Review

ANNALS OF MEDICINE & SURGERY

OPEN

National burden of Ebola virus disease in Democratic Republic of the Congo: the urgency to act

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Abstract

Ebola virus disease (EVD) has long been a major public health concern for Democratic Republic of the Congo (DR Congo). First identified in DR Congo in 1976, the country has witnessed more than 25 outbreaks of this deadly disease, which has a case fatality rate of nearly 90% and manifesting with symptoms such as diarrhoea, vomiting, stomachache and haemorrhagic fever. African fruit bats have been speculated to be the reservoir of this virus. DR Congo is currently facing another EVD outbreak simultaneously with other communicable diseases, rendering it vulnerable to a shortage of medical and paramedical staff along with distrust among remote communities towards local authorities due to armed conflict and political instability. Moreover, lack of ring vaccinations and inefficient surveillance of suspected individuals are some other significant hurdles in disease control. Despite the availability of rVSV-ZEBOV/Erbevo vaccine and many antibody-based vaccines, challenges including politicization, low access to remote communities, and illiteracy have limited their effectiveness. Recently, the Congolese govt. has put in efforts such as building local capacities at the health zone level, outbreak control intervention, community engagement and social mobilization to counter the rising EVD cases. Four successive Strategic Response Plans have been implemented to increase resource mobilization by DR Congo and her partners. The Spread of zoonotics such as EVD can be confronted by implementing the One Health approach, which involves medical staff, veterinarians and public health officials.

Keywords Democratic Republic of the Congo, disease, Ebola virus disease, epidemiology, risk factors

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2024) 86:4579–4585

Received 9 March 2024; Accepted 15 May 2024

Published online 21 June 2024

http://dx.doi.org/10.1097/MS9.0000000000002213

Introduction

The Ebola virus (EBOV) is the most prominent member of the *Filoviridae* family of viruses[1]. The *Filoviridae* is segregated into three different genera: EBOV, Marburg virus, and Caevavirus[1]. Five individual species have been categorized in the genus EBOV: Zaire EBOV, Sudan EBOV, Taï forest EBOV, Bundibugyo virus and Reston EBOV represented by EBOV, Sudan virus (SUDV), Taï forest virus, Bundibugyo virus (BDBV) and Reston virus, respectively[2]. EBOV has a thread-like virion that can change shape to circular or filamentous forms. These filaments can vary in length and structure, appearing as long or short, branched or unbranched, and forming configurations like "6" and "U". The viral genome is 19 kb long, consisting of non-segmented negative sense (NNS), single-stranded RNA encoding seven genes. Each gene, except for glycoprotein (GP), has a single open reading frame (ORF), while GP has three overlapping ORFs. During assembly, viral RNA forms a ribonucleoprotein (RNP) complex with NP, L, VP30, VP35, and VP24, creating a helical nucleocapsid (NC) that protects the viral RNA from degradation by host immune responses and endonucleases[3]. For the past several years, EBOV, SUDV and BDBV have caused EVD outbreaks with rising frequency and case fatality rates from 30% to 90% in central and west Africa[1]. In 1976, EVD was identified for the first

time following two simultaneous outbreaks in South Sudan and Zaire (now the Democratic Republic of Congo)[4]. Since then, more than 25 outbreaks of EVD have been reported, the majority being reported in central Africa[4]. Prior to 2010, EVD outbreaks were in the form of relatively small number of cases, mostly in far-flung and rural areas, which were successfully and timely contained by basic public health and quarantine measures[4].

As of May 2022, 13 EVD outbreaks have been witnessed in Democratic Republic of Congo (DR Congo). 2018 was the year that marked Ebola's largest outbreak in DRC[5]. Ever since, several international bodies such as the WHO, Center for Disease Control and Prevention (CDC), and United Nations International Children's Emergency Fund (UNICEF) have worked in liaison with the Congolese Government to eradicate the Ebola outbreak-which has now been classified as a Public Health Emergency of International Concern[5]. Despite the introduction of control measures to stop the further spread of EVD by Ministry of Health (MoH) and WHO and investment of more than 1 billion dollars by the international community for EVD from 2018 to 2020, 3481 confirmed EVD cases and 2299 deaths were reported[6]. This fact reflects the economic and social burden of the largest Ebola outbreak in the country's history, both on the international community and the nation itself. Worthy to mention are some costly interventions such as Rapid Response Teams (RRTs) and EVD case management[6]. But for a conflict zone like DR Congo, burdensome expenses in such serious epidemics, like staff salaries of members of RRTs along with the security provided to each team, have long-lasting consequences on the economy and financial stability. This narrative review highlights the pivotal measures that should be undertaken by the Congolese government as well as the international community to minimize the national burden of EVD both in terms of monetary and social aspects (Table 1).

HIGHLIGHTS

- Ebola virus disease, an enveloped virus with a single-stranded, negative sense RNA genome of ~19 kB, is the most prominent member of the *Filoviridae* family of viruses.
- The first cases of Ebola virus infection were reported in Zaire (now DR Congo) in 1976.
- Collateral efforts and stringent measures must be taken at both global and national levels to eradicate the disease from the country.

Main text

Epidemiology and burden of EBOV Disease in DR Congo

The first cases of EBOV infection were reported in Zaire (now DR Congo) in 1976. These cases consisted of about 318 reported cases and 280 deaths, having a case fatality rate of 88%. The use of contaminated needles in an outpatient clinic at Yambuku Mission Hospital was found to be originally responsible for this outbreak. The most common culprit of EBOV outbreaks has been Zaire EBOV species of EBOV. The Zaire EBOV caused the disease outbreak in West Africa from 2014 to 2016. The Zaire EBOV had a case fatality rate of up to 90% in previous outbreaks[7].

The specific host reservoir of EVD remains to be determined. After the first discovery of EVD, investigations targeted animals, plants and insects as possible reservoirs. Although primates and other animals were involved in the initial cases of EVD and the host reservoir has not yet been confirmed by scientists, African fruit bats are highly likely to be the candidate reservoir[8]. For instance, the 2014 outbreak of EVD in West Africa began when a 2-year-old boy had a single zoonotic spillover event from fruit bats[9]. In DR Congo, cases have been reported where people became infected with EVD while handling chimpanzees, gorillas and antelopes. The virus can penetrate the body through nose, mouth, ears or eyes as well as wounds or mucous membranes. Studies have shown that the virus has the capability to thrive in bodily fluids such as semen, vaginal fluids, sweat, aqueous humour, urine and breast milk of people who have recovered from the disease[9].

EVD manifests initially with flu-like symptoms, stomachache, diarrhoea and vomiting, followed with unexplained profuse bleeding because of damaged blood vessels, eventually resulting in high mortality. This bleeding is characteristic of EVD, which is termed as Ebola haemorrhagic fever. Recent outbreaks of EVD have been of large magnitude due to the current nature of global trade and tourism, which has led to a higher risk of spread to other continents[9]. The DR Congo has also recently eluded a Marburg virus outbreak. It has shares some clinical features with EVD, such as flu-like symptoms, vomiting and severe haemorrhagic fever; but there are also key differences in their clinical presentation. Marburg virus presents with high-grade fever, severe headache, and weight loss in the early (generalization) phase of the disease, which can progress to cause encephalitis, confusion and melena in the early organ phase, which can lead to convulsions, severe dehydration, and orchitis in late organ phase. Potential complications of the late organ phase include arthralgia, hepatitis, asthenia and even psychosis[10].

Being suffered from multiple large-scale EVD outbreaks, DR Congo has also been heavily impacted with COVID-19 and cholera simultaneous to the EVD outbreaks. This has compromised the country's control efforts to rapidly detect and tackle new EVD cases. In the past, a deep mistrust towards local authorities fuelled by political instability and armed conflict has been the major hurdle in reducing EVD outbreaks in the country. The DR Congo's public health infrastructure is clearly vulnerable to endemics such as EVD thanks to a hostile climate, deplorable road networks, merciless terrain of vast rainforests and extreme poverty[11].

Table 1

Summary of major Ebola virus outbreaks in the Democratic Republic of Congo

Year	Location	Cases	Deaths	Case fatality rate (%)
1976	Yambuku	318	280	88
1977	Tandala	1	1	100
1995	Kikwit	315	254	81
2007	Mweka	264	187	71
2012	Isiro	57	29	51
2014–2016	Various locations	66	49	74
2017	Bikoro, Iboko, Mbandaka	54	33	61
2018	North Kivu, Ituri	3,470	2,287	66
2021–2022	North Kivu, Ituri, Equateur	174	122	70

A cross-sectional study conducted on 144 EVD survivors in 2019 found that 1/4th of them suffered from post-traumatic stress disorder and the same proportion of them suffered from depression. Furthermore, 1/3rd of the study participants were anxiety patients. This implies that EVD not only depleted the financial and medical resources of DR Congo, but also brutally challenged the mental health and well-being due to the stigma associated with the disease[12].

Consequences and complications in eradicating EVD in DR Congo

The WHO and MoH have worked tirelessly in the eradication of EVD, but despite international public health initiatives and a vastly increasing vaccination campaign, the EVD epidemic in DR Congo remains uncontrolled. Insecurity in the region and with persistent acts and threats of violence towards healthcare members have suspended case findings and belated isolation of cases, tracing of contacts, the possibility to ensure safe and honourable burials and ring vaccinations essential for the epidemic control. This delay in the implementation of control measures has led to a continued rise in new confirmed cases over the years[13].

The predictions of a mathematical model developed by Wells *et al.*[14] suggest that a one- or two-week delay in ring vaccinations decreases the effectiveness of vaccines to ward off new cases by a whopping 50–80%, respectively. An additional challenge is that EVD survivors may require subspecialized services such as ophthalmic care and mental healthcare, which is not readily available in DR Congo[15].

A study estimated the monetary value of human losses in DR Congo from 8 May 2018 to 27 May 2019 to be Int$13 801 per death. As 1286 deaths related to EVD were reported, one can easily gauge the enormous loss of human lives in terms of money[16].

This fact also helps us to estimate how much human loss can be prevented by strengthening national health system including the disease surveillance system. In addition, EVD outbreaks put a huge stress on the country's health system, which ultimately results in decreased access to and utilization of health services. Hence, eradication of EVD in DR Congo will relieve the stress on the national health system and enable the country to treat other infectious diseases such as malaria and more importantly, COVID-19[17]. Moreover, EVD eradication will also alleviate the burden of mental health disorders on healthcare system that were a product of stigma associated with EVD[12].

Vaccination and treatment status of EVD in DR Congo

The two most promising candidates of being the EVD vaccine are the rVSV-ZEBOV/Erbevo vaccine and Zabdeno vaccine. The rVSV-ZEBOV/Erbevo vaccine is a live, attenuated recombinant vesicular stomatitis virus-based vector expressing the envelope GP gene of Zaire EBOV. On the other hand, the Zabdeno vaccine is a monovalent replication-incompetent adenoviral vector serotype 26 (Ad26) vaccine, which encodes the full-length GP of the EBOV Mayinga variant. The rVSV-ZEBOV/Erbevo vaccine has been approved by US Food and Drug Administration (FDA) in December 2019 and indicated for the prevention of EVD in adults $\geq$ 18 years. It is given as a single dose and protects against Zaire EBOV, which has been responsible for the most destructive EVD outbreaks till date[4].

History has witnessed several barriers to Ebola vaccination such as inadequate knowledge and politicization of EVD, doubts regarding vaccination efficacy and necessity, and safety concerns[18]. Despite these obstacles, in the epidemic from 2018 to 2020, over 250,000 doses of the rVSV-ZEBOV vaccine have been administered via a ring vaccination protocol, and WHO has revealed no incident of death among vaccinated individuals who manifested EVD 10 or more days after vaccination[19]. An emergency stockpile of 500 000 Ebola vaccines funded by Gavi is currently in progress, which will be available to countries in case of an outbreak. Most importantly, the primary focus of the vaccination were healthcare workers because it provided the dual benefit of protecting the frontline warriors and also increased the likelihood of heathcare workers to motivate others to take the vaccine[18].

A peculiar fact regarding the vaccination campaign in DRC was that pregnant and lactating women were deliberately ignored till June 2019, after which the rVSV-ZEBOV vaccine was approved by the DR Congo's MoH for administration to pregnant women after their first trimester of pregnancy and to lactating women only if they were identified as case contacts[20]. The PALM (Pamoja Tulinde Maisha) trial compared ZMapp (a triple monoclonal antibody agent) with three newer investigational agents that is remdesivir (a nucleotide analogue RNA polymerase inhibitor), MAb114 (a single human monoclonal antibody derived from an Ebola survivor), and REGN-EB3 (a coformulated mixture of three human IgG1 monoclonal antibodies). The patients were assigned in a 1:1:1:1 ratio to receive the above-mentioned pharmacological agents. All individuals including pregnant women who had a positive result on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay within 3 days before screening and had not received any of the investigational agents within the past 30 days were enroled in this trial[21]. The PALM trial has proven that both MAb114 and REGN-EB3 were superior to ZMapp in reducing mortality from EVD. It means that antibody-mediated protection from mortality demonstrates the therapeutic effectiveness of these antibodies targeting the glycoprotein of Zaire EBOV. The PALM trial also showed the importance of early diagnosis and treatment with respect to mortality[21,22].

The mainstay of the management of EVD is supportive treatment, which includes maintaining hydration, electrolyte balance, and oxygen levels, as well as treating symptoms such as pain, fever and nausea. The management of Marburg virus is similar to that of EVD, as it also relies on symptomatic management as well as supportive treatment. Over the past years, antibiotics, antipyretics and steroids have been utilized in outbreaks as supportive methods. However the key difference in the management of both viral diseases is the availability of effective vaccines. The vaccines designed to prevent Marburg virus infection, like cAd3 and MVA-BN-Filo, are still in experimental phase; whereas a variety of vaccines for EVD have been introduced into the market and have been utilized to vaccinate high-risk groups in DR Congo[10].

Strategies, efforts and health implications to fight EVD in DR Congo

After the recurring EBOV outbreaks in the DR Congo, the Ministry of Health (MoH) in the DR Congo and the WHO worked to put in place strict measures to contain the virus. Efforts

such as building local capacities at health zone level, outbreak control intervention, community engagement and social mobilization were put in place. Key to note was that after the MoH in the DR Congo announced a new confirmed case of EVD in the city of Beni, on 21 August 2022.

The following EVD interventions were put in place:-

- Strong engagement with communities focusing on EVD prevention, early recognition of symptoms and care seeking and vaccination.
- Case investigations, active case search and contact tracing activities.
- Re-activation of the alert system.
- Activation of points of control at key border crossings.
- Strengthening, as needed, the functional laboratory in Beni.
- Preparation for ring vaccination using the Ervebo licensed vaccine and targeting contacts of the confirmed case and their contacts along with frontline workers. The International Coordinating Group for Vaccine Provision approved the use of the remaining doses available in country. Vaccines are being shipped to Goma and Beni and ultra-cold chain being assessed and set-up as needed.
- Treatment course of monoclonal antibodies is available in country.
- Ongoing assessment and rehabilitation of Beni Ebola Treatment Centre and strengthening of screening, triage and isolation capacities of other health facilities.
- Infection Prevention and Control measures have been initiated and include decontamination of health facilities, assessment and support to health facilities and training of healthcare workers on implementation of IPC measures, and water and sanitation rehabilitation.
- Capacities for safe and dignified burials are being assessed[23].

Efforts have been seen in the research for more vaccines and treatments for other types of Ebola. Currently, there is an effective vaccine for the Zaire type of Ebola found mainly in Guinea and the DR Congo[24].

In addition to these, there has been an increase in resource mobilization by the DR Congo and her partners in responding to EVD. This was seen in the Strategic Response Plans. The initial strategic response plan (SRP-1) covered the period up to in October 2018, and then the second strategic response plan (SRP-2) for the period from October 2018 to January 2019 facilitated the deployment of the important resources of the Congolese Government and its partners. The third strategic response plan (SRP-3), which covered February through end of July 2019, considered the salient points and recommendations made during the operational review of the implementation of the SRP-2 and other guidance based on lessons learned and risk analysis[25]. SRP-1 aimed at rapid response, SRP-2 aimed at geographic containment, while SRP-3 aimed at building trust and breaking the vicious cycle[26]. SRP-4 analyzed strengths and weaknesses of SRP-3 then came up with a more defined approach to combat Ebola in these 3 main axes: Essential services of the response; Coordination; Administrative, financial and logistical support for Coordination[27].

The Implications of Ebola on the health status in DR Congo was so great it could not go without being noticed. This outbreak crippled the health system of eastern DR Congo and its ability to fight other disease outbreaks like malaria and measles, posing a potential global health security problem if DR Congo's health systems aren't strengthened[28]. Healthcare workers got attacked and 450 violence cases were reported against healthcare workers hence reducing the service delivery to the people[29].

One notable effect of Ebola is that, once an outbreak occurs, most focus shifts to it and many other preventable deaths occurs, especially those affecting children under 5 years. We definitely cannot deny the grave effects of Ebola on how fast it kills and spreads. Ebola has killed about 15 266 people globally since 1976. Most recently, 2267 people have died in the DR Congo. However, these numbers pale in comparison to the under-5 deaths globally and in the DR Congo over the same period[30].

EBOV disease and one health approach

One Health is an interdisciplinary, collaborative effort to attain optimal health for people, animals, and the environment. According to WHO, One Health is "an approach to designing and implementing programs, policies, legislation, and research in which multiple sectors communicate and work together to achieve better public health outcomes"[31]. Since time immemorial, the fields of human and animal medicine have been closely interlinked[32].

Newly emerging infections that are transmitted from animals to man known as zoonotic have been on the rise, for instance: EBOV. Most of these infections have their origins in animals, particularly in wild animals[33].

To understand and comprehend the ecology of each disease, a collaborative, interdisciplinary approach that involves environmental, human and animal health is required[34]. EBOV is a zoonotic pathogen that is transferred between man and animals thus highlighting the need for a comprehensive One Health approach to understand and control the transmission of the virus[35].

The One Health approach emphasizes the impacts, reactions, and measures taken at the interfaces between animals, humans, and ecosystems[36]. A crucial step in One health approach in setting public and animal health priorities and evaluating the success of prophylactic and control strategies involves properly measuring the burden of zoonotic diseases. The interdependent nature of animal, man and environmental health, emphasizes the inefficacy of a disjointed approach in combatting diseases, such as Ebola.

Several factors that influence this inter-relationship include demographics, ecology, behavioural and socioeconomic changes, and civil conflicts in this particular region of eastern DRC. Improved coordination among key ministries (health, livestock, fisheries, wildlife, environment, disaster response, and partners) guided by the One Health approach is necessary to match responses to disease ecology[37].

Successfully implementing the One Health approach also requires a global network of qualified individuals working locally, regionally, nationally and internationally to share information, conduct disease surveillance in human and animal populations, monitor the environment, improve food safety and security, and communicate effectively to the public. National and regional public health sectors should give priority to deploying surveillance systems and enhanced diagnostic tools regarding emerging pathogens. A broad collaboration among clinicians, public health workers, veterinarians, and veterinary public health officials is necessary for prompt response strategies and ensuring the prevention and management of zoonosis. The ongoing EVD outbreak in eastern DRC gives an insight into the integration of

the One Health approach into the implementation of infectious diseases control programs in DR Congo[38]. It is also worthy to note that chatbots are becoming more prevalent in medical education, especially during the COVID-19 lockdown, with ChatGPT emerging as one of the most sophisticated AI-driven chatbots. These chatbots and models based on GPT(Generative Pretrained Transformer) technology can greatly influence the learning and comprehension of veterinary anatomy. Understanding of veterinary anatomy of animals that is reservoirs that host the EBOV can enhance our comprehension of transmission and infectivity of virus[39].

Recommendations, challenges and the way forward to fight EVD in DR Congo

The first and foremost recommendation that needs to be put into action for the eradication of EVD is strengthening the surveillance systems that are critical for timely detection and swift containment of EVD outbreaks. This can be done by utilizing technological advances to support decentralized diagnostic testing capacity near the point of patient care[40]. Swift isolation of infected individuals to minimize onward transmission is only possible by early diagnosis. However, poor infrastructure and lack of resources in remote areas are major hurdles in establishing robust surveillance systems. Underdeveloped healthcare infrastructure and the issue of accessibility to remote communities impede timely detection and reporting of EVD cases[41].

Targeted vaccination campaigns can help limit the propagation of EVD and protect high-risk populations such as healthcare workers and frontline responders. In order to maximize the impact of vaccination efforts, it is critical to prioritize high-risk areas as well as ensure equitable vaccine distribution. But implementation of vaccination campaigns on such a large scale in a resource-limited country is hindered by the limited vaccine supply, logistical constraints and hesitancy of individuals to get vaccinated. It is also crucial to realize that in practical terms, as in case of SARS-COV-2, achieving herd immunity against EBOV is possible through vaccination rather than natural infection. However, it's essential that people who have recovered from the virus continue to follow mitigation measures just as diligently as those who haven't been exposed but are at risk[42]. The key challenges the government faces in achieving herd immunity against EVD are overcoming community skepticism, addressing safety concerns regarding the vaccine and affirming required vaccine coverage in remote areas of the country[43]. In addition, the underutilization of artificial intelligence to inculcate travel medicine at airports throughout the country is a great limiting factor in containing the spread of EVD across borders[44].

There is also an urgent need to implement safe and dignified burial protocols with trained burial teams using suitable personal protective equipment, which significantly lessens the possibility of EVD transmission during burials. But before this, we must promptly educate communities about the hazards associated with traditional burial practices that involve contact with bodies of people who died from EVD. For preventing nosocomial transmission of EBOV, strict infection prevention and control measures, including hand-hygiene protocols, necessary use of personal protective equipment and environmental decontamination, are crucial[45].

It is also imperative to engage communities by means of communication strategies that adhere to cultural norms for promulgating awareness about EVD transmission, symptoms and prophylactic measures. Risk communication messages should be modified to address regional beliefs and practices to help gain community trust and enhance active participation of the population in efforts of outbreak response[46–48]. But several factors such as overcoming mistrust, misinformation and fear within communities mount huge challenges to effective risk communication. Linguistic barriers, cultural and tradition differences, and scarce access to communication channels undermine efforts to disseminate accurate information and encourage community involvement in EVD prevention and control[46,49,50].

Apart from the aforementioned recommendations and challenges to fight EVD in DR Congo, there is also an urgent need improve coordination and cooperation among government agencies, international organizations, NGOs and local stakeholders for optimal allocation of resources, collective efforts, address logistical and operational gaps. In addition, it is also essential to collaborate with the neighbouring countries to facilitate cross-border surveillance. Moreover, the concerned authorities must also provide psychosocial support services to affected individuals and their families to address the trauma and stigma related to EVD outbreaks. There is also a dire need to foster research initiatives to improve understanding of different aspects of EVD such as transmission, immunity, diagnostics, therapeutics and vaccines[51–54].

Conclusion

It is the need of the hour for the Congolese government and global stakeholders to take stringent measures to eradicate the disease from this war-torn and underdeveloped country, as it cannot bear the healthcare and economic burden of another major EVD outbreak. It is imperative for healthcare authorities to devise systems for timely detection of infected individuals and restrict the spread of this deadly virus. There is an urgent need to launch a vaccination campaign that effectively encompasses all the high-risk communities of DR Congo. It is also essential to realize the importance of One Health approach in uniting medical professionals, veterinarians and public health authorities in order to handle the outbreak at a multi-faceted level. The Congolese government and MoH must take concrete steps to put an end to further EVD outbreaks, in a time when the burden of other communicable diseases such as AIDS and recently, COVID-19 is also alarmingly high. The most crucial factor in the rehabilitation and recovery of EVD patients is to promote public education regarding the virus and strengthen the health infrastructure and economic stability of the outbreak-stricken country.

Ethical approval

Ethics approval was not required for this review.

Consent

Informed consent was not required for this review.

Source of funding

The authors did not receive any financial support for this work. No funding has been received for the conduct of this study.

Author contribution

All authors contributed equally.

Conflicts of interest disclosure

The authors declare that there no conflict of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Aymar Akilimali.

Data availability statement

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed

Acknowledgements

The authors thank the direction of Medical Research Circle (MedReC) and the Standing Committee of Research and Exchange (SCORE) of the Medical Student Association (MSA) of Democratic Republic of the Congo for the realization of this present paper.

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