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Medical countermeasures against henipaviruses: a review and public health perspective

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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.

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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.[1] Like other viruses of the henipavirus genus, Nipah virus (NiV) and Hendra virus (HeV) are zoonotic viruses that can spillover from *Pteropus* spp bats—their natural hosts and reservoir—to other mammals including humans.[2,3] Transmission occurs via exposure to animal or human secretions or respiratory droplets.[2,3] 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.[4] Since 1994, henipavirus spillover events have caused human outbreaks in several countries, including Australia, Bangladesh, India, Malaysia, the Philippines, and Singapore.[5] 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[6,7] (encompassing Indo-Pacific territories across the southeast Asia and western Pacific regions) and covers half of the global population.[8] 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.[5] Although the reproduction number (R_0) for HeV has not been calculated, the R_0 for NiV ranges from 0·19 to 0·59 in nosocomial settings or in the community, including corpse-to-person transmission.[9,10]

In an outbreak situation, use of widespread sensitive rapid diagnostic tests (RDTs)[11] combined with appropriate prevention and non-pharmaceutical intervention control measures, can rapidly lower the R_0, buying precious time

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 Mojiang 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]

See Online for appendix

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.[14–17] 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 analyses[41] or biosafety level 2 pseudotyped virus assays[42] 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.[19] 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 pre-clinical 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,[43] 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;[18] 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 encephalitis[16,44] in which its use led to a possible reduction in viral load.[45] Soluble Ephrin-B2 receptors (EFBN2) have been shown to inhibit binding of NiV and HeV to target cells in vitro,[46] 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[18]	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%)* in Malaysian outbreak (1998)	Approved for hepatis C virus and respiratory syncytial virus in several countries
Remdesivir[19]	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[20]
Favipiravir[21]	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[22]
Chloroquine[23,24]	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[25]	Anticoagulant	Syrian golden hamsters (subcutaneous)	NiV, HeV	Inhibits cell-mediated viral trans-infection by binding to heparan sulfate	Inhibition of viral trans-infection in vitro. Heparin treatment restricts NiV infection in Syrian golden hamsters	Approved for coagulopathies in several countries. Experimental: preclinical (Syrian golden hamster study)
Rintatolimid[26]	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[27]
Griffithsin[28]	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[29]
VIKI-dPEG4-Toco, VIKI-PEG4-chol[30,31]	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[32]	Mycotoxin	In vitro	NiV, HeV	Viral RNA-dependent RNA polymerase inhibitor	Inhibition of infection and replication; Cytotoxic but possible topical applications	Experimental: exploratory
Bortezomib[33]	Anticancer	In vitro	NiV	Proteasome inhibitor	Inhibition of viral budding	Approved for multiple myeloma and mantle cell lymphoma by the US FDA
Balapiravir, R1479[34]	Antiviral	In vitro	NiV, HeV	Viral RNA-dependent RNA polymerase inhibitor	Inhibition of viral replication	Experimental, discontinued in phase 1 trials for dengue virus and hepatitis C virus[35]
Lumicitabine, ALS-8112[36]	Antiviral	In vitro	NiV	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[37]
CH25H[38]	Antiviral	In vitro	NiV	Intravenous-stimulated genes: catalyses oxidation of cholesterol to 25-hydroxycholesterol	Inhibition of viral membrane fusion and NiV replication	Experimental: exploratory
KIN1408[39]	Antiviral	In vitro	NiV	Immunomodulation of interferon regulatory factor 3	Inhibition of viral replication and decreased viral load in vitro	Experimental: exploratory
AB00991123, AB00992391, and AB00993210[40]	Antivirals	In vitro	NiV	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 BSL4 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.[50] 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 mild 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.[53]

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 WHO[55] 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".[55] 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[47–50]	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[51,52]	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[53]	Preclinical	HeV or NiV G glycoprotein (receptor-binding protein)	Vanderbilt Vaccine Center (Nashville, TN, USA)
Anti-G mAb, anti-F mAb	Hamsters[54]	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=monocolonal 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.[68,73,77] 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.[91,101] This candidate builds on existing knowledge gained from using the same soluble protein in several pre-clinical and veterinary studies,[79,80,82,83,85] including pivotal data used to develop the Equivac HeV vaccine approved for veterinary use in horses.[85] 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.[91]

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.[55] The low temperature requirement could create challenges for

	Vaccine regimen and administration route	Animal models used	Henipavirus challenge strain	Reference
Viral vectors				
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	NiV-M	57
Canarypox vector (ALVAC) expressing NiV-M G or F	2 doses, 14 days apart (intramuscular)	Pigs*	NiV-M	58,59
Venezuelan equine encephalitis virus expressing HeV or NiV-M G or 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)	Mice	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	NiV-M	63†
Adeno-associated virus vector expressing NiV-M G	Single dose (intramuscular)	Syrian golden hamsters	NiV-M and HeV	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	NiV-M	65
Live-attenuated rVSV-ZEBOV-GP vector expressing NiV-M G, F, or N	Single dose (intraperitoneal)	Syrian golden hamsters	NiV-M	66‡
Single-cycle replication VSV-DG vector expressing NiV-M G or F	Single dose (intramuscular)	Syrian golden hamsters	NiV-M	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	NiV-M	69‡
Live-attenuated rVSV-ZEBOV-GP vector expressing NiV-M G	Single dose (intraperitoneal)	Syrian golden hamsters	NiV-M	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)	Mice	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	NiV-B	74†
Chimpanzee adenovirus vector expressing NiV-B G	Single or two doses, 28 days apart (intramuscular)	Syrian golden hamsters	NiV-M, NiV-B, and HeV	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, $rERAG_{333E}$ 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)

	Vaccine regimen and administration route	Animal models used	Henipavirus challenge strain	Reference
(Continued from previous page)				
Protein subunits§				
sG_{NiV-M} or sG_{HeV} in CSIRO triple adjuvant (Montanide/QuilA/DEAE-dextran)	3 doses, 2 weeks apart (subcutaneous)	Cats	NiV-M	79
Recombinant soluble HeV G glycoprotein in CpG plus Alhydrogel adjuvant	2 doses, 21 days apart (intramuscular)	Cats	NiV-M	80
Soluble trimeric forms of HeV and NiV-M F proteins (sF_{GCN4}) in Sigma Adjuvant System adjuvant	4 doses, each 30 days apart (intraperitoneal or subcutaneous)	Mice	None	81
Recombinant soluble HeV G glycoprotein in CpG and Alhydrogel adjuvant	2 doses, 21 days apart (intramuscular)	African green monkeys	NiV M	82
Recombinant soluble HeV G glycoprotein in Alhydrogel and CpG adjuvant	2 doses, 20 days apart (subcutaneous)	Ferrets	NiV B	83
Recombinant soluble HeV G glycoprotein in Alhydrogel with or without CpG adjuvant	2 doses, 21 days apart (intramuscular)	African green monkeys	HeV	84
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)	Ferrets	HeV	88
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 aluminum hydroxide	2 doses, 3 weeks apart (intramuscular)	Mice	None	89
Monovalent, bivalent, and tetravalent Fc-linked G proteins from NiV-M, HeV, GhV, 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	Single dose or 2 doses, 4 weeks apart (intramuscular)	African green monkeys	HeV (Brisbane) and NiV B	91
Virus-like particles				
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)¶	Single dose or 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				
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				
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	NiV-M pseudovirus	98
mRNA				
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. rVSV=recombinant vesicular stomatitis virus. 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.

Table 3: **Chronological overview of henipavirus vaccines in development, by platform**

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.[102] 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.[75]

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.[103–105] 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.[106]

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.[107] 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.[112] 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.[113] If successful, this concept will fundamentally improve access to mAb treaments. Casirivimab and imdevimab (Regeneron [Tarrytown, NY, USA]) and bamlanivimab (Eli Lily [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,[114] 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.[114,115]

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.[111] These figures do not include delivery costs, which could add substantially to the immunisation costs depending on vaccine logistics, infrastructure, and regimens.[116] 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.

	Reference price* (US$)	Reference cost unit	Potential dose regimen	Estimated cost of regimen per person (US$)
Small molecules or therapeutics†				
Remdesivir	53 per vial (Cipla Limited, Mumbai, India)	100 µg vial	Ebola regimen; intravenous: 200 mg (loading dose) + 10 mg for 10 days	$640
Favipiravir	<0·50 per tablet (Mylan Laboratories Limited, Hyderabad, India)	200 mg tablet	Influenza regimen: oral: 1800 mg twice daily (loading dose) + 800 mg twice daily for 14 days	$31
Ribavirin	<1 per tablet	200 mg tablet (oral) or 10 mg vial (intravenous)	Chong et al[18] Nipah regimen; oral: 2 g (loading dose) + 1 g for 10 days Intravenous: 30 mg/kg (loading dose) + 16 mg/kg every 6 h for 4 days + 8 mg/kg every 8 h for 3 days	$20–60 (oral); $14–26 (intravenous)
Monoclonal antibodies‡				
Monoclonal antibodies produced in mammalian cell lines	1250–2100 per vial	700 mg–2·4 g per dose	COVID-19-like regimens; single intravenous infusion	$1250–2100 (intravenous)[108–110]
Vaccines§				
Viral vectors, protein subunits in adjuvant, and mRNA in liquid nanoparticles	4–37 per dose	Variable concentration per dose	Single or two-dose regimen	$8–74[111]

*Prices based on publicly available information of generic product costs, or products developed using similar platforms. †Costs exclude expenses related to hospital care infrastructure and administration, supportive therapy, and disposables, etc. ‡Reference data for monoclonal antibodies are based on data available in the public domain for bamlanimivab (Eli Lilly, Indianapolis, IN, USA) and casirivimab plus imdevimab (REGN-COV2 antibody cocktail [Regeneron, Tarrytown, NY, USA]).[90,92–99] §Costs exclude expenses related to vaccine delivery, transport, refrigeration, and administration.

Table 4: **Projected costs of henipavirus medical countermeasures**

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.[117,118] 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 NiV detection exist globally,[12] 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.[119] 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).[120] 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.[121] 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][122] or the animal efficacy rule[126] in the USA), and conditional approval or exceptional circumstances in the European Union (EU).[123] 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.[135] 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.

	Data package could include	Examples of approved vaccines for other indications
Current scenario: R_0 <1		
Accelerated approval (US FDA),[122] conditional marketing authorisation or exceptional circumstances approval (EMA),[123] 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;[124] conditional marketing authorisation for Ervebo (recombinant vesicular stomatitis virus–Zaire Ebola virus)[125]
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 (Ad26.ZEBOV [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
Alert phase: R_0 ~1		
Rapid response: potential shift to PHEIC and pandemic scenarios	..	..
Higher incidence scenarios: R_0 >1		
Accelerated approval (US FDA),[122] conditional marketing authorisation (EMA),[123] national regulatory authority emergency use authorisation, WHO EUL,[132,133] and other	Phase 1 data, phase 2 data, and assay validation data†	Ebola vaccines: Ervebo[125,134]

EMA=European Medicines Agency. EUL=emergency use listing. PHEIC=public health emergency of international concern. US FDA=US Food and Drug Administration.
*Phase 2 clinical trial material can become so-called "outbreak-ready" for an investigational stockpile. †Investigational stockpile deployed.

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

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 efficacy data instead of human clinical data.[126] To support licensure through this route, the efficacy of a medical countermeasure can be demonstrated using a disease endpoint in a relevant animal model that enables the selection of an effective dose and regimen in humans. The animal efficacy rule approval pathway is only available in a situation where licensure through the traditional or accelerated approval pathway is not feasible. Generating the data required for approval via this pathway is challenging. So far, there has been only one precedent for a vaccine approval using the animal rule (BioThrax [Emergent BioSolutions, Rockville, MD, USA] for post-exposure prophylaxis following suspected or confirmed anthrax exposure). The process and data requirements were substantial, taking at least 5 years from conception of the regulatory pathway to approval.[137,138] To gain approval via the animal rule, data must be generated to demonstrate a reasonably good understanding of the pathophysiology of the disease in a chosen animal model, and preferably in more than one animal species.[139] Well-designed natural history studies must be done, with solid evidence that the models can recapitulate key aspects 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 authorisation[123] 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.[123] 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[128] and Mvabea[129] (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_0>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[132,133,140] 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[141–144] 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[145] 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

use.[50] With scientific expertise in HeV, BSL4 capacity, and a renowned medical countermeasure consortia,[146] Australia could be a leading stakeholder in ensuring access through large-scale manufacturing and technology transfer of mAbs in the western Pacific region. In countries like Bangladesh, where Nipah outbreaks have predominantly affected poor populations in rural areas and health-care expenditures are generally out-of-pocket expenses,[147] central and local governments can prepare for future outbreaks by adapting strategies to reduce out-of-pocket expenses[148] or by devising mechanisms to share the costs of medical countermeasure procurement, deployment, and delivery, avoiding any undue delays to populations in need, regardless of their ability to pay for treatment.

Strategies to reduce the cost of medical countermeasure production while increasing the number of market players would help to increase access to medical countermeasures for low-income and middle-income countries; however, this approach is challenging in the face of a somewhat small henipavirus medical countermeasure portfolio. There might be little financial incentive perceived by multinational pharmaceutical companies, which have the most competitive resources and manufacturing capacity to invest in medical countermeasures.[149,150] Several initiatives have been set up to address this gap—for example, CEPI has invested more than $100 million in the pre-clinical and clinical development of four NiV vaccine candidates, including a protein subunit vaccine,[91] a measles vector-based vaccine,[64] a vesicular stomatitis virus vector-based vaccine,[66,69,70] and a chimpanzee adenovirus vector vaccine.[75] NiV investigational vaccine stockpiles and other medical countermeasures, together with operations for intervention in the field, should be in place before a major epidemic or pandemic.[151] However, more financial investment and continued participation from governments and the pharmaceutical private sector will be required to achieve this goal. The public, philanthropic, and private funding of active henipavirus vaccine development projects (appendix p 3) could help to decouple the price of the product from the cost of research and development, making it potentially more affordable. Efforts to increase supply and local manufacturing are also needed to potentially reduce prices and spur innovation. Funders must therefore include low-income and middle-income countries and strengthen their capacities in the crucial stages of vaccine development such as manufacturing, for example by establishing mechanisms to transfer technology and know-how to emerging developers in low-income and middle-income countries.[152]

Compared with vaccines, small molecules and antivirals are easier to generically produce. The COVID-19 pandemic has demonstrated that in some cases, prices can be set fairly low by overcoming intellectual property issues.[153] Therefore, both upstream and downstream strategies that address such issues across all the medical countermeasures will be vital for accessibility.

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.[13]

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.[154] 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, MLJ, DY, EM, and TTL contributed to conceptualidation 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, MLJ, DY, AH, EM, and TTL contributed to drafting of the manuscript. NT, MLJ, 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). All other authors are employees of 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.

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