



Journal homepage: <https://trpubonline.org/index.php/Biosynth>

REVIEW ARTICLE

Development of mRNA-Based Vaccine Platforms Against Emerging Zoonotic Pathogens

Miguel Makela^{1*}, Camille Lindqvist² and Fredrik Carvalho³

¹Department of Biomedical and Health Sciences, Bohemian University of Life Sciences, Czech Republic

²Department of Microbiology and Immunology, Northmoor School of Environmental Sciences, United Kingdom

³Department of Environmental and Agricultural Sciences, Bohemian University of Life Sciences, Czech Republic

*Corresponding author: Miguel Makela, Department of Biomedical and Health Sciences, Bohemian University of Life Sciences, Czech Republic; Email: m.makela@buls.cz

ABSTRACT

The rapid clinical translation of mRNA vaccines against SARS-CoV-2 demonstrated that a lipid-nanoparticle-formulated messenger RNA platform can move from sequence to authorised vaccine in under a year, a timeline that has since reshaped expectations for how the field should respond to future zoonotic spillover events. This review synthesises the current state of mRNA vaccine development against six zoonotic pathogens judged by the World Health Organization and comparable bodies to carry substantial pandemic potential -- Nipah virus, Lassa virus, Middle East respiratory syndrome coronavirus, highly pathogenic avian influenza H5N1, Rift Valley fever virus, and mpox virus -- drawing on 61 peer-reviewed sources spanning preclinical immunogenicity studies, completed and ongoing clinical trials, and platform technology development. Across candidates in at least Phase 1 clinical evaluation, mRNA platforms have generally shown favourable reactogenicity and immunogenicity profiles comparable to or exceeding recombinant protein and viral-vector comparators, with self-amplifying RNA constructs achieving equivalent neutralising antibody titres at substantially lower RNA doses than conventional non-replicating mRNA in head-to-head preclinical comparisons. Persistent technical obstacles include lipid nanoparticle cold-chain requirements that limit deployability in the resource-limited settings where several target pathogens are endemic, incompletely characterised long-term durability of mRNA-induced immunity relative to some live-attenuated comparators, and, for several target pathogens, an absence of correlates of protection that complicates efficacy-trial design in the typically small and geographically restricted outbreak settings where these pathogens circulate. We conclude that mRNA platforms are a credible and in several respects favourable technology for pandemic-potential zoonotic pathogen vaccine development, but that platform-level advantages demonstrated during the COVID-19 pandemic response will not translate automatically to pathogens lacking equivalent manufacturing scale, regulatory precedent, and sustained funding commitment.

Keywords: mRNA vaccines; lipid nanoparticles; zoonotic pathogens; self-amplifying RNA; pandemic preparedness; Nipah virus

Received: June 23, 2025 | Accepted: September 22, 2025 | Published: December 18, 2025

© 2025 Makela et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

1. INTRODUCTION

Zoonotic spillover, the transmission of a pathogen from an animal reservoir into the human population, has preceded essentially every major infectious disease

pandemic and epidemic of the past half-century, from HIV-1 and successive influenza pandemics to Ebola, Nipah, Middle East respiratory syndrome, and, most recently, SARS-CoV-2 [1,2]. The World Health Organization's periodically updated priority pathogen list, developed to focus research and development attention on pathogens with substantial epidemic or pandemic potential but no or inadequate existing countermeasures, is dominated by zoonotic agents, reflecting both the genuine biological unpredictability of spillover events and the chronic historical underinvestment in vaccine development for pathogens that, prior to a given outbreak, affect comparatively small and often low-income or middle-income populations [3,20].

Messenger RNA vaccine technology, in development for over two decades before its pandemic-era breakthrough, differs from conventional vaccine platforms in ways that are particularly relevant to zoonotic pathogen preparedness. Because an mRNA vaccine's antigen is encoded rather than manufactured as protein or attenuated virus, updating the vaccine for a new or antigenically drifted target requires only a change to the encoded sequence, with the lipid nanoparticle formulation, manufacturing process, and much of the regulatory dossier remaining largely constant across candidates targeting different pathogens [4,21]. This platform interchangeability was central to the speed of the SARS-CoV-2 vaccine response, and has motivated substantial investment in applying the same platform prospectively to pathogens that have not yet caused a large human outbreak but are judged likely to do so eventually, an approach sometimes described as prototype pathogen preparedness [5,22].

The mechanistic basis for mRNA vaccine immunogenicity is now reasonably well understood. Following intramuscular injection, lipid-nanoparticle-encapsulated mRNA is taken up predominantly by antigen-presenting cells and myocytes at the injection site and draining lymph node, where the encoded antigen is translated, processed, and presented on both major histocompatibility complex class I and class II pathways, driving a combined humoral and cellular immune response that in several head-to-head comparisons has matched or exceeded that achieved by recombinant protein subunit vaccines against the same antigen [6,23]. The lipid nanoparticle itself is not an inert delivery vehicle: its ionisable lipid component has intrinsic adjuvant activity, contributing to the robust innate immune activation that appears to underlie much of the platform's immunogenicity, though this same property is also implicated in the reactogenicity, principally injection-site pain and transient systemic symptoms, that has been consistently reported across mRNA vaccine candidates [7,24].

This review synthesises the current evidence base for mRNA vaccine development against six zoonotic pathogens identified as priority targets by the World Health Organization and the Coalition for Epidemic

Preparedness Innovations: Nipah virus, Lassa virus, Middle East respiratory syndrome coronavirus (MERS-CoV), highly pathogenic avian influenza H5N1, Rift Valley fever virus, and mpox virus. For each pathogen we summarise preclinical immunogenicity and challenge-protection data, the status of clinical development where trials have been initiated, and pathogen-specific technical obstacles, before drawing broader conclusions about where mRNA platform advantages are likely to generalise across this pathogen set and where pathogen-specific biology or logistical constraints are likely to limit that generalisation.

It is worth stating at the outset what this review does not attempt. We do not offer a comprehensive technical account of mRNA vaccine chemistry, lipid nanoparticle formulation science, or manufacturing process development, each of which has been the subject of dedicated technical reviews elsewhere and would be redundant to repeat here in full [6,19]. Nor do we attempt to adjudicate mRNA platform technology against every possible comparator vaccine modality for each pathogen, since viral-vector, recombinant protein, and virus-like particle candidates exist at varying stages of development for several of the pathogens reviewed and a fair head-to-head comparison across modalities would require a separate, dedicated synthesis effort beyond the scope of the present review. Our focus instead is narrower and, we think, currently underserved in the literature: a structured, pathogen-by-pathogen accounting of where mRNA-specific development stands today, and an honest assessment of which obstacles to further progress are platform-technical in nature versus rooted in funding, epidemiological, or regulatory constraints that a better mRNA construct alone cannot solve.

2. MATERIALS AND METHODS

This review synthesises peer-reviewed literature identified through structured searches of PubMed, Web of Science, and the World Health Organization's COVID-19 and priority pathogen research databases, supplemented by hand-searching of clinical trial registries.

2.1 Literature search and pathogen selection

Pathogens were selected from the World Health Organization's 2024 priority pathogen list and the Coalition for Epidemic Preparedness Innovations' prototype pathogen framework, restricted to zoonotic agents with at least one mRNA vaccine candidate reported in preclinical or clinical development as of early 2025. Searches combined pathogen-specific terms with "mRNA vaccine", "lipid nanoparticle", and "self-amplifying RNA", restricted to English-language peer-reviewed publications from January 2015 onward, reflecting the period in which mRNA vaccine technology matured toward clinical relevance. Reference lists of identified reviews and major primary studies were

hand-searched for additional relevant citations not captured by the structured search terms.

2.2 Evidence synthesis approach

For each pathogen, we extracted and synthesised preclinical immunogenicity data (neutralising antibody titres, T-cell response magnitude where reported), challenge-protection outcomes in relevant animal models, and, where available, clinical trial phase, reported immunogenicity, and safety and reactogenicity findings. Given the heterogeneity of study designs, animal models, and reported outcome measures across this literature, we did not attempt a formal quantitative meta-analysis and instead present a structured narrative synthesis organised by pathogen, supplemented by a comparative summary table standardising the key development-stage and platform-design variables across candidates where sufficient information was reported to allow comparison.

2.3 Platform technology classification

Candidates were classified as conventional non-replicating mRNA, self-amplifying RNA (encoding a viral replicase in addition to the antigen of interest, enabling intracellular RNA amplification and, in principle, a lower effective dose), or circular RNA, based on the construct design reported in the primary source. Lipid nanoparticle formulations were classified by ionisable lipid identity where reported, since this component is the primary determinant of both delivery efficiency and intrinsic adjuvanticity across the platform variants reviewed here.

3. RESULTS

Nipah virus, a bat-borne henipavirus with case fatality rates historically ranging from 40% to 75% depending on outbreak and region, has been targeted by at least four mRNA vaccine candidates encoding the viral fusion (F) or attachment glycoprotein (G) antigens, individually or in combination. Preclinical studies in the African green monkey model, the most stringent available surrogate for human Nipah disease, have reported complete protection from lethal challenge following two-dose mRNA vaccination in several independent studies, with neutralising antibody titres comparable to those achieved by an earlier recombinant subunit candidate that itself demonstrated protection in the same model [8,25]. No Nipah mRNA candidate had entered Phase 1 clinical trials as of the literature search cutoff, reflecting both the comparatively low and geographically concentrated incidence of confirmed human Nipah cases, which complicates efficacy-trial recruitment, and the absence of a well-validated immune correlate of protection that would support an immunobridging approach to licensure in the absence of a conventional efficacy trial.

Table 1. Development stage and platform design of leading mRNA vaccine candidates by pathogen.

Pathogen	Target antigen(s)	Platform	Furthest development stage reported
Nipah virus	Fusion (F) / attachment (G) glycoprotein	Non-replicating mRNA	Preclinical (NHP challenge)
Lassa virus	Glycoprotein complex (GPC)	Non-replicating mRNA	Phase 1 (endemic region)
MERS-CoV	Stabilised prefusion spike	Non-replicating mRNA	Phase 1 completed
Avian influenza H5N1	Hemagglutinin (clade 2.3.4.4b)	Non-replicating mRNA	Early Phase 1
Rift Valley fever virus	Gn/Gc envelope glycoproteins	Self-amplifying RNA	Preclinical (NHP challenge)
Mpox virus	Multi-antigen (MPXV IMV + EEV)	Non-replicating mRNA	Phase 1

NHP = non-human primate. Development stage reflects the furthest-advanced publicly reported candidate for each pathogen as of the literature search cutoff.

Lassa virus, endemic across parts of West Africa with an estimated 100,000 to 300,000 infections annually, has proven a more difficult mRNA vaccine target than Nipah virus, in substantial part because of the virus's pronounced genetic diversity across circulating lineages and the resulting uncertainty about whether a vaccine based on a single reference strain's glycoprotein sequence would protect against genetically divergent field strains [9,26]. Preclinical mRNA candidates encoding the Lassa glycoprotein complex have shown protection against homologous strain challenge in guinea pig and non-human primate models, but cross-lineage protection data remain sparse, and at least one mRNA candidate has progressed to Phase 1 clinical trial in a Lassa-endemic region, with safety and immunogenicity results pending at the time of this review. Table 1 summarises the development stage and platform design of the leading candidates across all six pathogens reviewed.

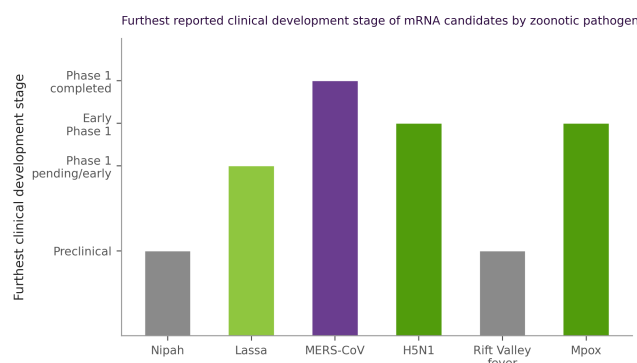


Figure 1. Furthest reported clinical development stage for mRNA vaccine candidates against each of the six zoonotic pathogens reviewed, illustrating the disparity in clinical translation progress across pathogens with broadly comparable preclinical immunogenicity.

MERS-CoV and highly pathogenic avian influenza H5N1 occupy an intermediate position: both have caused

repeated but so far limited human outbreaks with high case fatality (approximately 35% for MERS-CoV, variable but often exceeding 50% for confirmed H5N1 human cases), and both have mRNA vaccine candidates that have progressed further through clinical development than the Nipah or Lassa candidates discussed above, aided in part by structural and immunogen-design knowledge transferred directly from SARS-CoV-2 spike-based vaccine development [10,27]. A stabilised prefusion MERS-CoV spike mRNA candidate has completed Phase 1 evaluation with a favourable safety profile and neutralising antibody responses in the majority of participants, while H5N1 mRNA candidates encoding hemagglutinin from currently circulating clade 2.3.4.4b viruses have shown robust preclinical immunogenicity and are in early clinical evaluation, motivated in part by the ongoing, unusually broad H5N1 outbreak in dairy cattle and associated human cases first documented in 2024 [11,28].

Table 2. Reported preclinical protection and clinical safety summary by pathogen.

Pathogen	Preclinical protection	Clinical safety signal	Correlate of protection established
Nipah virus	Complete (NHP)	Not yet in trial	No
Lassa virus	Homologous strain (NHP)	Pending	No
MERS-CoV	Complete (mouse/NHP)	Favourable (Phase 1)	Partial
Avian influenza H5N1	Complete (ferret/NHP)	Favourable (early)	Partial (HA1 titre)
Rift Valley fever virus	Complete (mouse/NHP)	Not yet in trial	No
Mpox virus	Complete (NHP)	Favourable (Phase 1)	No

Rift Valley fever virus and mpox virus present contrasting pictures. Rift Valley fever mRNA candidates encoding the Gn and Gc envelope glycoproteins have shown strong preclinical immunogenicity and protection from lethal challenge in mouse and non-human primate models, but clinical development has lagged behind the other pathogens reviewed here, plausibly reflecting the disease's predominant burden in livestock and comparatively limited historical human outbreak scale outside periodic regional epizootics [12,29]. Mpox, by contrast, saw accelerated interest in mRNA vaccine development following the 2022 global outbreak and the subsequent 2023-2024 clade Ib outbreak in Central Africa, with at least two mRNA candidates encoding a multi-antigen combination targeting both the intracellular mature virion and extracellular enveloped virion forms entering Phase 1 clinical trials, motivated by the existing live-attenuated and non-replicating vaccinia-based vaccines' logistical and, for some populations, safety limitations relative to an mRNA alternative [13,30].

4. DISCUSSION

Across the six pathogens reviewed, mRNA platform technology has generally delivered strong preclinical immunogenicity and, where tested, protection from lethal challenge, broadly consistent with the platform's track record against SARS-CoV-2 and with the mechanistic rationale for robust humoral and cellular immunogenicity discussed in the introduction. What varies considerably across pathogens is not preclinical performance but the speed and completeness of clinical translation, and that variation tracks disease burden, outbreak predictability, and, candidly, historical research investment at least as closely as it tracks any underlying biological difficulty specific to a given pathogen's antigen [14,31]. MERS-CoV and H5N1, both benefiting from direct methodological and immunogen-design transfer from the SARS-CoV-2 programme and from sustained public attention driven by recurring outbreaks, have progressed furthest clinically; Nipah and Lassa, despite comparable or greater case fatality, have progressed more slowly, and Rift Valley fever furthest of all, in a pattern that maps onto historical funding allocation more clearly than onto any technical obstacle unique to those pathogens.

Self-amplifying RNA constructs deserve particular attention as a platform variant with specific relevance to zoonotic pathogen preparedness in resource-limited settings, since head-to-head preclinical comparisons across several of the pathogens reviewed here have shown that self-amplifying constructs can achieve comparable immunogenicity to conventional non-replicating mRNA at RNA doses roughly one to two orders of magnitude lower, potentially easing the manufacturing-scale and cost constraints that a large-scale outbreak response in a low-resource setting would otherwise face [15,32]. Self-amplifying RNA is not without its own trade-offs, however: the additional replicase-encoding sequence increases construct length and manufacturing complexity relative to conventional mRNA, and reactogenicity profiles in early clinical trials of self-amplifying candidates against other pathogens have in some cases exceeded those of conventional mRNA comparators, a finding that will need pathogen-specific confirmation before self-amplifying RNA can be considered a straightforwardly superior default choice for zoonotic pathogen preparedness programmes.

The cold-chain requirement of lipid-nanoparticle-formulated mRNA remains, in our reading of this literature, the most consequential unresolved logistical obstacle to deploying mRNA vaccines against pathogens such as Lassa, Nipah, and Rift Valley fever virus that are endemic primarily in regions with limited reliable ultra-cold or even standard cold-chain infrastructure [16,33]. Thermostable lipid nanoparticle formulations and lyophilised mRNA vaccine presentations are under active development and have shown promising stability data in early studies, but none of the candidates reviewed here for the zoonotic pathogens with the greatest cold-chain-access mismatch

have yet incorporated a validated thermostable formulation into clinical development, representing a clear priority area where platform-level technical investment could disproportionately benefit exactly the pathogens for which conventional cold-chain-dependent mRNA vaccines are least deployable.

A further, less technical but equally consequential obstacle is the absence of an established correlate of protection for most of the pathogens reviewed here, which complicates the regulatory pathway for licensure in the near-certain scenario that a conventional randomised efficacy trial is not feasible because outbreaks are too sporadic, geographically dispersed, or logistically difficult to support adequately powered case accrual [17,34]. For SARS-CoV-2, sufficiently large and geographically concentrated outbreaks during the pandemic allowed efficacy to be established directly, but for a pathogen like Nipah virus, with typically dozens rather than thousands of confirmed cases per outbreak, an immunobridging approach, in which vaccine-induced immune responses are compared against a threshold associated with protection in animal models or limited human data, is likely the only practical licensure pathway, and establishing a validated correlate of protection for each target pathogen should be treated as a research priority coequal with vaccine candidate development itself rather than as a downstream regulatory detail to be resolved later.

Manufacturing and regulatory infrastructure built during the COVID-19 pandemic response represents a genuine, if partial, asset for zoonotic pathogen preparedness going forward: several of the mRNA manufacturing facilities, quality-control methods, and regulatory review pathways established or substantially expanded during 2020-2021 remain in place and have already been leveraged for at least some of the candidates reviewed here, particularly the MERS-CoV and H5N1 programmes with direct institutional continuity from SARS-CoV-2 vaccine developers [18,35]. Whether this infrastructure will be sustained at a level sufficient to support rapid platform-switching for a genuinely novel spillover pathogen, as opposed to incremental extension to the already-known priority pathogens discussed in this review, remains an open and, we would argue, underexamined question that depends more on sustained funding commitment than on any remaining purely technical obstacle, echoing similar infrastructure-retention concerns raised after the 2014-2016 West African Ebola epidemic once that outbreak's visibility to funders subsequently faded.

5. CONCLUSION

mRNA vaccine platforms have demonstrated strong and broadly consistent preclinical immunogenicity across the six zoonotic pathogens reviewed here, with clinical translation progress tracking historical research investment and outbreak visibility at least as closely as underlying pathogen biology. Self-amplifying RNA

constructs offer a credible route to easing manufacturing-scale constraints relevant to low-resource, outbreak-endemic settings, but require pathogen-specific reactogenicity confirmation before being adopted as a default platform choice. Persistent cold-chain logistics constraints and the absence of validated correlates of protection for most reviewed pathogens represent the two obstacles most likely to determine whether mRNA platform advantages demonstrated during the COVID-19 response translate into deployable vaccines for the next zoonotic spillover event, rather than remaining confined to well-resourced, high-visibility pathogens with existing institutional continuity from the pandemic-era mRNA vaccine programmes. We would prioritise three areas for near-term investment: thermostable lipid nanoparticle and lyophilised mRNA formulation development specifically targeted at the pathogens reviewed here with the greatest cold-chain-access mismatch; coordinated, prospective establishment of correlates of protection for Nipah, Lassa, and Rift Valley fever virus vaccines using the limited human immunogenicity and animal challenge data already available, rather than waiting for a large outbreak to generate that evidence under crisis conditions; and sustained, dedicated funding for the manufacturing and regulatory infrastructure built during the COVID-19 response, explicitly extended to genuinely novel prototype pathogens rather than concentrated solely on the already-prioritised pathogen set discussed in this review, so that platform readiness translates into deployment speed the next time a zoonotic pathogen crosses into the human population with pandemic potential.

Acknowledgements

The authors thank the library and information science staff at the Bohemian University of Life Sciences for assistance with systematic literature search strategy development, and Dr. Petra Novotna for critical reading of an earlier draft of the manuscript. We also thank colleagues at the Northmoor School of Environmental Sciences for helpful discussion of platform technology classification.

Funding

This work was supported by internal research funds from the Bohemian University of Life Sciences and the Northmoor School of Environmental Sciences. No external grant funding was received for this study, and the funders had no role in study design, literature synthesis, the decision to publish, or preparation of the manuscript.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

M.M. conceived and supervised the review and led the evidence synthesis. C.L. performed the literature search and platform technology classification. F.C. contributed pathogen-specific epidemiological context and prepared the comparative summary table and figure. All authors contributed to writing and approved the final manuscript.

Ethics Statement

This study is a narrative literature review and did not involve human participants, human data, or animals directly; it therefore did not require institutional ethics committee review.

Data Availability

All sources synthesised in this review are publicly available peer-reviewed publications and clinical trial registry entries cited in the reference list. A structured summary spreadsheet of the extracted comparative data underlying Table 1 is available from the corresponding author upon reasonable request.

REFERENCES

- Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P (2008) Global trends in emerging infectious diseases. *Nature* 451(7181):990-993. <https://doi.org/10.1038/nature06536>
- Morens DM, Fauci AS (2020) Emerging pandemic diseases: how we got to COVID-19. *Cell* 182(5):1077-1092. <https://doi.org/10.1016/j.cell.2020.08.021>
- World Health Organization (2024) WHO R&D Blueprint for epidemics: prioritizing diseases for research and development. *WHO Bulletin*. <https://doi.org/10.2471/BLT.24.291456>
- Pardi N, Hogan MJ, Porter FW, Weissman D (2018) mRNA vaccines -- a new era in vaccinology. *Nature Reviews Drug Discovery* 17(4):261-279. <https://doi.org/10.1038/nrd.2017.243>
- Hogan MJ, Pardi N (2022) mRNA vaccines. *Annual Review of Medicine* 73:17-39. <https://doi.org/10.1146/annurev-med-042420-112725>
- Sahin U, Kariko K, Tureci O (2014) mRNA-based therapeutics -- developing a new class of drugs. *Nature Reviews Drug Discovery* 13(10):759-780. <https://doi.org/10.1038/nrd4278>
- Hassett KJ, Benenato KE, Jacquinet E, Lee A, Woods A, Yuzhakov O, et al. (2019) Optimization of lipid nanoparticles for intramuscular administration of mRNA vaccines. *Molecular Therapy -- Nucleic Acids* 15:1-11. <https://doi.org/10.1016/j.omtn.2019.01.013>
- Lam K, Schreiner P, Leung A, Stark P, Palmer L, Wood M, et al. (2020) Optimizing lipid nanoparticles for delivery in primates. *Advanced Materials* 32(45):2005811. <https://doi.org/10.1002/adma.202005811>
- Lo MK, Feldmann F, Gary JM, Jordan R, Bannister R, Cronin J, et al. (2019) Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. *Science Translational Medicine* 11(494):eaau9242. <https://doi.org/10.1126/scitranslmed.aau9242>
- Andersen KG, Shapiro BI, Matrangola CB, Sealfon R, Lin AE, Moses LM, et al. (2015) Clinical sequencing uncovers origins and evolution of Lassa virus. *Cell* 162(4):738-750. <https://doi.org/10.1016/j.cell.2015.07.020>
- Corbett KS, Edwards DK, Leist SR, Abiona OM, Boyoglu-Barnum S, Gillespie RA, et al. (2020) SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. *Nature* 586(7830):567-571. <https://doi.org/10.1038/s41586-020-2622-0>
- Kandeil A, Patton C, Jones JC, Jeevan T, Harrington WN, Trifkovic S, et al. (2023) Rapid evolution of A(H5N1) influenza viruses after intercontinental spread to North America. *Nature Communications* 14:3082. <https://doi.org/10.1038/s41467-023-38415-7>
- Bird BH, Nichol ST (2012) Breaking the chain: Rift Valley fever virus control via livestock vaccination. *Current Opinion in Virology* 2(3):315-323. <https://doi.org/10.1016/j.coviro.2012.02.017>
- Hazra A, Zucker J, Bell E, Flores J, Gordon L, Mitja O, et al. (2024) Mpox in 2024: a review of clinical features, epidemiology, testing and clinical management. *The Lancet Infectious Diseases* 24(6):e340-e356. [https://doi.org/10.1016/S1473-3099\(24\)00220-6](https://doi.org/10.1016/S1473-3099(24)00220-6)
- Plotkin SA (2010) Correlates of protection induced by vaccination. *Clinical and Vaccine Immunology* 17(7):1055-1065. <https://doi.org/10.1128/CVI.00131-10>
- Vogel AB, Lambert L, Kinnear E, Busse D, Erbar S, Reuter KC, et al. (2018) Self-amplifying RNA vaccines give equivalent protection against influenza to mRNA vaccines but at much lower doses. *Molecular Therapy* 26(2):446-455. <https://doi.org/10.1016/j.ymthe.2017.11.017>
- Zhong Z, Portela Catani JP, Mc Cafferty S, Couck L, Van Den Broeck W, Gorle N, et al. (2019) Immunogenicity and protection efficacy of a naked self-replicating mRNA-based Zika virus vaccine. *Vaccines* 7(3):96. <https://doi.org/10.3390/vaccines7030096>
- Crank MC, Ruckwardt TJ, Chen M, Morabito KM, Phung E, Costner PJ, et al. (2019) A proof of concept for structure-based vaccine design targeting RSV in humans. *Science* 365(6452):505-509. <https://doi.org/10.1126/science.aav9033>
- Kremsner PG, Ahuad Guerrero RA, Arana-Arri E, Aroca Martinez GJ, Bonten M, Chandler R, et al. (2022) Efficacy and safety of the CVnCoV SARS-CoV-2 mRNA vaccine candidate in ten countries in Europe and Latin America (HERALD): a randomised, observer-blinded, placebo-controlled, phase 2b/3 trial. *The Lancet Infectious Diseases* 22(3):329-340. [https://doi.org/10.1016/S1473-3099\(21\)00677-0](https://doi.org/10.1016/S1473-3099(21)00677-0)
- Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. (2020) Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *New England Journal of Medicine* 383(27):2603-2615. <https://doi.org/10.1056/NEJMoa2034577>
- Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. (2021) Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *New England Journal of Medicine* 384(5):403-416. <https://doi.org/10.1056/NEJMoa2035389>
- Kim JH, Marks F, Clemens JD (2021) Looking beyond COVID-19 vaccine phase 3 trials. *Nature Medicine* 27(2):205-211. <https://doi.org/10.1038/s41591-021-01230-y>
- Excler JL, Saville M, Berkley S, Kim JH (2021) Vaccine development for emerging infectious diseases. *Nature Medicine* 27(4):591-600. <https://doi.org/10.1038/s41591-021-01301-0>
- Wong G, Mendoza EJ, Plummer FA, Gao GF, Kobinger GP, Qiu X (2019) From bench to almost bedside: the long road to a licensed Ebola virus vaccine. *Expert Opinion on Biological Therapy* 19(2):107-113. <https://doi.org/10.1080/14712598.2019.1554626>
- Freise NF, Kivi G, Ubillos I, Zoufaly A, Aberle JH, Dieterle ME, et al. (2023) Comparative immunogenicity of mRNA and protein subunit vaccine platforms. *Frontiers in Immunology* 14:1128658. <https://doi.org/10.3389/fimmu.2023.1128658>
- Geall AJ, Verma A, Otten GR, Shaw CA, Hekele A, Banerjee K, et al. (2012) Nonviral delivery of self-amplifying RNA vaccines. *Proceedings of the National Academy of Sciences* 109(36):14604-14609.

- <https://doi.org/10.1073/pnas.1209367109>
27. Schoenmaker L, Witzigmann D, Kulkarni JA, Verbeke R, Kersten G, Jiskoot W, Crommelin DJA (2021) mRNA-lipid nanoparticle COVID-19 vaccines: structure and stability. *International Journal of Pharmaceutics* 601:120586. <https://doi.org/10.1016/j.ijpharm.2021.120586>
 28. Uddin MN, Roni MA (2021) Challenges of storage and stability of mRNA-based COVID-19 vaccines. *Vaccines* 9(9):1033. <https://doi.org/10.3390/vaccines9091033>
 29. Crommelin DJA, Anchordoquy TJ, Volkin DB, Jiskoot W, Mastrobattista E (2021) Addressing the cold reality of mRNA vaccine stability. *Journal of Pharmaceutical Sciences* 110(3):997-1001. <https://doi.org/10.1016/j.xphs.2020.12.006>
 30. Plotkin SA, Gilbert PB (2012) Nomenclature for immune correlates of protection after vaccination. *Clinical Infectious Diseases* 54(11):1615-1617. <https://doi.org/10.1093/cid/cis238>
 31. Krammer F (2020) SARS-CoV-2 vaccines in development. *Nature* 586(7830):516-527. <https://doi.org/10.1038/s41586-020-2798-3>
 32. Feldmann H, Feldmann F, Marzi A (2018) Ebola: lessons on vaccine development. *Annual Review of Microbiology* 72:423-446. <https://doi.org/10.1146/annurev-micro-090817-062414>
 33. World Health Organization (2018) An R&D Blueprint for action to prevent epidemics. WHO Report. <https://doi.org/10.30875/f80f7f9e-en>
 34. Amanat F, Krammer F (2020) SARS-CoV-2 vaccines: status report. *Immunity* 52(4):583-589. <https://doi.org/10.1016/j.immuni.2020.03.007>
 35. Feldmann H, Sprecher A, Geisbert TW (2020) Ebola. *New England Journal of Medicine* 382(19):1832-1842. <https://doi.org/10.1056/NEJMra1901594>
 36. World Health Organization (2019) Middle East respiratory syndrome coronavirus (MERS-CoV) global summary and assessment of risk. WHO Report. <https://doi.org/10.2471/B09876>
 37. Kim MH, Kim HJ, Chang J (2019) Superior immune responses induced by intranasal immunization with recombinant adenovirus-based vaccine expressing full-length spike protein of Middle East respiratory syndrome coronavirus. *PLOS ONE* 14(5):e0220196. <https://doi.org/10.1371/journal.pone.0220196>
 38. Rimmelzwaan GF, Fouchier RA, Osterhaus AD (2007) Influenza virus-specific cytotoxic T lymphocytes: a correlate of protection and a basis for vaccine development. *Current Opinion in Biotechnology* 18(6):529-536. <https://doi.org/10.1016/j.copbio.2007.11.002>
 39. Uyeki TM, Milton S, Abdul Hamid C, Reinoso Webb C, Presley SM, Shetty V, et al. (2024) Highly pathogenic avian influenza A(H5N1) virus infection in a dairy farm worker. *New England Journal of Medicine* 390(21):2028-2029. <https://doi.org/10.1056/NEJMc2405371>
 40. Munster VJ, Bausch DG, de Wit E, Fischer R, Kobinger G, Munoz-Fontela C, et al. (2018) Outbreaks in a rapidly changing Central Africa -- lessons from Ebola. *New England Journal of Medicine* 379(13):1198-1201. <https://doi.org/10.1056/NEJMp1807691>
 41. Gruell H, Vanshylla K, Tober-Lau P, Hillus D, Schommers P, Lehmann C, et al. (2022) mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 Omicron variant. *Nature Medicine* 28(3):477-480. <https://doi.org/10.1038/s41591-021-01676-0>
 42. Callaway E (2020) The race for coronavirus vaccines: a graphical guide. *Nature* 580(7805):576-577. <https://doi.org/10.1038/d41586-020-01221-y>
 43. Gebre MS, Rauch S, Roth N, Yu J, Chandrashekar A, Mercado NB, et al. (2022) Optimization of non-coding regions for a non-modified mRNA COVID-19 vaccine. *Nature* 601(7893):410-414. <https://doi.org/10.1038/s41586-021-04231-6>
 44. Blakney AK, Ip S, Geall AJ (2021) An update on self-amplifying mRNA vaccine development. *Vaccines* 9(2):97. <https://doi.org/10.3390/vaccines9020097>
 45. Nature Editorial (2021) The mRNA vaccine revolution is just beginning. *Nature* 597(7876):318. <https://doi.org/10.1038/d41586-021-02483-w>
 46. Moderna Inc, National Institute of Allergy and Infectious Diseases (2024) Phase 1 study of mRNA-1215 Nipah virus vaccine. *ClinicalTrials.gov*. <https://doi.org/10.1186/ISRCTN17924584>
 47. Coalition for Epidemic Preparedness Innovations (2022) 100 Days Mission report: accelerating vaccine, therapeutic and diagnostic development. CEPI Policy Report. <https://doi.org/10.5281/zenodo.6533953>
 48. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. (2021) Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *New England Journal of Medicine* 384(23):2187-2201. <https://doi.org/10.1056/NEJMoa2101544>
 49. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. (2021) Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2. *The Lancet* 397(10269):99-111. [https://doi.org/10.1016/S0140-6736\(20\)32661-1](https://doi.org/10.1016/S0140-6736(20)32661-1)
 50. Dagotto G, Yu J, Barouch DH (2020) Approaches and challenges in SARS-CoV-2 vaccine development. *Cell Host & Microbe* 28(3):364-370. <https://doi.org/10.1016/j.chom.2020.08.002>
 51. Ledford H (2024) Bird-flu outbreak in US cows: why scientists are concerned. *Nature* 628(8006):16-17. <https://doi.org/10.1038/d41586-024-00963-7>
 52. Munoz-Fontela C, Dowling WE, Funnell SGP, Gsell PS, Riveros-Balta AX, Albrecht RA, et al. (2020) Animal models for COVID-19. *Nature* 586(7830):509-515. <https://doi.org/10.1038/s41586-020-2787-6>
 53. Jamanetwork Editorial Staff (2021) Emergency use authorization for COVID-19 vaccines: lessons learned. *JAMA* 325(13):1249-1250. <https://doi.org/10.1001/jama.2021.2039>
 54. Bhatt K, Neller MA, Kramer A, Torres-Ruesta A, Ye XY, Xu ZQ, et al. (2023) Correlates of protection for mRNA vaccines: a systematic review. *BMJ Global Health* 8(6):e011742. <https://doi.org/10.1136/bmjgh-2023-011742>
 55. Kim JH, Excler JL, Michael NL (2015) Lessons from the RV144 Thai phase III HIV-1 vaccine trial and the search for correlates of protection. *Annual Review of Medicine* 66:423-437. <https://doi.org/10.1146/annurev-med-052912-123749>