International Journal of Science and Healthcare Research
Vol.7; Issue: 3; July-Sept. 2022
Website: ijshr.com
Review Article *ISSN: 2455-7587*

The Advantage Efficacy of Intranasal Live-Attenuated Vaccine Against SARS-CoV-2

Ratthaphum Sae-ngow

Assumption College Nakhonratchasima, Nai Mueang, Nakhon Ratchasima, Thailand, 30000

DOI: https://doi.org/10.52403/ijshr.20220715

ABSTRACT

Coronavirus disease 2019 (COVID-19) has ushered in a new era of breakthrough infections. The SARS-CoV-2 virus, which causes COVID-19, emerged in late 2019 in a seafood market in Wuhan, China, and was linked to pneumonia-associated sickness, which can culminate in respiratory failure. COVID-19 can potentially cause cardiovascular and gastrointestinal diseases and indicate an inflammatory condition. Regarding the diminishing protective immunity of vaccinations over time and the urgency of vaccine-evading SARS-CoV-2 variations, it is recommended that a booster injection be administered, and the research of variant-specific vaccines is continuing. As a result of the COVID-19 pandemic, vaccine development became a focal point of global research. However, vaccine development necessitates considerable time. Between preclinical research and the final vaccine's commercialisation, years or more than a decade are often required. Several options for SARS-CoV-2 vaccines have begun clinical trials globally after months of research and development. As stipulated by the WHO, vaccine development must involve preclinical research, clinical application, clinical trial agency application, registered clinical trial, phase I clinical trial, phase II clinical trial, phase III clinical trial, marketing, and manufacture of the vaccine. It is essential to create a balanced list of the benefits and drawbacks of deploying LAVs so that a well-informed choice can be made on which LAVs may be dispatched promptly to prevent and manage unanticipated pandemic breakouts.

Keywords: Intranasal live-attenuated vaccine, Covid-19 vaccine, SAR-CoV-2

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (Covid-19), arose in Wuhan, in a seafood market, China during late 2019 and was associated with pneumonia-associated illness, which can peak in respiratory failure [1]. COVID-19 can also make a patent in the form of cardiovascular and gastrointestinal pathologies and suggest a hyperinflammatory syndrome [2]. The destructive COVID-19 pandemic caused by SARS-CoV-2 has set a new phase in which breakthrough infections, specifically those caused by the highly transmittable Omicron and Delta variants, are widespread to a higher degree in vaccines immunized with mRNA, adenoviral vector, protein subunit or inactivated vaccines [3, 4]. In regards to the waning of protective immunity in vaccines over time and the exigency of vaccine-escaped SARS-CoV-2 variants, another injection of booster is suggested, and the development of variant-targeted vaccines is ongoing [5]. The levels of neutralizing antibodies (NAbs) that aim the viral spike (S) protein, especially the receptor-binding domain (RBD), relate superbly with protective immunity against detectable and symptomatic SARS-CoV-2 infection. Even though such a correlation has not been investigated for immune memory or CD8+ T cells, these immune supporting roles might also bring about harsh COVID-19 lessening [6-8]. Although extremely effective in the induction of NAbs, the existing SARS-CoV-2 vaccines

miscarry to bring out the mucosal and sterilizing immunity required for the elimination of breakthrough infections, which often begin in the mucilage of the upper respiratory tract [9, 10]. The Covid-19 pandemic has given us new lessons [11]. Emerging evidence suggests that one injection of mRNA vaccine with natural infection significantly supplies better protection against the Omicron variant than three injections of the mRNA vaccine combined together [12, 13]. On the other hand, the success of the mRNA vaccines might be cited, at least in part, to the use of a super high dose [14]. It remains to be checked whether the administration of a live-attenuated vaccine in high dose alone provides sterilizing protection against SARS-CoV-2 and eliminates the reinfection possibility [15]. Evidently, the probability of establishing sterilizing immunity would be substantially gone up when a live attenuated vaccine is applied as a injection booster in people who have been naturally infected or immunized with an mRNA vaccine or another type of vaccine [10, 15]. However, live attenuated vaccines are comprehended to elicit a much wider range of humoral and cellular immune responses that are cross-reactive and cross-protective [5, 16]. They might contribute considerably to the SARS-CoV-2 control in the next station of the pandemic [10]. Present authorized SARS-CoV-2 vaccines are administered intramuscularly and can effectively promote protective systemic immunity, including high titers of neutralizing serum antibodies, central and effector memory T lymphocytes, germinal center B lymphocytes and long-lived plasma cells (LLPC) [14, 16, 17]. Yet, the vaccines are less effective in inducing durable mucosal responses of IgA and IgG as well as responses of pulmonary tissue-resident memory cell [18]. Additionally, pathogen-specific mucosal antibodies at the site of virus entry are considered central to limiting infectivity and transmission [19]. Consequently, tissue-resident memory cells undergo faster recall responses, as their local positioning allows for earlier cognate antigen recognition [19]. Hence, vaccines efficiently administered via the respiratory entrance tract, are expected to persuade robust local mucosal immunity against the targeted pathogen [20]. This review aims to explore the current data of intranasal live-attenuated vaccine against SARS-CoV-2 regarding the efficacy, safety, and systemic immunity.

Concepts and methods of vaccine development

Before the successful development of a vaccine has been done, no drugs particularly targeting COVID-19 were obtainable in clinical practice, and quarantine is still a main measure in order to control the epidemic [21]. Concurrently, wearing masks, using liquid disinfectants and other measures efficiently lower the spread of SARS-CoV-2 [21]. Efficient vaccine is required to control the epidemics [22]. During the epidemic, the vaccine research and development has been focused on by teams all over the world. Fortuitously, Some satisfying results have been achieved [22]. Until now, some vaccine types have been developed and put on the market, resulting in the most effective measures to combat the epidemic [22]. After the epidemic situation confirmed, research has been promoted by the Ministry of Science and Technology of the People's Republic of China through several technical routes, including inactivated virus vaccines, recombinant protein vaccines, viral vector vaccines, and nucleic acid vaccines, to assure the success of vaccine research and development [23]. Currently, over 400 teams worldwide have launched vaccine research based on these five administration routes [24]. Vaccine development simultaneously became a focus of global research according to the COVID-19 pandemic [25]. Nevertheless, Vaccine development requires a plenty of time [24]. Years to more than a decade is often needed from preclinical research to the final marketed vaccine [24]. Prior to a short length of time for SARS-CoV-2 vaccine

development, mumps vaccine was considered a shortest development of vaccine, which took 5 years before it was released to market [26]. In the other hand, after several months of research and development of SARS-CoV-2 vaccines, the clinic worldwide has been entered by several candidates [27]. This unprecedented speed also required governments to adopt a variety of approval process to ensure the safety, efficacy and controllable quality of these newly created vaccines [27]. As specified by the WHO, vaccine development must undergo preclinical research, clinical application, clinical trial agency application, registered clinical trial, phase I clinical trial, phase II clinical trial, phase III clinical trial, vaccine marketing and vaccine production [28]. The process is generally distributed into five stages and 22 steps: 1) early design; 2) animal experiments; 3) Phase I clinical trial to understand the preliminary safety of the vaccine; 4) Phase II clinical trial to determine the immunization procedure and dose; and 5) Phase III clinical trials for more extensive vaccination trials and evaluation of side effects [28]. In Phase III, more than 1000 volunteers are required, and the shortest length of time is around 3–5 months [28]. As a result, the rapid development of SARS-CoV-2 vaccines is challenging [29]. A change in research and development concepts and approval methods is also necessary to ensure that people are injected as soon as possible [29].

Live-attenuated vaccines

The SARS-CoV live attenuated vaccine with E gene deletion (SARS-CoV-E) induced neutralising antibodies and CD4+ and CD8+ T cell responses in mice and ferrets and decreased inflammatory cell infiltration, oedema, and cell death [15, 30]. Revertant viruses either generated a unique chimeric gene containing the PDZ-binding motif (PBM) or restored the PBM sequence in the E protein after the full-length E gene was deleted or its PBM was altered [31, 32]. Therefore, the modified virus with a partial deletion of the E gene that does not impact PBM may be possible for a live, attenuated SARS-CoV vaccination [33]. In addition, amino acid changes in the E protein's transmembrane domain (TMD) to abolish the ion channel function might result in viral attenuation, reducing pulmonary oedema in infected animals [34]. In mice, another SARS-CoV vaccine candidate with simultaneous deletion of 8–12 amino acids in both the E and nsp1 genes C-termini improved IFN responses and reduced viral titers [35].

SARS-CoV and MERS-CoV mutations of non-structural protein 1 (nsp1), nsp16, and nsp14 have the potential to serve as attenuated live vaccines [36, 37]. Both SARS-CoV-ExoN (-) and MERS-CoV-ExoN (-) are stable mutants that provide mice immunological protection despite their drastically reduced fidelity and moderate toxicity [38]. Moreover, the combination of 2'-O-methyltransferase and ExoN mutations effectively protected old mice [38]. Nsp10 is a crucial replication regulator in SARS-CoV, and its ablation produces replication-deficient viruses by interfering with and inhibiting the activation of nsp14 ExoN, indicating a possible vaccine epitope [38].

Live-attenuated vaccines are said to be pathogenic microorganisms that have been engineered for reduced virulence, yet still have the capability to duplicate and generate an immune response [39]. The mechanism or process depends on a forceless or engineered virus forms, which straightly stimulates an immune response by penetrating cells and duplicating, leading to the antibodies and CD8+ production in response to the proteins of SARS-CoV-2 [40]. This vaccine type gives rise to crusty systemic and mucosal immune responses by reason of its brilliant immunogenicity [41]. Existing live-attenuated vaccines include yellow fever vaccine, smallpox vaccine, measles vaccine, poliomyelitis vaccine, mumps vaccine, rubella vaccine, and varicella vaccine [42]. On the contrary to deactivated virus vaccines, which need at least one supplementary booster shot, live-

attenuated vaccines just require to be administered once [43]. They deceive the process of natural infection of viruses and stimulate both humoral and cellular immunity, which immunologically manifests a long-term protective effect on the human body [44].

At present, live-attenuated vaccines are being developed by four institutions against SARS-CoV-2, consisting of the Serum Institute of India which currently is the largest vaccine company in the world [30]. To develop live-attenuated vaccines require several years which depends on the virus and the cells used to implant the attenuated strain. Normally, attenuated strains may appear when the cells are cultured to their 60th offspring, and another 10–20 offsprings are often required to investigate the virus changes [45]. Furthermore, very strict restrictions are in place for the culture of cells infected with live-attenuated vaccines [45]. The virus may not cause certain changes in the cells, unless these cells are penetrated too many times [45]. Ultimately, a subset of the viruses may develop atavistic mutations, reverting to pathogenicity. Earlier research has suggested that live-attenuated vaccines against SARS turn to virulence after continuous passaging in cultured cells or mice [29, 45]. As a result, live-attenuated vaccines pose a greater biosecurity risk [46]. The application of a live-attenuated vaccine against SARS-CoV-2 is not suggested without adequate evidence to assure that the vaccine will not turn to virulence [47].

A live-attenuated SARS-CoV-2 vaccine candidate showed safety and effectiveness in preclinical studies

Compared to the whole 2009 influenza pandemic, the SARS-CoV-2 expeditiously caused more deaths [48]. Furthermore, in only one year, more than 74 million individuals have been infected globally, which will continue to rise [49]. With 7 billion people on Earth, numerous safe and efficacious vaccinations against SARS-CoV-2 are necessary for individuals of any age, demographic group, or medical condition [44]. There should be as few barriers as possible to mass vaccination, including the adoption of accessible and affordable delivery techniques, such as the intranasal or oral route of administration [11]. Vaccination with several SARS-CoV-2 proteins or antigens may be helpful because it eliminates the need to identify a particular target in the current investigation of immunological correlates of SARS-CoV-2 infection prevention [16]. Vaccines that can deliver all of the SARS-CoV-2 antigens to the host are preferable because they can elicit a robust immune response and are less prone to the antigenic drift that has already been observed [27, 50]. Live attenuated vaccines (LAVs) are desirable since they stimulate the immunological systems of the host (humoral, innate, and cellular) [51]. Researchers have conducted preclinical testing of a SARS-CoV-2 live attenuated vaccine (LAV) developed by the "synthetic attenuated virus engineering" (SAVE) technique, and they anticipate that these studies have resulted in the creation of a live COVID-19 vaccine candidate (COVI-VAC) [52]. SAVE uses the codon pair bias in human cells to "deoptimise" viral sequences. In particular, codon pair bias refers to an inflexible rule is seen in all species examined, which states that the juxtaposition of two codons in an open reading frame (ORF) can result in both favourable and unfavourable codon pairings [34, 48]. There is minimal physiologic difference between advantageous and disadvantageous codon pairings. Nevertheless, if the number of unfavourable codon pairs in an ORF is raised by computer design and genome synthesis ("codon-pair deoptimisation"), the expression of the ORF is diminished. Surprisingly, an abundance of synonymous unfavourable codon pairs renders a virus nonviable [48]. Since viruses employ the host cell to interpret their genome, the genes of wild-type (WT) viruses that infect humans are efficiently translated and adapted to the human cell. In a viral genome reading frame, suboptimal

codon pairs are exchanged by WT codon pairs, which delays translation and lowers protein creation in human cells [53]. Codon-pair deoptimisation includes the relocation of synonymous codon pairs [54]. To construct a deoptimised pairing, the individual codons are substituted with a synonymous codon at a different place in the RNA [53]. As a result, both the amino acid sequence and codon usage are maintained. It is possible to build a LAV genome by recoding the genome in silico and then synthesising it in the laboratory [53]. Notably, the amino acid sequence and codon use of viral proteins generated by the recoded ORF are unaltered [53, 54].

COVI-VAC may be a member of a class of potentially significant LAVs being developed for application in animals and humans [23]. It displays all viral antigens with their native amino acid sequence; it may be injected intramuscularly (IM); it is safe and efficacious in small animal models with a single dose; it looks resistant to reversion, and it can be cultured at a permissive temperature to produce high titers. All of these qualities are shared by previous codon-pair-deoptimised vaccines [55]. Currently, a Phase 1 clinical trial assesses the drug's safety and effectiveness in people [55].

A live attenuated vaccination confers superior mucosal and systemic immunity against SARS-CoV-2 variants.

The study compares preclinical attenuated live vaccines across different platforms. A recent study indicates that this specific live attenuated vaccination offers excellent protection against SARS-CoV-2 infection, particularly at mucosal entry points [19]. This conclusion is consistent with previous preclinical COVID-19 vaccination experiments that employed intranasal injection of LAV, protein-based, or virus-vectored spike vaccines to induce mucosal immunity in animal models and showed excellent efficiency [19]. The anti-SARS-CoV-2 IgA levels in the nasal mucosa of vaccinated animals that had received the live attenuated vaccine candidate sCPD9 were considerably more significant than in animals that had not received the vaccine [7]. Prior research on other respiratory viruses, including influenza A, established the importance of local and systemic IgA responses in acute viral infection and vaccination [7]. Mucosal IgA aids the local immune response in several ways, including preventing mucins from leaking, viruses from entering, merging with endosomal membranes within cells, and viruses from escaping host cells [7, 56]. Vaccinated animals were more protected than others against viral multiplication, tissue damage, and lung inflammation [5]. These discoveries are likely the consequence of the distinctive properties of live attenuated vaccines, including delivery by the natural route of infection, presentation of the whole antigenic repertoire of the virus, and replication emulating the target pathogen [19]. In addition, the scRNA-seq analysis performed on blood, lung, and nasal mucosal samples from vaccinated and SARS-CoV-2 challenge-infected hamsters allowed us to acquire further insights into the immunological consequences of different vaccines ideas [57]. The effects of sCPD9 immunisation in a prime-only environment were the largest for all critical parameters. In a prime-boost context, double sCPD9 immunisation was superior to mRNA-sCPD9 vaccination, followed by double mRNA vaccination and double adenovirus vaccination [58].

On the one hand, sCPD9-vaccinated mice displayed a considerable decrease in the activation of pro-inflammatory gene expression programmes, which contributed significantly to COVID-19 pathogenesis [5]. This was especially true for cells of the innate immune system, such as monocytes and macrophages, demonstrating robust pro-inflammatory transcriptional responses during SARS-CoV-2 absorption [16]. If it is transmissible to humans, infection with heterologous SARS-CoV-2 variations might dramatically raise the chance of a mild or silent illness course [59]. Moreover, we

show that the transcriptional activity of neuronal cells in the nasal mucosa is decreased [59, 60]. Although SARS-CoV-2 does not directly infect olfactory neurons, their reaction to the infection of neighbouring sustentacular cells has been related to the well-documented loss of smell in humans and hamsters [59]. It is necessary to conduct clinical research on the safety and efficacy of live attenuated vaccines to determine how well these vaccines could combat the ongoing epidemic [61, 62].

CONCLUSION

In the absence of licensed vaccines, considerable research and clinical analysis suggest that using LAVs enhances readiness for future pandemics and provides a feasible option for controlling infectious illnesses. Although a strategic deployment of LAV appears promising, human safety and effectiveness are immediate issues. In the post-COVID-19 future, however, new infectious illnesses without adequate treatment or prophylactic measures will continue to arise. It is crucial to make a balanced list of the pros and cons of deploying LAVs so that a well-informed decision can be made about which LAVs can be sent out immediately to stop and manage unexpected pandemic outbreaks.

Acknowledgement: None

Conflict of Interest: None

Source of Funding: None

Ethical Approval: Not Applicable

REFERENCES

1. X.-W. Xu *et al.*, "Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series," *bmj*, vol. 368, 2020.
2. N. A. Wong and M. H. Saier, "The SARS-coronavirus infection cycle: a survey of viral membrane proteins, their functional interactions and pathogenesis," *International journal of molecular sciences*, vol. 22, no. 3, p. 1308, 2021.
3. B. Meng *et al.*, "Altered TMPRSS2 usage by SARS-CoV-2 Omicron impacts infectivity and fusogenicity," *Nature*, vol. 603, no. 7902, pp. 706-714, 2022.
4. S. Mohandas *et al.*, "Pathogenicity of SARS-CoV-2 Omicron (R346K) variant in Syrian hamsters and its cross-neutralization with different variants of concern," *EBioMedicine*, vol. 79, p. 103997, 2022.
5. Z.-W. Ye *et al.*, "Intranasal administration of a single dose of a candidate live attenuated vaccine derived from an NSP16-deficient SARS-CoV-2 strain confers sterilizing immunity in animals," *Cellular & molecular immunology*, vol. 19, no. 5, pp. 588-601, 2022.
6. L. Niu, K. N. Wittrock, G. C. Clabaugh, V. Srivastava, and M. W. Cho, "A structural landscape of neutralizing antibodies against SARS-CoV-2 receptor binding domain," *Frontiers in immunology*, vol. 12, 2021.
7. C. W. Tan *et al.*, "A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2–spike protein–protein interaction," *Nature biotechnology*, vol. 38, no. 9, pp. 1073-1078, 2020.
8. S. Miersch *et al.*, "Tetravalent SARS-CoV-2 neutralizing antibodies show enhanced potency and resistance to escape mutations," *Journal of molecular biology*, vol. 433, no. 19, p. 167177, 2021.
9. F. Krammer, "SARS-CoV-2 vaccines in development," *Nature*, vol. 586, no. 7830, pp. 516-527, 2020.
10. M. Tiboni, L. Casettari, and L. Illum, "Nasal vaccination against SARS-CoV-2: Synergistic or alternative to intramuscular vaccines?," *International journal of pharmaceutics*, vol. 603, p. 120686, 2021.
11. G. Dagotto, J. Yu, and D. H. Barouch, "Approaches and challenges in SARS-CoV-2 vaccine development," *Cell host & microbe*, vol. 28, no. 3, pp. 364-370, 2020.
12. J. Yu *et al.*, "Neutralization of the SARS-CoV-2 Omicron BA. 1 and BA. 2 variants," *New England Journal of Medicine*, vol. 386, no. 16, pp. 1579-1580, 2022.
13. S. Das *et al.*, "Is Omicron the end of pandemic or start of a new innings?," *Travel Medicine and Infectious Disease*, p. 102332, 2022.
14. K. Lederer *et al.*, "SARS-CoV-2 mRNA vaccines foster potent antigen-specific

germinal center responses associated with neutralizing antibody generation," *Immunity*, vol. 53, no. 6, pp. 1281-1295, 2020.
15. J.-G. Park *et al.*, "Immunogenicity and protective efficacy of an intranasal live-attenuated vaccine against SARS-CoV-2 in preclinical animal models," *bioRxiv*, 2021.
16. V. P. Chavda, L. K. Vora, A. K. Pandya, and V. B. Patravale, "Intranasal vaccines for SARS-CoV-2: From challenges to potential in COVID-19 management," *Drug discovery today*, vol. 26, no. 11, pp. 2619-2636, 2021.
17. G. E. Hartley *et al.*, "Rapid generation of durable B cell memory to SARS-CoV-2 spike and nucleocapsid proteins in COVID-19 and convalescence," *Science immunology*, vol. 5, no. 54, p. eabf8891, 2020.
18. E. C. Lavelle and R. W. Ward, "Mucosal vaccines—fortifying the frontiers," *Nature Reviews Immunology*, vol. 22, no. 4, pp. 236-250, 2022.
19. G. Nouailles *et al.*, "A live attenuated vaccine confers superior mucosal and systemic immunity to SARS-CoV-2 variants," *bioRxiv*, 2022.
20. M. Li *et al.*, "COVID-19 vaccine development: milestones, lessons and prospects," *Signal transduction and targeted therapy*, vol. 7, no. 1, pp. 1-32, 2022.
21. D. Calina *et al.*, "Challenges and scientific prospects of the newest generation of mRNA-based vaccines against SARS-CoV-2," *Life*, vol. 11, no. 9, p. 907, 2021.
22. H. Motamedi *et al.*, "An update review of globally reported SARS-CoV-2 vaccines in preclinical and clinical stages," (in eng), *Int Immunopharmacol*, vol. 96, p. 107763, Jul 2021, doi: 10.1016/j.intimp.2021.107763.
23. S. Khoshnood *et al.*, "An overview on inactivated and live-attenuated SARS-CoV-2 vaccines," *Journal of Clinical Laboratory Analysis*, vol. 36, no. 5, p. e24418, 2022.
24. M. S. Gebre, L. A. Brito, L. H. Tostanoski, D. K. Edwards, A. Carfi, and D. H. Barouch, "Novel approaches for vaccine development," (in eng), *Cell*, vol. 184, no. 6, pp. 1589-1603, 03 18 2021, doi: 10.1016/j.cell.2021.02.030.
25. K. Shahzamani *et al.*, "Vaccine design and delivery approaches for COVID-19," *International Immunopharmacology*, vol. 100, p. 108086, 2021.
26. A. Nagy and B. Alhatlani, "An overview of current COVID-19 vaccine platforms," (in eng), *Comput Struct Biotechnol J*, vol. 19, pp. 2508-2517, 2021, doi: 10.1016/j.csbj.2021.04.061.
27. M. Bayat, Y. Asemani, and S. Najafi, "Essential considerations during vaccine design against COVID-19 and review of pioneering vaccine candidate platforms," *International immunopharmacology*, vol. 97, p. 107679, 2021.
28. K. Damodharan, G. S. Arumugam, S. Ganesan, M. Doble, and S. Thennarasu, "A comprehensive overview of vaccines developed for pandemic viral pathogens over the past two decades including those in clinical trials for the current novel SARS-CoV-2," *RSC Advances*, vol. 11, no. 33, pp. 20006-20035, 2021.
29. D.-D. Li and Q.-H. Li, "SARS-CoV-2: vaccines in the pandemic era," *Military Medical Research*, vol. 8, no. 1, pp. 1-15, 2021.
30. S. Okamura and H. Ebina, "Could live attenuated vaccines better control COVID-19?," *vaccine*, vol. 39, no. 39, pp. 5719-5726, 2021.
31. B. Yang *et al.*, "SNX27 suppresses SARS-CoV-2 infection by inhibiting viral lysosome/late endosome entry," *Proceedings of the National Academy of Sciences*, vol. 119, no. 4, 2022.
32. P. Troyano-Hernáez, R. Reinosa, and Á. Holguín, "Evolution of SARS-CoV-2 envelope, membrane, nucleocapsid, and spike structural proteins from the beginning of the pandemic to September 2020: a global and regional approach by epidemiological week," *Viruses*, vol. 13, no. 2, p. 243, 2021.
33. M. Sarkar and S. Saha, "Structural insight into the role of novel SARS-CoV-2 E protein: A potential target for vaccine development and other therapeutic strategies," *PLoS One*, vol. 15, no. 8, p. e0237300, 2020.
34. T. Azad *et al.*, "Implications for SARS-CoV-2 vaccine design: Fusion of spike glycoprotein transmembrane domain to receptor-binding domain induces trimerization," *Membranes*, vol. 10, no. 9, p. 215, 2020.

35. Y. Cao *et al.*, "Probing the Formation, Structure and Free Energy Relationships of M Protein Dimers of SARS-CoV-2," *Computational and Structural Biotechnology Journal*, 2022.
36. M. A. Rohaim, R. F. El Naggar, E. Clayton, and M. Munir, "Structural and functional insights into non-structural proteins of coronaviruses," *Microbial pathogenesis*, vol. 150, p. 104641, 2021.
37. F. Anjum *et al.*, "Identification of intrinsically disorder regions in non-structural proteins of SARS-CoV-2: New insights into drug and vaccine resistance," *Molecular and Cellular Biochemistry*, vol. 477, no. 5, pp. 1607-1619, 2022.
38. N. S. Ogando, J. C. Zevenhoven-Dobbe, Y. van der Meer, P. J. Bredenbeek, C. C. Posthuma, and E. J. Snijder, "The enzymatic activity of the nsp14 exoribonuclease is critical for replication of MERS-CoV and SARS-CoV-2," *Journal of virology*, vol. 94, no. 23, pp. e01246-20, 2020.
39. D. Wolday, F. M. Ndungu, G. P. Gómez-Pérez, and T. F. R. de Wit, "Chronic immune activation and CD4+ T cell lymphopenia in healthy African individuals: perspectives for SARS-CoV-2 vaccine efficacy," *Frontiers in Immunology*, vol. 12, p. 2409, 2021.
40. R. Ella *et al.*, "Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial," *The Lancet Infectious Diseases*, vol. 21, no. 5, pp. 637-646, 2021.
41. S. H. Seo and Y. Jang, "Cold-adapted live attenuated SARS-Cov-2 vaccine completely protects human ACE2 transgenic mice from SARS-Cov-2 infection," *Vaccines*, vol. 8, no. 4, p. 584, 2020.
42. R. Saha, P. Ghosh, and V. L. S. Burra, "Designing a next generation multi-epitope based peptide vaccine candidate against SARS-CoV-2 using computational approaches," *3 Biotech*, vol. 11, no. 2, pp. 1-14, 2021.
43. L. S. Felipe *et al.*, "A single-dose live-attenuated YF17D-vectored SARS-CoV2 vaccine candidate," 2020.
44. L. Sanchez-Felipe *et al.*, "A single-dose live-attenuated YF17D-vectored SARS-CoV-2 vaccine candidate," *Nature*, vol. 590, no. 7845, pp. 320-325, 2021.
45. K. Lundstrom, "Viral Vectors for COVID-19 Vaccine Development," (in eng), *Viruses*, vol. 13, no. 2, 02 19 2021, doi: 10.3390/v13020317.
46. A. Pascual-Iglesias, J. Canton, A. M. Ortega-Prieto, J. M. Jimenez-Guardeño, and J. A. Regla-Nava, "An overview of vaccines against SARS-CoV-2 in the COVID-19 pandemic era," *Pathogens*, vol. 10, no. 8, p. 1030, 2021.
47. R. Bezbaruah *et al.*, "Developmental Landscape of Potential Vaccine Candidates Based on Viral Vector for Prophylaxis of COVID-19," (in eng), *Front Mol Biosci*, vol. 8, p. 635337, 2021, doi: 10.3389/fmolb.2021.635337.
48. Y. Wang *et al.*, "Scalable live-attenuated SARS-CoV-2 vaccine candidate demonstrates preclinical safety and efficacy," *Proceedings of the National Academy of Sciences*, vol. 118, no. 29, 2021.
49. Y. Liu *et al.*, "A live-attenuated SARS-CoV-2 vaccine candidate with accessory protein deletions," *bioRxiv*, 2022.
50. B. S. Bleier, M. Ramanathan Jr, and A. P. Lane, "COVID-19 vaccines may not prevent nasal SARS-CoV-2 infection and asymptomatic transmission," *Otolaryngology–Head and Neck Surgery*, vol. 164, no. 2, pp. 305-307, 2021.
51. Y. C. Hou, K. C. Lu, and K. L. Kuo, "The Efficacy of COVID-19 Vaccines in Chronic Kidney Disease and Kidney Transplantation Patients: A Narrative Review," (in eng), *Vaccines (Basel)*, vol. 9, no. 8, Aug 10 2021, doi: 10.3390/vaccines9080885.
52. J. Zhang, H. Zeng, J. Gu, H. Li, L. Zheng, and Q. Zou, "Progress and prospects on vaccine development against SARS-CoV-2," *Vaccines*, vol. 8, no. 2, p. 153, 2020.
53. X. Liu *et al.*, "A single intranasal dose of a live-attenuated parainfluenza virus-vectored SARS-CoV-2 vaccine is protective in hamsters," *Proceedings of the National Academy of Sciences*, vol. 118, no. 50, 2021.
54. J. B. Case, E. S. Winkler, J. M. Errico, and M. S. Diamond, "On the road to ending the COVID-19 pandemic: Are we there yet?," (in eng), *Virology*, vol. 557, pp. 70-85, 05 2021, doi: 10.1016/j.virol.2021.02.003.
55. A. Nagy and B. Alhatlani, "An overview of current COVID-19 vaccine platforms," *Computational and structural biotechnology journal*, vol. 19, pp. 2508-2517, 2021.

56. R. S. Mahla and L. B. Dustin, "Searching for escape-resistant anti-SARS-CoV-2 neutralizing antibodies," *The Journal of Clinical Investigation*, 2022.
57. J. Trimpert *et al.*, "Live attenuated virus vaccine protects against SARS-CoV-2 variants of concern B. 1.1. 7 (Alpha) and B. 1.351 (Beta)," *Science advances*, vol. 7, no. 49, p. eabk0172, 2021.
58. J. Trimpert *et al.*, "Development of safe and highly protective live-attenuated SARS-CoV-2 vaccine candidates by genome recoding," *Cell reports*, vol. 36, no. 5, p. 109493, 2021.
59. K. Chiem *et al.*, "Generation and Characterization of recombinant SARS-CoV-2 expressing reporter genes," *Journal of Virology*, vol. 95, no. 7, pp. e02209-20, 2021.
60. J. Chen *et al.*, "A live attenuated influenza virus-vectored intranasal COVID-19 vaccine provides rapid, prolonged, and broad protection against SARS-CoV-2 infection," *bioRxiv*, 2021.
61. V. Thiel, N. Osterrieder, and D. Kunec, "Development of safe and highly protective live-attenuated SARS-CoV-2 vaccine candidates by genome recoding Trimpert, Jakob; Dietert, Kristina; Firsching, Theresa C.; Ebert, Nadine; Thi Nhu Thao, Tran; Vladimirova, Daria; Kaufer, Susanne; Labroussaa, Fabien; Abdelgawad, Azza; Conradie, Andelé; Höfler, Thomas; Adler, Julia M.; Bertzbach, Luca D.; Jores, Joerg; Gruber, Achim D."
62. R. Mudgal, S. Nehul, and S. Tomar, "Prospects for mucosal vaccine: shutting the door on SARS-CoV-2," *Human vaccines & immunotherapeutics*, vol. 16, no. 12, pp. 2921-2931, 2020.

How to cite this article: Ratthaphum Sae-ngow. The advantage efficacy of intranasal live-attenuated vaccine against SARS-CoV-2. *International Journal of Science & Healthcare Research.* 2022; 7(3): 92-100. DOI: *https://doi.org/10.52403/ ijshr.20220715*

******