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Measles-derived vaccines to prevent emerging viral diseases

Phanramphoei N. Frantz [a, b], Samaporn Teeravechyan [b], Frédéric Tangy [a, *]

[a] Viral Genomics and Vaccination Unit, Department of Virology, Institut Pasteur, CNRS UMR 3965, Paris, France
[b] Virology and Cell Technology Laboratory, National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency, Pathumthani, Thailand

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ABSTRACT

Infectious disease epidemics match wars and natural disasters in their capacity to threaten lives and damage economies. Like SARS previously and Zika recently, the Ebola crisis in 2015 showed how vulnerable the world is to these epidemics, with over 11,000 people dying in the outbreak. In addition to causing immense human suffering, these epidemics particularly affect low- and middle-income countries. Many of these deadly infectious diseases that have epidemic potential can become global health emergencies in the absence of effective vaccines. But very few vaccines against these threats have been developed to create proven medical products. The measles vaccine is an efficient, live attenuated, replicating virus that has been safely administered to 2 billion children over the last 40 years, affording life-long protection after a single dose. Taking advantage of these characteristics, this attenuated virus was transformed into a versatile chimeric or recombinant vaccine vector with demonstrated proof-of-principle in humans and a preclinical track record of rapid adaptability and effectiveness for a variety of pathogens. Clinical trials have shown the safety and immunogenicity of this vaccine platform in individuals with preexisting immunity to measles. This review describes the potential of this platform to develop new vaccines against emerging viral diseases.

1. Introduction

Emerging viral diseases (EVDs) have been making the headlines for the past two decades. Each subsequent outbreak emphasizes the global lack of preparedness in controlling and minimizing the spread of these diseases to both human and animal populations. The burden of EVDs to public health and the global economy has been massive, with direct and indirect costs of zoonotic diseases estimated to exceed US$220 billion in the last decade alone, [1,2].

This rise in EVD cases can be traced to a number of causes. The growing global population, which is expected to reach 9.7 billion people by 2050, has resulted in expanding urbanization and deforestation, exposing populations to reservoirs of new viruses. Furthermore, high-density living conditions are often associated with low quality of life and insufficient health care, thus facilitating disease transmission. Climate change also plays a major role by enabling emergence of infections in new locations, with warmer weather increasing the range of arthropod disease vectors such as mosquitoes and ticks. Globalization and the dramatic growth of international travel also increase the rapidity and scale of emerging disease dissemination.

Of particular concern are the top seven priority pathogens designated by the World Health Organization (WHO) as likely to cause a major outbreak associated with high mortality rates due to the lack of effective medical treatments or countermeasures, [3]. These pathogens, all zoonotic, include the Crimean-Congo hemorrhagic fever virus (CCHFV), Ebola and Marburg viruses (EBOV), Lassa virus (LASV), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), Nipah virus (NiV), and Rift Valley fever virus (RVFV). Additionally, chikungunya virus (CHIKV) and Zika virus (ZIKV) have been declared health emergencies with epidemic potential by the WHO [4], despite their low mortality rates, as these mosquito-borne arboviruses can rapidly spread through large populations.

Zoonotic viruses can be transmitted directly to humans from their animal reservoirs. For example, NiV can be acquired from bat shedding, MERS-CoV from camels, and SARS-CoV from civets [5]. Alternately, transmission can occur through intermediate hosts such as NiV infection of pigs followed by transmission to other pigs or humans [6] and EBOV transmission from bats to non-human primates (NHPs) and then to humans [7]. Larger human

* Corresponding author.
E-mail address: ftangy@pasteur.fr (F. Tangy).

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outbreaks subsequently occur when individuals come in contact with body fluids (urine, saliva, aerosolized droplets or blood) of an infected person. Air travel and trading ships carrying infected persons, animals or vectors can result in intercontinental spread of diseases and pandemics.

Several vaccine platforms have been developed for preventative care of these diseases and preparedness for future outbreaks. In this review, we will discuss the measles virus (MV) vector as a promising alternative to conventional vaccine development methods and how its strengths as a vaccination platform for these emerging diseases compare with other approaches. This platform is based on a replicating MV vaccine vector with demonstrated proof-of-principle in humans and a preclinical track record of rapid adaptability and effectiveness for a variety of pathogens.

2. Virus-vectored vaccines as vaccination platforms for emerging viral diseases

Tackling the unpredictability regarding when and where EVDs will arise requires strong international disease surveillance networks as well as commitment to the development of preventative measures and post-exposure treatments. For this reason, in May 2015, the 68th World Health Assembly "welcomed the development of a blueprint for accelerating research and development in epidemics or health emergency situations where there are no, or insufficient, preventive, and curative solutions, taking into account other relevant work streams within WHO" [8]. The R&D Blueprint aims to reduce the time between the declaration of an international public health emergency and the availability of effective tests, vaccines, antivirals, and other treatments that can save lives and avert a public health crisis. Following that initiative, the Coalition for Epidemic Preparedness Innovations (http://cepi.net) was created. CEPI is an alliance between governments, industry, academia, philanthropy, intergovernmental institutions, such as the WHO, and civil society that aims to finance and coordinate the development of new vaccines to prevent and contain infectious disease epidemics. As epidemics disproportionately affect low-income countries, CEPI will ensure that the vaccines will be affordable and available to populations with the most need.

There are currently no drugs available to efficiently treat acute virus infection. Viral inhibitors such as Ribavirin and others can reduce and slow down viral replication, giving the host immune system a chance to develop and clear the virus. However, the treatment window for acute viral infections is short and symptoms often only appear late in the course of infection, during the viral clearance phase (Fig. 1) and after the host has become infectious. Passive immunization can be used in emergency cases in high exposure areas, as seen with EBOV [9], NiV [10] or Hendra virus [11] outbreaks, but this approach is not practical for general implementation due to high cost and limited efficacy. Therefore, prophylactic vaccination remains the most simple, safe and effective way to prevent viral infections and subsequent outbreaks.

Indeed, vaccines have been crucial to the control or elimination of many deadly viral diseases and represent the most efficient method to prevent viral infection. Inactivated (killed) viruses, live attenuated viruses, and subunit vaccines comprise the conventional mode of vaccination. Inactivated-virus vaccines are made of whole virus particles treated with chemicals, heat or radiation. Live attenuated virus vaccines are created by passaging virulent virus strains in animals or cell culture until the virus has adapted to its new host and are no longer pathogenic in target animals or humans (usually after 5 to 100 or 200 passages). Inactivated-virus and subunit vaccines are non-replication competent, so while there is no risk of reversion to infectivity, they are usually not effective enough to elicit strong host immune responses on their own. Immunization efficacy requires the use of adjuvants and several boosters, which can in turn cause side effects and severe allergic reactions. On the other hand, live attenuated vaccines elicit long-term protective immune responses because they can replicate inside the host. However, depending on the number of attenuation mutations and on the viral family, there is a risk of reversion where virulence can be regained through reassortment with pathogenic strains, as observed with the oral live polio vaccine [12]. Moreover, the conventional attenuation is a lengthy process requiring numerous passages that can take from 6 months to several years of work, rendering it impractical as a prompt response to ongoing outbreaks.

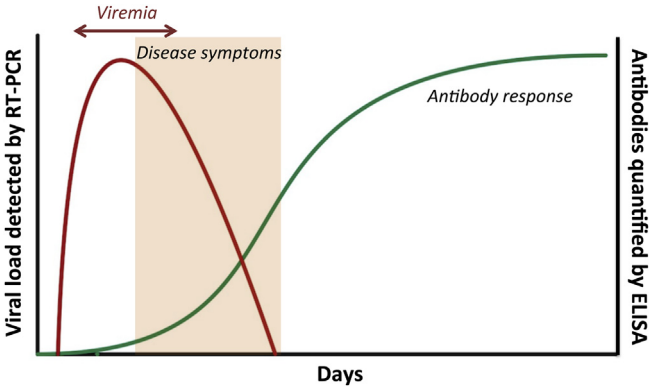

Fig. 1. Immune response during viral infection in an individual. During viral infection, symptoms generally appear after the decline in viral load. Viral clearance is the result of a developed immune response, which leads to recovery.

Nevertheless, given their efficacy, simple administration regimens, and ease in large-scale manufacture, live attenuated vaccines remain attractive choices for vaccine design. Highly successful examples of live attenuated vaccines include those developed against smallpox, yellow fever, poliomyelitis, and measles, with the latter three being successfully implemented in low- and middle-income countries through the Expanded Program on Immunization (EPI). Well-tested and effective live attenuated virus vaccines can be modified with modern recombinant DNA technology to combine the advantages of replicating viral vectors with the need for rapid methods of developing new vaccines for emerging or re-emerging diseases. Live replicating vectors, such as the MV vector, are characterized by induction of long-lived protective immunity after one or two administrations. With reverse genetics technology, a viral vector vaccine platform can be created to carry antigenic proteins from another circulating virus to yield a vaccine candidate that can be quickly tested in established animal models. Such a "plug-and-play" platform has the capacity to provide rapid responses to future emerging viral diseases.

3. Live attenuated measles virus-derived vaccination vector

Measles virus (MV) is a member of the genus *Morbillivirus* in the family of *Paramyxoviridae*. It is an enveloped virus with a non-segmented, negative-sense, single-stranded RNA genome of approximately 16 kb in length (Fig. 2a) encoding six structural proteins: nucleoprotein (N), phosphoprotein (P), matrix (M), fusion (F), hemagglutinin (H), polymerase (L), and two non-structural proteins: V and C. The accessory proteins V and C are essential in regulating viral replication and the host innate immune response. Envelope structure is comprised of H, F, and M proteins, which are responsible for virus attachment, membrane fusion and viral entry. Viral particles are pleomorphic with sizes

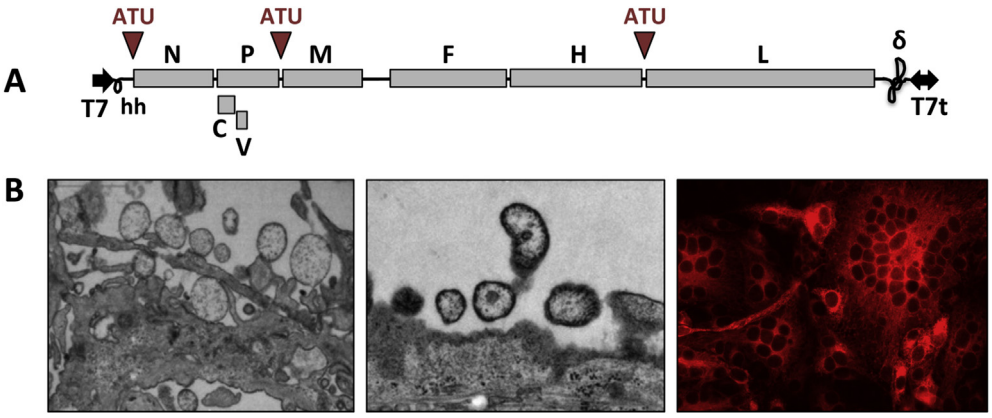

Fig. 2. Measles virus vector. A) Schematic representation of cloned measles virus vector genome (pTM-MVSchw) containing additional transcription units (ATU). Structural proteins genes (N, nucleoprotein; P, phosphoprotein; M, matrix protein; F, fusion protein; H, hemagglutinin; L, large polymerase), and accessory proteins genes (C and V proteins) are shown. T7, T7 RNA polymerase promoter; hh, hammerhead ribozyme; δ, hepatitis delta virus (HDV) genome ribozyme; T7t, T7 RNA polymerase terminator. **B)** Electron microscopy images of MV vector particles budding from infected Vero cells and immunostaining image of Vero cells infected with MVSchw vector; anti-N-MV mouse monoclonal antibodies and Cy3-conjugated anti-mouse IgG antibodies.

ranging from 150 to 350 nm due to the flexibility of envelope structure. Inside the particles, the genomic viral RNA is tightly wrapped with N, P and L to constitute a helicoidal ribonucleoprotein (RNP) complex, which is auto-replicative in the host cytoplasm. The RNP serves as the template for viral RNA synthesis, and with each N molecule associated with 6 nucleotides, efficient replication requires that the genome length respects the so-called 'rule of six', which means that the total number of genome nucleotides is dividable by 6 [13]. Since the helicoidal structure is highly flexible like a spring, the genome tolerates large insertions as long as the total length complies with the 'rule of six'. Viral genes are transcribed in succession from the N to L genes as the polymerase stops and restarts at intergenic regions. However, as efficiency of re-initialization is not 100%, mRNAs are produced in decreasing amounts from the 5′ to 3′ end of the genome, resulting in the greatest abundance of N and lowest abundance of L protein. Accumulation of intracellular N protein promotes a shift from transcription to replication. During replication, L synthesizes a complete copy of the entire genome as a positive-sense antigenome which serves as the template for generation of full-length negative-sense genomes for packaging. Viral particles are assembled with the N, P and L proteins synthesized in the cytoplasm before budding from the plasma membrane together with envelope proteins localized to the surface membrane.

Live attenuated MV vaccine is one of the safest and most effective vaccines available. Several MV vaccine strains, such as the Schwarz/Moraten, Edmonston-Zagreb, and AIK-C strains, have been developed from the pathogenic wild-type virus by multiple passages in various cellular substrates (chicken eggs, chicken embryo fibroblasts) under different conditions. In the past 40 years, the MV vaccine has been administered safely to over 2 billion children, with no case of reversion reported. It induces both humoral and cellular immune responses by efficiently stimulating long-lasting memory B– and T-cells and provides lifelong immunity. It has an efficacy rate of approximately 93% after one administration and 97% after two administrations. The virus only replicates in the cytoplasm, hence there are no possibility of viral genome integration into the host genome. Thanks to its non-segmented negative-sense RNA genome, there is no genomic recombination possible or observed with other viruses. Furthermore, the MV vaccine is currently produced on a large scale in many countries and is globally distributed at low cost through the EPI. Therefore, the MV vector platform provides a means of rapidly generating potent vaccine candidates against a broad spectrum of epidemic disease targets, and its accessible manufacturing process provides a means to rapidly scale-up vaccines at low cost for stockpiling purposes and as a rapid response vaccine countermeasure to epidemic threats.

Recombinant MV vectors generated from attenuated MV vaccine strains are attractive choices for developing vaccine candidates against other viral infections. Due to the helicoidal packaging of its genome, an MV vector can take up foreign genes up to 6 kb in size and possibly more. Heterologous proteins can be stably expressed at high levels for more than 12 passages and rescued recombinant viruses retain growth capabilities similar to the original MV strain [14]. The MV delivery platform has been developed from its preclinical stages to clinical proof-of-concept for several indications with a preclinical track record of fast and effective adaptability to a variety of pathogens. MV vectors are immunogenic in mice and NHPs, inducing long-term neutralizing antibodies and cellular immunity even in the context of preexisting immunity to the vector [15–18].

The initial and pioneer cloning of full-length infectious MV was achieved in 1995 by the group of M. Billeter in Zurich [19]. Later, the Schwarz strain of MV was cloned at Institut Pasteur (Paris) as it is a commercially and WHO approved, mostly attenuated, efficient and widely used MV vaccine strain [20]. To generate an infectious clone, its full-length antigenomic viral cDNA (Fig. 2b) was cloned into the pTM plasmid under the control of the T7 RNA promoter. DNA sequences containing a GGG motif, hammerhead and hepatitis delta viral ribozymes were added to facilitate accurate cleavage of the viral RNA and ensure production of full-length viral RNA. The virus can be produced or rescued by transfection of pTM-MVschw plasmid together with a plasmid expressing the Schwarz MV L gene into trans-complemented human cells (HEK293 cells constitutively expressing T7 RNA polymerase, MV N and MV P). Transfected cells are then further co-cultured with any MV permissive cell line such as Vero, MRC5 or chicken embryonic fibroblasts. Plaques are picked and seeded for amplification and characterization. Rescued viruses from the cDNA clone possess the same sequence as the parental Schwarz strain, demonstrating the stability of the negative-sense genome. To enable insertion of foreign antigens, several additional transcription units (ATUs) based on MV cis-acting sequences were introduced into pTM-MVschw at various sites in the genome. Cloning sites can accommodate inserts of over 6 kb in length, in

multiples of six base pairs to respect the 'rule of six' that is essential for measles genome replication [13].

One common concern regarding the use of MV as a vaccine vector is preexisting immunity, due to the broad coverage of MV vaccines in human populations worldwide. However, it was demonstrated that recombinant MV vaccines induce strong immune responses even in previously immunized animals or humans [15,21,22]. Although surprising, a few MV properties may account for this phenomenon. First, recombinant MV are replicating, therefore although low doses are used, the vaccine is amplified *in vivo*. Upon cell infection, the recombinant MV expresses measles proteins as well as heterologous antigens, and MV particles are assembled and released from the cell. Heterologous antigens are either secreted from the cell or expressed on the cell surface, depending on the nature of the antigen, and stimulate the immune response. Second, the virus delivers antigens directly to dendritic cells, macrophages and B cells (the most effective antigen presenting cells), and viral particles are transmitted from cell to cell by cell contacts. Lastly, we have recently shown that additional antigens expressed from replicating MV vectors are naturally adjuvanted through defective interfering genomes produced by the recombinant virus, contributing to robust induction of interferon and conferring vaccine efficacy [23].

This vaccine technology platform has the capacity to address the challenge of rapid vaccine development, combining a strong safety and immunogenicity profile demonstrated through multiple applications, the ability to target antigens from infectious pathogens in preclinical and clinical settings, and a robust, antigen-independent, scalable manufacturing process. Several recombinant measles vaccines against a number of viral pathogens have so far been generated and tested in animal models (Fig. 3). Target pathogens include HIV [24,15,25,16,17,26–28], West Nile Virus (WNV) [29,30], dengue virus (DENV) [31,32], hepatitis B virus (HBV) [33], human papilloma virus (HPV) [34], CHIKV [21], NiV [35], respiratory syncytia virus (RSV) [36], SARS-CoV [37], MERS-CoV [18], H5N1 influenza A virus (IAV) (unpublished), ZIKV (unpublished), LASV (unpublished) and EBOV (unpublished). Preclinical immunogenicity and protection from lethal challenges have been shown in mice and NHPs for WNV, CHIKV, HIV-1, SARS-CoV, H5N1 IAV, ZIKV, and LASV. In the cases of HIV-1, ZIKV, and CHIKV, recombinant vaccine candidates have successfully completed phase I clinical trials in adults, with the last progressing to phase II trials.

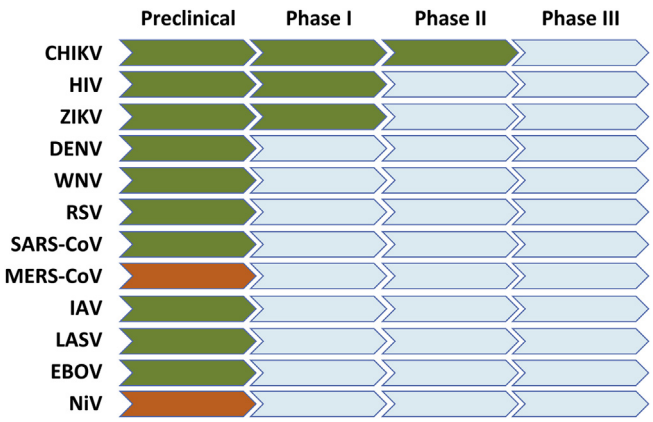

Fig. 3. MV-based vaccines pipeline. MV-based vaccines targeting viruses responsible for various emerging and re-emerging diseases are shown in relation to their current preclinical or clinical study phase. Green arrows indicate use of the Schwarz strain-based vector, while orange arrows indicate use of the Edmonston strain-based vector.

4. Vaccines against emerging viral diseases

4.1. Chikungunya virus

Chikungunya virus (CHIKV) is an enveloped, positive-sense, single-stranded RNA virus in the family of *Alphaviridae*. Approximately 30% of infected patients develop debilitating chronic polyarthralgia that can last months or even years. Initially thought of as an African virus, it emerged in 2005–2006 on La Reunion island in the Indian Ocean, infecting a third of the island population, before spreading throughout India, giving rise to the Indian Ocean lineage. In 2013, it reemerged on the Caribbean island of Martinique. Since then, CHIKV has been found in over 60 countries in the Americas, Africa, Asia, and Europe, with more than 1.7 million people infected.

An MV-based CHIKV vaccine has been developed expressing CHIKV structural genes (C, E3, E2, 6K, E1) cloned from the clinical isolate CHIKV 06.49 (ECSA strain) [21]. Expression of CHIKV structural genes results in formation of virus-like particles during infection in Vero cells. Preclinical studies in CD46+/IFNAR−/− mice showed full protection from lethal CHIKV challenge after a single immunization, even in presence of preexisting immunity to the vector [21]. The MV-CHIKV vaccine candidate was further introduced into clinical trials by Themis Bioscience (http://themisbio.com). Immunogenicity was demonstrated in phase I clinical trial with a 90% seroconversion rate after a single injection and 100% seroconversion after boosting (28 days or 3 months apart) [22]. There were no serious adverse reactions observed; even the group receiving a high dose (3×10^5 $TCID_{50}$) displayed only mild reactions such as headache, flu-like symptoms and mild muscle pain, similar to those observed with the control standard MV vaccine [22]. Most importantly, the study demonstrated that the immune response to measles and CHIKV VLP was not dampened by previous MV immunization since all volunteers were preimmune to measles [22]. The phase II clinical trial is ongoing with 400 volunteers in Austria and Germany (EudraCT No. 2013-001084-23). Additionally, two independent phase I studies have been initiated in the USA (NIH) and Puerto Rico (DoD) in June 2017 (ClinicalTrials.gov: NCT03028441, NCT02861586). The success of MV-CHIKV thus far reaffirms that the MV vector is an excellent platform for vaccine development.

4.2. Dengue virus

Dengue virus (DENV) is an enveloped, positive-sense, single-stranded RNA virus in the family *Flaviviridae* that causes a tropical disease endemic in Southeast Asia and Latin America. WHO identified dengue as a neglected disease with potential for emergence in new geographical areas due to climate change [3]. The major complication of dengue infection is that four distinct serotypes of the virus circulate. After the first DENV infection, the host acquires life-long immunity to that particular serotype, but this does not provide cross-protection against other serotypes. Rather, non-neutralizing antibodies enhance infection of cells carrying the Fc receptors used by DENV for host cell entry. This phenomenon is called antibody-dependent enhancement (ADE) [38,39]. Due to ADE complications, the strategy for DENV vaccine development is to focus on tetravalent vaccines that simultaneously stimulate immune responses against all four DENV serotypes.

The recently licensed DENV vaccine Dengvaxia (CYD-TDV) is a tetravalent YF17D-based recombinant vaccine that has completed phase 3 clinical trials and is now distributed in Southeast Asia and South America [40]. However, the vaccine poses a safety concern associated with increased risk of disease exacerbation in recipients who have not been previously exposed to DENV. Sanofi has pulled the vaccine from the Philippines after recent concerns, and vaccine

use is recommended only for individuals with prior exposure to DENV.

Given the limitations of the current vaccine, other options are still being explored. An MV-based tetravalent vaccine candidate is in development as well. The DENV antigen used consists of domain III of the E glycoprotein (EDIII) from each of the four serotypes, as it contains serotype-specific neutralizing epitopes, fused to the ectodomain of the membrane protein (M) [32]. This M ectodomain is essential for immunogenicity of the inserted tetravalent EDIII due to its adjuvant properties through induction of pro-inflammatory and antiviral cytokines and chemokines [31]. Preclinical trials revealed that immunized mice and macaques developed neutralizing antibodies against all four serotypes (unpublished data).

4.3. Zika virus

Zika virus (ZIKV) is a flavivirus closely related to DENV, with approximately 40% amino acid difference compared to the 30–35% difference between the four DENV serotypes [41,42]. ZIKV was first identified among humans, primates, and mosquitoes in the Zika forest of Uganda in 1947 [43]. In 1969, it emerged in Southeast Asia and became largely endemic in tropical regions. The first massive outbreak was seen on Yap Island in 2007, where more than 70% of the population became infected. In 2017, the disease reached Latin America with a major outbreak in Brazil.

ZIKV infection shares some common symptoms with other arbovirus infections such as fever, flu-like symptoms, and rashes. In the Brazilian outbreak, around half of the cases exhibited no symptoms but the virus could be detected in the saliva of infected individuals [44]. ZIKV was declared an emergency public health concern by the WHO in 2016 due to neurological complications associated with Guillain Barré Syndrome (as reported in French Polynesia) and microcephaly in newborns (as reported in Brazil) [45]. Congenital ZIKV syndromes suggested human-to-human transmission through sexual intercourse, breast milk or placental transfer [46,47].

With its close evolutionary relationship to DENV, ADE between both viruses has been reported *in vitro*; sera of DENV-infected individuals facilitate ZIKV infection in usually non-permissive cells [48]. Although not confirmed in humans, this phenomenon could complicate vaccine development against ZIKV and DENV. Vaccines currently in preclinical trials include an MV-based vaccine, which was developed by cloning the full-length prM and E genes (prM-E) of ZIKV into the pTM-MVschw vector. This vaccine candidate is highly immunogenic and conferred full protection to both mice and monkeys. A phase I clinical trial was initiated in 2017 (Themis Bioscience, http://themisbio.com).

4.4. Highly pathogenic coronaviruses

Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are enveloped, positive-sense, single-stranded RNA viruses possessing genomes approximately 27.9 and 30.1 kb in size respectively. While both viruses are thought to originate from bats, the first known case of SARS occurred through transmission from a palm civet [49] in Foshan, China in November 2002 before spreading throughout China and to other countries. WHO tallied 8096 reported cases in 27 countries in 2003. Due to a global effort in disease management, the outbreak was declared to be over by July of that year. Ten years after the first SARS incidence, MERS-CoV emerged in Saudi Arabia in 2012, with cases arising from transmission from dromedary camels to humans. As MERS-CoV has not been observed to spread from person to person like SARS-CoV, a localized outbreak arising from an imported case was observed only in South Korea as a result of nosocomial transmission from a single infected traveler [50].

The structural spike (S) proteins of CoVs have been identified as targets for neutralizing antibodies and are considered potential targets for subunit and viral vector vaccine development. At Institut Pasteur, an MV-based vaccine against SARS-CoV has been developed where a human codon-optimized gene encoding the native SARS-CoV S or its soluble form was inserted into the ATU between the P and M sequences of pTM-MVschw [37]. These gene insertions did not interfere with recombinant MV growth and titer. The vaccine was tested in mice and found to induce neutralizing antibodies. All immunized animals were protected from a lethal dose of SARS-CoV challenge delivered intranasally. Native S was observed to be more potent in eliciting antibodies than its soluble counterpart, and these antibodies were found to possess high neutralizing activity against both SARS-CoV and MV [51]. Higher IgG2a than IgG1 levels were observed, suggesting a Th1-biased response.

For MERS-CoV, an MV-based vaccine has been generated using a modified Edmonston strain backbone carrying either the full-length or soluble MERS-CoV S between the P and M genes [18]. Like the SARS-CoV version, this vaccine also induced neutralizing antibodies and antigen-specific cytotoxic T-cells. Both Elispot assays and intracellular cytokine staining by flow cytometry showed strong increase in specific $CD3^+$ $CD8^+$ T cells from vaccinated mice after *ex vivo* restimulation with the S antigen, as well as a positive killing assay [18]. The promising results thus far demonstrate that the MV vector has great potential for further SARS-CoV and MERS-CoV vaccine development.

4.5. Ebola and Marburg viruses

Ebola and Marburg viruses (EBOV and MARV) are enveloped, negative-sense, single-stranded RNA viruses in the *Filoviridae* family responsible for hemorrhagic fevers associated with high fatality rates of up to 50%. EBOV was first discovered in 1976 in Congo and Sudan. Its circulation has generally been restricted to central African countries where several EBOV strains and MARV cause frequent outbreaks. They continue to cause sporadic outbreaks, re-emerging regularly in eastern and central Africa. In December 2013, however, an unprecedented outbreak emerged in the western African country of Guinea, causing a major crisis with its rapid spread within the country as well as to the neighboring Sierra Leone and Liberia. Air travel led to imported cases in many countries (US, Spain, Mali and UK), turning the EBOV epidemic into a global public health emergency. From 2013 to 2016, WHO documents indicate a total of 28,464 reported cases of EBOV infection with 11,323 reported deaths. While a concerted international effort managed to stem the outbreak, EBOV outbreaks are predicted to persist into the next decade [52].

This recent outbreak re-energized EBOV vaccine development with a massive influx of funding, and several vaccine candidates were placed in accelerated development. Among them were two viral-vector vaccines targeting the envelope glycoprotein (GP) of EBOV, which are currently in phase II/III clinical trials. The first vaccine is based on the vesicular stomatitis virus (VSV) vector expressing the EBOV Zaire strain GP (rVSV-ZEBOV) [53,54]. This vector is based on a cattle virus not frequently associated with human infection. NHP experiments demonstrated that this vaccine protects against EBOV challenge and is also effective as post-infection treatment within a few days of infection. Drawbacks of the rVSV-ZEBOV vaccine include unknown duration of protection and possible adverse effects depending on the dose used. A phase I clinical trial was abruptly stopped due to serious joint pain and dermatitis [55]. For now, however, the vaccine has proven effective

in limiting disease spread when implemented in a "ring vaccination" scheme in Guinea [56,57,55].

The second vaccine candidate against EBOV is an adenovirus vector (Ad) expressing EBOV-GP. This vaccine vector provides the benefit of being non-pathogenic to humans and is naturally controlled by the immune system. However, the first generation of Ad-based vaccines had reduced effectiveness due to pre-existing immunity, which was later overcome by the use of a chimpanzee adenovirus strain (ChAd) [58]. Regardless of preexisting immunity, to confer a long-lasting immunity, HuAd and ChAd platforms require a booster delivered by a heterologous modified vaccinia virus Ankara (MVA) vector. Prime-boost protocols are difficult to set up in EBOV-emerging countries where healthcare systems are weak and unavailable in some areas. Moreover, the dose required for efficient protection is 10^{11} $TCID_{50}$, a highly challenging task for manufacturing a vaccine for millions of individuals.

The MV vector provides an attractive alternative for vaccine development that can circumvent possible safety issues associated with the rVSV vector and the manufacturing hurdles and complex regimen of the AdV vector approach. In particular, MV ability to elicit both humoral and cellular responses will be advantageous for efficient protection, as T-cell responses have been shown to play some role in controlling EBOV infection [59] and will probably be instrumental for maintaining long-term memory. Furthermore, the large insertion capacity of the MV vector enables development of a combined vaccine against both EBOV and MARV. MV expressing different forms of GP of EBOV (Zaire strain) are currently being tested for immunogenicity and efficacy in the NHP model at Institut Pasteur.

4.6. Lassa fever

Lassa virus (LASV) is a bi-segmented, negative-sense, single-stranded RNA virus in the family *Arenaviridae* that causes hemorrhagic fever in humans. The natal multimammate rat is its natural reservoir, with most infections occurring by rodent-to-human transmission. Human-to-human spread can occur through direct contact of infected body fluids and in nosocomial settings. Lassa fever causes non-specific symptoms but in severe cases, vascular leakage and multi-organ failure have been reported. The disease was first identified in Nigeria in 1969 and was detected throughout western and central Africa within a decade. Unlike EBOV infection, Lassa fever occurs annually, posing a major threat to local populations, travelers and healthcare workers. The US CDC estimates that LASV causes 100,000–300,000 cases and 5000 deaths yearly. Among hemorrhagic fever viruses, LASV causes the highest global burden due to its stability and aerosol transmission, which also render it a potential bioterrorism threat.

Several virus-based vectors including VSV [60], vaccinia virus [61] and yellow fever virus (YF17D) [62] carrying the surface glycoprotein complex (GPC) of LASV showed promising immunological results in guinea pig and NHP models. Ninety percent of NHP survived lethal LASV challenge after vaccination with vaccinia-LASV-GP [61]. This study also confirmed that cell-mediated immune responses are key to LASV protection. However, use of the vaccinia-based vaccine is not desirable for the high HIV prevalence regions of Africa, as it is still unclear whether immunosuppressed individuals face risks of increased vaccinia replication and generalized infection. On the other hand, the YF17D vector expressing LASV-GPC was observed to exhibit genetic instability of the antigen due to the vector's small insertion capacity [62]. Various versions of the GP1 and GP2 glycoproteins were tested in YF17D to resolve this issue, but loss of antigen expression was still observed after five passages of the recombinant virus.

An MV-based vaccine, MV-LASV-NP+GPC, is currently being developed at Institut Pasteur with no problem of antigen instability due to the high insertion capacity of this vector. Experiments in macaques have shown the great efficacy of this vaccine candidate to protect the animals after a single immunization from lethal LASV challenge (unpublished data).

4.7. Nipah virus

Nipah virus (NiV) is a henipavirus in the *Paramyxoviridae* family. It is an enveloped, negative-sense, single-stranded RNA virus that causes disease in both humans and animals. Its reservoir is the fruit bat, and transmission occurs through contact with bat saliva or urine, often through consumption of contaminated fruits or date palm sap. The disease first emerged with a fatal case of acute encephalitis in the town of Nipah in Malaysia in 1998, and was followed by a few hundred cases of disease with over 30% mortality. The virus re-emerged in India and Bangladesh in 2001–2008 with a higher fatality rate of 70–100%. Pigs act as amplifying hosts, where infection causes mostly respiratory symptoms and is known as the "barking pig disease". Direct transmission from infected pigs to humans has been reported [6]. In addition, the fact that a number of infected patients never came into contact with either bats or pigs indicates occurrence of human-to-human transmission of NiV [63,64].

Vaccine target antigens for NiV are its fusion protein (F) and glycoprotein (G), which are the surface proteins important for host cell attachment and viral entry. The various immunization strategies have been summarized in a previous review [11]. Canarypox virus carrying F and G was developed for use in animals and showed protection against intranasal challenge in piglets [65]. For human vaccination, vaccinia virus, adenovirus, MV and VSV [10,35,66,67] have all been used as viral vectors. These vaccine candidates all elicited specific neutralizing antibodies and protected against challenge in hamster and ferret models, with VSV-NiV-G demonstrating partial protection against lethal challenge in NHPs as well, although some lesions were observed in brain cells suggesting viral replication in the central nervous system [68].

The MV-based vaccine involved insertion of the NiV G gene into the Edmonston strain-based vector. Initial immunogenicity testing was performed in hamsters and showed full protection from lethal challenge after the second immunization. In NHP model, monkeys were vaccinated with 1×10^5 $TCID_{50}$ of rMV-NiV-G with one booster and showed no clinical signs after challenge with NiV, demonstrating full protection in vaccinated monkeys [35].

4.8. Rift Valley fever virus (RVFV)

Rift Valley fever virus (RVFV) is a phlebovirus with a tri-segmented, negative-sense, single-stranded RNA genome. It is transmitted by several *Aedes spp.* and *Culex spp.* mosquitoes to livestock and humans. Infection causes acute severe disease in ruminants with fever, loss of appetite, aborted fetuses and a high mortality rate in newborn animals. Humans are dead-end hosts, and infection results in a febrile illness with approximately 1% of those infected presenting with more severe symptoms such as encephalitis or hemorrhagic syndromes. It first appeared in the Rift Valley region of Kenya and the virus itself was isolated in 1930. Several major outbreaks were reported throughout Africa, before first appearing outside the region in 2000 with a large outbreak in the Arabian peninsula.

The three segments of the RVFV genome have been named the small (S), medium (M) and large (L) genes. The two envelope glycoproteins (Gn or Gc) serve as receptor-binding proteins to facilitate virus attachment and infection, rendering them targets for

vaccine development. Subunit vaccines targeting Gn or Gc have been shown to elicit specific RVFV neutralizing antibodies [69].

Many vaccine platforms have been used to develop vaccine candidates for RVFV. While there are no licensed vaccines for humans available yet, animal vaccines include the live attenuated Smithburn and inactivated RVFV in Africa [70]. Unfortunately, these are not DIVA (differentiating infected from vaccinated animals) vaccines, which can present a problem for the export of livestock and its products. Among the vaccines in the pipeline, clinical trials have been conducted for formalin-inactivated and attenuated vaccines, and these have demonstrated seroconversion and long-term protection against RVFV in both animals and humans [71,72]. Nevertheless, the attenuated vaccine retains the risk of reversion through reassortment with field strains.

While an MV vector has not yet been used in the development of an RVFV vaccine, considering the drawbacks of the current vaccine options and candidates, its advantages provide a strong argument to pursue this approach. Furthermore, MV has been shown to infect animals through the Nectin4 receptor without requiring CD46 (unpublished) making this platform viable for animal vaccines as well.

5. Conclusion

The MV platform is highly flexible, enabling easy modification to create a replicating delivery vector for various protective antigens. This platform benefits of the advantages of live attenuated vaccines without the risks and drawbacks. This “plug-and-play” property will help ensure the timely availability of preventive vaccines whenever a new epidemic occurs. The platform has a track record in safety and immunogenicity for other relevant antigens and pathogens and a well-established production process that allows substantial acceleration in development timelines. The various MV-vectored vaccines that have demonstrated solid performance in early phase clinical trials provide proof-of-concept that the MV platform is a powerful tool in the fight against current and emerging viral pathogens.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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