Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Medical countermeasures against henipaviruses: a review and public health perspective

Raúl Gómez Román, Nadia Tornieporth, Neil George Cherian, Amy C Shurtleff, Maina L’Azou Jackson, Debra Yeskey, Adam Hacker, Eric Mungai, Tung Thanh Le

Henipaviruses, including Nipah virus, are regarded as pathogens of notable epidemic potential because of their high pathogenicity and the paucity of specific medical countermeasures to control infections in humans. We review the evidence of medical countermeasures against henipaviruses and project their cost in a post-COVID-19 era. Given the sporadic and unpredictable nature of henipavirus outbreaks, innovative strategies will be needed to circumvent the infeasibility of traditional phase 3 clinical trial regulatory pathways. Stronger partnerships with scientific institutions and regulatory authorities in low-income and middle-income countries can inform coordination of appropriate investments and development of strategies and normative guidelines for the deployment and equitable use of multiple medical countermeasures. Accessible measures should include global, regional, and endemic in-country stockpiles of reasonably priced small molecules, monoclonal antibodies, and vaccines as part of a combined collection of products that could help to control henipavirus outbreaks and prevent future pandemics.

Introduction

Nipah and other henipaviral diseases are listed among the WHO research and development blueprint priority diseases that pose a substantial public health risk because of their epidemic or pandemic potential and the absence of specific medical countermeasures to control and mitigate them. Like other viruses of the henipavirus genus, Nipah virus (NiV) and Hendra virus (HeV) are zoonotic viruses that can spill over from Pteropus spp bats—their natural hosts and reservoir—to other mammals including humans. Transmission occurs via exposure to animal or human secretions or respiratory droplets. Human infections with NiV were originally described as a syndrome of fever and rapid neurological decline (ie, encephalitis) following contact with pigs. Since 2001, outbreaks (of Nipah virus Bangladesh strain [NiV-B]) report prominent respiratory symptoms (eg, atypical pneumonia and severe respiratory problems, including acute respiratory distress) and human-to-human transmission. Since 1994, henipavirus spillover events have caused human outbreaks in several countries, including Australia, Bangladesh, India, Malaysia, the Philippines, and Singapore. Although these outbreaks have thus far involved fewer than 1000 confirmed cases in total, the case–fatality rate for henipavirus infections can be as high as 100% depending on the context and constraints of the health-care systems where outbreaks occur. The geographical range where the various Pteropus bat species thrive is extensive (encompassing Indo-Pacific territories across the southeast Asia and western Pacific regions) and covers half of the global population. In addition to the tragic loss of human lives, henipavirus outbreaks can generate fear, stigma, loss of livestock (pigs and horses), and have a negative economic effect on affected communities. Although the reproduction number (R0) for HeV has not been calculated, the R0 for NiV ranges from 0.19 to 0.59 in nosocomial settings or in the community, including corpse-to-person transmission.

Key messages

• The pipeline for henipavirus countermeasures in development with clinical or preclinical data in the public domain includes at least eight small molecules, four monoclonal antibodies, and more than 15 vaccine candidates.

• Several of these potential henipavirus medical countermeasures employ molecules, concepts, or technologies that are being used, where available, to treat or prevent COVID-19.

• Access to henipavirus countermeasures will depend on various factors including cost and whether or not their use is authorised by the national regulatory authorities in henipavirus-affected countries.

• Given the sporadic and unpredictable nature of current henipavirus outbreaks, traditional phase 3 clinical trial regulatory pathways might not be feasible for vaccines; thus, national regulatory authorities might have to rely on alternative regulatory pathways such as conditional market authorisation, authorisation under exceptional circumstances, or the animal rule.

• To prepare for future henipavirus outbreaks, funding agencies, sponsors, and manufacturers of henipavirus medical countermeasures must jointly understand the regulatory requirements to apply for emergency use or relevant authorisation of henipavirus medical countermeasures in the affected countries where these measures are ultimately needed.

• Lessons learned from the current COVID-19 pandemic provide a platform to connect with several stakeholders and to better prepare for future virus threats, including those posed by henipaviruses.
to deploy medical countermeasures. Vaccines, antivirals, and other medical countermeasures must be developed and made available for use worldwide, especially to populations at the highest risk of henipavirus infection.

Internationally coordinated development of medical countermeasures against henipaviruses has mainly focused on NiV, but important progress has also been made in the development of such measures against HeV. Medical countermeasures against other henipaviruses have not been described. This Review will focus on publicly available evidence of potential medical countermeasures at any stage of development against both of these viruses. The aim is to provide a synthesis of available knowledge to aid epidemic preparedness. Potential costs and equitable access by all henipavirus-affected countries, including low-income and middle-income countries, are considered.

Scope and search strategy
We reviewed information available in the public domain on therapeutics, monoclonal antibodies, and vaccine candidates evaluated for prophylaxis or protection, primarily against NiV and HeV infection, with a small amount of information found for other henipaviruses such as Cedar henipavirus, Ghanaian bat henipavirus, and Mojijiang henipavirus. A targeted literature search was done in the English language following PRISMA guidelines and using “Nipah” OR “Hendra” OR “henipaviruses” as keywords with additional MeSH terms and selection criteria described in detail in the appendix p 1. Our search strategy did not include diagnostics. Although diagnostics are classified as medical countermeasures, they are mentioned here only in the context of other medical countermeasures. A detailed landscape analysis of the henipavirus diagnostic pipeline has been published elsewhere.12

Evidence for medical countermeasures
Small molecules and antivirals
No approved therapy exists for henipavirus encephalitis, and a target product profile for potential NiV therapeutics is currently being developed by WHO.13 Where available, intensive supportive therapy for severe respiratory and neurological complications is the current standard of care for individuals infected with henipavirus.14−16 Further evidence is required to generate substantive guidance protocols for pre- and post-exposure prophylaxis against henipavirus encephalitis. Available evidence regarding potential therapeutics against henipavirus encephalitis is displayed in table 1. Most of these compounds are broadly active antiviral therapeutics targeting a range of RNA and DNA viruses, rather than specifically developed as henipavirus medical countermeasures.

Although some of the compounds listed in table 1 are approved for other indications, none are yet WHO-prequalified for global procurement. Although a few of these have been shown to inhibit viral replication of henipaviruses in vitro and in vivo, there is still a paucity of evidence in animal models, partly due to the restricted access to biosafety level 4 (BSL4) laboratories required to do experiments. Thus, several research groups are doing in-silico analyses18 or biosafety level 2 pseudotyped virus assays19 to design and screen compounds for the potential treatment of henipavirus encephalitis before animal and clinical testing. Although animal challenge studies have mainly been against NiV, the evidence available for remdesivir, favipiravir, ribavirin, and griffithsin suggests that these agents could also offer broad protection against other henipaviruses (table 1). Only remdesivir and VIKI-dPEG-Toco are supported by non-human primate challenge data in African green monkeys, whereas all other experiments have been done in smaller animals such as mice, ferrets, or Syrian golden hamsters. Remdesivir has been shown to be protective against NiV challenge in African green monkeys when daily, intravenous treatment was initiated within 24 h of exposure to NiV and continued for 12 days.20 Favipiravir has been shown to be protective in Syrian golden hamsters when given immediately after NiV infection.21 Although these compounds have shown protection against challenge or post-exposure in animal models, demonstration of a therapeutic effect following symptom onset is still missing and merits further research.

For further development of these drugs as potential henipavirus medical countermeasures, additional preclinical and clinical studies are needed to determine the protective efficacy of the treatment regimen when initiated more than 24 h post-virus challenge, or even after symptom onset. Such studies will help define scenarios for prophylactic medical countermeasure use, as well as use of medical countermeasures as a post-infection intervention. The potentially narrow treatment window (within 24 h of exposure), timing of deployment, administration, and appropriate volumes of these products need to be considered for stockpiling. Notably, NiV can present with relapsing encephalitis,22 and such cases might also benefit from antiviral prophylaxis.

Ribavirin (approved for hepatitis C virus) remains the only therapeutic with supportive evidence from a human outbreak;23 mortality was reduced by 36% when ribavirin was used empirically in Malaysia during the outbreak of Nipah there in September, 1998–June, 1999.18 However, this evidence is limited due to the open-label nature of the study, the use of data from historical control patients who declined treatment or received standard treatment before ribavirin was available, and the simultaneous provision of intensive supportive care to patients. Ribavirin has since been used on a compassionate basis during the 2018 Indian outbreak of Nipah encephalitis24,25 in which its use led to a possible reduction in viral load.26 Soluble Ephrin-B2 receptors (EFBN2) have been shown to inhibit binding of NiV and HeV to target cells in vitro,27 but to our knowledge no EFBN2 analogues have been developed and specifically tested as potential therapeutics against henipaviruses.
| Classification | Available evidence so far (route of therapeutic administration) | Target | Mode of action | Finding | Development or licensure status and indication |
|----------------|------------------------------------------------------------------|--------|---------------|---------|-----------------------------------------------|
| Ribavirin[^1]  | Antiviral, Open-label clinical trial in humans (oral and intravenous) | NIV    | Viral replication inhibition | Reduced mortality of treated patients compared with non-treated patients (by 36%)[^6] in Malaysian outbreak (1998) | Approved for hepatitis C virus and respiratory syncytial virus in several countries |
| Remdesivir[^2] | Antiviral, African green monkeys (intravenous) | NIV    | Nucleotide analogue prodrug, inhibits viral replication | Protection against viral challenge | Approved for COVID-19 by the US FDA. Emergency use authorisation for COVID-19 in Australia, Bangladesh, India, Singapore, Japan, Taiwan, and the European Union[^7] |
| Favipiravir[^8] | Antiviral, Syrian golden hamsters (oral and subcutaneous) | NIV, HeV | Viral RNA-dependent RNA polymerase inhibitor | Protection against viral challenge | Approved for influenza A in Japan, and for COVID-19 in several countries. Emergency use authorisation for COVID-19 in India[^9] |
| Chloroquine[^10[^11] | Antimalarial, Syrian golden hamsters (intraperitoneal) and ferrets (route not stated) | NIV, HeV | Inhibition of F protein maturation | Inhibition of viral replication in vitro. No conclusive evidence in vivo challenge—in combination with ribavirin | Approved for malaria in several countries |
| Heparin[^12] | Anticoagulant, Syrian golden hamsters (subcutaneous) | NIV, HeV | Inhibits cell-mediated viral trans-infection by binding to heparan sulfate | Inhibition of viral trans-infection restricts NIV infection in Syrian golden hamsters | Approved for coagulopathies in several countries. Experimental: preclinical (Syrian golden hamster study) |
| Rintatolimid[^13] | Interferon inducer, Syrian golden hamsters (subcutaneous and intraperitoneal) | NIV | Induces IFN-α and IFN-β production, inhibition of viral replication | Inhibition of viral replication and protection against viral challenge | Approved for chronic fatigue syndrome in Argentina. Experimental (phase 1 and 2 trials) for HIV and chronic fatigue syndrome[^14] |
| Griffithsin[^4] | Antiviral lectin, Syrian golden hamsters (intranasal) | NIV | Inhibits viral entry, replication and syncytia formation | Reduced viral replication in vitro and provides partial protection against viral challenge | Experimental: phase 1 trials for HIV[^15] |
| VIKI-dPEG4-Toco, VIKI-PEG4-Chol[^16] | Viral fusion inhibitory peptide | African green monkeys and Syrian golden hamsters (intratracheal and intranasal) | NIV | Inhibition of F protein fusion and cell entry | Partial protection against viral challenge | Experimental: preclinical |
| Gliotoxin[^2] | Mycotoxin | In vitro | Viral RNA-dependent RNA polymerase inhibitor | Inhibition of infection and replication; Cytotoxic but possible topical applications | Experimental: exploratory |
| Bortezomib[^17] | Anticancer | In vitro | Proteasome inhibitor | Inhibition of viral budding | Approved for multiple myeloma and mantle cell lymphoma by the US FDA |
| Balapiravir, R147934[^18] | Antiviral | In vitro | Viral RNA-dependent RNA polymerase inhibitor | Inhibition of viral replication | Experimental, discontinued in phase 1 trials for dengue virus and hepatitis C virus[^19] |
| Lumicitabine, ALS-8112[^20] | Antiviral | In vitro | Nucleotide analogue prodrug, inhibits viral replication | Inhibition of recombinant and wild-type NIV replication, and reduced NIV infectious virus titre | Experimental: phase 1 and phase 2 trials for respiratory syncytial virus[^21] |
| CH25H[^22] | Antiviral | In vitro | Intra-venous-stimulated genes: catalyses oxidation of cholesterol to 25-hydroxycholesterol | Inhibition of viral membrane fusion and NIV replication | Experimental: exploratory |
| KIN1408[^23] | Antiviral | In vitro | Immunomodulation of interferon regulatory factor 3 | Inhibition of viral replication and decreased viral load in vitro | Experimental: exploratory |
| AB00991123, AB00992194, and AB00993210[^24] | Antivirals | In vitro | Sulfonamide compounds, unknown | Inhibition of NIV-induced cytopathic effect and virus replication | Experimental: exploratory |

HeV=Hendra virus. NIV=Nipah virus. *Patients also received intensive supportive treatment, and comparators were historical control patients.

Table 1: Available evidence on potential small molecules against henipavirus encephalitis

A major bottleneck in moving promising compounds to clinical development is access to BS14 facilities to conduct proof-of-concept challenge studies. Other key aspects for repurposed therapeutics include the need for further evidence on oral, intravenous, or intranasal routes of administration, the associated costs of intravenous administration, and the need for hospital infrastructure and supportive treatment. Regulatory requirements for repurposing approved medications, such as additional clinical trials for novel indications and...
reformulation of the product, must also be taken into account.

**Monoclonal antibodies**

Monoclonal antibodies (mAbs) could be a viable medical countermeasure option for deployment under compassionate use for prophylaxis, and this might remain the case until a vaccine is available for emergency use or licensed. Similar to small molecules and antivirals, mAbs can potentially be used for both pre-exposure and post-exposure prophylaxis and fill in a critical gap before vaccine availability. mAbs may even be deployed in an emergency situation even after a vaccine becomes available, given that many of the vaccines follow a two-dose regimen and would require several days to elicit protective immunity. Four main mAb projects constitute the current landscape of mAbs under development against henipaviruses (table 2). These mAbs have also been used as reagents to characterise antigens and inform vaccine design strategies.

mAb m102·4 is the furthest in development and is the only NiV mAb with published phase 1 data. It has been shown to protect African green monkeys against challenge with both Malaysia and Bangladesh NiV strains.47–49 m102·4 has been administered under compassionate use as post-exposure prophylaxis for HeV to 14 individuals in Australia and the USA.48 The phase 1 trial in Australia included 40 healthy adults, who received escalating single doses from 1 mg/kg to 20 mg/kg, or two 20 mg/kg infusions, 72 h apart, or placebo.50 No serious adverse events or adverse events leading to discontinuation were observed in this study. The most commonly reported adverse events included milder to moderate infections and infestations and headaches, occurring at a similar frequency in active treatment and placebo recipients. Another mAb, h5B3·1 (ie, the humanised version of mAb 5B3 originally derived from mouse hybridoma 5B3), neutralises HeV and NiV Bangladesh and Malaysia strains and inhibits viral fusion in vitro.51 In NiV and HeV post-exposure prophylaxis models in ferrets, mAb h5B3·1 protected animals against disseminated disease when administered intraperitoneally on days 3 and 5 post-infection.52 In 2020, mAb HENV-26 and mAb HENV-32, two naturally occurring human mAbs, were isolated from a donor immunised with a veterinary HeV protein subunit vaccine (Equivac; Zoetis, Rhodes, NSW, Australia) administered under compassionate use. These mAbs were shown to neutralise both HeV and NiV Bangladesh and Malaysia strains.53 In a NiV post-exposure prophylaxis model in ferrets, these mAbs also protected animals against disseminated disease when administered intraperitoneally on days 3 and 5 post-infection. Although their different epitope specificity would suggest that these mAbs could have synergistic properties if administered as a mAb cocktail, the mAbs were only tested separately in virus neutralisation assays and protective efficacy experiments. Furthermore, despite binding to NiV and HeV G proteins, the mAbs did not bind to G proteins from other henipaviruses such as Ghanaian bat henipavirus or Cedar henipavirus.54

The current engagement from academic, public, and biotechnology product developers is important for progression of the existing mAb pipeline. However, to further accelerate the development process and ensure that final products reach the target population, a clear strategy is required on the following four areas: scenario planning for product development and regulatory pathways in relation to disease epidemiology; further participation from industry, especially product developers with experience in the development of medical countermeasures against other pathogens, to lead and support henipavirus medical countermeasure development efforts; technical transfer and engagement of local manufacturers in endemic countries; and further progression of mAb development to clinical trials and potential licensure.

**Vaccines**

A draft Nipah vaccine target product profile published by WHO55 stipulates that a NiV vaccine be used for reactive immunisation (ie, active immunisation of at-risk individuals in the area of an ongoing outbreak) and “in conjunction with other control measures to curtail or end an outbreak”.56 In an outbreak scenario, key preferred

| Evidence available | Current development stage | Target | Developer |
|-------------------|---------------------------|--------|----------|
| mAb 102·4 | Human (phase 1 trial), ferrets, and African green monkeys | Phase 1 | HeV or NiV G glycoprotein | Henry M Jackson Foundation for the Advancement of Military Medicine (Bethesda, MD, USA) |
| mAb 5B3, mAb h5B3·1 | Mice and ferrets | Preclinical | HeV or NiV pre-fusion F glycoprotein | University of Washington (Seattle, WA, USA) and Uniformed Services University (Bethesda, MD, USA) |
| mAb HENV-26, mAb HENV-32 | Ferrets | Preclinical | HeV or NiV G glycoprotein (receptor-binding protein) | Vanderbilt Vaccine Center (Nashville, TN, USA) |
| Anti-G mAb, anti-F mAb | Hamsters | Preclinical | NiV G and F glycoprotein | INSERM (Paris, France), Université Claude Bernard Lyon 1 (Lyon, France), and Institut Pasteur (Paris, France) |

HeV=Hendra virus. mAb=monoclonal antibody. NiV=Nipah virus.

Table 2: Preclinical and clinical evidence for candidate monoclonal antibodies against henipaviruses
characteristics of a NiV vaccine include an ability to elicit protective immunity rapidly (preferably within 2 weeks) after a single dose, acceptable safety profile, high efficacy (>90%), thermostability (2–8°C), and an ability to confer immunity and protection against Malaysia and Bangladesh strains of NiV.

Table 3 shows the current landscape of the henipavirus vaccine pipeline. There are more than 40 candidates in development with data available in the public domain; however, eight of these are intended primarily for veterinary use. Nearly half (n=19) of henipavirus vaccine candidates are based on viral vector platforms, 17 are protein subunits or virus-like particles formulated in various adjuvants, and two are based on mRNA technology. The main targets of henipavirus vaccines in development are the surface G glycoprotein or the fusion F protein. All listed vaccines are highly immunogenic and elicit henipavirus binding antibodies, neutralising antibodies, or both, with at least 15 candidates conferring various levels of protection against challenge with homologous or heterologous henipavirus strains in African green monkeys, Syrian golden hamsters, or ferrets (table 3).

The recombinant, soluble HeV G glycoprotein candidate is the only vaccine candidate that has progressed to phase 1 clinical trials. This candidate builds on existing knowledge gained from using the same soluble protein in several pre-clinical and veterinary studies, including pivotal data used to develop the Equivac HeV vaccine approved for veterinary use in horses. In addition to good manufacturing practices and good clinical practices required to develop the soluble HeV G product for human use, a key difference between the vaccine intended for humans and its previous versions is the adjuvant formulation in Alhydrogel (Croda, USA) at a 1:10 ratio.

It is too early to ascertain whether any of these candidate vaccines will achieve licensure and meet the preferred product characteristics described in the draft WHO target product profile for a NiV vaccine. The low temperature requirement could create challenges for

| Viral vectors                                                                 | Vaccine regimen and administration route | Animal models used                                                                 | Henipavirus challenge strain | Reference |
|------------------------------------------------------------------------------|------------------------------------------|------------------------------------------------------------------------------------|-----------------------------|-----------|
| Recombinant vaccinia viruses (modified vaccinia virus Ankara) expressing NiV-M or HeV F, G, or N | Single dose (intraperitoneal)            | Mice                                                                               | None                        | 56        |
| Vaccinia virus vector (NYVAC) expressing NiV-M G or F                       | 2 doses, 1 month apart (subcutaneous)    | Syrian golden hamsters                                                             | None                        | 57        |
| Canarypox vector (ALVAC) expressing NiV-M G or F                            | 2 doses, 14 days apart (intramuscular)   | Pigs†                                                                              | None                        | 58,59     |
| Venezuelan equine encephalitis virus expressing HeV or NiV-M or G F          | 3 doses on weeks 0, 5, and 18 (footpad inoculation) | Mice                                                                               | None                        | 60        |
| Replication-defective VSV-DG vector expressing NiV-M G or F                  | Single dose (intranasal or intramuscular) | Mouse                                                                              | None                        | 61        |
| Newcastle disease virus vector expressing NiV-M F or G                       | 2 doses, 4 weeks apart (intramuscular)   | Mice, pigs*                                                                        | None                        | 62        |
| Single-cycle replication VSV-DG vector expressing NiV-B G and/or F           | Single dose (intramuscular)              | Ferrets                                                                            | None                        | 63        |
| Adeno-associated virus vector expressing NiV-M G                             | Single dose (intramuscular)              | Syrian golden hamsters                                                             | None                        | 64        |
| Measles virus vaccine vectors (HL and Ed strains) expressing NiV-M G         | 2 doses, 21 or 28 days apart (intraperitoneal [Syrian golden hamsters] or subcutaneous [African green monkeys]) | Syrian golden hamsters, African green monkeys | None                        | 65        |
| Live-attenuated rVSV-ZEBOV-GP vector expressing NiV-M G, F, or N             | Single dose (intraperitoneal)            | Syrian golden hamsters                                                             | None                        | 66        |
| Live-cycle replication VSV-DG vector expressing NiV-M G or F                 | Single dose (intramuscular)              | Syrian golden hamsters                                                             | None                        | 67        |
| Live-attenuated and beta-propiolactone-inactivated VSV or rabies virus vaccine vectors expressing codon-optimised HeV G | Single dose (live) or three doses (beta-propiolactone), on weeks 0, 2, and 3 (intramuscular) | Mice*                                                                              | None                        | 68        |
| Live-attenuated rVSV-ZEBOV-GP vector expressing NiV-M G                       | Single dose (intramuscular)              | African green monkeys                                                              | None                        | 69†       |
| Live-attenuated rHSV-ZEBOV-GP vector expressing NiV-M G                       | Single dose (intraperitoneal)            | Syrian golden hamsters                                                             | None                        | 70        |
| Canarypox vector (ALVAC) expressing HeV G or F                               | 2 doses, 21 days apart (intramuscular)   | Syrian golden hamsters and ponies (horses)                                        | None                        | 71        |
| Non-replicating VSV-DG vectors expressing NiV-M G and/or F                   | Single dose (intranasal or intracranial) | Mouse                                                                              | None                        | 72        |
| Live-attenuated and beta-propiolactone-inactivated rabies virus vaccine vector expressing NiV-B G | Single dose (live) or 2 doses (beta-propiolactone), 28 days apart (intramuscular) | Mice                                                                              | None                        | 73        |
| Single-cycle replication VSV-DG vector expressing NiV-B G and/or F           | Single dose (intramuscular)              | African green monkeys                                                              | None                        | 74†       |
| Chimpanzee adenovirus vector expressing NiV-B G                              | Single or two doses, 28 days apart (intramuscular) | Syrian golden hamsters                                                             | None                        | 75        |
| Modified vaccinia virus Ankara expressing NiV-M sG or G                       | Single or 2 doses, 21 days apart (intraperitoneal or intramuscular) | IFNAR -/- mice                                                                     | None                        | 76        |
| Recombinant rabies viruses Evelyn-Rokitnicki-Abelseth strain, rERAG, expressing NiV-M G or F | 2 doses, 8 weeks apart (oral)            | Mice and pigs*                                                                     | None                        | 77        |
| Bovine herpes virus 4 or canarypox vectors (ALVAC) expressing NiV-M G or F   | 2 doses, 3 weeks apart (intramuscular)   | Pigs*                                                                              | None                        | 5,78      |

(Table 3 continues on next page)
Table 3: Chronological overview of henipavirus vaccines in development, by platform

| Vaccine regimen and administration route | Animal models used | Henipavirus challenge strain | Reference |
|-----------------------------------------|--------------------|------------------------------|-----------|
| Recombinant soluble NiV-M G glycoprotein in CpG plus Alhydrogel adjuvant | African green monkeys | NiV-M | 82 |
| Soluble trimeric forms of HeV and NiV-M F proteins (sFGCNGt) in Sigma Adjuvant System adjuvant. | Ferrets | NiV-B | 83 |
| Recombinant soluble HeV G glycoprotein in CpG and Alhydrogel adjuvant 2 doses, 21 days apart (intramuscular) | African green monkeys | HeV | 84 |
| Recombinant soluble HeV G glycoprotein in Alhydrogel with or without CpG adjuvant 2 doses, 21 days apart (intramuscular) | None | | 81 |
| Recombinant soluble HeV G glycoprotein (produced in 293 or Chinese hamster ovary cells) in a proprietary adjuvant (Zoetis, Inc) 2–5 doses, weeks 0 and 3, then at 6 months and then yearly (intramuscular) | Horses* | HeV | 85, 86 |
| Recombinant soluble HeV G glycoprotein in a proprietary adjuvant (Zoetis, Inc) 2 doses, 21 days apart (intramuscular) | Pigs* | NiV-M and HeV | 87 |
| Recombinant soluble HeV G glycoprotein in alhydrogel + CpG adjuvant 2 doses, 20 days apart (subcutaneous) | Mice | None | 90 |
| Molecular clamp-stabilised F protein (mcsF) 2 doses, 3 weeks apart (intramuscular) | Pigs* | NiV-M | 5 |
| Multiple pre-fusion-stabilised F and oligomeric G proteins derived from NiV-M and formulated in aluminium hydroxide 2 doses, 3 weeks apart (intramuscular) | Mice | None | 89 |
| Monovalent, bivalent, and tetravalent Fc-linked G proteins from NiV-M, HeV, GnV, and MoJv formulated in CpG and Alhydrogel 2 doses, 3 weeks apart (intramuscular) | Mice | None | 90 |
| Recombinant soluble HeV G glycoprotein, produced in HEK-293 cells, formulated in Alhydrogel 2 doses or 2 doses, 4 weeks apart (intramuscular) | African green monkeys | HeV (Brisbane) and NiV B | 91 |

**Virus-like particles**

| Vaccine regimen and administration route | Animal models used | Henipavirus challenge strain | Reference |
|-----------------------------------------|--------------------|------------------------------|-----------|
| Virus-like particles containing NiV-M M, G, and F 3 doses on days 0, 15, and 29 (subcutaneous) | Mice | None | 92 |
| Virus-like particles containing NiV-M M, F, and G, formulated in various adjuvants (alum, monophosphoryl lipid A, and CpG) 3 doses on days 0, 21, and 42 (intramuscular) | Syrian golden hamsters | NiV-M | 93 |
| Virus-like particles containing NiV-M M and F or G in Sigma Adjuvant System 3 doses on weeks 0, 3, and 5 (intramuscular) | Rabbits | None | 94 |
| Virus-like particles containing NiV-M F and G and HeV M 3 doses on weeks 0, 3, and 6 (intraperitoneal) | Mice | None | 95 |

**Cellular debris**

| Vaccine regimen and administration route | Animal models used | Henipavirus challenge strain | Reference |
|-----------------------------------------|--------------------|------------------------------|-----------|
| Pellets and supernatants from sF9 cells expressing recombinant NiV-M F and G proteins in a baculovirus system 2 doses, 3 weeks apart (intramuscular and intraperitoneal) | Mice | None | 96 |

**DNA**

| Vaccine regimen and administration route | Animal models used | Henipavirus challenge strain | Reference |
|-----------------------------------------|--------------------|------------------------------|-----------|
| Plasmids encoding codon-optimised NiV-M F and/or G 2 doses, 4 weeks apart (intramuscular) | Mice | None | 97 |
| Plasmids encoding NiV-M F and/or G Single dose (intramuscular) followed by electroporation | Mice | None | 98 |

**mRNA**

| Vaccine regimen and administration route | Animal models used | Henipavirus challenge strain | Reference |
|-----------------------------------------|--------------------|------------------------------|-----------|
| HeV G codon-optimised mRNA in liquid nanoparticles Single dose (intramuscular) | Syrian golden hamsters | NiV-M | 99 |
| mRNA-1215, mRNA encoding NiV-M F and G in liquid nanoparticles To be determined | Undisclosed preclinical development | To be determined | 100 |

GHV=Ghanaian bat henipavirus. GP=glycoprotein. HeV=Hendra virus. MoJv=Mojiang henipavirus. NiV=Nipah virus. NiV-B=Nipah virus Bangladesh. NiV-M=Nipah virus Malaysia. VSV=vesicular stomatitis virus. ZEBOV=Zaire Ebola virus. *These vaccines are intended primarily for veterinary use. †The single-cycle replication VSV-DG vector expressing NiV-B G and/or F is identical in these studies. ‡The live-attenuated rVSV-ZEBOV-GP vector expressing NiV-M G is identical in these studies. §The soluble HeV G protein is identical in all studies using different adjuvant formulations. ¶The virus-like particles are identical in these studies using different formulations. **The live-attenuated rVSV-ZEBOV-GP vector expressing NiV-M G is identical in these studies.

some vaccine candidates; however, this problem is currently being addressed with COVID-19 vaccines and is not necessarily a barrier, as even a small amount of ultracold chain capacity can be established rapidly during vaccine deployment in response to an outbreak. The single-dose vaccine regimen and cross-protection characteristics as described in the WHO target product profile might be possible to achieve. For example, a single dose of the ChAdOx-NiV Bangladesh vaccine candidate cross-protects Syrian golden hamsters against challenge with HeV and the NiV-Malaysia strain. The global effort to develop COVID-19 vaccines might pose a substantial risk to henipavirus vaccine development capacity, including delays in animal studies and reduced manufacturing capacity and funding. However, COVID-19 vaccine development has also accelerated many of the vaccine platform technologies that could be applied to henipavirus vaccine development and rapid response. Among these, the henipavirus mRNA vaccine candidates are likely to benefit from the experience in COVID vaccine development, scale-up manufacturing, regulatory approval, and deployment.
Projected costs of henipavirus medical countermeasures in a post-COVID-19 era

The current henipavirus medical countermeasure pre-clinical and clinical landscape includes nine small molecules, four mAbs, and 15 vaccine candidates. Included candidates are those with clinical data in humans or proof-of-concept data in ferrets, Syrian golden hamsters, or African green monkeys. This list of candidates excludes those with only exploratory in-vitro data, or pre-clinical data without a known henipavirus challenge study. The development pipeline is heavily shifted towards vaccines because these are potentially the most effective public health intervention. The main funders of currently active henipavirus vaccine development projects are listed in appendix p 3. In addition to these, the National Institute of Allergy and Infectious Diseases has supported and continues to fund the development of henipavirus mAbs and other medical countermeasures.30–32 Furthermore, as part of its new strategic priorities, the Coalition for Epidemic Preparedness Innovations (CEPI) aims to support the development of a fully licensed vaccine or prophylactic mAb against Nipah by 2027.33,34

Despite this progress, the development of vaccines and treatments against infectious diseases is a lengthy, costly, and risky process. The development of medical countermeasures against COVID-19 has proved that at least the speed of product development can be partially overcome with broad mobilisation of public and philanthropic funding, and engagement of scientists, policymakers, epidemiologists, public and private vaccine developers, manufacturers, and regulators involved in emergency use processes. However, this advanced speed comes with additional costs due to a greater number of projects entering the pipeline, and at-risk costs needed for large-scale manufacturing of various leading products in parallel before conclusion of the clinical testing.35 COVID-19 medical countermeasure investments will probably increase the speed of product development and the number of medical countermeasure platform technologies against other pathogens, including those against henipavirus. Table 4 estimates the costs of potential henipavirus medical countermeasures in a post-COVID-19 era. Vaccines and small molecule regimens will continue to be more affordable per person than mAbs. However, vaccine impact at large, including vaccine effectiveness and cost-effectiveness of potential medical countermeasures, will need to be determined in a post-authorisation and post-licensure era.

Small molecules

For small molecules, we project costs ranging from US$14 to $600 per person per regimen (table 4). Advantages are associated with repurposing commercially available products for new indications, including the cost benefits of limited additional investments needed to ramp up supply, or in the cases of remdesivir and favipiravir, the leverage scale from demand generated by the current COVID-19 indication. Furthermore, commercialised drugs are likely to have a reliable supply chain of generic versions at substantially reduced costs, with the potential for a good investment case for pre-exposure or post-exposure prophylaxis for high-risk populations in affected areas. An example of a prophylaxis campaign during an outbreak would be the use of oseltamivir (Tamiflu; F Hoffmann-La Roche AG, Basel, Switzerland) during the 2009 influenza A (H1N1) pandemic.36 For henipavirus outbreaks, however, further supportive evidence in animal models and clinical trials will be needed in support of a mass prophylaxis concept. The route of administration will be especially relevant in an outbreak scenario—for example, daily intravenous administration of remdesivir would be limited by cost, infrastructure, and the need for hospital stays.

mAbs

For mAbs, we project costs of more than $1000 per person per regimen (table 4). Further funding will be required to advance henipavirus mAb programmes into early-stage and late-stage clinical development. Delivery of mAbs, especially via intravenous infusion, requires capacity and infrastructure, which could prove challenging in some outbreak settings. Subcutaneous administration of mAbs against COVID-19 is being tested and submitted for licensure.37 If successful, this concept will fundamentally improve access to mAb treatments. Casirivimab and imdevimab (Regeneron [Tarrytown, NY, USA]) and bamlanivimab (Eli Lilly [Indianapolis, IN, USA]) COVID-19 mAbs have rapidly completed phase 1 trials and received emergency use listings as treatment against mild and moderate COVID-19,38 setting the precedent for future emulation in a henipavirus outbreak. However, further data are needed regarding the added benefit to children and adolescents, and the prophylactic indication for mAbs.39,40

Vaccines

The cost of henipavirus vaccines in an epidemic or pandemic setting remains unclear; however, experience from COVID-19 vaccines using similar platforms suggests the price of vaccines could range between $4 per dose for viral vector vaccines to $37 per dose for mRNA vaccines.41 These figures do not include delivery costs, which could add substantially to the immunisation costs depending on vaccine logistics, infrastructure, and regimens.42 The cost per dose of a henipavirus vaccine in the scenario of a small number of outbreaks and a modest stockpile could also be higher as a result of the lower market potential. Although this price estimate is a wide range, vaccines might still be reasonably priced by comparison with other medical countermeasures such as mAbs. Public funding for research and development and advance purchase agreements could keep the cost affordable.
Further investments in diagnostics and virological surveillance

Laboratory-based diagnostic testing, contact tracing, and proactive quarantine and treatment of suspected cases, often collectively referred to as “test, track/trace, and treat” strategies, are indicated at the onset of an outbreak and can quickly isolate and treat patients to halt further spread of henipaviruses. Currently, however, no near-patient or point-of-care tests are currently used for Nipah or Hendra viruses, which is likely to be a major limitation for the development of other medical countermeasures. Incentivisation is therefore needed to commercialise diagnostic assays and to adapt them for early detection of henipavirus encephalitis in suspected epidemic or pandemic settings.

Although numerous in-house serological methods (ELISA) and nucleic acid amplification techniques (PCR) for Nipah detection exist globally, harmonisation of validation methods, standards, and reagents to facilitate development of commercial PCR kits is needed. A reverse transcription-loop-mediated isothermal amplification (RT-LAMP) assay for the NiV N gene has recently been developed and is significantly more sensitive than RT-PCR, demonstrating potential for a quicker and simple rapid diagnostic test for use in outbreak settings. Key barriers to the development of henipavirus diagnostic tests include: the scarcity of widely available sera from henipavirus survivors, which might be necessary to accelerate the evaluation, validation, and licensure of serologic diagnostics for human use; and the BSL4 laboratory requirements for diagnostics dependent on virus isolation and wild-type virus neutralisation assays.

Notably, all experimental knowledge on Nipah virus acquired over the past two decades is derived from only two virus strains (199902916 Malaysia and 200401066 Bangladesh). Investments in surveillance, virus isolation, and sequencing can further our understanding of the impact of Nipah virus strain variation on medical countermeasure efficacy.

Regulatory considerations

Modelling to evaluate the feasibility of conducting a phase 3 NiV vaccine trial in Bangladesh suggests that under the present low incidence scenario, traditional randomised, controlled efficacy trials are not feasible. Alternative licensure pathways in lieu of a traditional phase 3 vaccine efficacy trial, as described in the following paragraphs, should be considered.

Regulatory pathways

Various pathways exist for the licensure of new medical countermeasures or medical countermeasures for life-threatening diseases (table 5). These options include accelerated approval (by the Food and Drugs Administration [FDA] or the animal efficacy rule in the USA), and conditional approval or exceptional circumstances in the European Union (EU). These regulatory pathways might be suitable for the licensure of medical countermeasures against viruses that have unpredictable outbreak patterns and are not conducive to phase 3 human clinical efficacy trials. However, NiV outbreaks are very unlikely to occur where the US FDA or the European Medicines Agency (EMA) have jurisdiction. Therefore, further development of the regulatory procedures in potentially affected countries is paramount.
In the absence of specific regulatory mechanisms in affected countries, this article will reference the US FDA and the EMA regulatory procedures. The US accelerated approval pathway allows for surrogate or clinical intermediate endpoints and is used for therapies for serious conditions “as soon as it can be concluded that [their] benefits justify their risks”.136 For henipaviruses, an example of a surrogate endpoint could be a protective titre of virus-neutralising antibodies. Accelerated approval would only be granted with a post-marketing commitment to demonstrate efficacy in a well-controlled clinical trial at the time of an outbreak. Given the epidemiology of NiV, timely fulfilment of this commitment would be problematic.

The animal efficacy rule (US FDA) entails using animal disease comparisons might not reveal all features of human disease. There have been relatively few human cases of henipavirus encephalitis to enable description of the full human clinical and pathological basis of the disease; therefore, animal disease comparisons might not reveal all features of human disease. Finally, whether or not the available strains of henipavirus encephalitis (as well as the challenge dose and method of administration) used in the animal challenge studies are epidemiologically relevant remains unclear. Hence, using the the animal rule to obtain approval for a vaccine against NiV may be challenging.

In the European Union (EU), the conditional marketing authorisation133 has some similarities to the US accelerated approval procedure. The following

| Current scenario: $R_0 < 1$ | Data package could include | Examples of approved vaccines for other indications |
|-----------------------------|---------------------------|---------------------------------------------------|
| Accelerated approval (US FDA),122 conditional marketing authorisation or exceptional circumstances approval (EMA),138 or similar mechanisms | Phase 1 data, phase 2 data, phase 3 trial feasibility assessment (results from mathematical modelling), assay validation data, surrogate endpoint or correlates of protection data, passive transfer or adoptive transfer studies, bridging data for licensure, and post-approval confirmatory studies to demonstrate clinical benefit | Approvals based on surrogate endpoints;126 conditional marketing authorisation for Ervebo (recombinant vesicular stomatitis virus-Zaire Ebola virus)135 |
| Animal rule (US FDA)126 and exceptional circumstances (EMA)123 | Natural history study data and challenge data, additional requirements requested by national regulatory authorities for licensure, and post-approval confirmatory studies to demonstrate clinical benefit (if possible to conduct) | Approvals based on the animal rule;127 exceptional circumstances: Zabdeno (AA26.ZEOBV [adenovirus type 26 vector-based vaccine, expressing a Zaire Ebola virus glycoprotein])128 and Mvabea (MVA-BN-Filo [modified vaccinia Ankara vector-based vaccine, encoding glycoproteins from the Zaire Ebola virus])129 |
| Other, depending on specific national regulatory authority legislation. See Directorate General of Drug Administration, (Bangladesh)130 and the Central Drugs Standard Control Organization (India)131 as examples | To be defined by each national regulatory authority | Vary by different national regulatory authority |

**Table 5: Potential regulatory pathways to pursue henipavirus vaccine authorisation**

*Phase 2 clinical trial material can become so-called “outbreak-ready” for an investigational stockpile. †Investigational stockpile deployed.*

In the absence of specific regulatory mechanisms in affected countries, this article will reference the US FDA and the EMA regulatory procedures. The US accelerated approval pathway allows for surrogate or clinical intermediate endpoints and is used for therapies for serious conditions “as soon as it can be concluded that [their] benefits justify their risks”.136 For henipaviruses, an example of a surrogate endpoint could be a protective titre of virus-neutralising antibodies. Accelerated approval would only be granted with a post-marketing commitment to demonstrate efficacy in a well-controlled clinical trial at the time of an outbreak. Given the epidemiology of NiV, timely fulfilment of this commitment would be problematic.

The animal efficacy rule (US FDA) entails using animal disease comparisons might not reveal all features of human disease. There have been relatively few human cases of henipavirus encephalitis to enable description of the full human clinical and pathological basis of the disease; therefore, animal disease comparisons might not reveal all features of human disease. Finally, whether or not the available strains of henipavirus encephalitis (as well as the challenge dose and method of administration) used in the animal challenge studies are epidemiologically relevant remains unclear. Hence, using the the animal rule to obtain approval for a vaccine against NiV may be challenging.

In the European Union (EU), the conditional marketing authorisation133 has some similarities to the US accelerated approval procedure. The following
criteria must be met: the benefit–risk balance must be positive; the product must fulfil an unmet medical need; the benefit of making the product immediately available must be greater than the risk of additional data still being required; and comprehensive data post-authorisation must be provided in a timely manner. As is the case for the accelerated approval pathway, fulfilment of the latter is problematic given the epidemiology of NiV.

EU legislation also allows marketing authorisation to be granted in the absence of comprehensive data under exceptional circumstances. Unlike conditional marketing authorisation, where marketing approval is granted in the likelihood that the sponsor will provide such data post-approval within an agreed timeframe, the EMA can grant authorisation under exceptional circumstances when comprehensive data cannot be obtained even after authorisation. For example, approval under exceptional circumstances was granted in July, 2020, for Zabdeno and Mvabea (both Janssen-Cilag International NV, Beerse, Belgium) against Ebola virus in individuals 1 year of age or older. The fact that Zabdebo and Mvabea received approval under exceptional circumstances in the EU but is yet to be approved in the USA implies that the EU exceptional circumstances regulatory route may be less challenging than the animal rule in the USA.

Early discussions with the US FDA and EMA are critical to establish specific data requirements and map the most appropriate route to approval for the developer. Importantly, the aforementioned US and EU regulatory routes are defined within specific legislation and require robust technical capabilities, especially with regard to the review and acceptance of animal efficacy data. Further work will be needed to evaluate the extent to which existing legislation in henipavirus-affected countries provides an appropriate level of flexibility to allow the use of animal efficacy data as the basis for regulatory approval. If such mechanisms are not available, the development of similar legislation should be considered by those countries where future henipavirus outbreaks could occur.

Pre-licensure mechanisms: emergency use of vaccines

National regulatory authorities might consider the authorisation of vaccines in their jurisdiction by allowing the use of an investigational product in emergency situations (R>1), such as in the event of a henipavirus pandemic, or if a public health emergency of international concern (PHEIC) is declared by WHO. Preparedness efforts can speed up the time from the declaration of a PHEIC to the licensure of vaccines for emergency use. The WHO emergency use listing procedure has enabled rapid deployment of COVID-19 vaccines to a broad range of countries.

All countries with potential for a henipavirus outbreak must have emergency legislation to enable the rapid deployment of vaccines in the event an emergency use listing is granted by WHO. Since there might be a delay between the emergence of a henipavirus outbreak and declaration of a PHEIC, national regulatory authorities should also have legislation to enable the deployment of vaccines under their own emergency measures.

Data packages for vaccine candidates with some clinical data could be formally submitted to regulators in those countries where future outbreaks might occur and an authorisation could be requested based on existing clinical and non-clinical data, supplemented by data from the vaccine platform technology. These data could undergo a regulatory assessment based on anticipating the local benefit–risk in the country of deployment in the event of an outbreak. This would allow research to continue and additional data to be generated to support licensure. Such a licensed vaccine could be rapidly deployed in an attempt to control the emerging outbreak. Effectiveness and pharmacovigilance data could be collected in the real-world setting to confirm vaccine efficacy and safety. Although there is no current regulatory mechanism to support this, we advocate for an open debate on the feasibility of this approach. Case studies from the deployment of COVID-19 vaccines licensed in China, India, and Russia before the availability of phase 3 efficacy data, as well as learnings from undertaking clinical vaccine trials during the 2014–16 west African Ebola outbreak, could contribute to the framing of innovative regulatory frameworks in response to future pandemics.

A minimal dataset will be reviewed by regulatory authorities to enable rapid access and deployment of a vaccine during an emergency, irrespective of the regulatory mechanism used. As such, the ultimate objective of early deployment should be to continue to generate and collect the appropriate level of data to confirm effectiveness and achieve full licensure of the vaccine.

In the event that vaccines against NiV, HeV, or both do achieve licensure, it will also be important to advocate for implementation of accelerated regulatory approaches to enable the use of so-called core dossiers based on the pre-pandemic strains and manufacturing technology platform experience to rapidly enable a strain change in the event that the henipavirus outbreak contains mutations that make the licensed vaccines less efficacious due to insufficient cross-reactivity.

Ensuring equitable access

Crucially, affected populations must be able to access medical countermeasures irrespective of cost. Four countries (Bangladesh, India, Malaysia, and the Philippines) historically affected by henipaviruses are low-income or middle-income countries whereas two (Australia and Singapore) are high-income countries. Australia is the first country with a HeV vaccine and a documented, in-country stockpile of a henipavirus mAb, m102-4, which has been administered for compassionate...
Funding agencies, sponsors, and manufacturers of henipavirus medical countermeasures must share the responsibility of understanding regulatory requirements to apply for emergency use or relevant authorisation of henipavirus medical countermeasures in affected countries. Poor knowledge of country-specific regulatory pathways can potentially create authorisation delays and an access roadblock for affected countries. Communication between product developers and the appropriate national regulatory authorities is essential to obtain clarity and guidance on local clinical trial requirements, regulatory legislation, and import requirements. Regulatory pathways and national regulatory authority capabilities vary between henipavirus-affected countries; thus, early engagement with regulators, preferably as soon as a target product profile is conceived with defined target populations, is essential to identify country-specific considerations.

Coordination and cooperation among all stakeholders is crucial to ensure equitable access to henipavirus medical countermeasures. Although the price of the various measures could be reduced, supply might still be low in the case of a large outbreak or pandemic, as is the case with COVID-19. Improved mechanisms to facilitate mobilisation, coordination, and cooperation across all the stakeholders are required.

Conclusion

In this Review we have presented an overview of several medical countermeasures under development that have the potential to control henipavirus outbreaks. The pipeline of such measures is diverse (and mostly in the pre-clinical stage), with vaccines leading both in the number of candidates and the lowest anticipated cost per person per regimen. Investment in a combined portfolio of several medical countermeasures, including surveillance systems, should be part of a coordinated, multilateral strategy for epidemic and pandemic preparedness given the unpredictability of outbreaks and the high case–fatality rate. Given such risk, ethical considerations must feature prominently when planning clinical trials and establishing the trial design before the outbreak. Active exchange of data between developers of human and animal medical countermeasures should be encouraged. Regulatory agencies across different nations will require convincing data packages to approve the start of human clinical testing. Animal efficacy data collected in well-designed, high-quality studies could enable the start of these clinical studies and the collection of further data to support licensure via non-traditional regulatory pathways. For these efforts to be effective, multilateralism will be necessary. Multilateral strategies should be based on scenario planning and include an outbreak response plan that clearly delineates responsibilities for the coordinated, sequential deployment of medical countermeasures in the event of a henipavirus outbreak. The current COVID-19 pandemic
opens a timely and unique opportunity to implement lessons learned from SARS-CoV-2 and apply them to preparedness efforts against henipaviruses and other pathogens of pandemic potential.

**Contributors**

RGR, NT, NGC, ACS, MLIJ, DY, EM, and TTL contributed to conceptualization of the study. RGR did the literature search for the vaccines section, NGC did the search for the small molecules section, and TTL did the search for the monoclonal antibodies section. RGR verified the data in the small molecules section, NGC verified the data in the monoclonal antibodies section, and TTL verified the data in the vaccines section. RGR, NGC, ACS, MLIJ, DY, AH, EM, and TTL contributed to drafting of the manuscript. NT, MLIJ, DY, and AH critically reviewed the scientific content. All authors reviewed and approved the final version.

**Declaration of interests**

NT is an independent consultant to the Coalition for Epidemic Preparedness Innovations (CEPI). CEPI is supporting the research and development of a diverse portfolio of vaccine candidates (including vaccines against Nipah virus) based on a range of vaccine approaches.

**Acknowledgments**

We thank Amol Chaudhari, Gabrielle Breugelmans, and Georges Thiry for reviewing the manuscript, and Julia Granerod for providing scientific writing support.

**References**

1. WHO. Prioritizing diseases for research and development in emergency contexts. 2021. https://www.who.int/news-room/media-centre/events/prioritizing-diseases-for-research-and-development-in-emergency-contexts-(accessed April 28, 2021).

2. Lee B, Rota PA. Henipavirus: ecology, molecular virology, and pathogenesis. New York, NY: Springer, 2012.

3. Halpin K, Rota P. A review of Hendra virus and Nipah virus infections in man and other animals. In: Sing A, ed. Zoonoses – infections affecting humans and animals: focus on public health aspects. Dordrecht: Springer, 2015: 997–1012.

4. Hauser N, Gushiken AC, Narayanan S, Kottil S, Chua JV. Evolution of Nipah virus infection: past, present, and future considerations. Trop Med Infect Dis 2021; 6: 24.

5. Coalition for Epidemic Preparedness Innovations. Nipah@20. Proceedings from Nipah Virus International Conference, Singapore, 9 to 11 December 2019. 2019. https://cepi.net/wp-content/uploads/2020/06/2019-CEPI-Duke-WHO-NIAID-Nipah-Conference_FINAL.pdf (accessed April 28, 2021).

6. WHO. Nipah virus: risk of importation to the countries of EMR. Wkly Epidemiol Monitor 2018; 11: 23.

7. Encbery F, Horvat B. Understanding the interaction between henipaviruses and their natural host. Fruit bats: paving the way toward control of highly lethal infection in humans. Int Rev Immunol 2017; 36: 108–21.

8. WHO. Population data by WHO region. Global health Observatory database. 2016. https://apps.who.int/gho/data/view.main.POP2002language=en (accessed April 28, 2021).

9. Nikolay B, Salje H, Hossain MJ, et al. Transmission of Nipah virus—14 years of investigations in Bangladesh. N Engl J Med 2019; 380: 1804–14.

10. Sazzad HMS, Hossain MJ, Gurley ES, et al. Nipah virus infection outbreak with nosocomial and corpse-to-human transmission, Bangladesh. Emerg Infect Dis 2013; 19: 210–17.

11. Koczula KM, Gallotta A. Lateral flow assays. Essays Biochem 2016; 60: 111–20.

12. Mazzola LT, Kelly-Cirino C. Diagnostics for Nipah virus: a zoonotic pathogen endemic to Southeast Asia. BMJ Glob Health 2019; 4 (suppl 2): e001118.

13. WHO. Nipah virus research & development (R&D) roadmap. 2018. https://www.who.int/publications/m/item/nipah-research-and-development-(r-d)-roadmap (accessed April 28, 2021).

14. BMJ. BMJ best practice. Henipaviruses. 2021. https://bestpractice.bmj.com/topics/en-gb/1607-management-approach/(accessed April 28, 2021).

15. Institute of Epidemiology Disease Control And Research. National Guideline for management, prevention and control of Nipah virus infection. 2020. https://jdrdc.gov.bd/publication/guidelines/10adb7b531b6-4eb7-a375-7c81f4b88 (accessed June 2, 2021).

16. Central team Ministry of Health and Family Welfare, Government of India. Clinical management protocol for Nipah virus disease. 2018. http://cghael.nic.in/cghael/h17/Information/content/NipahVirus/Treatment.pdf (accessed June 2, 2021).

17. Indian Medical Association–Tamil Nadu State Branch. Surveillance, prevention and control of Nipah virus infection: a practical handbook. 2014. https://imatai.com/wp-content/uploads/2018/05/ surveillance-prevention-and-control-of-nipah-virus-infection-a-practical-handbook.pdf (accessed June 2, 2021).

18. Chong HT, Kamarturman A, Tao CT, et al. Treatment of acute Nipah encephalitis with ribavirin. Ann Neurol 2001; 49: 810–13.

19. Lo MK, Feldmann F, Gary JM, et al. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. Sci Transl Med 2019; 11: eaaw9242.

20. Reuters. FACTBOX–Countries where remdesivir is approved or supported for treating COVID-19. 2021. https://www.reuters.com/article/healthcoronavirus-gileadin-remdesivir-idUSL1N2HD1UX (accessed April 28, 2021).

21. Dawes BE, Kalveram B, Ilegami T, et al. Favipiravir (T-705) protects against Nipah virus infection in the hamster model. Sci Rep 2018; 8: 7604.

22. Agrawal U, Raju R, Udawadia ZF. Favipiravir: a new and emerging antiviral option in COVID-19. Med J Armed Forces India 2020; 76: 370–36.

23. Freberg AN, Worthy MN, Lee B, Hollbrook MR. Combined chloroquine and ribavirin treatment does not prevent death in a hamster model of Nipah and Hendra virus infection. J Gen Virol 2010; 91 (Pt 3): 765–72.

24. Pallister J, Middleton D, Crameri G, et al. Chloroquine administration does not prevent Nipah virus infection and disease in ferrets. J Virol 2009; 83: 1979–82.

25. Mathieu C, Dhideu KP, Chalons M, et al. Heparan sulfate-dependent enhancement of henipavirus infection. mBio 2015; 6: e02427.

26. Georges-Courbot MC, Contamin H, Faure C, et al. Poly(I)-poly(C12U) but not ribavirin prevents death in a hamster model of Nipah virus infection. Antimicrob Agents Chemother 2006; 50: 1768–72.

27. Hemisphér Biopharma. Executive informational overview. Nov 27, 2016. https://cdn2.hubspot.net/hubfs/150154/docs/Hemispher-Executive-Informational-Overview-11-27-16.pdf (accessed April 28, 2021).

28. Lo MK, Spengler JR, Krumpe LRH, et al. Griffithsin inhibits Nipah virus entry and fusion and can protect Syrian golden hamsters from lethal Nipah virus challenge. J Infect Dis 2020; 221 (suppl 4): S480–92.

29. ClinicalTrials.gov. Studies found for griffithsin. 2021. https://www.clinicaltrials.gov/ct2/results?recr=cdon&term=griffithsin&cntry=&state=&city=&dist (accessed April 28, 2021).

30. Mathieu C, Porotto M, Figueira TN, Horvat B, Moscona A. Fusion inhibitory lipopeptides engineered for prophylaxis of Nipah virus in primates. J Infect Dis 2018; 218: 218–27.

31. Porotto M, Rockx B, Yokoyama CC, et al. Inhibition of Nipah virus infection in vivo: targeting an early stage of paramyxovirus fusion activation during viral entry. PLoS Pathog 2010; 6: e1001168.

32. Aljosfan M, Sganga ML, Lo MK, et al. Antiviral activity of giotioxin, gentian violet and brilliant green against Nipah and Hendra virus in vitro. Viral J 2009; 6: 187.

33. Wang YE, Park A, Lake M, et al. Ubiquitin-regulated nuclear-cytoplasmic trafficking of the Nipah virus matrix protein is important for viral budding. PLoS Pathog 2010; 6: e1001186.

34. Hotard AL, He B, Nichol ST, Spiropoulou CF, Lo MK. 4'-azidocytidine (R1479) inhibits henipaviruses and other paramyxoviruses with high potency. Antiviral Res 2017; 144: 147–52.

35. ClinicalTrials.gov. A study of balapiravir in patients with dengue virus infection. 2021. https://clinicaltrials.gov/ct2/show/NCT01096576 (accessed April 28, 2021).
36 Lo MK, Amblard F, Flint M, et al. Potent in vitro activity of beta-D-4-chloromethyl-2-deoxy-2-fluorocytidine against Nipah virus. Antiviral Res 2020; 175: 104712.
37 ClinicalTrials.gov. 7 studies found for lumicitabin. 2021. https://clinicaltrials.gov/ct2/results?recrs=&cond=&term=lumicitabin&ctSID=&state=&city=&dist (accessed April 28, 2021)
38 Liu SY, Aliyari R, Chikere K, et al. Interferon-inducible cholesterol 25-hydroxybroadly inhibits viral entry by production of 25-hydroxysterol. Immunity 2013; 38: 92–105.
39 Pattabhi S, Wilkins CR, Dong R, et al. Targeting innate immunity for antiviral therapy through small molecule agonists of the RLR pathway. J Virol 2015; 90: 2722–87.
40 Tigabu B, Rasmussen L, White EL, et al. A BSL-4 high-throughput screen identifies sialofonamide inhibitors of Nipah virus. Assay Drug Dev Technol 2014; 12: 155–61.
41 Sen N, Kanitkar TR, Roy AA, et al. Predicting and designing therapeutics against the Nipah virus. PLoS Negl Trop Dis 2019; 13: e007419.
42 Porotto M, Orefice G, Yokoyama CC, et al. Simulating henipavirus multicyle replication in a screening assay leads to identification of a promising candidate for therapy. J Virol 2009; 83: 5168–55.
43 Tan CT, Goh KJ, Wong KT, et al. Relapsed and late-onset Nipah encephalitis. Ann Neurol 2002; 51: 703–08.
44 Banerjee S, Nivas VKM, Soneja M, et al. First experience of ribavirin postexposure prophylaxis for Nipah virus, tried during the 2018 outbreak in Kerala, India. J Infect 2019; 79: 493–503.
45 Times of India. Ribavirin effective in treating Nipah, say Pune scientists. 2018. https://timesofindia.indiatimes.com/india/ribavirin-effective-in-treating-nipah-say-pune-scientists/articleshow/64546561.cms (accessed July 1, 2021).
46 Bonaparte MJ, Dimitrov AS, Bossart KN, et al. Ephrin-B2 ligand is a functional receptor for Hendra virus and Nipah virus. Proc Natl Acad Sci USA 2005; 102: 10652–57.
47 Bossart KN, Geisbert TW, Feldmann H, et al. A neutralizing human monoclonal antibody protects african green monkeys from henipavirus infection challenge. Sci Transl Med 2011; 3: 105ra3.
48 Bossart KN, Zhu Z, Middleton D, et al. A neutralizing human monoclonal antibody protects against lethal disease in a new ferret model of acute nipah virus infection. PLoS Pathog 2009; 5: e1000642.
49 Geisbert TW, Mire CE, Geisbert JB, et al. Therapeutic treatment of Nipah virus infection in nonhuman primates with a neutralizing human monoclonal antibody. Sci Transl Med 2014; 6: 242ra82.
50 Playford EG, Munro T, Mahler SM, et al. Safety, tolerability, pharmacokinetics, and immunogenicity of a human monoclonal antibody targeting the G glycoprotein of henipaviruses in healthy adults: a first-in-human, randomised, controlled, phase 1 study. Lancet Infect Dis 2020; 20: 48–55.
51 Dang HV, Chan YP, Park YJ, et al. An antibody against the G glycoprotein inhibits Nipah and Hendra virus infections. Nat Struct Mol Biol 2019; 26: 980–87.
52 Mire CE, Chan YP, Borisevich V, et al. A cross-reactive humanized monoclonal antibody targeting fusion glycoprotein function protects ferrets against lethal Nipah virus and Hendra virus infection. J Infect Dis 2020; 221 (suppl 4): S71–79.
53 Dong J, Cross RW, Doyle MP, et al. Potent henipavirus neutralization by antibodies recognizing diverse sites on Hendra and Nipah virus receptor binding protein. Cell 2020; 183: 1536–50.e7.
54 Guillaume V, Contamin H, Loth P, et al. Antibody prophylaxis and therapy against Nipah virus infection in hamsters. J Virol 2006; 80: 1972–78.
55 WHO. WHO target product profile for Nipah virus vaccine. 2017. https://www.who.int/blueprint/priority-diseases/key-action/Nipah_virus_vaccineTPP.pdf?ua=1 (accessed April 28, 2021)
56 Tamin A, Harcourt BH, Ksiazek TG, Rollin PE, Bellini WJ, Rota PA. Functional properties of the fusion and attachment glycoproteins of Nipah virus. Virology 2002; 296: 190–200.
57 Guillaume V, Contamin H, Loth P, et al. Nipah virus: vaccination and protective studies in a hamster model. J Virol 2004; 78: 8344–40.
58 Weingart HM, Berhane Y, Caswell JL, et al. Reombinant Nipah virus vaccines protect pigs against challenge. J Virol 2006; 80: 7929–38.
59 Tamin A, Harcourt BH, Lo MK, et al. Development of a neutralization assay for Nipah virus using pseudotype particles. J Virol Methods 2009; 160: 1–6.
60 Defang GN, Khetawat D, Broder CC, Quinann GV Jr. Induction of neutralizing antibodies to Hendra and Nipah glycoproteins using a Venezuelan equine encephalitis virus in vivo expression system. J Virol 2010; 84: 212–20.
61 Chattopadhyay A, Rose JK. Complementing defective viruses that express separate paramyovirus glycoproteins provide a new vaccine vector approach. J Virol 2011; 85: 2004–11.
62 Kong D, Wen Z, Su H, et al. Newcastle disease virus-vectorised Nipah encephalitis vaccines induce B and T cell responses in mice and long-lasting neutralizing antibodies in pigs. Virology 2012; 432: 127–35.
63 Mire CE, Versteeg KM, Cross RW, et al. Single injection recombinant vesicular stomatitis virus vaccines protect ferrets against lethal Nipah virus infection. J Virol 2013; 10: e533.
64 Ploum A, Szeczi J, Mathieu C, et al. Protection against henipavirus infection by use of recombinant adeno-associated virus–vector vaccines. J Infect Dis 2013; 207: 697–708.
65 Yoneda M, Georges-Courbet MC, Ikeda F, et al. Recombinant measles virus vaccine expressing the Nipah virus glycoprotein protects against lethal Nipah virus challenge. PLoS One 2013; 8: e58414.
66 DeBuyschers BL, Scott D, Marzi A, Prescott J, Feldmann H. Single-dose live-attenuated Nipah virus vaccines confer complete protection by eliciting antibodies directed against surface glycoproteins. Vaccine 2014; 32: 2637–44.
67 Lo MK, Bird BH, Chattopadhyay A, et al. Single-dose replication-defective VSV-based Nipah virus vaccines provide protection from lethal challenge in Syrian hamsters. Antiviral Res 2014; 101: 26–29.
68 Kurup D, Wirblich C, Feldmann H, Marzi A, Schnell MJ. Hendravirus-based vaccine platforms against henipaviruses. J Virol 2015; 89: 144–54.
69 Prescott J, DeBuyschers BL, Feldmann F, et al. Single-dose live-attenuated vesicular stomatitis virus-based vaccine protects African green monkeys from Nipah virus disease. Vaccine 2015; 33: 2823–29.
70 DeBuyschers BL, Scott D, Thomas T, Feldmann H, Prescott J. Peni-exposure protection against Nipah virus disease using a single-dose recombinant vesicular stomatitis virus-based vaccine. NPJ Vaccines 2016; 1: 16002.
71 Guillaume-Vasselin V, Lernaire L, Dhondt KP, et al. Protection from Hendra virus infection with canarypox recombinant vaccine. NPJ Vaccines 2016; 1: 16003.
72 van den Pol AN, Mao G, Chattopadhyay A, Rose JK, Davis JN. Chikungunya, influenza, Nipah, and Semiliki Forest chimeric viruses with vesicular stomatitis virus: actions in the brain. J Virol 2017; 91: e02154–60.
73 Keshwara R, Shieles T, Postnikova E, et al. Rabies-based vaccine induces potent immune responses against Nipah virus. NPJ Vaccines 2019; 4: 15.
74 Mire CE, Geisbert JB, Agans KN, et al. Use of single-injection recombinant vesicular stomatitis virus vaccine to protect nonhuman primates against lethal Nipah virus disease. Emerg Infect Dis 2019; 25: 1144–52.
75 van Doremalen N, Lambe T, Sebastian S, et al. A single-dose ChAdOx1 vectored vaccine provides complete protection against Nipah Bangladesh and Malaysia in Syrian golden hamsters. PLoS Negl Trop Dis 2019; 13: e0007462.
76 Kalodimos G, Veit S, Jany S, et al. A soluble version of Nipah virus glycoprotein G delivered by vaccinia virus MVA activates specific CD8 and CD4 T Cells in mice. Viruses 2019; 12: 26.
77 Shuai L, Ge J, Wen Z, Wang J, Wang X, Bu Z. Immune responses in mice and pigs after oral vaccination with rabies virus vectored Nipah disease vaccines. Vir Microbiol 2020; 241: 108549.
78 Pedraza M, Macchi F, McLean RK, et al. Bovine herpesvirus-4 vectored delivery of Nipah virus glycoproteins enhances T cell immunogenicity in pigs. Vaccine 2020; 8: 115.
79 Mungall BA, Middleton D, Crameri G, et al. Feline model of acute Nipah virus infection and protection with a soluble glycoprotein-based subunit vaccine. J Virol 2006; 80: 12293–302.
80 McCormick JA, Birmingham J, Crameri G, et al. A recombinant subunit vaccine formulation protects against lethal Nipah virus challenge in cats. Vaccine 2008; 26: 3842–52.
81 Chan YP, Lu M, Datta S, et al. Biochemical, conformational, and immunogenetic analysis of soluble trimeric forms of henipavirus fusion glycoproteins. J Virol 2012; 86: 21427-71.
82 Bossart KN, Rockx B, Feldmann F, et al. A Hendra virus G glycoprotein subunit vaccine protects African green monkeys from Nipah virus challenge. Sci Transl Med 2012; 4: 146ra77.
83 Pallister JA, Klein A, Arkinstall R, et al. Vaccination of ferrets with a recombinant G glycoprotein subunit vaccine provides protection against Nipah virus disease for over 12 months. Viril J 2013; 18: e237.
84 Mite CE, Geisbert JB, Agans KN, et al. A recombinant Hendra virus G glycoprotein subunit vaccine protects nonhuman primates against Hendra virus challenge. J Virol 2014; 88: 6246-31.
85 Middleton J, Pallister J, Klein A, et al. Hendra virus vaccine, a one health approach to protecting horse, human, and environmental health. Emerg Infect Dis 2014; 20: 372–79.
86 Rn R, Hodge A, Klein R, et al. Viral-neutralising antibody responses in horses following vaccination with Equivac(RE) HeV: a field study. Aust Vet J 2018; 96: 161–66.
87 Pickering BS, Hardham JM, Smith G, et al. Protection against henipaviruses in swine requires both, cell-mediated and humoral immune response. Vaccine 2016; 34: 4777–86.
88 Pallister J, Middleton D, Wang LF, et al. A recombinant Hendra virus G glycoprotein-based subunit vaccine protects ferrets from lethal Hendra virus challenge. Vaccine 2011; 29: 5623–30.
89 Loomis RJ, Stewart-Jones GBE, Tsybovsky T, et al. Structure-based design of Nipah virus vaccines: a generalizable approach to paramyxovirus immunogen development. Front Immunol 2020; 11: 842.
90 Li Y, Li R, Wang M, et al. Fc-based recombinant henipavirus vaccines elicit broad neutralizing antibody responses in mice. Viruses 2020; 12: 480.
91 Geisbert TW, Bobb K, Borisievich V, et al. A single-dose investigational subunit vaccine for human use against Nipah virus and Hendra virus. NPJ Vaccines 2021; 6: 23.
92 Walpita P, Barr J, Sherman M, Basler CF, Wang L. Vaccine potential of Nipah virus-like particles. PLoS One 2011; 6: e18437.
93 Walpita P, Cong Y, Jahrling PB, et al. A VLP-based vaccine provides complete protection against Nipah virus challenge following multiple-dose or single-dose vaccination schedules in a hamster model. NPJ Vaccines 2017; 2: 21.
94 Schmidt R, Beltzig LC, Sawatsky B, et al. Generation of therapeutic antisera for emerging viral infections. NPJ Vaccines 2018; 4: 42.
95 Stroh E, Fischer K, Schwager T, et al. Henipavirus-like particles induce a CD8 T cell response in C57Bl/6 mice. Vir Microbiol 2019; 237: 108409.
96 Wang XJ, Hu S, Ge JY, Wang QH, Qin LT, Bu ZG. [Study of fusion protein and attachment glycoprotein of Nipah virus expressed in recombinant baculovirus]. Sheng Wu Gong Cheng Xue Bao 2006; 22: 418–24.
97 Wang X, Ge J, Hu S, et al. Efficacy of DNA immunization with F and G protein genes of Nipah virus. Ann N Y Acad Sci 2006; 1088: 241–45.
98 Nie J, Liu, Wang Q, et al. Nipah pseudovirus system enables evaluation of vaccines in vitro and in vivo using non-BSL-4 facilities. Emerg Microbes Infect 2019; 8: 272–81.
99 Lo MX, Spengler JR, Wachels SR, et al. Evaluation of a single-dose nucleoside-modified messenger RNA vaccine encoding Hendra virus-soluble glycoprotein against lethal Nipah virus challenge in Syrian hamsters. J Infect Dis 2020; 221 (suppl 4): S493–98.
100 Moderna. Press releases. Moderna provides business update and announces three new development programs in infectious disease vaccines. 2021. https://investors.modernatx.com/news-releases/news-release-details/moderna-provides-business-update-and-announces-three-new (accessed April 28, 2021).
101 Coalition for Epidemic Preparedness Innovations. CEPI-funded Nipah virus vaccine candidate first to reach phase 1 clinical trial. 2020. https://cepi.net/wp-content/uploads/2021/03/CEPI_3.5_billion_investment_case_.pdf (accessed April 28, 2021).
102 Jusu MO, Glauser G, Seward JF, et al. Rapid establishment of a cold chain capacity of −60°C or colder for the STRIVE Ebola vaccine trial during the Ebola outbreak in Sierra Leone. J Infect Dis 2018; 218 (suppl 1): S46–55.
103 NIH. NIH RePORTER. Project details. Project 2 – Vanderbilt University. 2021. https://reporter.nih.gov/project-details/9979483 (accessed April 28, 2021).
104 NIH. NIH RePORTER. Project details. Advance of vaccines and therapies for henipaviruses. 2021. https://reporter.nih.gov/project-details/10273019 (accessed April 28, 2021).
105 NIH. NIH RePORTER. Project details. Rapid development of vaccines for emerging viruses. 2021. https://reporter.nih.gov/project-details/10273019 (accessed April 28, 2021).
106 Coalition for Epidemic Preparedness Innovations (CEPI). The urgency of now. 2021. https://cepi.net/wp-content/uploads/2021/03/CEPI_3.5_billion_investment_case_.pdf (accessed April 28, 2021).
107 Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 vaccines at pandemic speed. N Engl J Med 2020; 382: 1169–73.
108 Clinical Trials Arena. Eli Lilly’s monoclonal antibody bamlanivimab value allows payor grace for Covid-19. 2020. https://www.clinicaltrialsetc.com/entry/els-lillys-monoclonal-antibody-bamlanivimab/#:~:text=Lilly%20will%20be%20supplying%20300%20000,press%20release%20and%20CEO%20note (accessed April 28, 2021).
109 Eli Lilly. News release. Lilly announces 650,000 additional doses of neutralizing antibody bamlanivimab (LY-CoV555) purchased by U.S. Government to treat COVID-19. 2020. https://investor.lilly.com/news-releases/news-release-details/lilly-announces-650000-additional-doses-neutralizing-antibody (accessed April 28, 2021).
110 Johnson CY, McGinley L. Experimental drug given to Trump to treat covid-19 wins FDA clearance. The Seattle Times. 2020. https://www.seattletimes.com/nation-world/experimental-drug-given-to-trump-to-treat-covid-19-wins-fda-clearance/ (accessed April 28, 2021).
111 Statista. The cost per jab of Covid-19 vaccine candidates. 2020. https://www.statista.com/chart/23658/reported-cost-per-dose-of-covid-19-vaccines/ (accessed April 28, 2021).
112 Lee V, Yap J, Cook AR, et al. Oseltamivir ring prophylaxis for containment of 2009 H1N1 influenza outbreaks. N Engl J Med 2010; 362: 2166–74.
113 Regenener. Press Release. Phase 3 prevention trial showed 81% reduced risk of symptomatic Sars-cov-2 infections with subcutaneous administration of Regen-cov™ (castrimivir) with imdevimab. 2021. https://investor.regenener.com/news-releases/news-release-details/phase-3-prevention-trial-showed-81-reduced-risk-symptomatic-sars (accessed April 28, 2021).
114 Cohen MS. Monoclonal antibodies to disrupt progression of early Covid-19 infection. N Engl J Med 2021; 384: 285–91.
115 Wolf J, Abzug MJ, Watter RL, et al. Initial guidance on use of monoclonal antibody therapy for treatment of COVID-19 in children and adolescents. J Pediatric Infect Dis Soc 2021; 10B: 629–34.
116 Vaughan K, Ozalpin A, Mallow M, et al. The costs of delivering vaccines in low- and middle-income countries: findings from a systematic review. Vaccine X 2019; 2: 100034.
117 Arunkumar G, Chandni R, Mourya DT, et al. Outbreak investigation of Nipah virus disease in Kerala, India. 2018. J Infect Dis 2019; 219: 1867–78.
118 Sahay RR, Yadav PD, Gupta N, et al. Experiential learnings from the Nipah virus outbreaks in Kerala towards containment of infectious public health emergencies in India. Epidemiol Infect 2020; 148: e90.
119 Ma L, Chen Z, Guan W, Chen Q, Liu D. Rapid and specific detection of all known Nipah virus strains’ sequences with reverse transcription-loop-mediated isothermal amplification. Front Microbiol 2019; 10: 418.
120 Gurley ES, Spiropoulou CF, de Wit E. Twenty years of Nipah virus research: where do we go from here? J Infect Dis 2020; 221 (suppl 4): S359–62.
121 Nikolay B, Lipsitch M, Rahman M, et al. Assessing the feasibility of Nipah vaccine efficacy trials based on previous outbreaks in Bangladesh. medRxiv 2020; published online Dec 8. https://doi.org/10.1101/2020.12.06.20244871 (preprint).
122 US Food and Drug Administration. Accelerated approval. 2018. https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review (accessed April 28, 2021).
123 European Medicines Agency. Conditional marketing authorisation. 2021. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation (accessed April 28, 2021).
