PROTOCOL

Protocol Number: INA-201

RESEARCH TITLE:

Implementing a Combination of Clinical Parameters (Rapid Diagnostic Tests, Biomarkers, and Standard of Care Procedures) for The Etiology Diagnoses of Pneumonia in Pediatric Patients to Improve Clinical Management in Indonesia

(PEER-PePPes)

Sponsored by:

Partnerships for Enhanced Engagement in Research (PEER Health)

Indonesia Research Partnership on Infectious Disease (INA-RESPOND)

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TABLE AND FIGURES

GLOSSARY

AE	Adverse Event
AFB	Acid Fast Bacilli
CBC	Complete Blood Count
CRF	Case Report Form
CRP	C-reactive protein
EC	Ethics Committee
EDMS	Electronic Data Management System
FU	Follow-Up
GRTK	Genetic Resources And Traditional Knowledge
GCP	Good Clinical Practice
Hib	Human Influenza Virus B
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INA-RESPOND	Indonesia Research Partnership on Infectious Diseases
IPR	Intellectual Property Rights
IRB	Institutional Review Board
MoP	Manual of Procedure
MTA	Material Transfer Agreement
NPS	Nasopharyngeal Swab
NPV	Negative Predictive Value
PCR	Polymerase Chain Reaction
PCT	Procalcitonin
PPV	Positive Predictive Value
RA	Research Assistant
RDT	Rapid Diagnostic Tests
ROC	Receiver Operating Characteristic
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
SDW	Source Document Worksheet
SAE	Serious Adverse Event
SoC	Standard of Care

RESEARCH SUMMARY

Full title
Implementing a Combination of Clinical Parameters (Rapid Diagnostic Tests (RDTs), Biomarkers, and Standard of Care Procedures (SoCs)) for the Etiology Diagnoses of Pneumonia in Pediatric Patients to Improve Clinical Management in Indonesia.
Short title
PEER PePPes (INA-201)
Study type
Prospective observational study
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Study objectives
Primary objective To develop an algorithm for the diagnosis of viral and bacterial pathogens in pediatric patients with pneumonia.

Secondary objectives

- To identify the etiologies of pneumonia in children in Indonesia, which are currently unavailable.
- To document outcomes in pediatric patients with pneumonia in Indonesia.
- To evaluate the performance of each rapid point of care test (to detect influenza and viral syncytial viruses, legionella urinary antigen, biomarkers of bacterial infections (C-Reactive Protein (CRP) and Procalcitonin (PCT)), and standard of care procedures (Chest X-ray) compared to the gold standard molecular assays in differentiating virus and bacterial infections.
- To analyze the performance of combined tests in differentiating virus and bacterial infections.
- To provide information regarding updated strains of circulating respiratory viruses and pathogens in children.

Study Population

Hospitalized patients with pneumonia whose ages range from 2 months to 5 years.

Sample size

The total sample is 275 participants.

Study duration

Study will accrue participants **up to September 2019**. Each participant will have follow up visits in a period of 30 days from the enrollment day.

Eligibility criteria

Inclusion criteria

- Pediatric inpatients whose ages range from 2 months to 5 years
- Meet the case definition for pneumonia which is cough **or** fever with at least one other following symptoms:
  - ✓ Shortness of breath
  - ✓ Tachypnea
  - ✓ Grunting
  - ✓ Crackles/rhonchi
  - ✓ Decreased vesicular breath sound
  - ✓ Bronchial breath sound
  - ✓ Chest x-ray consistent with pneumonia
- Comply with all study procedures including to store required specimens for diagnostic testing and archiving.

Exclusion criteria

- Being Hospitalized for more than 24 hours at enrollment
- Having a cancer or history of cancer
- Having a history of long term exposed of steroid (at the minimum of 2 months)
- Having any condition that might interfere with study procedure and compliance (based on clinicians' judgement)

Study Procedures
Participants who meet the inclusion and exclusion criteria will be enrolled and then having a daily follow up for maximum of 13 days' hospitalization. Next follow up will be taken time at day 14th after hospitalization date, either on ward or policlinic. The participations will be ended by day 30th after hospitalization date when the called follow up is done by the Research Assistant (RA). This study will collect demographic data, medical history, clinical data, treatment, and risk factors of pneumonia. The study also recorded the supporting examination results include but not limited to Complete Blood Count (CBC) results, blood gas analyses result, CRP, PCT, culture result, rapid test for influenza, Respiratory Syncytial Virus (RSV), legionella, and chest X-ray. In order to produce a robust data, this study will conduct the serological and molecular tests at the reference laboratory. Whole blood, serum, urine, Nasal Pharyngeal Swab (NPS), sputum/induced sputum, and other respiratory specimens (if available) will be collected for storage and testing at enrollment. Any left-over respiratory specimens and/ or plasma on day 2 and 3 of hospitalization will also be collected to be stored. For additional, at day 14th after hospitalization serum will be processed from 4 mL of blood for archiving and testing at the reference laboratory.

1. BACKGROUND

Pneumonia accounts for an estimated 920,136 fatalities or 16% of all deaths in children under five years of age.[1] Based on Indonesia National Basic Health Survey, period prevalence of pneumonia in children under 5 years is 18.5 per mil.[2] The high rate of morbidity in children with pneumonia may be prevented by promoting exclusive breastfeeding, vaccination, and an improved environment, whereas the mortality can be reduced by providing appropriate management including appropriate antibiotic treatment for bacterial infection which is now still very low (30%).[1]

Diagnosing pneumonia using current WHO pneumonia diagnostic criteria is challenging as no one clinical feature is sufficient to diagnose pneumonia definitively. To improve diagnostic performance, a combination of clinical features has to be used. [3] Chest X-rays are neither sensitive nor specific. Radiological findings lag behind clinical findings and are unable to differentiate between viral and bacterial etiologies of pneumonia. Differentiation between viral and bacterial pathogens is becoming more important since the introduction of Hib and pneumococcal vaccines that may shift the substantial causes of pneumonia to viruses. [3] This distinction is also important for guiding appropriate antibiotic treatment. [4] The gold-standard for microbiological pathogen assays require specimens that are difficult to collect such as

nasopharyngeal wash or bronchoalveolar lavage and may need several days for the results to be available.

Considering all the factors above, a combination of rapid diagnostic and biomarker tests, using non-invasive or relatively easily collected specimens, and standard of care procedures may help to differentiate between viral and bacterial pneumonia to better guide management (antiviral vs antibacterial treatment).

2. RESEARCH BENEFITS

This study will provide the data and algorithm to differentiating bacterial and viral pneumonia. This algorithm will be useful to transform the management of pneumonia cases and to determine the prevention strategies as well. Other benefit from this study is to obtain a better understanding of pathogen caused by pneumonia to provide the evidence that might change a clinical pathway, for example, for example, the identification of influenza or other viruses as the causes of pneumonia may have an impact on the perceptions of clinicians and health policy makers that these viruses may also cause severe illness and therefore antiviral should be provided. The importance of viral pathogens as the cause of pneumonia will also have an impact on the risk of nosocomial infection and the need of vaccination to health care workers and children. Thus, better understanding of identified pathogens, particularly the newly reported may bring us to new strains invention. Those benefits hopefully will give us the evidence to advice the policy maker, hospital management, and to increase the clinician awareness.

3. OBJECTIVE

3.1. Primary Objective

To develop an algorithm for the diagnosis of viral and bacterial pathogens in pediatric patients with pneumonia.

3.2. Secondary Objectives

- To identify the etiologies of pneumonia in children in Indonesia, which are currently unavailable.
- To document outcomes in pediatric patients with pneumonia in Indonesia.
- To evaluate the performance of each rapid point of care test (to detect influenza and viral syncytial viruses, legionella urinary antigen, biomarkers of bacterial infections (CRP and PCT), and standard of care procedures (Chest X-ray, O_2 saturation, CBC, blood Gas Analyses (if available) compared to the gold standard molecular assays in differentiating virus and bacterial infections.
- To analyze the performance of combined tests in differentiating virus and bacterial infections.
- To provide information regarding updated strains of circulating respiratory viruses and pathogens in children.

4. METHODS

4.1. Study Plan

For brief explanation of the study plan please go to Figure 1, the study plan.

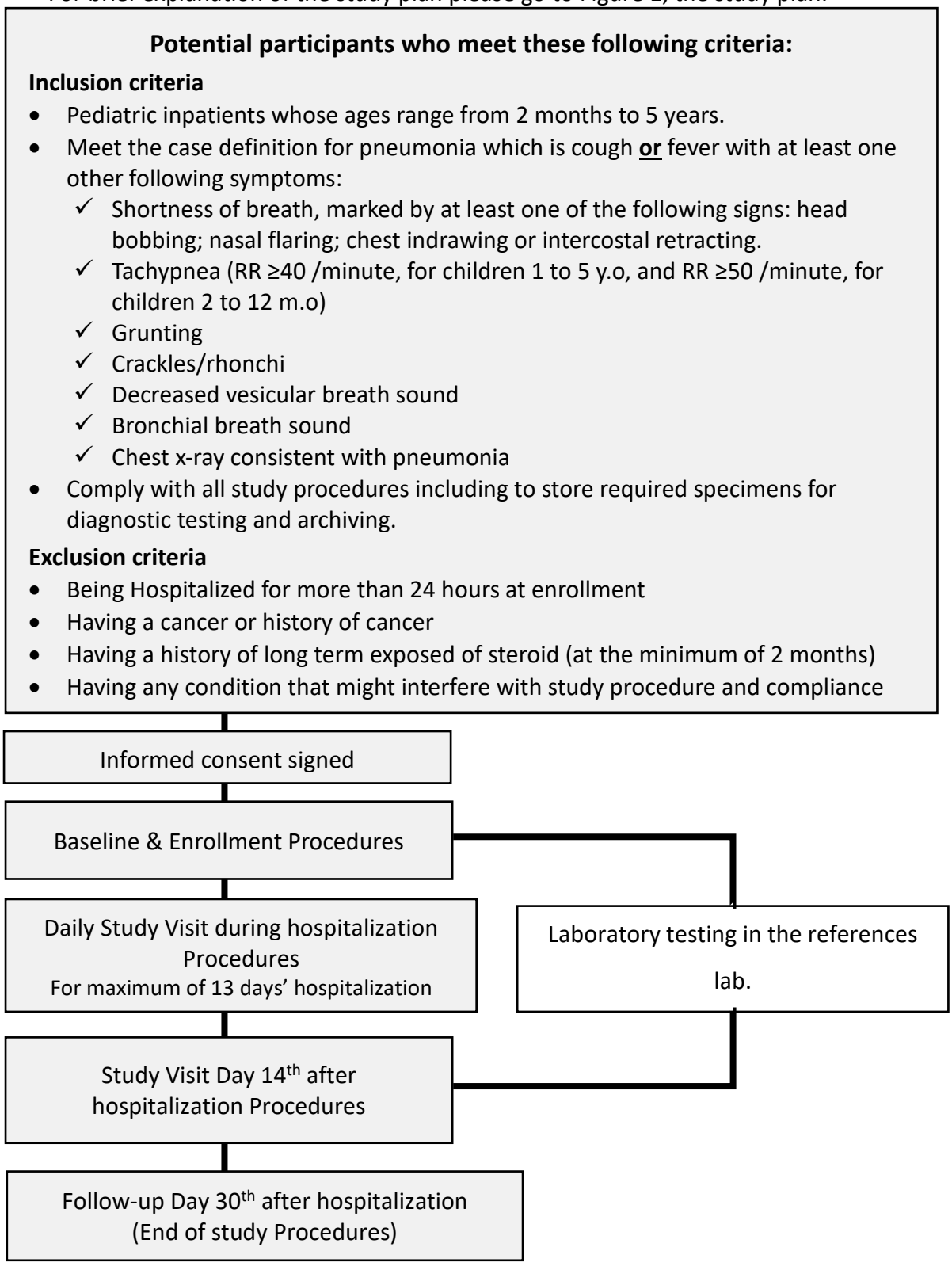

Figure 1. The Study Plan

4.2. Study Sites and Duration

This study will be conducted at following INA-RESPOND sites:

- RSU Kabupaten Tangerang, Tangerang
- RSUP Dr. Kariadi, Semarang
- RSUP Dr. Sardjito, Yogyakarta
- RS An Nisa, Tangerang
- **RSUD Dr. Adhyatma, MPH / RSUD Tugurejo, Semarang**
- **RS Bhakti Wira Tamtama, Semarang**
- **RSA UGM, Yogyakarta**

Maximum duration for participants' accrual will be **up to September 2019**. However, the study laboratory testing may take up to 6 months to be completed.

4.3. Type and Design of Study

This study is an observational study, conducted at the pediatric department at three hospitals in Indonesia. It will recruit hospitalized children aged between 2 months to 5 years who meet the inclusion and exclusion criteria. Participants will be followed up for maximum 13 days' hospitalization. At day 14th after hospitalization date each participant will be assessed for his/her symptoms, clinical data, clinical outcome, and serum specimen collection. The end of their participation will be ended on day 30th after hospitalization date, after followed up phone from RA.

Laboratory test procedures will be conducted during the study and/or after study completion. Chest X-Ray, CBC, blood and respiratory specimen cultures including antibiotic resistance test will be performed either as part of standard of care or study addition. Rapid tests for Influenza A and B; Respiratory Syncytial Virus (RSV); and Legionella will be performed as study requirement. C-reactive protein (CRP) and Procalcitonin (PCT) will also be measured for study interest. Molecular assays to identify bacterial and viral pathogens and serological assays to detect infections of several viruses and bacteria will be conducted at the reference laboratory. Any left-over respiratory specimens and/or plasma from day 2 and 3 hospitalization will be stored for archiving.

Specimen that will be stored for archiving, will be maintained for further laboratory testing for up to 5 years after the study is completed. After 5 years, with the decision of Steering

Committee and Governing Board, specimens in the INA-RESPOND specimen repository in NIHRD Jakarta, will either be destroyed, or after IRB approval, transferred to another existing protocol or a repository.

4.4. Population and Sample Size

This is a preliminary study to characterize the pathogens present in this cohort. The number of participants' that will be enrolled is based on the number of pneumonia cases in 5 years old children or less. This study plan to enroll with total of 275 participants.

With 275 participants, the 95% confidence interval for the prevalence of each pathogen will be no greater than ± 7%. The study is not powered to test the diagnostic accuracy of the algorithm. The algorithm developed from this study will be evaluated in a larger study, powered to estimate sensitivity and specificity. As a result, no formal power calculations have been provided.

4.5. Eligibility Criteria

4.5.1. Inclusion criteria

- Pediatric inpatients whose ages range from 2 months to 5 years.
- Meet the case definition for pneumonia which is cough **<u>or</u>** fever with at least one other following symptoms:
    - ✓ Shortness of breath, marked by at least one of the following signs: head bobbing; nasal flaring; chest indrawing or intercostal retracting.
    - ✓ Tachypnea (RR ≥40 /minute, for children 1 to 5 years old, and RR ≥50 /minute, for children 2 to 12 months old)
    - ✓ Grunting
    - ✓ Crackles/rhonchi
    - ✓ Decreased vesicular breath sound
    - ✓ Bronchial breath sound
    - ✓ Chest x-ray consistent with pneumonia
- Comply with all study procedures including to store required specimens for diagnostic testing and archiving.

4.5.2. Exclusion criteria

- Being hospitalized for more than 24 hours at enrollment
- Having a cancer or history of cancer
- Having a history of long term exposed of steroid (at the minimum of 2 months)
- Having any condition that might interfere with study procedure and compliance (based on clinicians' judgement).

4.6. Study Procedures and Evaluations

4.6.1. Screening and enrollment

Potential pediatric participants who come to the emergency room or outpatient clinic and have been admitted to the hospital will be referred by physicians at participating hospitals to be observed and screened according to the study eligibility criteria. If the patients meet the criteria, the parent/legal guardian will be offered information about the study. If agree, he/she must provide a documented informed consent form (ICF) and will undergo the enrollment procedures. Participants who have finished or completed the study can't be re-screened and re-enrolled into the study.

4.6.2. Baseline (study visit day 0 = day 1 hospitalization)

Following baseline procedures will be collected on all participants, these include:

1. Demographic data including age, sex, birth order, parent's education, parent's occupation, and family income.
2. Medical history including history of mother's pregnancy and breastfeeding, vaccination, vitamin A supplementation, growth and development, history of past and presence illness including congenital disease, and allergic.
3. Clinical data including chief complaint, sign and symptoms, vital signs, anthropometric, initial diagnosed, comorbidities, chest X-Ray (if available).
4. Treatment including antibiotic, steroid, and oxygen therapy.
5. Risk factors including smoking exposure, TB contact, poultry contact (contact with sick and/or dead poultry and contact with poultry's faeces

and/or derivative), contact with someone who has cold, air pollution exposure, going to daycare, living in a densely populated area.

6. Laboratory examinations including CBC test, CRP, PCT, Blood gas analysis, blood culture, respiratory culture (if available), antimicrobial sensitivity test, HIV test, influenza rapid test, legionella Ag, Gram negative test, AFB, Xpert MTB/RIF (according to SoC).
7. Laboratory examinations at the reference laboratory including molecular and serological tests.
8. Specimen archiving including left over specimens (whole blood, serum, urine, NPS, sputum/induced sputum) and isolate from culture (if available)

Whole blood and serum must be collected and processed during 24 hours after the enrollment. Other specimens' collection can be postponed up to 48 hours after the enrollment.

Blood culture should be performed on all participants prior to antibiotic administration in the study site, however any condition where blood culture is done after the antibiotic administer is still allowed. Blood culture worked prior to the enrollment will be recorded in the CRF and no repetition needed.

For the detail of study procedures, please check out the Manual of Procedures (MoP).

4.6.3. Follow up during hospitalization (Daily study visit day 1 up to day 12 = day 2nd up to day 13th hospitalization)

This follow up schedule will be conducted daily during hospitalization of participants, but limited up to daily study visit day 12 (day 13th hospitalization). The following procedures will be collected from each participant, if available:

1. Clinical data including sign and symptoms, vital signs, and chest X-Ray.
2. On-going treatment
3. Specimen archiving. Any respiratory left-over specimen and/or plasma from daily study visit day 1 & 2 (day 2 & 3 of hospitalization) will also be collected to be stored.

4.6.4. During discharge

Hospitalization and discharge information including complication, discharge diagnoses, and clinical outcome. Procedure will be collected at discharge day.

3.6.5. Follow up (Study Visit Day 14th after hospitalization)

This study follow up will be conducted at day 14th after hospitalization. There will be ± 4-days window period for this follow up schedule. The following procedures will be collected from each participant, if available:

1. Clinical data including sign and symptoms, vital signs, anthropometric, clinical outcome.
2. Laboratory examinations at the reference laboratory including serological tests.
3. Specimen archiving. Serum will be collected and stored.

3.6.6. Follow up (day 30th after hospitalization)

In this follow up schedule, the RA will conduct follow up by phone and the participants will be assessed for their self-reported health condition. If needed, home visit can be conducted for this visit. There will be ± 4-days window period for this follow up schedule. No specimen will be collected in this follow up.

3.6.7. Laboratory procedures for Molecular and Serological Testing

This study will carry out molecular and serological testing that will be done at the reference laboratory. The study will cover all the costs of those tests. Table 1 and Table 2 will furtherly explain the required specimen volume and tests needed. Also see appendix A for the work flow.

Table 1. The research specimen and laboratory testing

Visit /Time	Collected Specimen	Amount	Laboratory Testing at	
			Hospital	Reference Lab
Enrollment (up to 24 hours after enrollment)	Whole Blood	2 x 1 ml – 2 ml blood 1 x 3 ml blood	Blood culture (2 sides) CBC	PCR (Streptococcus pneumonia, Staphylococcus aureus, Haemophilus influenza)
	Serum	1 x 4 ml blood	CRP, Procalcitonin, HIV (can be done up to 5 days after enrollment)	Serology IgM and IgG (Influenza A, B, RSV, Parainfluenza virus, Adenovirus, Mycoplasma pneumonia, Chlamydia pneumonia, Bordetella pertussis, Legionella pneumonia)
Enrollment (up to 48 hours after enrollment)	Urine	1 ml – 3 ml urine	Rapid test Legionella antigen	PCR (Legionella pneumoniae, Leptospira)
	Nasopharyngeal swab	2 VTM (1.5 ml)	Rapid test Influenza Rapid test RSV	PCR (18- Viral Panel)
	Sputum/induced sputum	2 ml	Culture, MTB (genexpert, if AFB positive)	PCR (11 Bacterial and 18 viral panel)
	Other resp specimen (leftover – efusi pleura, BAL)	If available	Culture, MTB (genexpert, if AFB positive)	PCR (11 Bacterial and 18 viral panel)
Daily study visit during hospitalization	**Left-over respiratory specimen and/or plasma (Daily study visit day 1 & 2 (day 2 & 3 of hospitalization)**	**If available**	**None**	**TBD**
Study Visit Day 14th after hospitalization	Serum	4 ml blood	None	Serology IgM and IgG (Influenza A, B, RSV, Parainfluenza virus, Adenovirus, Mycoplasma pneumonia, Chlamydia pneumonia, Bordetella pertussis, Legionella pneumonia)
Follow-up Day 30th **after hospitalization**	None	None	None	None

NOTE: Maximum amount of blood drawn in pediatric patients weight 7.3 – 45.5 kgs is 10 ml - 30 ml at any one time or 60 ml – 350 ml cumulative during hospitalization or maximum 1 month (Garza D, Becan-McBride K).

Table 2. PCR Panel for Bacterial & Viral Pathogens

PCR Viral Panel	PCR Bacterial Panel
Human Influenza A virus	*Haemophilus influenza*
Human Influenza B virus	*Streptococcus pneumoniae*
Adenovirus	*Legionella pneumoniae*
Enterovirus	*Mycoplasma pneumoniae*
Respiratory Syncytial Virus A	*Chlamydia pneumoniae*
Respiratory Syncytial Virus B	*Chlamydia psittaci*
Human Metapneumo virus	*Bordetella pertussis*
Rhinovirus	*Moraxela catharalis*
Human Parainfluenza Virus 1	*Staphylococcus aureus*
Human Parainfluenza Virus 2	*Klebsiella pneumoniae*
Human Parainfluenza Virus 3	*Burkholderia pseudomallei*
Human Parainfluenza Virus 4	
Corona Virus 22E	
Corona Virus OC43	
Corona Virus SARS	
Corona Virus NL63	
Parechovirus	
Bocavirus	

4.7. Study Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The Investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Research Team.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or Institutional Review Board (IRB) terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to the planned termination time period, and study site team will record the reason(s) for all withdrawals from the study in participants' study records.

4.8. Study disposition status

Study disposition status will be completed by the Research Assistant when the participants considered as end of study. Participants followed until 30 days after hospitalization will be considered as completing the study procedure and end of study.

The rest of the Participants will be considered as end of study at the following time point:

- Participant is dead
- Participant withdraws consent
- Participant who can't be reached for follow-up visit (lost to follow-up)
- Based on investigator discretion
- Termination of study

4.9. Study Instruments

The following instruments will be used in this study. Further information will be found in the study MOP.

a. Forms
    - Informed consent
    - Source Document Worksheet (SDW)
    - Case Report Form (CRF)

b. Log
    - Screening log
    - Enrollment log
    - Specimen log

c. Electronic Database
    - OpenClinica
    - Manual Specimen Repository Database
    - INA-RESPOND Electronic Data Management System (EDMS)

5. LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

5.1. Universal Precaution and Biohazard Containment

As the transmission of blood-borne pathogens and air-borne pathogens can occur through contact with contaminated needles, blood, respiratory specimens and its products, appropriate blood and secretion precautions will be employed by all personnel

in the drawing of blood, collecting respiratory specimen, shipping and handling of all specimens for this study. These will be further described in the study MoP.5.2 Specimen Collection and Aliquots

Each study site will adhere to standards of good clinical laboratory practice and the study SOPs for specimen management including proper collection, processing, alliquoting, labeling, transport, and storage of specimens. In general, all laboratory procedures will be done locally in the study sites and in the reference laboratory for molecular and serological testing. These will be further described in the study MoP.

Samples will be collected at baseline and some follow-up visits according to the study procedures. If available, specimens will be tested either on hospital laboratory or reference laboratory. Samples will be coded with a unique identifier that does not contain any information capable of linking the sample to the participant. A code that links the unique identifier with the study volunteer will be kept in a locked file cabinet in a secure room or on a password-protected computer. Only authorized personnel will have access to the code.

Specimens from blood approximately will be divided into aliquot of 3. One will be stored at the site and two will be sent to the reference laboratory.

5.2. Specimen Repository and Destruction

Some of the specimens collect under this protocol would be stored for repository. Based on the clinical presentation and laboratory data, the researchers will determine further testing to be done on specimens from participants who are willing to allow storage of specimens for use in future studies of infectious disease. Upon this evaluation, researchers will develop a new protocol. Specimen will be maintained for further laboratory testing for up to 5 years after the study is completed. After 5 years, with the decision of Steering Committee and Governing Board, specimens in the INA-RESPOND specimen repository in NIHRD Jakarta, will either be destroyed, or after IRB approval, transferred to another existing protocol or a repository. The used and destruction of the archived specimens in the future, will be determined per INA-RESPOND SOP of Specimen Ownership, Access, and Use (see appendix C).

6. DATA MANAGEMENT AND ANALYSIS

6.1. Data Management

Participants' data will be coded with a unique identifier that does not contain any information capable of linking the data to the study participants. A code that links the unique identifier with the study participants will be kept in a locked file cabinet in a secure room. Only authorized study personnel will have access to the code and the data. Data will be keyed and tracked using the OpenClinica.

Data will be periodically sent to the INA-RESPOND Central Data Management Center. Site and national data will be analyzed by all investigators. The investigator is responsible for ensuring that the data collected is complete, accurate and recorded in a timely manner. Following each study visit, the investigator or designated site staff member will upload the completed Case Report Form (CRF) to INA-RESPOND EDMS. The data will then be entered into the database and reviewed for completeness and accuracy. The study team will be notified of any discrepancies for clarification.

The study team should also complete accurate source documentation to support the data collected on the CRF. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Source documents include, but are not limited to, the participant's medical records, laboratory reports, X-ray(s), radiologist reports, participant progress notes, pharmacy records and any other similar reports or records of procedures performed in accordance with the protocol.

It is not acceptable for the CRF to be the only record of the participant's participation in the study and participant progress should also be recorded in the participant medical records. This is to ensure that anyone who would access the participant's medical records has adequate knowledge that the participant is participating in a clinical study.

Any document that acts as a source document (the point of the initial recording of a piece of data) should be signed and dated by the person recording or reviewing the data for issues of medical significance (for example the review of laboratory reports). Persons signing the source documents should be listed as a site staff member.

6.2. Analysis

An interim analysis will be conducted every 3-6 months to discuss the operation and challenges of the screening and enrollment process, the collection of data and specimens, and to analyze the results of bacterial culture, biomarkers, rapid diagnostic tests, molecular and serogical assays.

It is expected that the gold standard measurements will fall into three categories: confirmed viral (33%), confirmed bacterial (20%), and mixed/unconfirmed (47%). For purposes of algorithm development and assessment, we will combine the latter two groups (confirmed bacterial and mixed/unconfirmed) into a single group. The justification for the grouping is that clinically, a patient who receives a mixed/unconfirmed diagnosis will likely be treated in the same manner as a patient with a confirmed bacterial diagnosis.

As this is a preliminary study, we will fit the data using a variety of different approaches for combining diagnostic tests, including classification and regression trees, random forests, and multivariate logistic regression. For models with binary outputs, we will calculate the sensitivity and specificity (defined using confirmed bacterial as "cases" and confirmed viral as "controls"). For models with continuous outputs, we will calculate the receiver operating characteristic (ROC) curve. The relative performance of the models will primarily be evaluated based on sensitivity and specificity. 10-fold cross- validation or similar methods will be used to account for potential over optimism from fitting multiple models.

While clinical relevance is of primary importance, we may also consider algorithms that perform three-category classifications (with the categories as originally defined), as such results may be of etiologic interest. Furthermore, for all analyses, we may consider calculating the positive predictive value (PPV) and negative predictive value (NPV); while sensitivity and specificity are of primary importance, PPV and NPV may provide further useful descriptive information.

6.3. Operational Definitions

- Fever : temperature recorded ≥ 37.5°C during the first 24 hours period of hospitalization or at home.
- Study specimens: specimens collected from study subjects.

- Respiratory samples: leftover respiratory samples (BAL, pleural fluid, etc) that are collected by the attending physician based on clinical presentation.
- Study clinical data: clinical data collected from study subjects.
- Study completion: Subjects followed until 30- days (± 4-days window period) after hospitalization or die.
- Subject withdrawal: if the subject's parents or legal guardians decides to voluntarily discontinue participation or the study physician decides to terminate subject participation at any time during the study.
- Missed visit: a scheduled study visit which a study subject fails to attend or a home visit does not occur.

7. REPORTING THE LOSS OR UNANTICIPATED DESTRUCTION OF SPECIMENS/ DATA TO THE IRB

Any loss or unanticipated destruction of data or samples (for example, due to freezer malfunction) that compromises the scientific integrity of the data collected for the study will be reported to the IRB. Additionally, participants may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the participant and to the IRB.

8. RESEARCH MONITORING

The study will be conducted in compliance with this protocol, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), and any applicable regulatory and ethical requirement(s). Independent monitors, under contract by the Sponsor, will visit the study sites to monitor all aspects of the study in accordance with the monitoring plan. The objective of a monitoring visit is to oversee the progress of the study, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., ICF, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related

documentation by authorized representatives of the local IRB or ethic committee (EC), the local and national regulatory authorities, and the sponsor representatives. A site visit log will be maintained at the study site to document all study monitoring and auditing visits.

9. SAFETY MONITORING AND REPORTING

All reportable adverse events (events that occur within 48 hours of the study specimen collection and are possibly, probably, or definitely related to the study specimen collection) that result in a serious outcome (Serious Adverse Event (SAE)) will be evaluated by Site PI within 24 hours of the investigator's awareness. The SAE will also be reported to the IRB within 10 working days, **or follows on local ethic requirement**, of the investigator's awareness.

All reportable adverse events (events that occur within 48 hours of the research blood draw and are possibly, probably, or definitely related to the research blood draw) will be reported in the summary form to the IRB at the time of Continuing Review.

All reportable event (RE) and unanticipated problem (UP) will be reported by the site PI to the IRB within 10 working days, or follows on local ethic requirement, of the investigator's awareness as required for US federally funded trials.

9.1. Definition of an Adverse Event

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject that occurs within 48 hours of a study-related study blood specimen collection that is possibly, probably, or definitely related to the study specimen collection. Any event outside of this 48 hours' window period will not be considered an AE for this study.

But for induce sputum collection, if the subject's conditions worsening from the original condition prior to the enrollmentis observed such as, but not limited to, increase in coughing or wheezing, it will be considered as AE for this study if occurred within 2 hours after sputum induction procedure. For every AE that occurs based on the subject's conditions, the RA needs to consult with the site PI or site Co-PI to determine AE or not.

9.2. Definition of a Serious Adverse Event

A serious adverse event (SAE) is defined as any AE related to study specimen collection that **meet one / more of the <u>seriousness criteria</u> below**:

- Death
- Life-threatening (places the subject at immediate risk of death from the event as it occurred);
- **Requires** in inpatient hospitalization **(unplanned hospitalization)** or prolongation of existing hospitalization**;**
- Persistent or significant **disability** / incapacity**;**
- Congenital anomaly/birth defect **or fetal/neonatal death;** or
- **Important Medical Event:** Based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition**.**

9.3. Definition of Reportable Event

A Reportable Event (RE) is defined as any event <u>outside</u> of an AE definition that meet one / more <u>seriousness criteria</u> as stated in the section 9.2.

9.4. Definition of an Unanticipated Problem

An unanticipated problem is defined as any incident, experience, or outcome that is defined as:

1. Unexpected in terms of nature, severity, or frequency in relation to:
    - the research risks that are described in the research protocol and informed consent document or other study documents; and
    - the characteristics of the subject population being studied; and
2. Related or possibly related to the participation in the research; and
3. Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized or is an SAE.

10. ETHICAL CONSIDERATION

10.1. Informed consent process

Informed consent is a process in which information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an ongoing conversation between the human research subject and the researchers covering the essential

information about the study which begins before consent is given and continues until the end of the subject's involvement in the research.

Their parents or legal guardians will sign an ICF after discussion of essential information about the research by the study staff. This will include the purpose of the study, duration, procedures, alternatives, risks, and benefits. Subjects and/or their parents or legal guardians will have the opportunity to ask questions about the study and have their questions answered.

Legal guardian is a person who has rights and responsibilities to look after / take care the child. They are usually related by blood, members of the family, or legal parents of an adopted child. Neighbor, friends, or maid of the family cannot serve as the child's legal guardian.

Subject's parent or legal guardian will sign/thumb print an appropriate informed consent document prior to any procedures being done specifically for the study. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the signing of the consent form in each subject's study record.

10.2. Illiterate Subject's parent or legal guardian

If the subject's parent or legal guardian is illiterate, oral consent will be obtained. The administrator of the oral consent will sign and date the form. The subject's parent or legal guardian will thumbprint the consent form. An impartial witness should be present during the entire informed consent discussion and should sign and date the consent form.

10.3 Parental Consent

Parental/legal guardian consent will be obtained for all study subjects. For further information, please refer to IRB checklist: studies involving children.

10.4. IRB Review

Prior to the implementation of the protocol, the protocol and ICF for this study will be submitted for approval to the appropriate IRB. Any change to the protocol, ICF, or a change of the site investigator, will only be made after approval from the IRB. Records of the IRB review and approval of all the documents pertaining to the study will be kept on file by the site investigator and are subject to inspection at any time during the study. Continuing

reviews or study progress report will be submitted according to the requirement of the appropriate IRB, but once a year at a minimum.

10.5. Participant Confidentiality

All records will be kept co*nfidential to* the extent provided by the law. The study monitors and other authorized representatives may inspect all documents and records required to be maintained by the site investigator, including, but not limited to, medical records. Records will be kept in a locked cabinet, and all computer entry and networking programs will be done with coded numbers only. Clinical information, attributable to the subject, will not be released without written permission of the subject, except as necessary for monitoring by INA-RESPOND and the EC/IRB.

10.6. Rationale for Subject Selection

Children under age 2 month are excluded from participating in the study due to concerns regarding blood volume.

10.7. Benefits

This study is meant as a pilot study to provide knowledge on the etiology of pneumonia among hospitalized pediatric patients in study hospitals and to identify areas of potential research in the future. It may not provide direct benefit to participants. All test may help the physician to establish diagnose.

The study will provide two blood cultures, sputum culture, CBC, CRP, Procalcitonin and rapid diagnostic test for Influenza, RSV, and Legionella as listed in section 4.6.6 and 4.6.7. Transportation costs and time compensation will be reimbursable up to Rp.150,000 for study Visit Day 14th after hospitalization. The study will not provide costs for routine care or hospitalization.

10.8. Risks and Discomforts

This is a minimal-risk, observational study and does not involve experimental interventions. The only study intervention is a blood draw and all other procedures are considered as part of standard care for hospitalized pneumonia patients.

The hazards of blood drawing are minimal and consist of mild discomfort and or bleeding at the venipuncture site, bruising and rarely fainting and local infection. In case of any immediate serious side effect like fainting the patient will be stabilized by the study team if needed.

The hazards of sputum collection are minimal and consist of mild discomfort when subjects tried to produce sputum to be collected.

10.9. Plan for Maintaining Privacy and Confidentiality of Subject Records

The information obtained during the conduct of this clinical study is confidential. The results of the research study may be published according to the INA-RESPOND policy, but subject names or identities will not be revealed. To maintain confidentiality, study documents, including case report forms will be kept in locked filing cabinets, in a secure room at each clinical research site.

10.10 Recording/Documentation

At each contact with the subject, assessment information will be elicited by appropriate questioning and examination, and they will be recorded on source documents. Source documents may include worksheets, progress notes, laboratory reports, consult notes, and data collection tools. Data is to be transcribed onto CRFs from source documents on an ongoing basis during the study. The study monitor may review and audit all documents and records required to be maintained by the site investigator.

Any type of corrections to study documents should be initialed and dated by the person who is making the correction. The site investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. All CRFs should be reviewed by the site investigator and signed as required with written signature. CRFs will be maintained and kept in locked cabinets at the site for at least 5 years after study completion.

Each subject's name will be paired with a numeric code in the enrollment log. Access to data identifying subjects will be kept in a locked file, accessible only by study staff. Finally, the importance of subject confidentiality will be impressed upon all research staff. The site investigator is responsible for the accuracy and completeness of the data reported.

11. PROTECTION OF INTELLECTUAL PROPERTY (IPR), MATERIAL TRANSFER AGREEMENT (MTA), AND GENETIC RESOURCES AND TRADITIONAL KNOWLEDGE (GRTK)

11.1. Publication and Dissemination Policy

Publication of the results of this study will be governed by the INA-RESPOND publication policy. Any presentation, abstract, or manuscript will be made available for review by the supporters prior to submission.

Publication and dissemination will be guided by the IPR terms as outlined in Article X and Annex I of the Science and Technology agreement between the Government of the Republic of Indonesia and the Government of the United States of America. Article X (Protection of Intellectual Property) states:

1. Provisions for the protection and distribution of intellectual property created or furnished in the course of cooperative activities under this Agreement are set forth in Annex I, which shall form an integral part of this Agreement.
2. Scientific and technological information of a non-proprietary nature resulting from cooperation under this Agreement (other than information which is not disclosed for commercial or industrial reasons) shall be made available, unless otherwise agreed, to the world scientific community through customary channels and in accordance with normal procedures of the participating agencies and entities.

and under Paragraphs III.A and III.B(1), (2)(a), (2)(b), (2)(c) of Annex I, Intellectual Protection Rights, of the Science and Technology agreement between the Government of the Republic of Indonesia and the Government of the United States of America.

11.2. Material Transfer Agreement

Research materials used in the collaborations under this protocol may, on agreement of the participants, be transferred using Material Transfer Agreements (MTAs) as appropriate in the particular collaborations, as outlines in Article VIII of the Science and Technology Agreement.

11.3. Genetic Resources and Traditional Knowledge

The collection, conservation and exchange of genetic resources and associated traditional knowledge under this protocol shall be subject to Article VI of the S and T Agreement and will be based on the following considerations:

- Obtaining informed consent from appropriate authority/institutional review board prior to accessing genetic resources collected during the conduct of this protocol.
- Equitably sharing the benefits arising from the use of traditional knowledge and genetic resources.

The complete Science and Technology agreement between the Government of the Republic of Indonesia and the Government of the United States of America is in Appendix B.

12. RESEARCH TEAM

ROLE	NAME, INSTITUTION & LOCATION	EXPERTISE	CONTACT INFORMATION
Principal Investigator	dr Herman Kosasih, PhD INA-RESPOND, Jakarta	Infectious Disease	Phone: 0816 1182 072 Email: hermaninarespond@gmail.com
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US Collaborator	Dr Sophia Siddiqui, MPH NIAID, Bethesda, Maryland, USA	Public Health	Phone: +1301 496 7196 Email: Sophia.siddiqui@nih.hhs.gov
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Co-Principal Investigator	dr. Arif Budiman, SpA RSU Kab. Tangerang, Tangerang	Pediatrician	Phone: 0817 0871 080 Email : abud_817@yahoo.com
Co-Principal Investigator	dr. Chakrawati Hayuningsih, Sp.PK, MARS RS An Nisa, Tangerang	Pathology Clinic	Phone: 08128343367 Email : chakrawati_h@yahoo.com
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Co-Principal Investigator	**Dr. Setya Dipayana, SpA** **RSUD Dr. Adhyatma, MPH / RSUD Tugurejo, Semarang** **RS Bhakti Wira Tamtama, Semarang**	**Pediatrician**	**Phone: 081325388788** **Email: doktersetya@gmail.com**
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INA-RESPOND Investigator	Dr M Karyana, MKes NIHRD, Jakarta	Public Health	Phone: 0816 789 817 Email: mkaryana@gmail.com

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	Jason Liang, PhD NIAID, Bethesda, Maryland, USA	Statistician	Email: Jason.liang@nih.gov

13. APPROXIMATE TIMELINE OF PLANNED RESEARCH ACTIVITIES

	2017												2018	2019										
	J	F	M	A	M	J	J	A	S	O	N	D		J	F	M	A	M	J	J	A	S	O	N	D
Protocol & ICF development	X	X																						
IRB submission & approval		X	X																					
Site feasibility, assessment	X	X																						
Study Preparation	X	X	X	X	**X**	**X**																		
Study duration							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**
Patient recruitment							X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**						
Specimen and Data collection							X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**						
Interim Analysis										X	X	X	X	X	X	X	**X**	**X**	**X**						
Data Analysis										X	X	X	X	X	X	X	X	X	X	X	X	X	**X**	**X**	**X**
Data Dissemination & Publication																	X	X	X	X	X	X	X	X	X

14. PRINCIPAL INVESTIGATOR'S CURICULUM VITAE

Herman Kosasih

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HKosasih@ina-respond.net

Experience	Scientific Lead, Indonesia Research Partnership on Infectious Diseases (INA-RESPOND) October 2010-now, INA RESPOND, Jakarta, Indonesia Secretary for the "WHO CC for influenza at the human and animal interface" establishment team October 2010-September 2011, NIHRD, Ministry of Health, Indonesia
	Medical Research Scientist, Head of Clinical Studies, Viral Diseases Program August 1998-May 2010, NAMRU#2, Jakarta, Indonesia
	Medical Advisor January 1998-August 1998, PT Darya Varia Laboratoria, (Pharmaceutical Company) Jakarta, Indonesia
	Head of Primary Health Center July 1996-December 1997, Puskesmas Dieng Kulon, Banjarnegara, Central Java, Indonesia Head of Primary Health Center February 1992-August 1993, Puskesmas Wawo Utara, Bima, NTB, Indonesia

Education	2014: PhD, Radboud University, Nijmegen, The Netherlands 2009: Emerging Infectious Disease Certificate, Iowa University 2008: Post Graduate Certificate in Medical Virology, Liverpool University, UK (by distance) 2002: Summer Training in Epidemiology, Erasmus University, Rotterdam, The Netherlands 1990: Medical Doctor, Padjadjaran University, Bandung, Indonesia
Organization	Indonesia Medical Association
References	Dr Kevin R Porter, NMRC, Silver Spring, US Patrick J Blair, PhD, NHRC, San Diego, US Prof Dr. David M Muljono, PhD, Eijkman Institute, Jakarta, Indonesia Dr. Bachti Alisjahbana, PhD, Medical Research Center, Padjadjaran University, Bandung, Indonesia
Peer-review publication	**Detection and identification of coxsackievirus B3 from sera of an Indonesian patient with undifferentiated febrile illness**. Wiyatno A, Antonjaya U, Ma'roef CN, et al. J Infect Dev Ctries. 2016 Aug 31;10(8):880-3 **Case report: Weil's disease with multiple organ failure in a child living in dengue endemic area.** Lokida D, Budiman A, Pawitro UE,et al.BMC Res Notes. 2016 Aug 15;9(1):407. **Comparison of the Hemagglutination Inhibition Test and IgG ELISA in Categorizing Primary and Secondary Dengue Infections Based on the Plaque Reduction Neutralization Test.** Lukman N, Salim G, Kosasih H, et al. Biomed Res Int. 2016;2016:5253842 **Global Influenza B Study. Temporal Patterns of Influenza A and B in Tropical and Temperate Countries: What Are the Lessons for Influenza Vaccination?** PLoS One. 2016 Mar 31;11(3) Caini S, Andrade W, Badur S, et al. **The Epidemiology, Virology and Clinical Findings of Dengue Virus Infections in a Cohort of Indonesian Adults in Western Java**. PLoS Negl Trop Dis. 2016 Feb 12;10(2) **Kosasih H**, Alisjahbana B, Nurhayati, et al. **Study of viremic profile in febrile specimens of chikungunya in Bandung, Indonesia.** J Clin Virol. 2016 Jan;74:61-5. Riswari SF, Ma'roef CN, Djauhari H, et al. **Epidemiological and virological characteristics of Influenza B: results of the global influenza B study**. Influenza Other Respir Viruses. 2015 Aug;9 Suppl 1:3-12. Caini S, Huang QS, Ciblak MA, et al; Global Influenza B Study. **INA-RESPOND: a multi-centre clinical research network in Indonesia.** Health Res Policy Syst. 2015 Jul 29;13:34. Karyana M, **Kosasih H**, Samaan G, Tjitra E, Aman AT, Alisjahbana B, Fatmawati, Gasem MH, Arif M, Sudarmono P, Suharto, Merati TP, Lane C, Siswanto, Siddiqui S.

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APPENDICES

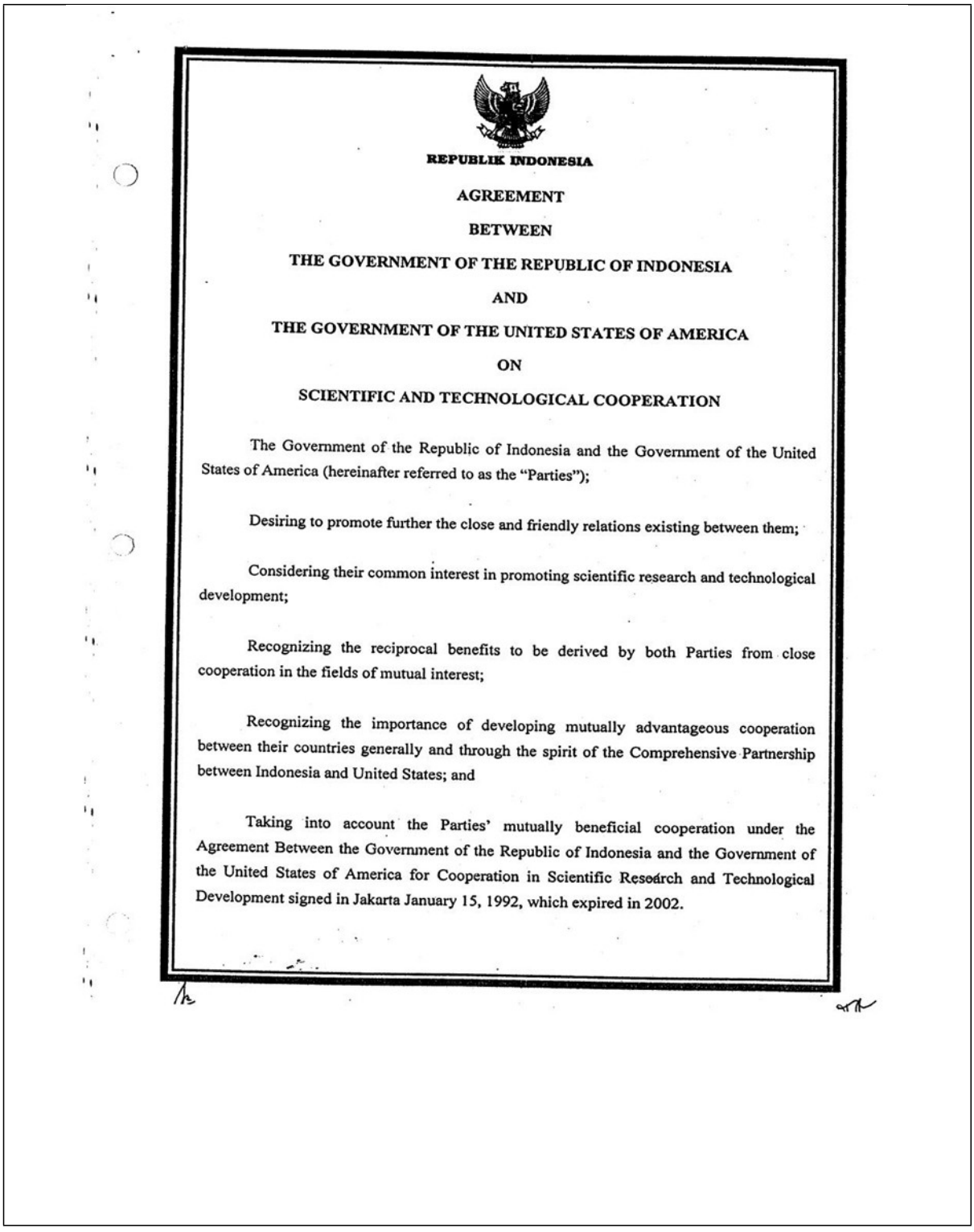
Appendix A. Laboratory Work Flow

<table>
<tr><th colspan="2">Enrollment Visit</th></tr>
<tr><td>Clinical Data collection (Demography, vital sign, initial information, oxygen therapy, signs and symptoms, pregnancy, vaccination and breast-feeding history, history of antibiotic and steroid administration, medical history, risk factors history, Chest X-ray, hematology, chemistry result, culture result, microscopic and Rapid test result, antibiotic sensitivity, collected and stored specimen)</td><td>Specimen collection for study: whole blood, Serum, Nasopharyngeal swab, Sputum/induced sputum, Urine, and isolate from culture (if available).

Lab testing:
a. SOC: Blood culture and culture from respiratory specimen
b. Study required:
- At the hospital: CBC, CRP, Procalcitonin, HIV, Rapid Diagnostic Test (Influenza A&B, RSV, Legionella)
- At reference lab:
• PCR (Streptococcus pneumonia, Staphylococcus aureus, Haemophilus influenzae, Legionella pneumoniae, Leptospira, 18- Viral panel, 11 bacterial panel)
• Serology IgM and IgG (Influenza A,B, RSV, Parainfluenza virus, Adenovirus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis, Legionella pneumoniae)</td></tr>
<tr><th colspan="2">Daily Study Visit during hospitalization
for maximum of 13 days' hospitalization</th></tr>
<tr><td>Clinical data collection:
-Daily: vital signs, signs and symptoms, chest x-ray, oxygen therapy, hematology, blood gas analysis, hematology, stored leftover specimen
-At discharge: Hospitalization information, clinical outcome at discharge</td><td>Specimen collection: If available store left-over respiratory specimens from daily study visit day 1 & 2 (day 2 & 3 of hospitalization)</td></tr>
<tr><th colspan="2">Study Visit Day 14th after hospitalization</th></tr>
<tr><td>Clinical data collection (vital sign, signs and symptoms, clinical outcome during day 14, collected specimen)</td><td>Specimen collection: serum
Lab testing at reference lab :
• Serology IgM and IgG (Influenza A, B, RSV, Parainfluenza virus, Adenovirus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis, Legionella pneumoniae)</td></tr>
<tr><th colspan="2">Follow-up Day 30th after hospitalization</th></tr>
<tr><td colspan="2">Clinical Data collection (Outcomes)</td></tr>
</table>

Study Outcome Analysis

Appendix B. Science and Technology agreement between the Government of the Republic of Indonesia and the Government of the United States of America.



REPUBLIK INDONESIA

AGREEMENT

BETWEEN

THE GOVERNMENT OF THE REPUBLIC OF INDONESIA

AND

THE GOVERNMENT OF THE UNITED STATES OF AMERICA

ON

SCIENTIFIC AND TECHNOLOGICAL COOPERATION

The Government of the Republic of Indonesia and the Government of the United States of America (hereinafter referred to as the "Parties");

Desiring to promote further the close and friendly relations existing between them;

Considering their common interest in promoting scientific research and technological development;

Recognizing the reciprocal benefits to be derived by both Parties from close cooperation in the fields of mutual interest;

Recognizing the importance of developing mutually advantageous cooperation between their countries generally and through the spirit of the Comprehensive Partnership between Indonesia and United States; and

Taking into account the Parties' mutually beneficial cooperation under the Agreement Between the Government of the Republic of Indonesia and the Government of the United States of America for Cooperation in Scientific Research and Technological Development signed in Jakarta January 15, 1992, which expired in 2002.

Have agreed as follows:

ARTICLE I
GEOGRAPHIC APPLICATION

For the purposes of this Agreement and for any implementing arrangements or agreements concluded pursuant to this Agreement, unless otherwise provided:

1. The term "Indonesia" means the territory of the Republic of Indonesia and the adjacent seas over which the Republic of Indonesia has sovereignty, sovereign rights or jurisdictions in accordance with the provisions of the 1982 United Nations Convention on the Law of the Sea.

2. The term "United States" means the United States of America. When used in a geographical sense, the term "United States" means the territory under the sovereignty of the United States and includes those parts of the continental shelf and adjacent seas over which the United States exercises sovereign rights in accordance with international law.

ARTICLE II
OBJECTIVES

1. The purposes of this Agreement are to strengthen scientific and technological capabilities of the Parties, to broaden and expand relations between the scientific and technological communities in both countries, and to promote scientific and technological cooperation in areas of mutual benefit for peaceful purposes.

2. Priority will be given to collaborations that provide opportunities to exchange ideas, information, skills, and techniques and to collaborate on scientific and technological endeavors of mutual interest on an equal basis including but not limited to:

a) science-based decision making;
b) agriculture, biotechnology and plant and animal health;

c) health sciences, including telemedicine, and biomedical and behavioral research;
d) medicinal science, including joint pharmaceutical research and vaccine research collaborations;
e) food safety;
f) biological sciences, including improving capacity building to strengthen biological laboratory safety and pathogen security;
g) information and communication technologies, including spatial data infrastructure;
h) transportation;
i) energy, including renewable and alternative energy;
j) marine research, including fisheries;
k) space, nanotechnology and advanced technologies, including remote sensing;
l) earth sciences, including geo-hazards, earth observation, and atmospheric sciences;
m) standards and metrology;
n) materials science;
o) social and humanities science;
p) natural and physical sciences, including mining and reclamation;
q) environment;
r) forestry, including forest fire prevention and forest industries;
s) biodiversity;
t) integrated watershed management;
u) science and technology education;
v) research and education exchanges;
w) science, technology and engineering for sustainable development; and
x) other areas of scientific and technological cooperation as may be mutually agreed upon.

3. Cooperative activity shall not proceed under this Agreement unless the Parties are satisfied that the relevant government agencies or other designees of the two

Parties have agreed to an implementing arrangement or agreement or the Parties have decided that an implementing arrangement or agreement is not necessary.

4. Cooperative activities shall be conducted in accordance with the applicable laws and regulations in each country.

ARTICLE III
MEANS OF COOPERATION

1. The Parties shall encourage and facilitate cooperation through appropriate means including:

a. exchanges of scientific and technical information;
b. exchanges of scientists and technical experts;
c. education, training and/or capacity building workshops of scientists and technical experts;
d. exchanges of best practices related to science and technology;
e. the convening of joint seminars and meetings;
f. the conduct of joint research projects;
g. the development of direct contacts and cooperation between government agencies, universities, research centers, institutions, private sector companies, and other entities of the two countries; and
h. other forms of scientific and technological cooperation as may be mutually agreed upon.

2. Cooperation under this Agreement shall be based on shared responsibilities and equitable contributions and benefits, commensurate with the Parties' respective scientific and technological strengths and resources.

ARTICLE IV
IMPLEMENTING AGENCY

Each Party will designate a point or points of contact for the coordination of requests for necessary authorizations for the purpose of scientific research, including requests for the

notification and approval of requests for authorizations for access to the waters and terrestrial airspace under national jurisdiction in accordance with international law, and will treat those requests with diligence, taking into account the significance of these activities to the advancement of scientific knowledge.

ARTICLE V
EXECUTIVE OFFICERS AND THE JOINT COMMITTEE

1. The Parties shall establish a Joint Committee for coordinating and facilitating cooperative activities under this Agreement composed of representatives designated by the Parties. The Committee shall conduct a joint review of activities, joint research projects, matters of importance in the fields of science and technology research, and policies related to the overall scientific and technological research relationship between the Parties under this Agreement periodically in a meeting that shall take place alternately in the United States and in Indonesia.

2. Each Party will select an Executive Officer responsible for the coordination and facilitation of cooperative activities under this Agreement, including coordination of Joint Committee meetings on scientific and technological cooperation between the Parties. For the United States, this shall be the Director of the Office of Science and Technology Cooperation in the Bureau of Oceans, Environment and Science of the U.S. Department of State. For Indonesia, this shall be the Director for International Research, Science and Technology Cooperation, the Ministry of Research and Technology of the Republic of Indonesia.

3. In the intervals between the sessions of the Committee, the Executive Officers of the Parties shall meet, if necessary, to discuss and further the implementation of this Agreement and to exchange information on the progress of programs, projects and activities of common interest, which may include review of intellectual property rights under this Agreement, and implementing arrangements under this Agreement, as outlined in Article X and Annex I.

ARTICLE VI
IMPLEMENTATION

1. The Parties may encourage, facilitate, and, where appropriate coordinate, the development of direct contacts and cooperation between government agencies, universities, research centers, institutions, and other entities as mutually agreed by the two countries.

2. The implementing arrangements or agreements concluded by government agencies or other designees of the Parties may cover, as appropriate, topics of cooperation in science and technology, means of cooperation, obligations and procedures for transfer and use of equipment and funds, genetic resources and associated traditional knowledge, Material Transfer Agreements (MTAs), the potential need for the temporary cessation of activities, and other relevant issues. The conclusion of those implementing arrangements or agreements shall be in accordance with prevailing laws, regulations and procedures of both Parties. Unless the Parties or their designees agree otherwise, the terms of this Agreement shall apply to any implementing arrangements or agreements.

3. Upon approval by both Parties, scientists, technical experts, governmental agencies and institutions of third countries, or international organizations may be invited to participate, at their own expense unless otherwise agreed, in projects and programs being carried out under this Agreement and its implementing arrangements or agreements.

ARTICLE VII
FINANCIAL ARRANGEMENTS

1. Cooperative activities under this Agreement shall be subject to the availability of funds.

2. Unless otherwise provided for in implementing arrangements or agreements, each Party or participating entity shall bear the cost of its participation and that of its personnel in cooperative activities under this Agreement. Should either Party or an entity thereof wish to use technical or professional services made available to it by the other Party,

the assumption of costs, both direct and indirect, shall be agreed upon by the entities involved.

ARTICLE VIII
MATERIAL TRANSFER AGREEMENT

Taking into account the applicable laws and regulations of the Parties, research materials used in the collaborations under this Agreement may, on agreement of the participants, be transferred using Material Transfer Agreements (MTAs) as appropriate in the particular collaborations.

ARTICLE IX
TRANSPARENCY

Cooperative activities under this Agreement shall be conducted with due regard for transparency. Each Party should provide the other Party with timely access to, and information about, the results of cooperative activities, consistent with the obligations set forth in this Agreement.

ARTICLE X
PROTECTION OF INTELLECTUAL PROPERTY

1. Provisions for the protection and distribution of intellectual property created or furnished in the course of cooperative activities under this Agreement are set forth in Annex I, which shall form an integral part of this Agreement.

2. Scientific and technological information of a non-proprietary nature resulting from cooperation under this Agreement (other than information which is not disclosed for commercial or industrial reasons) shall be made available, unless otherwise agreed, to the world scientific community through customary channels and in accordance with normal procedures of the participating agencies and entities.

ARTICLE XI
GENETIC RESOURCES AND ASSOCIATED TRADITIONAL KNOWLEDGE

The collection, conservation, and exchange of genetic resources and associated traditional knowledge under this Agreement may be subject to or the subject of negotiations in implementing agreements or arrangements as foreseen in Article VI. Such negotiations should take into account the applicable laws and regulations of the Republic of Indonesia and the United States of America.

ARTICLE XII
FACILITATION OF COOPERATION

1. Each Party shall facilitate, as appropriate, and in accordance with its laws and regulations, entry into and exit from its territory of appropriate personnel and equipment of the other Party, as well as other materials used or engaged as part of projects and programs under this Agreement.

2. Each Party shall facilitate, as appropriate, and in accordance with its laws and regulations, prompt and efficient access of persons of the other Party participating in cooperative activities under this Agreement, to its relevant geographic areas, institutions, data, materials, and individual scientists, specialists and researchers as needed to carry out those activities.

3. Customs duty and tax exemption and relief shall be in accordance with the prevailing laws and regulations of the Parties.

4. The Parties do not foresee the provision of foreign assistance under this Agreement. If they decide otherwise with respect to a particular activity, the relevant implementing arrangement would need to be consistent with the requirements of the laws of the respective countries that regulate activities related to foreign assistance, notwithstanding paragraph 3 of this Article.

3. Unless otherwise agreed by the Parties, termination of this Agreement shall not affect the implementation of any cooperative activity carried out under this Agreement and not completed upon termination of this Agreement.

IN WITNESS WHEREOF the undersigned, being duly authorized by their respective Governments, have signed this Agreement.

DONE at Jakarta, in duplicate, this twenty ninth day of March, 2010, in the Indonesian and English languages, which shall be equally authentic.

FOR THE GOVERNMENT OF THE REPUBLIC OF INDONESIA

SUHARNA SURAPRANATA
Minister for Research and Technology

FOR THE GOVERNMENT OF THE UNITED STATES OF AMERICA

CAMERON R. HUME
Ambassador Extraordinary and Plenipotentiary

ANNEX I

Intellectual Property Rights

I. General Obligation

The Parties shall ensure adequate and effective protection of intellectual property created or furnished under this Agreement and relevant implementing arrangements or agreements. Rights to such intellectual property shall be allocated as provided in this Annex.

II. Scope

A. This Annex is applicable to all cooperative activities undertaken pursuant to this Agreement, except as otherwise specifically agreed by the Parties or their designees.

B. For purposes of this Agreement, "intellectual property" shall mean the subject matter listed in Article 2 of the Convention Establishing the World Intellectual Property Organization, done at Stockholm, July 14, 1967 and may include other subject matter as agreed by the Parties.

C. Each Party shall ensure, through contracts or other legal means with its own participants, if necessary, that the other Party can obtain the rights to intellectual property allocated in accordance with this Annex. This Annex does not otherwise alter or prejudice the allocation between a Party and its nationals, which shall be determined by that Party's laws and practices.

D. Except as otherwise provided in this Agreement, disputes concerning intellectual property arising under this Agreement shall be resolved through discussions between the concerned participating institutions, or, if necessary, the Parties or their designees. Upon mutual agreement of the Parties, a dispute shall be submitted to an arbitral tribunal for binding arbitration in accordance with the applicable rules of international law. Unless the Parties or their designees agree otherwise in writing, the arbitration rules of the United Nations Commission on International Trade Law (UNCITRAL) shall govern.

E. Termination or expiration of this Agreement shall not affect any rights or obligations established under this Annex.

III. Allocation of Rights

A. Each Party shall be entitled to a non-exclusive, irrevocable, royalty-free license in all countries to translate, reproduce, and publicly distribute scientific and technical journal articles, reports, and books directly arising from cooperation under this Agreement. All publicly distributed copies of a copyrighted work prepared under this provision shall indicate the names of the authors of the work unless an author explicitly declines to be named.

B. Rights to all forms of intellectual property, other than those rights described in paragraph III.A above, shall be allocated as follows:

(1) Visiting researchers shall receive rights, awards, bonuses and royalties in accordance with the policies of the host institution.

(2) (a) Any intellectual property created by persons employed or sponsored by one Party under cooperative activities other than those covered by paragraph III.B(1) shall be owned by that Party. Intellectual property created by persons employed or sponsored by both Parties shall be jointly owned by the Parties. In addition, each creator shall be entitled to awards, bonuses and royalties in accordance with the policies of the institution employing or sponsoring that person.

(b) Unless otherwise agreed in implementing arrangements or agreements, each Party shall have within its territory all rights to exploit or license intellectual property created in the course of the cooperative activities.

(c) The rights of a Party outside its territory shall be determined by mutual agreement considering the relative contributions of the Parties and their participants to the cooperative activities, the degree of commitment in obtaining legal protection and licensing of the intellectual property and such other factors deemed appropriate.

(d) Notwithstanding paragraphs III.B(2)(a) and (b) above, if a particular project has led to the creation of intellectual property protected by the laws of one Party but not the other, the Party whose laws provide for this type of protection shall be entitled to all rights to exploit or license intellectual property worldwide although creators of intellectual property shall nonetheless be entitled to awards, bonuses and royalties as provided in paragraph III.B(2)(a).

(e) For each invention made under any cooperative activity, the Party employing or sponsoring the inventor(s) shall disclose the inventions promptly to the other Party together with any documentation and information necessary to enable the other Party to establish any rights to which it may be entitled.

(f) Either Party may request the other Party in writing to delay publication or public disclosure of such documentation or information for the purpose of protecting its rights in the invention. Unless otherwise agreed in writing, the delay shall not exceed a period of six months from the date of disclosure by the inventing Party to the other Party.

IV. Business Confidential Information

In the event that information identified in a timely fashion as business-confidential is furnished or created under this Agreement, each Party and its participants shall protect such

information in accordance with applicable laws, regulations, and administrative practices. Information may be identified as "business-confidential" if a person having the information may derive an economic benefit from it or may obtain a competitive advantage over those who do not have it, and the information is not generally known or publicly available from other sources, and the owner has not previously made the information available without imposing in a timely manner an obligation to keep it confidential.

Appendix C. SOP INA-RESPOND, Specimen Ownership, Access, and Use

Standard Operating Procedure
INA-RESPOND
Specimen Ownership, Access, and Use

1.0 Introduction

The Indonesian Research Partnership on Infectious Disease (INA-RESPOND) is a collaborative initiative between the *National Institute of Health Research and Development* (NIHRD) and the *National Institute of Allergy and Infectious Disease* (NIAID), along with 8 Schools of Medicine/ Hospitals (University of Indonesia/ Dr Cipto Mangunkusumo Hospital, Sulianti Saroso Infectious Disease Hospital, Padjadjajaran University/ Dr Hasan Sadikin Hospital, Diponegoro University/ Dr Kariadi Hospital, Gadjah Mada University/ Dr Sadjito Hospital, Airlangga University/ Dr Soetomo Hospital, Udayana University/ Sanglah Government Hospital, Hasanuddin University/ Dr Wahidin Sudirohusodo Hospital) in 7 cities in Indonesia that is formed to promote and conduct high-quality infectious disease clinical research in Indonesia.

INA-RESPOND is the sole owner of stored specimens for all network protocols conducted by INA-RESPOND. Access and usage of the specimens can only be granted upon approval of the Network Steering Committee and Governing Board.

2.0 Specimen Repository (Long-term storage)

The specimen repository for the INA-RESPOND Network will be located at the National Institute of Health Research and Development (NIHRD) in Jakarta, Indonesia. Samples may be stored the timeframe noted in section 6.0 and batched for future analysis. Specimens will be stored using a code and unique identifier that does not contain any information that can link the specimens to the subject.

3.0 Specimen Storage

Research specimens will be stored in a locked freezer with a temperature of -80^{0}C at the repository. Sample labeling will be done using a unique identifier that is decided by the data management team and laboratory. A code that links the unique identifier with the study subject will be kept in a locked file cabinet or on a password-protected computer in a secure room. Only authorized personnel will have access to the samples.

4.0 Specimen Tracking

Specimens will be tracked by a commercial software program and can only be accessed by authorized personnel.

5.0 Specimen Access and Usage

Collected samples may only be used for specific study research purposes in accordance with the protocols approved by the Institutional Review Board (IRB). Further studies by members of INA-RESPOND using the collected specimens may be conducted by submitting a new protocol, which is subject to EC's approval. Members of INA-RESPOND may conduct the studies using the collected specimens or data after getting INA-RESPOND Steering Committee and Governing Board's approval. Any clinical information shared about the sample, with or without patient's identifiers, would similarly require prior IRB approval.

6.0 Specimen Archiving

Specimens will be maintained for further laboratory testing for up to 5 years after the study is completed. After 5 years, with the decision of Steering Committee and Governing Board, specimens in the INA-RESPOND specimen repository will either be destroyed, or after IRB approval, transferred to another existing protocol or a repository.

7.0 Reporting Loss or Destruction of Specimens/ Data

Specimens are considered "damaged" if they experience a change from their initial state (contamination, change of color, etc.)

Any loss or unanticipated "destruction" of locally maintained specimens (for example, due to freezer malfunction, etc.) or data (for example, misplacing a printout of data with identifiers, etc.) will be reported to the corresponding site PI, protocol PI, and Data Management Center. The protocol PI, Steering Committee, and Governing Board will conduct further investigation.

Any loss or unanticipated "destruction" of repository maintained samples or data will be reported to all IRBs, protocol PI, Steering Committee, and Governing Board for further investigation.

Subjects may withdraw consent at any point to have their samples stored. In this case, the protocol PI will ensure the destruction of all known remaining samples and report what was done to both the subject and to the IRB in a written document.

Appendix D: Guidelines for maximum blood draw for pediatric patients

Patient's Weight Pounds	Patient's Weight Kilograms (approx.)	Maximum Amount to be drawn at any one time (mL)	Maximum Amount of blood–cumulative to be drawn during a given hospital stay (1 month or less-mL)
6-8	2.7-3.6	2.5	23
8-10	3.6-4.5	3.5	30
10-15	4.5-6.8	5	40
16-20	7.3-9.1	10	60
21-25	9.5-11.4	10	70
26-30	11.8-13.6	10	80
31-35	14.1-15.9	10	100
36-40	16.4-18.2	10	130
41-45	18.6-20.5	20	140
46-50	20.9-22.7	20	160
51-55	23.2-25.0	20	180
56-60	25.5-27.3	20	200
61-65	27.7-29.5	25	220
66-70	30.0-31.8	30	240
71-75	32.3-34.1	30	250
76-80	34.5-36.4	30	270
81-85	36.8-38.6	30	290
86-90	39.1-40.9	30	310
91-95	41.4-43.2	30	330
96-100	43.6-45.5	30	350

Reference: Becan-McBride, K., Phlebotomy Handbook - Blood Collection Essentials, Seventh Edition

Implementing a Combination of Clinical Parameters (Rapid Diagnostic Tests, Biomarkers, and Standard of Care Procedures) for the Etiology Diagnoses of Pneumonia in Pediatric Patients to Improve Clinical Management in Indonesia

Protocol Number:	INA201
Site Number:	[insert site number]
Protocol Title:	Implementing a Combination of Clinical Parameters (Rapid Diagnostic Tests, Biomarkers, and Standard of Care Procedures) for the Etiology Diagnoses of Pneumonia in Pediatric Patients to Improve Clinical Management in Indonesia
Subject Name	_____ (Subject's full name in CAPITAL LETTER
Protocol Principal Investigator:	
Site PI Name:	Name: [insert Site PI's name] Address: [insert site address] Telephone number: [insert Site PI's contactable phone number(s)]

INTRODUCTION

We invite your child to take part in a pneumonia study. The doctor in charge of this study at this site is (<<insert name of Site Investigator>>). Before you decide if you want your child to be a part of this study, we want you and your child to know about the study.

This is an information sheet. It gives you and your child information about the study. The study staff will inform you and your child about the study. You and your child are free to ask questions about this study at any time. If you agree that your child may take part in this study, you will be asked to sign the consent form. You will get a copy of the information sheet and informed consent of this study.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are: to develop a procedure for diagnosing pneumonia, to identify the causes of pneumonia in children in Indonesia and to evaluate the performance of each rapid diagnostic test. Results of this study will be beneficial because until now the causes of pneumonia in children are currently unavailable in Indonesia. This study may help better diagnosing pneumonia to better guide management.

WHAT WILL HAPPEN TO MY CHILD IN THIS STUDY?

1. Screening
This evaluation will be conducted to see whether your child is eligible to take part in this study. The screening evaluation will take about 15 minutes.

Your child may be enrolled into this study if he/she has meet the following criteria:

- He/she is between 2 months of age to 5 years old
- He/she has cough OR fever and at least one sign of lung infection
- Willing to follow all study procedure including allowing researcher to store and use his/her biological specimen for testing

However your child may not be enrolled into this study if:

- He/she has been hospitalized for more than 24 hours
- He/she has received intravenous antibiotic
- He/she has history of cancer or long term (at the minimum of 2 months) use of steroid
- Based on clinicians' judgement, the minimum required specimens are not possible to be collected
- They have any condition which might interfere with the compliance of the study.

If you agree to your child joining this study, you will be asked to sign this informed consent.

2. Entry (This evaluation may be combined with the Screening evaluation)
This evaluation may take about 30 minutes. At this evaluation, your child will have the following done:

- We will check your child's blood pressure, pulse, respiratory rate, temperature, signs and symptoms and your child will have a physical exam, unless these are already done by the doctor treating your child.
- About 8-10 mL (approximately two to three teaspoon) of your child's blood will be drawn for culture testing, CRP, Procalcitonin and Complete Blood Count (CBC). You and your child will be told the results of this test as soon as this information becomes available. The remaining specimen will be drawn for future research tests. All of these samples will be taken to the hospital laboratories or specimen repository for storage and analysis. We cannot ensure that you will be told the results of the research done on these samples.
- Besides blood, respiratory specimens and urine are also required for this study. These will be collected by trained laboratory technician for culture tests, rapid

diagnostic tests for some pathogens. You and your child will be told the results of this test as soon as this information becomes available. The remaining respiratory specimens will be stored for future research tests.

- Nasopharyngeal swab will be performed this way: Your child will be asked to cough before the test begins and then tilt your head back. A sterile cotton-tipped swab is gently passed into your nose. The swab is quickly rotated and removed. The sample is sent to a laboratory for rapid diagnostic test. You and your child will be told the results of this test as soon as this information becomes available. The remaining specimen will be stored for future research tests.

- Sputum induction will be performed if your child unable to produce sputum spontaneously. Your child will inhale fluid for around 30 minutes. Then the sputum will be collected while your child cough or by mucus extractor. This procedure can be repeated once again to reach sufficient amount of sputum.
- The doctor treating your child may decide to collect other biological samples (~~sputum, induced sputum~~, ~~urine,~~ pleural fluid, others) to determine why your child is sick. If some of the samples are left after the necessary testing, we will store for our study. These samples may be tested to look for infection caused by viruses and bacteria or parasites. We cannot ensure that you will be told the results of the research done on these samples.

3. Daily Follow-Up Visit

During daily follow-up at the hospital, daily clinical data will be collected until discharged from the hospital or up to maximum 14 days of hospitalization. Left over blood will be stored for the study from day 3 hospitalization.

4. Next Study Follow-Up Visits (These evaluations may be performed at this hospital site or your home):

a. Day 14 Visit (One Visit) Post Enrollment

This visit may take about 30 minutes. At this visit, your child will have the following done:

- We will check your child's blood pressure, pulse, respiratory rate, temperature, signs and symptoms.
- About 4 mL (approximately two teaspoons) of blood will be drawn for future research tests.

b. At 30 days Post Enrollment

We will contact or visit you to ask about your child condition. No specimen is taken at this visit.

4. Stored Samples and Future Research

At entry and Day 14 visits, respiratory specimens and blood will be collected for this research. The remaining specimens may be used for future research.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 200 children will take part in this study.

HOW LONG WILL MY CHILD BE IN THIS STUDY?

Your child will be in this study for one month.

WHY WOULD THE DOCTOR TAKE MY CHILD OFF THIS STUDY EARLY?

You may withdraw your child from the study at any time. Your child will not be asked for further information or blood samples.

The study doctor may need to take your child off the study early without your permission if:

- The study is cancelled or terminated by the sponsors or the site's Institutional Review Board (IRB)/Ethics Committee (EC).
- You and your child are not able to attend the study visits as required by the study.
- Continuing the study may be harmful to your child.

WHAT ARE THE RISKS OF THE STUDY?

The researchers believe that the risks or discomforts to your child are minimal and includes the risks associated with obtaining blood, nasopharyngeal swab and induced sputum. Blood drawing will cause slight pain and redness or bruising at the site where the blood is drawn and in rare cases, fainting. Bruising may be alleviated by a warm compress. There is a very small chance the site where the blood is drawn may become infected. This is unlikely since the person drawing the blood will clean the site with alcohol before blood is taken and use a sterile blood drawing material. In Nasopharyngeal swab procedure your child may gag a little or feel some pressure or discomfort. Your child's nose may feel irritated or bleed a little bit after the procedure. A humidifier may ease these symptoms. In sputum induction procedure your child may produce excessive sputum and gag a little. But these events are rare.

WHAT OTHER CHOICES DOES MY CHILD HAVE BESIDES THIS STUDY?

The alternative is not having your child participate in this study. If you decide not to have your child participate in this study, your physician will still provide similar treatment for your child's pneumonia.

ARE THERE BENEFITS FOR MY CHILD TO TAKE PART IN THIS STUDY?

The study will pay for the blood and sputum culture testing and other important diagnostic testings described in the protocol. You and your child's transportation costs and time compensation will be reimbursed for up to Rp 150,000 per visit (at enrollment and follow-up visit day 14), The study will not provide costs for routine care or hospitalization. The results of this study may help your child's clinician to provide better treatments and improve the management of pneumonia.

WILL WE RECEIVE ANY PAYMENT?

You and your child will not receive any payments for taking part in this study.

WHAT ABOUT CONFIDENTIALITY?

All information about your child will be kept confidential and will not be shared with anyone who is not responsible for their care. Your child's medical record will only be reviewed by those who are working on this study.

All the research documents and samples will be labeled using your child's study number. Your child's name will not be used for labeling samples and your child's name will not appear in study related reports or scientific publications.

WHAT HAPPENS IF MY CHILD IS INJURED?

We will provide immediate medical care for study related injuries e.g. an infection where blood has been taken. The study cannot pay for long term disability that may have resulted from the subject's illness.

WHAT ARE MY CHILD'S RIGHTS AS A RESEARCH PARTICIPANT?

Your child's participation in this study is completely voluntary. If you do not want your child to participate, your child will still get standard treatment. You may discontinue your child's participation in this study at any time you choose.

We will tell you and your child about new information from this or other studies that may affect your child's health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I OR MY CHILD HAS QUESTIONS OR PROBLEMS?

If you or your child has questions regarding this study, you may contact:

[Site PI's name & Phone number]
[Site Co-PI's name & phone number]
[Research assistant's name & phone number]

Implementing a Combination of Clinical Parameters (Rapid Diagnostic Tests, Biomarkers, and Standard of Care Procedures) for the Etiology Diagnoses of Pneumonia in Pediatric Patients to Improve Clinical Management in Indonesia

I have read the study information sheet or this information sheet has been read to me. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I have been explained that I have the right to withdraw my child from the study at any time.

I freely and voluntarily choose my child to participate in this study. I will be given a copy of this information sheet and signed consent form to keep for my reference.

Child's Name: _____ Age: _____

Parental relationship or legal custodianship with the child: _____

Name of Parent/Legal Guardian: _____

Signature*: _____ Date: ____/____/____
(dd/mm/yy)
Time of Consent: _____

**A thumb print can be used if the person cannot write.*

Name of the Investigator: _____ Signature: _____

Date: ____/____/____ Time of Consent: _____
(dd/mm/yy)

Name of Witness: _____ Signature*:_____

Date: ____/____/____ Time of Consent: _____
(dd/mm/yy)