EBOLA RESPONSE MULTI-PARTNER TRUST FUND
PROPOSAL

Proposal Title: **Vaccination cohort study: Preventing late transmission of Ebola from survivors to close contacts**	**Recipient UN Organization(s):** World Health Organization (WHO)
Proposal Contact: Address: Sarah Kline Telephone: +1 917 843 4275 E-mail: klinesa@who.int	**Implementing Partner(s) – name & type (Government, CSO, etc.):** Government of Guinea and a team of national and international experts including from Italy, UK, US, France and Germany.
Proposal Location (country): Please select one from the following ☒ Guinea ☐ Liberia ☐ Sierra Leone ☐ Common Services	**Proposal Location (provinces):** Guinea
Project Description: This study is designed to test the effectiveness of a vaccination program in preventing the transmission of Ebola from survivors to close contacts. It will determine the effect of natural seropositivity on the immunogenicity and safety of the VSV-ZEBOV vaccine. The funding from MPTF would be provided as an initial payment to enable the study to begin while additional funds are confirmed from other sources.	**Requested amount: USD$299,547** Other sources of funding of this proposal: Paul Allen Foundation (TBC). **Start Date: 01 January 2016** **End Date: 31 March 2016** **Total duration (in months): 3 months**

MISSION CRITICAL ACTIONS to which the proposal is contributing. For reporting purposes, each project should contribute to one SO. For proposals responding to multiple MCAs within 1 SO, please select the primary MCA to which the proposal is contributing to.

- ☐ Strategic Objective 1 MCA1: **Identifying and tracing of people with Ebola**
- ☐ Strategic Objective 1 MCA2: **Safe and dignified burials**
- ☒ Strategic Objective 2 MCA3: **Care for persons with Ebola and infection control**
- ☐ Strategic Objective 2 MCA4: **Medical care for responders**
- ☐ Strategic Objective 3 MCA5: **Provision of food security and nutrition**
- ☐ Strategic Objective 3 MCA6: **Access to basic services**
- ☐ Strategic Objective 3 MCA7: **Cash incentives for workers**
- ☐ Strategic Objective 3 MCA8: **Recovery and economy**
- ☐ Strategic Objective 4 MCA9: **Reliable supplies of materials and equipment**
- ☐ Strategic Objective 4 MCA10: **Transport and Fuel**
- ☐ Strategic Objective 4 MCA11: **Social mobilization and community engagement**
- ☐ Strategic Objective 4 MCA12: **Messaging**
- X Strategic Objective 5 MCA13: **Multi-faceted preparedness**

Recipient UN Organization(s)[1] World Health Organization	Management Committee Chair:
Name of Representative: Dr. Bruce Aylward Signature Name of Agency World Health Organization Date & Seal	Dr. David Nabarro Signature Date:

NARRATIVE

a) Rationale for this project:

While the original Ebola outbreak in West Africa has now dramatically slowed, late transmission of the virus from survivors to close contacts due to viral persistence remains a significant challenge to stopping all cases of Ebola in the region. WHO is already undertaking a landmark study funded by the Paul Allen Foundation that is examining viral persistence in survivors: it has shown that some men still produce semen samples that test positive for Ebola virus nine months after onset of symptoms. Better understanding of viral persistence is important for supporting survivors to recover and to move forward with their lives. Furthermore, it is crucial in prevention re-introduction of the Ebola virus. Post-recovery transmission events (PRTEs) due to EBOV carriage in semen or other body fluids of Ebola survivors have the potential to trigger clusters of disease and restart wider transmission. This poses an important risk to ending an epidemic of Ebola and could render inadequate the window of 42-day disease-free period plus 90 days of enhanced surveillance allowed before Ebola is declared eliminated from an area.(World Health Organization 2015a). Virus can persist in a range of body fluids.(Rowe et al. 1999) A particular concern is male-to-female sexual transmission, because the virus can persist in semen for many months, with documented transmission.(Christie et al. 2015; Deen et al. 2015; Mate et al. 2015). Ending Ebola requires diminishing the potential risk of late transmission from survivors to their close contacts.

VSV-EBOV was developed by the Public Health Agency of Canada. The vaccine was licensed to NewLink Genetics, and on 24 November 2014, Merck & Co., Inc and NewLink Genetics Corp. entered into an exclusive worldwide licensing agreement wherein Merck assumed responsibility to research, develop, manufacture, and distribute the investigational vaccine. Financial support was provided by the Canadian and US Governments, among others.

Results from an interim analysis of the Guinea Phase III efficacy vaccine trial show that VSV-EBOV (Merck, Sharp & Dohme) may be highly effective against Ebola. The independent body of international experts - the Data and Safety Monitoring Board – that conducted the review, advised that the trial should continue. Preliminary results from analyses of these interim data were published in July 2015 in the British journal The Lancet.

While the vaccine up to now shows 100% efficacy in individuals, more conclusive evidence is needed on its capacity to protect populations through what is called "herd immunity". To that end, the Guinean national regulatory authority and ethics review committee approved continuation of the trial.

A ring vaccination protocol was chosen for the trial, where some of the rings are vaccinated shortly after a case is detected, and other rings are vaccinated after a delay of 3 weeks. This is

[1] If there is more than one RUNO in this project, additional signature boxes should be included so that there is one for every RUNO.

an alternative to using a placebo by providing a randomized control group for comparison but at the same time ensures that all contacts are vaccinated within the trial.

Therefore this study is designed to test the effectiveness of a vaccination program in preventing the transmission of Ebola from survivors to close contacts. It will determine the effect of natural seropositivity on the immunogenicity and safety of the VSV-ZEBOV vaccine. The study would use rVSV-ZEBOV (Merck), following the very promising efficacy results in the interim analysis of the WHO-led ring vaccination trial (suggesting 100% protection, and unlikely to be less than 75% protective), and early indications of safety from the ring trial and studies in non-outbreak settings.

Primary objective:

To determine, in populations connected to Ebola survivors, if immunological responses observed at 28 days after Ebola vaccination vary with baseline antibody status.

Secondary objectives:

1. To determine if baseline antibody levels and vaccine immunological response at day 28 vary by prior exposure, including levels of contact with acute cases, and levels of contact with survivors, including by virus-persistence status of survivors' body fluids, or other epidemiological or demographic factors.
2. To assess the prevalence of viral persistence in survivors' semen, vaginal fluid, menstrual blood and/or breast milk, as applicable, and the relationship between serological immune markers and viral persistence.

Study Design

The study is expected to take place in Guinea, in locations defined based on an epidemiological review of confirmed cases. The cohort study would vaccinate and follow-up approximately 1,000 to 1,500 people closely connected to Ebola survivors. Baseline blood samples would be compared with samples collected at 28 days to examine how baseline antibody levels affect vaccine response. Safety data would be collected at days 3, 14 and 28 and through spontaneous reporting, with ongoing safety assessment and reporting to a data safety and monitoring board (DSMB). Body fluid samples from volunteer survivors would be tested for viral persistence with follow-up until clearance.

Consenting survivors of adolescent age and above with EVD onset in the last 9-15 months would be included. Rather than focusing only on sexual contacts of survivors, the study would vaccinate small clusters of contacts around survivors using a priori criteria. Vaccination would not depend on the body-fluid positivity status of the survivor, thus ensuring vulnerable contacts are protected even if a fluid positive contact declines to provide a sample. This approach also reduces identification and stigmatisation of sexual contacts, and provides sufficient recruitment to investigate the study hypotheses on antibodies. Consenting contacts from the age of six would be eligible for vaccination, provided they do not meet exclusion criteria such as pregnancy, breast-feeding or HIV infection.

Community engagement is critical, and advice from HIV research experts will be used to inform participatory processes. The study will be discussed with community leaders as to the expected benefits and how best to implement the study. Training would be given to study field workers, all of whom will be recruited from the GCP trained staff of the ring vaccination trial.

Survivors who became ill during the time window of interest will be identified through surveillance records and assessed for age and geography. They would be visited in their communities, the study explained, and careful definition of the cluster done with full regard for confidentiality and ensuring privacy. A private area for sample production or collection from survivors will be provided.

Informed consent will be sought from eligible contacts for enrolment, exclusion screening and vaccination. Participants will be given information sheets and researcher contact details. After vaccination, participants are observed for 30 minutes for immediate reactions. Participants are revisited at days 3, 14 and 28 following immunization to determine if any severe adverse events have occurred, with non-solicited adverse events documented on days 3 and 14 using standard questionnaires. Blood samples for serology would be collected on day 0 and day 28 from contacts and day 0 for survivors.

Laboratory analysis
Survivor fluid samples would be tested promptly using RT-PCR to detect Ebolavirus RNA. Virus isolation would also be attempted. Survivors would be informed of test results. Blood serum would be tested for immunoglobulin G and other immune markers if indicated. Blood samples will be collected only from a random subsample of survivors and contacts and oral fluid collection devices will be use to collect samples from others.

Statistical analysis
Regression analysis would be done of immunogenicity data, accounting for clustering and adjusting for participant baseline features. Adverse event rates, including serious adverse events, would be analysed by participant baseline features, including with near-real-time monitoring for safety signals through an independent data and safety monitoring board.

Project costs
The estimated project cost is USD$1,250,000 (excluding the in-kind contributions provided by the partners). The costs will cover local operation costs (staff salaries, perdiem, logistics operations), laboratory sample processing and testing costs. This proposal is for up to USD$300,000. The funding from MPTF would be provided as an initial payment to enable the study to begin while additional funds are confirmed from other sources.

b) **Coherence with existing projects:** This section lists any of the projects which are supporting the same SO or MCA in the same country or area of operation.

This study will be conducted in collaboration with the programs of the Government of Guinea, WHO and other partners that address the prevention of the spread of Ebola in Guinea. It will be coordinated with the Gouvernement de la Republique de Guinée. 2015. *Plan Strategique National De Gestion Des Survivants De La Maladie A Virus Ebola, 30 Octobre*. Conakry, Guinea.

Other relevant on-going studies include:
Sexual transmission of EVD: In addition to the work cited above, other research is ongoing. Investigations of several other recent Ebola cases in West Africa have suggested sexual transmission from survivors but have not been confirmed (CDC Emergency Operations Center, unpublished data, 2015). Genomic surveillance is likely to assist in determining if sexual transmission is relevant and its role (Gire et al. 2014)

Body fluid viral persistence in survivors: Additional studies are planned to determine clearance, persistence and shedding of Ebola virus in body fluids of survivors and to evaluate possible

sexual transmission of infection.(Deen et al. 2015). Studies on the role of antivirals in reducing semen carriage of EBOV are in planning in Liberia and Sierra Leone (personal communications with Stephen Kennedy and Robert Leitch).

Ebola vaccine immunology: A phase II study is planned in Guekedou, Guinea by the NIH-PREVAIL collaboration to provide immunological bridging data in support of vaccine licensure. This is expected to have 5000 participants, randomised 1:1:1 to rVSV (control), ChAd3 and Ad26-MVA vaccines.

c) Capacity of RUNO(s) and implementing partners:

The study design was developed by a group of experts from France, Germany, Guinea, Italy, Switzerland, United Kingdom, United States, and WHO.

From WHO the study activities will be coordinated by Dr. Ana Maria Henao Restrepo who has already led the *Ebola ca suffit* Ring vaccination trial . (Henao-Restrepo et al. 2015)

Other contributors & collaborators include:
Sakoba Keita, National Coordinator Ebola Response, Government of Guinea
Federica Ambrosini, Istituto Nazionale per le Malattie Infettive "Lazzaro Spallanzani" I.R.C.C.S., Direzione Scientifica, Via Portuense 292, 00149 Roma, Italy
Nathalie Broutet, Department of Reproductive Health and Research, World Health Organization, Switzerland
Miles Carroll, Deputy Director, Public Health England, London, UK
Gabriella De Carli, Department of Epidemiology, National Institute for Infectious Diseases L. Spallanzani IRCCS, Rome, Italy
Antonio Di Caro, National Institute for Infectious Diseases L. Spallanzani, Via Portuense 292 00149 Rome, Italy
Nathalie Dean, Department of Biostatistics, University of Florida, Gainesville, FL 32611, USA
John Edmunds, London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology, London, UK
Rosalind Eggo, School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology, London, UK
Stephen Guenther, Head, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
Brad Gessner, Agence de Medicine Preventive, Paris
Judith Glynn, London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology, London, UK
Ana Maria Henao Restrepo, Immunization, Vaccines & Biologicals, World Health Organization, Switzerland
Giuseppe Ippolito, Scientific Director, National Institute for Infectious Diseases, Lazzaro Spallanzani, Via Portuense 292, 00149 Rome, Italy
Simone Lanini, Specialist in Infectious Disease, Epidemiology and Preclinical Research Department INMI Lazzaro Spallanzani, Via Portuense 292 00149 Rome Italy
Ira Longini, Professor of Biostatistics, Department of Biostatistics, University of Florida, Gainesville, FL 32611, USA
Francesco Vairo, Clinical Epidemiology, National Institute for Infectious Diseases "L. Spallanzani", Rome, Italy
Conall Watson, London School of Hygiene and Tropical Medicine, Department of Infectious Disease Epidemiology, London, UK

d) Proposal management

This project will be conducted by the Government of Guinea (Sponsor) with technical and operational support by WHO. A Guinean researcher will act as the Principal investigator, there will be a Guinean coordinating the laboratory activities and all the field team will include Guinean nationals. The team will receive support from national and international experts listed above.

e) Risk management

The key risks and strategies to mitigate these risks are as follows:
The study will be conducted in compliance with Good Clinical Practice. A trial insurance will be sought.

Risks to the Achievement of Strategic Aims	Likelihood of Occurrence (high, medium, low)	Severity of Risk Impact (high, medium, low)	Risk Management and Mitigating Strategy	Responsible Partner/Unit
Insufficient numbers of volunteers	Low	Medium	Recruitment is already under way; experience of recent trial suggests ongoing engagement with the community will help ensure sufficient numbers recruited.	Dr. Ana Maria Henao Restrepo
Delayed recruitment of key staff	Low	Medium	Staff are already recruited and contracts completed for 12 months	Dr. Ana Maria Henao Restrepo
Rising costs of study	Low	Medium	Costs of study have already been carefully reviewed and contingency funds included	Dr. Ana Maria Henao Restrepo
Inability to secure full funding for the study	Low	High	Study subject of fundraising work with Paul Allen Foundation and other donors; WHO retaining flexible funding as last resort.	Dr. Ana Maria Henao Restrepo

f) **Monitoring & Evaluation:** This section sets the M&E arrangements and responsibilities for the proposal, including who will be responsible for the collection and analysis of data required in the result framework.

The study will be implemented between January and March 2016, with follow-up to 28 days, to the end of viral persistence/adverse events, and/or to a date indicated by study extensions, with consent from participants. Findings will be disseminated in a timely manner to relevant authorities and through the medical science literature. Monthly reports updating MPTF will be submitted as per usual MPTF grant agreements; the final outcome of the study will not be available in the three months of this project's duration and will be communicated to MPTF as soon as it is made public.

References

1. World Health Organization (n.d.) Ebola response roadmap - Situation report. Geneva: World Health Organization. Available: http://apps.who.int/ebola/ebola-situation-reports.

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PROPOSAL RESULT MATRIX

Proposal Title: Vaccination cohort study: Preventing late transmission of Ebola from survivors to close contacts					
Strategic Objective to which the Proposal is contributing[2]	MCA3, MCA13				
Effect Indicators	**Geographical Area (where proposal will directly operate)**	**Baseline[3] In the exact area of operation**	**Target**	**Means of verification**	**Responsible Org.**
% of Reduction in Ebola disease incidence among the vaccinated group of Survivors and close contacts in Guinea as a result of the vaccination programme	Guinea	To be collected at start of trial	More than 50%	Report of study published in peer review journal.	WHO and the Government of Guinea
Strategic Objective1 MCA3, MCA13					
Output Indicators	**Geographical Area**	**Target**	**Budget**	**Means of verification**	**Responsible Org.**
# Participants recruited for the initial phase of the vaccination Programme	Guinea	1,000	200,000	Interim Report produced	WHO and the government of Guinea
% of blood samples of selected participants systematically collected and analyzed at 28 day period	Guinea	100% blood samples collected & analyzed at 28 days	79,950	Monthly update report to MPTF	WHO and the government of Guinea
Coordination Fees[4]			**7[5]%**		
Staffing	Guinea		200,000		
Supplies, Commodities, Materials	Guinea		28,000		
Equipment, Vehicles Furniture	Guinea		27,450		
Travel	Guinea		24,500		
Direct Costs			279,950		
Indirect Cost max 7 %			19,597		
Total Project Cost in USD			299,547		

[2] Proposal can only contribute to one Strategic Objective
[3] If data are not available please explain how they will be collected.
[4] Should not exceed 20% including the indirect cost
[5] Refers to indirect cost ONLY

Project budget by UN categories

CATEGORIES	Description	Amount Recipient Agency	TOTAL (for 3 months) USD
1a. Field staff and other personnel	1 Guinean Principal investigator	WHO	10,000
	40 Guinean field staff to conduct trial activities (contact listing, informed consent, sample collection, vaccination, follow up, logistics)	WHO	120,000
	4 Guinean staff with supervisory functions	WHO	12,000
	2 international staff with supervisory functions (@ 25%)	WHO	18,000
	1 International Statistician (@25%)	WHO	9,000
	1 Guinean Lab coordinator and two lab technician	WHO	10,000
	1 International Lab coordinator @ 25%	WHO	9,000
	Subtotal		**188,000**
1b. Data collection staff	1 Guinean Data Manager coordinator to supervise the data management procedures	WHO	3,000
	2 Guinean staff for data management	WHO	2,000
	1 international Data Manager with supervisory functions to develop the database and provide support throught (@ 25%)	WHO	7,000
	Subtotal		**12,000**
2. Supplies, Commodities, Materials			
Laboratory supplies	Kits for oral fluids and blood sample sample collection	WHO	10,000
	Lab consumables for sample processing	WHO	9,000
Commodities and materials	Petrol for cars for field work	WHO	5,000
	Office consumables		2,000
	Petrol for cold chain generator		2,000
	Subtotal		**28,000**
3. Equipment, Vehicles, and Furniture, incl. depreciation (include details)	11 Tablets for data collection	WHO	4,950
	Rental fees for 5 four-wheel drive cars for 3 months (@ USD 150)	WHO	22,500

	Subtotal		**27,450**
4. Contractual services (include details)			
5.Travel (include details)	Travel Geneva-Conakry for 5 international staff (once each, 5 days trip @ USD 3500 per trip)) plus travel for Guinean PI from Conakry to Europe (2 trips 5 days trip @ 3500 per trip)	WHO	24,500
6. Transfers and Grants to Counterparts (include details)			
7. General Operating and other Direct Costs			
	Subtotal		**24,500**
Sub-Total Project Costs			**279,950**
8. Indirect Support Costs*	PSC@7%		19,597
TOTAL			**299,547**

* The rate shall not exceed 7% of the total of categories 1-7, as specified in the Ebola Response MOU and should follow the rules and guidelines of each recipient organization. Note that Agency-incurred direct project implementation costs should be charged to the relevant budget line, according to the Agency's regulations, rules and procedures.