Reviews

Two mRNA Platforms for Canine Rabies Vaccines: Advances, Limitations, and Field Application Prospects

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ABSTRACT

Canine rabies control in rural China faces logistical barriers such as multi-dose schedules, cold-chain requirements, and the recapture of free-roaming dogs, which impede progress toward 70% vaccination coverage. Although inactivated vaccines remain the cornerstone of rabies control, mRNA platforms offer both manufacturing and immunological advantages. This review compares non-replicating mRNA (nr-mRNA) and self-amplifying mRNA (saRNA) platforms. It also examines oral and vectored vaccines as comparators for free-roaming dogs beyond the reach of injectable products. LVRNA001 and ABO1005 are nr-mRNA candidates that provide complete protection in canine challenge models using two-dose regimens; neutralizing antibody geometric mean titers (GMTs) exceed the World Health Organization (WHO) 0.5 IU/mL threshold through day 125, with the LVRNA001 50-μg group reaching approximately 100 IU/mL versus approximately 16 IU/mL for the inactivated vaccine (P<0.05). Both elicited Th1-biased cellular and cross-neutralizing antibody responses; lyophilized ABO1005 was stable at 2–8 °C for 12 months. For saRNA, single-dose protection has been shown only in mice and no canine data exist; dose extrapolation and excessive innate immune activation remain unresolved. Licensure requires compliance with China's 2026 draft guideline for animal mRNA products. Evidence derives from human candidates in beagles; prospects are most immediate for owned or accessible dogs; translation remains contingent on target-animal safety data, delivery innovation, regulatory approval, and operational feasibility.

Rabies is a fatal zoonotic disease caused by the rabies virus (RABV), with a case fatality rate approaching 100% (*1*–*2*). Globally, rabies causes approximately 59,000 human deaths annually, more than 99% of which are attributable to dog-mediated transmission (*3*–*5*). In China, annual human rabies cases declined for 16 consecutive years following comprehensive control measures implemented in 2006, reaching a historic low of 122 in 2023 (*6*–*7*).

Maintaining canine vaccination coverage at or above 70% is recognized as the threshold required to interrupt dog-to-dog transmission (*7*–*11*). In China, rural canine vaccination coverage remains substantially below this threshold; a 2021 household survey in rural Guangxi reported that only 19.1% of dog owners had vaccinated their dogs (*12*). Although post-exposure prophylaxis (PEP) is life-saving for exposed individuals, it cannot interrupt the canine transmission cycle at the source (*9*). Three persistent barriers have impeded progress: poorly enumerated free-roaming and stray dog populations with unknown vaccination status (*13*); multi-dose schedules and cold-chain constraints, which compound the difficulty of recapturing free-roaming dogs (*14*–*17*); and limited financial resources and veterinary personnel shortages in endemic settings (*18*–*19*).

mRNA vaccine platforms have been the focus of intensive vaccine research (*20*–*21*). Several mRNA rabies vaccine candidates have been evaluated in animal models, including dogs (*22*–*23*). Two principal modalities have emerged: non-replicating mRNA (nr-mRNA) delivers a conventional transcript encoding the rabies glycoprotein, while self-amplifying mRNA (saRNA) encodes a viral replicase that amplifies the transcript intracellularly, permitting substantially lower input doses (*20*,*24*). This review compares the protective efficacy, manufacturing characteristics, immunogenicity, and safety profiles of these two modalities, particularly focusing on human vaccine candidates evaluated in canine models. This review also examines their implications for the development of veterinary mRNA rabies vaccines in China. Delivery, not immunogenicity, is the binding constraint for free-roaming dogs; oral and vectored platforms are therefore considered as comparators.

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FEATURES OF mRNA PLATFORMS

Protective Efficacy

LVRNA001, an nr-mRNA candidate encoding the CTN-1 strain RABV glycoprotein (RABV-G), has been evaluated in a canine model. Two intramuscular doses of 10 or 50 μg (days 0 and 7) conferred 100% protection against lethal challenge with 50 × LD_{50} of the BD06 street virus strain on day 35. Neutralizing antibody geometric mean titers (GMTs) exceeded the World Health Organization (WHO) protective threshold of 0.5 IU/mL by day 7 in all vaccinated groups. By day 125, the titer in the 50-μg group had risen to its peak, whereas the titer in the inactivated group declined to approximately 16 IU/mL (P<0.05) (*25*). In a canine post-exposure prophylaxis (PEP) model, lyophilized ABO1005 (15 μg, two-dose) achieved a virus neutralizing antibody GMT of 67.0 IU/mL at day 60, compared with 45.2 IU/mL for the five-dose inactivated vaccine regimen (*26*). Time-course GMT values are summarized in Table 1.

Manufacturing

Conventional inactivated rabies vaccine production requires the large-scale propagation of live viruses, typically under BSL-3 containment. Meanwhile, mRNA vaccines are manufactured through cell-free in vitro transcription, eliminating live-virus handling and reducing biosafety requirements (*22*,*25*–*26*). As this process is independent of the encoded antigen, the same facility can rapidly adapt to new targets (*31*). Lyophilized mRNA–lipid nanoparticles (LNP) formulations can remain stable in 2–8 °C storage (*26*), overcoming the ultra-cold requirements of earlier liquid mRNA vaccines. Per-dose costs currently exceed those of inactivated vaccines owing to proprietary LNP components and limited manufacturing scale; however, domestic supply chain development is expected to reduce costs over time (*32*).

Regulatory Landscape for Veterinary mRNA Vaccines

Translation from laboratory proof-of-concept to licensed veterinary products requires compliance with species-specific regulatory frameworks. In 2026, China Institute of Veterinary Drug Control issued the Technical Requirements for Registration Application of Animal mRNA Products (Draft for Comments) (*33*), specifying comprehensive data requirements including pharmaceutical characterization, target-animal safety (single-dose, repeated-dose, and reproductive toxicity), challenge-protection studies with at least three product batches, stability testing, and biosafety assessment. saRNA products are classified as genetically engineered veterinary biologics requiring an additional biosafety approval certificate — a requirement not applied to nr-mRNA products. EMA and WOAH have also established quality guidelines for veterinary mRNA vaccines and rabies biologics (*34*–*35*). Notably, all three frameworks require target-animal data, multi-batch consistency, and long-term stability. A complete dossier, including target-animal efficacy and safety data, is mandatory for acceptance.

Immunogenicity

In addition to challenge protection, mRNA rabies vaccines elicit immune responses that are not typically observed with inactivated vaccines. LVRNA001

TABLE 1. Comparative overview of three vaccine platforms for canine rabies control.

Dimension	Inactivated vaccine	nr-mRNA	saRNA
Schedule	2–3 doses + annual booster	2 doses (D0–7 or D0–21)	Single dose (mouse only)
Canine protection	Pre: 100%; PEP: 83–100% (*25*,*26*)	100% pre- & post-exposure (*25*,*26*,*27*)	No data
Immunogenicity	Humoral; limited cellular (*25*)	Th1-biased cellular + cross-NAb + plasma cells (*25*,*27*–*29*)	Mouse: humoral + cellular (*30*)
Canine evidence	Decades of field data	Beagle efficacy, safety, stability (*25*,*26*,*27*)	All key data absent
Canine GMT (IU/mL; doses in μg)	D7: approximately 4; D35: approximately 60 (peak); D125: approximately 16 IU/mL (*25*)	D7: 50 μg approximately 3, 10 μg approximately 1.5; D35: 50 μg approximately 78, 10 μg approximately 19; D125: 50 μg approximately 100* (peak), 10 μg approximately 75; ABO1005: 67.0 (PEP D60) (*25*,*26*)	No canine GMT data

Abbreviation: nr-mRNA=non-replicating mRNA; saRNA=self-amplifying mRNA; GMT=geometric mean titer; NAb=neutralizing antibody; PEP=post-exposure prophylaxis; Pre=pre-exposure; D=day.
* P<0.05 versus inactivated vaccine.

induced a pronounced Th1-biased cellular response in mice, with increased frequencies of interferon-gamma (IFN-γ)-secreting splenocytes and RABV-G-specific $CD4^+$ T cells (*25*,*27*). In cynomolgus macaques, two-dose LVRNA001 generated high-titer neutralizing antibodies within 7 days of the first dose and sustained RABV-G-specific bone marrow plasma cell responses (*25*). CureVac unmodified mRNA-LNP vaccines induced cross-neutralizing antibodies against heterologous lyssavirus strains lasting for at least 1 year in non-human primates (*28*–*29*). However, these features were observed exclusively in laboratory beagles and inbred mouse strains. Whether Th1 bias or cross-neutralizing breadth confers protection against heterologous street-virus exposure in genetically diverse free-roaming dogs remains to be established.

Reactogenicity

Repeated-dose toxicity studies of LVRNA001 in cynomolgus macaques reported transient elevations in fibrinogen and C-reactive protein levels with a decreased albumin-to-globulin ratio, all of which resolved after a 4-week recovery period; injection-site reactions were mild and self-limiting (*25*). A reproductive toxicity study in rats revealed no adverse effects on fertility or embryofetal development (*25*). These findings align with the known innate immune activation profile of LNPs, in which dose-dependent inflammatory responses are common (*36*). The reactogenicity of nr-mRNA vaccines is formulation- and dose-dependent: CV7202, another nr-mRNA rabies candidate, was discontinued at the 5-μg dose in its Phase I trial owing to unacceptable reactogenicity, whereas 1- and 2-μg doses were well tolerated (*37*). When developing veterinary mRNA products, injection site reactogenicity must be assessed in target animal studies, as owner acceptability under field conditions may be affected (*38*–*39*).

TARGET-SPECIES EVIDENCE: DATA AND GAPS

nr-mRNA Platform

nr-mRNA has generated more extensive canine evidence than saRNA. LVRNA001 has been evaluated in mice, dogs, and cynomolgus macaques, with two-dose regimens providing complete protection in both pre-and post-exposure canine challenge models (*25*). Lyophilized ABO1005 has demonstrated 12-month storage stability at 2–8 °C (*26*). SYS6008 has demonstrated cross-clade protection against China I–VII RABV strains in murine post-exposure models (*40*). Studies in non-human primates have confirmed durable cross-neutralizing antibody responses and bone marrow plasma cell induction (*28*–*29*), and Phase I data for CV7202 have established clinical proof of concept (*37*). Veterinary mRNA rabies vaccine candidates have recently entered early development; however, peer-reviewed data from these programs are not yet available.

saRNA Platform

Two saRNA candidates have provided proof-of-concept evidence. JJ-saRNA-RABV001 demonstrated single-dose protection in murine models: a 0.1-μg dose achieved 100% survival when administered 14 days before challenge (*30*). RBI-4000 has completed a Phase I human trial showing neutralizing antibody durability that matched or exceeded licensed inactivated rabies vaccines (*41*). Broader advances include protective efficacy against pseudorabies virus (*42*) and immunogenicity of a Rift Valley fever vaccine in mice (*43*). For canine rabies, however, no peer-reviewed study has reported neutralizing antibody GMTs, challenge protection, or repeated-dose safety in dogs for any saRNA construct. Dose extrapolation from rodents (approximately 20 g) to domestic dogs (5–40 kg) is unreliable because of differences in body mass, lymphatic drainage, and innate immune signaling (*44*–*45*). Canine saRNA studies, if undertaken, should prioritize species-specific dose determination and formal assessment of excessive innate immune activation risk in outbred populations, which requires specifically designed canine studies rather than extrapolation from existing murine data. The cross-species comparison is provided in Table 2.

Regulatory and Translational Barriers for saRNA

Beyond murine proof-of-concept, however, registration and field deployment in the short- to medium-term remain blocked by the absence of core target-animal data and by the additional biosafety approval required for genetically engineered veterinary biologics under China's current framework.

COMPARATOR APPROACHES AND FIELD DELIVERY

Oral administration offers an alternative route for

TABLE 2. Cross-species comparison of evidence for mRNA rabies vaccines.

Species	nr-mRNA key findings	saRNA key findings	Inactivated key findings	Data gaps	Peak neutralizing GMT
Mouse	2-dose: 100%; GMT > inact. (25,27)	0.1 μg single: 100% (D14) (30)	2–3 doses: 100%	saRNA: mouse-only, not extrapolable	nr-mRNA GMT > inact.; saRNA: mouse data only
Dog	LVRNA001: 100% pre-/post-exposure, ≥125 d (25); ABO1005: 12-mo 2–8°C (26)	GMT: N/A; Protection: N/A; Safety: N/A	Pre: 100% (25); PEP: ≥83% (26)	saRNA: all canine data missing	50 μg: approximately 100 IU/mL (D125)*; ABO1005: 67.0 (PEP D60); inact.: approximately 60 (D35) → approximately 16 (D125); saRNA: no data (25,26)
NHP	Cross-NAb ≥1 yr + plasma cells (28,29)	No data	Seroconversion	saRNA: no NHP data	nr-mRNA cross-NAb ≥1 yr (28,29); saRNA: no data
Human (Phase I)	CV7202: D43 100% seroconv.; 5 μg discontinued (37)	RBI-4000: durability ≥ inact. (41)	Seroconversion	–	CV7202: 100% D43 (37); RBI-4000 ≥ inact. (41)

Note: "–" means data not applicable.
Abbreviation: nr-mRNA=non-replicating mRNA; saRNA=self-amplifying mRNA; GMT=geometric mean titer; NAb=neutralizing antibody; PEP=post-exposure prophylaxis; NHP=non-human primate; inact.=inactivated vaccine; seroconv.=seroconversion; Pre=pre-exposure; D=day; mo=month; yr=year; N/A=not available.
* $P<0.05$ versus inactivated vaccine.

dogs that cannot be captured. In wildlife reservoirs, baits containing recombinant vaccinia virus expressing RABV-G contributed to rabies elimination in Belgium, France, and Luxembourg (46). Both WHO and WOAH position oral vaccination as complementary to parenteral vaccination for free-roaming populations that campaigns cannot reach (35,47–48). In a Chinese non-parenteral trial, a recombinant canine adenovirus type 2 vaccine expressing RABV-G, delivered in baits or as an intranasal solution, seroconverted 87.5% (119/136) of dogs; among seroconverted animals, 90.8% maintained virus-neutralizing antibodies above 0.5 IU/mL for 24 months, and all 10 dogs challenged with CVS-24 2 years after vaccination survived (49). Attenuated live rabies virus strains are an alternative oral candidate class, but require target-animal safety data and assessment of residual pathogenicity and non-target species exposure (47–48). These platforms therefore address delivery rather than immunogenicity, complementing injectable mRNA platforms rather than replacing them.

Injectable mRNA candidates, by contrast, require capture and, for nr-mRNA, two doses, and are therefore best suited to owned or accessible dogs presented at clinics or during centralized campaigns, when a second visit is feasible. Even a single-dose saRNA product would require parenteral administration; neither platform eliminates the need to recapture free-roaming dogs.

Vaccination alone is unlikely to eliminate rabies from free-roaming populations. The WOAH Terrestrial Animal Health Code states that mass culling of dogs is ineffective and may be counterproductive, and that dog population management contributes to rabies control by reducing population turnover and thereby sustaining the herd immunity established by vaccination (13,50). Under Article 30 of China's Animal Epidemic Prevention Law, owners are responsible for periodic vaccination and registration of their dogs, while local governments organize the control of free-roaming dogs and cats (51). mRNA vaccines are therefore best positioned as adjuncts to dog population management rather than as substitutes for it.

LIMITATIONS

This study has some limitations. First, the evidence base is both platform- and species-limited; no canine data are available for saRNA vaccines, and all available canine data are derived from controlled laboratory studies in beagles rather than from free-roaming dogs, which constitute the primary rabies reservoir in rural China. No veterinary mRNA rabies vaccine has been licensed, and no field delivery or effectiveness studies of mRNA rabies vaccines in dogs have been reported. Second, the immunogenicity follow-up for LVRNA001 did not extend beyond 125 days, and the 12-month stability of lyophilized ABO1005 was demonstrated only under constant-temperature conditions. Thus, long-term durability and performance under variable rural cold-chain logistics remain unverified. Third, no comparative cost-effectiveness or budget impact analyses of mRNA

versus inactivated canine rabies vaccines under Chinese field conditions are available. Finally, selection bias in literature inclusion cannot be excluded in this narrative review, and the 2026 draft guideline for veterinary mRNA products awaits formal promulgation.

CONCLUSIONS

In the short term, the nr-mRNA platform, which has accumulated canine efficacy data comparable to inactivated vaccines, can be developed for owned or accessible dogs, contingent on target-animal safety data, delivery feasibility, and regulatory approval. Remaining gaps include safety in juvenile, pregnant, and immunocompromised dogs, stability under variable rural cold-chain conditions, field trials clarifying vaccinator training and owner acceptability, and domestic LNP excipient development for cost compatibility with public immunization programs. In the medium term, bridging murine proof-of-concept to veterinary drug evaluation standards for saRNA requires systematic canine studies — dose escalation, repeated-dose safety, immunogenicity beyond one year, and biodistribution — together with empirical validation of cross-species dose extrapolation and formal assessment of excessive innate immune activation in outbred dogs. In the long term, products with superior thermostability, simplified dosing, and competitive cost could replace multi-dose inactivated vaccines in China's spring and autumn centralized campaigns. Such implementation, in alignment with the Zero by 30 strategic plan, will require coordinated investment in domestic mRNA supply chains and rigorous health-economic comparison. Therefore, contribution to the 2030 target depends on the availability of target animal safety data, delivery innovation for free-roaming dogs, regulatory approval under the 2026 draft framework, and operational feasibility in resource-limited rural settings.

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