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Ethical considerations for use of unregistered interventions for Ebola viral disease

Report of an advisory panel to WHO

World Health Organization

Summary

West Africa is experiencing the largest, most severe, most complex outbreak of Ebola virus disease in history. Previous Ebola outbreaks have been contained by existing interventions, such as early detection and isolation, contact tracing and monitoring, and adherence to rigorous procedures of infection prevention and control. Effective treatments and vaccines would, however, dramatically strengthen the ability to counter the disease.

During the past decade, research has been conducted to develop drugs and vaccines for Ebola virus disease. Some of these have shown promising results in the laboratory and in animal models, but they have not yet been evaluated for safety and efficacy in humans. The large number of people affected by the present outbreak in West Africa and the high case-fatality rate have prompted calls to accelerate the evaluation and development of these investigational medical interventions and to use them to try to save the lives of patients and curb the epidemic.

Therefore, on 11 August 2014, WHO convened a consultation to consider and assess the ethical implications for clinical decision-making of use of unregistered interventions that have shown promising results in the laboratory and in animal models but that have not yet been evaluated for safety and efficacy in humans.

The panel members deliberated the particular circumstances of this outbreak and weighed the different options. They concluded unanimously that it would be acceptable on both ethical and evidential grounds to use as potential treatments or for prevention unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans, provided that certain conditions are met. In reaching these conclusions, the panel members were mindful that this is a departure from the well-established, historically evolved system of regulation and governance of therapies and interventions.

Ethical and scientific criteria must guide the use of unregistered interventions. The ethical criteria include transparency about all aspects of care, so that maximum information is obtained about the effects of the interventions, fair distribution in the face of scarcity, promotion of cosmopolitan solidarity, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community. Use of these interventions should also be based on the best possible assessment of risk and benefit from the available information.

The group advised that, if and when these interventions are used to treat patients (or as prevention), the physicians overseeing their administration have a moral obligation to collect and share all scientifically relevant data generated, including from treatment provided for “compassionate use” (access to an unapproved drug outside a clinical trial), in order to establish the safety and efficacy of the interventions.

The group discussed how use of these investigational interventions in a clinical context can be evaluated scientifically to ensure timely, accurate information about their safety and efficacy. They agreed unanimously that investigators have a moral duty to evaluate these interventions (for treatment or prevention) in the best possible clinical studies that can be conducted under the circumstances of the epidemic in order to establish their safety and efficacy or to provide evidence to stop their use. Continuous evaluation should guide future interventions.

In addition to this advice, the panel identified areas that require more detailed analysis and discussion, including:

- ethical ways to gather data while providing optimal care under the prevailing circumstances;
- ethical criteria for prioritizing the use of unregistered experimental therapies and vaccines; and

- ethical criteria for achieving fair distribution in communities and countries of the growing number of investigational interventions, none of which is likely to meet the demand in the short term.

Introduction

West Africa is experiencing the largest, most severe, most complex outbreak of Ebola virus disease in history. Previous Ebola outbreaks have been contained with existing interventions, such as early detection and isolation, contact tracing and monitoring, and adherence to rigorous procedures of infection control. Effective treatments and vaccines would, however, dramatically strengthen the ability to counter the disease.

During the past decade, research has been conducted to develop drugs and vaccines for the disease. Some of these have shown promising results in the laboratory and in animal models of infection, but most have not yet been evaluated for safety and efficacy in humans. For many of these drugs and vaccines, phase-1 safety studies are planned during the next 2–6 months, and some are likely to progress to phase-2 clinical studies. The magnitude of the outbreak in West Africa, with large numbers of people affected, has prompted calls for use of investigational medical interventions that are not yet registered to try to save the lives of patients and to curb the epidemic.

Scope and purpose

On 11 August 2014, in the context of the current Ebola outbreak, WHO organized a consultation to consider and assess the ethical implications for clinical decision-making of the use of unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans**.** With this objective, the WHO Secretariat requested the panel to reflect on five questions:

1. Is it ethical to use unregistered interventions that have shown promising results in the laboratory and in animal models but have unknown adverse effects in humans for *possible treatment* of people who are infected? If yes, what criteria and conditions must be satisfied before they can be used?

2. Is it ethical to use unregistered interventions that have shown promising results in the laboratory and in animal models but have unknown adverse effects in humans for prophylaxis in people who are exposed but who show no signs of disease (i.e. *post-exposure prophylaxis*)? If yes, what criteria and conditions must be satisfied before they can be used?

3. Is it ethical to use unregistered interventions that have shown promising results in the laboratory and in animal models but have unknown adverse effects in humans for prophylaxis in people who may be exposed (i.e. *pre-exposure prophylaxis*)? If yes, what criteria and conditions must be satisfied before they can be used?

4. If it is ethical to use unregistered interventions that have shown promising results in the laboratory and in animal models under the circumstances described above, what criteria should guide the choice of intervention?

5. If it is ethical to use unregistered interventions that have shown promising results in the laboratory and in animal models under the above circumstances, who should receive priority for treatment or prevention?

Meeting procedure

A panel of 12 members (see list below) was invited to advise the WHO Director-General during a 3-h panel discussion, held by teleconferencing. They were invited on the basis of their varied, relevant background, expertise and geographical representation. The expertise of the panellists included: bioethics, scientific research methods, Ebola research, experience in Ebola management, experience

in humanitarian crises, patient safety advocacy and regulation of therapeutics. Four resource persons were invited to provide relevant input to the advisory panel when required.

At the start of the meeting, the Director-General invited Dr Philippe Calain to chair the panel.

All panellists and resource persons were asked to declare any relevant financial, academic or non-academic interests. Their written statements were assessed by the Secretariat, who found that none of the panellists had a relevant conflict of interest. Dr Frederick Hayden, one of the resource persons, declared that "he and his University have received compensation for his time in reviewing one patent case regarding Zanamivir (GSK) and medicolegal cases involving fatal influenza and delayed use of Oseltamivir (Roche)." Dr Hayden added that he had reviewed the cases while a full faculty member and that he had not received any remuneration for them in his personal capacity.

Meeting report

The meeting was opened by Dr Margaret Chan, Director-General of WHO, who thanked the participants for making themselves available at short notice to advise and assist the WHO in these difficult ethical questions. Dr Chan outlined the issues and invited the panel to begin their deliberations. Dr Marie-Paule Kieny, Assistant Director-General, explained the respective roles of the advisers and resource persons. The meeting was then handed to the Chair, who requested that, in order to use time effectively, the panel consider the first three questions together and then move to the last two. Each adviser was asked to give a short response to each question, summarizing his or her position, after which the discussion was opened to comments and questions. Panellists were invited to provide additional written comments within 24 h of the meeting closure.

While the panel discussion was structured around the five questions listed above, this report summarizes the discussions that ensued among the panel members.

Key points of discussion

1. Exceptional circumstances

- The panel members noted that the situation in West Africa is unprecedented. The Ebola virus disease outbreak is occurring in countries that have never previously experienced the disease, and it is placing extreme demands upon fragile health systems, to a point that exceeds their capacity. This outbreak is already the largest ever recorded of a filovirus disease. It is a complex outbreak, involving multiple locations, with much cross-border movement between communities and misconceptions about the origin of the disease, which render the international relief effort more difficult. The virus strain responsible for the outbreak induces a disease with a variable but very high fatality rate. The local health care community is in a critical situation because of the high risks to which medical and nursing personnel are being exposed.
- Before the outbreak, there was no commercial incentive to develop treatments or vaccines for filovirus diseases, and the lack of any such intervention has left public health authorities and clinicians in the affected countries with no specific prevention or treatment options, despite the fact that outbreaks have been occurring for nearly four decades.
- The only way of obtaining evidence on the safety and efficacy of any intervention in Ebola virus disease is during an outbreak, because identified sporadic disease is very rare. Therefore, frameworks to guide the most appropriate research study designs and procedures during an outbreak are urgently required.
- The panel noted that medical products are being developed for Ebola virus disease, comprising passive immunotherapy, antiviral drugs and vaccines, which are at an advanced preclinical stage

of development; some are ready for testing in humans. The panel strongly recommended that these investigational drugs or vaccines for patients with Ebola virus disease that have shown promising results in the laboratory and in animal models be urgently tested in humans by scientifically sound, rigorous methods. At the same time, the practical circumstances of outbreak response capacity call for exploration of innovative methods of rapid assessment, so that candidate interventions that show promise can quickly be tested in larger clinical studies. Without such testing, there is no certainty that experimental interventions are safe and effective.

- Having considered the points above, the panel agreed unanimously that, in the exceptional situation of the current Ebola outbreak, there is an ethical imperative to offer the available experimental interventions that have shown promising results in the laboratory and in relevant animal models to patients and people at high risk of developing the disease, with the proviso that the conditions listed below are met.

2. Essential considerations prior to use of unregistered interventions

- Investigational therapeutic or prophylactic options should not divert attention or resources from the public health measures that remain the main priority in outbreak control.
- Ethical criteria based on traditional research ethics, professional ethics, public health ethics and global health ethics should guide the use of such interventions. These include transparency about all aspects of care (including medical indications and selection criteria for use), so that the maximum information is obtained about the effects of the interventions, trust, fair distribution in the face of scarcity, promotion of cosmopolitan solidarity, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community.
- Use of such interventions should be based on the best possible assessment of risk and benefit from the information available at a given time.
- The unregistered interventions to be offered should have been demonstrated to be safe and efficaciouseffective in relevant animal models and in particular in non-human primates.
- There should be shared understanding of the criteria for compassionate use (access to an unapproved drug outside a clinical trial) by all those involved in the final decision (patients, clinicians, families and people entrusted to safekeeping of the materials), and this should be recorded before deployment of the intervention.
- The extent of uncertainty about the safety and efficacy of the intervention in humans should be clearly acknowledged and transparently communicated to all stakeholders, especially to the patients and communities involved, to avoid fostering unfounded expectations.
- Capacity should be available to administer the experimental therapy in conjunction with the necessary supportive treatment, to monitor and manage any side-effects and to monitor the progress of treatment, including, at a minimum, measuring when possible appropriate surrogate outcomes, such as disease and immune response markers.
- Appropriate scientifically useful data generated on clinical and other relevant outcomes resulting from use of these agents, including from compassionate use, should be collected and shared transparently and rapidly with the scientific community. The panel emphasized that this is a moral obligation.
- Compassionate use is justified as an exceptional emergency measure. It should not preclude or delay the initiation of more conclusive investigations of the intervention in properly designed clinical studies. Under the current evolving circumstances, no single ethical discourse can

adequately capture all the issues that justify compassionate use, and no single principle or normative consideration is likely to supersede the others.

- The panel acknowledged the impact of the outbreak on the health systems of the affected countries and advised that any decision to use experimental, unproven interventions should include consideration of the standard of care and feasibility in the setting in which they are used.

3. Criteria for the prioritization and allocation of investigational interventions

- The panel recommended that the priority should be to facilitate the access of affected countries to those candidate interventions that have already shown evidence of safety and efficacy in the laboratory, including in non-human primate models.
- As the number of candidate interventions is currently limited and doses of the most promising interventions are in extremely short supply, choices will have to be made, not only about who receives the intervention but also which country gets what and on the basis of what criteria. It was agreed that the principles used for setting priorities in resource-constrained settings should be applied to make such choices. Some of the criteria mentioned were:
  - distributive justice: fairness between countries and among populations within countries;
  - reciprocity and social usefulness: Although the panel was not unanimous, many members proposed that health care workers be considered of high priority, including for access to therapy. This proposal is based on two ethical principles: reciprocity (they put their life at risk to care for others) and social usefulness (they are instrumental to controlling the outbreak). The same principles should apply to other workers providing supportive services (such as sanitation and burial services) and to relatives who provide care to patients. Other panel members advocated that patients in the community should have the same priority as the groups mentioned above, particularly for therapy;
  - likelihood of a positive impact on both individual and public health outcomes;
  - clinical stage of the disease; and
  - the characteristics of the unregistered medical product.
- Because of their higher mortality rates, children and pregnant women should be considered particularly vulnerable to Ebola virus disease and given special protection when receiving such interventions.
- The principles used to prioritize administration of the very limited number of doses available should be fully transparent and involve the governments of the affected countries and communities in a participatory, inclusive manner.
- Other guiding principles were identified:
  - Standard supportive care must be provided when the unregistered product in question is used as a therapeutic agent;
  - Minimal infrastructure and equipment to administer the experimental therapy, monitor its efficacy and treat any severe adverse effects appropriately must be available;
  - Families and communities must be involved, to the extent possible, in decisions on priority allocation;
  - The ultimate choice of whether to receive the experimental intervention must rest with the patient, if the patient is in a condition to make the choice. If the patient is unconscious or too unwell to understand the risks, provision should be made to seek consent from the family and/or the community;

- As consent is of paramount importance, information should be provided in easy-to-understand, culturally appropriate language. For minors, assent should be obtained whenever possible, in addition to the consent of the parents or surrogate guardian;
- Understanding and support by the community of use of experimental interventions in this context may engender trust in medical care in general and encourage patients to seek early treatment. These interventions may benefit individual patients and could also benefit the entire community by promoting health-seeking behaviour.

4. Further steps

The panellists agreed that a number of issues should continue to be discussed and analysed in the very near future, as new data become available.

- How can data on the interventions be gathered ethically while at the same time providing the best possible care under the prevailing circumstances and respecting confidentiality?
- What ethical criteria should be used to prioritize the use of unregistered experimental therapies and vaccines that have shown promising results in the laboratory and in animal models?
- What ethical criteria should be used to achieve fair distribution of the interventions in communities and among countries, with a growing number of possible new interventions, none of which is likely to meet demand in the short term?

The panellists recommended that discussion should continue with ethicists, in conjunction with reviews of (i) new scientific evidence on potential therapeutic and preventive options for Ebola virus disease; (ii) the minimal pragmatic conditions for proper trials; and (iii) the trial designs that are the most appropriate for accommodating the current constraints of the international outbreak response, including use of pragmatic trial designs and exploration of innovative methods for rapid assessment of efficacy and safety.

Conclusion

In the particular context of the current Ebola outbreak in West Africa, it is ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention.

Ethical, scientific and pragmatic criteria must guide the provision of such interventions. The ethical criteria include transparency about all aspects of care, so that the maximum information is obtained about the effects of the interventions, fairness, promotion of cosmopolitan solidarity, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity, involvement of the community and risk–benefit assessment.

If and when unproven interventions that have not yet been evaluated for safety and efficacy in humans but have shown promising results in the laboratory and in animal models are used to treat patients, those involved have a moral obligation to collect and share all the scientifically relevant data generated, including from treatments provided for “compassionate use”.

Researchers have a moral duty to evaluate these interventions (for treatment or prevention) in clinical trials that are of the best possible design in the current exceptional circumstances of the West African Ebola outbreak, in order to establish the safety and efficacy of the interventions or to provide evidence to stop their use. Continuous evaluation should guide future interventions.

List of participants

Advisers

Name	Affiliation	Expertise	Country
Dr Juan Pablo Beca	Professor, Bioethics Centre, Faculty of Medicine, Universidad del Desarrollo Member of the Chilean Academy of Medicine	Bioethics, research ethics, clinical ethics	Chile
Dr Helen Byomire Ndagije	Head, Drug Information Department, Ugandan National Drug Authority	Drug regulatory issues	Uganda
Dr Philippe Calain (Chair)	Senior Researcher, Unit of Research on Humanitarian Stakes and Practices, Médecins Sans Frontières	Filovirus diseases, humanitarian ethics, public health ethics, global public health surveillance, disaster ethics	Switzerland
Dr Marion Danis	Head, Section on Ethics and Health Policy, Chief, Bioethics Consultation Service, National Institutes of Health	Bioethics, health policy, strategies for public engagement in rationing	USA
Professor Jeremy Farrar	Director, Wellcome Trust	Emerging infections, influenza, central nervous system infections, dengue, typhoid, tuberculosis and opportunistic infections related to HIV infection, ethics of research in epidemics	United Kingdom
Professor Ryuichi Ida	Member, Expert Panel on Bioethics (National Bioethics Committee)	Bioethics	Japan
Professor Tariq Madani	Professor, Medicine and Infectious Diseases Chairman, Section of Infectious Diseases, Faculty of Medicine Chairman, Viral Haemorrhagic Fever Scientific Chair, King Fahd Medical Research Centre	Viral haemorrhagic fever, infectious diseases, infection control	Saudi Arabia
Professor Michael Selgelid	Director, Centre for Human Bioethics, Monash University	Ethical issues associated with infectious disease	Australia
Professor Peter G. Smith	Professor of Tropical Epidemiology, London School of Tropical Medicine and Hygiene	Epidemiological and statistical research, large-scale intervention studies against tropical diseases, including vaccine trials	United Kingdom
Ms Jeanine Thomas	Patient safety champion	Patient advocate	USA

Dr Aisssatoue Touré	Head, Immunology Department, Pasteur Institute Member, National Ethics Committee	Malaria immunology	Senegal
Professor Ross Upshur	Canada Research Chair in Primary Care Research Professor, Department of Family and Community Medicine and Dalla Lana School of Public Health, University of Toronto	Communicable disease epidemiology, public health ethics, global health ethics, ethical issues in epidemics and pandemics, research ethics	Canada

Resource persons

Dr Daniel Bausch, United States Naval Medical Research Unit No. 6, Lima, Peru

Professor Luciana Borio, United States Food and Drug Administration

Dr Frederick Hayden, University of Virginia, USA

Dr Stephan Monroe, United States Centers for Disease Control and Prevention, USA