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SHORT COMMUNICATION

# Multi-Pathogen Innovative (5 in 1) Vaccine for Viral Haemorrhagic Fevers will Save More Lives

## *Un Vaccin Innovant Multi Pathogène (5 in 1) Contre les Fièvres Hémorragiques Virales Permettra de Sauver Plus de Vies*

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**ABSTRACT**

Mankind has developed strategies to mitigate calamitous pandemics, by using vaccines. Eradication of some diseases was successful through usage of vaccines. Lassa, Yellow, Crimean-Congo, Marburg and Ebola viruses need special attention. Lassa fever, that now has a candidate vaccine, was discovered in 1969 when two missionary nurses died in Nigeria, while Yellow fever has a vaccine from its 17D attenuated strain. Crimean-Congo haemorrhagic fever is a widespread tick-borne viral disease, and the nucleoprotein and glycoproteins are identified for inclusion in a vaccine. Marburg virus is highly pathogenic with mortality rate of 90%. Ebola virus outbreak in West Africa in 2013-2016 necessitated an early introduction of a vaccine. The classical vaccine platforms are commonly used for human vaccines, and next-generation platforms, are being developed. Development of a novel multivalent vaccine against viral haemorrhagic fevers will eliminate the difficulties of single vaccines and may lead to the eradication of these diseases.
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**Keywords:** Innovative; Multi-pathogen; Vaccine development; Viral haemorrhagic fevers.

**RÉSUMÉ**

L'Humanité a développé des strategies pour atténuer les pandémies calamiteuses, en utilisant des vaccins. L'éradication de certaines maladies a été réussie grâce à l'utilisation de vaccins. Les virus de Lassa, de la fièvre jaune, de la fièvre de Crimée-Congo, de Marburg et d'Ebola méritent une attention particulière. La fièvre de Lassa, qui dispose aujourd'hui d'un candidat vaccin, a été découverte en 1969 lors du décès de deux infirmières missionnaires au Nigeria, tandis que la fièvre jaune dispose d'un vaccin à partir de sa souche atténuée 17D. La fièvre hémorragique de Crimée-Congo est une maladie virale répandue, transmise par les tiques, et la nucléoprotéine et les glycoprotéines sont identifiées pour être incluses dans un vaccin. Le virus de Marburg est hautement pathogène avec un taux de mortalité de 90 %. L'épidémie de virus Ebola en Afrique de l'Ouest en 2013-2016 a nécessité l'introduction rapide d'un vaccin. Les plateformes vaccinales classiques sont couramment utilisées pour les vaccins humains, et des plateformes de nouvelle sont en cours de développement. Le développement d'un nouveau vaccin multivalent contre les fièvres hémorragiques virales éliminera les difficultés des vaccins uniques et pourrait conduire à l'éradication de ces maladies.
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**Mots clés:** Innovant ; Multi-pathogène ; Développement de vaccins; Fièvres hémorragiques virales.

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**Abbreviations: EBOV,** Ebola Virus; **HF,** Haemorrhagic Fever; **Hib,** *Haemophilus influenzae* type b; **rVSV,** Recombinant Vesicular Stomatitis Virus; **LASV,** Lassa Virus; **YELMC,** Yellow Fever, Ebola Fever, Lassa Fever, Marburg and Crimean-Congo Haemorrhagic Fever Viruses.

## INTRODUCTION

Humans have suffered sufficient dangerous and catastrophic deadly epidemics/pandemics like the Spanish flu that killed over 20 million people and the plague that wiped out unimaginable millions of people.[1] The threats of pandemics are real, presently and in the future. Now, mankind has developed strategies to mitigate such calamitous pandemics, by using vaccines to stimulate the immune system which is the body's defence against infections. Basically, the body's immune system comprises of – macrophages that engulf the infectious agents, B-lymphocytes that produce antibodies that neutralize the antigens left by the macrophages and T-lymphocytes that attack the cells in the body that have been infected. The body after an encounter with an infectious agent keeps some T-Lymphocytes as memory cells that quickly go into action if the same infectious agent invades the body again. Vaccines make the body to develop immunity by tricking the immune system into believing that an infectious agent is attacking leading to production of antibodies. Enough memory T-lymphocytes, and also B-lymphocytes will be left behind that will remember how to fight the real disease in the future.

Vaccines may require more than one dose. Some peoples' immune system may not sufficiently respond actively to the first dose, or the immunity may wear off, so booster doses are administered to make sure everybody is protected. Eradication of some diseases like smallpox was successful through the usage of vaccines. Inovio pharmaceutical INC. has produced INO_4500, a DNA candidate vaccine to prevent infection from Lassa virus which is currently undergoing clinical trials. The intra-dermally delivered vaccine provided 100% protection in non-human primates challenged with a lethal dose of the virus.[2]

Lassa virus belongs to the family *Arenaviridae*, and Lassa fever is a zoonotic infection, that can be transmitted to humans. The illness is common in West Africa[3] and was discovered in 1969 when two missionary nurses died in Nigeria, West Africa.[4] Lassa fever illness is mild or has no observable symptoms in about 80% of infected people. In the remaining 20%, there is a severe multisystem disease consisting of haemorrhages, diarrhoea and other manifestations, with a case fatality rate of about 50% seen during outbreaks.[5–7] In occasional epidemics, the virus is sporadically transmitted to humans by direct contact with a rodent's urine or faeces, or eating food contaminated with a rodent's excretions, or sometimes when rodents (*Mastomys natalensis)* are caught and prepared for food.[7]

Yellow fever virus belongs to the family of *Flaviviridae* and is transmitted by infected mosquitoes (*Aedes aegypti*). The "yellow" in the name refers to jaundice that affects some patients. Symptoms of yellow fever include fever, headache, jaundice, muscle pain, nausea, vomiting and fatigue. A small proportion of patients who contract the virus, develop severe symptoms, and approximately half of those die within 7 to 10 days. By 1937, Max Theiler discovered an effective vaccine against yellow fever.[8] He created a watered-down yellow fever virus that would not affect the brain. Trial testing for Theiler's vaccine started the next year in Brazil. Max Theiler's development of the 17D strain of the attenuated virus, which could be used as a live vaccine, earned him a Nobel Prize in 1951 and has paved the way to save the lives of many millions of people.[8] A single dose of yellow fever vaccine is sufficient to confer sustained immunity and life-long protection against yellow fever disease. A booster dose of the vaccine is not needed.[8]

Crimean-Congo haemorrhagic fever (CCHF) is a widespread tick-borne viral disease in the family of *Bunyaviridae*. The interaction of the virus with host cells is most likely responsible for the pathogenesis of CCHF. There are two theories underlying the CCHF pathogenesis: first, the virus interacts with the endothelial cells directly, and secondly, it interacts indirectly via immune cells with subsequent release of soluble mediators. As the key structural components of the virus, the nucleoprotein and glycoproteins are identified as potential antigenic targets for inclusion in a vaccine against CCHF .[9]

Marburg virus (MARV) is a highly pathogenic virus associated with severe disease and mortality rate as high as 90%. Outbreaks of MARV are sporadic, deadly, and often characterized by a lack of resources and facilities to diagnose and treat patients.[10]

The devastating Ebola virus (EBOV) outbreaks in West Africa in 2013–2016 killed more than 11,000 people leading to infrastructural and economic chaos in Liberia, Guinea and Sierra Leone.[11] The current outbreak in DRCongo has flagged the need for timely development of vaccines for high-threat pathogens.[1] Findings indicate that vaccination with attenuated recombinant vesicular stomatitis virus (rVSV) vectors, each expressing a single haemorrhagic fever (HF) virus glycoprotein, may provide protection against these Filoviruses and Lassa virus (LASV) most commonly responsible for outbreaks of severe HF in Africa.[2,12]

Future threats of outbreaks and consequent creation of effective vaccines could drastically bring down the impact of deadly diseases like Lassa fever, Ebola and Marburg.[13] Viral genetic code is located in its RNA, which elicits the production of proteins. These proteins, known as antigens, make our immune system to respond by producing antibodies that successively identify the invading pathogens, and try to eliminate them. Researchers in Cambridge have developed and successfully tested a vaccine in animals that protects against Ebola and Marburg viruses.[13] Yellow fever, Ebola, Lassa, Marburg and Crimean Congo viruses independently cause haemorrhagic fever disease with high mortality rates.[13]

## DISCUSSION

Recent occurrences of filoviruses and the arenavirus in the overlapping endemic areas of Africa highlights the need for a prophylactic vaccine that could confer protection against all these viruses that cause lethal HFs. As a vaccine platform, the vesicular stomatitis virus (VSV) had been established as a robust vaccine vector backbone for infectious diseases for well over a decade.[2] The required attributes to qualify as a vaccine vector are as follows: stable insertion of coding sequences into the genome, induction of a protective immune

response, a proven safety record, and the potential for large-scale production. The recent clinical trials testing the vaccine candidate VSV-EBOV against EBOV disease now have added a substantial amount of clinical data and suggest VSV to be an ideal vaccine vector candidate for outbreak pathogens (including Yellow fever virus, Marburg virus, Lassa virus, Ebola virus and Crimean Congo haemorrhagic fever virus).[2]

Besides the traditional inactivated or live attenuated, virus-vectored and subunit vaccines,[16] emerging non-viral vaccine technologies, such as viral-like particle and nanoparticle vaccines, DNA/RNA vaccines, and rational vaccine design, offer innovative approaches to address existing challenges of vaccine development.

There are various stages of development for each of these vaccine platforms for pathogens like COVID-19. The novel strategies and technologies developed in response to the challenges presented by a universal influenza vaccine will be applicable to the structure-based design of vaccines for a wide range of pathogens. It is an incredibly exciting time for the field of vaccine development, and a structure-based, design-driven renaissance that recalls or even surpasses the original golden age of vaccines is predicted.[17] Technological advances in immunology, protein design, and genetic delivery have unlocked new possibilities for vaccine concepts and delivery technologies that were previously inaccessible. Approaches to vaccine design and engineering-based on recent insights into immunology, structural biology, computational biology, and immune engineering – are emerging.[9] It is anticipated that these cutting-edge, interdisciplinary approaches will lead to breakthrough vaccine concepts for the ever evolving and re-emerging diseases like influenza viruses, with important ramifications for global public health.[17]

Vaccines have enormous effect on human and animal health. The need to develop new vaccines for infectious diseases, increase vaccine accessibility, reduce health costs, and simplify overloaded immunization schedules has driven the idea to combine antigens from the same or various pathogens. Other novel strategies propose an antigen combination of different pathogens to protect against several diseases at once (multi disease or multi pathogen vaccines). The development of new combined vaccines requires reflection on the terminology that is currently used to describe this new class of chimeric vaccines. There is the problematic ambiguity in definition. In general parlance, "multivalent/polyvalent" (with valency in Greek or Latin) refers to an agent that is effective against different types of the same organism. In accordance with this terminology, an infection consisting of multiple pathogens is generally described as a multi pathogen disease or simply multi disease. Multi disease/multi pathogen vector vaccine refers to key protective antigens from two or more pathogens in a single vector to immunize against several diseases.[18] The technology for multi pathogen vaccine production is in use. MMR (measles, mumps, and rubella) has a 3 in 1 combination, just like the 6 in 1 vaccine for diphtheria, tetanus, whooping cough (pertussis), polio, *Haemophilus influenzae* type b (Hib) and hepatitis B in use in the United Kingdom.[18] There is a need for the development of a multi pathogen vaccine for the following viruses together; Yellow fever, Ebola fever, Lassa fever, Marburg and Crimean-Congo haemorrhagic fever viruses (YELMC) (Figure 1).

The multi-pathogen vaccine is an innovative combination proposal. The vaccine will reduce costs, pain and difficulties of multiple injections for the five viruses as single vaccines. This multi disease vaccine for YELMC is advocated for use in sub-Saharan and central Africa. The cost-effective trend vaccine is aimed at eradicating the five viral haemorrhagic fever diseases in Africa and other continents, hence saving more lives. Yellow fever and Ebola vaccines are already in use in West Africa, and currently in central/East Africa. Lassa fever, Marburg and Crimean Congo vaccines are in developmental stages.[16]

The development of the multi-pathogen vaccine needs a planned procedure. The African heads of government need make an input maybe through the Organization of African Unity (OAU). They should initiate partnership with their vaccine related research institutes, ministries of health or other agencies, interested non-African countries and technically renowned vaccine producing companies, in conjunction with the World Health Organization (WHO) as a monitoring agency. This coalition will work out details on funding, research methodology (including vaccine platform), trials, and assessment of the finally approved vaccine and cost of administering it to the people. African countries (especially West, Central and Eastern parts) will gain immensely from the introduction of this innovative 5 in 1 vaccine. These African countries, unfortunately, are engulfed by civil strife, insurgency, ethnic/ religious conflicts, unchecked hunting of wildlife and worse still, climatic and political turmoil, with devastating economic/ health consequences. Strong global external persuasive influence should be the way out for them to benefit from this 5 in 1 vaccine, instead of being the pathogens' breeding ground with consequent catastrophic Armageddon that the world will face. This 5 in 1, YELMC vaccine should be seriously considered.

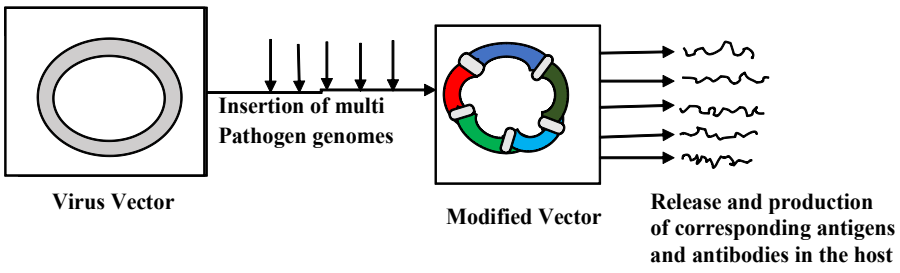


**Fig. 1: Scheme for Multi-Pathogen Vaccine Development.**

The acceptability of YELMC vaccine among the populations of endemic countries in Africa and elsewhere will be significant as it will be like using one vaccine to control and possibly eradicate the five lethal diseases.

## CONCLUSION

The presentation and delivery of antigens are crucial for inducing immunity and, desirably, lifelong protection. Recombinant viral vectors are ideal shuttles to deliver foreign proteins to induce an immune response with protective antibody levels by mimicking natural infection. The introduction of a novel multi pathogen vaccine against viral haemorrhagic fevers will reduce costs, pain and difficulties of multiple injections for single vaccines. It will drastically improve compliance, wide population overall coverage, save more lives with the potential to eradicate the five pathogens and bring on a ripple effect, leading to the production of more potent vaccines against other existing emerging and re-emerging pathogens.

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