

SHORT PAPER

Ebola Virus Disease Outbreak: What's going on

G. Giraldi*, L.T. Marsella**

Key words: Ebola virus disease, Ebola treatment, healthcare professional workers, outbreak, transmission

Parole chiave: Ebola, trattamento, professionisti sanitari, epidemia, trasmissione

Abstract

The current West African Ebola Virus Disease (EVD) outbreak was confirmed in March, 2014, and after months of slow, fragmented responses, the EVD has been recognized as a public health emergency of international concern.

The early diagnosis of the disease is difficult without laboratory testing, because its symptoms can be seen in many other infections. In the wake of international agencies advices, the Italian Ministry of Health, on October 1, 2014, released to the Healthcare Professional Workers (HPWs) the Protocol about the management of cases and contacts within the national territory.

Due to the increasing number of humanitarian groups and HPWs involved in the field, the probability to have new cases of contamination is higher than ever. Proven specific treatments against EVD are not yet available, however, a variety of compounds have been under testing. The most effective are select monoclonal antibodies that have a high neutralizing potential against epitopes of Ebola Virus. For facing the matter, it is important a comprehensive approach according to the recommendations proposed by the international agencies because no single institution or country has all the capacities to respond to a new and emerging infectious disease.

Introduction

Today, there is growing recognition that an outbreak anywhere can potentially represent an emergency for public health concern, with the potential to burst into a worldwide pandemic.

Ebola Virus Disease (EVD) is a severe, often fatal illness in humans, which first appeared in 1976 in two simultaneous outbreaks, one in a village near the Ebola River in the Democratic Republic of Congo, and the other in a remote area of Sudan.

While initial cases of EVD was contracted by handling infected animals or carcasses, secondary cases occurred by direct contact with the bodily fluids of an ill person, either through unsafe case management or unsafe burial practices. During this outbreak, most of the disease has spread through human-to-human transmission.

Recently, the first case of this West African epidemic was confirmed in March, 2014, and after months of slow, fragmented responses, a meeting of the World Health Organization (WHO) International Health

* Department of Public Health and Infectious Diseases, Sapienza University of Rome, Italy

** Department of Biomedicine and Prevention, Tor Vergata University, Rome, Italy

Regulations Emergency Committee on August 8, declared the outbreak a public health emergency of international concern and a clear threat to global health security. Actually, up to the 11 January 2015, a total of 21,296 confirmed, probable, and suspected cases of EVD have been reported worldwide. The intense transmission countries are Guinea, Liberia, Sierra Leone; six countries (Mali, Nigeria, Senegal, Spain, United Kingdom and the United States of America) have reported exclusively one or more cases imported from a country with widespread and intense transmission.

The outbreak continues to evolve in alarming ways, with the severely affected countries, Guinea, Liberia, and Sierra Leone, struggling to control the escalating outbreak against a backdrop of severely compromised health systems. Reported cases in the past 21 days were: 230 in Guinea, 48 in Liberia, and 769 in Sierra Leone. The case fatality rate across the three most-affected countries in all cases with a recorded definitive outcome is 71%; in hospitalized patients the case fatality rate is between 57% and 60% (1, 2).

Realizing the aftermaths associated with the EVD, the WHO has advocated the development of a systematic framework to tackle the appearance of even a single case, in nations, where no suspect/confirmed case of has been detected till date. Steps for an appropriate response such as alert system in well-defined sites, creation of a rapid response team trained in case definitions, reporting, infection prevention and control measures, and periodic monitoring and evaluation has been also recommended (3).

Disease diagnosis and management

The early diagnosis is difficult without laboratory testing, because such symptoms can be seen in many other infections, including malaria, typhoid, and influenza. The incubation period varies from 3 to 21 days;

patients initially present with general flu-like symptoms, intense weakness, muscle pain, headache and sore throat. This is followed by vomiting, diarrhea, rash, impaired kidney and liver function, and in some cases, both internal and external bleeding.

Laboratory findings include low white blood cell and platelet counts, and elevated liver enzymes. Distinguishing a case of EVD requires testing a patient's blood with PCR (Polymerase Chain Reaction). During acute disease the assays include a) virus isolation using Vero or Vero E6 cell lines, b) RT-PCR and real time quantitative PCR assays with appropriate false negative and false positive controls, c) antigen capture ELISA, and d) IgM ELISA (4).

Many countries have implemented disease control measures including the creation of specialized referral centers equipped with negative air pressure isolation rooms or wards for containment of patients in the context of imported disease. WHO does not recommend home care and strongly advises individuals and their family members to urgently seek professional care in a treatment center. The national governments' role is preeminent, and could be strengthened but not replaced by international agencies (5).

In the wake of international agencies advices, the Italian Ministry of Health, on October 1st, released to the healthcare professional workers (HPWs) the Protocol (6) about the management of cases and contacts within the national territory (updated in October 6) indicating the procedures for handling suspected, probable and confirmed cases of EVD.

The protocol shows classification cases, initial evaluation, the taking charge of suspicious cases and their transfer to treatment center, in which the patients can be managed adequately. The aim of the indications is to reduce the risk of transmission during patient support, the spreading of the infection to other patients, HPWs and visitors. Additionally, the document defines the management of

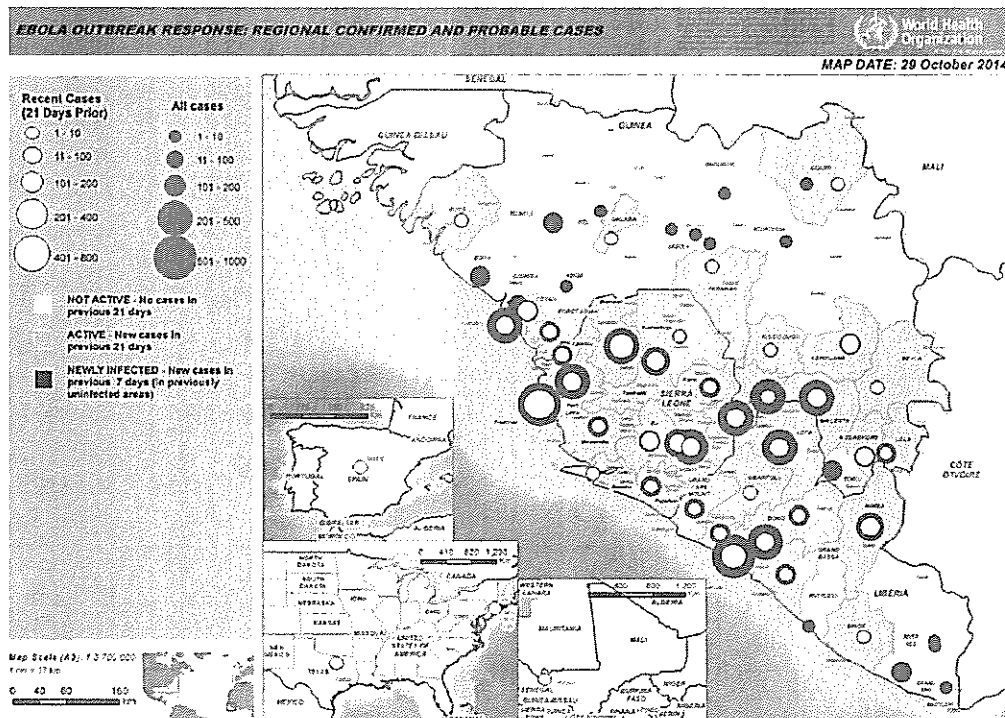


Figure 1 - Ebola outbreak response: Regional Confirmed and probable cases. [Available at www.who.int/esr/disease/ebola/maps/en/]

verified cases, the measures for contacts and for the reduction of the risk of transmission. Individuals with Ebola-like symptoms must be tested early, confirmed patients should be transported by dedicated vehicles that have protective equipment, disinfectants, and trained local transport operators.

Due to the increasing numbers of humanitarians and HPWs in the field, the probability to have new cases of contamination is higher than ever. At the time of writing a total of 843 HPWs are known to have been infected with Ebola Virus, 493 of whom have died. The total case count in countries with intense transmission includes 159 HPWs in Guinea, 370 HPWs infected in Liberia and 296 HPWs infected in Sierra Leone (2).

In most countries, field-exposed personnel on return are subject to voluntary body temperature self-surveillance for 21 days at home as a quarantine measure. To stem the importation and travel related cases of Ebola, some authors proposed the following

strategies: 1) an urgent need to reinforce traceability and training of humanitarians and HPWs who provided assistance in epidemic countries, 2) to provide better training for HPWs in charge of caring for imported cases at referral centers ex-Africa, 3) to ensure safe handling of samples and validated diagnostic tests in hospital laboratories, and 4) to take immediate action with restriction of travel into the epidemic countries and limit this travel to medical and humanitarian aid (7).

Treatment

Proven, specific treatments or vaccines against Ebola Virus are not yet available. The control of the infection still hinges on supportive medical care to increase the survival of those who are infected and on basic non-pharmaceutical public health measures to prevent transmission, namely:

1. infection control measures including standard precautions in health care settings;

2. rapid contact tracing and isolation of infectious individuals;

3. social distancing interventions in the community which may include the dissemination of awareness campaigns to inform the population on how to avoid contracting the disease, quarantining people potentially exposed to infectious individuals and restricting the movement of communities exhibiting local transmission to prevent onward transmission; and

4. providing intravenous fluids and balancing electrolytes to affected individuals (8).

Recent experiments in monkeys provide promising evidence that experimental drugs could have a significant impact on mortality burden during Ebola outbreaks (9) and a promising bivalent Ebola vaccine against the Zaire and Sudan Ebola strains has entered human safety trials in September 2014 with an initial goal of building a stockpile of 10,000 doses by November 2014 (10).

A number of chemotherapeutic agents have been tested in humans as candidates for post-exposure therapy: antibodies, siRNAs (small interfering RNAs), interferons and chemical substances, i.e. neplanocin A derivatives (i.e. 3-deazaneplanocin A), BCX4430, favipiravir (T-705), endoplasmic reticulum (ER) α -glucosidase inhibitors that have been found to inhibit EVD infection blocking viral entry or by a mode of action that still has to be clarified (11). The most effective have been select monoclonal antibodies that have a high neutralizing potential such as the ones against epitopes of Ebola Virus. These antibodies termed MB-003 (12) and the ZMAb (9) have shown to be quite effective in infected nonhuman primates when administered 24-72 hours after the exposure.

Nevertheless, careful studies could be useful for assessing the impacts of treatment

on contact, transmission and diagnosis as well as on the disease burden.

Conclusion

Outbreaks require regional and global alert, response mechanisms to ensure rapid access to technical advice and resources to support national public health capacity. The key for epidemic control is rapid diagnosis, isolation and treatment of infected individuals. Control strategies based on the previous mainstays may reduce the transmission under one additional person per infected case, thereby rapidly containing the epidemic.

This approach was used in past Ebola outbreaks through contact tracing, in which anyone exposed to a person with Ebola was monitored, tested if they developed symptoms, and, if positive, securely transported to a health facility for treatment. These actions could be conducted in close collaboration with local community leaders to effectively reach the population at large (13, 14).

Due to the observed differences compared to the previous Ebola outbreaks, available epidemiological data to infer the natural history parameters of EVD remain limited and no single institution or country has all the capacities to respond to international public health emergencies caused by epidemics and by a new and emerging infectious disease.

For facing the matter, it is important a comprehensive approach according to the recommendations proposed by the international agencies. However, this does not mean at all that the unaffected nations can relax under the misconception that the threat no more exists. Whereas most developed countries certainly have the capacities to implement such a framework, many low-income and middle-income countries, and especially fragile states, do not. Increasing

capacity for contact tracing will be necessary to end local chains of transmission (15).

Riassunto

L'epidemia da Virus Ebola: Che cosa sta succedendo

L'attuale focolaio di Ebola nell'Africa occidentale è stato confermato a Marzo 2014, e dopo mesi di lente e frammentate risposte, è stato riconosciuto come un'emergenza sanitaria di rilevanza internazionale.

La diagnosi precoce è problematica in assenza di test di laboratorio, poiché i sintomi possono riscontrarsi in molte altre infezioni. Sulla scia delle raccomandazioni internazionali, il Ministero della Salute italiano, il primo Ottobre 2014, ha emanato ai professionisti sanitari il protocollo per la gestione dei casi e dei contatti all'interno del territorio nazionale.

A causa dell'aumento dei volontari e dei professionisti sanitari coinvolti, la possibilità che si verifichino nuovi casi di contagio è in aumento. Non sono disponibili trattamenti di provata efficacia, tuttavia, una varietà di composti sono in fase di sperimentazione. I più efficaci sono anticorpi monoclonali selettivi che hanno un elevato potenziale neutralizzante verso gli epitopi di Ebola virus. Per affrontare la questione, è importante un approccio globale secondo le raccomandazioni proposte dalle agenzie internazionali, perché nessuna singola istituzione o paese ha tutte le capacità per affrontare una malattia infettiva nuova ed emergente.

References

- [no authors listed] Ebola: what lessons for the International Health Regulations? [Editorial]. *Lancet* 2014; **384**: 1321.
- www.who.int/csr/disease/ebola/situation-reports/en/ [Last access January 15, 2015].
- Green A. WHO and partners launch Ebola response plan. *Lancet* 2014; **384**: 481.
- Ansari AA. Clinical features and pathobiology of Ebolavirus infection. *J Autoimmun* 2014; **55C**: 1-9.
- Iyengar R, Mahal AR, Aklilu L, et al. The use of Technology for large-scale education planning and decision-making. *Information Technol Dev* 2014; DOI:10.1080/02681102.2014.940267.
- Circolare pr. 26377 del 1/10/14 "Malattia da Virus Ebola (MVE) – Protocollo centrale per la gestione dei casi e dei contatti sul territorio nazionale".
- Brouqui P, Ippolito G. Ebola and travel - Management of imported cases. *Travel Med Infect Dis* 2014; **12**(6PA): 561-2.
- Frieden TR, Damon I, Bell BP, Kenyon T, Nichol S. Ebola 2014 - new challenges, new global response and responsibility. *N Engl J Med* 2014; **371**: 1177-80.
- Qiu X, Wong G, Audet J, et al. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. *Nature* 2014; **514**: 47-53.
- Kroll D. GSK/NIAID Ebola vaccines to enter US, UK human safety trials. *Forbes* 2014. Available at: www.forbes.com/sites/davidkroll/2014/08/28/gsk-niaid-ebola-vaccine-to-enter-uk-human-safety-trials-broad-international-collaboration/ [Last access December 10, 2014].
- De Clercq E. Ebola virus (EBOV) infection: therapeutic strategies. *Biochem Pharmacol* 2014; pii: S0006-2952(14)00689-3.
- Qiu X, Audet J, Wong G, et al. Successful treatment of Ebola virus-infected cynomolgus macaques with monoclonal antibodies. *Sci Transl Med* 2012; **4**: 138ra81.
- Meltzer MI, Atkins CY, Santibanez S, et al. Estimating the future number of cases in the Ebola epidemic—Liberia and Sierra Leone, 2014–2015. *MMWR Surveill Summ* 2014; **63**: 1-14.
- Dhillon RS, Srikrishna D, Sachs J. Controlling Ebola: next steps. *Lancet* 2014; **384**: 1409-11.
- Kanopathipillai R. Ebola virus disease—current knowledge. *N Engl J Med* 2014; **371**: e18.

Corresponding author: Guglielmo Giraldi, MD, Department of Public Health and Infectious Diseases, Sapienza University of Rome, P.le A. Moro 5, 00185 Rome, Italy
e-mail: guglielmo.giraldi@uniroma1.it