Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)

Overview on Ebola Research

Update February 2015

Prepared in the context of the

Ebola R&D Funders' Meeting on 11 December 2014

jointly organised by

the European Commission, Directorate-General for Research & Innovation

and the Bill & Melinda Gates Foundation

EUROPEAN COMMISSION

DIRECTORATE-GENERAL FOR RESEARCH & INNOVATION

Directorate E - Health

E.3 - Fighting infectious diseases and global epidemics

GLOPID-R

Global Research Collaboration for Infectious Disease Preparedness

Table of content

THE EUROPEAN COMMISSION

Directorate-General for Research & Innovation including IMI and EDCTP1

In order to address urgent research needs in relation to the current Ebola crisis the Commission has quickly mobilised €24.4 million from Horizon 2020 via an exceptional procedure to support urgent Ebola research. This was the first time that this special exceptional procedure (grants awarded without a specific call for proposals, Art. 128 of Financial Regulation, Art. 190 of its Rules of Application) has been used by DG RTD. In the preparation of this procedure and the evaluation of proposals, DG RTD has worked closely with the WHO and the European Medicines Agency.

Five projects are being funded, including a trial of the most advanced vaccine against Ebola being developed by GSK (with an EU financial contribution €15.1 million). This vaccine is already being tested in humans, with very promising results being seen so far. Other projects will study the potential therapeutic effect on Ebola patients of an existing treatment against influenza, plasma from survivors, and serum from antibody-producing horses. A further project will work on the transmission of the virus and the clinical importance of its mutations.

[1] http://ec.europa.eu/research/health/infectious-diseases/emerging-epidemics/Ebola-projects_en.html

Table with details on the five projects funded by the EU Commission (DG RTD)

Title	Coordinator	Amount	Project Scope
EbolaVac	GlaxoSmithKline Biologicals, BE	€15,153,216	Conduct clinical trials in Europe and Africa on the most advanced vaccine candidate ChAd3-EBOV. These trials will provide extended evidence on the safety and ability to elicit a protective immune response, as well as on the most appropriate vaccination schedule. Five small phase I trials in of candidate vaccine in healthy-volunteer trials have been completed (UK, USA, Switzerland, Mali). Initial safety and immunogenicity data enabled selection of the most appropriate dose. Further safety/immunogenicity healthy-volunteer phase II studies start in March (Mali, Ghana, Nigeria, Cameroon, Senegal). If data from 100 adults shows acceptable safety, a study in children would follow.
REACTION	Institut National de la Santé et de la Recherche Médicale (INSERM), FR	€2,575,810	Study the safety and efficacy of Favipiravir, an antiviral already licensed for influenza, first in an animal model of the disease and then on patients with Ebola virus disease. First results expected after 6 months. At least 80 individuals with Ebola have now been treated with favipiravir, in order to test its effectiveness against Ebola. The REACTION project has recently announced preliminary results that show that favipiravir halves mortality (from 30% to 15%) in patients with early Ebola disease. If these results are further confirmed by the ongoing clinical trial, it will be the first time ever that a treatment against Ebola will be deployed during the current outbreak. The dosage used in this study has been published in The Lancet. Press release Commissioner Moedas welcomes encouraging results – 24 February 2015
Ebola_Tx	Prins Leopold Instituut voor Tropische Geneeskunde, BE	€2,892,171	Study the safety, efficacy, and practical aspects of using whole blood or plasma from survivors, as a treatment for patients with Ebola virus disease. The objective is to find out whether this therapy improves patients' survival chances. At the same time, the trial will also be studying if and how the approach can be scaled up. Anthropologists from the Institute of Tropical Medicine in Antwerp have established contact with Ebola survivors in view of plasma donation. While blood transfusion is a well-known procedure in Guinea, both the survivors and the community at large need to be sensitized about the donation of plasma in the context of a clinical trial. As the trial preparations are in the final stages, Ebola-Tx researchers now await the green light to start treating patients. The trial will take place at the Donka Ebola Treatment Centre run by Médecins sans Frontières in Conakry, Guinea.

Title	Coordinator	Amount	Project Scope
EVIDENT	Bernhard-Nocht-Institut für Tropenmedizin, DE	€1,759,326	Research on interactions between the Ebola virus and the host. This will provide urgently needed answers regarding the pathophysiology and transmissibility of the disease, and will help better guide the planned clinical trials on vaccines and potential treatments, as well as the management of patients with Ebola virus disease. EVIDENT has so far identified novel biomarkers of outcome with potential to be used in clinical management and in vaccine correlates of immunity which will serve to inform current vaccine trials. These new biomarkers have opened up the possibility to develop post-exposure immunotherapy against Ebola virus disease, a highly sought medical countermeasure for treatment of acute patients. The consortium continues to work in the field and in the laboratory to gather, for the first time, significant insight into the pathogenesis and transmission of EVD.
IF-Ebola	Institut de recherche pour le développement, FR	€1,992,770	Study the safety and efficacy of using antibodies produced in horses against Ebola, as a passive immunity treatment for patients with Ebola virus disease. The IF-EBOLA action benefits from the expertise of 9 partners from Europe, North America, Middle-East & Africa to operate in Sierra-Leone & Guinea. Early diagnostic by ultrasensitive virus detection will lead to an early treatment (supported by WHO & EMA) of contact-patients with horse anti-Ebola polyclonal antibodies expecting to reduce the EVD fatality rate. The immune response will be monitored.

Actions under the Innovative Medicines Initiative (IMI2)

The Innovative Medicines Initiative 2 (IMI2), a partnership between the European Union and the European pharmaceutical industry, represented by the European Federation of Pharmaceutical Industries and Associations (EFPIA), has launched a new research and innovation programme, Ebola+, on Ebola and other filoviral haemorrhagic fevers. The programme will cover urgent actions addressing the current epidemic and put in place a long-term strategy to manage any future outbreaks. The call for proposals launched on 6 November 2014 has a total budget of €215 million which will go towards eight projects[2] addressing development and manufacturing of vaccines (VSV-EBOVAC, EBOVAC1, EBOVAC2, EBOMAN), ensuring compliance with vaccine regimens (EBODAC), and the development of rapid diagnostic tests (MOFINA, FILODIAG, EbolaMoDRAD). €114 million comes from Horizon 2020, and the remaining €101 million from the pharmaceutical companies involved in the projects. The first projects have started working as of 1 January 2015, and the hope is that they will deliver results that will contribute to tackling both the current and future outbreaks. It is expected that additional calls will be launched under the Ebola+ programme in 2015 and 2016 to address additional topics, e.g.: Multivalent filovirus vaccine development; Formulation for cold chain; Immunotherapy; Rapid diagnostic tests – long term; Antivirals development and repurposing; as well as discovery and early development of other products.

[2] The Grant Agreements for some projects selected under the first call of the Ebola+ programme are still being finalised. Final information on all selected projects, including budget details, will be published once the Grant Agreements have been signed.

Project Acronym	Coordinator	Funding	Abstract
Vaccine development			
VSV-EBOVAC	Sclavo Vaccines Association, IT	IMI: €3.9 million	VSV-EBOVAC will build on existing work to advance the development of the Ebola vaccine candidate VSV-ZEBOV ('vesicular stomatitis virus-vectored Zaire Ebola vaccine'). The VSV-EBOVAC project will use cutting-edge technologies to carry out in-depth analyses of samples taken from clinical trial participants before and after vaccination. This will allow them to gather vital information on both the strength of the immune responses triggered by the vaccine and vaccine safety. Already started working.
EBOVAC 1 **EBOVAC 2**	London School of Hygiene & Tropical Medicine, UK INSERM Transfert, FR	IMI: €58.3 million EFPIA in kind: €32.7 million IMI: €22.8 million EFPIA in kind: €15.1 million	Between them, the two EBOVAC projects will assess, through clinical trials in Europe and Africa, the safety and tolerability of the 'prime-boost' Ebola vaccine regimen (Ad26.ZEBOV and MVA-BN-Filo) in development at the Janssen Pharmaceutical Companies of Johnson & Johnson. In a prime-boost vaccine regimen, patients are first given a dose to prime the immune system, and then a boost dose which is intended to enhance the immune response over time. Phase I trials will be carried out by the EBOVAC1 project. These trials will gather preliminary information on the safety and tolerability of the vaccine regimen. The immune response generated by the regimen will also be evaluated longer term. The Phase II and III trials, subject to review of the preliminary Phase I data, will be carried out in parallel by the EBOVAC2 and EBOVAC1 projects respectively to speed up the clinical development of the vaccine regimen. In these trials, larger groups of people will receive the vaccine regimen, allowing the projects to gather further information on the regimen's safety and immunogenicity, including in specific groups such as children and the elderly, and to assess its efficacy against Ebola virus.
Vaccine manufacture capability			
EBOMAN	Vibalogics GmbH, DE	IMI: €1.0 million EFPIA in kind: €47.6 million	Accelerate the development and manufacturing of a promising new 'prime-boost' Ebola vaccine regimen Ad26.ZEBOV and MVA-BN®-Filo. Ensure the delivery of sufficient quantities of Ad26.ZEBOV and MVA-BN®-Filo vaccines to support the clinical trials to be performed under EBOVAC 1 and EBOVAC 2. Establish a platform capable of rapidly producing sufficient quantities of the Ad26.ZEBOV and MVA-BN®-Filo vaccine, while adhering to stringent quality and safety requirements. Create additional vaccine production capacity to allow for the rapid preparation of large quantities of vaccines in case the outbreak further escalates.

Deployment and compliance of vaccination regimens			
EBODAC	London School of Hygiene and Tropical Medicine, UK	IMI: €20.3 million EFPIA in kind: €5.4 million	The EBODAC project will develop a communication strategy and tools to promote the acceptance and uptake of new Ebola vaccines. One of the project's most important products will be a platform, based on mobile technology, dedicated to Ebola vaccines. As well as providing local communities with information on Ebola and vaccines, the platform will send reminders to people receiving the 'prime boost' vaccine to return to get their second 'booster' dose and facilitate the tracking of vaccination coverage. EBODAC will also set up local training programmes to make sure the communication strategy tools will be ready for deployment in the local setting.
Rapid diagnostic tests			
MOFINA	Altona Diagnostics GmbH, DE (TBC)	IMI: €1.0 million	The project will develop a new diagnostic test that will deliver results in under 45 minutes on whether the patient has Ebola or a related disease such as Marburg virus. Crucially, the device is designed to work well in sites where high-end laboratory infrastructures are simply not available, while also protecting users from infection. The project will draw on two existing technologies: a conventional Ebola virus test, and a point-of-care molecular diagnostics platform. After testing a prototype of the system, the project partners will validate it in the field.
FILODIAG	GNA Biosolutions GmbH, DE	IMI: €2.3 million	The FILODIAG project aims to deliver an ultra-fast, accurate diagnostic instrument that will test for Ebola in less than 15 minutes. Such a system could be used in both healthcare settings and at critical infrastructures like airports. This project will replace the heating/cooling PCR steps with a technology based on laser-heated nanoparticles. Early tests of this technology have worked well. The project will add a step to concentrate the virus and refine and test the system before evaluating it in the field.
EbolaMoDRAD	Folkhälsomyndigheten (The Public Health Agency of Sweden), SE	IMI: €4.3 million	The EbolaMoDRAD project aims to develop and validate in the field a rapid diagnostic tool that will be both simple and safe to use in low resource settings by people who may not have specialist training. At the same time, the project will implement a large-scale capacity building programme in West Africa with a strong focus on diagnostics, biosafety, and outbreak management.

EDCTP[3]

The European & Developing Countries Clinical Trials Partnership (EDCTP) was launched in 2003 by the European Union (EU) to accelerate the development of new or improved drugs, vaccines and diagnostics against poverty-related diseases, with a focus on HIV/AIDS, tuberculosis and malaria. It currently involves 13 African countries and 13 European countries. At the Commission's request made on 23 September, EDCTP has included

[3] www.edctp.org

emerging infectious diseases of particular relevance for Africa, such as Ebola, in the list of pathogens referred to in their work plan. This will allow EDCTP to fund clinical trials on drugs, vaccines and diagnostics for Ebola and other emerging epidemics in calls issued under the second EDCTP programme (EDCTP2), which was launched in December 2014. Reflecting this, the first call for Research and Innovation Actions (RIA) under EDCTP2, which aims to fund "diagnostic tools for poverty-related diseases", includes diagnostic tools for Ebola. In the first quarter of 2015, EDCTP intends to launch two other RIA calls that will include Ebola in its remit, namely on "improved treatment and clinical management of poverty-related diseases" and "strategic projects with major cofounding". Finally, a call for proposals on "operational research in support of Ebola virus diseases clinical studies" is also foreseen to be published in early 2015. This latter call aims to support clinical site preparedness and community engagement in clinical studies.

The Commission has also urged EDCTP to mobilise funding from the Participating States to increase the EDCTP budget for 2014 and 2015 and to coordinate relevant research activities.

On-going funding under FP7

The European Commission is funding several research projects that are addressing Ebola under the EU's Seventh Framework Programme for Research and Development.

ANTIGONE

ANTIGONE - *Anticipating the global Onset of Novel* Epidemics, EU funding €11,997,709[4] - identifies factors promoting the emergence of pandemics from zoonotic pathogens including related prevention strategies studies a number of zoonotic viruses and bacteria such as filo-viruses, including the Ebola virus, with the aim of identifying the key factors that make zoonotic viruses and bacteria with human pandemic potential prone to cross the species barriers, adapt to human hosts, and to gain human-to human transmissibility. The research on Ebola virus and another important filovirus, Marburg virus, concentrates on the molecular mechanism of the high pathogenicity of these viruses, with the ultimate goal to develop new antiviral drugs against them. The project discovered how soluble proteins produced by the Ebola virus cause damage to blood vessel walls and contribute to the internal bleeding characteristic of the disease. This finding could clear the way to produce a new treatment for Ebola in the future and could also help scientists to develop treatments for other diseases that operate the same way (*PLoS Pathogens – accepted*). Moreover, given the current Ebola outbreak situation in West Africa the consortium reallocated some of its resources towards Ebola research. It was agreed to use these funds for two projects as new ANTIGONE supported Ebola Research Response projects: *(1) Therapy against shed glycoprotein in Ebola virus infection (INSERM/EMC):* the overall goal of this project is to explore therapeutic strategies to alleviate the septic shock-like syndrome caused by human Ebola virus infection. The proposed research will make use of well-established animal models for Ebola virus infection to determine the effect of shed glycoprotein on cytokine response and vascular permeability, and to determine the efficacy of therapeutic candidates on the reduction of the clinical signs of septic shock-like syndrome. The first results of this research are expected after 12 months. (2) *Tracking Ebola virus in Ghana, West Africa (IOZ, UCAM, INSERM, UK-*

[4] www.antigonefp7.eu; from 2011-11-01 till 2016-10-31

*BONN).*The overall goal of this project is to understand how people in West Africa come into contact with Ebola virus and Ebola-like viruses, and specifically to understand the role of different fruit bat populations as reservoirs, the role of domestic animals, particular pigs, as intermediate hosts, and risk factors for people to become infected. The results of this research are expected after 18 to 24 months. Two new research projects to improve preventive and therapeutic strategies against Ebola are being planned within the Antigone consortium. One is to identify the infection dynamics of filoviruses between fruit bats, livestock and people in West Africa. This information may help to prevent Ebola by identifying risk factors for contracting Ebola virus infection. The other is to study the role of one of the proteins, GP, that Ebolavirus releases into the bloodstream and its contribution to the septic shock-like syndrome caused by Ebolavirus infection. The intention is to use the knowledge gained to develop therapeutic strategies against this detrimental effect of Ebola virus infection.

PREDEMICS

The FP7 project PREDEMICS - *Preparedness, Prediction and Prevention of Emerging Zoonotic Viruses with Pandemic Potential using Multidisciplinary Approaches*'[5] - addresses the prevention of emerging zoonotic viruses with pandemic potential. For this purpose the project is studying a number of zoonotic viruses to identify risk patterns of emergence of practical relevance for disease surveillance, control, intervention and pandemic preparedness. Final results are expected in 2016. In case of emergence of a zoonotic virus with pandemic potential, PREDEMICS partners have the possibility to engage in research within the scope of PREDEMICS based on expertise, knowhow and methodologies developed within PREDEMICS. Given the current Ebola virus crisis the consortium has been involved in outbreak intervention and development of point of care molecular diagnostic tests. It has also been contributing to analysis of the interhost and intrahost genetic evolution of the Ebola virus providing insights into the source and time of introduction of the virus in Guinea[6] and Sierra-Leone[7] and defining patterns of transmission. Contributions are also made through modelling and analysis based on epidemiological data to estimate key transmission parameters, document trends in the epidemic in the affected countries[8], and assess the effect of the currently implemented travel bans on the risk of importation worldwide. Additional studies on virus-host interactions and innate or serological responses are on-going.

PREPARE

PREPARE - *Platform foR European Preparedness Against (Re-)emerging Epidemics*, EU funding €24,000,000[9] - is an initiative, funded by the European Commission, to establish a European clinical research framework covering over primary care and hospital care in 27 EU member States. PREPARE implements 'inter-epidemic' large-scale clinical studies and patient-oriented pathogenesis studies and develop novel diagnostics. In addition the project develops and tests solutions to bottlenecks that prevent rapid clinical research responses in the face of new infectious disease threats. The project has the goal of mounting a rapid,

[5] http://predemics.biomedtrain.eu/cms/default.aspx; from November 1, 2011 till 31 October 2016
[6] http://currents.plos.org/outbreaks/article/phylogenetic-analysis-of-guinea-2014-ebov-Ebolavirus-outbreak-2/
[7] www.sciencemag.org/content/345/6202/1369
[8] http://www.nejm.org/doi/full/10.1056/NEJMoa1411100
[9] www.prepare-europe.eu; from 2014-02-01 till 2019-01-31

coordinated deployment of Europe's clinical investigators within 48 hours of a severe infectious disease outbreak in Europe.

An electronic survey on healthcare preparedness for Ebola in 736 European hospitals in 40 countries was completed in August-September 2014. The survey showed that patient transfer agreements were in place for the majority of hospitals that would not admit patients. Admitting hospitals were more frequently engaged in preparedness activities and more often contained basic infrastructural characteristics such as admission rooms and laboratories considered important for infection control. Some gaps and concerns were also identified.

TELL ME

The FP7 project TELL ME[10] - *Transparent communication in Epidemics: Learning Lessons from experience, delivering effective Messages, providing Evidence*, EU funding €1,900,342 - aimed to develop evidence-based models for improved risk communication during infectious disease outbreaks. Even if conceived before the last Ebola crisis in 2014, some of the outcomes served for the response at communications level. In November 2014 a document with the project's contribution to Ebola response was submitted to the European Commission, with a set of proposed actions. Meanwhile a dedicated e-learning course for primary care professionals was adopted by the Italians Associations of Doctors and Nurses respectively, reaching about 30,000 Italian health professionals, including a dedicated course on Ebola. The TELL ME Communication Kit also offers practical guidance at different levels which can be useful to consider in order to overcome communication obstacles in the context of the Ebola crisis.

[10] http://tellmeproject.eu ; from 1-2-2012 till 31-1-2015

BILL & MELINDA GATES FOUNDATION

The Bill & Melinda Gates Foundation has been working in support of the broader US and Global response to the Ebola crisis to prioritize Research & Development activities that hold the most promise for near term impact on the epidemic, and pave the way for longer term benefit to West Africa. Our goal is to work closely and urgently with UN agencies, public and private sector partners, and other funders to support the global response and end the Ebola epidemic as soon as possible. Our current R&D efforts are focused on developing and delivering meaningful therapeutic, diagnostic, and preventive interventions to sick patients and individuals at high risk. We are investing in those interventions that have the highest likelihood for early implementation and breaking the transmission cycle with an emphasis on achieving proof of concept as quickly as possible.

Key Considerations

- Interventions available to confirmed infected patients in developed countries should be introduced in West Africa on the same basis.
- An intense and ongoing focus on reducing transmission by contact tracing and quarantine is central to all control efforts and should be maximally supported. Rapid, accurate diagnostic tools that can be deployed in field settings are urgently needed to support this.
- Contacts of infected individuals are at high risk of developing disease (beyond that of trained HCW) and there currently are no therapies available to reduce this risk.

Gates Foundation R&D Priorities

- Given the urgency of the situation, a key area of focus is on identifying one or more therapies from currently available options that would be safe and effective in reducing risk of symptomatic infection in this group (and hence reducing R0 to < 1, dampening the epidemic).
- There are at least 3 therapeutic interventions that merit evaluation at this point and have sufficient supply for study:

Intervention	Organization	Stage of Development	Foundation Support to Date
Convalescent Plasma	ClinicalRM, Inc.	Preclinical	$5.8M
Brincidofovir	Chimerix, Inc.	Preclinical (EBOV)	Under Consideration
rVSV-EBOV	NewLink Genetics/Merck	Phase 1	Under Consideration

- Supply remains a constraint for other potentially promising interventions:

Intervention	Organization	Stage of Development	Foundation Support to Date
ZMapp™	Mapp Biopharmaceutical	Preclinical	$0.7M
Ebola Immune Globulin	TBD	N/A	Under Consideration

- FDA approved drugs for other indications (e.g. Favipiravir, Zoloft, Chloroquine, Azithromycin) with evidence of anti-Ebola activity in vitro that could potentially be repurposed for treatment of Ebola Virus Disease are also under consideration.
- Rapid Diagnostic Tests, Nucleic Acid Tests and Supportive Technologies are all being considered carefully for funding with a priority for triage and contact tracing as the most important intended uses. Diagnostic investments to date include the following:

Intervention	Organization	Stage of Development	Foundation Support to Date
Xpert® Ebola Test (NAT)	Cepheid	Development	$3.4M*
Fionet™ Cloud Based ICT	Fio Corp.	Development	$0.7M
Nanotrap®	Ceres Nanosciences	Development	$0.4M

*Co-Funded by the Paul G. Allen Family Foundation

- Vaccine development investments to date include GSK ChAd3-EBOV ($3M) and WHO ($3M).

Adaptive Clinical Trial Platform Design

- All of these treatment options have unknown efficacy in this setting and some have poorly defined safety profiles, hence data supporting their broader use is urgently required.
- We are therefore considering supporting an adaptive clinical trial platform design that most efficiently looks for evidence of efficacy across and between these options, allowing us to rapidly eliminate ineffective or unsafe options and providing a basis for broader deployment.
- The adaptive platform design allows patients to receive the best treatment during the course of a single trial, and provides data on multiple interventions.

- Potential treatments could be efficiently compared using pre-defined criteria for continuation or abandonment by an independent data monitoring committee. This approach has been used in the clinical evaluation of neo-adjuvant treatments for breast cancer[11].

Key Design Elements

Fixed randomization initially, followed by adaptive randomization based on observed endpoints.

- Trial begins with fixed randomization with equal allocation to the initial treatment regimens, stratified according to disease severity (i.e., fever duration and diarrhea)
- The fixed stage of the randomization lasts until the ability to observe endpoints, and the trial enters adaptive randomization
- A probability for each of the treatment regimens is created and this randomization is used for randomizing all patients for the duration of the first treatment regimen (i.e. 2 weeks)
- After the first treatment regimen, the full data for the trial on outcomes (e.g., mortality at 14 days) are updated and a new randomization probability is created for the following regimen

Perpetual continuation of the trial for as long as needed, allowing new treatments to be added as trial evolves

Potential Benefits

- Treatments that do not meet endpoint criteria can be replaced, allowing patients to receive the best treatment in a single trial
- New treatments can be added to the trial as developed, allowing flexibility to adopt to fast moving R&D of new products
- Establishing the adaptive platform, setting up the clinical infrastructure, and obtaining field experience equip affected countries to manage any future epidemics more effectively

[11] Barker AD1, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. Clin Pharmacol Ther. 2009 Jul;86(1):97-100.

PARTNER ORGANIZATION	DESCRIPTION	AMOUNT
Clinical Research Management, Inc.	Ebola Convalescent Plasma: To conduct phase I/II clinical trials for Ebola Virus Disease treatment in West Africa providing important clinical, immunologic and virologic data to inform strategic planning, design of further clinical trials and potential future treatments	$5,774,202
Cepheid	To rapidly develop an Xpert® Ebola assay for use in the GeneXpert instrument system in response to the urgent epidemic in West Africa. The product will be suitable for use in low resource settings for triage care and for contact tracing where possible	$3,385,451
WHO	To support WHO in its convening and coordinating role to accelerate development, licensure and use of high quality, safe and effective ebola interventions	$2,985,234
GlaxoSmithKline Biologicals	ChAd3-EBOV: To accelerate Ebola Vaccine Production and Development in order to treat those affected by the Ebola epidemic in West Africa	$2,952,386
Fio Corporation	To adapt Fionet™ for Rapid Deployment to Ebola Crisis Areas to Provide Mobile Diagnostic Solutions Integrated with Real-Time Information Services	$736,048
Mapp Biopharmaceutical, Inc.	ZMapp™ antibody production in tobacco plants: To accelerate the production of an experimental drug in order to treat those affected by the Ebola epidemic in West Africa	$627,000
Ceres Nanosciences, Inc.	Nanotrap®: To support effective detection of Ebolavirus using a noninvasive oral fluid collection tool, coupled with a highly sensitive diagnostic approach as a solution for rapid identification and confirmation of infected individuals without requiring highly-trained personnel	$432,762

AUSTRALIA
National Health & Medical Research Council

- NHMRC is considering the need for a specific research call on Ebola Research and is consulting with the Australian Government.
- NHMRC recently held a national teleconference of interested members of the Australian research community to discuss how Australia could assist international EVD research efforts. It is evident that Australia has significant research capacity that could contribute to the current situation and there are a number of researchers working closely with international initiatives. Australian research capabilities have been identified including those through the Australian Animal Health Laboratory - a high containment facility with 'biosafety level four' classification necessary for working with pathogens such as EVD.
- NHMRC is also working together with the Australian Chief Medical Officer and relevant Commonwealth, state and territory bodies on this issue. The CMO and the State 12.

BRAZIL

Fiocruz

Fiocruz will host the Red de Institutos Nacionales de Salud de la Unión de Naciones Suramericanas - Network of National Health Institutes of South American Nations - of the Union of South American Nations (RINS / UNASUR) Seminar "Facing the Ebola Epidemics", programmed to be held on November 25 – 27, in Rio de Janeiro, with participation of 3 specialists per country (infectology, epidemiology and Laboratory).

Fiocruz participates in the coordination of efforts for the surveillance and care for Ebola cases in Brazil.

There are no known Brazilian plans of funding research in Ebola so far. Fiocruz is discussing that in contact with the Brazilian Minister of Health.

Butantan Institute

A horse hyperimmune serum anti-rabies/Ebola viruses for therapy of infected patients with Ebola and/or rabies virus and an inactivated rabies and Ebola vaccine for human use against infection by rabies and Ebola viruses.

Throughout its more than one hundred years of existence, the Instituto Butantan has been developing vaccines for public health, contributing to the control and eradication of transmissible diseases such as bubonic plague and smallpox, among others. Butantan Institute has today 2,140 direct employees, which 180 of them are researchers and at least 80% of them are PhD. The technological development of the institution's products achieved greater increase in the mid-1980's, when the Biotechnology Center of IB (Butantan Institute) was created, with the purpose of approaching and increasing R&D and Production activities, and thereby boosting the Self-Sufficiency in Immunobiology Program of the Ministry of Health (PASNI), helping to reduce the country's dependence on imported vaccines.

The production of recombinant Hepatitis B vaccine is an example of success of Instituto Butantan. All the development was carried out throughout Instituto Butantan, in a laboratory of the Biotechnology Center, in collaboration with Russian researchers. A few years later, it was the production of seasonal influenza vaccine from the multinational industry (Sanofi-Pasteur), with all technology of production of the vaccine being internalized in IB. Currently, new vaccine plants are being completed and/or put into service, as the case of human rabies vaccine produced in cell culture.

The Instituto Butantan runs the entire route for the product, once it is strategic in a policy of technological innovation to have the entire production performed in the country and not only the formulation and bottling of the active ingredients. For this, it has a production infrastructure dedicated to each of the vaccines and a production plant for horse hyperimmune sera, besides formulation and filling laboratories, quality control, quality assurance, and a central animal house. The Instituto Butantan has been heavily investing in actions of quality control and quality assurance, aiming at achieving international standards, in order to be qualified by the WHO.

Moreover, the Instituto Butantan is able to carry out pharmacovigilance actions and clinical trials from Phase I to Phase IV for all its innovative products, which differentiates the Institute from other institutions that rely on multinational companies for performance of these tests. The incorporation of these clinical trials activities within the Butantan Institute streamlines and accelerates the registration of new products, which is essential when it comes to technological products that benefit public health.

The Instituto Butantan also counts on a team of regulatory affairs that provides all regulatory support necessary for the development of clinical study phases at ANVISA, a national regulatory agency with roles similar to FDA.

Regarding more specific interaction of the research area with private companies, such interaction has occurred after granting the Butantan Institute with a CEPID (Research, Innovation and Diffusion Centers) Program by FAPESP, in 2000. This program encourages interaction between research and private companies, and through this, a relationship among the Butantan Institute, FAPESP and a consortium of private companies, called COINFAR, which is made up by the laboratories Biolab/Sanusat, União Química Farmacêutica Nacional and Biosintética Ltda, was established.

Since then, the interaction of Butantan Institute with private companies is increasing more and more, and it is possible to conclude more partnership agreements. This approach with the private sector is due to the enactment of laws that flexibilize such interaction, as well as government incentives by means of programs that encourage technological development, and even the maturity and professional relationship of Butantan Institute´s staffs, which become more structured and prepared to interact with private companies.

We are going to use the object of the patent presented above, not to a commercial aim, but to an internal development. We hope to develop, with the Ebola rabies vaccine, a serum against Ebola/rabies and, eventually, an Ebola/rabies vaccine. Probably we are not going to commercialize it, but we are going to supply it to the Brazilian Ministry of Health and the WHO, as Ebola is a global health problem.

The aim of this proposal is to develop and to produce two products, in collaboration with NIH: 1) a horse hyperimmune serum anti-rabies/Ebola viruses for therapy of infected patients with Ebola and/or rabies virus; 2) an inactivated rabies and Ebola vaccine for human use against infection by rabies and Ebola viruses.

1. A horse hyperimmune serum anti-rabies/Ebola viruses for therapy of infected patients with Ebola and/or rabies virus

Butantan Institute (Butantan) produces horse hyperimmune sera against snake bites, scorpions, spiders and caterpillar envenomations as well as against rabies virus infection, diphtheria, botulism and tetanus. The production of horse hyperimmune sera started more than 100 years ago and the current technology is basically as described [1] comprising antigen preparation, horse immunization, blood collection, plasma purification, formulation, filling and packing, quality control tests and release of the final product to Brazilian Ministry of Health.

Butantan also produces several vaccines, among them, rabies vaccine in Vero cells for human use, that will be discussed later, but also rabies antigens in BHK21 cells for horse

immunization and production of horse anti-rabies hyperimmune serum (Product registered at ANVISA, numbers 1.2234.0010.002-6 and 1.2234.0010.003-9).

Taking this into account, Butantan aims to develop a horse anti-rabies/Ebola hyperimmune serum to be used as therapeutic intervention for Ebola infection treatment. This is especially important in the light of the epidemic episode in several countries in Africa, representing a worldwide threat [2]. The produced serum can be used to treat patients infected by Ebola virus in Africa, to control the spread of imported cases in Brazil and in other countries. The potential use of this serum as therapeutic tool against Ebola infection is supported by the reports describing the efficacious use of a combination of three different monoclonal antibodies in a unique formulation known as ZMapp in nonhuman primate trials [3] as well as in a few number of infected patients [4]. In contrast to ZMapp, this proposal will produce horse policlonal antibodies Fab´2, which can be obtained in higher yields, titers and the technology for its production is already established and this kind of therapy is being used for more than 100 years with clinical success in Brazil and all over the world.

For the production of this serum, the antigen can be prepared by NIH and delivered to Butantan for horse immunization. Alternatively, a virus seed can be delivered to Butantan for antigen preparation under NIH instructions. Briefly, horses will be submitted to a basic immunization protocol (primming) to create an immunological memory, followed by boost inoculations of the antigen. This prime/boost protocol is able to induce the production of horse high affinity IgG instead of IgM. The titer will be determined and the animals will be bled. Three bleedings will be performed for each horse. Each bleeding is expected to provide 3-4 L of plasma. The total plasma volume is fractionated by ammonium sulfate, digested with pepsin, precipitated by caprylic acid at 55°C, 30 kDa diafiltrated and finally purified by ion exchange, concentrated in a tangential filtration (30 kDa cut off) and sterilized by filtration. The resulted serum is formulated, filled and packed. Yields can vary from 400 vials to 20 vials/liter of hyperimmune plasma, depending on the initial plasma titer. The samples are assayed for sterility as well as for potency before batch release. It becomes clear that collaboration with NIH will be necessary in the following steps: a) antigen preparation or support by NIH for antigen production at Butantan; b) Potency test with Ebola virus to be performed by NIH for lot release; c) development of a new potency method that does not involve the use of Ebola virus (for instance, VLPs carrying the Ebola glycoprotein and a reporter) to be used as a potency assay for quality control of the final product at Butantan.

The antisera will be assayed in animals in pre-clinical studies followed by clinical trial which will describe the safety and efficacy endpoints.

The timeline for this project:

1) Antigen production: 1 month (with NIH collaboration)

2) Horse immunizations and plasma obtaining: 5 months (by Butantan)

3) Plasma fractionation, formulation, filling and packing: 1 month (by Butantan)

4) Quality control release: 2 months (by Butantan)

5) Pre-clinical assay: 4 months (with NIH collaboration)

6) Clinical Trial: 18 months

2. An inactivated rabies and Ebola vaccine for human use against infection by rabies and Ebola viruses

NIH has developed inactivated rabies/Ebola vaccines for human use and also live attenuated rabies/Ebola vaccines to protect wildlife, which may indirectly serve to interrupt transmission to humans [5-8]. On the other hand, Butantan also has a rabies vaccine produced in VERO cells (under ANVISA registration no 1.2234.0038.001-0). The Butantan vaccine is produced in serum-free medium with one of the highest yield [9]. Currently, the rabies vaccine production plant is being finished, starting operation in the beginning of the second semester of 2015.

Therefore, Butantan is also interested to produce the inactivated rabies/Ebola virus vaccine developed at NIH for human pre-exposure use. It is also clear that we will need support from NIH to define the production processes. This will be developed by Butantan's team, but the efficacy of the vaccine in animal models, especially for Ebola will need NIH support and collaboration. As pointed out, Butantan will need to establish locally a potency assay that does not involve the use of Ebola virus (as described above, item c, "development of a new potency method that does not involve the use of Ebola virus (for instance, VLPs carrying the Ebola glycoprotein and a reporter) to be used as a potency assay for quality control of the final product at Butantan". We envision that the production of inactivated rabies/Ebola virus will be very similar to that established at Butantan for the production of the human rabies vaccine.

Briefly, Vero cells will be grown in defined medium and will be inoculated with rabies/Ebola virus in bioreator. Following the virus production, it is expected to collect continuously the media (supernatant) during six days (the media will be replaced to keep the initial volume). The medium containing the virus will be concentrated by tangential filtration, purified by ion exchange cromatography, and the virus will be inactivated by beta-propiolactone treatment. This concentrated and inactivated virus bulk will be formulated, filled in vials. The vaccine can be delivered in a liquid form with an expected validity of 18 months. On the other hand, the vaccine can be lyophilized to increase the validity time (to be determined). Our current rabies production plant has the capacity to produce 8 – 9 million doses of rabies vaccine/year. The rabies/Ebola vaccine will be assayed in animals in pre-clinical studies followed by Phase I, II and III clinical trials.

The timeline for this project:

1) Production of master and seed banks: 1-2 months

2) Production of three vaccine lots: 1 month (by Butantan) (each lot with an expected yield of 90,000 doses of vaccine)

3) Quality control release: 2 months (by Butantan)

4) Pre-clinical assay: 4 – 8 months (by NIH collaboration)

5) Phase I: 12 months

6) Phase II: 12 months

7) Phase III: 12-18 months

References [12]

Butantan Institute is currently negotiating with NIH the Rabies-Ebola experimental vaccine license to start the development of horse polyclonal antibody and large-scale GMP vaccine for clinical trials. They hope to obtain the first lots of antibodies within 7 months and for the vaccine within 12 months in order to initiate phase I clinical trial in Brazil.

CANADA

Ebola Vaccine Trial Phase I[12]

A phase 1 trial of the VSV-EBOV vaccine is currently being conducted in Canada by the Canadian Immunization Research Network (CIRN); and jointly funded by CIHR and the Public Health Agency of Canada (PHAC). CIRN investigators are conducting a 3-arm trial in healthy adults aged 18-65, with each arm receiving a different dose. Total enrolment of 40 subjects was completed in December 2014, and all participants have received their injections and have completed the initial monitoring phase. Monitoring and sampling will continue until 6 months post-vaccination (May 2015). This trial has been announced publicly*.

International Consortium to conduct a phase III vaccine clinical trial against the Ebola virus in Guinea

On November 28th the Canadian Institutes of Health Research (CIHR), in partnership with the International Development Research Center (IDRC) and the Public Health Agency of Canada (PHAC), launched a call for Expressions of Interest for Canadian researchers wishing to participate in an International Consortium to conduct a phase III clinical trial of an Ebola vaccine in Guinea.

This trial will be led by researchers from Guinea as part of a team that includes collaborators from a number of different countries including Canada, Norway, the United States and Mali, amongst others. This group will work under the supervision of the Health Ministry of Guinea and in coordination with a number of other groups, including the WHO, Médecins sans Frontières (MSF), and international relief organizations working in Guinea as a part of the international response to Ebola.

Researchers from the team that submitted the successful Expression of Interest will participate in the trial on a number of fronts, including: chairing the Data and Safety Monitoring Board (DSMB); co-chairing and providing anthropological expertise on the Scientific Advisory Group (SAG); and mathematical modelling of disease transmission. Canada will also be providing support for the development of clinical research capacity in Guinea, through researchers at the University of Maryland and CVD-Mali. This trial is expected to be launched in late February or early March 2015.

Innovative Ebola Research

CIHR is developing a Request for Applications (RFA) for innovative research on various issues related to Ebola in late December. Research proposals across will be solicited from a number of priority research areas, namely: Ebola biology; Ebola treatment; transmission, spread, containment and prevention of Ebola; and health system impacts of the Ebola crisis. The focus is on 1-year projects, to support research with the potential to create new knowledge, and be rapidly implemented to effect changes in practice and preparedness.

[12] http://webapps.cihr-irsc.gc.ca/cfdd/db_search?p_language=E&p_competition=201409EVR

* http://news.gc.ca/web/article-en.do?nid=904689

FRANCE

French Ebola research program: AVIESAN's activities

In the current epidemic of Ebola hemorrhagic fever (EHF), 10,141 cases – 4,926 (49%) of them fatal - have been reported from the three most affected West African countries (as of 16th September) and the burgeoning rate of increase in incidence continues at an alarming pace. The diagnostic of the epidemic was performed in the French National Reference Centre for Viral Haemorrhagic Fever in the BSL- 4 laboratory in Lyon (*Baize S et al, N Engl J Med. 2014 Apr 16)*.

This alarming situation can be reversed by a major increase in highly qualified personnel for diagnosis, epidemiology, clinical trials and socio-anthropology, backed by greatly improved laboratory and hospital facilities, and research.

Apart from The Gambia, Ghana and Guinea-Bissau, all the countries that adjoin the main affected region are francophone and these in turn are contiguous with six more French ex-colonies. Nearly all these countries retain strong links with France, and a range of French institutions are actively involved in health-related research. These include the Pasteur Institute and its international network (3 centres in West Africa), the National Institute for Research for Development (IRD); the National Institute for Health and Medical Research (INSERM), the National Institute for Research on AIDS and Hepatitis (ANRS) and Fondation Mérieux. All of these are members of the National Alliance for Life Sciences and Health (AVIESAN). The French agency ESTHER, it's European Alliance, and the international medical association SOLTHIS are also involved.

In response to the current EHF outbreak, REACTing has held several scientific meetings to review existing collaboration with scientists in the affected West African countries and to identify research needs and interventions to halt the expansion of the disease in the affected areas. We have initiated an operational program of collaborative research (in accordance with recommendations by the World Health Organization (WHO) that involves the institutions listed above in partnership with local African scientists and National authorities, and in close contact Doctors Without Borders (MSF), Public Health workers.

This integrated and multidisciplinary program falls under four main topics:

1. Improvement of diagnostic tools

There is a need for diagnostic tools that are applicable for large-scale interventions. We propose:

- To develop a standardize qualitative and quantitative molecular protocol for filovirus infections—freeze-dried and ready-to-use—that will differentiate filoviruses from other haemorrhagic diseases that are endemic in the affected and surrounding regions
- To evaluate in West Africa, two rapid diagnostic tests for the detection of Ebola virus in blood or urine; the first one developed by the French Alternative Energies and Atomic Energy Commission (CEA) and the second one by bioMérieux

Other proposals will be discussed in a near future.

These projects would be complementary to a proposal of mobile BSL-4 lab, coordinated by INSERM in cooperation with Pasteur Institute and Fondation Mérieux. This has been submitted to the European Commission. The objective is to strengthen diagnostic capabilities and train local laboratory staff.

2. Therapeutic interventions

Several molecules that have been tested in animal models (monoclonal antibodies, siRNA-based drugs, and small antiviral molecules) appear promising. However, the efficacy and safety of such drugs in humans are unknown and existing supplies limited. For these reasons their use is not feasible in the short term. However, in a consultative group convened by the WHO (September 4-5th, 2014), experts identified several therapeutic interventions that should be given priority for evaluation. Among those, Favipiravir (T-705) was recently approved for treatment of novel or resistant influenza in Japan and has demonstrated effectiveness in mice model infected with Ebola virus. More than 10,000 doses are available.

2.1. Assessment of the efficacy of Favipiravir

This will be done by reducing mortality and decreasing Ebola plasma viral load in 60 adults at early stage of infection in a pilot non-randomized phase IIb sequential trial. The protocol includes interim analysis and futility stopping rules. The study will be launched in Guinea and is coordinated jointly by a Guinean and a French scientist. The study will include several French, African and European partners, in collaboration with MSF. Training of clinicians and epidemiologists will be a major component. An anthropological module will be included to assess the acceptability of Phase II trials of this kind i.e. during an epidemic for which (as in the present emergency) no specific treatments exist.

In parallel, we will assess the antiviral activity of Favipiravir in non-human primates at different doses and at different stages of disease: preventive use, post-exposure use, and use at early clinical stages of infection. This study will be conducted at the BSL-4 laboratory in Lyon, France, in collaboration with several European partners.

The European Commission has recently selected the overall study for a grant.

2.2. Evaluation of convalescent blood and plasma for EHF in affected West African Countries

The WHO has put transfusion of whole blood or plasma from convalescent patients as one of the most promising therapeutic strategies on the very short term. In response to the dramatic escalation of the epidemic, we joined a consortium led by the Tropical Medicine Institute in Antwerp to investigate how convalescent plasma can be produced and used in Guinea in order to treat Ebola patients

The objective of the proposal is to determine the efficacy and safety of CWB and CP therapy as treatment for patients with EHF. The trial will take place in three consecutive phases; i) initial phase to initiate harmonized standard supportive care, ii) evaluation of CWB and iii) evaluation of CP.

France will investigate how convalescent plasma can be produced and used in Guinea in order to treat Ebola patients, and will explore the feasibility to use plasma from blood donors in order to determine whether they could constitute a valuable source of immune plasma.

3. Follow-up of recovered patients

Many aspects of EHF survival are not understood nor the frequency of sequellae, clinical or psychologic and only very few data on the outcome of the survivors are available. One of the rare report concerns the Kikwit outbreak in DRC with a follow-up of patients for 6 weeks. In this report, an important rate of severe persistent asthenia, arthralgia, ocular and hearing disturbance was described among the survivors.

We will set up a prospective cohort of EHF survivors patients in the Republic of Guinea to evaluate in adults and children several outcomes; i) Clinical (sequelae, co-infections, quality of life), ii) Virological (kinetics of Ebola virus clearance in the different body fluids), iii) Immunological (kinetics of antibodies and cellular immunity), iv) Social (experience of illness and healing) and v) Public Health (to explore how survivors can contribute to raise awareness in the population and eventually participate as community-based caregivers)

4. Public response to epidemics

In addition to their direct impact on Public Health, epidemic crises have important social, economic and political consequences through disruption of activities that are shaped and amplified by key features of local society. For these reasons, crisis management must include the interaction of many heterogeneous players: public authorities, scientists, physicians and the lay population, as well as international organizations, NGOs and private companies.

We propose two independent and complementary studies to:

1. Document the use of digital technology to circulate EHF information by health and humanitarian authorities (governmental and non-governmental, local and international). This will include several African countries affected by the epidemic and three countries of the North: France, USA and Canada.

2. Analyse social constructs of trust among the key actors (health professionals) in accordance with the current plan to combat EHF in Senegal, and to support the ownership of recommendations, in particular in people under surveillance (contact cases). This project will be partly extended to Benin and Ivory Coast.

3. Other proposals include:

- two proposals that have been recently submitted to the National Research Agency
- development of Dendritic Cell-based prophylactic and therapeutic Ebola vaccines
- genetic diversity, modalities of cross-species transmission and risk assessment of outbreak emergence in Central Africa
- a study of the characteristics and care's trajectories of patients with suspected Ebola infection in France
- a study to exploit specimens collected from Ebola virus infected patients to gather knowledge on B an T cell immunology, biomarkers, virus evolution, virulence determinants and transmission on the virus. This study, funded by the EC, is led by Germany and includes BSL-4 lab in Lyon.

Discussions are eventually on-going on other priorities such as neutralizing tests, vaccine candidates, immunotherapy, and clinical trial in children.

The program outlined above is an exercise in collaboration between research organisations in an emergency situation, coordinated by AVIESAN. ANRS teams in France and Africa will be encouraged to participate, especially those involved in operational research and in the human and social sciences.

Collaboration with African partners and NGOs is crucial. A major component will involve training via the African Network of HIV Practitioners, and capacity-building in the affected countries and in peripheral Francophone countries.

GERMANY

The German Federal Government has responded to the Ebola outbreak with a catalogue of various measures. In terms of research the **Federal Ministry of Health (BMG)** supports

- A field study in West-Africa to investigate the **virus distribution in the regional fauna** by the Robert-Koch-Institute, Berlin
- A **clinical phase I trial with Ebola vaccine rVSV-Zebov** (together with DZIF and BMBF, see below)
- A study dedicated to the use of **hyperimmune plasma** undertaken by the Paul-Ehrlich-Institut (PEI), Langen, Germany

The **Federal Ministry of Education and Research** (BMBF)[13] supports

A) The development of a diagnostic platform by the Product Development Partnership "FIND (Foundation for new innovative Diagnostics)" together with Alere Technologies, Jena, Germany and

B) Funding to the German Center for Infection Research (DZIF) for an Ebola targeted research network "EBOKON" to strengthen Ebola research and close the knowledge gaps as quickly as possible in the fight against the epidemic.

The ten EBOKON projects will be conducted until end of 2015. These projects will be supported in addition to other ongoing DZIF projects working on Ebola. This broadly based collaboration project will be brought together and strategically aligned under the roof of the German Center for Infection Research (DZIF)[14].

1. Developing MVA vector vaccines to prevent Ebola virus infections

The aim of this project is the preclinical development and characterisation new vaccines against Ebola virus infections, based on recombinant vaccinia viruses MVA. There are currently two promising candidate vaccines against the Ebola virus available, which are yet to be tested in humans. Clinical trial preparations are underway and an implementation is expected at the beginning of 2015. These vaccines are either effective against two subtypes of the Ebola virus (adenovirus-based vaccine), or monovalently effective against the Zaire Ebola virus only (VSV-based vaccine).

[13] www.bmbf.de/en/
[14] www.dzif.de

2. Developing and validating pan-Ebola vaccination strategies

The antibody cocktail (ZMAPP) seems to cause significant improvement in some people with Ebola infections. However, the cocktail is globally no longer available and the production of a few new doses takes months. There is currently a lack of concepts for rapidly developing and producing passive immune therapies. This project compares different vaccination strategies and validates the most promising ones with further experiments in Marburg.

3. Analysing and inhibiting Ebola virus entry into host cells

There are currently no antiviral drugs available against Ebola viruses. One potential mechanism of anti-Ebola virus therapy could be to inhibit its entry into target cells. Ebola viruses contain glycoprotein GP, a substance which mediates their entry into host cells. In order to identify potentially highly effective antiviral drugs, this project will investigate the interaction between the virus and host cells and how it can be inhibited.

4. Developing fluorescing recombinant Ebola viruses (Guinea strain) to enable rapid testing of emerging mutations in the virus genome and their pathogenic implications; Testing vaccine effectiveness and antibody therapies under BSL-4 conditions

In the Ebola virus outbreak in West Africa, several mutations in the Ebola virus genome which occurred during human-to-human transmission have been discovered. The significance of these mutations for the biology of the virus and its pathogenic effects is currently totally unclear. This project aims to characterise emerging mutations.

5. Using chimeric mouse models to investigate Ebola virus immunity and pathogenesis

Immune responses to Ebola viruses are not well understood because insufficient numbers of patient samples have been available up to now. For example, it is not known how the T cell response of patients who survive Ebola infections differs to immune responses in cases where infection was fatal. Mouse models in which the virus can replicate will be used to help investigate these questions. This project is in collaboration with the Heinrich Pette Institute in Hamburg.

6. Systems vaccinology: Hereditary predictors of Ebola virus induced adaptive immunity

There is very little data available about immune responses to Ebola virus vaccines. A clinical phase I trial with an Ebola virus vaccine (VSV-EBOV) in Hamburg has already been planned, which will also allow for more insight into the immune responses. It is expected that investigations into the initial post-immunisation stage, in which the innate immune system triggers the acquired immune response, will deliver valuable information regarding vaccination success.

7. Conducting a phase I Ebola vaccination trial

The VSV-based Ebola vaccine is a promising candidate vaccine, being clinically tested at four locations coordinated by the WHO. A trial is due to be conducted at the UKE in Hamburg. Besides this, the Albert-Schweitzer Hospital in Gabon will also be conducting a phase I trial sponsored by the University of Tübingen.

8. Investigating the filovirus transmission chain in an industrialised West African country

Fruit bats are known to be the natural reservoir of Ebola virus. However, the exact route of transmission to humans is unknown, as is the question of whether other infected animals play a role in the spread of the epidemic. The project will investigate the entire possible transmission chain of Ebola viruses and other so-called filoviruses with existing patient samples in Ghana - a relatively well-industrialised West African country - without having to do elaborate field work.

9. Minimising the risk of further Ebola virus spread

9a: Investigating a possible secondary reservoir in animals in West Africa: In this project, animals in the outbreak areas will be tested for Ebola viruses as well as for Ebola antibodies, in order to identify possible secondary reservoirs and the consequent risks. The results could be used to implement appropriate measures against this.

9b: Developing adaptive, interactive software to assess absolute risk of Ebola imports in global air traffic network hubs: Individual cases of Ebola infections may be transported into further countries. Besides being dependent on air traffic movements, the risk of transporting the virus also depends on other factors (e.g. the number of cases in West Africa) which have so far not been sufficiently taken into consideration in the respective mathematical models. In this project, an existing model for risk assessment will be developed further.

9c: Developing, implementing and evaluating a follow-up tool for staff in Ebola treatment centres and returning travellers from Ebola epidemic regions: Health monitoring for helpers and other persons who return from missions in regions with Ebola is to be made simpler by means of mobile data entry, an optional follow-up network is to be developed.

10. Ebola surveillance with mobile real-time data transmission in Nigeria

In past Ebola outbreaks, monitoring people who had had contact with people suffering from Ebola infections was an essential tool for containing the epidemic. However, the current outbreak has taken on a scale where such measures can only be implemented by means of very modern technology, especially under West African conditions. A new system using centrally connected mobile telephones as a steering instrument is being developed in Germany, together with Nigerian partners and due to be piloted in Nigeria.

NORWAY

Research Council of Norway (RCN)

The Norwegian Ministry of Foreign Affairs and Norad earmarked funding for an Ebola Vaccine trial (phase 2/3) in Guinea. Funding for the project ***Efficacy and safety evaluation of Ebola vaccines in Guinea*** is channeled through the Research Council of Norway and its Programme for Global Health and Vaccination Research (GLOBVAC)[15]. The application was submitted 20 November 2014, and following a rapid scientific review and assessment by the GLOBVAC Programme Board funding was granted on 26 November 2014. The project application was updated and revised in December 2014 in parallel with project start up. The phase III study with vaccination will first start when all ethical and regulatory approvals in Guinea are obtained, at earliest in March 2015.

The Norwegian Institute of Public Health (NIPH) is chairing the consortium consisting of the Ministry of Health in Guinea, Doctors Without Borders, the World Health Organization (WHO) and the NIPH. In addition to Norwegian experts the Trial involves leading scientists from universities in Mali (Bamako), Switzerland (Bern), USA (Florida and Maryland) and the UK (LSHTM).

Coordinators/PIs: John Arne Røttingen (NIPH), Ana Maria Henao Restrepo (WHO), Rebecca Grais (MSF). WHO will be the study sponsor, and the PIs will be from West Africa.

The RCN granted NOK 20 million (approximately Euro 2.2 million) in funding, which is co-funded by significant contributions from Wellcome Trust and Canadian health authorities. MSF, WHO and the NIPH have also made significant in kind contributions.

Two vaccine candidates will be considered to be tested in the trial: cAd3-EBOV (cAd3) from GlaxoSmithKline (GSK) and the U.S. National Institute of Allergy and Infectious Diseases (NIAID), and rVSV_G-EBOV-GP (rVSV), from NewLink Genetics/Merck and the Public Health Agency of Canada. The choice of which of these to be prioritized first will be made based on criteria vetted by the WHO Scientific and Technical Advisory Committee for Ebola Experimental Interventions (STAC-EE).

Ring vaccination study

Primary objective

To assess vaccine efficacy against laboratory-confirmed Ebola virus disease (EVD) by performing a clinical trial comparing immediate versus delayed ring vaccination.

Secondary objectives

a) To assess vaccine efficacy against death from laboratory-confirmed EVD.

[15] http://www.forskningsradet.no/globvac

b) To assess vaccine efficacy against probable and suspected EVD.

c) To evaluate vaccine safety by assessing severe adverse events (SAEs) over 90 days.

d) To assess vaccine effectiveness in preventing laboratory-confirmed EVD at the level of the ring after 90 days of follow-up.

Frontline worker (FLW) study

Primary objective

To evaluate vaccine safety by assessing SAEs over 90 days in frontline workers

Secondary objectives

Samples and data will be collected at study timepoints and stored for future analyses of immunogenicity as and when a correlate of protection is known or to contribute to the scientific development of a correlate.

SOUTH AFRICA
South African Medical Research Council (SAMRC) Ebola Research Strategy

The South African Medical Research Council is a Science Council in South Africa that funds and conducts health related research. The SAMRC is supporting research into point of care testing and/or rapid diagnostics for Ebola. The SAMRC will fund the National Institute of Communicable Diseases (NICD) to develop rapid testing as well as the evaluation of rapid diagnostics developed by other institutions that have been co-funded by the SAMRC.

Since the outbreak of the current Ebola epidemic in West Africa the NICD has a mobile laboratory facility in Sierra Leone and has been assisting with diagnostic testing in Freetown. The capacity of the laboratory allows for up to 60 tests per day. According to the RSA Ministry of Health, there is a need to scale up testing to 200 tests per day. This is only achievable using rapid diagnostic techniques. The RSA MOH has requested the SAMRC also to fund the scale up and field implementation of rapid diagnostics.

EVD Diagnostics

Diagnosis of EVD generally requires demonstration of IgM antibody or/an IgG seroconversion or virus detection (virus isolation, detection of viral nucleic acid or antigen). Ebolavirus is poses a high risk for laboratory personnel, thus certain diagnostic assays, such as virus isolation can only be performed in BSL4. These factors compound the problem with early diagnosis required for patient containment and the tracing of case contacts. At present, the primary diagnostic platform being used for EVD is the PCR to detect viral RNA in blood samples. However viraemia may be often brief and/or present at a low level hence diagnosis by this methodology is not always definitive. Thus the development of wider ranging diagnostic capacity remains a priority. Immunoassay based tests such as enzyme linked immunosorbent assays (ELISA), or indirect immunofluorescence assay's (IFA) are an alternative's to the PCR, and have been used with success, but they require specialized equipment in addition to inactivated virus culture stocks, that have to be prepared in BSL4 containment, which are unavailable in the countries where the virus is endemic.

Diagnostic challenges

Efforts to contain the EVD epidemic in West Africa are currently hampered by the use of rather complex diagnostic tests requiring highly trained staff, laboratory biosafety and the use of sophisticated diagnostic equipment. The molecular assays utilized in mobile and other laboratories supporting the EVD outbreak response usually include the real-time reverse-transcriptase polymerase chain reaction (RT-PCR). The RT-PCR test, which involves a number of laborious and cumbersome procedures, provides accurate results only when performed by highly trained staff. Each test requires collection of a tube of blood, and takes on average 4 hours for completion, and is expensive (~$100). These requirements are difficult to meet in resource-constrained West African settings, thus severely limiting diagnostic capacity. Other important constrain is the time lost when transporting specimens from remote locations to limited number of laboratories. This situation also poses the risk of their deterioration during prolong transport, misplacement, and delay in diagnosis. Lost time means that infected people may remain in the community and unintentionally transmit the

virus to others. Moreover, in the absence of rapid laboratory support, people with other common infectious diseases, which have similar early symptoms, may be held in an Ebola holding centres as a precautionary measure, and consequently if they were not infected when entering the centre, they may unfortunately be at increased risk of acquiring infection within this facility.

Point-of-care tests (POCTs)

The development of point-of-care tests (POCTs) based on the detection of specific virus antigen and/or antibodies would vastly improve the rapid detection of EVD cases. Clinical decisions guided by results from rapid POCT could significantly improve timely implementation of containment measures and patient management, including treatment outcomes. Additional advantage of having POCTs in place could be rebuilding trust and confidence in West African health systems, which have been devastated by fear of contagion as well as by the demands of managing a deadly and dreaded disease.

POCTs developed for the purposed of diagnosing of infectious diseases, often provide a qualitative ‘yes’ or ’no’ answer in the form a visible colour change of line development. The most common POCT format available is that of the immunochromatographic lateral flow (ILF) device. In this format, the sample reacts with dried virus specific reagents that have been immobilized on a solid matrix, such as nitrocellulose membrane. A positive result is indicated by a colour change which can be read by the user within 10-15 minutes. The biomarkers used for these devices differ from proteins, nucleic acids, metabolites, and microbes to microbe antigens found in various clinical samples which require only minimal or no preparation such as blood, saliva, urine and other bodily excretions.

Although the development of rapid and simple to use POCT is technically achievable, their implementation and successful use in the field depends not only on technical design and availability of high quality biomarkers/immunereagents but also on their diagnostic performance characteristics (sensitivity and specificity).

Validation of diagnostic performance of newly developed assays is often hampered by unavailability of well characterized clinical materials. Successful operationalization of the NICD Ebola Mobile Laboratory in Sierra Leone makes it possible that clinical materials from EVD cases will be transported for further analysis and research purposes to the BSL4 facility at the NICD. Permit for shipping clinical specimens from suspected EVD cases to BSL4 at NICD which are tested on daily basis at the NICD Mobile Laboratory in Freetown-Lakka has been recently granted by Sierra Leone health authorities.

Project 1: Molecular epidemiology of Ebola virus disease in West Africa and the development of diagnostic capacity by NICD, Johannesburg

Project I: Investigate serological, virological, and epidemiological aspects of the current EVD outbreak in West Africa.

Project II: Development and validation of recombinant protein POCTs based and ELISAs for EVD rapid diagnosis.

Project 2: Differential diagnosis of 5 febrile illnesses (including EBOLA) on a multi-lateral flow point-of-care assay by Life Assay Diagnostics (Pty) Ltd, Cape Town.

This project aims to develop a POCT diagnostic platform that will accurately and rapidly (~10 to 15 minutes) differentiate between EBV and typhoid fever, falciparum malaria, dengue fever, and leptospira infection, so as to guide the immediate and appropriate patient management in an effective and expeditious manner. The diagnostic platform will be a 5-in-1 lateral flow cassette able to detect pathogens associated with the five illnesses, making it very user friendly and easy to use. Alternatively, a single EBV lateral flow assay can be produced should this be required.

The simple lateral flow assay can offer the following:

1. Detect EBV antigen from a finger prick (minimally invasive - 25µl whole blood only),
2. Yield a qualitative result in 10-15 minutes
3. Differentiate EBV from 4 other febrile illnesses commonly found in West Africa (typhoid fever, falciparum malaria, dengue fever, leptospira)
4. Be performed as a true point-of care (POC) assay at any place, anytime, anywhere
5. Requires minimal training and can be done by a lay person after 10 minutes train-ing
6. Can be used under African conditions, not requiring refrigeration, and having a 24 month shelf life when stored at up to 30˚C
7. Yield high reproducible results with acceptable sensitivity and specificity compared to current testing methods;
8. Be able to detect EBV infection as soon as symptoms start.

SPAIN
Ebola Related Activities in Spain - Date: 24/10/2014

Research activities in the field of Filoviruses as well as those related to the clinical and epidemiological aspects of these pathogens show that in the last few years a number of Spanish researchers are incorporating into their strategic agendas, the global threat represented by Ebola Virus as well as other pathogens that produce hemorrhagic fevers.

These activities can be categorized into the following groups.

1. Research related to diagnostic methods for Filoviruses

The *National Center of Microbiology/CNM (Instituto de Salud Carlos III)* has a long tradition in the development of PCR-based diagnostic methods for Ebola and other hemorrhagic viruses. The arboviruses group works in close collaboration with other Spanish and European Groups and participates in a European project and the QUANDHIP European Network for Biosafety.

2. Research activities related to the study of vectors and reservoirs

A number of groups in the *National Center for Tropical Medicine/CNTrop (Instituto de Salud Carlos III)* that also coordinates the thematic research network of tropical diseases: from genomics to control(funded by the *(Instituto de Salud Carlos III)*, *Valencia University*, and the *Instituto Universitario de Investigación en Enfermedades Tropicales* y *Salud Pública* of Tenerife have an active role in the study of the biology of Ebola and other viruses in some animal reservoirs, studying potential reservoirs and seroprevalence patterns in European and African animals.

The *University of Castilla la Mancha* – Health and Biotechnology group, is contributing to a European Project financed in FP7 with the acronym ANTIGONE with the goal to identify the key factors that contribute to the emergence of pathogens with human pandemic potential from pathogens with a zoonotic background, including Ebola. SaBio-IREC participates with primary research and horizontal actions, with emphasis on vector-borne diseases, Mycobacterium bovis and Escherichia coli.

3. Research activities related to the study of Ebola pseudotyped viral models:

- Platform of screening of Ebola Virus cell-entry inhibitors: *Instituto de Investigación Hospital Universitario 12 de Octubre*, Madrid.
- Rapid measurement and follow up of neutralizing-antibody (Nab) titer of plasma from Ebola Virus Disease convalescent patients: *Instituto de Investigación Hospital Universitario 12 de Octubre*, Madrid and *Instituto de Investigación Hospital Universitario La Paz-Hospital Carlos III*.
- Study of the interaction of Ebola Virus species with C-type Lectin DC-SIGN and related molecules in Dendritic, Langherhans and Endothelial Cells: *Instituto de Investigación Hospital Universitario 12 de Octubre*, Madrid.
- Design of specific Ebola Virus antivirals based in DC-SIGN blockage through glycan nanotechnology: *Instituto de Investigación Hospital Universitario 12 de Octubre*, Madrid; *Instituto de Investigaciones Químicas*, CSIC, Sevilla; *Universidad Complutense*, Madrid

and *University of Oxford*, UK. Our screening platform allows rapid evaluation of antiviral potency to improve design of candidate compounds.

4. **Research of novel instruments for the epidemiological control of case studies**

The *Spanish virtual center (CIBER): Network for Epidemiology and Public Health (funded by the Instituto de Salud Carlos III)* is currently developing in partnership with Telefonica (one of the main international telecommunications group) an IT-based project for telematic control and epidemiological survey of contacts with Ebola patients that can be implemented in the monitoring of real outbreaks.

The National Centre for Epidemiology /CEE (Instituto de Salud Carlso III) is the central Hub responsible for the epidemiological surveillance in Spain.

5. **Research of Clinical aspects of Ebola Virus infection:**

The recent experience of three cases of EV infection in the *Hospital Universitario La Paz – Carlos III* has given the clinical team in charge of the management of these patients an enormous amount of scientific evidence on the characteristics of the clinical course of the disease in a health-care system of a developed country, far away from the evidence accumulated in countries where the current outbreak is still active.

6. **Industrial capabilities:**

Spanish Industry has a leading position in plasma-derived therapies (Grifols) as well as relevant developments in clinical diagnostics reagents and systems (Biokit, Biotools, Master Diagnostica, Progenika Biopharma, Vircell, MECWINS), vaccines and immunotherapy (Laboratorios Leti, Laboratorios farmacéuticos Rovi, Bial-industrial Farmacéutica, Nanotherapix, Laboratorios Diater, Canvax Biotech, VLPBio).

THAILAND

Preventative measures and control of Ebola epidemic and Thailand's aid to West Africa

The Cabinet approved the Ministry of Public Health's proposal as followed:

1. Approved the proposed preventative measures and control of the Ebola virus.
2. Approved the use of Federal budget to send medical and public health experts to West Africa to lend assistance. The Ministry of Public Health will be implementing the program with technical support from related agencies.
3. Approved of monetary aid for necessary materials and tools, and humanitarian aid through public-private cooperation.

Thailand's action relating to Ebola

1. The Ministry of Public Health has been actively following the situation of the outbreak via the World Health Organisation and other countries to assess the threat.
2. There are 9 health control points across the country such as the ones at the international airport, the port and along the borders has been screening travellers who have visited countries where Ebola is present. A total of 1,689 people were screened between 8 June 2014 and 25 September 2014. In addition, a device measuring body temperature has been installed at Suvarnabhumi airport.
3. Thailand is on the lookout for patients who have the virus. At present, there is no case of Ebola virus in Thailand.
4. Thailand has provided 5,000 sets of protective gear to medical and public health personnel. Another 29,640 sets will be ordered using the Federal budget of around 11 million Baht (268,000 EUROS) in October 2014.
5. The government is preparing Thailand's treatment potential in terms of facility and personnel training, laboratory testing, monitoring, examining and quarantine.
6. The government is working with universities to prepare laboratories to meet international standards.
7. Thailand has practiced on emergency preparedness response to the spread of Ebola at all levels.
8. Thailand has initiated of an integrated plan in response to the spread of the Ebola virus.
9. There is a need to communicate threats of the virus to personnel, citizens and travellers.
10. The Ministry of Foreign Affairs has issued a warning to Thai citizens to avoid travelling to countries affected by the virus, and has registered Thais living in such countries. In addition, the Ministry has increased immigration screening measures for persons travelling from such countries.

11. The Ministry of Natural Resources and Environment and the Ministry of Agriculture and Cooperatives are monitoring animals and wild animals for signs of the virus.
12. The government coordinates international cooperation with entities such as the WHO and the United States of America.

The Ministry of Public Health and associated agencies have prepared specific guidelines for preventing and controlling the spread of Ebola virus in all sectors under 3 possible scenarios as follows:

- No patient infected with the Ebola virus in Thailand, and no cases found of persons infected with the virus travelling into the country from abroad
- A patient infected with the virus has been identified, but the virus has not yet spread within the country
- The case of an outbreak of the virus in the country

Aid

The Thai government should play an international role in assisting countries suffering from the Ebola outbreak to quickly confine the spread of the disease at the origin, with the goal to end the outbreak that threatens all nations including Thailand ASAP.

Thus, increased aid measures have been proposed as follows:

1. Monetary aid as estimated by the United Nations through funding from the Federal budget, and will collect addition funds from organisations such as the government, the Thai Red Cross and the public sector.
2. Provide tools and materials that are produced in Thailand such as protective gear, disinfectant, scientific materials for laboratory examinations.
3. Provide policy support such as policy on the outbreak of the virus, and support policies will be lifted up to the higher level of the prohibition on travelling and international trade.
4. Support through air transport in delivering goods or personnel.
5. Medical and public health personnel support among others will be sent to countries near the affected areas to organise trainings and coordinate preparedness for personnel in such countries, or to participate in the UN's crisis centres. Alternatively, 3 sets of medical personnel will be supported to the affected countries such as Guinea, Liberia and Sierra Leon for a period of 1 month each.

UK
Department for International Development (DFID)

Vaccines

DFID is supporting a Phase 1 clinical trial of a GSK vaccine candidate in partnership with the Wellcome Trust and the Medical Research Council (MRC). The trial is led by the University of Oxford. A candidate Ebola vaccine is being tested as part of a series of safety trials of potential vaccines. This candidate vaccine is against the Zaire species of Ebola, and uses a single Ebola virus protein to generate an immune response. Pre-clinical research has indicated that it provides promising protection in non-human primates exposed to Ebola without significant adverse effects.

Research for Health in Humanitarian Crises (R2HC) Call for Ebola Research (DFID and Wellcome Trust)

DFID are also supporting projects through a joint initiative with the Wellcome Trust through Research for Health in Humanitarian Crises (R2HC). The six projects cover diagnostics, modelling, anthropology, behaviour change and surveillance and are managed by Enhancing Learning & Research for Humanitarian Assistance (ELRHA).

1. EbolaCheck – Portable Device which tests bodily fluids for Ebola

University of Westminster – Dr. Sterghios Moschos

This project looks at the development of a cost-effective, portable, battery-powered device which can provide reliable, rapid and safe diagnostic tests suitable for use in the field. EbolaCheck aims to test bodily fluids for Ebola in a single process, providing results within 40 minutes – over eight times quicker than some existing laboratory techniques.

2. Predicting the geographic spread of Ebola virus disease in West Africa

University of Oxford – Professor Simon Hay & Dr. Nick Golding

Using data on human mobility, population density and transport infrastructure in West African countries, this piece of research will make predictions about disease spread. This will enable resources to be deployed more effectively to contain the epidemic. The information will be mapped out and contain summaries of health centres most likely to see new cases. This will be continuously updated as data becomes available and shared through an online tool.

3. Behaviour change to help infection prevention and control

International Rescue Committee – Dr. Lara Ho

This research, being carried out in Sierra Leone, analyses the levels of knowledge and risks perceptions amongst health workers. The aim to help overcome barriers that staff may face in adhering to standard precautions. This will ensure that safety procedures and training for health workers is effective as possible to reduce the risk of infection while working on the front line.

4. Modelling the Ebola epidemic in West Africa

London School of Hygiene & Tropical Medicine – Professor John Edmunds

This piece of research uses statistical modelling to analyse data collected by MSF in West Africa to look at how many cases and deaths from Ebola might be expected over time. The study will look at what health care facilities will be needed to cope with different scenarios.

5. Ebola Response Anthropology Platform

London School of Hygiene & Tropical Medicine – Dr. Melissa Parker

An Ebola Response Anthropology Platform will look at developing locally-appropriate interventions. The project aims to provide rapid, practical advice on how to engage more effectively with affected populations.

6. Rapid, point-of-care diagnostic test for the Ebola virus

Pasteur Institute in Dakar, Senegal – Dr. Amadou A. Sall

A rapid, point-of-care diagnostic test for the Ebola virus will be trialled in the coming weeks at the Ebola treatment centre in Conakry, Guinea. The trial will be deployed using a 'mobile suitcase laboratory' which is designed for low-resource settings. The portable laboratory includes a solar panel, a power pack and a results reader which is the size of a small laptop.

Wellcome Trust

Below is a summary of the trials and programmes the Wellcome Trust has funded under two different rapid response mechanisms (Ebola Trials and R2HC).

Projects funded under Ebola Trials call

This call for research proposals would evaluate experimental therapies and vaccines for Ebola, focusing on clinical studies that could begin during the current epidemic. The Trust is encouraging rapid applications for funding, which it will evaluate and peer-review urgently so that appropriate projects can start without delay. To date, we have committed £9.14M - the call is still open and receiving enquiries.

Vaccines

1) **Adrian Hill** (University of Oxford): £2.82M (co-funded between the Wellcome Trust, Department for International Development and Medical Research Council)

Accelerated Clinical Evaluation of a Monovalent Vectored Ebola vaccine

This is a phase 1 trial to assess the safety and immune response of different doses of a GSK manufactured adenovirus vectored Ebola vaccine, for the Zaire strain of Ebola virus and shows significant promise in pre-clinical studies conducted at the NIH. The vaccine will be assessed in 2 sites in healthy adults, starting in Oxford, UK, (Sept 2014) and followed by trials in Mali (Oct 2014) to determine any differences between European and African populations. 10,000 doses of this vaccine are being manufactured at risk in order to vaccinate more widely to health care workers if shown to be safe and elicit appropriate immune response.

2) **Marie-Paule Kieny** (World Health Organisation + international partners): £3.12M.

Coordinated Clinical Trials of VSV-Ebola Virus Vaccine

This is a Phase I trial to assess the safety and immune response of a vesicular stomatitis vectored vaccine, for the Zaire strain of Ebola donated to the WHO by the Canadian government. Different doses of the vaccine will be assessed in three sites, starting in Hamburg, Germany, followed by a larger dose finding trial in Kenya. A final trial will be completed in Switzerland focussing on health care workers who expect to be deployed to West Africa. Discussions with Industrial partners with manufacturing expertise for large scale production of the vaccine are ongoing.

Therapeutics / Interventions

1) **Peter Horby** (University of Oxford + international partners): £3.2M.

Emergency Evaluation of Treatments for Ebola Virus Disease

Establishment of a clinical trials platform in two or more Ebola Virus Disease (EVD) treatment centres in West Africa to rapidly assess the efficacy and safety of un-registered therapeutic products to provide data for potential regulatory approval. The first stage will be to determine the most appropriate sites for the trial in an observational stage (Oct 2014). The medium term objective is to provide a platform for the evaluation of potential therapeutics- currently the trial will examine Brincidofovir.

Timeline of research activities Action	Date
Ebola Trials funding call announced for research proposals that would evaluate experimental therapies and vaccines for Ebola, focusing on clinical studies that could begin during the current epidemic	**21 Aug 2014**
First UK healthy volunteer receives monovalent vectored Ebola vaccine in Oxford trial	**17 Sept 2014**
First healthy volunteer receives VSV-Ebola Virus vaccine	**22 Oct 2014**
First health workers in Mali receive monovalent vectored Ebola vaccine	**09 Nov 2014**
Evaluation of Brincidofovir at sites to be announced. Trials to begin from December onwards.	**Nov 2014**
First trial data for monovalent vectored Ebola vaccine (GSK) released by NIH	**26 Nov 2014**
170 Ebola Trials enquiries received	**04 Dec 2014**

Projects funded under the Research for Health in Humanitarian Crises programme (R2HC)

This call focusses on rapid-response funding for humanitarian research into combating the Ebola outbreak in West Africa. This is jointly funded by the Wellcome Trust and the UK Department for International Development (DFID), administered by Enhancing Learning and Research to Humanitarian Assistance (ELRHA). DFID and the Wellcome Trust have committed £1.85M amount to date. This covers research in areas such as epidemiology, clinical management, ethics, diagnosis, disease control and prevention, health systems and surveillance.

Surveillance and modelling

Two projects cover modelling the outbreak to help resource allocation and planning, as well as reduction in transmission and improving contact tracing and tracking survivors.

1. **Simon Hay** (University of Oxford, UK): £95K

Predicting the geographical spread of Ebola virus disease in West Africa

Providing continuously updated, high-resolution maps of Ebola virus disease importation risk in West Africa to guide allocation of resources and surveillance for disease control.

2. **John Edmunds** (London School of Hygiene and Tropical Medicine, UK): £258K

Modelling Ebola in West Africa

We will analyse detailed line-lists collected by MSF in West Africa to assess the spread of Ebola and the potential impact of alternative interventions. We will estimate key epidemiological quantities, such as the reproduction number and project the course of the outbreak under different scenarios.

Prevention

These applications address barriers to treatment seeking behaviour and behaviour change to support infection prevention and control for Ebola virus (both in Sierra Leone).

1. **Lara Ho** (International Rescue committee, UK): £181K

Participatory behavioural change to reinforce infection prevention and control for Ebola virus disease in Sierra Leone

This project aims to identify effective behavioural change and logistical models to enable health workers to practice standard precautions in health facilities in responding to the Ebola virus. The research, conducted in Sierra Leone, will produce relevant outcomes for this and future outbreaks.

Diagnostics

1. **Sterghios Moschos** (University of Westminster, Public Health England and Ghana (KNUST) team): £620K

Ebolacheck

Can a device suitable for Africa detect Ebola in saliva in <40min? - The project will validate known reagents on a cheap, robust, portable, battery-powered device for detecting RNA in biofluids. Public Health England & the projects Ghana team will confirm function to make the technology available for field use.

2. **Amadou Sall** (Institut Pasteur of Dakar, Senegal): £500K

Point of care diagnostic testing for Ebola virus disease in Ebola treatment centers in Guinea, for suspect cases screening, patient management and support for clinical trials

The project aims to develop a point of care diagnostics tests for Ebola that will be available in the Ebola treatment centers in Guinea for suspect cases screening, patient management and support for clinical trials.

Anthropology Platform

1. **Melissa Leach** (University of Sussex): £200K

Establishment of an anthropology platform to address social issues such as mistrust of the heath service and authorities and behaviours that have been instrumental in transmission, such as funeral practises.

Action

Ebola call announced through the £6.5 million Research for Health in Humanitarian Crises (R2HC) initiative. – 21/8/2014

Deadline for preliminary applications (n=218) to the R2HC initiative – 8/9/2014

R2HC funding decisions made – 5/11/2014.

UNITED STATES OF AMERICA

The Administration is taking a whole-of-government approach under a comprehensive strategy to respond to the threat of Ebola, in the form of an S&T task force being led by the Office of Science and Technology Policy (OSTP) in the Office of the President.

OSTP had created two roadmaps, prior to the Ebola outbreak, which have provided some strategic guidance on key science challenges; those include the National Bio-surveillance Science and Technology Roadmap and the Biological Response and Recovery Science and Technology Roadmap (you can find them here). Also, to help frame the key scientific research agency, HHS sponsored a rapidly convened Institute of Medicine (IOM) workshop on needs for the Ebola challenge, with a focused interest on informing decisions through government and foundational science investment (summary of this workshop is available here). Our modeling team is also scoping priority research questions.

Across the US Government, there are several areas of focus for which all agencies are collaborating, including:

- **Personal Protective Equipment (PPE)**

Scientific questions include the use and application of PPE; pipeline and supply of PPE in both domestic and international contexts; and enabling proper PPE selection based on specified applications). Additional efforts already underway are supporting test and evaluation of innovative ideas in support the USAID grand challenge review on PPE.

- **Data connectivity**

The objective is to support response and satellite enabled in-country access to data networks, which can be expanded to create an enduring capacity for network access. (US Agency for International Development)

- **Data access and sharing of scientific findings**

Agency representatives indicated document markings are hindering data accessibility and sharing needed to support the Ebola response in West Africa (Department of Defense (DoD) and Department of State).

- **Diagnostics**

DoD, the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC) are handling the coordination of diagnostics activities. Scientific goals include application and access to common validation panels, consistent test protocols and sharing of validation protocols and procedures, and interagency efforts to prioritize evaluation of diagnostic performance in BSL3 and BSL4 environments. Our partners at CDC and DoD have developed and are continuing to refine Ebola diagnostic tests for use in various settings. The FDA has approved the use of four of these tests under Emergency Use Authorization and they are deployed both in US and West African laboratories.

The Office of the Assistant Secretary for Preparedness and Response (ASPR) leads the Science Preparedness initiative, an interagency coordinated effort to identify and implement priority research in the immediate aftermath of disasters or other public health related events. An Ebola virus research working group has been created under the initiative to explore how

investigators can address scientific questions associated with Ebola virus, including viral persistence studies on contaminated surfaces (e.g., PPE, steel, plastics, air handling filters, etc.) and aerosolisation studies characterizing liquid droplet and droplet nuclei deposition and potential for transmission. These scientific questions have important implications for public health safety, and through coordination of the OSTP Task Force the Department of Homeland Security has taken on some of these experiments in their BSL-4 facility. Comparative sequence analysis of circulating West African strain(s) of Ebola virus, non-West African strains, and non-contemporary strains can provide additional evidence-based information on transmission and pathogenesis characteristics of Ebola virus to support medical countermeasure development. The outcome of those experiments will be shared with us this week.

The U.S. Department of Health and Human Services also specifically has the lead for monitoring the outbreak and developing new and improved Ebola countermeasures. Underpinning these efforts are investigations of the basic biology and genetics of the Ebola virus supported by the National Institutes of Health (NIH). The National Institute of Allergy and Infectious Diseases (NIAID), the lead institute of the NIH for research on Ebola virus, conducts and supports basic research to understand how Ebola virus causes illness in animals and in humans as well as applied research to develop diagnostics, vaccines, and therapeutics. ASPR, through the Biomedical Advanced Research and Development Authority, is directly supporting the development and manufacturing of candidate Ebola therapeutics and vaccines, and is partnered with the NIAID and DoD in their longstanding efforts to develop these products. ASPR is also involved in the interagency and international discussion of the planning, design and execution of clinical trials for these products.

We are supporting the development of five Ebola vaccine candidates in various stages of development. Two vaccine candidates—cAd3 and rVSV—have been in Phase 1 human clinical trials; three others are still a few months away from the start of trials.

We achieved a major milestone on November 26th when the initial National Institutes of Health's (NIH) Phase 1 clinical trial for the cAd3 Ebola vaccine candidate, which was developed by the National Institute of Allergy and Infectious Diseases (NIAID) and GlaxoSmithKline, was completed successfully, with results published in the New England Journal of Medicine. The results indicate that the vaccine candidate is safe and induces an immune response. Additional clinical trials of the vaccine are underway or imminent in Atlanta, Baltimore, the United Kingdom, Switzerland, and Mali, among other sites.

Phase 1 clinical trials of a second vaccine, rVSV, are underway at the Walter Reed Army Institute of Research and at NIH, with results expected in December. Additional Phase 1 studies are underway or planned to begin in the near future at clinical research centers in Switzerland, Germany, Kenya, and Gabon in a WHO-coordinated effort, and in Canada. Merck and NewLink Genetics Corporation are collaborating to research, develop, manufacture, and distribute this investigational rVSV vaccine candidate.

The National Insitutes of Health collaborating with Liberian health authorities initiated a Phase 2 clincial studies Liberia in early February 2015 using a randomized controlled trial protocol to evaluate the safety and efficacy of two Ebola vaccine canddiates aginst a placebo control. In Sierra Leone, the Centers for Diease Control and Prevcention with the Sierra Leone health authorities and the BiomedioclAdvanced Research and Development Authority will start a

Phase 2 clinical trial in March 2015 evaluating one of these two Ebola vaccine candidates using an adaptive clinical trial protocol randomized against time.

NIH, DOD, and HHS' Biomedical Advanced Research and Development Authority (BARDA) are supporting production of tens of thousands of doses of these vaccines on a pilot scale for planned trials. BARDA with FDA assistance is supporting the rapid scale-up and optimization of vaccine manufacturing for these vaccine candidates to ensure that the capacity exists to produce millions of vaccine doses in a timely way if mass vaccination campaigns are able to occur in 2015 in Africa.

BARDA is currently funding three Ebola vaccine candidates:

- Profectus has a rVSV vaccine that is being developed by BARDA and DOD. BARDA will support manufacturing activities and DOD will support evaluation of the vaccine in Phase 1 trials in late spring 2015.
- Newlink/Merck is developing the rVSV vaccine developed by PHAC. BARDA is supporting manufacturing activities with the potential to evaluate alternative formulations of the vaccine, such as lyophilized formulation.
- GSK is commercializing the ChAd3 vaccine that was developed by NIH/VRC. BARDA is supporting process improvements and scale-up activities. BARDA also anticipates using the Fill/Finish and Manufacturing Network to assist with the filling of vaccine.

BARDA is currently evaluating proposals for additional Ebola vaccine candidates and will make decisions for potential funding based on availability of funds.

In addition to these vaccine candidates, there are three other candidates supported during early stage development by NIH and DOD that are a few months away from the start of Phase 1 clinical trials. Additionally, the U.S. Government is supporting the development of several investigational candidate therapeutics to treat patients infected with the disease. Some have already been employed in patients in the United States and Africa.

ZMapp: Under contract with DOD's Defense Threat Reduction Agency (DTRA) and BARDA, ZMapp's antibodies are produced in specially grown tobacco plants and have only been produced in limited quantities. BARDA is sponsoring the manufacturing of ZMapp for Phase 1-2 clinical studies. ZMapp has shown evidence of antiviral activity in animal models of infection. Clinical studies are expected to start in early 2015 at NIAID. Other clinical studies are slated to begin in affected African countries in early 2015. This therapeutic candidate has been used under an emergency investigational new drug (eIND) application in Ebola-infected patients in the United States, Africa, and elsewhere. Mapp Biopharmaceutical produces ZMapp.

BARDA, NIAID, and DoD (DTRA) have collaborated to support the data necessary for submission of the investigational new drug (IND). DTRA has evaluated ZMapp in NHP studies, looking at fewer number of doses and lower concentrations of antibodies/dose for efficacy. The data is currently being reviewed. NIAID has supported toxicology and other studies necessary to support the IND. BARDA continues to manufacture ZMapp in tobacco plants and is utilizing one of our core-services, the Fill/Finish and Manufacturing Network to assist in the filling of product at Baxter/Nano. The IND was approved by the FDA (February 2015) to support use of the product under the master protocol. Product has been filled and has been sent to Liberia for inclusion in the Phase 2 master protocol.

BARDA has also initiated efforts with two additional tobacco plant manufactures, Medicago and Fraunhofer, to evaluate production of the antibodies that comprise ZMapp utilizing their expression systems and tobacco plants.

BARDA has partnered with two large pharmaceutical companies to evaluate the expression of the antibodies that comprise ZMapp expressed in CHO cells.

- Genentech has humanized the three monoclonal antibodies that comprise ZMapp and cloned them into a proprietary CHO cell line. BARDA anticipates utilizing the Centers for Innovation and Advanced Development and Manufacturing (CIADMs) to evaluate expression in the CHO cells and to perform non-clinical studies to evaluate efficacy.
- Regeneron has cloned the identical antibody constructs that are expressed in tobacco plants into their proprietary CHO cell line.
- Regeneron has also used their proprietary human mouse model to generate novel antibodies.

BARDA is collaborating with USAMRIID to evaluate the Regeneron antibodies, both the "ZMapp-Like" and novel antibodies, in NHP challenge studies.

BARDA will utilize one of our core-services, the Non-Clinical Development Network, to evaluate additional novel antibodies generated by Regeneron.

- **TKM-Ebola**

TKM-Ebola has undergone testing in nonhuman primates and showed a significant benefit in terms of survival. This therapeutic candidate has been used under an eIND in some Ebola-infected patients in the United States. Plans for studying this drug in clinical trials are under discussion. TKM-Ebola is produced by the Canadian company Tekmira Inc. under a contract from DTRA.

- **BCX4430**

BCX4430 is a small molecule drug with recent NIH support that, in preliminary investigations, has been reported to have some antiviral activity against a range of viruses, including Ebola. NIH and the U.S. Army Medical Research Institute of Infectious Diseases are collaborating to evaluate activity in nonhuman primate models of Ebola virus disease as well as human clinical safety trials. Potential for clinical trials has been under discussion depending on assessment of animal study results.

- **NIAID**

NIAID is supporting Phase 1 single ascending dose and multi-ascending dose studies in the UK.

- **BARDA**

BARDA anticipates support for manufacturing activities in the near future.

- **Brincidofovir (CMX001)**

Brincidofovir, originally supported by BARDA as a potential smallpox drug, was reported in one study to show possible inhibition of Ebola virus replication in infected cells. This therapeutic candidate has been used under an eIND in some Ebola-infected patients in the United States. Potential for clinical trials has been under discussion depending on assessment of animal study results. The drug is under development by Chimerix. This candidate is no longer being evaluated for efficacy against Ebola.

- **Favipiravir (T-705)**

Favipiravir has been in clinical trials for treatment of influenza but also been reported to show some activity against other viruses, including in Ebola-infected cells. This therapeutic candidate was developed by Toyama and is licensed to Fujifilm and Medivector with support from DTRA. Potential for clinical trials has been under discussion, and it has reportedly been used in some Ebola-infected patients in Europe.

Contact persons:

Maria Klimathianaki: maria.klimathianaki@ec.europa.eu

Irene Plank: irene.plank@ec.europa.eu

Birgit Van Tongelen: Birgit.van-tongelen@ec.europa.eu