

**HUMANITARIAN ALTERNATIVES****Ebola research: an encounter between science and humanitarian action**

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**The authors of this text have been involved in caring for patients and conducting clinical research in Ebola Treatment Centres (ETCs) in Liberia, Guinea and Sierra Leone at different periods between October 2014 and July 2015. Focusing on therapeutic research during infectious disease outbreaks, they share here their experiences and reflections on the encounter between science and humanitarian action that took place in the ETCs of West Africa.**

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**M**edical science and humanitarian medicine share the same objectives: improving the health of populations and individuals. However, the two disciplines usually operate independently, and the medium- and long-term goals of the researchers differ most of the time from the short-term aims of the humanitarians (although humanitarian missions can also be long-term). When collaborating, their actions must satisfy both the ethics of healthcare and medical research, which are not necessarily synonymous.

The Declaration of Helsinki, which sets the principles of medical research, affirms that the patient's health prevails over any other consideration. The treating physician has the duty to "promote and safeguard the health, wellbeing and rights of patients": his or her actions aim at immediate benefits. The medical researcher has a duty to "protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects"<sup>1</sup> while pursuing a research objective that may not necessarily imply an immediate benefit for the patient. The West African Ebola epidemic, which began in late 2013 and continues well into 2015, has raised both moral and technical debates concerning the ability to deliver medical care, public health and research activities simultaneously during a humanitarian crisis<sup>2</sup>.

**The meeting of two urgencies**

The greatest priority during the West African Ebola outbreak has been, understandably, humanitarian, involving the need to provide urgent medical care and social support for affected populations, and the need to bring the epidemic under control. In March 2014, when the non-governmental organisation (NGO) Médecins sans Frontières (MSF) faced an unusual outbreak of an illness consistent with viral hemorrhagic fever in the Forest region of Guinea, samples were sent quickly to the Jean-Mérieux-Inserm BSL4 laboratory in Lyon and the Bernhard Nocht

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<sup>1</sup> World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects adopted in June 1964, amended for the last time in October 2013.

<http://www.wma.net/en/30publications/10policies/b3/index.html>

<sup>2</sup> Note of the Inserm ethics committee in collaboration with the consultative committee of deontology and ethics of IRD, « Du VIH à Ebola, réflexions éthiques sur la recherche en santé dans les pays du "sud", juin 2015. <http://www.inserm.fr/qu-est-ce-que-l-inserm/1-ethique-a-l-inserm/saisines-et-notes-du-comite-d-ethique>

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Institute in Hamburg. The laboratories confirmed the presence of a well-known filovirus, but one never before associated with a confirmed outbreak in humans in this region: the Ebola virus<sup>3</sup>. Subsequently, an outbreak of Ebola Virus Disease (EVD) was notified by Guinea to the World Health Organisation (WHO) on March 23rd 2014.

Building on its experience in Central Africa, MSF opened the first ETCs to support the health authorities, which faced overwhelming challenges in the face of this new and significant outbreak, which by now had been affecting rural populations for several months. But poor healthcare infrastructure, an inadequate number of national healthcare workers, a distrust of authorities and NGOs, and significant population mobility were as many barriers against efforts to control the outbreak. Secondary EVD foci were declared soon after in Sierra Leone and Liberia and, for the first time in the history of Ebola, the disease reached major urban areas and capital cities. At this time, the international community still had a wait-and-see approach, expecting the end of the epidemic in just a few months, based on experience from previous epidemics in Central and Eastern Africa. By the end of June, the health authorities of the three affected countries and the few international and local NGOs active in the field became increasingly overwhelmed by the number of new cases, compounded by significant losses of local health care workers to EVD. On June 23rd 2014, MSF announced that the epidemic was “out of control” and called for an exceptional mobilization of the governments in the West African region, and increased assistance from international aid organisations<sup>4</sup>. The NGO made a fervent request for more qualified medical personnel and for contact tracing and population sensitisation to be intensified. Only on August 8th 2014, after the EVD outbreak had reached Nigeria, did WHO declare a “Public Health Emergency of International Concern”<sup>5</sup> triggering greater global awareness and greater external intervention. At this point in time, international humanitarian aid support increased, and additional NGOs commenced operational control of ETCs, including GOAL Global in Sierra Leone and the French Red Cross in Guinea.

Alongside the humanitarian emergency there was a “scientific emergency” however, triggered by the conjunction of two events. The first was the awareness of the availability of experimental treatments for EVD. This came to the forefront when two EVD-infected American healthcare workers received one of these experimental treatments, ZMapp, following medical evacuation from Liberia at the end of July 2014. Until then, the drug had only been administered to non-human primates. The two American health-care workers survived. By contrast, one of their Liberian colleagues died in Lagos, having received antipyretic and rehydration treatment alone and no experimental drugs. Subsequently, other international health care workers infected with EVD were also repatriated to specialist centres in Europe and North America to receive intensive care and, in most cases, experimental drugs. The extent to which these investigational agents may have contributed to patient outcomes cannot be determined outside of a clinical trial. However, the use of experimental treatments for western healthcare workers provoked an ethical argument regarding equitable access to treatment, particularly in the affected countries<sup>6</sup>. In response to the use of experimental drugs for western healthcare workers, Liberia’s assistant health minister stated that it made their job very difficult, as patients and their relatives demanded the same

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<sup>3</sup> Baize et al., Emergence of Zaire Ebola Virus Disease in Guinea, *New England Journal of Medicine*, 371:1418-1425, October 9, 2014. [http://www.nejm.org/doi/full/10.1056/nejmoa1404505?query=featured\\_home&#t=articleTop](http://www.nejm.org/doi/full/10.1056/nejmoa1404505?query=featured_home&#t=articleTop)

<sup>4</sup> Médecins sans Frontières, Ebola en Afrique de l’Ouest : l’épidémie s’étend et requiert une mobilisation exceptionnelle au niveau régional, 23 juin 2014. <http://www.msf.fr/presse/communiqués/ebola-en-afrique-ouest-epidemie-s-etend-et-requiert-mobilisation-exceptionnelle-a>

<sup>5</sup> WHO statement on the 1st meeting of the IHR Emergency Committee on the 2014 Ebola outbreak in West Africa 8 August 2014. <http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/>

<sup>6</sup> Laura Seay, “Ebola, research ethics, and the ZMapp serum”, *The Washington Post*, August 6, 2014.

<http://www.washingtonpost.com/blogs/monkey-cage/wp/2014/08/06/ebola-research-ethics-and-the-zmapp-serum/>

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potential treatments for EVD: “You said there was no cure for Ebola, but the Americans are curing it”<sup>7</sup>.

The second trigger for this “scientific emergency” stemmed from the magnitude and duration of the EVD outbreak in West Africa, which allowed, for the first time, to plan robust clinical research protocols to evaluate the efficacy of experimental treatments for EVD.

On August 11th 2014, the WHO convened a panel of international experts to consider and assess the ethical implications of using unproven and unlicensed therapies. The experts declared that “given the particular circumstances of this outbreak, it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention. Ethical criteria must guide the provision of such interventions. These include transparency about all aspects of care, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community”<sup>8</sup>. There was unanimous agreement amongst the experts that “there is a moral duty to also evaluate these interventions, for treatment or prevention, in the best possible clinical trials under the circumstances in order to definitively prove their safety and efficacy or provide evidence to stop their utilisation”.

From that moment, the scientific urgency combined with the humanitarian emergency in a race against the epidemic. Whilst the different phases of clinical research<sup>9</sup> usually take many years, it was estimated that the Ebola epidemic would last one to two years. Action had to be taken rapidly. Research stakeholders quickly met under the coordination of the WHO. Research institutions, NGOs, health industries, important research sponsors (e.g. European Commission, Wellcome Trust, Bill & Melinda Gates Foundation) and national regulatory agencies for medicines, as well as the African Vaccine Regulatory Forum – AVAREF, began unprecedented collaborations to expedite clinical trials. In general, the protocols were approved quickly by the ethics committees. But despite the speed with which the different stakeholders reacted and coordinated, the first therapeutic trials only started recruiting EVD patients in Guinea in December 2014, when that country’s epidemic peak had passed. INSERM was the first to implement clinical research on favipiravir in Guinea, whilst Oxford University followed with brincidofovir in Liberia and TKM-130803 in Sierra Leone, and the National Institute of Health (NIH) subsequently started investigated ZMapp in Liberia and Sierra Leone.

### **The encounter of two missions**

ETCs serve two main purposes: to diagnose, care for and treat patients with EVD, and to isolate patients with EVD to prevent the spread of the epidemic. In general the management of EVD in West Africa has consisted of rehydration, electrolyte replacement, analgesia, and the treatment of co-infections such as bacterial sepsis and malaria. Despite such treatment, mortality has ranged between 29% and 67% during the West Africa outbreak, depending on the country<sup>10</sup>. At the end of 2014, several ETCs began implementing therapeutic EVD research. For many NGOs, collaborating with clinical research during an outbreak was a new experience. For many

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<sup>7</sup> Adam Withnall, “Ebola virus: British experts urge US and WHO to ‘give Africans cure’”, *The Independent*, 6 August 2014, <http://www.independent.co.uk/news/world/africa/ebola-outbreak-british-experts-urge-us-and-who-to-give-africans-experimental-cure-9650937.html>

<sup>8</sup> WHO, Ethical considerations for use of unregistered interventions for Ebola virus disease, statement of the 12 August, <http://www.who.int/mediacentre/news/statements/2014/ebola-ethical-review-summary/en/>

<sup>9</sup> Phase I: toxicity evaluation among healthy human volunteers, phase II: dose-ranging for safety and efficacy among few sick patients and phase III: Evaluation of efficacy against the disease in large comparative studies.

<sup>10</sup> WHO, <http://apps.who.int/ebola/ebola-situation-reports>, last consulted 19/9/2015.

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humanitarian healthcare workers, frustrated at not being able to save more lives with current treatment strategies, the promise of potential treatments gave hope.

However, when the standard method for evaluating the efficacy of a new drug – the placebo-controlled randomised trial<sup>11</sup> – was proposed by some members of the scientific community, MSF objected: “those who are most in need should have access to the product under investigation. Trials for treatments should not include a placebo and exposed and vulnerable people in Ebola-affected and low-resource settings shouldn’t be led to think they are being treated when they’re not”<sup>12</sup>. Such a position was supported by the excellent survival rates observed in non-human primate models of EVD for the most promising agents, and by the use of several experimental treatments for Ebola workers treated in Europe and North America without knowledge of safety or effectiveness in humans with EVD. The position of MSF was primarily to make sure that medical ethics be respected.

From a scientific perspective, exposing a patient to a medication that lacks appropriate, disease-specific safety and effectiveness data is also an ethical concern, however. Compassionate use of an investigational product may be permitted on a case-by-case basis, but it would be difficult to justify a blanket approval of compassionate use that could jeopardise the chances of assessing a potential treatment. Indeed, this was pointed out by the expert panel convened by the WHO on the 11th of August 2014 to assess ethical considerations relating to the use of experimental treatments for EVD. The panel recommended that the best possible clinical trials, appropriate to the exceptional circumstances, should be implemented to assess efficacy and safety of the most promising potential treatments.

From a regulatory perspective, a new treatment cannot be said to be more effective than a placebo until efficacy has been demonstrated stringently, and a controlled randomised trial of an investigational drug versus placebo, or versus the best available drug, is the standard method in clinical trials. However, the exigency of a research protocol is very much part of scientific ethics and the risk of failing to reach the research objective within the narrow time frame of an outbreak must be minimised. Therefore, alternative pragmatic designs needed to be considered alongside traditional designs. A project of limited quality that doesn’t answer the research question is a waste of resources and may mean that important research opportunities are missed, in addition to failing those who take part in the study. Therefore, the ethical evaluation of a research protocol should also include thorough assessments of scientific quality and the likelihood that study endpoints can be met. This is the debate that took place, the pros and cons of randomised and non-randomised controlled trials, in the context of the West African EVD epidemic. Some researchers have proposed that randomised controlled trial designs are the obvious and only choice<sup>13</sup>, whereas others have questioned whether RCTs are ethically appropriate or capable of delivering results within the context and timescale of an EVD outbreak<sup>14</sup>.

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<sup>11</sup> In this type of clinical trial, there is a random drawing to appoint the participants in a group that will receive the experimental drug or a group that will receive a placebo. This method allows evaluating the real efficacy of the drug.

<sup>12</sup> MSF, October 17, 2014, <http://www.doctorswithoutborders.org/article/ebola-experimental-treatments-and-vaccines>

<sup>13</sup> Edward Cox et al., “Evaluating Ebola Therapies – The Case for RCTs”, *n engl j med* 371;25 [nejm.org](http://www.nejm.org) december 18, 2014, <http://www.nejm.org/doi/full/10.1056/NEJMp1414145>

<sup>14</sup> Clement Adebamowo et al., “Randomised controlled trials for Ebola: practical and ethical issues”, *www.thelancet.com* Vol 384 October 18, 2014, [http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(14\)61734-7.pdf](http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(14)61734-7.pdf)

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Faced with logistical and time-dependent challenges associated with an EVD outbreak, scientists had to look beyond traditional RCTs. The concepts of adaptive randomised trial<sup>15</sup> and of Multi-Stage Approach<sup>16</sup> have been introduced in the debate as solutions enabling faster access to effective treatment. They allow, within the framework of an evolving study design integrating several research phases, to immediately analyse and use the results obtained during the course of the research implementation.

Separate studies of favipiravir, brincidofovir, and TKM-130803, implemented by INSERM and the University of Oxford at ETCs in Guinea, Liberia and Sierra Leone, have offered access to experimental drugs (in addition to standard care) to all participants without randomisation. The results obtained will be compared to expected death rates derived from large historical control data sets obtained from the same outbreak. The brincidofovir trial was terminated for logistical reasons after recruiting for four weeks<sup>17</sup>, whereas the TKM-130803 trial reached a pre-specific endpoint in less than three months and ceased recruitment accordingly<sup>18</sup>. Interim results from the favipiravir study were announced in early 2015<sup>19</sup>. A trial assessing ZMapp is being conducted by the NIH, initially recruiting patients at ETCs in Liberia and then in Sierra Leone. This open-label phase I/II study follows a traditional randomised controlled trial design, with the ability to progress to pairwise comparisons of novel interventions once the initial ZMapp assessment phase has been completed. Patients in this trial are randomised to standard care, or standard care and ZMapp. With the decrease in EVD cases seen in 2015, the ZMapp trial and other continuing treatment trials now face the challenge of recruiting enough patients to meet predefined endpoints and produce meaningful conclusions.

**Challenges in implementing research in the ETC**

Despite communication campaigns highlighting the advantages for people with suspected EVD of accessing medical care at an ETC as quickly as possible, resistance and fear towards ETCs and medical personnel have remained high amongst some populations. Rumours still persist in some areas contributing to the continuation of the epidemic. Such rumours are easy to understand given the management of patients with EVD at the start of the outbreak, which was often palliative. Still now, despite the best supportive care possible under the circumstances, only between one third and two thirds of the patients admitted to an ETC with EVD walk out again. Early in the outbreak, the social, psychological, and cultural aspects of managing EVD patients were also often overlooked. Relatives had little opportunity to visit and communicate with their sick family members whilst they were in the ETC; burials were often conducted without regard for traditional funeral rites and the wishes of family members; and there was little access to psychosocial support. These initial mistakes contributed, at least in part, to long lasting suspicions about NGOs and healthcare workers in ETCs, which in turn have resulted in challenging conditions for obtaining informed consent from EVD patients to participate in clinical research.

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<sup>15</sup> Simone Lanini et al., “Are adaptive randomised trials or non-randomised studies the best way to address the Ebola outbreak in west Africa?”, *www.thelancet.com/infection* Vol 15 June 2015 [http://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099\(15\)70106-4.pdf](http://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(15)70106-4.pdf)

<sup>16</sup> Ben S. Cooper et al., “Evaluating Clinical Trial Designs for Investigational Treatments of Ebola Virus Disease”, *PLOS Medicine* | DOI:10.1371/journal.pmed.1001815 April 14, 2015 <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001815>

<sup>17</sup> Wellcome Trust-funded Ebola treatment trial stopped in Liberia, <http://www.wellcome.ac.uk/News/Media-office/Press-releases/2015/WTP058609.htm>

<sup>18</sup> Helen Branswell, Trial of Canadian Ebola drug stopped after no overall benefit shown, TORONTO – The Canadian Press, Jun. 19, 2015, <http://www.theglobeandmail.com/news/national/trial-of-canadian-ebola-drug-stopped-no-overall-benefit-shown-from-tkm-ebola/article25035127/>

<sup>19</sup> INSERM press release, <http://www.inserm.fr/espace-journalistes/ebola-resultats-preliminaires-de-l-essai-jiki-pour-tester-l-efficacite-du-favipiravir>

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Usually exhausted, having often lost several relatives, and faced with medical personnel in full personal protective equipment, the patients are in conditions of extreme distress. The checks and balances to protect potential subjects must be particularly strict, even though they may seem heavy and the duration of the consent very long, given the health status of the participants and the unfavourable conditions for researchers and healthcare workers. Protocols may be misunderstood by healthcare workers if they are not acquainted with the requirements of research. Therefore, good communication between the researchers and ETC staff is of paramount importance. Explaining the design, aims and limitations of a study to all healthcare workers, including psychologists and social workers, who are an important link with patients and their relatives, is essential to avoid misunderstanding.

The monitoring of a research subject differs from the usual medical care of a patient. A closer monitoring of subjects is necessary to identify the onset of potential serious adverse events, which may be difficult to differentiate from the manifestations of EVD itself. Once again, good coordination and communication between researchers and healthcare workers is essential in this regard. It requires sharing the patient's health information and the biological results to avoid duplication of blood and data collection. The ETC is thus a place where the different teams really meet around a combined project of care and research.

The EVD outbreak in West Africa has represented an opportunity for an encounter between two worlds, on the one hand that of humanitarian action and the other that of medical research. As a result of the ethical issues that it has raised, the West African EVD outbreak has led to novel and creative ways of devising and implementing clinical research in outbreak situations. Firstly, it has fostered novel collaborations between researchers, humanitarian organizations, the pharmaceutical industry and regulators, to accelerate the phases of research while preserving the quality of the clinical trials process and protecting participants. Secondly, it has resulted in a fruitful debate among health-care workers and researchers, leading to the adaptation of clinical research methods and the use of innovative study designs to try and answer questions of drug efficacy and safety whilst optimising the opportunities for patients with EVD to receive experimental treatments, in a way that is most acceptable to the countries affected. The results of the different clinical trials remain to be published, but for some it is clear already that other treatment options need to be considered, for example antiviral combinations and immunomodulatory treatments aiming to mitigate the immunopathology that occurs secondary to ebolavirus infection.

What could we have done differently to advance the therapeutic research agenda during this outbreak? There are many potential answers to this question and a detailed analysis is required once the epidemic has ended and the different trials have reported their findings. Needless to say, two pitfalls have been avoided: the accusation that patients were treated as “Guinea pigs”, which could have arisen if experimental drugs had been administered on a large scale outside of rigorous research protocols; and the accusation that patients in West Africa were being deprived of potentially life-saving medicines, even though the arrival of experimental drugs in the field took some time.

Several important future challenges remain however. One is the ability to react rapidly in the context of an outbreak and implement research. This is the objective of initiatives such as, ISARIC<sup>20</sup> – the International Severe Acute Respiratory and emerging Infection Consortium – which aims to ensure that clinical researchers have the open access protocols and data-sharing

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<sup>20</sup> ISARIC, <https://isaric.tghn.org/>

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processes needed to facilitate a rapid response to emerging diseases that may turn into epidemics or pandemics; GLOPID-R<sup>21</sup>, which brings together research funding organisations from a dozen countries to facilitate an effective and rapid research response following an outbreak; and REACTING<sup>22</sup>, an international initiative aiming at promptly mobilising research teams and projects in case of emerging infectious diseases. The other critical future challenge, and one which was poorly addressed during the West African EVD outbreak, is the integration of the humanitarian and research response with the strengthening of facilities and infrastructures in countries with limited resources, both in terms of research and health-care, to better deal with future outbreaks autonomously. This is a key area that needs to be addressed in future outbreaks.

### Biographies

**Jake Dunning** • is a Consultant in Infectious Diseases and General Internal Medicine, and a Senior Clinical Researcher at the Centre for Tropical Medicine and Global Health, University of Oxford. His research focuses on emerging and re-emerging infections, including studies of pathogenic mechanisms and clinical characteristics, in addition to performing clinical trials of potential therapeutics during outbreaks. Since October 2014, he has worked in West Africa as the Lead Clinician for the RAPIDE clinical trials of potential treatments for Ebola virus disease. As a member of ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium), he is committed to improving outbreak research.

**Christophe Longuet** • is a medical doctor, specialising in Public Health and Tropical Medicine. Since 2007 he has been the medical director of the Mérieux Foundation. In 2014, he became member of the INSERM Ethics Committee. He keeps a clinical activity at the Infectious Diseases Department of Croix Rousse Hospital in Lyon, and contributes to the teaching of Humanitarian Medicine and International Health at the universities of Claude Bernard, Lyon, Pierre & Marie Curie and Denis Diderot, Paris. He participated, as a clinician and medical advisor, in the opening of the Ebola Treatment Centre of Macenta, Guinea, with the French Red Cross in November 2014, and in clinical research with the Centre for Tropical Medicine and Global Health, University of Oxford, at the Mathaska Ebola Treatment Centre, Sierra Leone, in May 2015.

**Alex Salam** • is a Specialist Registrar in Infectious Diseases and General Internal Medicine, based in London. He is currently a NIHR/Crick Clinical Research Fellow based at King's College London and the Francis Crick Institute, and the Ebola Clinical Research Supervisor for GOAL Global. In December 2014 and January 2015 he was a doctor and clinical advisor at the Kerry Town Ebola Treatment Centre in Sierra Leone with Save the Children. From March 2015 to June 2015 he was the medical director of the Mathaska Ebola Treatment Centre with GOAL Global.

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<sup>21</sup> GLOPID-R, <http://www.glopid-r.org/>

<sup>22</sup> REACTING, <http://www.aviesan.fr/fr/aviesan/accueil/toute-l-actualite/ebola-le-point-sur-la-recherche-en-france>