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MINI-REVIEW

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A second-generation, self-amplifying COVID-19 Vaccine: World's first approval and distribution in the Japanese market with vaccine hesitancy

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ABSTRACT

The mRNA vaccine is a milestone in immunotherapeutics, as symbolized by the 2023 Nobel Prize for Physiology or Medicine awarded to Drs. Karikó and Weissman. Whereas the conventional, "first-generation" mRNA vaccine was globally distributed to hundreds of millions of people to decrease COVID-19 prevalence, further advanced constructs have been pursued by researchers and pharmaceutical manufacturers. The key feature of the "second-generation" mRNA vaccine is a self-amplifying replicon that may allow a low dose to ensure durable immunogenicity. In clinical trials, ARCT-154 indeed showed effectiveness (magnitude, persistence, and breadth) superior to conventional mRNA vaccines, with similar or less frequent adverse responses, and acquired its world's first approval in November 2023 in Japan (brand name: KOSTAIVE manufactured by Meiji Seika Pharma, Tokyo, Japan) to prevent COVID-19 infection. Real-world distribution of KOSTAIVE was started in October 2024, and researchers are collecting data on its effectiveness and safety despite nonscientific, but persistent, antivaccine skepticism.

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The development of mRNA vaccines, established by Drs. K. Karikó and D. Weissman, is a milestone in the immunotherapeutic field,[1] for which they won the 2023 Nobel Prize for Physiology or Medicine.[2] The technique is characterized by applicability, short-term development, easy industrialization, and responsiveness to the mutation of pathogens.[3] Indeed, COVID-19 mRNA vaccines became available worldwide as early as approximately one year after industrialization was addressed by pharmaceutical manufacturers. The vaccine is now widely accepted as a countermeasure to control the pandemic.

The "first-generation" mRNA vaccine was simply based on the mRNA encoding the protein of the target (i.e., spike protein for COVID-19 vaccine) that is flanked by 5' and 3' untranslated regions (Figure 1a). Once the mRNA is translated into its corresponding protein, immunogenicity is induced via cellular and humoral mechanisms in the human body.[3] The prototypic technique was further advanced recently by introducing replicon RNA, as shown in Figure 1b.[3–6] The replicon includes sequences that encode non-structural proteins of the virus, such as alphavirus, followed by the second open reading frame that encodes the immunogenic protein. The sophisticated design allows self-amplification of mRNA itself, and longer duration of immunogenicity of the target viral protein is therefore expected. This means that a lower vaccine dose than that of the conventional, first-generation mRNA vaccine is needed to achieve effectiveness with a comparable or lower risk of adverse events.[5] Thus, researchers and manufacturers have begun to develop "second-generation," self-amplifying mRNA vaccines as preventive or treatment measures in multiple disease fields (e.g., infectious diseases and cancer), using multiple delivery systems and multiple animal species, as well as humans.[4–16] After multiple clinical trials conducted domestically and outside Japan, KOSTAIVE (Meiji Seika Pharma, Tokyo, Japan) was approved by the Japanese authorities in November, 2023 for the prevention of COVID-19 disease. This is the first case of a self-amplifying vaccine in the world.[17,18] Lipid nanoparticles are used as delivery vehicles for the vaccine. In this paper, the effectiveness and safety of this vaccine in comparison with conventional vaccines and an accompanying issue of vaccine hesitancy in Japanese society are described. This article may be a reference for the development and distribution of upcoming self-amplifying vaccines.

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

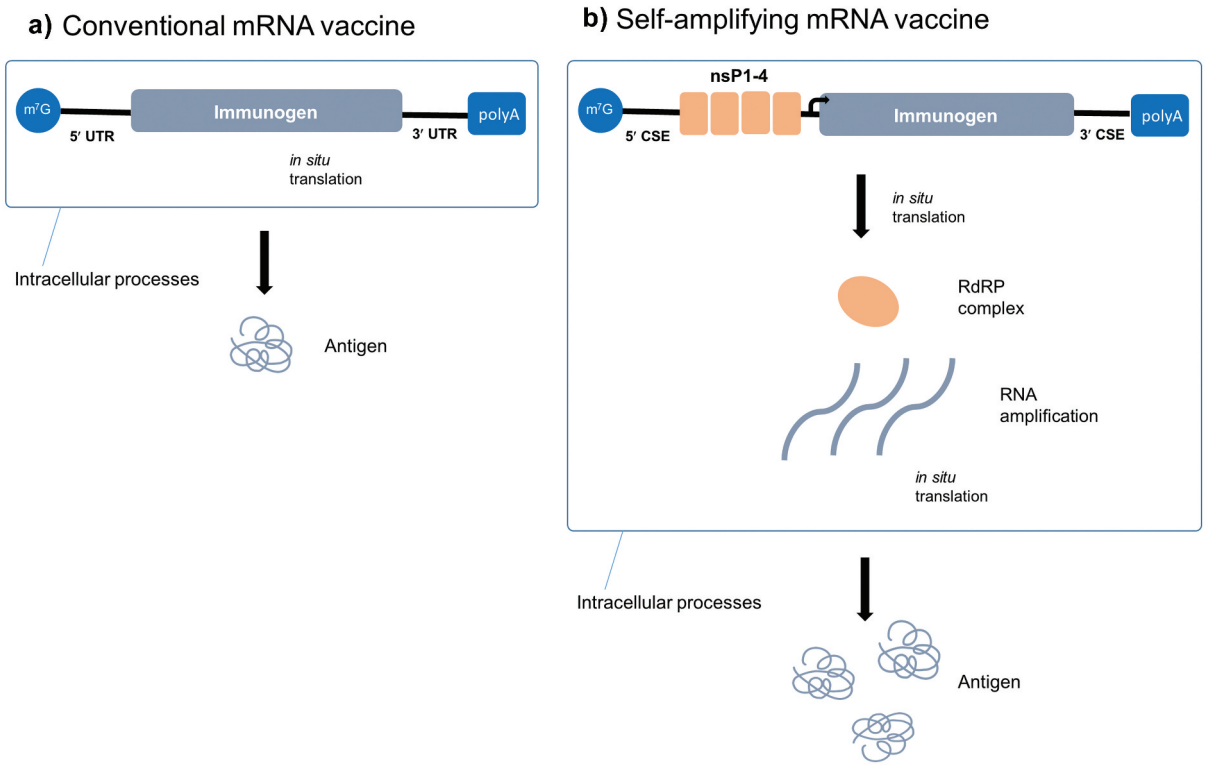

Figure 1. Schematic comparison of conventional and self-amplifying mRNA vaccines. The schemas of the conventional mRNA vaccine and the self-amplifying mRNA vaccine are shown in panels (a) and (b), respectively. m^7G = 7-methylguanosine, UTR = untranslated region, polyA = polyadenylated tail, CSE = conserved sequence element, nsP = non-structural protein, RdRP = RNA-dependent RNA polymerase.

In a clinical trial, in which two representative variants, Wuhan-Hu-1 and Omicron BA.4–5, were used, researchers showed that both the self-amplifying vaccine (ARCT-154) and the conventional, non-self-amplifying vaccine (BNT162b2) increased the geometric mean neutralizing titers (GMTs) in the participants one month post-vaccination. At three months, ARCT-154 maintained the antibody titer levels, but the levels already started to decrease in the BNT162b2 subset.[19] Though the titer gradually decreased during the later period (Six and 12 months post-vaccination) in the ARCT-154 subset, the GMT ratio was greater (approximately Two-fold) in this group than in the BNT162b2 group, irrespective of participants' age category, i.e., <50 or ≥50 y (Figure 2).[19,20] Persistent, longer-lasting (≥12 months) production of neutralizing antibodies was similarly observed for the self-amplifying vaccine against other viral variants.[20] It is notable that, for ARCT-154, its effectiveness increased according to the severity of COVID-19 disease.[21] Overall, adverse events observed in ARCT-154 recipients were similar or less frequent than those of recipients of licensed mRNA vaccines.[21–23]

Mainly mild or moderate adverse events were reported after the dose of ARCT-154. They were either local or systemic, and they resolved within several days or in the follow-up period post-injection.[21,23] The observed adverse events were much less lasting compared with the durability of effectiveness. Moreover, both serious adverse events and deaths were less frequent in the ARCT-154 subset than in the control subsets.[21,23] Thus, the vaccine was well tolerated in multiple clinical trials.

The superiority of ARCT-154 to conventional mRNA vaccines (e.g., BNT162b2) was observed for immune responses (magnitude, persistence, and breadth), in combination with a good safety profile. This may lead healthcare professionals to preferentially use self-amplifying vaccines.[20] Given its authorization, real-world use of the second-generation vaccine (KOSTAIVE) was started on October 1, 2024 in Japan, and researchers are addressing the next issue, which is whether the new type of vaccine indeed suppresses the occurrence and symptomatic worsening of COVID-19 disease with a safety profile superior (or at least comparable) to that of the conventional mRNA vaccines. Through collecting effectiveness and safety information, the profile of KOSTAIVE use will be seen sooner or later.

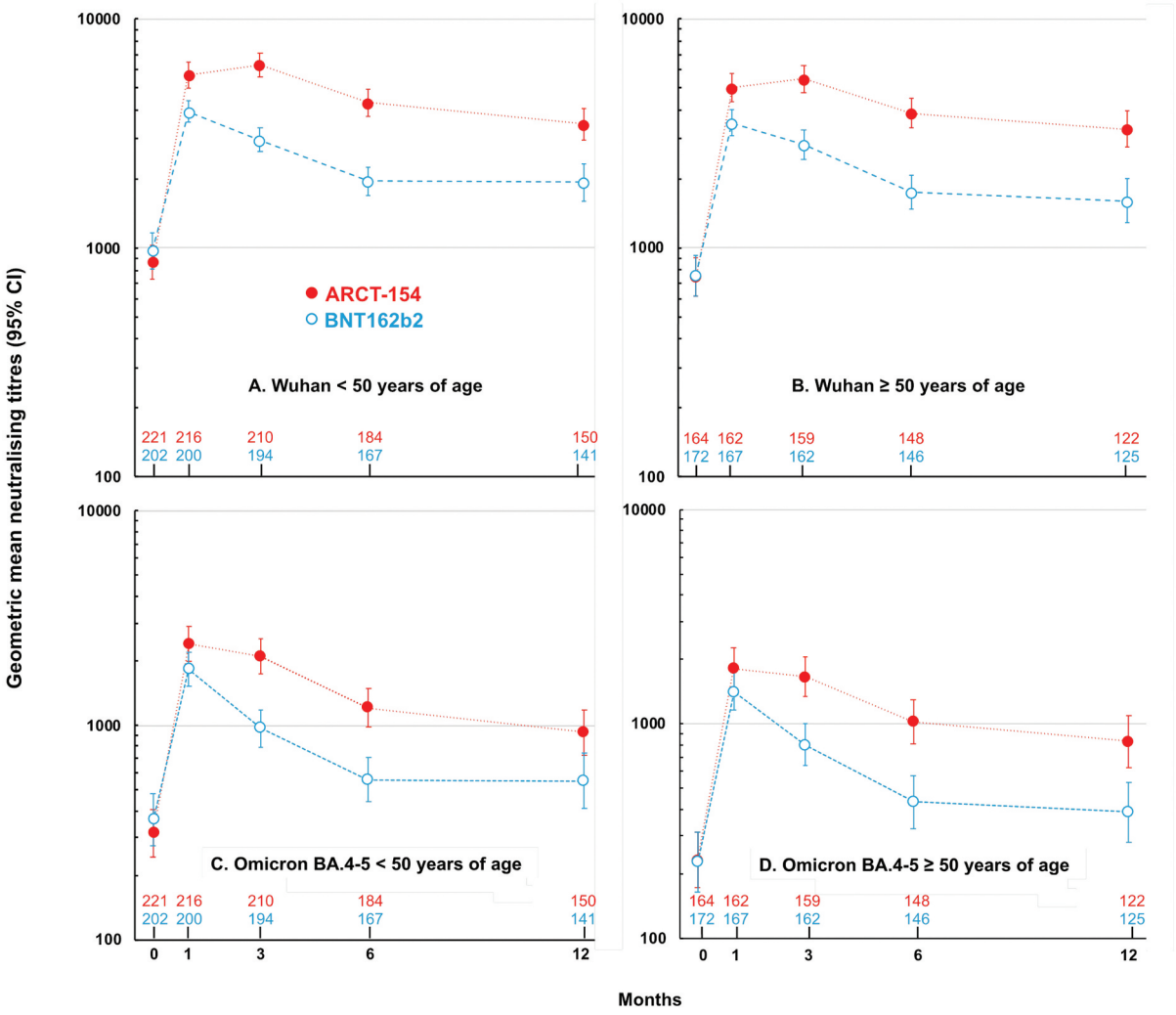

Figure 2. Geometric mean neutralizing antibody titers (with 95% CI) up to 12 months after vaccination with a booster dose of ARCT-154 or BNT162b2.[19] Values are shown for titers against Wuhan-Hu-1 strain (A and B) and Omicron BA.4-5 variant (C and D) for the trial participants grouped by age, <50 y (A and C) and ≥50 y (B and D). Numbers of at-risk participants are denoted in the figure at each timepoint post-vaccination. GMT ratios and their 95% CIs (ARCT-154 vs. BNT162b2) are given. GMT = geometric mean titer. This figure is reprinted from *The Lancet Infectious Diseases*, Yoshiaki Oda, Yuji Kumagai, Manabu Kanai, Yasuhiro Iwama, Iori Okura, Takeshi Minamida, Yukihiro Yagi, Toru Kurosawa, Pad Chivukula, Ye Zhang, Judd L Walson, 12-Month persistence of immune responses to self-amplifying mRNA COVID-19 vaccines: ARCT-154 versus BNT162b2 vaccine, 24:e729-e731, Copyright (2024), with permission from Elsevier.

COVID-19 mRNA vaccines, including KOSTAIVE, are provided by four manufacturers at present in Japan, and all target the viral spike protein. Other protein components may be alternative choices for vaccine development. COVID-19 vaccine is merely one example, and the concept of self-amplifying mRNA may allow us to construct multi-antigenic vaccines, using a single replicon. The concept may also be applicable to other therapeutic fields, including other infectious diseases and cancer, as well as to the veterinary field, including zoonotic infectious diseases such as Venezuelan equine encephalitis.[24] Vaccines for zoonotic infections should be developed through collaborations between medical and veterinary communities. Genetic disorders may also show benefits, because they are likely to achieve remission by the technique. Thus, the self-amplifying mRNA technique will be versatile in the future from wide and attractive perspectives. Approval applications for self-amplifying mRNA vaccines are currently under review by authorities in other nations.

Despite the features noted above, objections to the approval of KOSTAIVE have been raised by the Japan Nursing Ethics Association, alleging that viral shedding may occur in the community with vaccination.[25] The replicon construct encodes only the spike protein as a structural component, but it does not include the whole

viral genome. Therefore, viral shedding should be unlikely.[26] Furthermore, Meiji Seika Pharma, the manufacturer of KOSTAIVE, found no shedding events reported to date from the results of domestic and overseas clinical trials, which involved approximately 18,000 participants. A member of parliament who developed malignant lymphoma insists that cancer risk may be increased by mRNA vaccines. However, there have been no such reports to date according to the Japanese government in its reply to his claim.[27] Given his continuing claim, Meiji Seika Pharma recently filed a lawsuit.[28,29] Further, an employee of the manufacturer wrote a book anonymously, also claiming that the use of mRNA vaccines was associated with risk.[30] However, the book seems misleading with regard to its authorship and the scientific information contained therein.[31,32] These social movements are likely due to the skeptical attitude commonly observed in Japanese society,[33,34] as a worldwide survey reported that the percentage of respondents strongly confident about vaccines' safety was the lowest (8.9%) in Japan in late 2015, compared with the highest (>85%) in Argentina, Liberia, and Bangladesh.[33] This poor confidence in vaccines in Japan originated most likely from the safety scare related to the human papillomavirus (HPV) vaccine.[35] Japanese health officials once suspended proactive recommendation of HPV vaccine, causing applause from anti-vaccination groups. Though the recommendation was later re-instated, the vaccine scare still persists and remains as a serious issue to be resolved in Japan. It is absolutely essential that any concerns related to risks to health or life be addressed on a scientific basis.

Finally, it should be noted that the concept of *cis*-encoded innate inhibiting proteins may provide a strategic key for developing further advanced self-amplifying mRNA constructs.[4,36,37]

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Ethics approval

Ethics approval was not required for this research as it does not involve human participants.

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