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A potential roadmap to overcome the current eastern DRC Ebola virus disease outbreak: From a computational perspective

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ABSTRACT

The ongoing Ebola virus disease (EVD) outbreak in the eastern Democratic Republic of Congo is raising unprecedented health concerns, with potential to wipe out large proportions of the population in this part of the world. Established control strategies to contain the outbreak are failing due to several reasons, including lack of a data/information repository and ongoing violence and armed conflict. In this paper, we propose a potential roadmap from a computational perspective, which may provide solutions to contain the current outbreak, predict future outbreaks and facilitate development of novel solutions and therapeutics. This roadmap includes the implementation of an integrated information system through a centralized data coordinating center unifying existing and future EVD data and information to enhance innovative EVD translational research. This work will leverage off tools, guidelines and protocols developed by established data coordinating centers based in Africa or centers that address infectious disease outbreaks. The proposed EVD computational strategy is expected to inform optimal strategies at the national or global level towards strengthened responses to future EVD outbreaks and potential emergency of therapy resistant.

Brief EVD outbreak history

Since the discovery of the Ebola virus disease (EVD) in 1976, there have been 27 recurrent sporadic EVD outbreaks in several parts of the African continent. These include the largest outbreak which occurred between 2014 and 2016 in Western African countries, Guinea, Liberia and Sierra Leone, with approximately 11,000 deaths [1]. This 27th Africa outbreak has been

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ongoing since August 1, 2018 and is the tenth Democratic Republic of Congo (DRC) outbreak. This ongoing outbreak has reached approximately two thousand cases [2] with a fatality rate of 67% and is affecting the North Kivu and Ituri provinces in DRC (https://www.cdc.gov/vhf/ebola/outbreaks/drc/east-drc-map.html). This situation has raised an unprecedented health concern for this part of Africa, with the potential to wipe out large proportions of the population. Considering the psycho-socio-environmental context driven by community violence and armed conflict [3], it seems impossible to break the disease transmission and contain this outbreak. This led the World Health Organization (WHO) to declare this EVD outbreak a public health emergency on July 17, 2019 [4]. Strategies to curb and eradicate the Ebola virus (EV) have thus far, not been as effective as expected. Thus, this outbreak may become the worst ever in the EVD history. The EV infection progresses rapidly to disease, with an incubation period ranging from 2 to 21 days. This virus replicates at an unusually high rate, defeating the anti-viral immune mechanisms of host cells and leaving the host with a very small opportunity to develop acquired immunity [5]. The disease is spread through human-to-human transmissions, which leads to epidemics with an average fatality rate varying from 25% to 90% to date [6].

Computational approaches to EVD management, prevention and control

Several mathematical models have been developed to understand EVD transmission dynamics in a population [7]. These models focus on estimating the epidemiological index or basic reproduction number (R_0), predicting the disease evolution and assessing the effectiveness of management, prevention and control measures to help public-healthcare policy makers in decision making. Commonly implemented models consist of three or four compartments: susceptible (S), exposed (E), infectious (I) and recovered (R) individuals, known as SIR or SEIR [8]. Generally, these models are extended to include other aspects, such as case isolation or quarantine [9], vaccination [10,11], asymptomatic immunity [12], uncertainty around the epidemiological index [13]. However, the effectiveness of these models are compromised as they are simulation based [14], i.e., they rely on guessing parameters instead of estimations based on real datasets. Thus, there is need to use data-driven approaches which enable the estimation of parameters that best fit data for more accurate predictions of EVD related health-care and health impact.

At the molecular level, the release of the complete EV genome [15] was a big step towards providing valuable insights into the EV dynamics driving its pathogenic mechanisms and numerous virulence factors. This shed light on the specific mechanisms underlying its transmission and evolution. The use of genomic computational models revealed a rapid accumulation of EV inter-host and intra-host genetic variations. These analyses detected multiple non-synonymous mutations that alter protein sequences and established a catalog of 395 mutations, including 50 fixed non-synonymous changes with 8 at positions with high levels of conservation across EVs [16]. A functional enrichment analysis was performed [17] to enable the identification and validation of EVD targets. Furthermore, a restricted survival analysis based on the patient transcriptomic profiles was conducted to identify early stage host factors that are associated with acute illness and those that differentiate patient survival from fatality [18]. However, there are no longitudinal EVD cohort studies aimed at identifying differentially expressed genes at each stage of the disease to enhance the current EVD diagnosis, prognosis analysis and treatment strategy.

EVD translational research outcome: EVD prevention and therapy

EVD was identified by WHO and global experts as a priority "Blueprint" for research and development given its ability to cause public health emergencies [19]. Since the western Africa epidemic in 2014–2016, remarkable translational research progress has been made, a new EVD vaccine, namely recombinant vesicular stomatitis virus–Zaire Ebola virus (rVSV-ZEBOV) [20], and several drugs, including Remdesivir, ZMapp, REGN-EB3, mAb-114 and favipiravir [21], have been developed for prevention and treatment. These EVD drugs were tested in a clinical trial or will be tested after safety checks and risk assessments by the WHO and other experts. The assessment of efficacy and safety of antiviral drugs, Remdesivir and Favipiravir is still needed in appropriate randomized controlled trials [22]. These drugs should be used only in absence of monoclonal antibody-based drugs: ZMapp, REGN-EB3 and mAb-114. Currently, EVD seems to be treatable using two drugs REGN-EB3 and mAb-114 which have 90% efficacy. A clinical trial with 700 participants which supported the efficacy of REGN-EB3 and mAb-114 also concluded that two other drugs, namely ZMapp and Remdesivir, be discontinued [23]. Initially there was some evidence on the efficacy of ZMapp for the EVD treatment, based on an under-powered clinical trial. However, its use in low-resource settings was also limited by the temperature sensitiveness of the drug, it required negative 20 °C during distribution and storage [24]. The availability of these new drugs with minimal logistical requirements could change the state of the ongoing outbreak and the future of EVD.

A computational drug repurposing study [17] has predicted the potential effectiveness of monoclonal antibody approved drugs such as infliximab, adalimumab and golimumab for EVD treatment. These drugs are categorized as anti-inflammatory agents, tumor necrosis factor (TNF) and TNF-alpha inhibitors. In addition, anti-inflammatory, anti-malarials and amebicide-related drug, namely chloroquine, was predicted as drug therapy due to their similarity to human proteins associated with EVD. These human proteins include Probable ATP-dependent RNA helicase DDX58 (DExD/H-Box Helicase 58); essential human protein interacting with EV 'matrix protein' VP40, one of the targets of the EVD vaccine, rVSV-ZEBOV. VP40 is an essential EV protein that ensures structural integrity of the virion, promoting virus assembly and virus budding from the infected host cell [25]. VP40 has been predicted to interact with host proteins [17], regulating viral transcription inside the infected

human cells [26] with the ability to release itself from the cells even in the absence of other viral functional proteins [27]. Successful computational drug repurposing that targets VP40 could be a breakthrough for EVD control and eradication.

Major progress has been achieved towards providing valuable insights into EV pathogenicity, transmission mechanisms and virulence factors. Advances in genomics have enabled the EVD genetic epidemiology for genomic surveillance and EV evolution [15]. However, four decades of efforts are still challenged by the violence and armed conflict. In addition, there are high chances of therapy resistance due to rapid EV evolution. The main question is: What should be done now to contain the ongoing eastern DRC EVD epidemic as implementation of lessons learnt are compromised by the ongoing conflict? How best can existing research data and sequences be catalogued for research to curb future outbreaks and promote development of new therapies which are required due to the viral evolution which may lead to therapy resistant strains?

Current EVD outbreak challenges and potential roadmap to optimal solution

Based on EVD outbreaks, especially the 2014 western Africa outbreak, we learnt lessons and strategies to control person-to-person transmission and contain EVD outbreaks. There is increased awareness of the disease signs and symptoms, early diagnosis and symptomatic individual isolation, and tracing and monitoring contacts [1]. However, realization of the true impact of experiences and lessons acquired during the past four decades are challenged and compromised by the prevailing political situation and humanitarian crisis. This complex humanitarian crisis is characterized by violence and armed conflict [3] associated with attacks on health-care centers and workers, patients, and local mistrust and internal population displacements. This EVD outbreak is just another complex public health concern on the top of a risk factor in public health emergencies, which is violent conflict zone. This conflict is the particularity of this EVD outbreak and the biggest impediment to the existing control strategies.

Research on the knowledge, attitudes and practices in EVD affected populations have revealed that displaced populations are more susceptible to the EVD and other infectious diseases [1]. Considering the high acceptance of the new vaccine, rVSV-ZEBOV, and its efficacy [6], vaccinating displaced populations and awareness should be prioritized. Additionally, since the EVD initial signs and symptoms are often mistaken for malaria, we suggest that an anti-malaria drug, chloroquine, predicted as a potential drug for treating EVD [17], be initiated immediately in combination with analgesics [28] while waiting for a confirmed EVD diagnostics. For the mistrust and unwillingness to report EVD cases, community targeted health education initiatives and advocacy-patient engagement are needed. We also recommend that human health organizations update existing guidelines and protocols to inform ethical and culturally respectful engagement of communities by healthcare workers assigned to outbreak zones.

Future of EVD outbreaks and perspectives

The eastern DRC EVD outbreak seems to be a lost battle evident from the increasing average fatality rate [2] despite the availability of medical therapeutic and preventive tools, as never before in the history of the EVD outbreak. However, with the advent of new treatment and prevention options, EV infections should now evolve from an alarming public health emergency to a manageable disease. This should lead to an optimal control of the spread of new infections to achieve full epidemic control with reduced risk of transmission. There should be more efforts into ending the armed conflict given the complex environment created by this conflict in responding to the current EVD outbreak. The Congolese government, the United Nations (UN) Security Council's and other stakeholders' mandate to keep international peace and security in this part of the world have never been more challenged than now.

Finally, we propose strengthening health and research systems through Information and Communication Technology Services (ICTS) and multi-disciplinary collaboration. Such ICTS systems have potential to yield greater results especially if each outbreak is not considered as an isolated one-off event. Thus, we propose the implementation of a sustainable and integrated information system and a centralized data coordinating center unifying existing EVD information. This ICTS system intends to make existing EVD data, findable, accessible, interoperable and reusable (FAIR). Such data includes experimental, clinical and genomic (genetic and expression data), as well as environmental data. Making data publicly available has potential to enhance innovative EVD translational research by supporting the design of novel computational tools or pipelines. More importantly, knowledge and lessons learnt from different EVD outbreaks could inform policies, protocols and programmes. Such a strategy has potential to facilitate research towards improving existing experimental drugs and vaccine candidates as well as developing rapid diagnostic tools.

Building such ICTS portals comes with numerous ethical, legal and social implications (ELSIs) including informed consent, privacy and data sharing, benefit sharing and intellectual property. Adapting existing Africa-centric ELSI protocols and procedures would save efforts and funds [29,30]. Other lessons that could be learnt from existing data centers include the use of ontologies to facilitate harmonization of existing data and prospective across different sites [31]. To keep costs to a minimal and to tailor the ICTS solutions to low-resource settings such as Congo, the proposed EVD coordinating center could make use of mobile phone-based technology whose effectiveness is well-established. An example is a mobile SMS-based disease outbreak alert system which was shown to be effective in improving disease outbreak alerts in Kenya based on a randomized trial [32].

Conclusion

Over four decades of enduring the EVD outbreaks has resulted in enormous amount of data generated at different levels. These datasets have been translated into evidence-based outbreak responses and EVD targeted therapies. Thus, it is important to design an open-source and FAIR centralized knowledge-based system which includes up to date data and cutting edge methods to enable collaborations, effective leadership and efficient coordination of health services. This system is expected to be a research interface that informs optimal strategies at the national or global panel level, providing information on new EVD therapy options and data to policy makers to strengthen responses to future EVD outbreaks and potential emergency of therapy resistant EV.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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