付　属　資　料

１．討議議事録（R/D）

２．詳細計画策定調査協議議事録（M/M）

RECORD OF DISCUSSIONS

ON THE PROJECT

FOR

DEVELOPMENT OF RAPID DIAGNOSTICS AND THE ESTABLISHMENT OF AN ALERT SYSTEM FOR OUTBREAKS OF YELLOW FEVER AND RIFT VALLEY FEVER IN KENYA

AGREED UPON BETWEEN

MINISTRY OF PUBLIC HEALTH AND SANITATION

AND

JAPAN INTERNATIONAL COOPERATION AGENCY

Nairobi, 14th December 2011

Signed:

Masaaki Kato Chief Representative JICA Kenya Office	Mark Bor, CBS Permanent Secretary Ministry of Public Health and Sanitation

Countersigned by;

Joseph Kinyua, CBS
Permanent Secretary
Office of the Deputy Prime Minister
and Ministry of Finance

THE PERMANENT SECRETARY
MINISTRY OF FINANCE
P. O. Box 30007
NAIROBI

Witnessed by;

Yoshio Ichinose
Chief Representative
NUITM-KEMRI Project
Kenya Research Station
Institute of Tropical Medicine
Nagasaki University

Solomon Mpoke
Director
Kenya Medical Research Institute

ATTACHED DOCUMENT

Based on the minutes of meetings of the Detailed Planning Survey on the "Development of Rapid Diagnostic Test Kits in KEMRI and the Establishment of an Alert System for Outbreaks of Priority Arbovirus in Kenya" signed on 2nd September 2011 among Ministry of Public Health and Sanitation (hereinafter referred to as "MOPHS"), Kenya Medical Research Institute (hereinafter referred to as "KEMRI"), Nagasaki University, Institute of Tropical Medicine (hereinafter referred to as "NUITM") and the Japan International Cooperation Agency (hereinafter referred to as "JICA"), JICA and MOPHS (hereinafter referred to as "the parties") held a series of discussions with KEMRI, NUITM and other relevant organizations to develop the detailed plan and completed the diplomatic procedure for change of the project title to "the Project for Development of Rapid Diagnostics and the Establishment of an Alert System for Outbreaks of Yellow Fever and Rift Valley Fever in Kenya" (hereinafter referred to as "the Project").

Both parties agreed to the details of the Project and the main points discussed as described in Appendix 1.

Both parties also agreed that MOPHS, the counterpart to JICA, will be responsible for the implementation of the Project in cooperation with JICA, coordination with KEMRI, NUITM, and other relevant organizations, and ensure that the self-reliant operation of the Project is sustained during and after the implementation period, in order to contribute towards both social and economic development, and national response through new technology for tackling global issues (e.g. cross-border infectious diseases) in the Republic of Kenya.

The Project will be implemented within the framework of the Agreement on Technical Cooperation signed on 29th April 2004 and the Note Verbales exchanged on 24th August 2011 between the Government of Japan (hereinafter referred to as "GOJ") and the Government of the Republic of Kenya (hereinafter referred to as "GOK").

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Appendix 1: Project Description

Appendix 2: Minutes of Meetings on the Detailed Planning Survey for "Development of Rapid Diagnostic Test Kits in KEMRI and the Establishment of an Alert System for Outbreaks of Priority Arbovirus in Kenya"

PROJECT DESCRIPTION

Both parties confirmed that there is no change in the Project Description as agreed on in the Minutes of Meetings concerning the Detailed Planning Survey for the Project signed on 2nd September 2011(Appendix 2).

I. BACKGROUND

Outbreaks of arthropod-borne viral (arbovirus) infections such as Yellow Fever (YF) virus, Rift Valley Fever (RVF) virus, Chikungunya (CHIK) virus and Dengue (DEN) virus are periodically reported with high case fatality rate in Kenya and its neighboring countries.

It was reported that in all of these outbreaks, it took several days for diagnosis to be confirmed.

Based on this observation, it was hypothesized that if the rapid diagnostics (test kits) had been available at the right time, these outbreaks could have been prevented from spreading in Kenya and East Africa, while the rapid diagnostics (test kits) are commercially available only for CHIK and DEN virus.

In addition, an alert system network for early response to outbreaks of arbovirus infections is also required in order to report outbreaks of the diseases.

This project was requested to develop and produce rapid diagnostic test kits for YF virus and RVF virus at KEMRI Production Department (PD) in Nairobi, to build a field surveillance system at KEMRI-Centre for Infectious and Parasitic Diseases Control Research (CIPDCR) in Alupe, and to establish an early vigilance model against outbreaks of arbovirus infections in partnership with MOPHS.

II. OUTLINE OF THE PROJECT

Details of the Project are described in the Project Design Matrix (hereinafter referred to as "PDM") (Annex I) and the tentative Plan of Operation (hereinafter referred to as "PO") (Annex II).

1. Title of the Project

The Project for Development of Rapid Diagnostics and the Establishment of an Alert System for Outbreaks of Yellow Fever and Rift Valley Fever in Kenya

2. Project Purpose

Outbreak containment system of YF and RVF is strengthened in Kenya through the development of rapid diagnostics and establishment of a sustainable outbreak vigilance and response mechanism

3. Outputs

(1) Rapid diagnostics (test kits) for YF and RVF are developed in collaboration between researchers from Kenyan and Japanese sides

(2) Advanced rapid and accurate reference activities are in place and functional in KEMRI headquarters as well as CIPDCR-KEMRI (Alupe) in collaboration between Kenyan and Japanese sides

(3) Bidirectional early vigilance and rapid response mechanism model for YF and RVF outbreaks is established and evaluated in collaboration with MOPHS officials, selected health facilities officials and JICA Experts.

4. Inputs

(1) Inputs by JICA and NUITM

(a) Dispatch of Experts

-Chief Advisor/Development of Rapid Diagnostics and Alert System
-Research Management
-Project Coordinator
-Researchers
-Genetic Engineering
-Viral Experiments

(b) Training in Japan

-Virology (Recombinant Viral Protein Expression)
-Monoclonal Antibody Development
-Laboratory Diagnosis
-Quality Management System (QMS) for Production
-Molecular Epidemiology
-Other necessary trainings.

(c) Machinery and Equipment

- Necessary equipment for research and development activities in the Project, as shown in Annex IV
- Necessary equipment and/or devices for development of the bidirectional early vigilance and rapid response mechanism, as shown in Annex IV

Inputs other than those indicated above will be determined through consultations among JICA, MOPHS, KEMRI, and NUITM during the implementation of the Project, as necessary.

(2) Inputs by MOPHS and KEMRI

MOPHS and KEMRI will take necessary measures to provide at their own expense:

(a) Services of MOPHS's counterpart personnel, and KEMRI's counterpart researchers as referred to in II-5 (1),
(b) Suitable office, laboratory and research space with necessary equipment,
(c) Available data, clinical specimens and information related to the Project; and
(d) Running expenses necessary for the implementation of the Project.

5. Implementation Structure

The Project Implementation Structure is shown in Annex III. The roles and assignments of both sides are as follows.

(1) Kenyan side will assign:

(a) Project Director (who will bear overall responsibility for the administration and implementation of the Project): Director, KEMRI headquarters,
(b) Project Manager (who will be responsible for the managerial and technical matters of the Project): Director, CIPDCR-KEMRI (Alupe),
(c) Project Co-managers (who will be responsible for the managerial and technical matters of the Project, in collaboration with the Project Manager): Director of Department of Diseases Prevention and Control, MOPHS, Production Manager of Production Department, KEMRI; and Head of Arbovirology and Viral Hemorrhagic Fevers Laboratory, KEMRI.
(d) Researchers (Ph.D., MSc.) in Virology, Immunology, and

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Communicable disease surveillance; and
(e) Health Personnel engaged in early vigilance and rapid response for disease outbreaks.

(2) Japanese side will dispatch:
(a) Chief Advisor (who will provide necessary recommendations and advice to the Project Director and the Project Manager and the Project Co-managers on any matters pertaining to the implementation of the Project),
(b) JICA Project Coordinator (who will coordinate the Project, supporting the Chief Advisor); and
(c) Other JICA experts (who will give necessary technical guidance and advice to KEMRI counterpart researchers and MOPHS personnel on technical matters pertaining to the implementation of the Project).

(3) Joint Coordinating Committee
A Joint Coordinating Committee (hereinafter referred to as "JCC") will be established in order to facilitate inter-organizational coordination. JCC meeting will be held at least once a year and whenever deemed necessary. JCC will approve the annual work plan, review overall progress, conduct monitoring and evaluation of the Project, and exchange opinions on major issues that arise during the implementation of the Project. A list of proposed members of JCC is shown in Annex V.

6. Project Target Area, Implementers and Beneficiaries

Project Target Area: Endemic areas of priority arbovirus infectious diseases in Kenya

Project Implementers: Approximately 200 researchers and health personnel engaged in early vigilance and rapid response for outbreaks of YF and RVF composed of Researchers from Production Department (PD), Centre for Virus Research (CVR), Centre for Infectious and Parasitic Diseases Control Research (CIPDCR) (Alupe) of KEMRI and health personnel engaged in early vigilance and rapid response for outbreaks of MOPHS

Beneficiaries: Residents at risk of arbovirus infection in Kenya: Central Province: Approx. 3.9 millions, Coast Province: Approx. 3.0millions, Nairobi Province: Approx. 2.8 millions, North Eastern Province: Approx. 1.3 millions, Western Province: Approx. 4.0 millions.

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7. Duration

The duration of the technical cooperation for the Project will be five (5) years starting from January 2012.

8. Reports

JICA, MOPHS, KEMRI, and NUITM will jointly prepare the following reports in English.

(1) Progress Report on semiannual basis until the project completion; and

(2) Project Completion Report at the time of project completion.

9. Environmental and Social Considerations

MOPHS, KEMRI, and NUITM agreed to abide by 'JICA Guidelines for Environmental and Social Considerations' in order to ensure that appropriate considerations will be made for the environmental and social impacts of the Project.

III. UNDERTAKINGS OF MOPHS

1. MOPHS will take necessary measures to:

(1) Ensure that the technologies and knowledge acquired by the Kenyan nationals as a result of Japanese technical cooperation contributes toward both economic and social development and national response through new technology to the global issues (e.g. borderless infectious diseases) of Kenya, and that the knowledge and experience acquired by the personnel of Kenya from technical training as well as the equipment provided by JICA will be utilized effectively in the implementation of the Project; and

(2) Grant privileges, exemptions and benefits to the JICA experts referred to in II-4 (1) above and their families, which are no less favorable than those granted to experts and members of the missions and their families of third countries or international organizations performing similar missions in Kenya.

2. Other privileges, exemptions and benefits will be provided in accordance with the Agreement on Technical Cooperation signed on 29th April, 2004 between the GOJ and the GOK.

IV. EVALUATION

JICA, MOPHS, KEMRI and NUITM will jointly conduct the following reviews and evaluations:

1. Mid-term review at the middle of the cooperation term based on the Ex-ante Evaluation Sheet, as is shown in the Annex VI; and
2. Terminal evaluation at least the last six (6) months before the end of the cooperation term.

JICA, on its part, will conduct the following evaluations and surveys to mainly verify sustainability and impact of the Project and draw lessons. KEMRI is required to provide necessary support for these activities:

1. Ex-post evaluation three (3) years after the project completion, in principle; and
2. Follow-up surveys on necessity basis.

V. PROMOTION OF PUBLIC SUPPORT

For the purpose of promoting support for the Project, MOPHS and KEMRI will take appropriate measures to make the Project widely known to the people of Kenya.

VI. CONSULTATION

JICA MOPHS, KEMRI, and NUITM will consult one another whenever any major issues arise in the course of Project implementation.

VII. AMENDMENTS

The Record of Discussions may be amended by the minutes of meetings between Japanese and Kenyan sides.

The minutes of meetings will be signed by authorized representatives of each side who may be different from the signatories to the Record of Discussions.

Annex I	PDM (Version 1)
Annex II	Tentative PO
Annex III	Project Implementation Structure
Annex IV	Tentative List of Equipment
Annex V	Joint Coordinating Committee
Annex VI	Ex-ante Evaluation Sheet

Annex I

Project Design Matrix (PDM) (Version 1)

Date: (month) (date), (year)

Project Duration: 5 years starting from January 2012

Project Title: The Project for Development of Rapid Diagnostics and the Establishment of an Alert System for Outbreaks of Yellow Fever and Rift Valley Fever in Kenya

Target Area :Endemic areas of priority arbovirus infection in Central, Coast, Nairobi, North Eastern, and Western Provinces, the Republic of Kenya

Target Group :

Project Implementers: Approx. 200 researchers and health personnel engaged in early vigilance and rapid response for outbreaks of Yellow Fever (YF) and Rift Valley Fever (RVF).

【Kenya Medical Research Institute (KEMRI)】 Researchers: Production Department (PD), Centre for Virus Research (CVR), Centre for Infectious and Parasitic Diseases Control Research (CIPDCR) (Alupe)

【Ministry of Public Health and Sanitation (MOPHS)】 Health Personnel engaged in early vigilance and rapid response for outbreaks

Beneficiaries: Residents at risk of arbovirus infection in Kenya: Central Province: Approx. 3.9 millions, Coast Province: Approx. 3.0 millions, Nairobi Province: Approx. 2.8 million, North Eastern Province: Approx. 1.3 millions, Western Province: Approx. 4.0 millions

Narrative Summary	Objectively Verifiable Indicators	Means of Verification	Important Assumptions
Project Purpose			
Outbreak containment system of YF and RVF is strengthened in Kenya through the development of rapid diagnostics and establishment of a sustainable outbreak vigilance and response mechanism.	1. Rapid diagnostic test kits for YF and RVF are stably available in the target area. 2. The Operational Manual is integrated into the national surveillance and response system for priority diseases by the MOPHS by the end of project period. 3. The time taken from the first clinical suspicious cases to confirmation of diagnosis is 1 week or less.	(1) Experts' project reports (2) Steering committee meeting minutes (3) Monthly progress reports (4) Integrated Disease Surveillance and Response (IDSR) Technical Guidelines	
Outputs			
1 **Rapid diagnostics (test kits) for YF and RVF are developed in collaboration between researchers from Kenyan and Japanese sides.**	1-1. Rapid diagnostic test kits and ELISA test kits using viral antigens with more than 90% sensitivity and specificity are produced in KEMRI by the end of 2013. 1-2. Rapid diagnostic test kits using genetically engineered antigens with more than 90% sensitivity and specificity are produced in KEMRI by the end of 2014. 1-3. KEMRI-PD receives the qualification of ISO 13485: 2003 by the end of 2014.	(1) Experts' project reports (2) Steering committee meeting minutes (3) Monthly progress reports (4) ISO 13485: 2003 certificate for KEMRI-PD	1. Kenyan side properly proceeds with third-party accreditation, in terms of quality evaluation of diagnostics by National Public Health Laboratory Services (NPHLS) as well as ISO certification for KEMRI, necessary for official use of the rapid diagnostic test kits in Kenya.
2 **Advanced rapid and accurate reference activities are in place and functional in KEMRI headquarters as well as CIPDCR-KEMRI (Alupe) in collaboration between Kenyan and Japanese sides.**	2-1. Entire KEMRI receives the qualification of ISO 9001: 2008 by the end of 2012. 2-2. Sensitivity and specificity of laboratory diagnosis by ELISA and gene amplification technique in KEMRI are as same level as that in WHO collaborating centers by the end of 2014.	(1) Experts' project reports (2) Steering committee meeting minutes (3) Monthly progress reports (4) ISO 9001: 2008 certificate for KEMRI	2. Cooperation from relevant authorities for official authorization of the Operational Manual as a part of the national surveillance response system is gained.
3 **Bidirectional early vigilance and rapid response mechanism model for YF and RVF outbreaks is established and evaluated in collaboration with MOPHS officials, selected health facilities officials and JICA Experts.**	3-1. Sensitivity/specificity, completeness and timeliness of reporting are improved in comparison to the baseline data. (*target values will be determined on the basis of baseline investigation by the Joint Coordinating Committee meeting in 2014*) 3-2. Results from POC testing for YF and RVF are reflected in the DDSR Weekly Bulletin by the end of 2015. *3-3. Indicators for the measurement of spreading rate of communicable diseases and its responses will be determined by the Joint Coordinating Committee meeting in 2014.* 3-4 Ratios of laboratory confirmed cases of YF and RVF reach 80% among all the suspicious cases in the target areas of the Project by the end of 2016. 3-5. The Operational Manual is officially authorized by the MOPHS by the end of 2016.	(1) Experts' project reports (2) Steering committee meeting minutes (3) Monthly progress reports (4) DDSR Weekly Bulletin (5) Document(s) for authorization of the Operational Manual	

Activities	Inputs		
	Japan	Kenya	
1 Rapid diagnostics (test kits) for YF and RVF are developed in collaboration between researchers from Kenyan and Japanese sides.	Experts (1) Chief Advisor/Development of Rapid Diagnostics and Alert System (Short-term experts) (2) Research Management (Long-term expert) (3) Researchers (Long-term expert) (4) Project Coordinator (Long-term expert) (5) Genetic Engineering (Short-term experts) (6) Viral Experiments (Short-term experts), etc. Training in Japan (1) Virology (Recombinant viral protein expression) (2) Monoclonal Antibody Development (4) Quality Management System (QMS) for Production (5) Molecular Epidemiology (6) Other necessary training Equipment and materials (1) Necessary equipment for research and development activities in the Project (2) Necessary equipment and/or devices for development of the bidirectional early vigilance and rapid response mechanism. Local costs Running expenses necessary for implementation of the project activities other than those that borne by the Kenyan side.	Counterparts (1) Project Director (2) Project Manager (3) Project Co-managers (4) Researchers (PhD, MSc) in Virology, Immunology, and Communicable Disease Surveillance. (5) Health Personnel engaged in Early Vigilance and Rapid Response for Outbreaks Land, Facilities, equipment and materials (1) Office space at KEMRI headquarters and CIPDCR-KEMRI (Alupe) (2) Laboratory space at KEMRI-PD (3) BSL-3 laboratory at KEMRI (4) BSL-2 laboratory at CIPDCR-KEMRI (Alupe) (5) Clinical specimens from YF and RVF suspected cases Local costs Running expenses necessary for implementation of the project activities such as personnel costs of researchers, research activity costs including travel expenses, consumables, and supplies, utility costs such as water, electricity and communication, etc.	1. Kenyan side allocates an adequate budget and personnel for the project activities. 2. Trained counterparts do not leave their position so as to affect the outputs of the Project. 3. Necessary cooperation is gained by health facilities and relevant agencies for the project activities.
1-1. Preparation of reference antigens of YF and RVF by large-scale cell culture systems.			
1-1-1. Establish a large-scale viral antigen preparation system using eukaryotic cells in KEMRI-PD.			
1-1-2. Prepare viral antigens by purifying virus particles from the system.			
1-2. Preparation of genetically-engineered antigens of YF virus and RVF virus for development of antibody-detecting rapid diagnostic test kit.			
1-2-1. Establish a large-scale expression system of viral protein antigens with cultured prokaryotic cells in KEMRI-PD.			
1-2-2. Prepare genetically-engineered diagnostic antigens, designed on the basis of preliminary study, by affinity chromatography technique.			
1-3. Production of conjugated monoclonal and polyclonal anti YF virus and RVF virus antibodies.			
1-3-1. Purify polyclonal antibodies from sera of experimental animals sensitized by YF and RVF viral antigens prepared by activity 1-1.			
1-3-2. Prepare monoclonal antibodies from large scale culture of hybridoma cells provided from the Institute of Tropical Medicine, Nagasaki University.			
1-3-3. Label polyclonal and monoclonal antibody by conjugating with Horseradish Peroxidase (HRP) or colloidal gold particles.			
1-4. Production of rapid diagnostic test kits for point-of-care (POC) testing of YF and RVF using immunochromatography technology.			
1-4-1. Coat each antigen on immunochromatography membrane using spraying machine.			
1-4-2. Fabricate rapid diagnostic test kits by assembling relevant parts produced in KEMRI-PD.			
1-4-3. Evaluate specificity, sensitivity and stability of the YF- and the RVF-rapid diagnostic test kits by comparative reviewing with advanced reference diagnostics of ELISA (Enzyme-Linked Immunosorbent Assay).			
1-4-4. Validate the rapid diagnostic test kits for POC testing at field level, developed by the Production Department, using clinical specimens at KEMRI-CVR and CIPDCR-KEMRI (Alupe).			
1-5. Preparation of ELISA tests for YF and RVF as higher reference diagnostics.			

	1-5-1.	Fabricate ELISA test kits by assembling relevant parts produced in KEMRI-PD.
	1-5-2.	Validate the ELISA kits, developed by the Production Department, by using clinical specimens at KEMRI-CVR and CIPDCR-KEMRI (Alupe).
2	**Advanced rapid and accurate reference activities are in place and functional in KEMRI headquarters as well as CIPDCR-KEMRI (Alupe) in collaboration between Kenyan and Japanese sides.**	
2-1.	Strengthening reference capacity for rapid confirmation of YF and RVF at KEMRI headquarters.	
	2-1-1.	Enhance the function of existing Biosafety Level (BSL)-3 laboratory in the KEMRI headquarters by renovating it and supplying necessary research instruments.
	2-1-2.	Set up safe virus isolation system in BSL-3 laboratories targeting on YF virus and RVF virus for monitoring of antigenic variation and genetic mutation.
	2-1-3.	Set up and standardize gene amplification and detection system (e.g. real-time PCR) of YF virus and RVF virus as reference diagnostics at field laboratories.
	2-1-4.	Collect and analyze specimens for monitoring of antigenic variation and genetic mutation of YF virus and RVF virus.
2-2.	Establishment of primary reference capacity for confirmation of YF and RVF at CIPDCR-KEMRI (Alupe).	
	2-2-1.	Enhance the function of existing BSL-2 laboratory in CIPDCR-KEMRI (Alupe) by renovating it and supplying necessary research instruments.
	2-2-2.	Set up safe virus inoculation and RNA extraction system in the BSL-2 laboratory targeting on arboviruses.
	2-2-3.	Set up and standardize gene amplification and detection system at field laboratory level (e.g. real-time LAMP, conventional PCR).
	2-2-4.	Collect and analyze clinical specimens for diagnosis YF and RVF at field laboratory level.
3	**Bidirectional early vigilance and rapid response mechanism model for YF and RVF outbreaks is established and evaluated in collaboration with MOPHS officials, selected health facilities officials and JICA Experts.**	
3-1.	Integration of YF and RVF outbreak response network model into the existing communicable diseases response system in MOPHS/DDSR (Division of Disease Surveillance and Response).	
	3-1-1.	Set up a working group for development of YF and RVF outbreak response network model, composed of representatives from MOPHS, KEMRI, health facilities, other relevant agencies and Japanese experts.

	3-1-2. Develop a mobile networking system using verbal and Short Message Service (SMS) communication for communicable diseases vigilance and response system including YF and RVF.			
	3-1-3. Develop a draft Operational Manual of mobile phone-based bidirectional early vigilance and response for YF and RVF outbreaks.			
	3-1-4. Distribute mobile phones to health personnel engaged in communicable diseases outbreak vigilance and response system, followed by test operation of reporting system in accordance with the draft Operational Manual in a limited scale.			
3-2.	Set up the mobile phone linked to network of selected health facilities and laboratories in Central, Coast, Nairobi, North Eastern, and Western, Provinces.			
	3-2-1. Enroll 200 selected health facilities and laboratories in the pilot areas identifying a responsible personnel for each institution.			
	3-2-2. Provide trainings for manipulation of the rapid diagnostic test kits after its distribution to relevant facilities.			
3-3.	Conduct outbreak report and response simulation including table-top exercises in collaboration with DDSR, KEMRI, selected health facilities and other relevant agencies.			
3-4.	Verify the effectiveness of the novel outbreak vigilance and response system on spreading rate of communicable diseases and its responses by evaluating the data from the simulation in 3-3.			
3-5.	Revise and finalize the Operational Manual on the basis of the assessment results from the test operations and the simulations.			

Pre-conditions
1. Approval is obtained by the Scientific Steering Committee (SSC) and the Ethical Review Committee (ERC) for the research subjects conducted in the Project. 2. Approval is obtained from relevant ministry/authority for genetic engineering. 3.Clearance for animal use is obtained from SSC, ERC and the Animal Care and Use Committee: ACUC of KEMRI.

【Abbreviations】 JICA: Japan International Cooperation Agency, LAMP: Loop-mediated Isothermal Amplification, PCR: Polymerase Chain Reaction, RNA: Ribonucleic Acid

Annex II Tentative Plan of Operation (PO)

Date: (month) (day) (year)

Project Title: The Project for Development of Rapid Diagnostics and the Establishment of an Alert System for Outbreaks of Yellow Fever and Rift Valley Fever in Kenya

Output 1:
Rapid diagnostics (test kits) for YF and RVF are developed in collaboration between researchers from Kenyan and Japanese

Activities	Plan of Operation																					Institution in Charge		Remarks
	2012				2013				2014				2015				2016				2017	Japan	Kenya	
	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan			
	2010 (J.F.Y.)	2011 (J.F.Y.)			2012 (J.F.Y.)				2013 (J.F.Y.)				2014 (J.F.Y.)				2015 (J.F.Y.)							
	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q			
1-1. Preparation of reference antigens of YF and RVF by large-scale cell culture systems.																								
1-1-1. Establish a large-scale viral antigen preparation system using eukaryotic cells in KEMRI-PD.																						NU	KEMRI-PD	
1-1-2. Prepare viral antigens by purifying virus particles from the system.																						NU	KEMRI-PD	
1-2. Preparation of genetically-engineered antigens of YF virus and RVF virus for development of antibody-detecting rapid diagnostic test kit.																								
1-2-1. Establish a large-scale expression system of viral protein antigens with cultured prokaryotic cells in KEMRI-PD.																						NU	KEMRI-PD	
1-2-2. Prepare genetically-engineered diagnostic antigens, designed on the basis of preliminary study, by affinity chromatography technique.																						NU	KEMRI-PD	
1-3. Production of conjugated monoclonal and polyclonal anti YF virus and RVF virus antibodies.																								
1-3-1. Purify polyclonal antibodies from sera of experimental animals sensitized by YF and RVF viral antigens prepared by activity 1-1.																						NU	KEMRI-PD	
1-3-2. Prepare monoclonal antibodies from large scale culture of hybridoma cells provided from the Institute of Tropical Medicine, Nagasaki University.																						NU	KEMRI-PD	
1-3-3. Label polyclonal and monoclonal antibody by conjugating with Horseradish Peroxidase (HRP) or colloidal gold particles.																						NU	KEMRI-PD	
1-4. Production of rapid diagnostic test kits for point-of-care (POC) testing of YF and RVF using immunochromatography technology.																								
1-4-1. Coat each antigen on immunochromatography membrane using spraying machine.																						NU	KEMRI-PD	
1-4-2. Fabricate rapid diagnostic test kits by assembling relevant parts produced in KEMRI-PD.																						NU	KEMRI-PD	
1-4-3. Evaluate specificity, sensitivity and stability of the YF- and the RVF-rapid diagnostic test kits by comparative reviewing with advanced reference diagnostics of ELISA (Enzyme-Linked Immunosorbent Assay).																						NU	KEMRI-PD KEMRI-CVR	

Activities	Plan of Operation																					Institution in Charge		Remarks
	2012				2013				2014				2015				2016				2017	Japan	Kenya	
	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan			
	2010 (J.F.Y.)	2011 (J.F.Y.)			2012 (J.F.Y.)				2013 (J.F.Y.)				2014 (J.F.Y.)				2015 (J.F.Y.)							
	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q.	4Q	1Q	2Q	3Q	4Q			
1-4-4. Validate the rapid diagnostic test kits for POC testing at field level, developed by the Production Department, using clinical specimens at KEMRI-CVR and CIPDCR-KEMRI (Alupe).						→				→				→				→				NU	KEMRI-PD KEMRI-CVR CIPDCR-KEMRI (Alupe)	
1-5. Preparation of ELISA tests for YF and RVF as higher reference diagnostics.																								
1-5-1. Fabricate ELISA test kits by assembling relevant parts produced in KEMRI-PD.			→					→				→				→				→		NU	KEMRI-PD	
1-5-2. Validate the ELISA kits, developed by the Production Department, by using clinical specimens at KEMRI-CVR and CIPDCR-KEMRI (Alupe).			→	→	→			→	→	→		→	→	→		→	→	→	→	→	→	NU	KEMRI-PD KEMRI-CVR CIPDCR-KEMRI (Alupe)	

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Annex II Tentative Plan of Operation (PO)

Date: (month) (day) (year)

Project Title: The Project for Development of Rapid Diagnostics and the Establishment of an Alert System for Outbreaks of Yellow Fever and Rift Valley Fever in Kenya

Output 2:
Advanced rapid and accurate reference activities are in place and functional in KEMRI headquarters as well as CIPDCR-KEMRI (Alupe) in collaboration between Kenyan and Japanese sides.

Activities	Plan of Operation																					Institution in Charge		Remarks
	2012				2013				2014				2015				2016				2017			
	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan			
	2010 (J.F.Y.)	2011 (J.F.Y.)				2012 (J.F.Y.)				2013 (J.F.Y.)				2014 (J.F.Y.)				2015 (J.F.Y.)						
	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	Japan	Kenya	
2-1. Strengthening reference capacity for rapid confirmation of YF and RVF at KEMRI headquarters.																								
2-1-1. Enhance the function of existing Biosafety Level (BSL)-3 laboratory in the KEMRI headquarters by renovating it and supplying necessary research instruments.	→	→	→	→																		NU	KEMRI-CVR	
2-1-2. Set up safe virus isolation system in BSL-3 laboratories targeting on YF virus and RVF virus for monitoring of antigenic variation and genetic mutation.			→	→	→	→	→															NU	KEMRI-CVR	
2-1-3. Set up and standardize gene amplification and detection system (e.g. real-time PCR) of YF virus and RVF virus as reference diagnostics at field laboratories.				→	→	→	→	→														NU	KEMRI-CVR	
2-1-4. Collect and analyze specimens for monitoring of antigenic variation and genetic mutation of YF virus and RVF virus.				→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	NU	KEMRI-CVR	
2-2. Establishment of primary reference capacity for confirmation of YF and RVF at CIPDCR-KEMRI (Alupe).																								
2-2-1. Enhance the function of existing BSL-2 laboratory in CIPDCR-KEMRI (Alupe) by renovating it and supplying necessary research instruments.	→	→	→	→	→																	NU	CIPDCR-KEMRI (Alupe)	
2-2-2. Set up safe virus inoculation and RNA extraction system in the BSL-2 laboratory targeting on arboviruses.				→	→	→																NU	CIPDCR-KEMRI (Alupe)	
2-2-3. Set up and standardize gene amplification and detection system at field laboratory level (e.g. real-time LAMP, conventional PCR).			→	→	→																	NU	CIPDCR-KEMRI (Alupe)	
2-2-4. Collect and analyze clinical specimens for diagnosis YF and RVF at field laboratory level.					→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	NU	CIPDCR-KEMRI (Alupe)	

[Abbreviations] CIPDCR: Centre for Infectious and Parasitic Diseases Control Research (Alupe), CVR: Centre for Virus Research, J.F.Y.: Japanese Fiscal Year, LAMP: Loop-mediated Isothermal Amplification, NU: Nagasaki University, KEMRI: Kenya Medical Research Institute, PCR: Polymerase Chain Reaction, PD: Production Department, RVF: Rift Valley Fever, YF: Yellow Fever

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Date: (month) (day) (year)

Annex II Tentative Plan of Operation (PO)

Project Title: The Project for Development of Rapid Diagnostics and the Establishment of an Alert System for Outbreaks of Yellow Fever and Rift Valley Fever in Kenya

Output 3:
Bidirectional early vigilance and rapid response mechanism model for YF and RVF outbreaks is established and evaluated in collaboration with MOPHS officials, selected health facilities officials and JICA Experts.

Activities	Plan of Operation																					Institution in Charge		Remarks
	2012				2013				2014				2015				2016				2017	Japan	Kenya	
	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan - Mar	Apr - Jun	Jul - Sep	Oct - Dec	Jan			
	2010 (J.F.Y.)	2011 (J.F.Y.)			2012 (J.F.Y.)				2013 (J.F.Y.)				2014 (J.F.Y.)				2015 (J.F.Y.)							
	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q	1Q	2Q	3Q	4Q			
3-1. Integration of YF and RVF outbreak response network model into the existing communicable diseases response system in MOPHS/DDSR (Division of Disease Surveillance and Response).																								
3-1-1. Set up a working group for development of YF and RVF outbreak response network model, composed of representatives from MOPHS, KEMRI, health facilities, other relevant agencies and Japanese experts.		→																				NU	MOPHS-DDSR KEMRI	NPHLS
3-1-2. Develop a mobile networking system using verbal and Short Message Service (SMS) communication for communicable diseases vigilance and response system including YF and RVF.			→																			NU	MOPHS-DDSR KEMRI	NPHLS
3-1-3. Develop a draft Operational Manual of mobile phone-based bidirectional early vigilance and response for YF and RVF outbreaks.			→																			NU	MOPHS-DDSR MOPHS-DVBD KEMRI	NPHLS
3-1-4. Distribute mobile phones to health personnel engaged in communicable diseases outbreak vigilance and response system, followed by test operation of reporting system in accordance with the draft Operational Manual in a limited scale.					→			→		→				→					→			NU	MOPHS-DDSR KEMRI	NPHLS
3-2. Set up the mobile phone linked to network of selected health facilities and laboratories in Central, Coast, Nairobi, North Eastern, and Western, Provinces.																								
3-2-1. Enroll 200 selected health facilities and laboratories in the pilot areas identifying a responsible personnel for each institution.			→																			NU	MOPHS-DDSR KEMRI	NPHLS
3-2-2. Provide trainings for manipulation of the rapid diagnostic test kits after its distribution to relevant facilities.					→				→				→				→					NU	MOPHS-DDSR KEMRI	NPHLS
3-3. Conduct outbreak report and response simulation including table-top exercises in collaboration with DDSR, KEMRI, selected health facilities and other relevant agencies.						→				→				→				→				NU	MOPHS-DDSR KEMRI	NPHLS
3-4. Verify the effectiveness of the novel outbreak vigilance and response system on spreading rate of communicable diseases and its responses by evaluating the data from the simulation in 3-3.							→				→				→				→			NU	MOPHS-DDSR KEMRI	NPHLS
3-5. Revise and finalize the Operational Manual on the basis of the assessment results from the test operations and the simulations.								→				→				→				→		NU	MOPHS-DDSR MOPHS-DVBD KEMRI	NPHLS

[Abbreviations] CIPDCR: Centre for Infectious and Parasitic Diseases Control Research (Alupe), CVR: Centre for Virus Research, DVBD:Division of Vector Borne Diseases, DDSR: Division of Disease Surveillance and Response, J.F.Y.: Japanese Fiscal Year, MOPHS: Ministry of Public Health and Sanitation, NPHLS: National Public Health Laboratory Services, MOPHS, NU: Nagasaki University, KEMRI: Kenya Medical Research Institute, PD: Production Department, RVF: Rift Valley Fever, YF: Yellow Fever

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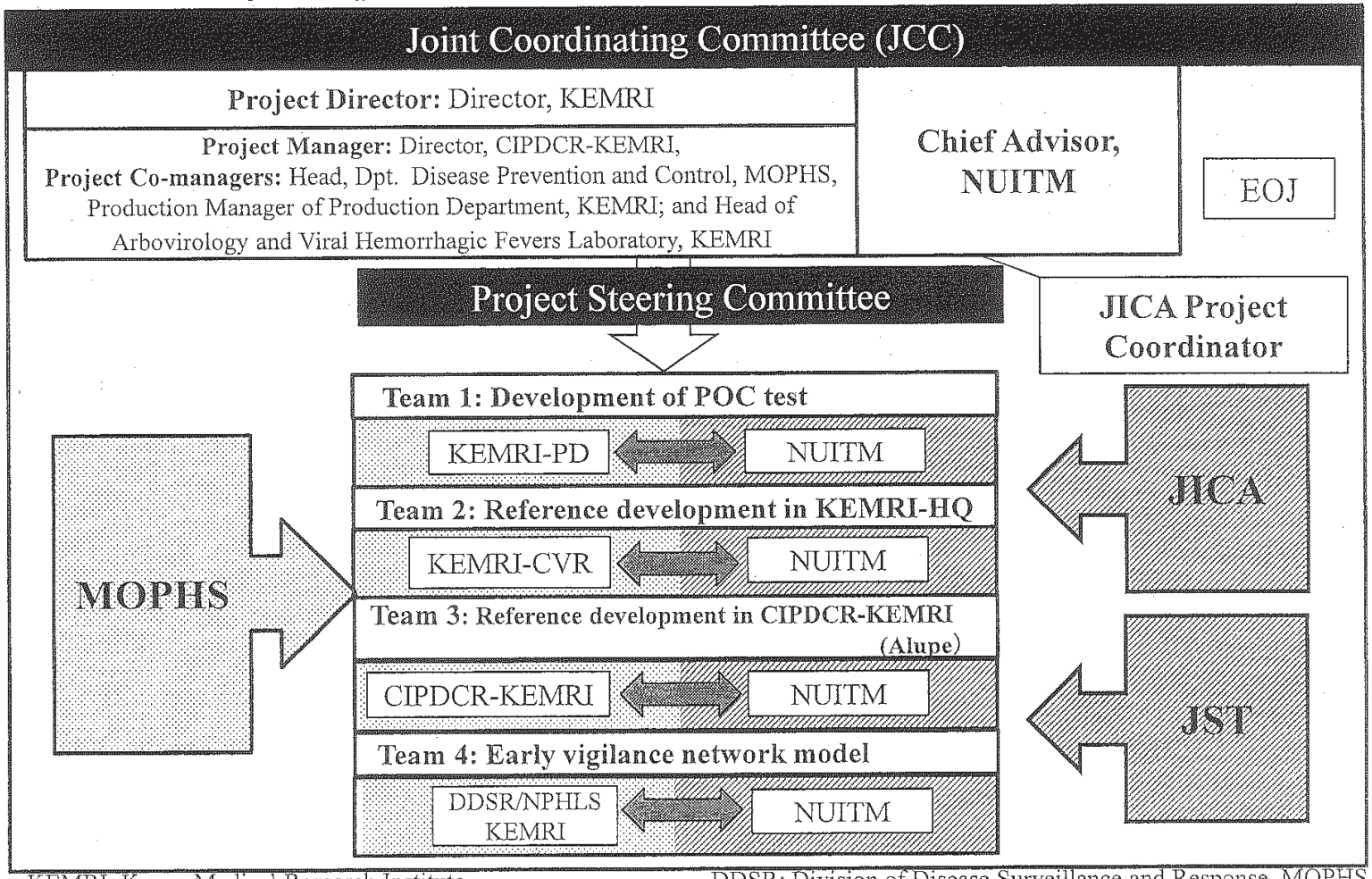
Annex III : Project Implementation Structure



KEMRI: Kenya Medical Research Institute
KEMRI-PD: Production Department, KEMRI
KEMRI-CVR: Centre for Virus Research, KEMRI
CIPDCR-KEMRI (Alupe):
Centre for Infectious and Parasitic Diseases Control Research, (Alupe) KEMRI

DDSR: Division of Disease Surveillance and Response, MOPHS
NPHLS: National Public Health Laboratory Services, MOPHS
NUITM: Nagasaki University, Institute of Tropical Medicine
EOJ: Embassy of Japan
MOPHS: Ministry of Public Health and Sanitation
POC test: Point-of-Care test

Annex VI

Tentative List of Equipment

Location	Item
DDSR	Mobile Phone
	Printer for SMS

KEMRI-PD	Vehicle
	Deep Freezer (-80°C)
	Freezer (-30°C)
	Autoclave
	Biosafety Cabinet
	Celan Bench
	Immunochromatography Spraying machine and its apparatus
	Lyophilizer
	Shaker Incubator
	Ordinary Incubator
	CO_2 Gas Incubator
	Slow-speed Anti-humid Stirrer
	Personal Computer
	Printer for PC
	Thermal Cycler (Gradient Type)
	Loop Amplification machine
	UV Trans-Illuminator
	Gel Image Analyzer with PC
	Minigel Electrophoresis set for DNA
	Gel Electrophoresis Set for Protein
	Blotting Machine
	Inverted Microscope
	Ultra-pure Water Sytetem
	Ice Crasher
	Low-speed Refrigerated Centrifuge
	High-speed Refrigerated Microcentrigue
	Desk-top Micro-centrifuge
	Large Capacity AVS
	Small Capacity AVS
	DNA Sequencer
	Apparatus for DNA Sequencer
	DNA Analysis Software
	Electrical Chemical Balance
	Spectrophotometer
	Digital Camera with adaptor set
	Air-conditioner for Materials Room

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KEMRI-CVR	Spare parts of UPS for BSL-3 lab. System
	HEPA Filters for Biosafety Cabinet in BSL-3 Lab.
	Real time PCR Thermal Cycler
	Deep Freezer (-80°C) Small in BSL-3 Lab.
	Deep Freezer (-80°C) Large in BSL-2 Lab.
	Inverted Microscope

KEMRI-CIPDCR (Alupe)	Vehicle
	BSL-2 Laboratory System Unit
	Racks for Deep Freezer (-80°C)
	Freezer (-30°C)
	Refrigerator (4°C)
	Autoclave
	Biosafety Cabinet
	Clean Bench
	Ordinary Incubator
	CO_2 Gas Incubator
	Large Capacity AVS
	Small Capacity AVS
	Personal Computer
	Printer for PC
	Thermal Cycler (Gradient Type)
	Loop Amplification machine
	Minigel Electrophoresis Set for DNA
	Inverted Microscope
	Stereo Microscope
	Digital Camera with Adaptor Set
	Water Deionization System
	Water Purification System
	Ultra-pure Water System
	Crashed Ice Maker
	Low-speed Refrigerated Centrifuge
	High-speed Refrigerated Micro-centrifuge
	Blood Counter
	Blood Chemical Analyzer
	Electrical Balance
	Electrical Chemical Balance
	Generator for BSL-2 Lab.
	Air-conditioner for BSL-2 Lab.
	pH Meter

ANNEX V Joint Coordinating Committee

For the effective and successful implementation of technical cooperation for the Project, a Joint Coordinating Committee will be established whose functions and composition are described as follows:

(1) Functions

1) To formulate and authorize the annual activity plan of the Project,

2) To endorse major achievements and products of the Project,

3) To monitor and review overall progress and supervise the Project; and

4) To review and discuss on major issues arising from or concerning the Project.

(2) Composition

1) Chairperson: Project Director

2) Members:

-Kenyan side

Project Manager, Project Co-managers

KEMRI counterpart researchers

MOPHS counterpart personnel

-Japanese side

Chief Advisor, JICA Project Coordinator, and other JICA Experts

Representative(s) from JICA Kenya Office

Representative(s) from Embassy of Japan (Observer)

Representative(s) from JST (Observer)

-Other stakeholders appointed by the Chairperson

Ex-Ante Evaluation (Science and Technology Research Partnership for Sustainable Development)

Date: November 07, 2011
JICA Division in Charge: Health Division 1, Human Development Department

1. Project Title: The Project for Development of Rapid Diagnostics and the Establishment of an Alert System for Outbreaks of Yellow Fever and Rift Valley Fever in Kenya

2. Background and the Justification of the Project

(1)Current Situation and Agenda of the Health Sector of the Country:

In the Republic of Kenya and the neighboring Eastern African countries, Arboviruses (multiple types of arthropod–borne viruses) often cause disease outbreaks, adversely affecting human beings and livestock respectively. In particular, damages caused by Yellow Fever (YF) and Rift Valley Fever (RVF) are often serious. In the year 2005, 555 YF cases were reported in the north western region of Kenya and the southern region of Sudan (with 142 casualties–case fatality rate of 25.6%). As for RVF, in the year of 2006-2007, 1,062 RVF cases were reported in Kenya, Somalia, and Tanzania (with 315 casualties–case fatality rate of 29.7%). In addition, 12,500,000 head of cattle, 11,000,000 head of sheep, and 850,000 head of camels were also infected. Although YF and RVF outbreaks in developing countries have been recognized as an important social issue, the development of the diagnostic techniques as well as the early vigilance and rapid response for control of YF and RVF diseases are considered to be significantly delayed with comparison to "Neglected Tropical Diseases: NTDs" as defined by the World Health Organization (WHO).

Arboviruses are found primarily in natural environment such as jungles and make sudden invasion into human communities, causing widespread infection. Taking countermeasures such as early detection of viruses and emergency vaccination and elimination of vector mosquitoes (aggregately referred to as "early containment") in areas where human contact with the viruses is frequent is thought to be more cost effective than a usual vaccination program. However, response to NTDs including researches of YF and RVF targeted by this project is lagging far behind. Rapid diagnostics have already been developed on a commercial level in pandemic diseases or those attracting high interest of economically advanced countries and are made available even in developing countries. On the other hand, inexpensive rapid diagnostics for NTDs such as YF and RVF are not made available on a commercial level, and in reality, companies in developed countries do not show any signs of producing them for use in developing countries. Kenya and other developing countries where these NTDs are widespread are in urgent need to come up with an inexpensive diagnostics on their own.

Alert system models of developed countries cannot be utilized due to differences in infrastructure between the countries. Thus, development of a sustainable alert system model that is well adapted to the social and economic infrastructure of developing countries is highly anticipated.

Under these circumstances, the promotion of studies is strongly required with regard to development of rapid diagnostics including introduction of POC (Point-of-Care) testing, strengthened referral functions for diagnosis, and establishment of early vigilance system towards the cost-effective "early containment" of patients for early response to the outbreaks of Arboviruses such as YF and RVF.

Arboviral infection control is a common issue for all East African countries. As the diagnostic technique and the alert system model developed by this project will be well designed for social and economic infrastructure of not only Kenya but all the East African countries, it is expected that the benefits derived from the project will be able to contribute to each country's fight against the infection.

(2)Development Policy of the Health Sector of the Country and the Position of the Project.

In "*the Second National Health Sector Strategic Plan (2005-2010) (NHSSP II)*" and "*the Strategic Plan of the Ministry of Public Health and Sanitation (2008-2012)*", capacity development in disease surveillance and research for infectious diseases covering not only HIV/AIDS, Malaria and Tuberculosis but YF and RVF is mentioned as areas of priority. The interviews conducted by JICA with the leadership of the Ministry of Public Health and Sanitation (MOPHS) brought out the importance of responses to YF and RVF for the reasons that RVF is regarded as a zoonotic infection threatening people's health and that YF has negative impact on the tourism industry. Moreover, as the Strategic Plan includes improvement of access to health services and strengthened functions of health facilities; this project aiming at

establishment of early vigilance system is affirmed to contribute indirectly to the implementation of the plan.

(3)Japan's and JICA's Aid Policy and Achievements for Health Sector

In "*the Yokohama Action Plan*" adopted by the fourth Tokyo International Conference on African Development (TICAD IV) in 2008, infectious disease control is listed on the priorities of the health sector. The Government of Japan revealed its commitment to encourage medical studies and researches for combating infectious diseases in Africa by dispatching Japanese researchers especially for facilitation of joint researches of infectious diseases. At the G8 Toyako Summit of the same year, global effort for infectious disease control was agreed on together with maternal and child health and human resource for health in the concept of "the Health Systems Strengthening (HSS)". "*Japan's Global Health Policy 2011-2015*" (September 2010) presented at the United Nations Millennium Development Goals (MDGs) at the World Summit, also, showed the vision; "*in order to help achieve the MDGs through realizing human security, Japan's new policy aims to deliver results effectively and efficiently by addressing bottlenecks impeding progress on the health MDGs*".

Kenya is playing a critical role for Japan's diplomacy in East Africa and is considered to be one of the priority countries for Japanese ODA. Health sector has a priority in the country assistance policy for Kenya.. "*JICA's Cooperation in Health Sector – Present and Future*" published in September 2010 also highlights the fight against infectious diseases that have impact beyond borders as a priority global issue.

(4)Assistance of Other Development Partners

In view of the strategic importance of Kenya in East Africa, many development partners have continued supporting the country. Especially, health sector support is considered to be critical by many development partners. U.S. Center for Disease Control and Prevention (CDC) and World Health Organization (WHO) are potentially inter-complementary collaborators without any duplication of activities observed.

3. Project Overview

(1)Purpose of the Project

This project, through its scientific joint research activities, aims at supporting the Kenya Medical Research Institute (KEMRI) in developing rapid diagnostics which includes introduction of POC (Point-of-Care) testing and in improving referral functions in the arbovirus infection high-risk provinces. . Furthermore, this project also aims at strengthening early containment system by establishing an early vigilance and rapid response system for YF and RVF, which connects the local health facilities, KEMRI and MOPHS, based on the results from the joint research.

(2)Period of Cooperation

The project period is five (5) years starting from January 2012

(3)Beneficiaries of the Project (Target Groups)

Residents at risk of arbovirus infection in Kenya: Central Province: Approx. 3.9 millions, Coast Province: Approx. 3.0millions, Nairobi Province: Approx. 2.8 millions, North Eastern Province: Approx. 1.3 millions, Western Province: Approx. 4.0millions

(4)Total Cost (JICA's budget)

The project has budget of approximately three hundred and sixty millions (360,000,000) Japanese Yen from JICA.

(5)Research Institution and Implementing Organization on the Kenyan side

KEMRI serves as the research institution of the Project with its Production Department (PD), Centre for Virus Research (CVR) in HQ, and Centre for Infectious and Parasitic Diseases Control Research (CIPDCR) in KEMRI-Alupe.

MOPHS serves as the implementing organization of the Project with its Department of Disease Prevention and Control, Division of Disease Control and Surveillance, National Public Health Laboratory Services.

(6)Research Institution on Japanese side

Institute of Tropical Medicine of Nagasaki University (NUITM) serves as the Japanese research

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institution of the Project.

(7)Inputs

① Japanese Side

＜Dispatch of Experts＞

(i) Chief Advisor/Development of Rapid Diagnostics And Alert System (Short-term Experts)
(ii) Research Management (Long-term Expert)
(iii) Researchers (Long-term Expert)
(iv) Project Coordinator (Long-term Expert)
(v) Genetic Engineering (Short-term experts)
(vi) Viral Experiments (Short-term Experts), etc.

＜Training in Japan＞

(i) Virology (Recombinant Viral Protein Expression)
(ii) Monoclonal Antibody Development
(iii) Laboratory Diagnosis
(iv) Quality Management System (QMS) for production
(v) Molecular Epidemiology
(vi) Other Necessary Training

＜Provision of Equipment＞

(i) Necessary equipment for research and development activities in the Project
(ii) Necessary equipment and/or devices for development of the bidirectional early vigilance and rapid response mechanism.

＜Local Costs＞

Running expenses necessary for implementation of the project activities other than those that are borne by the Kenyan side.

② Kenyan Side

＜Counterparts＞

(i) Project Director
(ii) Project Manager
(iii) Project Co-managers
(iv) Researchers (Ph.D., MSc.) in Virology, Immunology, and Communicable disease surveillance.
(v) Health Personnel engaged in early vigilance and rapid response for disease outbreaks

＜Land, Facilities, equipment and materials＞

(i) Office space at KEMRI headquarters and KEMRI-CIPDCR (Alupe)
(ii) Laboratory space at KEMRI-PD
(iii) BSL-3 laboratory at KEMRI
(iv) BSL-2 laboratory at KEMRI-CIPDCR (Alupe)
(v) Clinical specimens from YF and RVF suspected cases

＜Local Costs＞

Running expenses necessary for implementation of the project activities such as personnel costs of researchers, research activity costs including travel expenses, consumables, and supplies, utility costs such as water, electricity and communication, etc.

(8)Special Considerations for Environmental Society, Poverty Reduction, Social Development

Through the research activities conducted by the project, experimental waste disposal must be properly processed both at KEMRI Headquarters and KEMRI-CIPDCR (Alupe). Solid waste is generally disposed at KEMRI HQ with its own incinerator, but KEMRI-CIPDCR (Alupe) is using an incinerator of a neighboring medical facility. Construction of appropriate incinerator within the space available at the KEMRI-CIPDCR (Alupe) should be considered. Regarding the liquid waste, wastewater sewerage system of both facilities are placed independently from the general sewerage system, and designed not to affect the general environment. In the KEMRI Headquarters, special liquid waste is segregated and processed in accordance with the regulation. KEMRI-CIPDCR (Alupe) will have to take proper disposal procedures in accordance with the same regulation in waste treatment as the KEMRI HQ.

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(2) Related Aid Activities

① Japan's Aid Activities

JICA Expert (Dr. Shingo INOUE) was dispatched in 2008 by Nagasaki University to KEMRI-PD for development of new diagnostics in Arboviruses and assisted JICA and KEMRI in keeping up preparation of this project.

② Aid Activities of Other Development Partners

CDC has a base in KEMRI, and provides the KEMRI-CVR with technical assistances including confirmed diagnosis on YF and RVF (viral antibody detection-ELISA[1] and genetic detection -PCR[2] method) for suspected cases and supporting KEMRI-RD to obtain the WHO accreditation.

4. Framework of the Project

(1) Project Outline

① Project Purpose

Outbreak containment system of YF and RVF is strengthened in Kenya through the development of rapid diagnostics and establishment of a sustainable outbreak vigilance and response mechanism.

＜Objectively Verifiable Indicator (OVI)＞

1. Rapid diagnostic test kits for YF and RVF are stably available in the target area.
2. The Operational Manual is integrated by the MOPHS into the national surveillance and response system for priority diseases by the end of project period.
3. The time taken from the first clinical suspicious cases to confirmation of diagnosis is 1 week or less.

② Outputs and Activities

＜Output 1＞

Rapid diagnostics (test kits) for YF and RVF are developed in collaboration between researchers from Kenyan and Japanese sides.

＜OVI for Output 1＞

1. Rapid diagnostic test kits and ELISA test kits using viral antigens with more than 90% sensitivity and specificity are produced in KEMRI by the end of 2013.
2. Rapid diagnostic test kits using genetically engineered antigens with more than 90% sensitivity and specificity are produced in KEMRI by the end of 2014.
3. KEMRI-PD receives the qualification of ISO 13485: 2003 by the end of 2014.

＜Activities under Output 1＞

1-1. Preparation of reference antigens of YF and RVF by large-scale cell culture systems.
  1-1-1. Establish a large-scale viral antigen preparation system using eukaryotic cells in KEMRI-PD.
  1-1-2. Prepare viral antigens by purifying virus particles from the system.

1-2. Preparation of genetically-engineered antigens of YF virus and RVF virus for development of antibody-detecting rapid diagnostic test kit.
  1-2-1. Establish a large-scale expression system of viral protein antigens with cultured prokaryotic cells in KEMRI-PD.
  1-2-2. Prepare genetically-engineered diagnostic antigens, designed on the basis of preliminary study, by affinity chromatography technique.

1-3. Production of conjugated monoclonal and polyclonal anti YF virus and RVF virus antibodies.
  1-3-1. Purify polyclonal antibodies from sera of experimental animals sensitized by YF and RVF viral antigens prepared by activity 1-1.
  1-3-2. Prepare monoclonal antibodies from large scale culture of hybridoma cells provided from the Institute of Tropical Medicine, Nagasaki University.
  1-3-3. Label polyclonal and monoclonal antibody by conjugating with Horseradish Peroxidase

[1] ELISA: Enzyme-Linked Immunosorbent Assay

[2] PCR: Polymerase Chain Reaction

(HRP) or colloidal gold particles.

1-4. Production of rapid diagnostic test kits for POC testing of YF and RVF using immunochromatography technology.
- 1-4-1. Coat each antigen on immunochromatography membrane using spraying machine.
- 1-4-2. Fabricate rapid diagnostic test kits by assembling relevant parts produced in KEMRI-PD.
- 1-4-3. Evaluate specificity, sensitivity and stability of the YF- and the RVF-rapid diagnostic test kits by comparative reviewing with advanced reference diagnostics of ELISA.
- 1-4-4. Validate the rapid diagnostic test kits for POC testing at field level, developed by the Production Department, using clinical specimens at KEMRI-CVR and KEMRI-CIPDCR (Alupe).

1-5. Preparation of ELISA tests for YF and RVF as higher reference diagnostics.
- 1-5-1. Fabricate ELISA test kits by assembling relevant parts produced in KEMRI-PD.
- 1-5-2. Validate the ELISA kits, developed by the Production Department, by using clinical specimens at KEMRI-CVR and KEMRI-CIPDCR (Alupe).

＜Output 2＞

Advanced rapid and accurate reference activities are in place and functional in KEMRI headquarters as well as KEMRI-CIPDCR (Alupe) in collaboration between Kenyan and Japanese sides.

＜OVI for Output 2＞

1. Entire KEMRI receives the qualification of ISO 9001: 2008 by the end of 2012.
2. Sensitivity and specificity of laboratory diagnosis by ELISA and gene amplification technique in KEMRI are as same level as that in WHO collaborating centers by the end of 2014.

＜Activities under Output 2＞

2-1. Strengthening reference capacity for rapid confirmation of YF and RVF at KEMRI headquarters.
- 2-1-1. Enhance the function of existing Biosafety Level (BSL)-3 laboratories in the KEMRI headquarters by renovating it and supplying necessary research instruments.
- 2-1-2. Set up safe virus isolation system in BSL-3 laboratories targeting on YF virus and RVF virus for monitoring of antigenic variation and genetic mutation.
- 2-1-3. Set up and standardize gene amplification and detection system (e.g. real-time PCR) of YF virus and RVF virus as reference diagnostics at field laboratories.
- 2-1-4. Collect and analyze specimens for monitoring of antigenic variation and genetic mutation of YF virus and RVF virus.

2-2. Establishment of primary reference capacity for confirmation of YF and RVF at KEMRI-CIPDCR (Alupe)
- 2-2-1. Enhance the function of existing BSL-2 laboratory in KEMRI-CIPDCR (Alupe) by renovating it and supplying necessary research instruments.
- 2-2-2. Set up safe virus inoculation and RNA extraction system in the BSL-2 laboratory targeting on arboviruses.
- 2-2-3. Set up and standardize gene amplification and detection system at field laboratory level (e.g. real-time LAMP[3], conventional PCR).
- 2-2-4. Collect and analyze clinical specimens for diagnosis of YF and RVF at field laboratory level.

＜Output 3＞

Bidirectional early vigilance and rapid response mechanism model for YF and RVF outbreaks is established and evaluated in collaboration with MOPHS officials, selected health facilities officials and JICA Experts.

＜OVI for Output 3＞

1. Sensitivity/specificity, completeness and timeliness of reporting are improved in comparison to the baseline data. (*target values will be determined on the basis of baseline investigation by the Joint Coordinating Committee meeting in 2014*)
2. Results from POC testing for YF and RVF are reflected in the DDSR Weekly Bulletin by the end of 2015.

[3] LAMP: Loop-Mediated Isothermal Amplification

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3. Ratios of laboratory confirmed cases of YF and RVF reach 80% among all the suspicious cases in the target areas of the Project by the end of 2016.
4. The Operational Manual is officially authorized by the MOPHS by the end of 2016.

＜Activities under Output 3＞

3-1. Integration of YF and RVF outbreak response network model into the existing communicable diseases response system in MOPHS/DDSR (Division of Disease Surveillance and Response).
  3-1-1. Set up a working group for development of YF and RVF outbreak response network model, composed of representatives from MOPHS, KEMRI, health facilities, other relevant agencies and Japanese experts.
  3-1-2. Develop a mobile networking system using verbal and Short Message Service (SMS) communication for communicable diseases vigilance and response system including YF and RVF.
  3-1-3. Develop a draft Operational Manual of mobile phone-based bidirectional early vigilance and response for YF and RVF outbreaks.
  3-1-4. Distribute mobile phones to health personnel engaged in communicable diseases outbreak vigilance and response system, followed by test operation of reporting system in accordance with the draft Operational Manual in a limited scale.
3-2. Set up the mobile phone linked to network of selected health facilities and laboratories in Central, Coast, Nairobi, North Eastern, and Western, Provinces.
  3-2-1. Enroll 200 selected health facilities and laboratories in the pilot areas identifying responsible personnel for each institution.
  3-2-2. Provide trainings for manipulation of the rapid diagnostic test kits after its distribution to relevant facilities.
3-3. Conduct outbreak report and response simulation including table-top exercises in collaboration with DDSR, KEMRI, selected health facilities and other relevant agencies.
3-4. Verify the effectiveness of the novel outbreak vigilance and response system on spreading rate of communicable diseases and its responses by evaluating the data from the simulation in 3-3.
3-5. Revise and finalize the Operational Manual on the basis of the assessment results from the test operations and the simulations.

③ Considerations for Project Implementation

1. The application for this technical cooperation project was submitted by MOPHS, but this project will be managed jointly among chiefs of the participating institutions and organizations. They are Director of KEMRI, Director of KEMRI-CIPDCR (Alupe), Director of Department of Diseases Prevention and Control (MOPHS), while the initiative is taken by Director of KEMRI. Whether this project goes smoothly or not will have an influence on the success of the project from the viewpoint of efficiency. Thus, in order to coordinate the activities among the implementers and to monitor the progress of the research activities, a Project Steering Committee (PSC) will be established under the Joint Coordinating Committee. Additionally, research teams will be set up under the PSC and each researcher will be required to submit a quarterly research progress report. It is necessary to check whether this system will function after the project starts.
2. It is important for MOPHS to purchase the rapid diagnostic test kits produced through the project and to materialize the domestic distribution in Kenya from the viewpoint of sustainability and impact on the infection control in Kenya as well as other East African countries. Thus, the quality evaluation of the rapid diagnostics by the National Public Health Laboratory Service, MOPHS and accreditations by the third party including ISO certification of the KEMRI-PD must be conducted appropriately. The Kenyan side took note of the fact that these evaluation and accreditation should be adequately processed.
3. Originally, Central, Nairobi, Western and Coast Provinces, were considered as target areas for establishing an alert system for outbreaks. However, the Kenyan side strongly requested the addition of North Eastern Province that borders Somalia for reasons that the province is geographically important to monitor the invasion of -infectious diseases from the neighboring countries, and that previously the province had an outbreak of RVF. The detailed planning survey team agreed to add the North Eastern Province, but the implementation of the concrete activities need to be discussed on the basis of the latest JICA personnel safety measures after the project starts,

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because access to parts of the province is still restricted by JICA's safety regulations,.

4. There is an existing surveillance system in which the reports are sent up to the central level from health facilities via district disease surveillance coordinators. The early vigilance and rapid response system will be established in line with the existing one and eventually integrated because of sustainability of the Kenyan side. Therefore, it is important to obtain the right understanding and support by administrative organizations in charge of district and provincial health services.

(2) Other Impacts

Basic techniques of rapid diagnostics of YF and RVF to be developed by the Project will be available to other diseases. Joint research activities of the Project will focus on only the two diseases, but it is highly expected that diagnostics of other arboviruses and infectious diseases will be strengthened if capacities of researchers are developed. Also, if the rapid diagnostic test kits are produced and commercialized in East Africa after receiving third-party accreditation, significant positive impacts in the region will be realized with regard to control of YF and RVF

5. Pre-conditions and Important Assumptions (Risk Control)

① Pre-conditions

1. Approval is obtained by the Scientific Steering Committee (SSC) and the Ethical Review Committee (ERC) for the research subjects conducted in the Project.
2. Approval is obtained from relevant ministry/authority for genetic engineering.
3. Clearance for animal use is obtained from SSC, ERC and the Animal Care and Use Committee: ACUC of KEMRI.
4. Clearance for material transfer or export/import is obtained from relevant ministry/authority.

② Important Assumptions for Outputs

1. Kenyan side allocates an adequate budget and personnel for the project activities.
2. Trained counterparts do not leave their position so as to affect the outputs of the Project.
3. Necessary cooperation is obtained from health facilities and relevant agencies for the project activities.

③ Important Assumptions for Project Purpose

1. Kenyan side properly proceeds with third-party accreditation, in terms of quality evaluation of diagnostics by National Public Health Laboratory Services (NPHLS) as well as ISO certification for KEMRI, necessary for official use of the rapid diagnostic test kits in Kenya.
2. Cooperation from relevant authorities for official authorization of the Operational Manual as a part of the national surveillance response system is gained.

6. Evaluation Results

The project is fully aligned to the development policy and needs of Kenya as well as Japan's assistance policy to Kenya. Accordingly, significance of implementing the Project is highly recognized.

Kenya and neighboring East African countries have suffered tremendous loss of not only human lives but also those of livestock caused by Arbovirus outbreaks such as YF and RVF. As expressed in NHSSP II and MOPHS Strategic Plan, though measures against the three major infectious diseases HIV/AIDS, malaria and tuberculosis are being coordinated with other development partners, YF and RVF are way behind in all areas of surveillance, diagnosis and treatment. However, MOPHS officials added emphasis on enforcing the measures against YF and RVF not only in protecting the people's health but also in terms of zoonosis and its effect on tourism. There are high expectations for the implementation of this project notably in developing rapid diagnostics, strengthening referral functions for diagnosis and establishing outbreak alert system for YF and RVF. This project is in line with the needs of the Kenyan government's health policy and fulfills the needs of the Kenyan population residing in the endemic area. It is also highly consistent with the Japan's ODA policy, which values the importance of infectious disease control, and;

This project aims at improvement of capacity for "early containment" (Project Purpose) of YF and RVF, by developing rapid diagnostics that enable POC testing (Output 1), strengthening referral diagnostic functions including confirmed diagnosis conducted after field-level diagnosis (Output 2) and strengthening bidirectional outbreak alert system starting from the POC testing (Output 3). These

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Outputs efficiently cover all the elements necessary for "early containment" such as rapid and accurate diagnosis and bidirectional information system, responding to the global demand for research on infectious disease control. This project is theoretically feasible without logical discrepancy between the project purpose and outputs. Commercialization of YF and RVF rapid diagnostics within the project period is strongly expected for not only domestic sales but to other endemic areas in East African countries in the future.

7. Lessons Learned from Past Project

'*The Research and Control of Infectious Diseases Project*' (Technical Cooperation Project) and '*the Project for Improvement of Facilities for Control of Infectious and Parasitic Diseases at Kenya Medical Research Institute*' (Grant Aid Project) were implemented in Kenya for effective control of HIV/AIDS, and viral hepatitis as well as strengthened research capacity and production of test kits by KEMRI. As a result of these projects, blood-screening kits for HIV and hepatitis B were developed and produced. Subsequently, KEMRI obtained a marketing license of succeeding rapid diagnostic test kits for HIV and hepatitis B for domestic sales in Kenya, and started production of the kits.

The post evaluation reports of the two projects revealed that foreign-made test kits occupied a great deal of marketing shares in HIV and hepatitis B because the Project had been slow in responding to change of MOPHS procurement policy that suppliers were required to have pre-qualification by WHO, and due to insufficient sales capacity of KEMRI. On the other hand, the reports concluded that the capacity in technical research and the production of KEMRI were found to be reinforced.

The project will proceed for acquiring the WHO pre-qualification by establishing system of quality management regarding the production process of rapid diagnostic kits of YF and RVF by utilizing strengthened capacity in technical research and the productivity of KEMRI. Consequently, the kits will be available on domestic and regional market for sales after they are purchased by MOPHS.

8. Future Evaluation Plan・Mid-term Review; June, 2014・Terminal Evaluation:; June,2016