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Review

2014 SPREAD/UNCONTROLLED EBOLA OUTBREAK

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ABSTRACT

It is interesting to determine the underlying factors contributing to the emergence, rapid spread and uncontrolled nature of 2014 virus outbreak, the first to display a distinct epicentre in West Africa. Novel treatment and precautionary approaches are explored. The model of Ebola virus transmission dynamics is reviewed, with the aim to provide a broad sketch of the fundamental human–Ebola-virus biophysical forces that enable and constrain EVD. Kumar group reported a model of Ebola evading the immune system. What are the factors of the emergence, rapid spread and uncontrolled nature of 2014 virus outbreak? How to treat EVD?

Keywords: Ebola virus disease, seasonal distribution, deforestation, socio-political infrastructure, micronutrient deficiency.

1. INTRODUCTION

Two thirds of human pathogens are of zoonotic origin, *e.g.*, Ebola (identified in 1976), human immunodeficiency virus (HIV). A pathogen spread relies on perpetual contact with new groups of susceptible individuals. Ideal conditions for zoonotic-viruses emergence and spread are socio-economic/environmental changes, long-distance mobility (air travel) and changing climate. Ideas in biology should be valued by number of questions they generate. Questions (Qs), answer (A) and hypothesis (H) on Ebola virus disease (EVD) follow.

Q1. How is EVD contagious?

A1. It passes on by contact with secretions of a patient that be in active phase, *i.e.*, fever.

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Q2. What does it happen at the host/pathogen interface?

Q3. Why are certain viruses capable of jumping to new species?

H1. The genetic plasticity [ribonucleic acid (RNA) polymerase has no proofreading activity and is highly error-prone] is key if the virus is to overcome a host immune attack.

Q4. Is EVD a growing threat?

Q5. What will happen if phase-3 trials have insufficient power to determine efficacy?

Double-stranded (ds)RNA, an intermediate in viral replication, triggers release of cytokines, primarily interferons, which in turn causes upregulation of antiviral genes and antibodies. Viruses developed ways to inhibit interferon response: interferon antagonists [in Ebola, viral membrane-associated (VP24) and polymerase complex (VP35) proteins].

Mas-Coma and González-Candelas raised questions on EVD arrival at Spain on 2014 [1].

Q6. What are causes of the infection?

Q7. What is the risk for the health staff?

Q8. What is the possibility of an outbreak in Spain?

Q9. Is there a possibility that the virus mutate and become its transmission by the air?

Q10. Is it necessary to put to sleep the dogs of infected people?

Martín-Moreno raised the following questions on 2014 EVD outbreak [2].

Q11. What steps must one take before potentially infected people?

Q12. What is the alert level that can have a country as Spain?

Q13. Does the Law of Labour Risks observe the protocol?

Q14. Why has this infection happened?

Q15. What has it happened?

Q16. Was there a human error?

Q17. What health action must be activated after an infection?

Q18. The suits that were used, are the adequate ones for this type of virus?

Q19. Had a suit of higher-level protection better covered the exposure to the virus?

Q20. What information must be provided to worried neighbours?

In earlier publications it was reported anthropoid-apes phylogeny [3], fractal [4]/hybrid-orbital [5] analyses of protein tertiary structure, tumour‑immune cells competition [6], information-entropy classification of molecules [7–9], classification, diversity, complexity and emergence [10–12], periodic classification of HIV inhibitors [13], molecular classifications of thiocarbamates with cytoprotection activity *vs*. HIV [14], styrylquinolines as HIV integrase inhibitors [15] and *N*-aryloxazolidinone-5-carboxamides as HIV protease inhibitors [16], hypothesis on how acquired immunodeficiency syndrome (AIDS) destroys immune defences [17], interrogation of molecular structure [18], hyaluronan as a drug delivery vehicle [19,20]. In the present report, the model of Ebola virus transmission dynamics is reviewed, with the aim to provide a broad sketch of fundamental human–Ebola-virus biophysical forces that enable and constrain EVD.

2. 2014 EBOLA VIRUS DISEASE OUTBREAK

Elena raised the following questions on 2014 EVD outbreak [21].

Q1. Are there equipment and experience needed to treat EVD patients?

Q2. What is a virus?

Q3. What factors do favour the appearance of new viral diseases?

Q4. Why is it difficult to control infections or find vaccines *vs*. viruses-caused diseases?

Q5. How does one interfere a virus without doing anything to the cell?

Q6. Why have people no vaccine?

Q7. Ebola virus was identified in 1976 but, why is the most virulent outbreak nowadays?

Q8. Could the epidemic be spread to Europe?

Q9. Could an epidemic begin?

Q10. Double level. Must one be critical with protocols followed by Spanish Government?

Q11. To put to sleep the dogs of infected people?

Q12. Does it represent a danger or an opportunity?

Q13. Is there the equipment needed to have a dog infected by Ebola?

Q14. Are the media sensationalist?

Q15. Laying on of hands, seawater, essential oils of cinnamon/oregano, Ag^{+} or ozone therapy *via* rectal are some of the supposed cures *vs*. EVD. How must one act *vs*. the calls?

Q16. In who have they tested them?

Q17. With what probability do they function?

Q18. Are people close to eradication of viral diseases or is it a long way to cover?

3. ZOONOSES

3.1. Ecology of Zoonoses: Natural and Unnatural Histories

Karesh *et al*. proposed Qs and Hs on ecology of zoonoses (*e.g*., EVD, original HIV) [22].

Q1. How do zoonotic diseases result from natural pathogen ecology?

Q2. How do other circumstances (*e.g*., animal production, natural-resources extraction, antimicrobial application) change the dynamics of disease exposure to human beings?

Q3. Where does one stand in zoonoses and marginalized infectious diseases of poverty?

Q4. How do these pathogens survive and change?

Q5. Why do pathogens what they do?

H1. H of competitive exclusion. The ecological principle of competitive exclusion is the basis for common approaches to control of zoonotic pathogens in livestock and poultry.

Q6. What techniques are animals slaughtered and processed with?

Q7. How are products stored, packed, transported and prepared at the consumption place?

H2. Antimicrobial-resistance genes originated as evolutionary response to drugs produced by free-living bacteria, fungi and plants to protect from infection or competition.

H3. (Bennett). Resistance patterns and genes are much the same in wildlife and livestock.

H4. Whatever sources of resistant bacteria/genes, differences in wildlife-species ecology (*e.g*., diet, physiology) cause selection pressure on microbes, rather than differential exposure to anthropogenic antimicrobials or presence of different resistant strains in environment.

Q8. Has the use of antibiotics in agriculture exacerbated drug resistance in people?

Q9. What is transfer extent of antimicrobial-resistant organisms from animals to people?

Q10. What is the potential for reversal of resistance?

Q11. Would it occur in clinical settings after a change in antimicrobial use?

H5. Reversion to drug susceptibility depends on occurrence of natural dilution of microbial populations with susceptible strains and fitness costs of resistance.

H6. No approach to search for potential new human pathogens, *e.g*., tracing back source host of a human disease, would identify simian immunodeficiency virus (SIV) as a risk.

Q12. How is the environment changing?

Q13. How do these changes affect microbial dynamics across the system?

H7. Enhancing the role ecologists play in control programmes includes model-outputs production by collaboration with clinicians with real-time data, participation in prospective and retrospective study design, and field studies to identify risk factors to target surveillance.

H8. Disease ecology drives advances in prediction of novel-zoonoses emergence/spread.

Q14. How can dynamics of a pathogen in a wildlife host change seasonally?
Q15. How does it function the microbiome from people?
Q16. How does it function the microbiome from animals they contact?
Q17. What does it cause zoonotic microbes to proliferate in some conditions?
H9. One Health approach provides a wider, holistic view with which to achieve this aim.
Q18. Where do zoonoses occur?
Q19. How do zoonoses occur?

3.2. Drivers/Dynamics/Control of Emerging Vector-Borne Zoonotic Diseases

Kilpatrick and Randolph proposed Hs/Q on control of zoonotic diseases [23].

H1. Climate change leads to more widespread and abundant vector-borne pathogens (VBPs) as more of the planet starts to resemble closely the tropics.

H2. The arrival of exotic and upsurges of endemic VBPs are because of climate changes.

H3. Effects of climate change on VBPs are variable, as expected from complex systems.

Q1. What will global warming do?

H4. Feeding on additional alternative hosts results in risen vector densities, which result in higher transmission even if a smaller proportion feed on people.

H5. Dilution effect. Natural biodiversity diverts vectors from infectious hosts.

3.3. Prediction and Prevention of the Next Pandemic Zoonosis

Morse *et al*. proposed Hs/Qs on prediction/prevention of next pandemic zoonosis [24].

H1. Efforts to co-ordinate global strategy to fight pandemics are timely and important.

H2. Disease emergence is driven by anthropogenic changes, *e.g*., agriculture expansion.

H3. Human populations are exposed to a wide variety of non-human-animal pathogens.

H4. Viruses have the potential to evolve more rapidly than do other kinds of pathogen.

H5. Simple behavioural precautions greatly reduce risk.

H6. Risks to hunters, food handlers and livestock workers from occupational exposure are reduced in hotspots of emerging infectious diseases though routine sanitation and biosafety precautions, as was tried with A/H5N1 flu in agricultural settings.

H7. Nosocomial spread is prevented by infection control practices, *e.g*., sterile injections.

H8. Viral-relatedness analysis as a predictor of emergence. Wildlife viruses that are more closely related to known human pathogens are more likely to infect people than not similar.

Q1. How do viral traits/phylogenetic relations correlate with pathogenicity?

Q2. Why have some pathogens a high propensity for host jumps?

Q3. Why do some viruses that are benign in their natural hosts induce a severe or lethal hyperinflammatory response in a new host (*e.g*., Ebola, sin nombre virus)?

H9. Strong patterns of co-evolution during recent evolutionary time indicate stable long-term interactions with little host-switching, but pathogens that frequently moved from one host to another have poorly aligned co-evolutionary trees.

Q4. How feasible is a programme for identification of the many thousands of novel pathogens that are probably in wildlife globally?

Q5. How to address the underlying drivers that are essentially ecological (*e.g*., livestock production–wildlife populations juxtaposition) or occur on large spatial scales because of economic activity (*e.g*., change in land use related to development of tropical forests)?

Q6. Could the seemingly opposing forces of economic development and public health be reconciled before rather than after these outbreaks occurred?

H10. Expansion of so-called health impact assessments is an approach.

H11. Incentives for industries propagating pandemics is linked to development initiatives.

H12. Efforts to curtail wildlife trade for food and pets in hotspot and other countries include consumers incentives creation that lead to certification of healthy-practices industries.

Q7. Can researchers intervene before a pathogen reaches human population?

Q8. How can researchers intervene before a pathogen reaches human population?

4. VIRAL VIRTUOSOS OF PERSISTENT *VS*. ACUTE INFECTION

Sullivan raised some questions on viral virtuosos of persistent *vs*. acute infection [25].

Q1. How do viruses orchestrate lifelong infections?

Q2. How do human-body viruses use micro (mi)RNAs and their own to infect?

Q3. How could miRNAs/noncoding (nc)RNAs function spawn therapies, while yielding insights into evolutionary forces dictating parasitism/mutualism/multiorganismal relations?

Q4. Does RNAinterference (i) serve as a meaningful antiviral response in mammals?

Q5. How does the human virome contribute to health and disease?

5. VIRUSES AND CELL DEATH PROGRAMMES

Lamkanfi group raised a question on the regulation of apoptosis during infection [26].

Q1. How do viruses evade host cell apoptosis?

Kaminskyy and Zhivotovsky revised/proposed a Q/H on cell-death consequences [27].

Q2. How do viruses interact with the cell death machinery?

H1. Necrotic cell death is regulated by a specific set of signal transduction pathways.

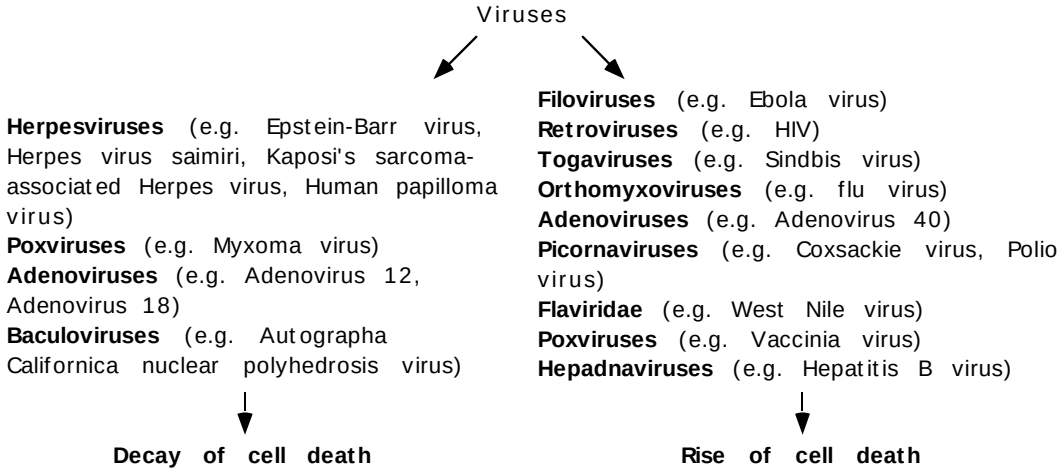
Figure 1 shows cell death-related consequences of viral infection.

Q3. How does the Ebola virus induce massive apoptosis of lymphocytes?

H2. Inflammatory mediators/NO secreted by macrophages induce bystander cell death.

H3. Viral proteins induce lymphocytic cell death.

Figure 1: Cell death-related consequences of viral infection



6. INTRACELLULAR EVENTS/CELL FATE IN FILOVIRUS INFECTION

Mühlberger group proposed Qs/Hs on intracellular events/cell fate in this infection [28].

Q1. What is known about intracellular events leading to virus amplification in infection?

Q2. How may cellular dysfunction and cell death correlate with disease pathogenesis?

H1. Adaptive immune responses may occur.

H2. Lymphopenia from apoptosis contributes to failure to clear infection.

H3. A well-regulated cytokine response early in infection is critical to disease outcome.

Q3. How do filoviruses enter, replicate and assemble exploiting cellular machineries?

Q4. How do filoviruses interact with cellular signalling pathways?

Q5. What is the current understanding of non/infected-cells fate in filovirus detection?

Q6. What changes are in ultrastuctural data of non/infected cells, in infection?

Q7. Why does little or no inflammatory cellular response occur at viral-replication sites?

Q8. What does it happen in the infected cell?

H4. The folate receptor is a significant filovirus receptor.

H5. Thymus-dependent lymphocyte (T-cell) immunoglobulin and mucin domain-1 (TIM-1) is a receptor for Ebola and Marburg viruses type-I transmembrane glycoprotein (GP).

Q9. What is the fate of infected and non-infected cells in filovirus infection?

Q10. How do viruses interact with the cell death machinery?

H6. In extensive filovirus infection, cells are unable to keep a normal water‑ion balance.

Q11. Do filoviruses manipulate signalling pathways in apoptosis or cell survival?

H7. Inhibition of retinoic acid-inducible gene-1 (RIG-I) by VP35 stops apoptosis.

H8. Cells using Toll-like receptors (TLR)-mediated antiviral pathways, *e.g.*, plasmacytoid dendritic cells (DCs), are less prone to the inhibitory effects of VP35 Ebola virus than cells relying on RIG-like signalling pathways.

H9. The GP-induced cytotoxicity is caused by GP‑guanosine-5'-triphosphate (GTP)ase dynamin interaction, interfering with intracellular trafficking of cell surface proteins.

Q12. What is the involvement of dynamin in GP-induced cytopathic effect (CPE)?

H10. Extracellular signal-regulated kinase-2 (ERK2) is involved in CPEs induction.

H11. A mechanism of cytotoxicity is induction of endoplasmic-reticulum (ER) stress.

Q13. Are the different proposed mechanisms to explain GP-mediated CPE connected?

Q14. How are different proposed mechanisms to explain GP-mediated CPE connected?

Q15. What is the ability of GP to induce cell death?

Q16. What does it happen in the infected cells?

H12. Host-derived proteins contribute to cluster of differentiation (CD_4) T-cell death.

H13. An accumulation of incomplete viral transcripts during abortive infection of resting CD_4 T-cells activates intrinsic pathways, which lead to apoptosis during HIV infection.

H14. Generalized mechanisms contribute to lymphocyte apoptosis in filovirus disease.

H15. Both intrinsic and extrinsic apoptotic pathways contribute to lymphocyte depletion.

H16. Loss of lymphocytes contributes to failure to generate adaptive immune responses.

H17. Dysregulated DCs/macrophages contribute in other ways to lymphocyte apoptosis.

H18. Programmed death-1 (PD-1) signalling results in decayed T-cell proliferation because of induction of apoptosis *via* PD ligand-1 (PD-L1) binding.

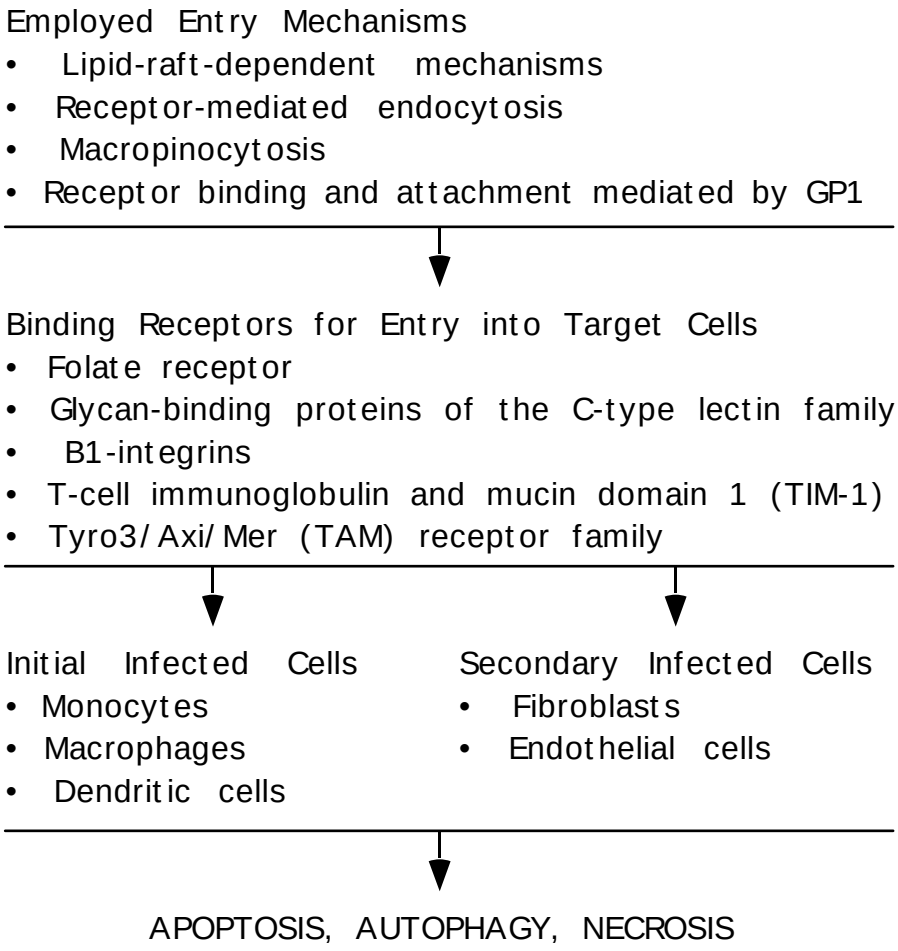
7. EVADING THE HOST'S IMMUNE RESPONSE

Kumar group reviewed emergence of 2014 EVD outbreak and proposed Qs and Hs [29].

Q1. What factors are contributing to emergence, rapid spread and uncontrolled nature?

Q2. How to treat EVD?
Q3. How does the Ebola virus replicate?
H1. Different genes related to early immune response to virus, impart bats resistance.
H2. Bat genes co-evolve with virus genes.
Q4. Could redirection of non/human primates immune system reduce Ebola's death rate?
Q5. Why have bats evolve to resist fatality in the face of the Ebola virus?
Q6. How have bats evolve to resist fatality in the face of the Ebola virus?
H3. The virus strain in 2014 epidemic shows signs of genetic mutations.
Q7. Did Ebola Zaire exist in Africa before 1976, or evade detection and documentation?
H4. All emergences between 1976 and 2005 are descendants of Yambuku-like virus.
H5. The descendents spread *via* outbreak regions.
H6. Ebola Zaire employs a mechanism of spread.
H7. Ebola Zaire-West African virus has a substitution rate 8×10^{-4} per site, per year.
H8. Outbreaks are indeed representative of independent zoonotic transmissions.
H9. The VP24 is critical in contributing to virulence and plays a role in host adaptation.
Q8. How does Ebola evade the immune system?
Mononuclear phagocyte system is the first one to be manipulated by virus (*cf*. Fig. 2).

Figure 2: Ebola evades the immune system



H10. Higher virulence levels exist in initial cases rather than infection successive waves.
Q9. What is the cause for risen initial virulence and subsequent risen chance of survival?
H11. Currently 22 million Central and West Africans are at risk of an Ebola infection.
H12. Previous H. Strain virulence is solely a product of viral genetics.
H13. Socio-political/environmental climates create flux in mortality rates and spread.
H14. The second outbreak was initiated by an ill imam traveling from Guinea to Mali in an attempt to receive better care at the Pasteur Clinic in Bamako.
H15. The 2013-2014 epidemic varies in trends and final outbreak size between Sierra Leone, Guinea and Liberia, which share common cultural and geographical traits.
H16. Bats are natural reservoir of Ebola and have behavioural associations with seasons.
H17. A trigger in the 2014 outbreak is the shift in the seasonal migratory route of bats.
H18. Ebola Zaire virus creates Se demand on infected host, depleting hosts stores in days.
H19. Survival of Ebola virus *via* replication is increased by low Se concentrations.
H20. Disabling T-cell from Ebola Zaire is similar to Se-deficient hosts infected with flu.
H21. Fibrinogen levels, procalcitonin and cross matching of blood assays are unsafe.
H22. Colloid solutions, human albumins and synthetic starches are associated with adverse renal outcomes and provide no benefit to EVD infected patient.
Q10. A dead-end host: Is there a way out?
Q11. Why was not Zmapp made more widely available in Africa?
H23. Ethical H. Administering an experimental drug without safety data is unethical.
H24. An advantage to the blood-transfusion recipient exists if the donor is from the same geographical region as EVD infected.
H25. Health care workers treating EVD outside treatment units are at an increased risk.
Q12. What role should pharmacy play in epidemics like this?
Q13. Ethical Q (EQ)1. Why to transport aid workers to native countries for treatment?
Q14. EQ2. What are the benefit *vs*. risk profiles of experimental therapies?
Q15. EQ3. Is practice of rushing an experimental agent to control an epidemic adequate?
Q16. EQ4. Is drug impact on transmission/containment of an epidemic positive/negative?

8. DISTINCT LINEAGES OF EBOLA VIRUS IN GUINEA: 2014 EPIDEMIC

Simon-Loriere *et al*. raised questions on distinct lineages of Ebola virus in Guinea [30].
Q1. What rate did Ebola virus evolve during the West African outbreak of EVD?
Q2. What may this mean for the virus adaptive capacity, *e.g*., changes in virulence?

9. DISCUSSION

Ebola is a dangerous virus that could cause in people a grave disease, which could reach the dead. The virus comes from Africa, where it causes the greatest problems. The population of the entire world is worried by EVD, and took measures to contain it and trait the persons that be infected. No signal exists that EVD expand widely to other continents. The first time that EVD was described was in 1976 and the most surprising of the virus is that it is aggressive: it has a mortality ranged in 40–90% (in Ebola Zaire strain, 85–95%). In the future, a holistic examination of the full spectrum of viral diversity, not just of the viruses that make humans ill, may be factored into medical decisions; *e.g*., a rise in the levels of a benign persistent virus was suggested as an indicator for monitoring therapeutic immune suppression. Beneficial altering host viral communities, so-called provirotics, could

contribute to improved human health. Advancing the notion will require effort to catalog and exploit the human virome, and decipher the contributions of the humble but elegant persistent viruses (and ncRNAs that regulate them).

Humans are not prepared for viral outbreaks: (1) the state of knowledge about host–pathogen interactions is selective; (2) a deficit of trained medical and scientific personnel delays deployment to the established Ebola treatment centres in West Africa; (3) the public is unaware of the threat of emerging viral diseases. Funding for basic research in virology is insufficient. The Ebola outbreak remembers people that a more thorough understanding of zoonotic viral infections is necessary, especially in the face of the changing environment. Interferon research is an emerging avenue, which helps achieving the understanding and improving the quality of viral infection management.

Genomic surveillance is a complement to local epidemiological research. Deployment of additional next-generation sequencing (NGS) facilities in West African surveillance net, avoiding the logistical and regulatory hurdles associated with long-distance sample transportation, will contribute to control the current epidemic and help limit future outbreaks.

10. CONCLUDING REMARKS

From the present review and discussion the following remarks can be drawn.

1. Safe-practices guidelines, *e.g*., ecology to reduce disease risk, are needed.

2. New understanding of noncoding ribonucleic acids may solve a long-standing puzzle about how viruses orchestrate lifelong infections. Microribonucleic acids can be thought of as tools that viruses use to manipulate key aspects of human biology and immune response, in order to hitchhike with people throughout their evolutionary history. The co-existence of virus and host involves careful control of the viral life cycle: whereas Ebola virus infection is flashy, persistent infection is elegant. Viral microribonucleic acids can optimize the location and timing of virus replication to fly under the radar of the host immune response.

3. Lesson to be learned: How little one knows about why and how certain viruses spill over from their natural hosts, and how they interact with the human immune system.

4. Transmission among humans occurs *via* blood and body-secretions exchange. Triggers in outbreaks are low temperatures, high humidity, seasonal change and its relation with animal behaviours, socio-economic decline leading to deforestation, *etc*. Contributing to success is delayed identification of outbreak, which initially spread unsuspectedly to neighbouring regions. While multiple candidate vaccines and antiviral therapies are in development, preventative public health interventions (*e.g*., risk communication, protective-principles implementation) are a means to mitigate spread of Ebola virus disease.

5. While one is alive, he is subjected to threats, which could kill him. However, to live frightened by the dangers, when the reply does not depend on oneself, is little recommendable. It is essential to get the needed means to control the outbreak in its origin.

6. Trials would need to reassume rapidly when and where the next Ebola outbreak occur.

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