urgent care to facilitate a rapid assessment of danger signs and assist in arranging transportation by the study to the health center or local hospital, as required. While the event may or may not be attributable to the study vaccines, study staff will follow the ethical imperative of

assisting ill participants once aware of severe illness. After referral, it will be the responsibility of a study clinician to assess and document all signs and symptoms.

8.1.4. Illness Diagnosis and Treatment

Participants will be instructed to seek care at the study sites and referred to RITM when necessary. The care provided to study participants presenting for outpatient consultation services at the sites will be recorded directly to the subject medical record. For participants visiting sites during non-working RITM hours, hospitalized at RITM, or visiting another facility, the study team will request the medical abstract. In the event this information cannot be obtained from the facility, as much information as possible will be obtained from the family of the participant. If the event is classified as an SAE, medical records regarding the event must be obtained.

While parents will be encouraged to seek care for their child at the sites or RITM, for participants presenting to a health center or transported to a health center or hospital other than RITM, a clinical assessment will be performed by a non-study health practitioner per routine community practice. Data on participant illness history, physical examination, diagnosis, and treatment will be documented. If necessary, staff will assist in arranging transportation for higher level care if necessary in their clinical judgment.

8.2. Laboratory Evaluations

8.2.1. Clinical Laboratory Evaluations

There will be no clinical (safety) laboratory evaluations scheduled in this study. However, laboratory testing will be provided if required for the assessment of an AE. Laboratory assays specified in Section 8.2.2. are for research purposes only and are not to be used for clinical diagnosis.

8.2.2. Serum Assays

8.2.2.1. Anti-Japanese Encephalitis Immunogenicity Testing

JE vaccine immunogenicity will be assessed by measurement of serum anti-JE neutralizing antibody. Testing will be performed at the Department of Virology, Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand. A 50% PRNT will be used to measure neutralizing antibodies for JE. Seroprotection will be defined as a serum JE PRNT titer of ≥1:10.[62]

8.2.2.2. Measles

Measles vaccine immunogenicity will be assessed by measurement of serum anti-measles neutralizing antibody. Testing will be performed at the Laboratory of Pediatric and Respiratory Viral Diseases, US FDA, in Silver Spring, MD. A 50% PRNT will be used to measure neutralizing antibodies for measles virus. Seroprotection will be defined as a serum measles plaque reduction neutralization concentration of ≥120 mIU/mL, as measured by the PRNT (dilution converted to concentration using the 3rd International Standard Reference serum).

8.2.2.3. Mumps

Mumps vaccine immunogenicity will be assessed by the presence of serum anti-mumps IgG antibody. Testing will be performed at the Laboratory of Pediatric and Respiratory Viral Diseases, US FDA, in Silver Spring, MD. A commercial IgG ELISA will be used to measure anti-mumps IgG antibody. Seroprotection will be defined as a serum anti-mumps IgG OD ratio ≥1.10 per the package insert.

8.2.2.4. Rubella

Rubella vaccine immunogenicity will be assessed by measurement of serum anti-rubella IgG concentration. Testing will be performed at the Laboratory of Pediatric and Respiratory Viral Diseases, US FDA, in Silver Spring, MD. A commercial IgG ELISA will be used to measure anti-rubella antibody concentration. Seroprotection will be defined as a serum anti-rubella IgG concentration corresponding to ≥10 IU/mL per the package insert.

8.2.3. Specimen Preparation, Handling, and Shipping

8.2.3.1. Specimen Collection

Blood draws of 3-5 mL will be collected during study visits as outlined in Section 7. The identity of the child will be verified immediately prior to the blood draw using the child's study participant number. Aliquot labels will be generated that indicate the participant ID, a designation for the type of test required (MMR and/or JE), and timepoint of collection (pre or post). One label will be affixed onto the vacutainer tube immediately following the blood sample drawing.

After collection, blood samples must clot for 60 minutes to 2 hours at room temperature. Samples will be maintained at 2°C to 8°C until processed in the site laboratory.

8.2.3.2. Specimen Preparation, Handling, and Storage

After centrifugation, the serum will be aliquoted. To ensure that samples are not mixed or inaccurately labelled, the child's study participant number, date of blood collection, number of aliquots obtained, and the date and time of aliquoting will be specified on the sample identification log. Comments may be made on the quality of samples (e.g., hemolyzed, contaminated). A label will be affixed onto each of the aliquots to indicate participant ID, a designation for the type of test required (MMR or JE), and timepoint of collection (pre or post).

All serum aliquots will be kept under appropriate conditions at the local study site. Study staff will monitor and record temperature on the appropriate form during the entire trial. For anti-JE testing, serum aliquots collected on D0 and D28 for Group 1 and D56 and D84 for Group 2 will be shipped to the Department of Virology, Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand. For anti-measles, anti-mumps, and anti-rubella testing, serum aliquots obtained on D0 and D56 for both groups will be shipped to the Laboratory of Pediatric and Respiratory Viral Diseases, US FDA, in Silver Spring, MD. A backup aliquot from each timepoint of collection will be retained for five years following study completion. Only authorized study staff will have access to the samples.

8.2.3.3. Specimen Shipment

Specimens will be shipped according to the International Air Transport Association regulations. Following the testing of specimens, all remaining back-up specimens will be stored for five years at a location designated by the sponsor following study completion.

9. ASSESSMENT OF SAFETY

9.1. Specification of Safety Parameters

Study vaccine safety profiles will be parameterized as the proportion of participants experiencing specific adverse events categorized into one of the following categories:

- Immediate reactions occurring within 30 minutes of administration of each study vaccine, as observed by study staff or reported by the participant to study staff.
- Solicited signs and symptoms occurring greater than 30 minutes after administration of each study vaccine through 14 days following vaccination, as observed by the parent/guardian and indicated on the diary card or observed by study staff.
- All other adverse events occurring within 28 days of receipt of each study vaccine, as observed by study staff or reported by the participant's parents to study staff.
- All SAEs occurring during the course of the study, as observed by study staff or reported by the participant's parents to study staff.

9.2. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1. Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

Information to be collected on adverse events includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event.

Any medical condition that was present at the time that the patient was enrolled should not be reported as an AE. However, if it deteriorates during the study safety recording periods, it should be recorded as an AE.

AEs should be graded for severity and relationship to vaccine.

Severity of Event: Any AE which is not a local and systemic sign or symptom occurring within 14 days of vaccination will be assessed to quantify intensity using the following guidelines[63]:

Grade	Categorization	Definition
Grade 1	Mild	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
Grade 2	Moderate	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated.
Grade 3	Severe	Symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.
Grade 4	Potentially life-threatening	Symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

**Intervention defined as medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.*

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

Relationship to Study Vaccines: The clinician's assessment of an AE's relationship to test vaccine is part of the documentation process, but it is not a factor in determining what is or is not recorded in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded. All AEs must have their relationship to study vaccines assessed using the following guidelines:

Categorization	Definition
Definitely Related	An adverse event or unanticipated problem clearly related to the research procedures.
Possibly Related	There is a reasonable possibility that the adverse event or unanticipated problem, incident, experience, or outcome may have been caused by the procedures involved in the research.
Not Related	Any adverse event or unanticipated problem clearly not related to study procedures.

9.2.2. Immediate Reactions

All participants will be observed for immediate reactions for 30 minutes following the first doses of each vaccine, with appropriate medical treatment readily available in case of an anaphylactic reaction following the administration of study vaccine. Immediate reactions will be assessed by a study clinician. All reactions that occur during this time will be recorded. Any immediate reaction which meets the criteria for a serious adverse event must also be documented on an SAE form.

9.2.3. Reactogenicity

Reactogenicity post-vaccination will be assessed from 30 minutes through 14 days following vaccination. All solicited local and systemic signs recorded from 30 minutes through 14 days post vaccination will be considered “related” to study vaccination. The parent will use a structured reactogenicity diary card for recording solicited (pre-listed) and unsolicited reactogenicity. Any reactogenicity continuing beyond 14 days will be documented as an adverse event and followed until resolution.

Any reactogenicity will be managed in accordance with good medical practices by the clinical study site team who will assess and treat or refer the child for medical care as appropriate. If needed to monitor or treat reactogenicity, additional study visits may be conducted. If any acute treatment or medical care is required as a result of harm caused by the study vaccine or study procedure, this care will be provided by the site free of charge. All children reporting reactogenicity will be followed clinically until the condition resolves (returns to baseline) or stabilizes. Conditions likely to be related to the product, whether serious or not, which persist at the end of the trial will be followed up by the study clinician until resolution or stabilization.

The parents of infants enrolled in this study will be instructed to contact the study site staff to report any reactogenicity of concern that their child experiences. In the case of a life-threatening event, they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, parents will be encouraged to seek medical care for the child at the RITM clinic, and to request that the study physician be contacted upon their arrival.

9.2.3.1. Local and Systemic Signs and Symptoms

All participants will be monitored at home for assessment of local and systemic signs and symptoms occurring from 30 minutes through 14 days following receipt of study vaccines. Parents will be instructed to record reactogenicity on diary cards. Study staff will call parents 2 days following vaccination to check on the participant and ensure the parent is completing the diary card.

Using a standardized data collection instrument, the following local and systemic signs and symptoms will be documented and graded on predefined scales based on functional assessment or magnitude of reaction[64]:

Local reactions (at injection site):

- Ecchymosis (bruising)
- Erythema (redness)
- Edema (swelling)
- Induration (hardness)
- Pain/tenderness

Local ecchymosis, erythema, edema, and induration, if present, will be graded as follows:

Grade 1: ≤2.5 cm in diameter.

Grade 2: >2.5 cm in diameter with 50% of surface area of extremity segment involved (upper arm or thigh).

Grade 3: ≥50% surface area of extremity segment involved (upper arm or thigh) OR ulceration OR secondary infection OR phlebitis OR sterile abscess OR drainage.

Grade 4: potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue).

Injection site pain/tenderness (pain without touching or tenderness when the area is touched), if present, will be graded as follows:

Grade 1: pain or tenderness causing no or minimal limitation of use of limb.

Grade 2: pain or tenderness causing greater than minimal limitation of use of limb.

Grade 3: pain or tenderness causing inability to perform usual social and functional activities.

Grade 4: pain or tenderness causing inability to perform basic self-care function OR hospitalization indicated.

Systemic reactions:
General Signs/Symptoms:

- Fever
- Rash
- Cough
- Runny nose
- Change in eating habits
- Diarrhea
- Sleepiness
- Irritability
- Unusual crying
- Vomiting

Fever if present will be recorded and graded as follows (axillary temperature):

- Grade 1: 37.5°C to 37.9°C
- Grade 2: 38.0°C to 38.4°C
- Grade 3: 38.5°C to 40.0°C
- Grade 4: >40.0°C

Rash, cough, runny nose, change in eating habits, diarrhea, sleepiness, irritability, unusual crying, vomiting, and any other unsolicited reaction occurring from 30 minutes through 14 days post vaccination will be graded as follows:

Grade 1: symptoms causing no or minimal interference with usual social and functional activities.

Grade 2: symptoms causing greater than minimal interference with usual social and functional activities.

Grade 3: symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.

Grade 4: symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death.

9.2.4. Serious Adverse Events

An SAE is defined as an AE that meets one of the following conditions:

- Death.
- Life threatening (participant at immediate risk of death) (*The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).*
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in a persistent or significant disability or incapacity.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Medical and scientific judgment should be exercised in deciding whether reporting is appropriate.

All SAEs occurring at any time during the study must be reviewed and evaluated by a study clinician (SAE relationship to study vaccine must be evaluated as outlined in Section 9.2.1) and recorded on an SAE form and reported (as specified in Section 9.3). All SAEs should be followed until satisfactory resolution or until the study clinician deems the event to be chronic or the patient to be stable.

9.3. Reporting Procedures

9.3.1. Serious Adverse Events

All SAEs occurring at any time during the study must be reported, even if the investigator considers that the SAE is not related to treatment. The study clinician will complete a Serious Adverse Event Form and send it to the medical monitor with copy to the Sponsor and CRO within 24 hours of site awareness, as outlined in a reporting SOP.

9.3.2. Regulatory Reporting

Collected SAEs will be reported to responsible ethical review committees according to requested timelines. Collected local and systemic reactions and adverse events not meeting the criteria of an SAE will be summarized at the end of the study, and a summary report will be sent to responsible ethical review committees and CDIBP.

9.4. Type and Duration of Follow-up of Participants after Adverse Events

Serious adverse events occurring throughout the study will be recorded. Adverse events likely to be related to the product, whether serious or not, which persist at the end of the trial will be followed up by the study clinician until resolution. The study clinician will document the date of final disappearance of the adverse event on a data clarification form. However, any AE not resolved at the time of data lock will be classified as “unresolved” for data cleaning and locking purposes.

9.5. Safety Oversight

Additional safety oversight will be conducted by a Safety Monitoring Committee (SMC). The SMC will operate under rules of an SMC-approved charter that will be finalized at the organizing meeting of the SMC (first meeting). PATH will draft this charter, and the SMC will approve it, after any modification by the SMC. The draft charter will embody the elements of the following sections.

9.5.1. SMC Roles and Responsibilities

An SMC will be constituted for independent safety review of this trial. The SMC will review individual and cumulative participant safety data when making recommendations regarding the safe continuation of the study. SMC members will not participate in the study, nor will they fall under the direct supervision of any investigator participating in the study.

PATH will, prior to any review of data, confirm that no conflicts of interest exist with any SMC member. Interests that might create a potential conflict of interest should be disclosed to PATH prior to any review of safety data. PATH will determine if the relationship is in conflict or gives the appearance of a conflict such that the individual should not serve on the SMC. PATH will determine how to handle such potential conflicts. PATH might dismiss an SMC member in the event of an unmanageable potential conflict.

9.5.2. Study Materials for SMC Review

The primary focus of the SMC will be to independently review all SAEs and items that PATH refers to it. The SMC will accomplish this by evaluating all such events against the known or expected safety profile of the study vaccine. Clinical and laboratory data, clinical records, and other study-related records will be made available for the SMC, as appropriate and available. If necessary, special reports will be prepared by the investigator or PATH.

It is the responsibility of the investigator and PATH to ensure that the SMC is apprised of all new safety information relevant to the study vaccines and the study. Summary safety and enrollment data will be forwarded periodically to the SMC. The SMC will receive all protocol revisions and might receive other documents related to the study.

9.5.3. Reports from the SMC

9.5.3.1. Review Report

According to pre-specified criteria agreed upon by PATH, the SMC will communicate in writing its findings and any concerns and recommendations to PATH. Unless otherwise specified, the written report will then be forwarded to the investigator, who may, in turn, submit the report as per local independent ethics committee (IEC) policy.

9.5.3.2. Immediate Action Report

The SMC will notify PATH of any findings of a serious and immediate nature including any recommendations to discontinue all or part of the trial. In addition to any verbal communications, recommendations to discontinue or substantially modify the design or conduct of a study must be conveyed in writing on the day of the SMC review. This written, confidential report may contain unmasked supporting data and include the SMC's rationale for the recommendations.

9.6. Halting Rules

Given the experience with CD-JEV and MMR vaccine, no safety issues are anticipated which would result in the suspension of enrollment in the study. However, the trial might be suspended at any time by PATH or any ethical review committee overseeing this study for any safety concern. This includes, for example, and without limitation, an SAE resulting in death, an unexpectedly high number of persons experiencing a similar event after receipt of any dose, or an unusually high rate of SAEs. PATH may suspend the study in the event that study conduct is found to be below GCP standards.

Should an SAE occur which is likely related to administration of study vaccine, the decision whether the study should continue per protocol, proceed with caution, be suspended pending further investigation, be discontinued, or be modified and then proceed will be made by PATH in consultation with the investigator, the SMC, the RITM institutional review board (IRB), and/or Western IRB (WIRB). However, no rules will be pre-specified to define these conditions.

If the study is halted, participants will be contacted immediately explaining why the study has been halted and the implications for their medical well-being.

In the event of the appearance of new data that indicate an increased level of risk to study participants, the clinical trial will be suspended until PATH, the SMC, and all ethical review committees have reviewed relevant data and agreed that the trial may proceed.

10. CLINICAL MONITORING

10.1. Site Monitoring Plan

Qualified and appropriately trained individuals will carefully monitor the study. The study monitor will periodically contact the site and perform on-site visits. The extent, nature, and frequency of site visits will be based on such considerations as study objectives, study design and complexity, and enrollment rate; periodicity and nature of monitoring activities will be described in the Monitoring Plan. PATH may

also include representatives of the Bill & Melinda Gates Foundation (the Foundation) in site contacts and visits, as appropriate, and will keep the Foundation program officer apprised of study progress.

10.1.1. Site Initiation Visit

Prior to study start, the monitor or PATH representative will ensure specific regulatory documents are available, such as IEC approvals, other IRB required approvals, and curriculum vitae for investigator and study staff. PATH will inform the investigator which documents need to be provided according to the applicable regulatory requirements. Prior to initiating recruitment, obtaining informed consent, and enrolling participants, the monitor or PATH representative will visit the site to train site personnel on the protocol and data collection procedures and to ensure the site meets all requirements for study start.

10.1.2. Follow-up Visits

Monitoring will be conducted according to PATH's requirements. The individuals responsible for monitoring the study will periodically review the progress of the study and should have access to all records necessary to ensure the ethical and safe conduct of the study and the integrity/validity of the recorded data.

During site visits and contacts, the monitor will:

- Check and assess the progress of the study.
- Review study data collected.
- Perform source data verification.
- Review regulatory files.
- Evaluate adherence to standard operating procedures.
- Identify any issues and address their resolution.

This will be done in order to verify that:

- The data are authentic, accurate, and complete.
- The safety and rights of participants are being protected.
- The study is conducted in accordance with the approved protocol (and any subsequent amendment) and all applicable regulatory requirements.

As part of study conduct, the investigator agrees to allow the monitor or PATH representative direct access to all relevant documents and to allocate time and the time of staff to discuss findings and any relevant issues. The investigator also agrees to allow representatives of the Foundation, authorized by PATH, to occasionally accompany the monitor or PATH representative during site visits.

10.1.3. Close-out Visit

Upon completion of the study, the study monitor or PATH representative and the investigator will conduct the following activities:

- Data clarification and/or resolution.
- Accounting, reconciliation, and destruction at sites of used and unused vaccines.
- Review of site study records for completeness.

PATH and any regulatory body retain the right to temporarily suspend or prematurely discontinue this study at any time related to safety. If the study is stopped or suspended prematurely, PATH will inform the investigator as well as regulatory authorities about the decision and the reasons for termination or

suspension. If such action is taken, all efforts must be made to ensure the safety of the participants enrolled in the study. The investigator will inform the responsible IEC and provide the reason for the suspension or termination. In case of premature study or study site closure, the monitor or PATH representative will conduct all activities as indicated above.

10.2. Audits and Inspections

For the purpose of compliance with applicable regulatory guidelines it may be necessary for PATH or national or foreign regulatory authorities to conduct a site audit. This may occur at any time from start to after conclusion of the study.

The investigator agrees to allow the auditor direct access to all relevant documents and to allocate her time and the time of her staff to the auditor to discuss findings and any relevant issues.

National and foreign regulatory authorities may conduct a regulatory inspection of this study. If a regulatory authority requests an inspection, the investigator must inform PATH immediately about this request. The investigator agrees to allow the inspector(s) direct access to all relevant documents and to allocate her time and the time of her staff to discuss findings and any relevant issues.

10.3. Archiving

In accordance with applicable regulatory requirements, following closure of the study, the investigator/institution will maintain a copy of study documents in a secure and designated location at the study site. Essential documents shall be retained for at least five years after the completion or discontinuation of the study.

11. STATISTICAL CONSIDERATIONS

11.1. Study Hypothesis

The primary study hypotheses are to prove that CD-JEV does not interfere with the immune response to measles and rubella antigens contained in the MMR vaccine.

11.2. Definition of Analysis Sets

All immunogenicity analyses and summaries will be performed on a per-protocol basis which will be considered as the primary approach to immunogenicity analyses. Supportive intention-to-treat immunogenicity analyses will also be conducted on all enrolled participants who received at least one dose of study vaccines and have at least one post-vaccination serology result. Safety analyses will be conducted on an intention-to-treat basis. In the event that there are participants who do not receive the vaccine(s) to which they were randomized, safety analyses will be performed on the safety analysis set as well. Analyses set definitions are provided below.

11.2.1. Intention-to-Treat Analysis Set

The Intention-To-Treat (ITT) set will include all participants who received a study vaccine. Participants in the ITT data set will be analyzed in the group to which participants have been assigned (not based on

the actual vaccine received). Participants who withdraw or are terminated from the study will be included in the ITT data set until the time of withdrawal or termination. Participants in the ITT analysis set who have at least one post-vaccination serology result will be included in the supportive immunogenicity analysis.

11.2.2. Safety Analysis Set

The Safety Analysis Set (SAS) will include all participants who received a study vaccine and have at least one post-vaccination safety result. Participants in the safety data set will be analyzed based on the actual vaccine received rather than the group to which they have been randomized.

11.2.3. Per-Protocol Analysis Set

The Per-Protocol (PP) sets will include the participants in the ITT set who are compliant with the protocol. This data set will be used for immunogenicity analysis only.

11.2.3.1. Measles Per-Protocol Analysis Set (measles-PP)

The measles-PP analysis set will be based on participants that meet all of the following criteria:

- Fulfilled the eligibility (inclusion/exclusion) criteria set forth in Sections 5.1. and 5.2.
- Received all study vaccines as assigned.
- Provided a valid measles serology laboratory result at baseline and at 56 days post-vaccination with MMR vaccine, with specimens taken within the windows prescribed by Section 7.14.
- Did not take any prohibited concomitant medication within 28 days post-vaccination.
- Did not show seropositivity for measles at baseline.

11.2.3.2. Mumps Per-Protocol Analysis set (mumps-PP)

The mumps-PP analysis set will be based on participants that meet all of the following criteria:

- Fulfilled the eligibility (inclusion/exclusion) criteria set forth in Sections 5.1. and 5.2.
- Received all study vaccines as assigned.
- Provided a valid mumps serology laboratory result at baseline and at 56 days post-vaccination with MMR vaccine, with specimens taken within the windows prescribed by Section 7.14.
- Did not take any prohibited concomitant medication within 28 days post-vaccination.
- Did not show seropositivity for mumps at baseline.

11.2.3.3. Rubella Per-Protocol Analysis Set (rubella-PP)

The rubella-PP analysis set will be based on participants that meet all of the following criteria:

- Fulfilled the eligibility (inclusion/exclusion) criteria set forth in Sections 5.1. and 5.2.
- Received all study vaccines as assigned.
- Provided a valid rubella serology laboratory result at baseline and at 56 days post-vaccination with MMR vaccine, with specimens taken within the windows prescribed by Section 7.14.
- Did not take any prohibited concomitant medication within 28 days post-vaccination.
- Did not show seropositivity for rubella at baseline.

11.2.3.4. JE Per-Protocol Analysis Set (JE-PP)

The JE-PP analysis set will be based on participants that meet all of the following criteria:

- Fulfilled the eligibility (inclusion/exclusion) criteria set forth in Sections 5.1. and 5.2.
- Received all study vaccines as assigned.
- Provided a valid JE serology laboratory result at baseline and at 28 days post-vaccination with CD-JEV vaccine, with specimens taken within the windows prescribed by Section 7.14.
- Did not take any prohibited concomitant medication within 28 days post-vaccination.
- Did not show seropositivity for JE at baseline.

11.3. Analysis Plan

A full and final Statistical Analysis Plan will be specified prior to the first participant first visit and finalized before locking of the database.

11.3.1. Immunogenicity

11.3.1.1. Primary Hypotheses

Non-inferiority of the concomitant administration of MMR and CD-JEV vaccines (Group 1) to MMR and CD-JEV vaccines given 2 months apart (Group 2) in children 9 months of age at 56 days is established in terms of percentage (or proportions) of participants achieving seropositivity to measles and rubella assuming a non-inferiority margin of 10%.

The following co-primary hypotheses will be tested:

$$H_{0M}: (P_{(M1)} \text{ minus } P_{(M2)}) \leq -10\%$$
$$H_{1M}: (P_{(M1)} \text{ minus } P_{(M2)}) > -10\%$$

and

$$H_{0R}: (P_{(R1)} \text{ minus } P_{(R2)}) \leq -10\%$$
$$H_{1R}: (P_{(R1)} \text{ minus } P_{(R2)}) > -10\%$$

where $P_{(M1)}$ refers to the percentage of participants seroconverting to measles in Group 1 and $P_{(M2)}$ refers to the percentage of participants seroconverting to measles in Group 2 and where $P_{(R1)}$ refers to the percentage of participants seroconverting to rubella in Group 1 and $P_{(R2)}$ refers to the percentage of participants seroconverting to rubella in Group 2.

11.3.2. Safety

To evaluate safety, proportions of participants experiencing any category of adverse event will be calculated with corresponding 95% confidence intervals using the Exact test.

11.3.3. Analysis and Reporting of Withdrawals

Participants may withdraw from the study at any time and for any reason. The investigator may withdraw participants from the study for various reasons. These reasons and how to handle withdrawals are detailed in Section 5.3. Regardless of reason for withdrawal, it is the obligation of the investigator and sponsor to report these withdrawals as part of the analyses, the clinical study report, and peer-reviewed

publication(s) summarizing study results. Withdrawals will be summarized with their reasons in these reports.

11.4. Sample Size Considerations

An enrollment size of 628 participants (314 per treatment group) was targeted to achieve an overall power of 90% (approximate individual power of 95% for each co-primary objective). This estimation is based upon a non-inferiority margin of 10% and a one-sided type-one error rate of 2.5% or less, and assumes (based on historical data) a 95% seropositivity rate for measles vaccine, a 90% seropositivity rate for rubella vaccine, and approximately 20% non-evaluable rate (exclusion for baseline seropositivity and loss to follow-up) at 56 days post-vaccination. Individual sample size calculations were based on Farrington-Manning score test.

11.5. Final Analysis Plan

11.5.1. Primary Analyses

Non-inferiority will be achieved when both H_{0M} and H_{0R} are rejected, that is, if the lower limit of the 95% CI for the differences in percentage of the participants achieving seropositivity between Group 1 and Group 2 >–10% for both measles and rubella outcomes. The 95% CI will be calculated using the Farrington-Manning method. Within-group exact 95% binomial confidence intervals for the proportion (or percentage) of seropositivity will be calculated.

11.5.2. Secondary Analyses

1. Non-inferiority of the concomitant administration of MMR and CD-JEV vaccines (Group 1) to MMR and CD-JEV vaccines given 2 months apart (Group 2) is established in terms of percentage (or proportions) of participants achieving seropositivity to mumps 56 days after vaccination, assuming a non-inferiority margin of 10%. The 95% CI will be calculated using the Farrington-Manning method. Within-group exact 95% binomial confidence intervals for the proportion (or percentage) of seropositivity will be calculated.

2. The ratio of anti-measles and anti-rubella GMCs between both treatment groups with 95% CI obtained 56 days after vaccination (ratio of concurrent administration to separate administration) will be calculated using parametric models after log transformation of the concentrations where applicable.

3. The difference with 95% CI between the anti-measles, anti-mumps, and anti-rubella seroconversion rates 56 days after vaccination for the two groups (concurrent administration minus separate administration) will be calculated using the Farrington-Manning method.

4. The difference with 95% CI between the anti-JE seropositivity rates 28 days after vaccination for the two groups (concurrent administration minus separate administration) will be calculated using the Farrington-Manning method.

5. The ratio of anti-JE GMTs between both treatment groups with 95% CI obtained 28 days after vaccination (ratio of concurrent administration to separate administration) will be calculated using parametric models after log transformation of the titers where applicable.

6. Safety endpoints will be descriptively summarized in terms of frequency counts and percentages by treatment group, where applicable.

11.5.3. Exploratory Analyses

Post-vaccination serologic responses will be analyzed for any association between the baseline anti-dengue antibody response and the anti-JE antibody response 28 days after vaccination with CD-JEV.

11.5.4. Timing of Analyses

Due to an expected delay in MMR testing, JE testing will be completed first. According to this order of available serology testing results, two independent final analyses will be conducted stepwise as follows:

- The first final analysis will include all safety data and JE immunogenicity results. The estimates of the JE immunogenicity endpoints and safety endpoints and statistical tests associated with relevant secondary objectives and exploratory objective will be provided. This analysis will be performed after anti-JE antibody results are available and database is cleaned and locked at the end of the study.

- The second final analysis will include all MMR immunogenicity results. The estimates of the MMR-related immunogenicity endpoints and statistical tests associated with primary and relevant secondary objectives will be presented. This analysis will be performed as soon as MMR results are available, cleaned, and locked.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Prior to the start of the trial it will be determined and documented which documents or data fields completed by the investigative team will be considered source documents. Only authorized study staff and representatives of PATH and authorized regulatory agencies may have direct access to source documents containing study data. Participant identification will be revealed to authorized representatives of these organizations only when necessary.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The study will be conducted in accordance with procedures identified in the protocol and staff will be guided by procedural activities detailed in the SOP.

Site monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet International Conference on Harmonisation Good Clinical Practice (ICH-GCP), sponsor standards, and regulatory guidelines, and that the study is conducted in accordance with the protocol and sponsor SOPs.

All site staff will be required to have had training in GCP, informed consent, and protocol implementation prior to work on the project. All study staff, including temporary staff such as nurses, phlebotomists, and interviewers will attend mandatory training prior to participant enrollment.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, ICH-GCP, and/or with local regulatory requirements, whichever affords the greater protection to the participant.

14.2. Institutional Review Board

The protocol will be reviewed and approved by all of the following bodies before recruitment begins:

1. Western Institutional Review Board (WIRB). PATH subcontracts its ethical review for clinical trials to WIRB.

2. The RITM Institutional Ethical Review Board.

The investigator, with the help of PATH and the CRO, shall be responsible for obtaining IRB and ethics committee(s) approval of the protocol and any subsequent amendments in compliance with local law before the start of the trial. The investigator must forward copies of these approvals to PATH with the composition (names and qualification of the members) of the ethics committee.

In addition, the protocol will be reviewed and approved by the FDA Research Involving Human Subject Committee before samples are sent to the FDA laboratory for testing.

14.3. Independent Ethics Committee

Per the Philippines Food & Drug Circular 2012-07, the protocol and other pertinent documents will be reviewed and approved by an Ethical Review Board/Committee selected by the Philippine Health Research Ethics Board.

The CRO, with the help of PATH, shall be responsible for obtaining independent ethics committee(s) approval of the protocol and any subsequent amendments in compliance with local law before the start of the trial. The CRO must forward copies of these approvals to PATH with the composition (names and qualification of the members) of the ethics committee.

14.4. Informed Consent Process

Prior to receipt of study vaccine, written informed consent will be obtained from a parent/guardian for all participants. Informed consent documents will embody the elements of consent as described in the Declaration of Helsinki and the ICH Harmonised Tripartite Guidelines for Good Clinical Practice.

Original Informed Consent Forms must be kept on file by the investigator for possible inspection by regulatory authorities and PATH. The participant or the participant's legally acceptable representative must receive a copy of the signed and dated Informed Consent Form(s), and any subsequent updates or amendments.

The study monitor shall check the documentation of the individual Informed Consent Form(s) during each monitoring visit.

Monetary incentives will not be provided to participants or their parent(s)/guardian(s) in exchange for participation. However, parents/guardians of participants will be paid 1,000 to 1,500 pesos per scheduled clinic visits after Day 0 to reimburse for transport costs and loss of wages. The scheduled clinic visits will require the parent/guardian to attend the vaccination clinic for specific follow-up procedures. To ensure that compensation does not risk becoming an inducement for participation, the parent/guardian will not be compensated for the study visit to the clinic at Day 0 for study enrollment.

Given the local social structure, information about the study and informed consent process will be conducted via a series of procedures: 1) consent forms will be in the local language and written within the eighth grade reading level or lower; 2) meetings will be scheduled with the community and government leaders and the study will be explained in detail by trained study staff fluent in the local language; 3) after the community leaders provide approval for conduct of the study, 4) the investigator, or a person designated by the investigator, will fully inform the participant's parent(s) of all pertinent aspects of the study and direct interested persons to the vaccination sites; and 5) individual consent will be documented by a signature and/or signature of an impartial literate witness of the consent form.

14.5. Inclusion of Women and Children

Children of any race/ethnicity and residing in the study area will be recruited for participation in the study. No special recruitment methods will be used to ensure certain levels of participation by any specific minorities residing in the source population. The investigator will emphasize during information sessions that girls and boys are at equal risk of JE and its complications.

14.6. Participant Confidentiality

14.6.1. Confidentiality of Data

By signing the protocol, the investigator agrees that the study protocol, documentation, data, and all other information generated regarding the vaccines will be held in strict confidence. The investigator may divulge such information within regulatory restrictions and ethical considerations only to ethical review committees or similar expert boards or committees, and their affiliated institutions and employees, only under an appropriate understanding of confidentiality with such board or committee, and their affiliated institutions and employees. No information concerning the study or the data may be released to any unauthorized third party without prior written approval of PATH. The investigator will ensure that all employees involved in the study respect the same rules.

Documents and data pertaining to the study will be kept in a locked cabinet under the responsibility of the investigator. PATH will conduct periodic monitoring visits to ensure that the data is safe and stored in this secure place and that only those authorized study staff have access to the data. Study data will be kept for five years after completion of the study.

Study participants will not be reported by name in any report or publication resulting from data collected in this study.

14.6.2. Confidentiality of Patient Records

Participant confidentiality is strictly held in trust by the participating investigator, her staff, and the sponsor(s) and their agents. This confidentiality pertains to a participant's personal and health information and extends to information on any biological specimen of the participant. Medical information about individual participants obtained during the course of this study is confidential and may not be disclosed to third parties, except authorized monitors, sponsors, auditors, or inspectors. Confidentiality will be ensured by the use of participant numbers coding for the identification of each participant's personal, health, and specimen information. Access to this linkage and other confidential data will be strictly controlled.

The investigator will keep individual results confidential to the extent permitted by law. Information will not be released to anyone other than the participant, their parent or their medical provider, unless required to do so by law.

14.6.3. Notification of Primary Care Physician

If agreed by the participant's legally acceptable representative, the study staff shall notify the participant's primary clinician, if applicable, of child's participation in the study. Participation in the study and study team contact numbers will be reported on the participant's study identification card as applicable.

14.7. Study Discontinuation

Study discontinuation is not expected to occur. However, if the study is discontinued for safety reasons, parents of participants will be informed of the reasons for discontinuation and of the implications/potential consequences for the child.

14.8. Future Use of Stored Specimens

Aliquots of participant's back-up serum specimens will be maintained for five years after the completion of the study. This is to allow the samples to be stored long enough to support any requests for additional information from WHO or other agencies. Following completion of this period, all samples will be destroyed. No personal identifying information associated with the study will be stored on site with the specimens. After the data analysis for the study is complete, the master linking document will be destroyed, thus removing the possibility of identifying the individual from whom the data and sample were collected. Samples will not be used for unrelated, future studies without appropriate ethics committee approvals and consent from participants (if deemed required by ethics committees and the master linking document with identifiers has not yet been destroyed).

15. DATA HANDLING AND RECORD KEEPING

15.1. Data Management Responsibilities

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. Data collection is the responsibility of the clinical study staff at the site under the supervision of the investigator.

Adverse events must be graded, assessed for severity and causality, and reviewed by the investigator or designee.

15.2. Data Capture Methods

Clinical data and laboratory data will be recorded. All children will be assigned a unique study participant number at study enrollment; this study participant number will be included on all forms and in the computer database and will serve to link study data to specific individuals. Data forms will be verified for accuracy, linked by study participant number, and managed using database management software.

The study will utilize DataFax software, an electronic data capture (EDC) system uniquely suited for international clinical research developed by DF/Net Research. Site staff will use the EDC tool to securely enter data into electronic case report forms (eCRFs) from source documents, or from medical or clinical records, directly into the database. The software utilizes workflows and specifically programmed edit checks to ensure that data is entered correctly and on time within expected parameters. The data validation process continues with routine batch edit checks initiated at the data management center to detect data issues.

The EDC system will distribute data entry and validation tasks to the research sites to optimize quality data collection at the point of entry. It will encompass an extensive edit check language to enforce legal ranges, field requirements, and other per-field attributes as well as higher-level concepts such as visit and form timing, conditional data, and data consistency across visits and forms. The data management system is ISO 9001:2008 certified and is routinely audited. It includes a 21 CRF Part 11-compliant audit trail and is implemented in accordance with Good Clinical Data Management Practices, all applicable regulations, and recognized best practices.

15.3. Types of Data

Data for this study will include biographical, medical history, clinical (signs, symptoms, prescription and non-prescription medical treatments, and non-study vaccinations), safety data, and immunologic laboratory data.

15.4. Timing/Reports

No interim analysis are planned. SMC reports will be completed within two weeks of each SMC meeting. The full Clinical Study Report (CSR) will be completed approximately six months after the completion of the analyses.

15.5. Study Records Retention

It is planned that the study data will be kept for five years after completion of the study. No records will be destroyed without the written consent of PATH. It is the responsibility of PATH to inform the investigator when these documents no longer need to be retained.

15.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, GCP, or the site manual of procedures. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of any deviations, corrective actions are to be developed by the site and implemented promptly. Examples of protocol deviations include the following:

- Non-adherence to inclusion and/or exclusion criteria.
- Irregular or improper implementation of the trial product.
- Unnecessary repeated performance of any planned procedures or tests.
- Changing the interval between two visits or procedures more than allowed by the protocol.
- Incorrect or careless documentation of study procedures on primary documents or required logs.
- Premature withdrawal of a participant for any reason, even if withdrawal is in the best interest of the well-being of the participant.

Trial procedures shall not be changed without the consent of PATH. Insignificant violations of the protocol will be examined on an individual basis taking into account information documenting the reason(s) that the deviation occurred.

It is the responsibility of the site to use continuous vigilance to identify and report deviations to PATH in a timely manner after identification. Reports of protocol deviations must be sent to WIRB and the RITM IRB, as required per their respective guidelines. The investigator and study staff are responsible for knowing and adhering to IRB and IEC requirements. PATH will assist the investigator in all reporting to WIRB or file reports on behalf of the investigator.

16. PUBLICATION POLICY

A CSR comprised of text and results tables reflecting all safety and immunogenicity data will be generated. The CSR will be reviewed, approved, and signed by the investigator. The CSR will be compliant with ICH guidelines.

All data, documents, any recordings and information transferred by PATH to any contractor or obtained or prepared by any contractor, his/her consultants or persons associated by contractual relationships with any contractor during the trials, belong to PATH.

All confidential information communicated to the investigator by PATH shall be kept strictly confidential by her or any other person connected with the study and shall not be disclosed, either orally or in written form, to any third party without prior written consent of the organization of which the information is the exclusive property.

Following completion of the CSR, the investigator, working with PATH representatives, is expected to publish the results of this research in peer-reviewed scientific journal(s). In no way may anyone or any organization prohibit the public dissemination of valid results of this trial.

The International Committee of Medical Journal Editors' member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry. It will be the responsibility of PATH representatives to register this trial in an acceptable registry preferably before enrollment but no later than 30 days following the enrollment of the first participant. Likewise, all clinical trials are required to be uploaded in the Philippine Clinical Trial Registry. It is the responsibility of the study sponsor to upload information related to the clinical trial to the registry (http://registry.healthresearch.ph) 30 days after the application to conduct the clinical trial has been granted. International Committee of Medical Journal Editors' authorship criteria will be strictly followed for publication of any manuscript(s) arising from this trial.

17. REFERENCES

1. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. Stat Med 9(12):1447–1454. 1990.

2. World Health Organization. Measles vaccines: WHO position paper. Weekly Epidemiological Record 84(35):349–360. 2009.

3. World Health Organization. The Immunological Basis for Immunization Series – Module 7: Measles. 2009. Immunization, Vaccines and Biologicals.

4. World Health Organization. Measles Fact Sheet. 2013.

5. World Health Organization. Measles vaccines: WHO position paper. Weekly Epidemiological Record 84(35):349–360. 2009.

6. World Health Organization. Measles vaccines: WHO position paper. Weekly Epidemiological Record 84(35):349–360. 2009.

7. World Health Organization. Meeting of the Strategic Advisory Group of Experts on immunization, November 2013 -- conclusions and recommendations. Weekly Epidemiological Record 89(1):1–20. 2014.

8. World Health Organization. The Immunological Basis for Immunization Series – Module 16: Mumps. 2010. Immunization, Vaccines and Biologicals.

9. World Health Organization. Mumps virus vaccines. Weekly Epidemiological Record 82(7):51–60. 2007.

10. World Health Organization. Rubella vaccines: WHO position paper. Weekly Epidemiological Record 86(29):301–316. 2011.

11. Enders G, Nickerl-Pacher U, Miller E, Cradock-Watson JE. Outcome of confirmed periconceptional maternal rubella. Lancet 1(8600):1445–1447. 1988.

12. Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. Lancet 2(8302):781–784. 1982.

13. World Health Organization. Rubella vaccines: WHO position paper. Weekly Epidemiological Record 86(29):301–316. 2011.

14. Cutts FT, Vynnycky E. Modelling the incidence of congenital rubella syndrome in developing countries. Int J Epidemiol 28(6):1176–1184. 1999.

15. World Health Organization. Status Report on Progress Towards Measles and Rubella Elimination: SAGE Working Group on Measles and Rubella. 2013. Immunization, Vaccines and Biologicals.

16. Fischer M, Lindsey N, Staples JE, Hills S. Japanese encephalitis vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR.Recomm.Rep. 59(RR-1):1–27. 2010.

17. Halstead S, Jacobson J. Plotkin SA, Orenstein WA, Offit PA, editors. Japanese encephalitis vaccines. Vaccines. Fifth(17):311–352. Saunders Elsevier; 2008.

18. Igarashi A. Epidemiology and control of Japanese encephalitis. World Health Statistics Quarterly 45(2-3):299–305. 1992.

19. Halstead SB, Thomas SJ. New Japanese encephalitis vaccines: alternatives to production in mouse brain. Expert Review of Vaccines 10(3):355–364. 2011.

20. Tsai TF. Mandell GL, Bennett JE, Dolan RD, editors. Flaviviruses (Yellow Fever, Dengue, Dengue Hemorrhagic Fever, Japanese Encephalitis, St. Louis Encephalitis, Tick-Borne Encephalitis. Principles and Practices of Infectious Diseases.(2):1714–1736. New York, NY: Churchill Livingston; 2000.

21. Campbell GL, Hills SL, Fischer M, Jacobson JA, Hoke CH, Hombach JM et al. Estimated global incidence of Japanese encephalitis: a systematic review. Bull World Health Organ 89(10):766–774E. 2011.

22. Innis BL. Porterfield JS, editor. Japanese encephalitis. Kass Handbook of Infectious Diseases: Exotic Virus Infections. 1:147–174. London: Chapman & Hall Medical; 1995.

23. Rosen L. The natural history of Japanese encephalitis virus. Annual Review of Microbiology 40:395–414. 1986.

24. Scherer WF, Buescher EL. Ecologic studies of Japanese encephalitis virus in Japan. I. Introduction. The American Journal of Tropical Medicine and Hygiene 8(6):644–650. 1959.

25. Soman RS, Rodrigues FM, Guttikar SN, Guru PY. Experimental viraemia and transmission of Japanese encephalitis virus by mosquitoes in ardeid birds. The Indian Journal of Medical Research 66(5):709–718. 1977.

26. Gould DJ, BYRNE RJ, Hayes DE. Experimental infection of horses with japanese encephalitis virus by mosquito bite. The American Journal of Tropical Medicine and Hygiene 13:742–746. 1964.

27. Wang YJ, Gu PW, Liu PS. Japanese B encephalitis virus infection of horses during the first epidemic season following entry into an infected area. Chinese Medical Journal 95(1):63–66. 1982.

28. World Health Organization. Japanese Encephalitis Vaccines: WHO position paper - February 2015. Weekly Epidemiological Record 90(9):69–87. 2015.

29. World Health Organization. Global Advisory Committee on Vaccine Safety, 9-10 June 2005. Weekly Epidemiological Record 80(28):241–248. 2005.

30. World Health Organization. Global Advisory Committee on Vaccine Safety, 29-30 November 2006. Weekly Epidemiological Record 82(3):18–24. 2007.

31. World Health Organization. Global Advisory Committee on Vaccine Safety, 12-13 December 2007. Weekly Epidemiological Record 83(4):37–44. 2008.

32. Chen HY, Ma FB, Zhang JL, et al. Observation on safety of the live attenuated SA 14-14-2 Japanese encephalitis vaccine. Japanese encephalitis Vaccine, Live.:33–34. China: National Institute of Pharmaceutical and Biological Products, Chengdu Institute of Biological Products; 2004.

33. Gatchalian S, Yao Y, Zhou B, Zhang L, Yoksan S, Kelly K et al. Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants. Vaccine 26(18):2234–2241. 2008.

34. Glovax. Summary of Live attenuated SA14-14-2 Japanese Encephalitis vaccine PMS study in Korea (2002-2008).:1–4. Seoul: Glovax Clinical Research and Regulation Affairs; 2008.

35. Liu ZL, Hennessy S, Strom BL, Tsai TF, Wan CM, Tang SC et al. Short-term safety of live attenuated Japanese encephalitis vaccine (SA14-14-2): results of a randomized trial with 26,239 subjects. The Journal of Infectious Diseases 176(5):1366–1369. 1997.

36. Ma FB, Zheng L, Bi C, Tao H, Zhou YL, Zhang JL et al. Study on the strategy of Japanese encephalitis immunization using live attenuated vaccine combined with inactivated vaccine. Zhonghua Liu Xing Bing Xue Za Zhi 24(2):113–115. 2003.

37. SAS. Post Marketing Study of primary immunization in Burdwan, West Bengal and Bellary, Karnataka (2006-2007). 2008. 2008.

38. Sohn YM, Park MS, Rho HO, Chandler LJ, Shope RE, Tsai TF. Primary and booster immune responses to SA14-14-2 Japanese encephalitis vaccine in Korean infants. Vaccine 17(18):2259–2264. 1999.

39. Victor JC, Yao Y, Zhou B, Zhang L, Yoksan S, Kelly K et al. Corrigendum to "Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants". Vaccine 32(2):306–308. 2014.

40. Wijesinghe PR, Abeysinghe MR, Yoksan S, Yao Y, Zhou B, Zhang L et al. Safety and immunogenicity of live-attenuated Japanese encephalitis SA 14-14-2 vaccine co-administered with measles vaccine in 9-month-old infants in Sri Lanka. Vaccine 32(37):4751–4757. 2014.

41. Zeng Y, Zhou B, Yang Y, Fang G, Liu Y, Qi Q. A safety study on JE-MV combined vaccine. Journal of Preventative Medicine and Information [in Chinese] 19(2) 2003.

42. Zhou B, Min Z, XiaoMing L. Clinical safety observation of JE live vaccine (SA 14-14-2) for children aged from 6 to 12 months. Journal of Preventive Medicine Information 21(3):284–286. 2005.

43. Zhou B, Jia L, Xu X. A large-scale study on the safety and epidemiological efficacy of Japanese encephalitis (JE) live vaccine (SA14-14-2) in the JE endemic areas. Chinese Journal of Epidemiology 20(1):38–41. 1999.

44. Chotpitayasunondh T, Sohn YM, Yoksan S, Min J, Ohrr H. Immunizing children aged 9 to 15 months with live attenuated SA14-14-2 Japanese encephalitis vaccine in Thailand. Journal of the Medical Association of Thailand 94 Suppl 3:S195–S203. 2011.

45. World Health Organization. Global Advisory Committee on Vaccine Safety,12-13 June 2013. Weekly Epidemiological Record 88(29):301–312. 2013.

46. Sohn YM, Tandan JB, Yoksan S, Ji M, Ohrr H. A 5-year follow-up of antibody response in children vaccinated with single dose of live attenuated SA14-14-2 Japanese encephalitis vaccine: immunogenicity and anamnestic responses. Vaccine 26(13):1638–1643. 2008.

47. Zaman K, Naser AM, Power M, Yaich M, Zhang L, Ginsburg AS et al. Lot-to-lot consistency of live attenuated SA 14-14-2 Japanese encephalitis vaccine manufactured in a good manufacturing practice facility and non-inferiority with respect to an earlier product. Vaccine 32(46):6061–6066. 2014.

48. Bista MB, Banerjee MK, Shin SH, Tandan JB, Kim MH, Sohn YM et al. Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case control study. Lancet 358(9284):791–795. 2001.

49. Tandan JB, Ohrr H, Sohn YM, Yoksan S, Ji M, Nam CM et al. Single dose of SA 14-14-2 vaccine provides long-term protection against Japanese encephalitis: A case-control study in Nepalese children 5 years after immunization. Vaccine 25(27):5041–5045. 2007.

50. Ohrr H, Tandan JB, Sohn YM, Shin SH, Pradhan DP, Halstead SB. Effect of single dose of SA 14-14-2 vaccine 1 year after immunisation in Nepalese children with Japanese encephalitis: a case-control study. Lancet 366(9494):1375–1378. 2005.

51. Lopez AL, Aldaba JG, Roque VG, Jr., Tandoc AO, III, Sy AK, Espino FE et al. Epidemiology of Japanese encephalitis in the Philippines: a systematic review. PLoS Negl Trop Dis 9(3):e0003630 2015.

52. Lopez AL, Aldaba JG, Roque VG, Jr., Tandoc AO, III, Sy AK, Espino FE et al. Epidemiology of Japanese encephalitis in the Philippines: a systematic review. PLoS Negl Trop Dis 9(3):e0003630 2015.

53. Lopez AL, Aldaba JG, Roque VG, Jr., Tandoc AO, III, Sy AK, Espino FE et al. Epidemiology of Japanese encephalitis in the Philippines: a systematic review. PLoS Negl Trop Dis 9(3):e0003630 2015.

54. Lopez AL, Aldaba JG, Roque VG, Jr., Tandoc AO, III, Sy AK, Espino FE et al. Epidemiology of Japanese encephalitis in the Philippines: a systematic review. PLoS Negl Trop Dis 9(3):e0003630 2015.

55. Lopez AL, Aldaba JG, Roque VG, Jr., Tandoc AO, III, Sy AK, Espino FE et al. Epidemiology of Japanese encephalitis in the Philippines: a systematic review. PLoS Negl Trop Dis 9(3):e0003630 2015.

56. UNICEF. Measles Mumps & Rubella: Technical and Supply Information Note. 2015.

57. UNICEF. Measles-Containing Vaccines (MCV): Supply & Demand Outlook. 2014.

58. Nascimento S, Jr., Camacho LA, Siqueira MM, Freire MS, Castro YP, Maia ML et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella. Vaccine 29(37):6327–6334. 2011.

59. World Health Organization. The Immunological Basis for Immunization Series - Module 11: Rubella. 2008. Immunization, Vaccines and Biologicals.

60. World Health Organization. The Immunological Basis for Immunization Series - Module 13: Japanese Encephalitis. 2010. Immunization, Vaccines and Biologicals.

61. **Japanese Encephalitis Vaccine, Live [Package Insert].** Chengdu, China. Chengdu Institute of Biological Products Co. Ltd China; 2013. http://www.who.int/immunization_standards/vaccine_quality/pq271_jev_5dose_chengdu_insert.jpg?ua=1 2013.

62. Hombach J, Solomon T, Kurane I, Jacobson J, Wood D. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2-3 September, 2004. Vaccine 23(45):5205–5211. 2005.

63. U.S.Department of Health and Human Services Division of AIDS. Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf 2014. February 24, 2014.

64. U.S.Department of Health and Human Services Division of AIDS. Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf 2014. February 24, 2014.