Science, Public Health Policy, and the Law
Volume: v8.2019-2025
August 2025
Public Health

An Institute for Pure and Applied Knowledge (IPAK)

Public Health Policy Initiative (PHPI)

Regulatory and Safety Assessment of COVID-19 mRNA-LNP Genetic Vaccines in Japan: Evidence for Revocation of Approval and Market Withdrawal

Jun Ueda[1*], Miki Gibo[2], Takayuki Kikuchi[3], Yuriko Hirai[4], Mariko Miyokawa[5], Akiko Kitagawa[5], Isamu Shima[6], Shinichiro Kodama[7], Masanori Fukushima[3]

Abstract

This paper examines critical safety issues of mRNA lipid nanoparticle formulations (hereinafter referred to as genetic vaccines and mRNA vaccines) for coronavirus disease 2019 (COVID-19)—including Comirnaty (development code BNT162b2), Spikevax (development code mRNA-1273), and Kostaive (development code ARCT-154) for intramuscular injection—and discusses the necessity for revocation of approval and market withdrawal. The genetic vaccines that received special approval for emergency were widely recommended for administration as a public health measure during the COVID-19 pandemic, with approximately 103.46 million people in Japan (79.5% of the population) receiving the genetic vaccine. Despite numerous reports of health injuries both domestically and internationally as of June 2025, the Japanese government has not conducted a nationwide health injury survey into these adverse health effects. These vaccines were approved without adequate non-clinical testing and long-term safety evaluation, and administration continued without sufficient disclosure of adverse events. This paper discusses in detail the scientific deficiencies in the regulatory review of genetic vaccines, inadequacies in post-marketing risk management, and issues concerning significant adverse drug reactions and potential DNA contamination in genetic vaccines. It is evident that genetic vaccines that received special approval for emergency by the Japanese government lack sufficient evidence of efficacy, and their potential risks to public health cannot be overlooked. A comparison with previous cases of pharmaceutical approval revocations indicates that revoking the approval and withdrawing genetic vaccines from the market is not only reasonable but also necessary. Therefore, we call upon the Japanese government and relevant regulatory agencies to implement prompt measures and conduct a thorough reassessment.

Keywords

COVID-19 vaccine, DNA contamination, excess mortality, Genetic Vaccine, market withdrawal, mRNA Vaccine, mRNA-LNP, negative efficacy, pharmaceutical recalls, policy critique, Self-amplifying RNA Vaccine

Introduction

This paper addresses the mRNA lipid nanoparticle formulations (hereinafter referred to as genetic vaccines and mRNA vaccines) that received special approval for emergency in May 2021 during the COVID-19 pandemic under Article 14-3, paragraph 1 of the Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as the "Pharmaceuticals and Medical Devices Act. [PMD Act]") (Table 1). It describes the significant public health event that occurred in Japan related to these formulations and discusses the grounds for revocation of approval (Article 74-2 and Article 75-3 of the PMD Act) (Table 1) and the necessity to withdraw these products from the market. All legislation mentioned in this paper refers to Japanese law unless otherwise specified.

The genetic vaccines that received special approval for emergency as a public health measure during the COVID-19 pandemic [1] were promoted for widespread administration to the Japanese population [2-4]. However, despite numerous reports of adverse reactions following administration both domestically and internationally (Figure 1), as of June 2025, the Japanese government (hereinafter referred to as "the government") has not conducted a nationwide investigation of adverse health effects caused by genetic vaccine administration. Following the report of multiple fatalities, the government should have immediately suspended administration or implemented appropriate measures (Article 69-3 of the PMD Act) (Table 1), conducted nationwide post-marketing surveillance, and scientifically evaluated the results, as were done previously with the diphtheria-pertussis-tetanus (DPT) vaccine, measles-mumps-rubella (MMR) vaccine, and mouse brain-derived Japanese encephalitis vaccine. When a large number of deaths have been reported following the administration of a pharmaceutical product, review of approval or product recall measures should be considered in accordance with relevant laws and regulations. Furthermore, an "Opinion on the Safety Evaluation of the COVID-19 Vaccine" had already been issued by the Pharmaceutical Administrative Evaluation and Surveillance Commission [5]. Although this opinion urged a careful assessment of the risks associated with administration, the government did not respond with sufficient seriousness. Instead, it continued to promote administration, during which time the number of reported health-related adverse events continued to rise [6].

The Japanese regulatory authorities have emphasized the need for rapid vaccine deployment during a national crisis [7, 8]; however, this approach does not exempt oversight bodies from their ongoing responsibilities to ensure transparency, update safety assessments, and disclose relevant risks to the public. The failure of Japanese administrative agencies to adhere to fundamental principles of public health policy, such as "evidence-based decision-making," and "prioritizing public health and safety above all else," and their failure to implement appropriate risk management, have resulted in adverse drug reactions of unprecedented scale in both number and medical severity among the Japanese population. This paper provides a critical analysis of structural deficiencies in Japan's regulatory

response to genetic vaccines during the COVID-19 pandemic and presents scientific grounds for the revocation of approval and market withdrawal of mRNA vaccines.

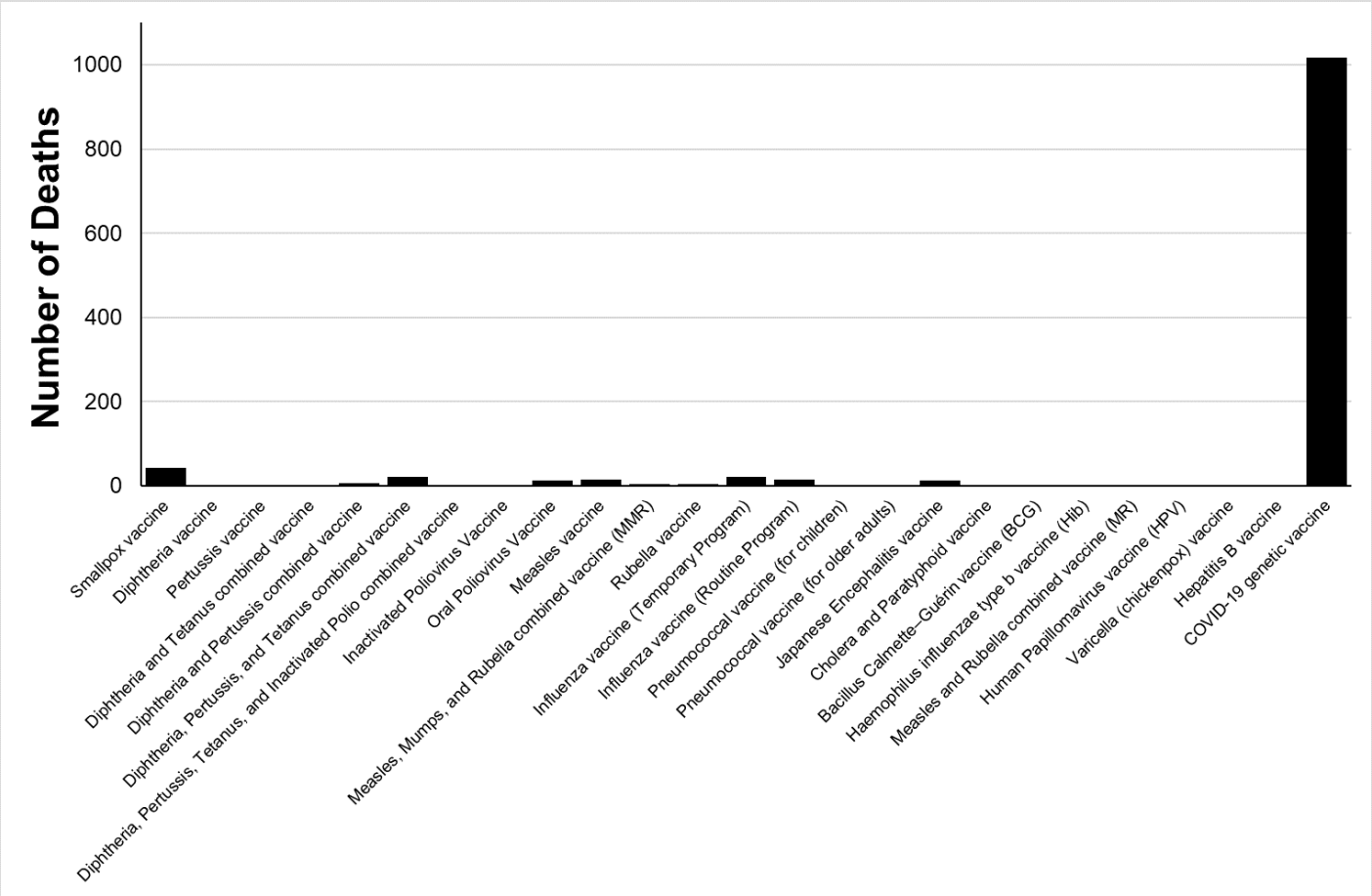

Figure 1. Number of deaths recognized under Japan's Vaccine Adverse Reaction Relief System administered by the MHLW (as of June 2, 2025). The cumulative number of approved cases under Japan's Vaccine Adverse Reaction Relief System is publicly available on the MHLW website for the period from February 1977 through 2021 [169]. For data from 2022 onward, the figures presented in this study were independently compiled based on individual records released on the same website, including those from each fiscal year and each meeting of the review committee.

Defects in Review Report and Package Insert

One contributing factor to the large-scale adverse drug reactions caused by genetic vaccines is that the Pharmaceuticals and Medical Devices Agency (PMDA) directly applied the "Guideline for Non-clinical Studies on Vaccines for the Prevention of Infectious Diseases," which had been used for reviewing conventional vaccines, to these first-in-human genetic vaccines (Tables 2 and 3). This guideline mandates a narrower scope of testing and less rigorous standards compared to requirements for general pharmaceutical products [9-23]. Genetic vaccines should properly be classified as gene therapy products based on their mechanism of action [24, 25] (Table 4), yet they were reviewed under the same regulatory framework as conventional vaccines despite not being pharmacologically or structurally equivalent [26].

Consequently, several key elements typically evaluated in non-clinical safety studies—such as biodistribution, pharmacokinetics, organ-specific toxicity, placental transfer, fetal toxicity, and immunogenicity—were not assessed. Studies on carcinogenicity and genotoxicity were also omitted. Given the extremely short follow-up period in clinical trials (only several weeks to several months), approval was granted without sufficient evaluation of long-term safety in either non-clinical or clinical settings. Additionally, sufficient information on adverse events observed in clinical trials—particularly the potential for a broad spectrum of adverse reactions—was not adequately communicated to Japanese healthcare professionals or the general public. The monovalent mRNA vaccine corresponding to the Omicron strain XBB.1.5 spike protein was approved based solely on non-clinical data without conducting sufficient clinical trials, on the grounds that antibody titer increases and safety profiles were similar to those of previously approved genetic vaccines [27].

According to the Ministry of Health, Labour and Welfare (MHLW)'s initial explanation, mRNA-LNP formulations remain at the injection site and the modified mRNA is rapidly degraded. Modified mRNA refers to mRNA that has been modified with methyl pseudouridine (m1Ψ), resulting in enhanced RNA stability and reduced immunogenicity. This was used in genetic vaccines (Pfizer, Moderna) to enhance spike protein production efficiency. (This explanation was previously available on the MHLW website but has since been removed.) However, subsequently published studies using rats and mice revealed that lipid nanoparticles (LNPs) accumulate in numerous organs including bone marrow and ovaries (in descending order of accumulation: liver, spleen, adrenal glands, ovaries, bone marrow, small intestine, lymph nodes, large intestine, lungs, thyroid, etc.) [28, 29], reach the fetus via the placenta and umbilical cord in pregnant mice [30], and remain in the bloodstream for at least two weeks following administration [31]. Although the PMDA had access to pharmacokinetic data in rats—submitted by pharmaceutical companies around February 2021 [28, 32]—it did not provide this information to medical institutions or the public. The failure to disclose that LNPs distribute systemically, cross the blood-brain barrier, and accumulate in organs such as the ovaries and adrenal glands represents a serious lapse in responsibility and may constitute regulatory oversight failure.

Furthermore, LNPs themselves have been reported to be highly inflammatory substances [33], and the production of anti-polyethylene glycol (PEG) antibodies has been confirmed [34]. Research demonstrating that LNPs remain in the bloodstream for at least two weeks post-administration clearly indicates that the two-day deferral period for blood donation—adopted by the Japanese Red Cross Society and similar organizations [35]—lacked a sufficient scientific basis. Since genetic vaccines were approved as pharmaceutical products, information regarding their pharmacokinetics should have been clearly documented in the package insert and thoroughly communicated to healthcare professionals. However, the package inserts for mRNA vaccines provide only minimal pharmacokinetic information, and dissemination of relevant data to healthcare institutions was significantly insufficient. Such circumstances may be evaluated as a failure by marketing authorization holders (MAHs) to fulfill their "duty to warn." When both the MAH and regulatory authorities failed to provide accurate and necessary information in a timely manner, such omissions may have presented a potential violation of Article 68-10 of the PMD Act (Table 1), which requires the disclosure of safety-related information. Notwithstanding these concerns and the emergence of multiple safety issues, the Japanese government proceeded to grant full

marketing approval for Pfizer's genetic vaccine in 2024.

Despite being aware of numerous adverse events during clinical trials of its mRNA vaccine (Comirnaty; development code BNT162b2), Pfizer did not disclose this important safety information to regulatory authorities, including Japan's MHLW. This fact was revealed through a freedom of information lawsuit filed by a U.S. citizen group. In 2021, the court ordered the FDA (U.S. Food and Drug Administration) to disclose materials that Pfizer had submitted, revealing that an unprecedentedly wide spectrum of adverse events had been reported from the outset. These adverse events span an extremely broad range, from common diseases to rare and intractable conditions [36]. A wide variety of adverse events, including thrombocytopenia and myocarditis, have been reported worldwide following genetic vaccine administration [37-42].

For adverse events that were originally of concern regarding genetic vaccines, these possibilities should have been clearly documented in the pharmaceutical package insert from the initial stages, with appropriate warnings provided to healthcare professionals, as part of the "duty to warn." However, actual package inserts contained almost no explicit documentation of the numerous adverse events (e.g., myocarditis, thrombosis, autoimmune reactions, etc.) being reported following genetic vaccine administration. Consequently, it became difficult for physicians to provide recipients with adequate explanations, including risks, creating a situation where the principle of informed consent could not function effectively. Information necessary for citizens to make informed decisions regarding genetic vaccine administration was not appropriately provided, compromising the foundation of medical ethics—the guarantee of the right to self-determination.

Particular attention should be drawn to PFSB/SD (Safety Division, Pharmaceutical and Food Safety Bureau) Notification No. 0328007 (March 28, 2005), titled "Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting [43]." Section 2.2, "Adverse Drug Reaction (ADR)," clearly states that "For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction." This explicitly indicates that adverse events should be treated as adverse drug reactions at the time they are reported.

All adverse event reports published on the MHLW website [6]—including those documenting adverse reactions, deaths (Figure 1), and serious health injuries following COVID-19 vaccination—as well as adverse events presented at academic conferences, should be regarded as "adverse drug reactions" irrespective of proven causality. Consequently, the inclusion of such adverse event information in pharmaceutical package inserts is a regulatory and ethical imperative. A failure to reflect this data appropriately constitutes a serious breach of the duty of MAHs and regulatory authorities to ensure adequate safety communication.

An administrative document disclosure request to MHLW (Disclosure No. 3333; Administrative Document Disclosure Decision Notice, MHLW PSEHB Notification No. 0403-37) revealed that MHLW and PMDA had obtained similar data prior to this information being disclosed. Since the initiation of genetic vaccine administration, MHLW has received diverse spontaneous adverse event reports from medical institutions nationwide. However, MHLW has not adequately established systems to disseminate this information to medical institutions and the general public in a timely and appropriate manner. Furthermore, there appears to be a significant problem with the approach of positioning

these formulations equivalently with conventional "vaccines," not treating spontaneously reported adverse events as "side effects" or "adverse drug reactions" and promoting administration without adequate causal relationship assessment or safety verification. When administrative bodies tasked with safeguarding public health and safety fail to respond transparently to scientifically recognized risks, their institutional and ethical accountability becomes a matter of utmost concern. In this context, MHLW bears institutional accountability for its failure to ensure transparency regarding adverse event data, for promoting genetic vaccines under the label of "vaccines," and for neglecting to appropriately categorize spontaneously reported adverse events as "adverse drug reactions." The dereliction of duty by an agency entrusted with protecting citizens' lives—particularly its failure to disclose critical safety information and to conduct proper verification— should be subject to thorough and independent review processes, with appropriate public accountability mechanisms.

Had it been disclosed during the regulatory review process that an unprecedentedly wide spectrum of distinct types of disorders had been reported as adverse events, it is questionable whether Pfizer's genetic vaccine would have received special approval. The transparency and integrity of the approval process for genetic vaccines must be subject to renewed and rigorous scrutiny. To prevent recurrence, it is imperative to promptly initiate a comprehensive investigation by independent third-party bodies and to ensure full accountability.

Despite receiving information from pharmaceutical companies and adverse event reports from physicians, the government took no specific countermeasures and instead openly ignored these concerns, reviewing and approving genetic vaccines with novel mechanisms of action, including self-amplifying mRNA (saRNA)-LNP formulations (commonly called replicon vaccines), as infectious disease prevention vaccines, and announced a policy to initiate routine administration for high-risk groups (elderly individuals, etc.) beginning in October 2024 (details will be discussed in Section 5). Such responses are inappropriate for public health policy that requires careful judgment based on scientific evidence and represent serious problems from the perspective of ensuring public safety.

As demonstrated above, both during the approval review process and in the post-marketing surveillance of adverse reactions to genetic vaccines, the PMDA and MHLW appear to have withheld critical safety information. Given their institutional responsibility to safeguard public health, such actions raise serious concerns regarding the potential infringement of the public's right to know and right to self-determination. The result was the occurrence of serious and extensive health injuries. Given the protections enshrined in Article 13 and Article 25 of the Constitution of Japan—respectively safeguarding individual dignity and the right to maintain a standard of wholesome and cultured living—the government's inaction may constitute a violation of constitutionally protected human rights. From a legal standpoint, such conduct may reasonably be characterized as regulatory oversight failure and a breach of statutory obligations.

In addition to these legal and ethical concerns, the absence of any reference to this serious structural risk in the PMDA's review report suggests a significant limitation in the current evaluation framework, raising concerns regarding the robustness of scientific assessment and compliance with established pharmaceutical regulatory standards. Therefore, a violation of the obligation to conduct a proper safety evaluation, as stipulated in Article 14 of the PMD Act, is strongly suspected. A rigorous and comprehensive reassessment by the Ministry of Education, Culture, Sports, Science and

Technology (MEXT), the MHLW, as well as independent third-party institutions, is urgently warranted to determine whether the scientific and ethical standards essential for ensuring safety have been properly fulfilled.

Suppression of Contradictory Real-World Data in Vaccine Policy-Making

When genetic vaccines for SARS-CoV-2 first received special approval [1], these products were widely promoted as being effective in preventing infection. In Japan, approximately 103.46 million people (79.5% of the population) received their second dose of genetic vaccines within a short period (Figure 2) [4]. Although Japan lagged behind other countries in initiating administration, it eventually became the country with the highest genetic vaccine administration rate worldwide (Figure 2) [44].

However, since 2023, it has been claimed that "there is no protective effect against the infection, but there is protection against severe disease [45]." Documents prepared by the MHLW and submitted to its own Advisory Board clearly illustrate the unsubstantiated and arbitrary nature of this statement.

One of the documents prepared by MHLW and submitted to the 50th COVID-19 Advisory Board presents comparative data on the COVID-19 case fatality rates among unvaccinated individuals and those who received one or two doses of genetic vaccines. The case fatality rates across all age groups were 0.12% (unvaccinated), 0.41% (single dose), and 0.58% (two doses), respectively, showing a trend of increasing case fatality rates with increasing doses of genetic vaccines (Table 5) [46]. This trend is more pronounced in specific age groups. Nevertheless, the document emphasizes only the data for the 65 years and older age group in red text, presenting figures that appear to show reduced case fatality rates following genetic vaccine administration in that age group. This exploits a phenomenon statistically known as "Simpson's Paradox" [47], which is a typical method for creating misleading impressions.

Subsequently, no nationwide case fatality rate data disaggregated by number of genetic vaccine doses has been published. At the 92nd Advisory Board meeting held on July 27, 2022, Document 2-5 presented data on the number of new positive cases instead of case fatality rates (Table 6) [48]. According to this data, in most age groups, the number of new positive cases (per 100,000 population) among unvaccinated individuals was lower than among those who had received genetic vaccines. For example, in the 65-69 age group, unvaccinated individuals had 66.5 new positive cases, compared to 265.5 cases among those who received two doses and 169.5 cases among those who received three doses. These figures make it difficult to conclude that genetic vaccine administration was effective in preventing the infection; rather, it is evident that individuals who received the administration had higher infection rates. Perhaps due to confronting these inconvenient real-world data findings (Figure 3), no similar administration history-stratified data have been published since.

MHLW did not disclose data in response to freedom of information requests concerning infection and case fatality rates stratified by genetic vaccine administration history. In ongoing litigation (Case Nos. 44 and 297 of 2023 [Gyo-U]), the Ministry explained that it had not repeated such tabulations because members of the Advisory Board had raised concerns regarding the tabulation methodology.

As a result of this litigation, both the Tokyo District Court and Tokyo High Court rendered decisions to "dismiss the plaintiff's claims." The following

extraordinary reasons were presented: "no relevant documents exist," and "at the 90th COVID-19 Advisory Board meeting, the view was expressed that 'it is inappropriate to simply compare severity rates and case fatality rates of infected individuals by vaccination history when conducting post-hoc evaluation and verification of the epidemiological effects of vaccination.' Therefore, it was decided not to create documents comparing severity rates and case fatality rates thereafter."

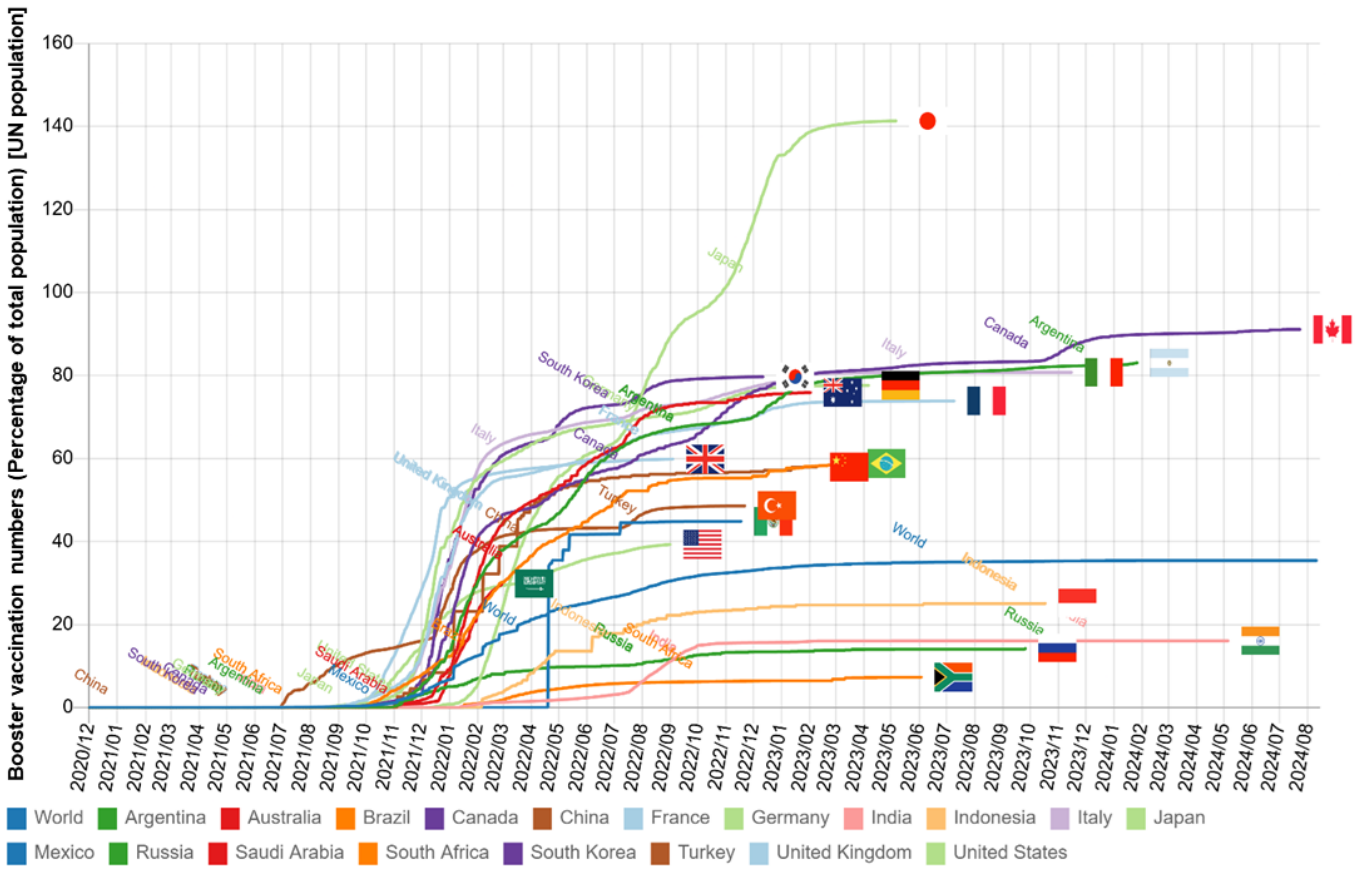

Figure 2. Number of booster doses of vaccines (including mRNA and viral vector vaccines) per 100 population in G20 countries. Figure created using data from the Sapporo Medical University website [44]. International comparison of COVID-19 booster vaccination coverage by country (2020–2024). This figure shows the cumulative number of COVID-19 booster vaccinations administered as a percentage of each country's total population, based on UN population estimates. The data span from December 2020 to August 2024 and includes 19 countries and the global average (blue line). Each line represents a country's booster rollout trajectory, with flags and label markers indicating approximate plateaus or the most recent values as of mid-2024. Notably, Japan (green line) reached a markedly high cumulative rate exceeding 140%, indicating multiple booster doses per capita. Canada, South Korea, Germany, France, and Argentina also show high coverage levels above 80%, whereas countries such as Russia, India, and South Africa show significantly lower uptake. The graph highlights stark disparities in booster coverage and reveals temporal trends in national vaccination strategies.

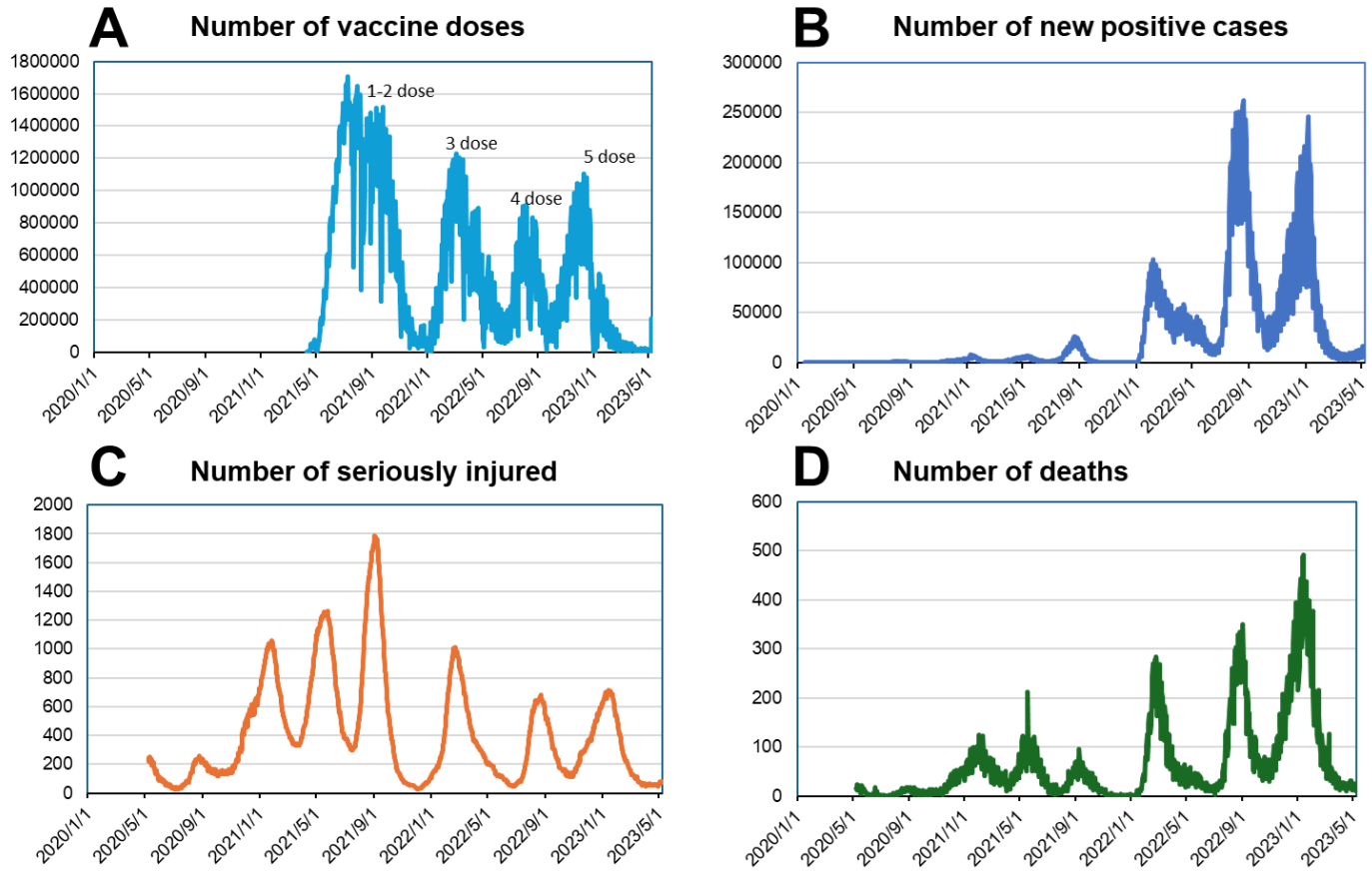

Figure 3. Trends in COVID-19 epidemiological indicators in Japan (2020–2023). This figure shows time-series trends of four key COVID-19 epidemiological metrics in Japan from 2020 to 2023. (A) Number of new positive cases per day. (B) Number of new severe cases per day. (C) Number of new hospitalizations per day. (D) Number of new deaths per day. All data were sourced from the Ministry of Health, Labour and Welfare (MHLW), Japan and are based on cumulative public health reports up to May 8, 2023, when aggregation of new case counts was officially discontinued following the reclassification of COVID-19 as a Category V infectious disease. Data from 'COVID-19 Information — Insights from Data' [170].

In fact, within six months of the rollout of genetic vaccines, data had already begun to reveal elevated case fatality rates in specific age cohorts. Accordingly, the claim that "vaccines prevent severe disease" was no longer tenable based on the available evidence at that time. Citing public epidemiological data from New South Wales, Australia, Parry *et al*. point to the possibility of a dose-dependent relationship between the number of COVID-19 genetic vaccine doses and severity indicators (number of hospitalizations and ICU admissions) [28]. According to the state's official report, COVID-19-related hospitalization and ICU admission rates progressively increased as the number of genetic vaccine doses increased from one to two, three, and four doses. This observation is noteworthy as it suggests the accumulation of immune abnormalities or spike protein-related toxicity in some individuals receiving genetic vaccines.

Similarly, given that data on new positive cases published in July 2022 demonstrated that vaccinated individuals tended to have higher infection rates than unvaccinated personals, claims that "vaccine benefits outweigh the risks" and that "approved

vaccines have benefits that far outweigh possible risks" [49, 50] lack objective foundation and cannot be justified to the public.

Therefore, although real-world data collected and acknowledged by MHLW itself contained evidence unfavorable to vaccine effectiveness, the Ministry consistently failed to disclose this information to the public and continued to conceal it. These actions appear inconsistent with the principles of governmental accountability and the public's right to know, potentially undermining the Ministry's obligations to maintain transparency and uphold evidence-based policymaking.

Structural Bias and Immune Mechanisms Undermining Vaccine Efficacy

One critical concern in evaluating the efficacy of genetic vaccines arises from the definition of the case counting window in pivotal trials [51]. As Doshi pointed out, excluding cases that occur within the first 7–14 days after the initial dose may introduce a systematic bias that inflates the apparent efficacy [52]. In an observational study by Kitano *et al.*, case counting was initiated 14 days after the second dose [53], suggesting that a similar bias structure may also be present in those data. These early cases likely occurred during a period of maximal susceptibility, when the immune response remained incomplete [51]. While such cases are often omitted from the efficacy denominator, they are typically included in safety assessments. This methodological choice may result in an overestimation of efficacy, particularly if early post-vaccination reactogenicity correlates with transient immunosuppression. Acknowledging this limitation is essential when interpreting headline efficacy results, especially in the context of emergency use authorizations.

Importantly, a disproportionately high number of deaths have been reported within the first few days following mRNA vaccine administration (Figure 4) [54-57]. This temporal clustering follows a pattern consistent with a discrete Erlang distribution, suggesting a non-random concentration of events shortly after exposure [58]. Notably, both 2021 and 2024 datasets display a consistent temporal profile, with a peak on Day 2 post-vaccination followed by a gradual monotonic decline. By June 2021, the reported post-vaccination mortality rate had reached approximately 0.002% [59], remaining relatively stable through 2024 [54]. The reproducibility of this pattern across independent datasets underscores the need for timely signal detection, robust causal inference, and transparent risk communication. Failure to incorporate such early adverse event patterns into safety and efficacy evaluations may introduce bias, particularly under emergency authorization frameworks.

Another potential source of bias in the interpretation of early trial and observational data relates to the diagnostic criteria used to confirm SARS-CoV-2 infection. As emphasized in the World Health Organization (WHO) Information Notice for IVD (In Vitro Diagnostic Medical Device) Users issued in January 2021 [60], RT-PCR–based diagnosis should be interpreted in conjunction with clinical presentation and cycle threshold (Ct) values. High Ct values (e.g., >35) are known to correlate poorly with viral infectivity and are more likely to reflect residual, non-viable viral RNA fragments rather than active infection [61, 62]. However, during the initial phases of mass testing, many clinical studies and public health surveillance systems did not report cycle threshold (Ct) values or applied high Ct cutoffs without adequate clinical contextualization. In Japan, available evidence indicates that no nationally standardized Ct threshold was established for RT-PCR diagnostics during the COVID-19 pandemic. Instead, Ct cutoffs varied considerably across laboratories and testing platforms, with some institutions reportedly considering values as high as

<40 as positive [63, 64]. This diagnostic heterogeneity critically undermined the reliability and comparability of SARS-CoV-2 case definitions. As a result, there is a credible possibility that early baseline cases, particularly among asymptomatic individuals, were likely inflated due to the inclusion of PCR-positive results that lacked clinical significance. Such diagnostic inflation could have distorted estimations of baseline infection and mortality risk, thereby affecting the perceived effectiveness of vaccination, especially if pre-vaccine risk levels were overstated. Accordingly, future revisions to diagnostic protocols must address this structural vulnerability to ensure consistency, reliability, and scientific integrity in pandemic response policy.

In parallel, mortality attribution practices also present serious concerns. Substantial institutional and procedural challenges remain in the causal assessment of deaths following COVID-19 vaccination. According to the WHO guidelines for causality assessment of adverse events following immunization (AEFI) [65, 66], a robust determination requires systematic evaluation of temporal relationships, biological plausibility, exclusion of alternative causes, and integration of supportive evidence such as autopsy findings. While PMDA has developed causality assessment guidelines in line with international standards, questions remain regarding the uniform application of these criteria and the transparency of their implementation, particularly in cases involving post-vaccination fatalities.

The absence of a standardized and rigorously applied evaluation framework undermines the scientific credibility of vaccine safety surveillance. In practice, although over 2,000 post-vaccination deaths have been reported by physicians in Japan, autopsies have been performed in only approximately 10% of cases. Consequently, nearly 99% of these reports have been classified as “causality indeterminable.” This systematic lack of post-mortem investigation has prompted strong concern among forensic and clinical experts, highlighting the urgent need for a nationally coordinated system of cause-of-death determination [67-69].

In the early phase of the COVID-19 pandemic, Japan faced considerable administrative disruptions and infection control priorities that severely limited the capacity to conduct autopsies [70]. These constraints likely impaired accurate cause-of-death assessments for both COVID-19–related and post-vaccination deaths, thereby compromising the validity of subsequent causal evaluations.

Moreover, in Japan and many other countries, it became common practice to classify deaths as “COVID-19–related” based solely on positive PCR test results, even in the absence of corroborating clinical or pathological evidence. Such a failure to distinguish between deaths *from* COVID-19 and deaths *with* COVID-19 risks a substantial overestimation of mortality statistics and poses a threat to the integrity of epidemiological indicators [71, 72].

For accurate assessment of vaccine risk–benefit profiles, mortality data should be stratified based on standardized causality determination criteria, including autopsy findings, comorbid conditions, and temporal proximity between symptom onset and death [55]. When vaccine efficacy is evaluated in the absence of such diagnostic and attributional rigor, doubts regarding the validity of such efficacy estimates are not only understandable, but arguably unavoidable.

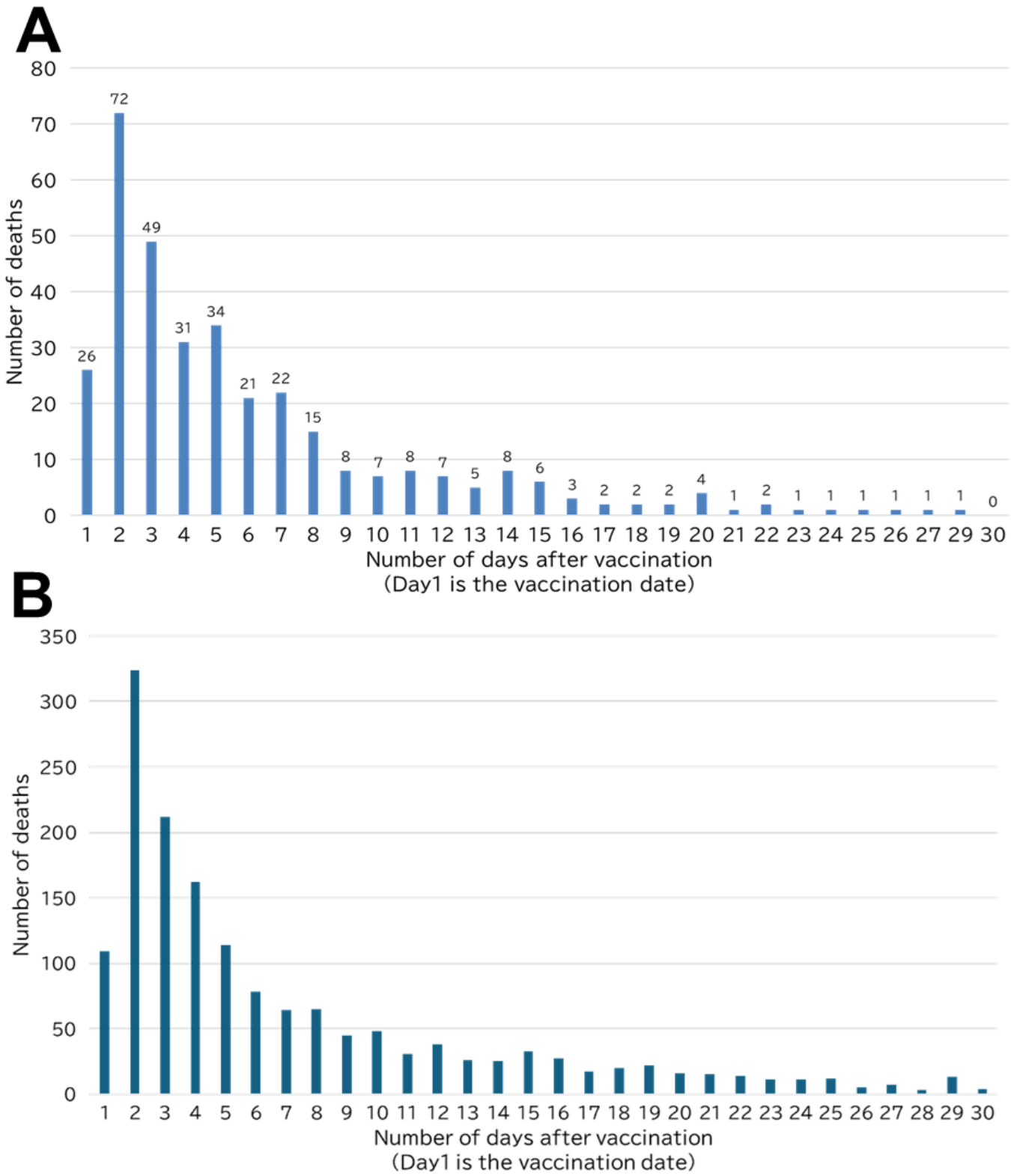

Figure 4. Temporal distribution of reported deaths following COVID-19 vaccination: (Panel A) as of June 18, 2021, (Panel B) as of January 28, 2025. Adapted from Fukushima [57] (Panel A) and Hirai et al. [54] (Panel B), with axis labels translated into English and the observation period for Panel A shortened to 30 days to ensure consistency with Panel B. These bar graphs

illustrate the daily incidence of reported deaths following COVID-19 vaccination, irrespective of confirmed causality, based on publicly accessible pharmacovigilance data compiled by the Japanese health authorities. Despite being based on datasets collected in different years (2021 and 2024, respectively), both graphs exhibit a remarkably consistent temporal pattern: a pronounced peak in reported deaths on Day 2 post-vaccination, followed by a gradual monotonic decline. This right-skewed distribution closely approximates a discrete Erlang distribution, commonly used in modeling time-to-event data, and suggests a reproducible, biologically constrained pathological process [58]. As early as June 2021—within six months of vaccine rollout—the post-vaccination mortality rate had already reached approximately 0.002% [59], a figure that remained largely unchanged through 2024 [54]. The reproducibility of this pattern across independent datasets underscores a missed opportunity for early regulatory intervention. Had standard pharmacovigilance practices been applied, reasonable warnings could have been issued to the public by mid-2021. The failure to do so constitutes a serious breach of pharmacovigilance obligations and a violation of individuals' right to informed self-determination.

Despite these limitations, expert advisory panel members entrusted with shaping national health policies failed to sufficiently disclose the underlying scientific uncertainties to the public [73]. Given their significant involvement in policymaking, any failure by such entities to uphold accountability standards merits serious scrutiny, potentially to a degree comparable to or exceeding that applied to governmental bodies.

Meanwhile, at the European Parliament in October 2022, Pfizer's vaccine development director testified under oath that "infection prevention efficacy was not investigated during the clinical trial stage" [74]. Subsequently, real-world data analysis revealed that the more genetic vaccines individuals received, the more likely they were to contract SARS-CoV-2 [50, 75, 76]. This may be attributable to genetic vaccines causing original antigenic sin due to prolonged antigen persistence in the body compared to conventional vaccines, as well as IgG4 class switching of anti-spike protein antibodies [77-81].

Original antigenic sin refers to a phenomenon whereby the immune system responds strongly to antigens from an initially encountered pathogen (virus or bacteria), and subsequent immune responses to similar pathogens become suboptimal.

Indeed, spike proteins derived from mRNA vaccines have been reported to persist in the human body for an extended duration following vaccination, particularly within lymphoid tissues, the bloodstream, and various organs [82-86]. Repeated administration of mRNA vaccines has been associated with elevated IgG4 responses, which may modulate immune reactivity [87]. This raises concerns regarding the potential for immune tolerance, although the extent to which this contributes to recurrent SARS-CoV-2 infections remains to be clarified.

In Japan, COVID-19 cases have continued to occur at substantial levels since the introduction of genetic vaccines (Figure 3). Time-series analysis of epidemiological indicators based on publicly available MHLW data from 2020 to 2023 revealed no sustained downward trend in positive cases, severe cases, or deaths following widespread vaccine administration. The recurrence of infection waves, particularly from 2021 onward, suggests that the infection suppression effect of genetic vaccines at the population level may have been limited, warranting further investigation.

This observation is consistent with the potential immunosuppressive mechanisms discussed above and the capacity of formulations to induce original antigenic sin. Specifically, increased IgG4 possesses anti-inflammatory properties that may, under certain circumstances, impact infection defense, potentially leading to reduced immune responses against

certain pathogens [88]. Normal antiviral immune responses are predominantly mediated by IgG1 and IgG3 subclasses, which are associated with strong pro-inflammatory and neutralizing activity [89]. However, chronic or repeated antigenic stimulation—such as sustained exposure to the SARS-CoV-2 spike protein—has been shown to induce a relative increase in IgG4 subclass antibodies specific to the spike protein. Several studies have reported that the frequency of anti–spike protein IgG4 antibodies rises in a dose-dependent manner with successive administrations of genetic vaccines [77-79, 81]. This finding is consistent with results showing that higher numbers of genetic vaccine doses are associated with repeated SARS-CoV-2 infections [50]. Furthermore, it is theoretically conceivable that excessive antigen production by the formulation could enhance Treg (regulatory T cell) function, resulting in diminished immune responses [90]. Particularly, it has been suggested that an increase in IgG4 and the induction of immune tolerance observed after genetic vaccine administration may lead to reduced protection against infection [87], warranting further investigation.

Supporting these concerns, mortality rates for specific cancers—including ovarian cancer, leukemia, lip/oral cavity/pharyngeal cancer, and pancreatic cancer— have shown a notable increase in Japan since the initiation of genetic vaccine administration [91]. In line with this concern, Abue *et al*. recently reported an association between repeated mRNA vaccination and reduced overall survival in patients with pancreatic cancer. This observation was accompanied by elevated IgG4 levels and increased infiltration of Foxp3-positive immunoregulatory cells in tumor tissues, suggesting a possible immunomodulatory effect [92]. While these findings raise important questions, further studies are warranted to determine causality and underlying mechanisms. Furthermore, recent statistics show that Japan's life expectancy, which had increased consistently over previous decades, peaked in 2020—the onset year of the COVID-19 pandemic—and has shown a declining trend since the introduction of genetic vaccines in 2021 [93, 94]. This decline corresponds with a rise in overall mortality observed during the same period. Age-adjusted mortality rates, which reached their lowest point in 2020, began increasing in 2021 and accelerated further in 2022 [93, 95]. These temporal patterns may indicate a shift in public health dynamics around 2020, warranting further investigation into potential contributing factors.

Currently, direct causal relationships with genetic vaccines remain unknown, but the characteristics of repeatedly administered genetic vaccines strongly suggest the likelihood of long-term immunosuppression or immune dysfunction in recipients. These findings highlight the urgent need for independent re-evaluation of genetic vaccine safety, efficacy, and long-term public health impact based on transparent and stratified data.

Biosafety Risks Associated with Self-Amplifying mRNA Vaccine Platforms

Among next-generation genetic vaccine technologies, saRNA platforms have attracted attention for their enhanced antigen expression efficiency (Figure 5) [96, 97]; however, concerns have been raised regarding their safety, regulatory classification, and insufficient clinical evaluation [98].

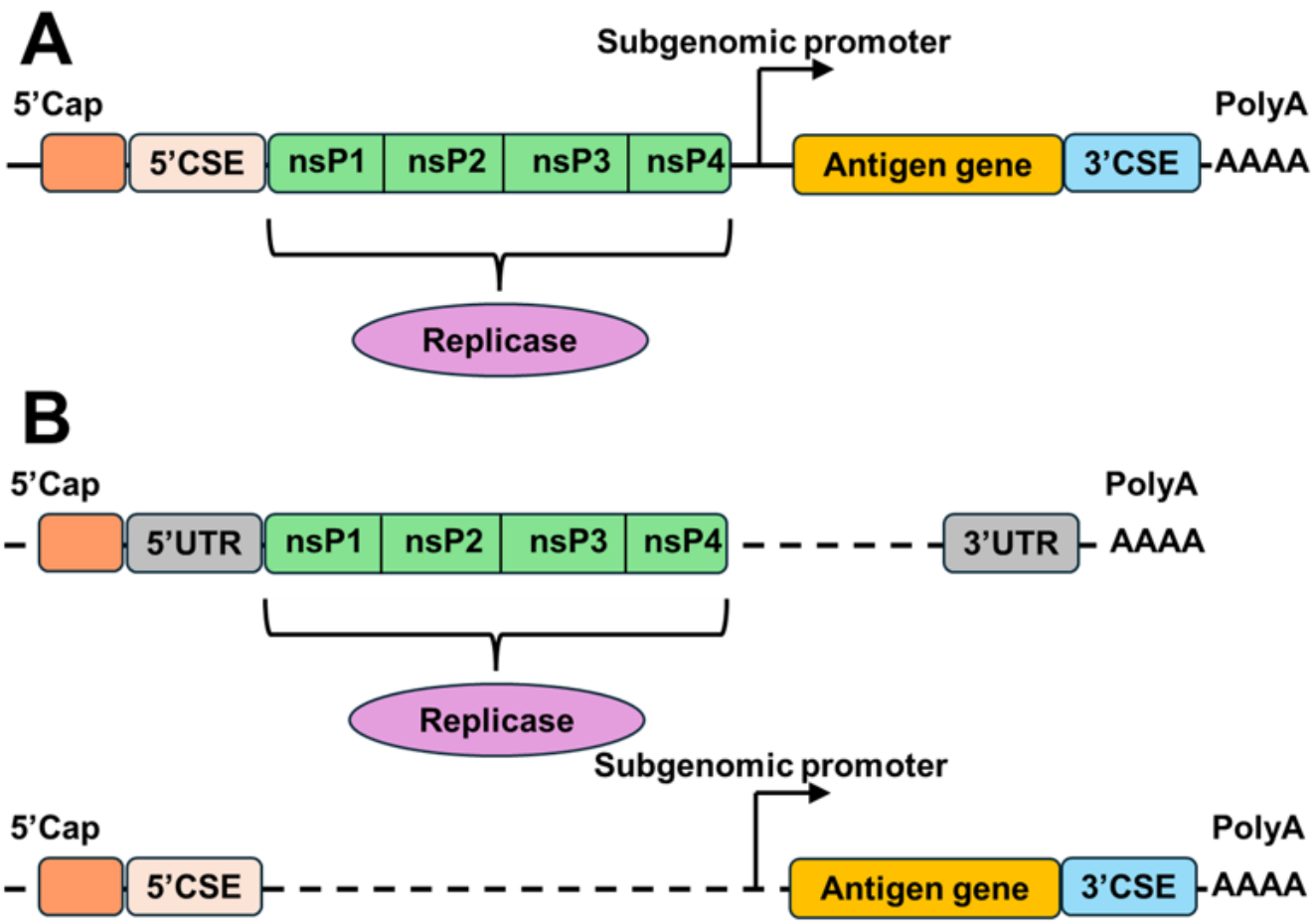

Figure 5. Structure of self-amplifying mRNA (saRNA) and trans-amplifying mRNA (taRNA). (A) Self-amplifying RNA (saRNA) encodes a viral-derived RNA-dependent RNA polymerase (replicase; nsP1–4), enabling intracellular amplification of RNA in human cells. In currently marketed saRNA–LNP genetic vaccines, both the replicase and antigen-encoding sequences are carried on a single RNA molecule. This design allows for potent antigen expression at lower doses but may also carry theoretical risks of sustained antigen production and unintended or non-specific translation, since both elements are co-expressed. Additionally, because RNA replicases lack proofreading activity, unlike DNA polymerases, they are prone to replication errors [109], raising concerns about replication fidelity and potential off-target cellular effects. (B) An alternative platform known as trans-amplifying mRNA (taRNA) separates the replicase RNA and the antigen-encoding RNA into two distinct molecules [97]. While saRNA constructs are typically large (exceeding 9–12 kb), taRNA systems divide the replicase and antigen-encoding components into separate RNA molecules, resulting in a substantially smaller size for each RNA strand. This structural division enhances biosafety by reducing the risk of prolonged or unregulated expression. Furthermore, it allows independent dose optimization of each RNA component, providing better control over replicase activity and antigen output. Because efficient amplification in the taRNA system requires co-delivery and co-localization of both RNAs within the same cell, the likelihood of uncontrolled amplification is substantially minimized. In both saRNA and taRNA platforms, a critical concern lies in the in vivo expression of antigen-encoding sequences that have not been attenuated or detoxified. This raises safety considerations, as these antigens—despite being intended to elicit immune responses—may themselves possess intrinsic biological activity or toxicity that could contribute to adverse effects following administration. CSE stands for "conserved sequence element"; nsP refers to "nonstructural protein"; UTR denotes "untranslated region."

According to clinical trials and the review report [99, 100], the adverse reaction profile of the saRNA

vaccine (trade name Kostaive for intramuscular injection, development code ARCT-154), developed by Arcturus Therapeutics and marketed by Meiji Seika Pharma, was similar to Pfizer's mRNA vaccine; thus the formulation was evaluated as "non-inferior" to existing formulations.

Non-inferiority refers to the concept that a new pharmaceutical product is "not statistically inferior in efficacy or safety" compared to existing standard treatments.

In other words, this means it could reasonably have been anticipated that adverse events similar to those observed with Pfizer and Moderna (trade name Spikevax, development code mRNA-1273) mRNA vaccines might occur. Therefore, it was sufficiently predictable that adverse events like those of conventional mRNA vaccines would occur with saRNA vaccines. Indeed, according to a document published by Meiji Seika Pharma Co., Ltd. in May 2025, multiple adverse events were reported within just a few months after initiating the administration of this formulation, including four fatalities [101, 102]. These facts indicate the necessity for rigorous investigation of whether appropriate preliminary risk assessments were conducted and whether adequate warnings and countermeasures were implemented in anticipation of these adverse events.

Moreover, Arcturus Therapeutics and Meiji Seika Pharma conducted a non-inferiority trial comparing a saRNA vaccine with a conventional mRNA vaccine (Pfizer) as a fourth-dose booster to evaluate the efficacy of the replicon-based formulation [103]. However, the trial cohort consisted exclusively of individuals who had previously received multiple doses of genetic vaccines, raising concerns that preexisting immune modulation or waning immunity may have confounded the evaluation of vaccine efficacy. This design limitation potentially undermines the appropriateness of the trial for assessing the standalone performance of the saRNA platform.

Amidst this situation, the vaccine formulation introduced for routine clinical use in October 2024 contains the spike protein of the JN.1 variant—an antigen for which comprehensive non-clinical and clinical safety evaluations had not yet been completed at the time of approval [99, 104]. These updated formulations were approved via the "partial change approval" pathway as stipulated under Article 14, paragraph (15) of the PMD Act (Table 1) [99, 105]. However, the JN.1 spike protein differs from the ancestral strain by approximately 3.5% at the amino acid level, resulting in alterations to structural and immunological properties [106]. If evaluated under the regulatory framework applicable to gene therapy or nucleic acid-based pharmaceuticals, such a degree of antigenic divergence would likely warrant independent non-clinical and clinical studies to reassess safety and efficacy.

The reliance on regulatory categorization as an "infectious disease vaccine," rather than as a gene therapy or nucleic acid pharmaceutical, may have permitted streamlined approval without rigorous reassessment. This regulatory classification discrepancy raises important questions regarding the sufficiency of existing approval pathways for next-generation genetic vaccines with evolving antigenic profiles. Given that saRNA vaccines arguably fall within the conceptual and mechanistic domain of gene therapy products [107], their evaluation without genotoxicity or carcinogenicity studies [9], and with shortened follow-up durations [102], may represent a gap in regulatory oversight. A reappraisal of regulatory categorization criteria is warranted to ensure alignment between product mechanism, safety requirements, and public health protections.

On the other hand, genetic recombination

experiments conducted at research institutions such as universities and companies require strict risk management from a biosafety perspective to avoid infection risks and unexpected recombination risks. As part of this approach, measures are implemented to minimize risks, such as dividing genes within viral vectors across multiple plasmids [108]. In contrast, the saRNA vaccine approved in Japan incorporates both the mRNA replication enzyme (replicase) and the antigen gene on a single vector (Figure 5), suggesting that biosafety safeguards may be insufficient for pharmaceutical products intended for human use. This co-localization raises concerns about sustained replicase activity [109], which may result in prolonged antigen expression and potential dysregulation of the immune system. Such effects could increase the risk of adverse immune responses, including hyperinflammation and autoimmunity, especially in vulnerable individuals. Furthermore, the single-vector design introduces structural risks that may elevate the likelihood of unintended recombination or horizontal gene transfer, posing substantial biosafety and infection control concerns.

From a pharmacokinetic and pharmacodynamic perspective, the immature design of current genetic vaccine formulations (both mRNA- and saRNA-LNPs) raises three fundamental concerns—referred as the "three Os": **O**ff-target expression, **O**verproduction of antigenic proteins, and **O**ut-of-control in bioreactivity and the host reaction [24]. These risks are particularly salient in mRNA–LNP platforms, where cellular uptake and translation are not confined to targeted tissues, antigen production may far exceed physiological levels, and systemic dissemination, unintended action, host responses in any place remains poorly characterized. Without rigorous evaluation of these dimensions in nonclinical studies, the overall safety profile remains inadequately defined.

In May 2025, President Donald Trump signed an Executive Order titled "Improving the Safety and Security of Biological Research," which drew considerable attention by instituting a moratorium on high-risk gain-of-function (GOF) research involving infectious pathogens and toxic agents, as well as by mandating a complete suspension of federal funding for such research conducted in foreign countries [110]. This Executive Order aims to rebuild risk management for life science research triggered by the COVID-19 pandemic and indicates a progressing trend toward strengthened international regulation of high-risk GOF research and experiments lacking biosafety measures [111, 112]. Given that saRNA vaccines, including conventional mRNA vaccines, have similar high-risk characteristics [113], comparable regulatory reassessments are strongly warranted in countries beyond the United States.

Safety Issues (Defects in Adverse Event Reporting, Recognition of Health Injuries, and Risk Assessment)

The SARS-CoV-2 spike protein used as an antigen in genetic vaccines has been reported to contribute to vascular endothelial cell injury, thrombosis, inflammatory response induction, and mitochondrial dysfunction, with multiple studies documenting spike protein-related toxicity across various organ systems [28, 114, 115]. Structural analyses have further suggested that the original Wuhan strain spike protein contains motifs homologous to gp120 and prion-like domains [116], may be capable of crossing the blood-brain barrier [117], and exhibits amyloidogenic properties *in vitro* [118]. The continued use of mRNA platforms encoding such biologically active and potentially pathogenic proteins as pharmaceutical agents raises important safety considerations, particularly regarding their long-term effects.

In parallel, suggestions have emerged that SARS-CoV-2 may be of artificial origin [119-121], further underscoring the necessity of rigorous oversight regarding the handling and dissemination of related genetic materials.

Shortly after the initiation of genetic vaccine administration, myocarditis and pericarditis were identified as adverse drug reactions [40] and added to the package insert for genetic vaccines [122]. In December 2021, the Minister in Charge of Promoting Vaccinations stated, "Some people develop myocarditis from vaccines, but the probability is low, and the condition is mild. Most people recover" [123]. This statement minimized these inherently serious conditions. Subsequent analysis by Japanese research groups reported a significantly increased incidence of myocarditis and pericarditis in individuals under 30 years of age who received genetic vaccines [124]. Adverse events have been reported successively not only in Japan but also in countries where genetic vaccines have been administered [38-42], and the number of cases with health injuries recognized by MHLW is overwhelmingly higher than for conventional vaccines such as influenza vaccines (Figure 1) [56, 125]. The number of recognized cases continues to increase, and the ultimate extent of health injuries in Japan remains unclear.

Until the end of 2021, the MHLW routinely published cumulative data on post-vaccination deaths officially certified under the government relief program. Starting in 2022, these cumulative updates ceased, compelling researchers to reconstruct the data manually from individual review committee minutes and annual reports (Figure 1). This interruption in transparent data dissemination appears to reflect a broader institutional tendency where information potentially deemed politically or administratively sensitive is selectively disclosed or withheld.

Furthermore, in May 2022, MHLW classified vaccinated individuals without recorded vaccination dates as unvaccinated, and following accusations of data misuse [126], discontinued public release of HER-SYS (Health Center Real-time Information-sharing System on COVID-19) data [127]. Such practices hinder independent verification and weaken the foundations of scientific discourse in public health. Ensuring transparency in the disclosure of public health data is essential to safeguard scientific integrity, uphold public trust, and support evidence-based policy decisions.

Additionally, it has been disclosed that members of the Study Group on Adverse Reactions under the Health Sciences Council of the Subcommittee on Immunization and Vaccination received funding from pharmaceutical companies [128]. Although this clearly constitutes a conflict of interest (COI), MHLW failed to undertake remedial reconstruction of a neutral committee by disinterested third parties. This inaction may constitute violations of multiple Japanese statutes, including the National Public Service Ethics Act, the Administrative Procedure Act, and the State Redress Act. Moreover, these actions may amount to breaches of official duties under the Penal Code, potentially involving bribery and breach of trust, thereby raising the possibility of criminal liability under Japanese law.

This case also raises serious concerns under international regulatory and ethical norms, potentially violating conflict of interest management guidelines established by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) [129]. In public health policy, transparency, accountability, and appropriate management of conflicts of interest in decision-making processes are essential [130, 131]. The lack of transparency in institutional operations and inadequate information disclosure observed in this

case represent significant issues from an international perspective.

The available evidence indicates that substantial safety concerns remain regarding these pharmaceutical products.

Inadequate Real-World Evidence and Pharmacovigilance

Immediately following the initiation of genetic vaccine administration in February 2021, numerous deaths were reported by physicians on a voluntary basis [6]. Post-marketing surveillance results also documented numerous adverse events. Nevertheless, the continued non-disclosure of these facts by the government may be regarded as a significant omission inconsistent with its institutional duty to ensure public health transparency. This constituted a violation of the duty to warn, which is a fundamental principle of medical care (Medical Care Act), resulting in persistent impediments to physicians' fulfillment of their duty to provide adequate explanations to patients. This can be evaluated as substantial state interference with physicians' professional judgment and obstruction of medical practice autonomy.

Countries that promoted genetic vaccine administration have experienced alarming increases in excess mortality [95, 132-134] (Figure 6), and Japan has experienced a marked decline in life expectancy and a concerning upward trend in cancer incidence [91]. Despite multiple warnings concerning the potential risks associated with genetic vaccines, the Japanese government has continued their routine administration [104].

Japan failed to operationalize a robust, adaptive pharmacovigilance system capable of near real-time detection and evaluation of vaccine-related adverse events, despite possessing a universal healthcare framework and advanced digitized infrastructure such as HER-SYS. In contrast, countries such as Israel rapidly leveraged national health insurance databases and hospital networks to facilitate real-time safety monitoring and outcome tracking [135, 136]. Japan's inadequate response reflects a missed opportunity for early signal detection and suggests structural inertia within regulatory and public health institutions. Integrating existing medical information systems could have enabled more responsive safety assessments, thereby enhancing transparency and facilitating evidence-based policy decisions.

In evaluating the safety of genetic vaccines, it is essential to contextualize reported adverse events by comparing them with established baseline incidence rates in the unvaccinated population. Without such reference points, temporal associations alone may lead to misinterpretation of vaccine-attributable risks. Cases of myocarditis, thrombosis, and sudden cardiac death must be assessed against background rates stratified by age and sex to determine whether observed frequencies exceed expected norms [137, 138]. In Japan, publicly available pharmacovigilance reports have seldom provided stratified baseline rates [139], limiting the capacity for risk quantification and hindering transparent risk–benefit assessments. Future evaluations should incorporate rigorous epidemiological frameworks that include background incidence rates to more accurately characterize the safety profile of genetic vaccine products.

The ongoing administration of pharmaceutical products without established long-term safety profiles raises substantial ethical concerns, potentially conflicting with established principles of medical ethics established in the Declaration of Geneva and Declaration of Helsinki: "The health and well-being of my patient will be my first consideration" (Declaration of Geneva); "In medical research involving human subjects, the well-being of the individual

research subject must take precedence over all other interests" (Declaration of Helsinki, Paragraph 6); and "Medical practitioners are to contribute to the improvement and promotion of public health through the administration of medical care and health guidance, and thereby ensure the healthy lives of the citizens" (Medical Practitioners' Act, Article 1) [140, 141].

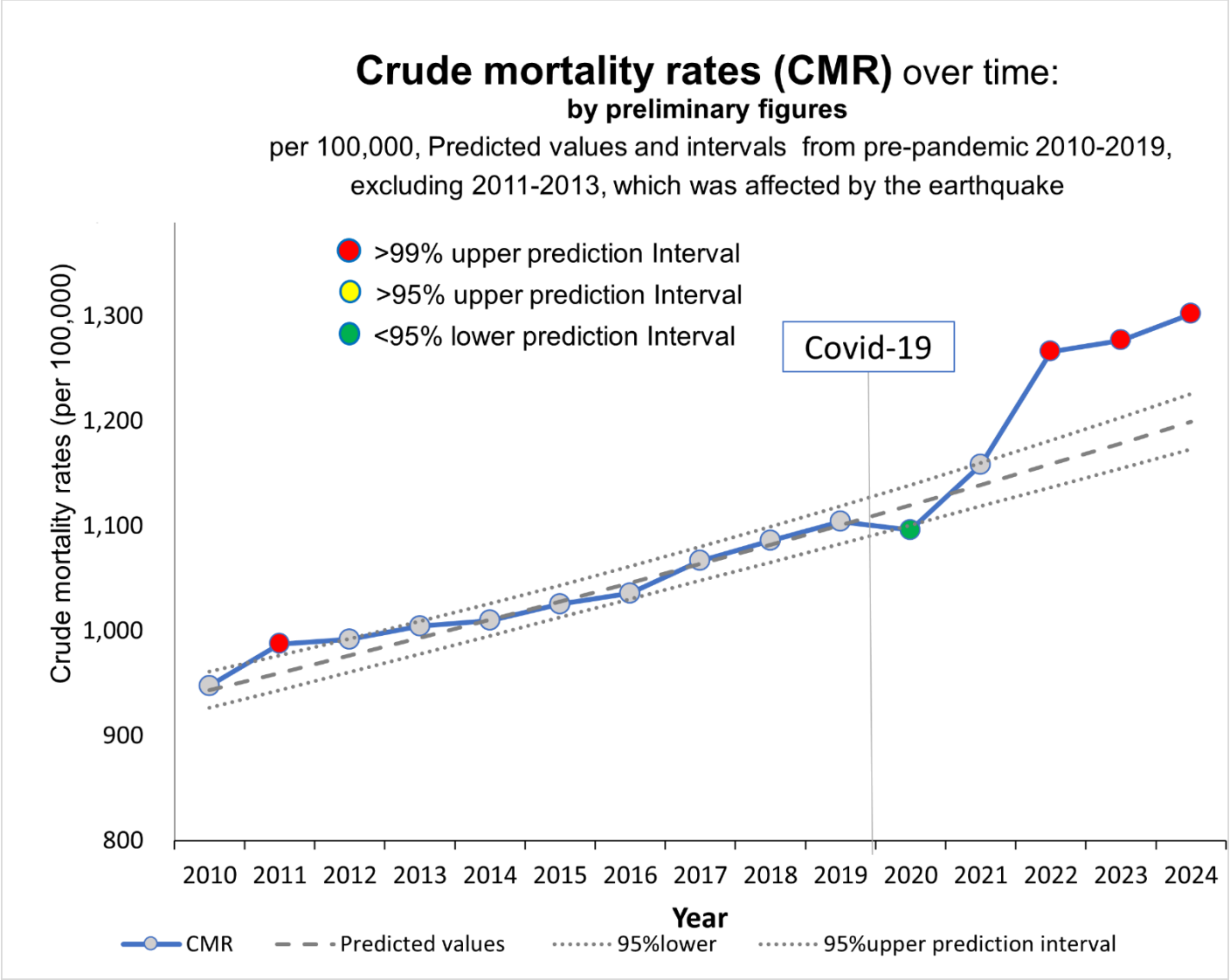

Figure 6. Crude mortality rates (CMRs) over time: all causes. The CMR in 2020 was below the 95% lower prediction interval (PI). In 2021, when the massive vaccination campaign started in Japan, it rose but within intervals. From 2022, it rose above 95% upper PI, following continuous excesses in 2023 and 2024. Preliminary mortality numbers and population projections have been officially obtained from the Japanese government websites [168, 171]. The predicted mortality rates and intervals from the pre-pandemic crude mortality (CMR) for all causes were calculated using logistic regression analysis, based on the period from 2010 to 2019, excluding the years 2011–2013 when mortality rates were exceptionally high due to the major earthquake and tsunami.

In view of accumulating safety signals and the continued lack of transparent, long-term post-marketing data, urgent regulatory reassessment is warranted. Consideration should be given to the

immediate suspension of current authorizations and potential market withdrawal of genetic vaccines. Such regulatory measures must be accompanied by rigorous, independent epidemiological investigations to comprehensively assess the scope, magnitude, and temporal dynamics of potential adverse health outcomes associated with their administration.

Public Health Risks of Potential Residual DNA in mRNA-LNP Vaccines: Necessity for Regulatory Oversight and Corporate Transparency

Emerging evidence from multiple countries, including Germany and the United States that vials of Pfizer/BioNTech and Moderna mRNA vaccines contained DNA fragments (plasmid DNA used in mRNA production) exceeding European Medicines Agency (EMA) regulatory limits (Table 7) [56, 142-149]. Notably, current regulatory thresholds for residual DNA were originally established prior to the introduction of advanced delivery systems such as liposomes and LNPs and have since been progressively relaxed [150]. However, these legacy standards are no longer appropriate for LNP-based formulations, which exhibit markedly enhanced transfection efficiency [151]. As a result, the existing regulatory framework is inadequate to accurately assess the residual DNA risk posed by these novel delivery systems. Therefore, discussions over whether LNP vaccines merely exceed or remain within outdated thresholds may be scientifically uninformative and risk obscuring the more pressing issue of actual biological hazard.

There has been considerable discussion among researchers regarding DNA contamination levels, with some criticism that accurate DNA measurement is difficult using Qubit fluorometry and quantitative PCR methods [152]. Nevertheless, MAHs have a responsibility under the Product Liability Act for providing scientific evidence to resolve these concerns. Additionally, the PMDA bears supervisory responsibility for requiring pharmaceutical companies to submit sufficient verification data to demonstrate that such issues are not present in their products. When DNA contamination exceeds regulatory limits, genetic vaccines fail to meet pharmaceutical product standards. This factor alone necessitates immediate discontinuation of genetic vaccine administration and product recall. Furthermore, if the PMDA failed to require pharmaceutical companies to submit data on potential DNA contamination during the regulatory review process, such an omission would reflect a critical deficiency in the new drug approval framework and a failure on the part of the regulatory authority to uphold its pharmacovigilance obligations.

While Pfizer and Moderna used degradation-resistant mRNA modified with methylpseudouridine to stabilize mRNA [153], it has been noted that methylpseudouridine causes translational frameshifting [154, 155]. This suggests that proteins other than the intended targets may be produced from methylpseudouridine-modified mRNA, which is extremely of concern [156]. Since there is no evidence that this possibility was investigated during the pharmaceutical review process, pharmaceutical companies have an obligation to provide data addressing both this issue and the DNA contamination concerns discussed above.

Requirements for Revocation of Approval and Market Withdrawal, and Past Cases

Past cases of pharmaceutical approval revocation and market withdrawal have involved serious deficiencies in efficacy or safety, as well as the detection of carcinogenic substances exceeding

regulatory limits. Following approval, pharmaceutical products undergo continuous evaluation of efficacy and safety through post-marketing surveillance (PMS) and reexamination. When serious problems are identified through this evaluation process, approval may be revoked by MHLW [157, 158]. Market withdrawal (recall) may also be implemented when quality issues are identified.

Genetic vaccines have already caused extensive harm worldwide following administration [56, 125]. Furthermore, given the absence of scientific evidence demonstrating efficacy in preventing the infection or severe disease, these formulations should be recognized as "not found to have the efficacy or effects indicated in the application" (PMD Act, Article 14, paragraph (2), item (iii), (a)) or "found to have no value as a pharmaceutical or quasi-pharmaceutical product as they have harmful effects which outweigh their efficacy or effects" (PMD Act, Article 14, paragraph (2), item (iii), (b)). Accordingly, the approval of these formulations should be revoked pursuant to Article 74-2, paragraph (1) of the PMD Act, on the grounds that they have come to fall under one or more of the conditions specified in Article 14, paragraph (2), item (iii), subitems (a) through (c) of the same Act (Table 1).

In Japan, although the pharmaceutical approval process should be based on scientific standards, decisions regarding revocation of approval may, in practice, be subject to administrative discretion. For example, gefitinib (Iressa), which had over 700 reported deaths, maintained its approval [159], while polysaccharide K (Krestin) was withdrawn from the market due to insufficient scientific evidence of efficacy rather than mortality risk [160]. Therefore, the criteria for revocation of approval lack consistency, and it is an undeniable fact that administrative judgments sometimes take precedence over scientific evidence. The case of sorivudine, which preceded the gefitinib (Iressa) incident, provides a critical precedent in Japan's pharmaceutical regulatory history [161]. Although sorivudine was initially approved, it was rapidly withdrawn from the market following reports of serious adverse reactions [162]. This incident should have served as a foundational lesson for establishing more robust and fail-safe regulatory practices. Yet over time, with personnel turnover and a lack of institutional memory, the lessons learned were not embedded into the system, and the opportunity to strengthen regulatory governance was ultimately lost. This reflects a persistent challenge within Japanese administrative culture: it remains difficult to ensure that lessons from past failures are consistently carried forward within regulatory institutions.

Information on pharmaceutical products with revoked approval is partially published on MHLW and PMDA websites. However, this information is scattered across websites and, unlike unified databases such as those of the FDA and EMA, is not easily accessible to the public. To improve this situation, it is necessary to enhance transparency in Japan's pharmaceutical review and approval processes, clarify the review criteria, and establish systems based on scientific evidence. It would be desirable to establish more transparent mechanisms by referencing the review data disclosure policies adopted by the FDA and EMA.

Despite strong scientific and legal grounds for revoking the approval of certain pharmaceutical products, regulatory action has been hindered by structural obstacles, including institutional conflicts of interest between the MHLW and industry, rapid personnel turnover, and judicial deference to administrative discretion. The discretionary nature of revocation under Article 74 of the PMD Act further contributes to regulatory inaction. To

address these issues, we propose the establishment of an independent investigatory commission, strengthened parliamentary oversight, and international collaboration to ensure transparent, evidence-based governance and restore scientific integrity in regulatory decision-making.

Conclusion

Given regulatory precedents for the revocation of drug approvals and product withdrawals from the market [56, 125], there is a compelling basis to assert that the SARS-CoV-2 genetic vaccines developed by Pfizer and Moderna, as well as Meiji Seika Pharma's saRNA vaccine approved on a non-inferiority basis, fulfill the conditions warranting such regulatory actions. Accordingly, it is necessary that the MHLW and other relevant authorities promptly consider revoking the approval and initiating the market withdrawal of these pharmaceutical products.

In the United States, over 81,000 physicians, scientists, researchers, and citizens, along with 240 government officials, 17 public health and medical organizations, 2 state Republican organizations, 17 Republican county committees, and 6 scientific studies, have issued statements calling for market withdrawal of genetic vaccines [56, 163]. Furthermore, legislative efforts to prohibit SARS-CoV-2 genetic vaccines are underway in multiple U.S. states, including Florida, South Carolina, Tennessee, Iowa, Texas, Montana, Idaho, Washington, Kentucky, North Dakota, and Minnesota, with bill consideration and drafting beginning at various levels of government. For example, in Montana, legislation prohibiting genetic vaccine administration to humans was introduced in the state legislature in January 2025 [164, 165]. Given these developments, the movement for market withdrawal and revocation of approval of genetic vaccines is no longer confined to a single country but is becoming an international trend. Considering the lack of transparency and inadequate information disclosure identified in the approval review process and post-marketing surveillance of genetic vaccines, continuing administration of genetic vaccines with serious safety concerns poses profound problems from scientific and ethical perspectives and constitutes an infringement upon individual autonomy and human rights.

The risks and adverse events associated with SARS-CoV-2 genetic vaccines far exceed initially anticipated efficacy and adverse drug reactions, warranting immediate market withdrawal. Latest analyses based on real-world data demonstrate serious safety concerns regarding genetic vaccines (notable excess mortality, decreased efficacy and negative effects, increased autoimmune disease risk, DNA contamination and potential carcinogenic risk, risks substantially exceeding FDA recall criteria) [166, 167], making reassessment of vaccination policy and implementation of independent investigations essential. Based on the accumulated evidence to date, the continued administration of SARS-CoV-2 genetic vaccines poses significant public health concerns. Therefore, the revocation of their regulatory approval and immediate market withdrawal should be seriously considered by relevant authorities.

	Statute and article number	Description	Relevance to vaccine regulation, approval, or withdrawal procedures under Japanese law
1	Article 14 of PMD Act	Defines the statutory framework governing marketing authorization for pharmaceutical products. According to this provision, the MHLW may approve the manufacture and sale of a drug only if it meets rigorous standards of quality, efficacy, and safety, and aligns with the nation's public health objectives. Article 14 serves as the foundational legal framework for Japan's drug approval system and includes multiple sub-paragraphs addressing various aspects such as: Paragraph (1): General approval requirements. Paragraph (15): Procedures for partial change approval of an already authorized product.	This article plays a central role in the regulation of vaccines, including mRNA-LNP formulations, and determines the legal threshold for their entry into the Japanese pharmaceutical market. It is also the statutory basis from which special approval mechanisms and post-approval modifications are derived.
2	Article 14, paragraph 15 of PMD Act	This provision establishes the legal framework for partial change approval (Ichi-bu Henkō Shōnin). This allows pharmaceutical manufacturers (MAHs) to implement specific changes to already approved drugs without having to submit a new approval application. This provision applies to changes such as: Change in active ingredients (e.g., changing the sequence of the spike protein to match a new virus strain). Changes in dosage form, route of administration, or manufacturing process. Updates to indications or target populations.	While this mechanism facilitates agile responses to emerging public health needs—such as adapting vaccines to new variants—it does not require full-scale clinical trials, provided that the change is deemed minor or supported by existing data. This regulatory flexibility, however, may raise concerns when applied to genetic vaccines, particularly if the modified product significantly differs in antigenic structure or mechanism of action from the original formulation. In the context of mRNA-based COVID-19 vaccines, this clause has been used to authorize updated formulations (e.g., targeting JN.1 or Omicron subvariants) without new clinical trials in Japan, relying instead on extrapolated data from previous versions.
3	Article 14-2-2 of PMD Act	This provision authorizes conditional and time-limited approval of pharmaceutical products in response to pressing public health emergencies, such as pandemics, in cases where full evidentiary requirements for conventional approval have not been completely fulfilled. Specifically, this provision enables regulatory authorities to grant marketing authorization based on limited clinical or non-clinical data, provided that: There is a clear medical necessity for the product. No alternative treatment or prevention method is available. The product is reasonably presumed to be effective and safe based on available scientific evidence. The sponsor commits to conducting post-marketing studies to confirm safety and efficacy.	This regulatory mechanism is analogous to the Emergency Use Authorization (EUA) in the United States or Conditional Marketing Authorization (CMA) in the European Union. In Japan, several COVID-19 genetic vaccines were granted special approval under this clause, despite the absence of comprehensive long-term safety data.

Table 1. Summary of Cited Statutory Provisions. This table provides an overview of the key statutory provisions under the Pharmaceutical and Medical Device Act (PMD Act) regarding the regulation, approval, conditional approval, and potential suspension of sales of pharmaceuticals (including mRNA-LNP genetic vaccines). Each provision is concisely explained, and specific applications to Japan's regulatory response during the COVID-19 pandemic are also noted. The provisions highlighted in this table comprehensively establish the legal framework for marketing approval (Article 14), emergency use approval (Article 14-3), drug surveillance and adverse reaction reporting (Article 68-10), emergency order (Article 69-3), and revocation of product approval (Articles 74-2 and 75-3). Article 14-3(1) served as the legal basis for the rapid approval in Japan of foreign-developed genetic vaccines based on special approval (emergency use). This table also clearly outlines the methods by which the Japanese government can legally intervene (suspend or revoke approval) in cases where post-marketing safety concerns arise, as well as the legal obligations of manufacturers to report such risks and respond appropriately. Table continues onto the next page.

4	Article 14-3 of PMD Act	This provision constitutes the statutory basis for Japan's Special Approval for Emergency Use (Tokurei Shōnin), which allows unapproved medical products to be conditionally authorized under specific emergency circumstances, provided that the following criteria are satisfied: A public health emergency exists that poses a serious risk to human life or health (e.g., pandemic or bioterrorism event). There are no adequate alternative products legally approved in Japan. The product in question has been approved for use in a country with a regulatory system equivalent to Japan's, such as the United States or the European Union.	This special approval mechanism bypasses the standard domestic clinical trial requirements, enabling expedited access to foreign-approved medical products. It was the primary legal foundation for the approval and distribution of mRNA-based COVID-19 vaccines in Japan beginning in 2021. However, because this pathway permits market entry without the full non-clinical and clinical review normally required under Japanese law, it places heightened importance on post-marketing surveillance, risk communication, and regulatory transparency to ensure patient safety.
5	Article 68-9 of PMD Act	Article 68-9 stipulates that if an MAH becomes aware of serious adverse events or other safety concerns related to an approved product, they are obligated to take necessary actions, including suspension of distribution and reporting to regulatory authorities. Failure to comply with this duty may result in administrative sanctions, including withdrawal of the product's approval.	In the case of vaccines—particularly genetic vaccines such as mRNA-LNP formulations—this article underscores the MAH's post-marketing responsibilities and serves as a statutory basis for regulatory intervention, including the potential initiation of market withdrawal procedures if safety risks are deemed substantial and inadequately managed.
6	Article 68-10 of PMD Act	Obligates MAHs and manufacturers to immediately notify the MHLW of any serious adverse events, infections, or quality defects associated with a pharmaceutical product. This duty extends across all stages of the product lifecycle—from clinical trials to post-marketing surveillance. The provision serves as a cornerstone of Japan's pharmacovigilance framework, enabling regulatory authorities to detect early safety signals, assess risk–benefit balance, and initiate timely regulatory interventions when necessary.	In the context of vaccines—including genetic vaccines such as mRNA-LNP formulations—Article 68-2 ensures that real-world safety data are systematically collected and reviewed, forming the evidentiary basis for actions under Articles 69-3 (suspension) or 74-2 (revocation). Failure to comply with Article 68-2 may result in administrative penalties and undermines the integrity of the post-marketing surveillance system.
7	Article 69-3 of PMD Act	Establishes the statutory authority for the MHLW to temporarily suspend or restrict the sale, or distribution of a pharmaceutical product upon the emergence of serious safety concerns. This allows the MHLW to take preemptive risk management actions—including halting further administration—based on preliminary signals of adverse events or quality issues, without awaiting the outcome of a formal inquiry or revocation procedure.	In the context of vaccine regulation, Article 69-3 functions as a precautionary legal mechanism that allows authorities to act rapidly to protect public health, particularly in cases involving serious adverse events or unexpected safety signals. The provision is especially relevant when post-marketing surveillance data or case reports indicate the need for immediate regulatory intervention, prior to or independent of a full withdrawal process under Article 74-2.
8	Article 74-2 of PMD Act	Article 74-2 empowers the MHLW to revoke or suspend the marketing authorization of a pharmaceutical product if post-marketing evaluations reveal that the product is no longer considered safe or effective, or if it fails to meet the conditions specified at the time of approval. This article serves as a legal basis for regulatory action in cases where new evidence indicates unacceptable risk.	In the context of genetic vaccines such as mRNA-LNP formulations, Article 74-2 serves as the principal statutory mechanism by which the Japanese government may initiate formal procedures for regulatory revocation or market withdrawal to protect public health.
9	Article 75-3 of PMD Act	Empowers MHLW to revoke the special approval of pharmaceutical products—such as those granted under Article 14-3—if any of the following conditions are met: The product no longer meets the original emergency use criteria. The marketing authorization holder fails to comply with obligations imposed under the approval. Such action is deemed necessary to prevent public health risks.	This provision enables the withdrawal of mRNA-based vaccines if the conditions justifying their expedited approval are no longer satisfied or if serious safety concerns arise.

Table 1. concluded.

	General Pharmaceutical Products	Infectious Disease Prevention Vaccines
Toxicology Studies		
Single-dose toxicity studies	In accordance with ICH M3(R2), single-dose toxicity studies evaluate mortality, clinical signs, body weight, autopsy findings, and histopathological changes in rodents and non-rodents over an observation period of at least 14 days. Two or more dose groups including determination of the No Observed Adverse Effect Level (NOAEL) are required, with administration conducted in principle according to the human route of administration.	Although acute toxicity evaluation is necessary, it can typically be assessed based on findings from the initial dose in repeated-dose toxicity studies.
Repeated-dose toxicity studies	The test substance administration duration is determined according to the expected clinical use duration of the substance as a pharmaceutical product (e.g., if expected clinical use duration is "single dose or continuous dosing within 1 week," the toxicity study duration is "1 month"). Administration is conducted 7 days per week as a general rule. At least three dose groups should be established to clearly characterize the test substance toxicity profile, including doses that produce toxic changes and doses that do not produce toxic changes (no-observed-adverse-effect level), with settings designed to demonstrate dose-response relationships. Additionally, a control group not receiving test substance (vehicle control) is established, with untreated control and positive control groups added as necessary.	Typically, administration exceeding the intended number of clinical doses is required. The dose should be equivalent to a single clinical dose as a guideline. However, when administering the same dose as humans is physically difficult, it is necessary to establish a dose (mg/kg or mL/kg) that at least exceeds the human body weight-adjusted dose (mg/kg or mL/kg).
Animal species/model selection	At least 2 species. One species should be selected from rodents and one from non-rodents other than rabbits.	At least one animal species that shows an immune response to the vaccine's active ingredients should be used. Selection of non-human primates is not always necessary.
Gender	Both males and females for at least one species should be examined.	Not specified.
Route of administration	In principle, the clinically intended route of administration should be used.	In principle, the clinically intended route of administration should be used.
General Pharmacology Studies		
Animal species/model selection	Use animal species appropriate for each test, such as mice, rats, guinea pigs, rabbits, cats, and dogs.	At least one animal species that shows an immune response to the vaccine's active ingredients should be used. Selection of non-human primates is not always necessary.
Strain, gender, age	Consider factors such as strain, gender, and age.	Not specified.
Route of administration	Use the clinically intended route of administration or an equivalent route.	In principle, the clinically intended route of administration should be used.
Test methods	A. In principle, all test substances should be evaluated for the following: Effects on general symptoms and behavior Effects on the central nervous system Effects on the autonomic nervous system and smooth muscle Effects on respiratory and circulatory systems Effects on the gastrointestinal system Effects on water and electrolyte metabolism Other important pharmacological effects B. Conduct tests as necessary based on results from A above: Effects on the central nervous system Effects on the somatic nervous system Effects on the autonomic nervous system and smooth muscle Effects on respiratory and circulatory systems Effects on the gastrointestinal system Other effects	Use test methods with sensitivity and specificity appropriate for the study objectives.

Table 2. continues onto the next page.

Evaluation of Immunotoxicity		
Evaluation methods	In accordance with ICH S8, additional immunotoxicity studies are conducted in addition to standard repeated-dose toxicity studies and may include, as appropriate: T-cell-dependent antibody response (TDAR), lymphocyte subset analysis ($CD4^+$, $CD8^+$, B-cell, etc.), NK cell/macrophage activity, complement function, and pathological evaluation of lymphoid tissues. Detailed evaluation is required when immunotoxicity risk is indicated.	Standard immunotoxicity studies and additional immunotoxicity studies are conducted, as necessary. The decision on whether to conduct immunotoxicity studies should be based on evaluating factors to be considered in immunotoxicity assessment according to their importance.
Evaluation of Host Defense against Infection		
Evaluation methods	Not specified.	When an animal model reflecting human infection or disease exists, it is desirable to evaluate protection against infection or disease caused by pathogenic microorganisms targeted by the vaccine.
Safety Pharmacology Studies		
Test methods	*In vivo* studies intended to clarify the dose-response relationship of recognized adverse effects. *In vitro* studies intended to establish concentration-effect relationships. Studies on metabolites, isomers, and the final formulation. Safety pharmacology core battery.	In non-clinical safety evaluation of vaccines, effects on major physiological functions (central nervous system, respiratory system, and cardiovascular system) can usually be evaluated through observations and examinations within toxicity studies. When these evaluations identify safety concerns regarding major physiological functions, conducting independent safety pharmacology studies should be considered.
Pharmacokinetic Studies		
Test methods	Appropriate animal species and in vitro test systems should be used considering correspondence with toxicity, pharmacology, and clinical studies.	Vaccines generally do not require pharmacokinetic studies. However, for vaccines containing expression plasmid DNA as an active ingredient, biodistribution studies should generally be conducted prior to clinical trials. For new live attenuated vaccines, examining excretion is useful for planning clinical shedding studies. When sufficient knowledge has been obtained from animal studies in pharmacological studies using the vaccine, or from human infections with wild-type viruses, it is not necessary to conduct independent shedding studies using the vaccine for this evaluation.
Reproduction Toxicity Studies		
Test methods	There are basically no differences as infectious disease vaccines are included in the scope of the Guidelines for Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (ICH-S5[R3]). Vaccine-specific considerations for animal species selection, dose setting, and study design are provided within this guideline.	
Genotoxicity Studies		
Test methods	The standard combination of tests is as follows: Evaluation of mutagenicity using bacterial reverse mutation tests. Evaluation of *in vitro* and/or *in vivo* genotoxicity in mammalian cells.	Vaccines generally do not require genotoxicity studies.
Carcinogenicity Studies		
Test methods	The basic concept is to conduct one new short- and medium-term *in vivo* rodent test system in addition to a long-term carcinogenicity study using one rodent species.	Vaccines generally do not require carcinogenicity studies.
Local Tolerance Studies		
Test methods	It is desirable to evaluate via the intended clinical route of administration as part of general toxicity studies, and evaluation in independent studies is not recommended.	Local tolerance can sometimes be evaluated by incorporating it into single-dose toxicity studies or repeated-dose toxicity studies; in such cases, independent local tolerance studies are not necessarily required.
Toxicokinetics		
Test methods	Toxicity studies requiring supporting toxicokinetic data include single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, and reproduction toxicity studies, and toxicokinetic studies must be conducted as part of these studies.	Vaccines generally do not require toxicokinetic evaluation.

Table 2. Differences in non-clinical study requirements between general pharmaceutical products and infectious disease

prevention vaccines in Japan. This table summarizes the key differences in non-clinical study requirements between general pharmaceutical products and infectious disease prevention vaccines under Japanese regulatory frameworks. It covers toxicology, pharmacology, immunotoxicity, host defense evaluation, pharmacokinetics, genotoxicity, carcinogenicity, local tolerance, and toxicokinetics. Adapted from Ueda et al. References [9-23].

	Description in the Guidelines for Nonclinical Studies of Preventive Vaccines for Infectious Diseases https://www.pmda.go.jp/files/000269127.pdf	**Guideline Compliance**	**Comirnaty IM Review Report** https://www.pmda.go.jp/drugs/2021/P20210212001/672212000_30300AMX00231_A100_6.pdf
Toxicology Studies			
Single-dose toxicity studies	Although acute toxicity evaluation is necessary, it can typically be assessed based on findings from the initial dose in repeated-dose toxicity studies.	Yes	Evaluated based on results after the first dose in repeat intramuscular administration toxicity studies in rats.
Repeated-dose toxicity studies	Typically, administration exceeding the intended number of clinical doses is required. The dose should be equivalent to a single clinical dose as a guideline. However, when administering the same dose as humans is physically difficult, it is necessary to establish a dose (mg/kg or mL/kg) that at least exceeds the human body weight-adjusted dose (mg/kg or mL/kg).	Yes	Duration of Administration: 2 weeks (once/week for a total of 3 doses) + 3-week recovery Dose (μg RNA/body): 0, 100 0, 30
Animal species/model selection	At least one animal species that shows an immune response to the vaccine's active ingredients should be used. Selection of non-human primates is not always necessary.	Yes	Rats
Gender	Not specified.	Yes	Male and Female
Route of administration	In principle, the clinically intended route of administration should be used.	Yes	Intramuscular
Pharmacology Studies			
Animal species/model selection	At least one animal species that shows an immune response to the vaccine's active ingredients should be used. Selection of non-human primates is not always necessary.	Yes	BALB/c mice
Strain, gender, age	Not specified.	Yes	8 females/group
Route of administration	In principle, the clinically intended route of administration should be used.	Yes	Intramuscular
Test methods	Use test methods with sensitivity and specificity appropriate for the study objectives.	Yes	The following immune responses were evaluated: Examination of specific IgG antibodies against S protein S1 and RBD Examination of neutralizing antibodies using pseudovirus Examination of IgG subtypes Examination of cytokine production in spleen cells

Table 3. Assessment of Comirnaty's compliance with Japanese non-clinical study guidelines. Although Pfizer's Comirnaty cleared all test items required by the Guidelines for Nonclinical Studies of Preventive Vaccines for Infectious Diseases, there was a problem with the lower standards of this guideline compared to general pharmaceutical product review criteria. Carcinogenicity and genotoxicity studies were not conducted because they are not required by Japanese regulatory authorities. *Table continues onto the next page.*

Evaluation of immunogenicity			
Evaluation methods	Studies to evaluate vaccine immunogenicity include assessment of antibody production levels expected to be highly relevant to infection prevention or disease prevention, the class and subclass of antibodies produced, cellular immunity, and cytokine production that affects the immune system.	Yes	The following immune responses were evaluated: Examination of specific IgG antibodies against S protein S1 and RBD Examination of neutralizing antibodies using pseudovirus Examination of IgG subtypes Examination of cytokine production in spleen cells
Evaluation of Host Defense against Infection			
Evaluation methods	When an animal model reflecting human infection/disease exists, it is desirable to evaluate protection against infection or disease caused by pathogenic microorganisms targeted by the vaccine.	Yes	Immune responses and infection protection/disease prevention effects after SARS-CoV-2 exposure were evaluated when rhesus macaques (6 males/group) received two intramuscular administrations of the formulation at 21-day intervals.
Safety Pharmacology Studies			
Test methods	In non-clinical safety evaluation of vaccines, effects on major physiological functions (central nervous system, respiratory system, and cardiovascular system) can usually be evaluated through observations and examinations within toxicity studies. When these evaluations identify safety concerns regarding major physiological functions, conducting independent safety pharmacology studies should be considered.	Yes	Evaluated based on general condition observations in repeated intramuscular administration toxicity studies in rats.
Pharmacokinetic Studies			
Test methods	Vaccines generally do not require pharmacokinetic studies. However, for vaccines containing expression plasmid DNA as an active ingredient, biodistribution studies should generally be conducted prior to clinical trials. For new live attenuated vaccines, examining excretion is useful for planning clinical shedding studies. When sufficient knowledge has been obtained from animal studies in pharmacological studies using the vaccine, or from human infections with wild-type viruses, it is not necessary to conduct independent shedding studies using the vaccine for this evaluation.	Yes	Non-clinical pharmacokinetic studies were not conducted.
Reproduction Toxicity Studies			
Test animal species	Animal species used in non-clinical testing of vaccines must show immune responses to the vaccine (regardless of adjuvant presence). The appropriateness of the type of reproduction toxicity studies to be conducted and animal species selection should be demonstrated based on observed immune responses and the feasibility of administering appropriate doses. Rabbits, rats, and mice are commonly used in reproduction toxicity studies of vaccines. Although qualitative and quantitative species differences may exist in immune responses (such as humoral and cellular immunity), conducting reproduction toxicity studies using one animal species is usually sufficient.	Yes	Rats
Dose selection	It is sufficient to evaluate with a single dose capable of inducing an immune response in animals. This dose should be the maximum human dose without body weight conversion (i.e., single human dose = single animal dose).	Yes	0 μg RNA/body 30 μg RNA/body
Route of administration	Clinical route of administration.	Yes	Intramuscular
Genotoxicity Studies			
	Vaccines generally do not require genotoxicity studies.	Yes	Since the mRNA contained in this formulation is composed of naturally occurring nucleic acids and new excipients have no genotoxicity concerns, genotoxicity studies using this formulation were not conducted.
Carcinogenicity Studies			
	Vaccines generally do not require carcinogenicity studies.	Yes	Since this formulation is not a pharmaceutical product with clinical use continuing for 6 months or longer, carcinogenicity studies using this formulation were not conducted.
Local Tolerance Studies			
	Local tolerance can sometimes be evaluated by incorporating it into single-dose toxicity studies or repeated-dose toxicity studies; in such cases, independent local tolerance studies are not necessarily required.	Yes	Evaluated based on results of repeated intramuscular administration toxicity studies in rats.
Toxicokinetics			
	Vaccines generally do not require toxicokinetic evaluation.	Yes	Not conducted.

Table 3. concluded.

	Gene Therapy Drugs	Infectious Disease Prevention Vaccines
Pharmacokinetics		
Biodistribution	Required	Not required
Target organ identification	Required	Not required
Toxicity associated with protein expression	Required	Not required
Genotoxicity		
Insertional mutagenesis	Required	Not required
Tumor formation	Required	Not required
Embryo/fetal toxicity	Required	Not required
Shedding Studies		
Semen/breast milk excretion	Required	Not required
Transmission to third parties	Required	Not required
Clinical Trials		
Development of autoimmune/hematologic diseases	Required	Not required
Development of new infections/cancer	Required	Not required
Observation period (follow-up period)	30 years (EMA: European Medicines Agency), ≥5 years (FDA: Food and Drug Administration) Appropriate periods should be established based on vector type, disease characteristics, etc. For integrating chromosome vectors, persistence of the target gene and, when feasible, clonality of gene-transduced cells should be evaluated, both with observations conducted at least once annually. Consider that follow-up study results may require extending the observation period.	42 days for mRNA-LNP formulations (FDA). For inactivated vaccines, approximately 2 weeks post-vaccination; for live vaccines, approximately 4 weeks post-vaccination. However, depending on vaccine characteristics, it may be necessary to establish appropriate periods of 2 weeks to 4 weeks or longer, such as conducting 1-year follow-up studies post-vaccination for vaccines with novel modalities or novel antigens.

Table 4. Comparison of test items for gene therapy drugs and vaccines. This table provides a regulatory comparison between gene therapy drugs and vaccines in terms of required preclinical and clinical test items. Notably, gene therapy products are subject to rigorous evaluations—including biodistribution, genotoxicity, shedding, and long-term follow-up—due to concerns such as insertional mutagenesis, tumorigenesis, and persistent vector expression. In contrast, infectious disease prevention vaccines, including mRNA-LNP formulations, are generally exempt from such assessments, with substantially shorter post-vaccination observation periods. This discrepancy underscores a critical regulatory gap, particularly in the context of nucleic acid–based vaccines with gene-delivery characteristics.

Age Group	Unvaccinated Case Fatality Rate	1 Dose Case Fatality Rate	2 Doses Case Fatality Rate
90 years and older	8.45% (18/213)	3.39% (2/59)	1.03% (1/97)
80–89 years	5.42% (39/719)	5.53% (12/217)	2.03% (6/296)
70–79 years	1.68% (23/1,366)	2.04% (11/538)	1.03% (4/387)
65–69 years	1.31% (13/991)	0.60% (2/334)	0.49% (1/203)
60–64 years	0.32% (10/3,098)	0% (0/715)	0.85% (1/117)
55–59 years	0.16% (9/5,728)	0.13% (1/787)	0% (0/117)
50–54 years	0.18% (15/8,257)	0% (0/806)	0% (0/146)
45–49 years	0.083% (8/9,588)	0.14% (1/726)	0% (0/132)
40–44 years	0.030% (3/9,847)	0.18% (1/568)	0% (0/127)
30–39 years	0.018% (4/22,764)	0.09% (1/1,063)	0% (0/244)
19–29 years	0.002% (1/41,375)	0% (0/1,605)	0% (0/352)
18 years and younger	0% (0/16,394)	0% (0/101)	0% (0/11)
All Age Group	0.12% (143/120,340)	0.41% (31/7,519)	0.58% (13/2,229)
65 years and older	2.83% (93/3,289)	2.35% (27/1,148)	1.22% (12/983)
Under 65 years old	0.04% (50/117,051)	0.06% (4/6,371)	0.08% (1/1,246)

*Table 5. COVID-19 Positive Patients: Number of Vaccine Doses and Case Fatality Rates (July 2021). Reprinted from reference [46]. Notes: These are survey results for a specific period, and it should be noted that the number of deaths is low, especially among those under 65 years of age. Due to significant differences in the number of infected persons by age group, it is preferable to compare each age group rather than all ages. *HER-SYS data totals: Deaths were counted as of August 31, 2021. Please note that the death reporting rate is approximately 70%.*

Age Group	Unvaccinated	2 Doses Only (excluding 3rd dose recipients)	3 Doses Completed	Vaccination Status Unknown
	New Cases (July 1 – July 17, 2022) / Unvaccinated Population (July 17, 2022) (New Cases per 100,000 Population)	New Cases (July 1 – July 17, 2022) / 2 Dose Vaccinated Population (July 17, 2022) (New Cases per 100,000 Population)	New Cases (July 1 – July 17, 2022) / 3 Dose Vaccinated Population (July 17, 2022) (New Cases per 100,000 Population)	New Cases (July 1 – July 17, 2022)
0–11 years	83,304 / 10,702,008 (778.4)			
12–19 years	19,220 / 2,177,023 (882.9)	30,075 / 3,846,574 (794.9)	11,699 / 2,917,567 (401.0)	19,190
20–29 years	15,855 / 2,403,781 (659.6)	31,268 / 4,306,981 (726.0)	31,015 / 6,012,155 (515.9)	19,497
30–39 years	13,648 / 2,811,723 (485.4)	26,493 / 4,202,769 (630.4)	33,461 / 7,281,233 (459.6)	20,447
40–49 years	9,882 / 3,141,838 (314.5)	22,562 / 4,249,005 (531.0)	41,775 / 10,965,616 (381.0)	19,536
50–59 years	5,479 / 1,251,177 (437.9)	10,391 / 2,591,318 (401.0)	35,955 / 12,922,885 (278.2)	12,128
60–64 years	1,262 / 616,652 (204.7)	1,988 / 604,356 (328.9)	13,225 / 6,177,151 (214.1)	3,754
65–69 years	687 / 1,033,539 (66.5)	953 / 363,017 (262.5)	10,665 / 6,687,911 (159.5)	3,109
70–79 years	1,179 / 865,189 (136.3)	1,342 / 595,475 (225.4)	17,222 / 14,734,058 (116.9)	4,954
80–89 years	626 / 51,335 (1219.4)	812 / 413,436 (196.4)	8,732 / 8,562,739 (102.0)	3,081
90 years and older	277 / - (-)	310 / 141,847 (218.5)	3,291 / 2,249,696 (146.3)	1,467

Table 6. Number of New COVID-19 Positive Cases by Vaccination Status (July 1–17, 2022). Notes: New positive cases registered in HER-SYS are categorized based on vaccination history (including unknown status) and reported, with the total number of new positive cases over the past 7 days calculated as of the reporting date. For cases where vaccination history is not recorded, those reported in ADB data submitted up to April 20, 2022, were classified as unvaccinated, while those reported in ADB data submitted on or after May 11, 2022, are classified as vaccination history unknown. Individuals without age information in HER-SYS are excluded. Additionally, individuals reported as being older than the oldest person in Japan (as of July 19, 2022) are excluded from all categories. New positive cases include asymptomatic infections. The number of new positive cases per 100,000 people is calculated by dividing the total number of new positive cases over a 7-day period by the population of 100,000, based on whether or not vaccination was administered on the final day of the period (July 17). Caution is required when interpreting the results. The number of vaccinated individuals is calculated based on reported data from the Vaccine Administration Record System (VRS). (Data as of July 19. Data is updated daily, so there may be a time lag between vaccination and recording, and the latest data will be reflected in the future.) The number of unvaccinated individuals is calculated by subtracting the number of vaccinated individuals from the total population of each age group. In addition, the age group population is based on data published on the Prime Minister's Office website (using the "Population by Age Group in the Basic Resident Register for the Year 2021 (by municipality)" published by the Ministry of Internal Affairs and Communications, which aggregates the gender and age group figures for each municipality). If the number of vaccinated individuals exceeds the age-specific population, the number of unvaccinated individuals and the number of new positive cases per 100,000 people are indicated as "-". Due to a change in the reporting format on June 30, 2022, data from July 1, 2022, onwards is based on HER-SYS data using the revised reporting format. This data simply aggregates the number of new positive cases reported during the specified period and does not consider the time interval between vaccination and testing, nor does it account for potential background factors such as prior COVID-19 infection history. Therefore, this data does not clearly demonstrate the preventive efficacy of vaccination. Note that decisions regarding vaccination are based on academic papers analyzing efficacy, following discussions at the Ministry of Health, Labour and Welfare's Expert Panel on Vaccination, and are not determined based on this data.

Researcher	Affiliation, Country	Pharma Company	# of Vials	First reported	Methods	DNA/dose (limit 10 ng)	DNA/RNA ratio (limit 1/3030)	Concerns	Source (Publication etc.)
McKernan K., *et al.*	Medicinal Genomics, US	Pfizer, Moderna	12	2023 Feb-23	Electrophoresis (Agilent)	2,250 ng – 3,390 ng *	1/8 – 1/2	Adverse Events, Gene Integration	Preprint [146] Reported to and presented at FDA Presented at the World Council for Health ※Found gene integration in OvCar3 cancer cells transfected by Kämmerer ※Found SV40 enhancer in tumors of vaccinated (※reported in Substack)
					Fluorometer (Qubit)	312 ng – 843 ng *	1/47 – 1/8		
					qPCR/RT-qPCR	12 ng	1/161 – 1/43		
		Pfizer, Moderna, Daiichi-Sankyo (Japan)	5	2023 Nov-23	Fluorometer (Qubit)	17.5 ng – 61.8 ng (after Tritton-X/RNase A)			
					qPCR	88.8 ng (Pfizer)			
Buckhaults P.J.	USC, US	Pfizer, Moderna	Some	2023 Jul-23	qPCR	0.6 ng – 18.7 ng		Adverse Events, Gene Integration	Presented in South Carolina Senate [148] ※Presented gene integration to normal human epithelial stem cells
		Pfizer 2020, Pfizer 2023, Moderna 2020, Moderna 2023	4	2024 Apr-24	qPCR	7.7 ng (SV40e, Pfizer) 4.5 – 5.5 ng (Neo/Kan, Pfizer) 1.5 – 9.0 ng (ORI, Pfizer) 2.5 – 18.7 ng (Spike, Pfizer) 0.002 – 0.004 ng (ORI, Moderna 2023)			
König B., Kirchner J.O.	Magdeburg Molecular Detections, Germany Indep., Germany	Pfizer, Moderna	7	2023 Sep-23	Fluorometer (Qubit)	3,600 ng – 5,340 ng	1/12 – 1/7	Adverse Events, Gene Integration	Reported to the German Ministry of Health Published in Methods Protocol [147]
Speicher D.J., McKernan K., *et al.*	University of Guelph, Canada Medicinal Genomics, US	Pfizer, Moderna	27	2023 Oct-23	Fluorometer (Qubit)	1,896 ng – 5,100 ng		Adverse Events, Gene Integration	Preprint [145] Presented at the World Council for Health
					qPCR	0.22 ng – 2.43 ng (Spike) 0.01 ng – 4.27 ng (ORI)			
Speicher D.J.	University of Guelph, Canada	Pfizer, Moderna (Australia)	3	2024 Jun-2	Fluorometer (Qubit)	451 ng – 1,420 ng (after RNase A/DNase I)		Adverse Events, Gene Integration	Reported to Therapeutic Goods Administration (TGA, Australia) Under litigation
					qPCR	6.46 ng – 163.68 ng (Spike) 0.54 ng – 12.97 ng (ORI) 3.70 ng – 14.69 ng (SV40e, Pfizer)			
Raoult D.	Aix-Marseille Univ (Former Prof), France	Pfizer	Some	2024 Nov-24	Fluorometer (Qubit)	216 ng (Avg) 5,160 ng (Avg, after Triton-X-100)		Gene Integration	Preprint [143]
Kämmerer U., *et al.*	Univ. Hospital of Würzburg, Germany	Pfizer	4	2024 Dec-24	Fluorometer (Qubit)	2,712 – 3,683 ng (after Triton-X-100) 32.71 – 42.09 ng (after Triton-X-100/RNase A)		Adverse Events, Gene Integration	Published in Science, public health policy and the law [142]
Wang T.J., Kim A., Kim K.	Centreville High School	Pfizer	6	2024 Dec-24	Fluorometer (Qubit)	41.4 – 109.5 ng (extracted by Monarch Plasmid DNA Miniprep, which includes RNase A)		Gene Integration	Published in Journal of High School Science [144], Technically supported by the FDA researchers

Table 7. Verification of DNA contamination in mRNA-LNP-based vaccine vials worldwide (as of March 24, 2025). This table compiles independent findings by researchers from multiple countries who reported residual DNA contamination in mRNA-

*LNP vaccine vials (Pfizer, Moderna, Daiichi-Sankyo) using various analytical methods. DNA quantities per dose and DNA/RNA ratios are compared against internationally referenced thresholds (10 ng/dose; 1/3030), alongside reported safety concerns such as adverse events and potential genomic integration. Updated from Gibo et al [95]. *Multiplied the value by 300 for µL.*

Acknowledgments

We would like to express our sincere gratitude to Drs. Akinori Fujisawa, Masayasu Inoue, Masato Yoshino, and Yasufumi Murakami for their invaluable guidance and support. We are also grateful to Mr. Masamitsu Fujie for sharing data on the number of individuals certified under the Japan's Vaccine Adverse Reaction Relief System, and to Dr. Kenji Fujikawa for providing data on DNA contamination in vaccine vials.

Author Contributions: Conceptualization, J.U. and M.F.; investigation, J.U., M.G., T.K., M.M., A.K., I.S., and M.F.; resources, T.K., Y.H., and M.F.; data curation, J.U., M.G., T.K., and M.F.; writing—original draft preparation, J.U.; writing—review and editing, J.U., M.G., T.K., Y.H., M.M., A.K., I.S., S.K., and M.F.; visualization, J.U., M.G., T.K. M.M., and A.K.; supervision, J.U. and M.F.; project administration, J.U. and M.F. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest: The authors declare no potential conflicts of interest.

Funding Statement: This study did not receive any funding.

Ethics: Since only published data were used, it was determined that ethics committee approval was not required in Japan.

Data Availability: This study utilizes only officially published data available from websites.

References

1. Ministry of Health Labour and Welfare [Special Approval of Novel Coronavirus Vaccine]; Tokyo(JP): MHLW: 2021/12/16 2021/11/11, 2021. https://www.mhlw.go.jp/stf/newpage_22126.html

2. Francis, A. I.; Ghany, S.; Gilkes, T.; Umakanthan, S., Review of COVID-19 vaccine subtypes, efficacy and geographical distributions. Postgraduate Medical Journal 2022, 98, (1159), 389-94.

3. Patel, R.; Kaki, M.; Potluri, V. S.; Kahar, P.; Khanna, D., A comprehensive review of SARS-CoV-2 vaccines: Pfizer, Moderna & Johnson & Johnson. Human Vaccines & Immunotherapeutics 2022, 18, (1).

4. Japan Broadcasting Corporation (NHK) [Vaccination status in Japan]. https://www3.nhk.or.jp/news/special/coronavirus/vaccine/ Access Date (2025-03-23).

5. Committee on Oversight of Pharmaceuticals and Medical Devices Safety Regulation Ministry of Health, L. a. W., ; [Opinions on Safety Evaluation of the Novel Coronavirus Vaccine]; Tokyo(JP): MHLW: 2021-12-24, 2021.

6. Ministry of Health Labour and Welfare [The Health and Science Council [Subcommittee on Immunization and Vaccines, Adverse Reaction Review Committee], Ministry of Health, Labour and Welfare]; Tokyo(JP): MHLW: 2013-05-16.

7. Prime Minister's Office of Japan [Press Conference by Prime Minister Yoshihide Suga (June 17, 2021)]. https://www.kantei.go.jp/jp/99_suga/statement/2021/0617kaiken.html Access Date (2025-03-24).

8. Cabinet Secretariat; Ministry of Health, L. a. W., ;, [Interim Report on COVID-19 Vaccination Policy (September 25, 2020)]. In 2020.

9. Director of Pharmaceutical Evaluation Division Pharmaceutical Safety Bureau Ministry of Health Labour and Welfare [Guidelines for nonclinical study of vaccines to prevent infections PSB/PED Notification No. 0327-1]; Tokyo(JP): MHLW: 2024-03-27, 2024.

10. Welfare, D. o. N. D. D. P. A. B. M. o. H. a.; Director of Examination Division Pharmaceutical Affairs Bureau Ministry of Health and Welfare [Revision of "Guidelines for Single and Repeated Dose Toxicity Studies" PAB/NDD No. 88]; Tokyo(JP): MHLW: 1993-08-10, 1993.

11. Director of Evaluation and Licensing Division Pharmaceutical and Food Safety Bureau Ministry of Health Labour and Welfare [Guideline on Safety Pharmacology Studies for Human Pharmaceuticals PMSB/ELD Notification No. 902]; Tokyo(JP): MHLW: 2001-06-21, 2001.

12. Director of New Drugs Division Pharmaceutical Affairs Bureau Ministry of Health and Welfare [Guidelines for General Pharmacology Studies Necessary for Application for Manufacturing (Import) Approval of New Drugs, etc. PAB/NDD No. 4]; Tokyo(JP): MHLW: 1991-01-29, 1991.

13. Director of Evaluation and Licensing Division Pharmaceutical and Food Safety Bureau Ministry of Health Labour and Welfare [Guidelines for Immunotoxicity Studies of Drugs PFSB/ELD Notification No. 0418001]; Tokyo(JP): MHLW: 2006-04-18, 2006.

14. Director of Evaluation and Licensing Division Pharmaceutical and Medical Safety Bureau Ministry of Health and Welfare [Guidelines for Nonclinical Pharmacokinetic Studies PMSB/ELD No. 496]; Tokyo(JP): MHLW: 1998-06-26, 1998.

15. Director of Pharmaceutical Safety and Environmental Health Bureau Ministry of Health Labour and Welfare [Guideline for Evaluation of Reproductive and Developmental Toxicity of Drugs PSEHB/PED Notification No. 0129-8]; Tokyo(JP): MHLW: 2021-01-29, 2021.

16. Director of Evaluation and Licensing Division Pharmaceutical and Food Safety Bureau Ministry of Health Labour and Welfare [Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use PFSB/ELD Notification No. 0920-2]; Tokyo(JP): MHLW: 2012-09-20, 2012.

17. Director of Pharmaceutical Evaluation Division Pharmaceutical Safety and Environmental Health Bureau, M. o. H. L. a. W., ; [Revision of "Guidelines for Carcinogenicity Studies of Drugs" PSEHB/PED Notification No. 0310-1]; Tokyo(JP): MHLW: 2023-03-10, 2023.

18. Director of Evaluation and Licensing Division Pharmaceutical and Food Safety Bureau Ministry of Health Labour and Welfare [Guidance on the Conduct of Nonclinical Safety Studies for Clinical Trials and Application for Marketing Approval for Pharmaceuticals PFSB/ELD Notification No. 0219-4]; Tokyo(JP): MHLW: 2010-02-19, 2010.

19. Director of Examination Division Pharmaceutical Affairs Bureau Ministry of Health and Welfare [Guidance on Toxicokinetics (Evaluation of Systemic Exposure in Toxicity Studies) PAB/ED Notification No. 443]; Tokyo(JP): MHLW: 1996-07-02, 1996.

20. European Medicines Agency, ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. In 2009.

21. European Medicines Agency, ICH Topic S 8 Immunotoxicity Studies for Human Pharmaceuticals. 2006.

22. European Medicines Agency, ICH Topic S 4 Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing). In 1999.

23. European Medicines Agency, ICH-S5 Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals S5(R3). In 2020.

24. Oldfield, P. R. G., L. Maria; McCullough, Peter A.; Speicher, David J. , Pfizer/BioNTech?s COVID-19 modRNA Vaccines: Dangerous Genetic Mechanism of Action Released before Sufficient Preclinical Testing. Journal of American Physicians and Surgeons 2024, 29, (4).

25. Director of Medical Device Evaluation Division Pharmaceutical Safety and Environmental Health Bureau Ministry of Health Labour and Welfare Ensuring the Quality and Safety of Gene Therapy Products PSEHB/MDED Notification No. 0709-2; Tokyo(JP): MHLW: 2019-07-09, 2019.

26. Director of Pharmaceutical Evaluation Division Pharmaceutical Safety Bureau Ministry of Health Labour and Welfare [Guidelines for clinical study of vaccines to prevent infections PSB/PED Notification No. 0327-4]; Tokyo(JP): MHLW: 2024-03-27, 2024.

27. Pharmaceutical Evaluation Division Pharmaceutical Safety Bureau Ministry of Health Labour and Welfare [Results of the Regulatory Review of the Monovalent (Omicron XBB. 1.5) Novel Coronavirus Vaccine (e.g., Cominati RTU Intramuscular Injection)]; Tokyo(JP): MHLW: 2023-08-31, 2023.

28. Parry, P. I.; Lefringhausen, A.; Turni, C.; Neil, C. J.; Cosford, R.; Hudson, N. J.; Gillespie, J., ?Spikeopathy?: COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA. Biomedicines 2023, 11, (8).

29. Luo, J.; Molbay, M.; Chen, Y.; Horvath, I.; Kadletz, K.; Kick, B.; Zhao, S.; Al-Maskari, R.; Singh, I.; Ali, M.; Bhatia, H. S.; Minde, D. P.; Negwer, M.; Hoeher, L.; Calandra, G. M.; Groschup, B.; Su, J.; Kimna, C.; Rong, Z.; Galensowske, N.; Todorov, M. I.; Jeridi, D.; Ohn, T. L.; Roth, S.; Simats, A.; Singh, V.; Khalin, I.; Pan, C.; Arus, B. A.; Bruns, O. T.; Zeidler, R.; Liesz, A.; Protzer, U.; Plesnila, N.; Ussar, S.; Hellal, F.; Paetzold, J.; Elsner, M.; Dietz, H.; Erturk, A., Nanocarrier imaging at single-cell resolution across entire mouse bodies with deep learning. Nat Biotechnol 2025.

30. Chen, J.-C.; Hsu, M.-H.; Kuo, R.-L.; Wang, L.-T.; Kuo, M.-L.; Tseng, L.-Y.; Chang, H.-L.; Chiu, C.-H., mRNA-1273 is placenta-permeable and immunogenic in the fetus. Molecular Therapy Nucleic Acids 2025.

31. Kent, S. J.; Li, S.; Amarasena, T. H.; Reynaldi, A.; Lee, W. S.; Leeming, M. G.; O'Connor, D. H.; Nguyen, J.; Kent, H. E.; Caruso, F.; Juno, J. A.; Wheatley, A. K.; Davenport, M. P.; Ju, Y., Blood Distribution of SARS-CoV-2 Lipid Nanoparticle mRNA Vaccine in Humans. ACS Nano 2024.

32. Malfitano, N., Dr. Robert Redfield on COVID vaccine mandate 'mistakes': 'They don't prevent infection'. The Sconi Jul 23, 2024. https://thesconi.com/stories/661844844-dr-robert-redfield-on-covid-vaccine-mandate-mistakes-they-don-t-prevent-infection Access Date (2025-04-22).

33. Ndeupen, S.; Qin, Z.; Jacobsen, S.; Bouteau, A.; Estanbouli, H.; Igyártó, B.Z, The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory. iScience 2021, 24, (12).

34. Ju, Y.; Lee, W. S.; Pilkington, E. H.; Kelly, H. G.; Li, S.; Selva, K. J.; Wragg, K. M.; Subbarao, K.; Nguyen, T. H. O.; Rowntree, L. C.; Allen, L. F.; Bond, K.; Williamson, D. A.; Truong, N. P.; Plebanski, M.; Kedzierska, K.; Mahanty, S.; Chung, A. W.; Caruso, F.; Wheatley, A. K.; Juno, J. A.; Kent, S. J., Anti-PEG Antibodies Boosted in Humans by SARS-CoV-2 Lipid Nanoparticle mRNA Vaccine. ACS Nano 2022, 16, (8), 11769-80.

35. Japan Red Cross Society [People who have been vaccinated within a certain period of time]. https://www.jrc.or.jp/donation/about/refrain/detail_08 Access Date (2024-12-12).

36. Pfizer, 5.3.6 CUMULATIVE ANALYSIS OF POST-AUTHORIZATION ADVERSE EVENT REPORTS OF PF-07302048 (BNT162B2) RECEIVED THROUGH 28-FEB-2021. In 2021.

37. Konishi, N.; Hirai, Y.; Hikota, H.; Miyahara, S.; Fujisawa, A.; Motohashi, H.; Ueda, J.; Inoue, M.; Fukushima, M., Quantifying side effects of COVID-19 vaccines: A PubMed survey of papers on diseases as side effects presented at academic conferences in Japan. Rinsho Hyoka (Clinical Evaluation) 2024, 51, (3).

38. Faksova, K.; Walsh, D.; Jiang, Y.; Griffin, J.; Phillips, A.; Gentile, A.; Kwong, J. C.; Macartney, K.; Naus, M.; Grange, Z.; Escolano, S.; Sepulveda, G.; Shetty, A.; Pillsbury, A.; Sullivan, C.; Naveed, Z.; Janjua, N. Z.; Giglio, N.; Perala, J.; Nasreen, S.; Gidding, H.; Hovi, P.; Vo, T.; Cui, F.; Deng, L.; Cullen, L.; Artama, M.; Lu, H.; Clothier, H. J.; Batty, K.; Paynter, J.; Petousis-Harris, H.; Buttery, J.; Black, S.; Hviid, A., COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals. Vaccine 2024, 42, (9), 2200-11.

39. Kim, H. J.; Suh, J. H.; Kim, M. H.; Choi, M. G.; Chun, E. M., Broad-Spectrum Adverse Events of Special Interests Based on Immune Response Following COVID-19 Vaccination: A Large-Scale Population-Based Cohort Study. J Clin Med 2025, 14, (5).

40. Bozkurt, B.; Kamat, I.; Hotez, P. J., Myocarditis With COVID-19 mRNA Vaccines. Circulation 2021, 144, (6), 471-84.

41. Mead, M. N.; Rose, J.; Makis, W.; Milhoan, K.; Hulscher, N.; McCullough, P. A., Myocarditis after SARS-CoV-2 infection and COVID-19 vaccination: Epidemiology, outcomes, and new perspectives. International Journal of Cardiovascular Research & Innovation 2025, volume_3, (issue_1).

42. Karimi, R.; Norozirad, M.; Esmaeili, F.; Mansourian, M.; Marateb, H. R., COVID-19 Vaccination and Cardiovascular Events: A Systematic Review and Bayesian Multivariate Meta-Analysis of Preventive Benefits and Risks. Int J Prev Med 2025, 16, 14.

43. Director of Safety Division Pharmaceutical and Food Safety Bureau Ministry of Health Labour and Welfare [Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2D) PFSB/SD Notification No. 0328007]; Tokyo(JP): MHLW: 2005-03-28, 2005.

44. Idogawa, M.; Tange, S.; Nakase, H.; Tokino, T., Interactive Web-based Graphs of Coronavirus Disease 2019 Cases and Deaths per Population by Country. Clin Infect Dis 2020, 71, (15), 902-03.

45. National Institute of Infectious Diseases [Preliminary results from a case-control study on the ability of the novel coronavirus vaccine to prevent severe illness: efficacy during the Delta and early Omicron epidemics]; Tokyo(JP): NIID: 2023-04-28, 2023.

46. Ministry of Health Labour and Welfare [The 50th Advisory Board Meeting on Novel Coronavirus Infectious Disease Control (COVID-19)]; Tokyo(JP): MHLW: 2021-09-03, 2021.

47. Pearl, J., Comment: Understanding Simpson?s Paradox. The American Statistician 2014, 68, (1), 8-13.

48. Ministry of Health Labour and Welfare [The 92nd Advisory Board Meeting on Novel Coronavirus Infectious Disease Control (COVID-19)]; Tokyo(JP): MHLW: 2022-07-27, 2022.

49. Pharmaceuticals and Medical Devices Agency

[ICMRA statement on the safety of COVID-19 vaccines]. https://www.icmra.info/drupal/en/strategicinitiatives/vaccines/safety_statement Access Date (2025-03-24).

50. Shrestha, N. K.; Burke, P. C.; Nowacki, A. S.; Simon, J. F.; Hagen, A.; Gordon, S. M., Effectiveness of the Coronavirus Disease 2019 Bivalent Vaccine. Open Forum Infectious Diseases 2023, 10, (6).

51. Polack, F. P.; Thomas, S. J.; Kitchin, N.; Absalon, J.; Gurtman, A.; Lockhart, S.; Perez, J. L.; Perez Marc, G.; Moreira, E. D.; Zerbini, C.; Bailey, R.; Swanson, K. A.; Roychoudhury, S.; Koury, K.; Li, P.; Kalina, W. V.; Cooper, D.; Frenck, R. W., Jr.; Hammitt, L. L.; Tureci, O.; Nell, H.; Schaefer, A.; Unal, S.; Tresnan, D. B.; Mather, S.; Dormitzer, P. R.; Sahin, U.; Jansen, K. U.; Gruber, W. C.; Group, C. C. T., Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020, 383, (27), 2603-15.

52. Doshi, P., Covid-19 vaccines: In the rush for regulatory approval, do we need more data? BMJ 2021, 373, n1244.

53. Kitano, T.; Thompson, D. A.; Engineer, L.; Dudley, M. Z.; Salmon, D. A., Risk and Benefit of mRNA COVID-19 Vaccines for the Omicron Variant by Age, Sex, and Presence of Comorbidity: A Quality-Adjusted Life Years Analysis. Am J Epidemiol 2023, 192, (7), 1137-47.

54. Hirai, Y.; Hikota, H.; Kikuchi, T.; Nakamura, T.; Fukushima, M., [Aortic dissection following COVID-19 vaccination: A case study, analysis of voluntary death reports submitted to MHLW, and literature review]. Rinsho Hyoka?Clinical Evaluation 2024, 52, (2).

55. Hulscher, N. A., P.E.; Amerling, R.; Gessling, H.; Hodkinson, R.; Makis, W.;Harvey, A.R.; Trozzi, M.; McCullough, P.A., A Systematic Review Of Autopsy Findings In Deaths After COVID-19 Vaccination. Science, Public Health Policy and the Law. 2024, (v5.2019-2024). https://publichealthpolicyjournal.com/a-systematic-review-of-autopsy-findings-in-deaths-after-covid-19-vaccination/

56. Hulscher, N.; Bowden, M. T.; McCullough, P. A., Review: Calls for Market Removal of COVID-19 Vaccines Intensify as Risks Far Outweigh Theoretical Benefits. Science, Public Health Policy and the Law. 2025, Jan 28; v6.2019-2025. https://publichealthpolicyjournal.com/review-of-calls-for-market-removal-of-covid-19-vaccines-intensify-risks-far-outweigh-theoretical-benefits/

57. Fukushima, M., [Ongoing paradigm shift in BioHealth science and technology.]. Rinsho Hyoka [Clinical Evaluation] 2021, 49, (2).

58. Nakamura, T., A Mathematical Model for the Pattern of COVID-19 Post-Vaccination Mortality. Jxiv 2023.

59. Fukushima, M.; Hirai, Y.; Nakatani, E.; Nishimura, T., [Overview of COVID-19 post-vaccination mortality and pharmacoepidemiological evaluation: nation-wide view and a proposal.]. Rinsho Hyoka [Clinical Evaluation] 2022, 49, (3).

60. WHO, WHO INFORMATION NOTICE FOR IVD USERS. In 2021.

61. Bullard, J.; Dust, K.; Funk, D.; Strong, J. E.; Alexander, D.; Garnett, L.; Boodman, C.; Bello, A.; Hedley, A.; Schiffman, Z.; Doan, K.; Bastien, N.; Li, Y.; Van Caeseele, P. G.; Poliquin, G., Predicting Infectious Severe Acute Respiratory Syndrome Coronavirus 2 From Diagnostic Samples. Clin Infect Dis 2020, 71, (10), 2663-66.

62. La Scola, B.; Le Bideau, M.; Andreani, J.; Hoang, V. T.; Grimaldier, C.; Colson, P.; Gautret, P.; Raoult, D., Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. Eur J Clin Microbiol Infect Dis 2020, 39, (6), 1059-61.

63. Oba, J.; Taniguchi, H.; Sato, M.; Takamatsu, R.; Morikawa, S.; Nakagawa, T.; Takaishi, H.; Saya, H.; Matsuo, K.; Nishihara, H., RT-PCR Screening Tests for SARS-CoV-2 with Saliva Samples in Asymptomatic People: Strategy to Maintain Social and Economic Activities while Reducing the Risk of Spreading the Virus. Keio J Med 2021, 70, (2), 35-43.

64. Suzuki, T.; Aizawa, K.; Shibuya, K.; Yamanaka, S.; Anzai, Y.; Kurokawa, K.; Nagai, R., Prevalence of Asymptomatic SARS-CoV-2 Infection in Japan. JAMA Netw Open 2022, 5, (12), e2247704.

65. WHO, Assessment of causality of individual adverse events following immunization (AEFI), User manual for the revised WHO classification, Second edition 2019 update. In 2019.

66. Pomara, C.; Sessa, F.; Ciaccio, M.; Dieli, F.; Esposito, M.; Giammanco, G. M.; Garozzo, S. F.; Giarratano, A.; Prati, D.; Rappa, F.; Salerno, M.; Tripodo, C.; Mannucci, P. M.; Zamboni, P., COVID-19 Vaccine and Death: Causality Algorithm According to the WHO Eligibility Diagnosis. Diagnostics (Basel) 2021, 11, (6)

67. Yazawa, H.; Nakajima, A., Why can't Japan evaluate 99% of the 1,325 deaths following COVID vaccinations? The Mainichi 2021. https://mainichi.jp/english/articles/20211119/p2a/00m/0na/042000c Accessed on: 2025-06-21.

68. Shintani, C.; Yamane, K., [Only 10% of Deaths After COVID-19 Vaccination Undergo Autopsy ? 'A National System for Determining Causes of Death is Needed']. The Asahi Shimbun August 3, 2023, 2023. https://www.asahi.com/articles/ASR706DZBR7MOXIE01J.html Accessed on: 2025-06-20.

69. Yamamoto, K., Need for validation of vaccination programs. Discover Medicine 2025, 2, (1).

70. Hirata, Y.; Iida, S.; Arashiro, T.; Nagasawa, S.; Saitoh, H.; Abe, H.; Ikemura, M.; Makino, Y.; Sawa, R.; Iwase, H.; Ushiku, T.; Suzuki, T.; Akitomi, S., Impact of the COVID-19 pandemic on pathological autopsy practices in Japan. Pathol Int 2023, 73, (3), 120-26.

71. Ioannidis, J. P. A., Reconciling estimates of global spread and infection fatality rates of COVID-19: An overview of systematic evaluations. Eur J Clin Invest 2021, 51, (5), e13554.

72. Ioannidis, J. P. A., Over- and under-estimation of COVID-19 deaths. Eur J Epidemiol 2021, 36, (6), 581-88.

73. Giubilini, A.; Gur-Arie, R.; Jamrozik, E., EXPERTISE, DISAGREEMENT, and TRUST IN VACCINE SCIENCE AND POLICY. The importance of transparency in a world of experts. Diametros 2025, 22, (82), 7-27.

74. Reuters Fact Check, Fact Check: Preventing transmission never required for COVID vaccines? initial approval; Pfizer vax did reduce transmission of early variants. Reuters February 13, 2024. https://www.reuters.com/fact-check/preventing-transmission-never-required-covid-vaccines-initial-approval-pfizer-2024-02-12 Accessed on: 2025-03-03.

75. Nakatani, E.; Morioka, H.; Kikuchi, T.; Fukushima, M., Behavioral and Health Outcomes of mRNA COVID-19 Vaccination: A Case-Control Study in Japanese Small and Medium-Sized Enterprises. Cureus 2024, 16, (12), e75652.

76. Feldstein, L. R.; Ruffin, J.; Wiegand, R.; Grant, L.; Babu, T. M.; Briggs-Hagen, M.; Burgess, J. L.; Caban-Martinez, A. J.; Chu, H. Y.; Ellingson, K. D.; Englund, J. A.; Hegmann, K. T.; Jeddy, Z.; Kuntz, J.; Lauring, A. S.; Lutrick, K.; Martin, E. T.; Mathenge, C.; Meece, J.; Midgley, C. M.; Monto, A. S.; Naleway, A. L.; Newes-Adeyi, G.; Odame-Bamfo, L.; Olsho, L. E. W.; Phillips, A. L.; Rai, R. P.; Saydah, S.; Smith, N.; Tyner, H.; Vaughan, M.; Weil, A. A.; Yoon, S. K.; Britton, A.; Gaglani, M., Protection From COVID-19 Vaccination and Prior SARS-CoV-2 Infection Among Children Aged 6 Months-4 Years, United States,

September 2022-April 2023. J Pediatric Infect Dis Soc 2025, 14, (1).

77. Irrgang, P.; Gerling, J.; Kocher, K.; Lapuente, D.; Steininger, P.; Habenicht, K.; Wytopil, M.; Beileke, S.; Schafer, S.; Zhong, J.; Ssebyatika, G.; Krey, T.; Falcone, V.; Schulein, C.; Peter, A. S.; Nganou-Makamdop, K.; Hengel, H.; Held, J.; Bogdan, C.; Uberla, K.; Schober, K.; Winkler, T. H.; Tenbusch, M., Class switch toward noninflammatory, spike-specific IgG4 antibodies after repeated SARS-CoV-2 mRNA vaccination. Sci Immunol 2023, 8, (79), eade2798.

78. Uversky, V.; Redwan, E.; Makis, W.; Rubio-Casillas, A., IgG4 Antibodies Induced by Repeated Vaccination May Generate Immune Tolerance to the SARS-CoV-2 Spike Protein. Vaccines 2023, 11, (5).

79. Kiszel, P.; Sík, P.; Miklós, J.; Kajdácsi, E.; Sinkovits, G.; Cervenak, L.; Prohászka, Z., Class switch towards spike protein-specific IgG4 antibodies after SARS-CoV-2 mRNA vaccination depends on prior infection history. Scientific Reports 2023, 13, (1).

80. Tortorici, M. A.; Addetia, A.; Seo, A. J.; Brown, J.; Sprouse, K.; Logue, J.; Clark, E.; Franko, N.; Chu, H.; Veesler, D., Persistent immune imprinting occurs after vaccination with the COVID-19 XBB.1.5 mRNA booster in humans. Immunity 2024, 57, (4), 904-11 e4.

81. Gelderloos, A. T.; Verheul, M. K.; Middelhof, I.; de Zeeuw-Brouwer, M. L.; van Binnendijk, R. S.; Buisman, A. M.; van Kasteren, P. B., Repeated COVID-19 mRNA vaccination results in IgG4 class switching and decreased NK cell activation by S1-specific antibodies in older adults. Immun Ageing 2024, 21, (1), 63.

82. Mörz, M., A Case Report: Multifocal Necrotizing Encephalitis and Myocarditis after BNT162b2 mRNA Vaccination against COVID-19. Vaccines 2022, 10, (10).

83. Yonker, L. M.; Swank, Z.; Bartsch, Y. C.; Burns, M. D.; Kane, A.; Boribong, B. P.; Davis, J. P.; Loiselle, M.; Novak, T.; Senussi, Y.; Cheng, C. A.; Burgess, E.; Edlow, A. G.; Chou, J.; Dionne, A.; Balaguru, D.; Lahoud-Rahme, M.; Arditi, M.; Julg, B.; Randolph, A. G.; Alter, G.; Fasano, A.; Walt, D. R., Circulating Spike Protein Detected in Post-COVID-19 mRNA Vaccine Myocarditis. Circulation 2023, 147, (11), 867-76.

84. Sano, S.; Yamamoto, M.; Kamijima, R.; Sano, H., SARS-CoV-2 spike protein found in the acrosyringium and eccrine gland of repetitive miliaria-like lesions in a woman following mRNA vaccination. J Dermatol 2024, 51, (9), e293-e95.

85. Patterson, B. K.; Yogendra, R.; Francisco, E. B.; Guevara-Coto, J.; Long, E.; Pise, A.; Osgood, E.; Bream, J.; Kreimer, M.; Jeffers, D.; Beaty, C.; Vander Heide, R.; Mora-Rodriguez, R. A., Detection of S1 spike protein in CD16+ monocytes up to 245 days in SARS-CoV-2-negative post-COVID-19 vaccine syndrome (PCVS) individuals. Hum Vaccin Immunother 2025, 21, (1), 2494934

86. Ota, N.; Itani, M.; Aoki, T.; Sakurai, A.; Fujisawa, T.; Okada, Y.; Noda, K.; Arakawa, Y.; Tokuda, S.; Tanikawa, R., Expression of SARS-CoV-2 spike protein in cerebral Arteries: Implications for hemorrhagic stroke Post-mRNA vaccination. J Clin Neurosci 2025, 136, 111223.

87. Perez, C. M.; Ruiz-Rius, S.; Ramirez-Morros, A.; Vidal, M.; Opi, D. H.; Santamaria, P.; Blanco, J.; Vidal-Alaball, J.; Beeson, J. G.; Molinos-Albert, L. M.; Aguilar, R.; Ruiz-Comellas, A.; Moncunill, G.; Dobano, C., Post-vaccination IgG4 and IgG2 class switch associates with increased risk of SARS-CoV-2 infections. J Infect 2025, 106473.

88. Rispens, T.; Huijbers, M. G., The unique properties of IgG4 and its roles in health and disease. Nat Rev Immunol 2023, 23, (11), 763-78.

89. Napodano, C.; Marino, M.; Stefanile, A.; Pocino,

K.; Scatena, R.; Gulli, F.; Rapaccini, G. L.; Delli Noci, S.; Capozio, G.; Rigante, D.; Basile, U., Immunological Role of IgG Subclasses. Immunol Invest 2021, 50, (4), 427-44.

90. Gao, F. X.; Wu, R. X.; Shen, M. Y.; Huang, J. J.; Li, T. T.; Hu, C.; Luo, F. Y.; Song, S. Y.; Mu, S.; Hao, Y. N.; Han, X. J.; Wang, Y. M.; Li, L.; Li, S. L.; Chen, Q.; Wang, W.; Jin, A. S., Extended SARS-CoV-2 RBD booster vaccination induces humoral and cellular immune tolerance in mice. iScience 2022, 25, (12), 105479.

91. Gibo, M.; Kojima, S.; Fujisawa, A.; Kikuchi, T.; Fukushima, M., Increased age-adjusted cancer mortality after the third mRNA-lipid nanoparticle vaccine dose during the COVID-19 pandemic in Japan. Rinsho Hyoka (Clinical Evaluation) 2024, 52, (1), 65-90.

92. Abue, M.; Mochizuki, M.; Shibuya-Takahashi, R.; Ota, K.; Wakui, Y.; Iwai, W.; Kusaka, J.; Saito, M.; Suzuki, S.; Sato, I.; Tamai, K., Repeated COVID-19 Vaccination as a Poor Prognostic Factor in Pancreatic Cancer: A Retrospective, Single-Center Cohort Study. Cancers 2025, 17, (12).

93. Ministry of Health Labour and Welfare [Overview of the 2022 Life Table].

94. Fukushima, M., Unveiling Excess Mortality: How to know the fact as it is. Rinsho Hyoka (Clinical Evaluation) 2024, 52, (1), 63-64.

95. Gibo, M. K., Seiji; Murakami, Yasufumi; Teramukai, Satoshi; Fukushima, Masanori, Excess Cancer Mortality after mRNA-Lipid Nanoparticle SARS-CoV-2 Vaccination in Japan: Observation until 2023. 2025.

96. Blakney, A. K.; Ip, S.; Geall, A. J., An Update on Self-Amplifying mRNA Vaccine Development. Vaccines (Basel) 2021, 9, (2).

97. Yildiz, A.; Raileanu, C.; Beissert, T., Trans-Amplifying RNA: A Journey from Alphavirus Research to Future Vaccines. Viruses 2024, 16, (4).

98. Kitonsa, J.; Serwanga, J.; Cheeseman, H. M.; Abaasa, A.; Lunkuse, J. F.; Ruzagira, E.; Kato, L.; Nambaziira, F.; Oluka, G. K.; Gombe, B.; Jackson, S.; Ssebwana, J. K.; McFarlane, L. R.; Joseph, S.; Pierce, B. F.; Shattock, R. J.; Kaleebu, P., Safety and Immunogenicity of a Modified Self-Amplifying Ribonucleic Acid (saRNA) Vaccine Encoding SARS-CoV-2 Spike Glycoprotein in SARS-CoV-2 Seronegative and Seropositive Ugandan Individuals. Vaccines 2025, 13, (6).

99. Pharmaceuticals and Medical Devices Agency Review Report [Brand name] KOSTAIVE intramuscular injection; Tokyo(JP): PMDA: 2024-09-06, 2024.

100. Ho, N. T.; Hughes, S. G.; Ta, V. T.; Phan, L. T.; Do, Q.; Nguyen, T. V.; Pham, A. T. V.; Thi Ngoc Dang, M.; Nguyen, L. V.; Trinh, Q. V.; Pham, H. N.; Chu, M. V.; Nguyen, T. T.; Luong, Q. C.; Tuong Le, V. T.; Nguyen, T. V.; Tran, L. T.; Thi Van Luu, A.; Nguyen, A. N.; Nguyen, N. T.; Vu, H. S.; Edelman, J. M.; Parker, S.; Sullivan, B.; Sullivan, S.; Ruan, Q.; Clemente, B.; Luk, B.; Lindert, K.; Berdieva, D.; Murphy, K.; Sekulovich, R.; Greener, B.; Smolenov, I.; Chivukula, P.; Nguyen, V. T.; Nguyen, X. H., Safety, immunogenicity and efficacy of the self-amplifying mRNA ARCT-154 COVID-19 vaccine: pooled phase 1, 2, 3a and 3b randomized, controlled trials. Nat Commun 2024, 15, (1), 4081.

101. Meiji Seika Pharma Co Ltd [KOSTAIVE intramuscular injection 4th Interim Report of Early Post-marketing Phase Vigilance]; Tokyo(JP): Meiji Seika Pharma Co., Ltd.j: 2025-02-14, 2025.

102. Meiji Seika Pharma Co Ltd [KOSTAIVE intramuscular injection: Post-marketing surveillance, Final report]; 2025.

103. Oda, Y.; Kumagai, Y.; Kanai, M.; Iwama, Y.; Okura, I.; Minamida, T.; Yagi, Y.; Kurosawa, T.; Greener, B.; Zhang, Y.; Walson, J. L.,

Immunogenicity and safety of a booster dose of a self-amplifying RNA COVID-19 vaccine (ARCT-154) versus BNT162b2 mRNA COVID-19 vaccine: a double-blind, multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet Infect Dis 2024, 24, (4), 351-60.

104. Ministry of Health Labour and Welfare [Routine Vaccination from October]; Tokyo(JP): MHLW: 2024-09-24, 2024.

105. Division of Molecular Target and Gene Therapy Products National Institute of Health Sciences [mRNA drugs in clinical development or approved]; Kanagawa(JP): NIHS: 2025-05-23, 2025.

106. Paciello, I.; Maccari, G.; Pierleoni, G.; Perrone, F.; Realini, G.; Troisi, M.; Anichini, G.; Cusi, M. G.; Rappuoli, R.; Andreano, E., SARS-CoV-2 JN.1 variant evasion of IGHV3-53/3-66 B cell germlines. Sci Immunol 2024, 9, (98), eadp9279.

107. Banoun, H., mRNA: Vaccine or Gene Therapy? The Safety Regulatory Issues. Int J Mol Sci 2023, 24, (13).

108. Dull, T.; Zufferey, R.; Kelly, M.; Mandel, R. J.; Nguyen, M.; Trono, D.; Naldini, L., A third-generation lentivirus vector with a conditional packaging system. J Virol 1998, 72, (11), 8463-71.

109. Poirier, E. Z.; Mounce, B. C.; Rozen-Gagnon, K.; Hooikaas, P. J.; Stapleford, K. A.; Moratorio, G.; Vignuzzi, M., Low-Fidelity Polymerases of Alphaviruses Recombine at Higher Rates To Overproduce Defective Interfering Particles. J Virol 2015, 90, (5), 2446-54.

110. THE WHITE HOUSE, IMPROVING THE SAFETY AND SECURITY OF BIOLOGICAL RESEARCH. In 2025. https://www.whitehouse.gov/presidential-actions/2025/05/improving-the-safety-and-security-of-biological-research/ Accessed on: 2025-05-08.

111. Evans, N. G.; Lipsitch, M.; Levinson, M., The ethics of biosafety considerations in gain-of-function research resulting in the creation of potential pandemic pathogens. J Med Ethics 2015, 41, (11), 901-8.

112. Potential Risks and Benefits of Gain-of-Function Research. 2015. https://doi.org/10.17226/21666

113. Hick, T. A. H.; Geertsema, C.; Nguyen, W.; Bishop, C. R.; van Oosten, L.; Abbo, S. R.; Dumenil, T.; van Kuppeveld, F. J. M.; Langereis, M. A.; Rawle, D. J.; Tang, B.; Yan, K.; van Oers, M. M.; Suhrbier, A.; Pijlman, G. P., Safety concern of recombination between self-amplifying mRNA vaccines and viruses is mitigated in vivo. Mol Ther 2024, 32, (8), 2519-34.

114. Lei, Y.; Zhang, J.; Schiavon, C. R.; He, M.; Chen, L.; Shen, H.; Zhang, Y.; Yin, Q.; Cho, Y.; Andrade, L.; Shadel, G. S.; Hepokoski, M.; Lei, T.; Wang, H.; Zhang, J.; Yuan, J. X.; Malhotra, A.; Manor, U.; Wang, S.; Yuan, Z. Y.; Shyy, J. Y., SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2. Circ Res 2021, 128, (9), 1323-26.

115. Bhardwaj, T.; Gadhave, K.; Kapuganti, S. K.; Kumar, P.; Brotzakis, Z. F.; Saumya, K. U.; Nayak, N.; Kumar, A.; Joshi, R.; Mukherjee, B.; Bhardwaj, A.; Thakur, K. G.; Garg, N.; Vendruscolo, M.; Giri, R., Amyloidogenic proteins in the SARS-CoV and SARS-CoV-2 proteomes. Nature Communications 2023, 14, (1).

116. Tetz, G.; Tetz, V., Prion-like Domains in Spike Protein of SARS-CoV-2 Differ across Its Variants and Enable Changes in Affinity to ACE2. Microorganisms 2022, 10, (2).

117. Rhea, E. M.; Logsdon, A. F.; Hansen, K. M.; Williams, L. M.; Reed, M. J.; Baumann, K. K.; Holden, S. J.; Raber, J.; Banks, W. A.; Erickson, M. A., The S1 protein of SARS-CoV-2 crosses the blood–brain barrier in mice. Nature Neuroscience 2020, 24, (3), 368-78.

118. Nystrom, S.; Hammarstrom, P., Amyloidogenesis of SARS-CoV-2 Spike Protein. J Am Chem Soc 2022, 144, (20), 8945-50.

119. Arakawa, H., The Natural Evolution of RNA Viruses Provides Important Clues about the Origin of SARS-CoV-2 Variants. SynBio 2024, 2, (3), 285-97.

120. AFTER ACTION REVIEW OF THE COVID-19 PANDEMIC: The Lessons Learned and a Path Forward. In U.S. House of Representatives, S. S. o. t. C. P. C. o. O. a. A., Ed. 2024. https://oversight.house.gov/wp-content/uploads/2024/12/2024.12.04-SSCP-FINAL-REPORT-ANS.pdf

121. Kakeya, H.; Matsumoto, Y., A Probabilistic Approach to Evaluate the Likelihood of Artificial Genetic Modification and Its Application to SARS-CoV-2 Omicron Variant. IPSJ Transactions on Bioinformatics 2022, 15, (0), 22-29.

122. Pharmaceutical Safety Division Pharmaceutical and Food Safety Bureau Ministry of Health Labour and Welfare [Update of Prescribing Information for Coronavirus Modified Uridine RNA Vaccine (SARS-CoV-2)]; Tokyo(JP): MHLW: 2021-12-03, 2021.

123. Kono, T., [Taro Kono's live broadcast] Taro-to-Kataro. In Tokyo(JP): Liberal Democratic Party: 2021. https://www.youtube.com/watch?v=4_tj824Nl4Q Access Date (2025-03-23).

124. Takada, K.; Taguchi, K.; Samura, M.; Igarashi, Y.; Okamoto, Y.; Enoki, Y.; Tanikawa, K.; Matsumoto, K., SARS-CoV-2 mRNA vaccine-related myocarditis and pericarditis: An analysis of the Japanese Adverse Drug Event Report database. J Infect Chemother 2025, 31, (1), 102485.

125. Rhodes, P.; Parry, P. I., Pharmaceutical product recall and educated hesitancy towards new drugs and novel vaccines. Int J Risk Saf Med 2024, 35, (4), 317-33.

126. TBS NEWS DIG [COVID-19 vaccine recipients were treated as 'unvaccinated'. Ministry of Health, Labour and Welfare: "The reason is unknown, but it was not intentional."].

127. Ministry of Health Labour and Welfare [Health Center Real-time Information-sharing System on COVID-19 (HER-SYS)].

128. Ministry of Health Labour and Welfare [Examination Committee for Certification of Sickness and Disability The 180th Meeting (Subcommittee on Infectious Diseases and Immunization Review) Compliance and Related Matters (Donation Receipt Records)]; Tokyo(JP): MHLW: 2025-02-21, 2025.

129. Council for International Organizations of Medical Sciences (CIOMS), International Ethical Guidelines for Health-related Research Involving Humans. In 2016.

130. Meghani, Z.; Kuzma, J., The “Revolving Door” between Regulatory Agencies and Industry: A Problem That Requires Reconceptualizing Objectivity. Journal of Agricultural and Environmental Ethics 2010, 24, (6), 575-99.

131. Kariya, H., [Pharmaceutical Capture]. The Hitotsubashi journal of law and international studies 2023, 22, (2).

132. Mostert, S.; Hoogland, M.; Huibers, M.; Kaspers, G., Excess mortality across countries in the Western World since the COVID-19 pandemic: ‘Our World in Data’ estimates of January 2020 to December 2022. BMJ Public Health 2024, 2, (1).

133. Rancourt, D. G.; Baudin, M.; Hickey, J.; Mercier, J., COVID-19 vaccine-associated mortality in the Southern Hemisphere. CORRELATION Research in the Public Interest 2023.

134. Kakeya, H.; Nitta, T.; Kamijima, Y.; Miyazawa, T., Significant Increase in Excess Deaths after Repeated COVID-19 Vaccination in Japan. JMA J 2025, 8, (2), 584-86.

135. Barda, N.; Dagan, N.; Ben-Shlomo, Y.; Kepten, E.; Waxman, J.; Ohana, R.; Hernan, M. A.; Lipsitch, M.; Kohane, I.; Netzer, D.; Reis, B. Y.; Balicer, R. D., Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med 2021, 385, (12), 1078-90.

136. Rossman, H.; Shilo, S.; Meir, T.; Gorfine, M.; Shalit, U.; Segal, E., COVID-19 dynamics after a national immunization program in Israel. Nat Med 2021, 27, (6), 1055-61.

137. Bots, S. H.; Riera-Arnau, J.; Belitser, S. V.; Messina, D.; Aragon, M.; Alsina, E.; Douglas, I. J.; Duran, C. E.; Garcia-Poza, P.; Gini, R.; Herings, R. M. C.; Huerta, C.; Sisay, M. M.; Martin-Perez, M.; Martin, I.; Overbeek, J. A.; Paoletti, O.; Palleja-Millan, M.; Schultze, A.; Souverein, P.; Swart, K. M. A.; Villalobos, F.; Klungel, O. H.; Sturkenboom, M., Myocarditis and pericarditis associated with SARS-CoV-2 vaccines: A population-based descriptive cohort and a nested self-controlled risk interval study using electronic health care data from four European countries. Front Pharmacol 2022, 13, 1038043.

138. Li, X.; Ostropolets, A.; Makadia, R.; Shoaibi, A.; Rao, G.; Sena, A. G.; Martinez-Hernandez, E.; Delmestri, A.; Verhamme, K.; Rijnbeek, P. R.; Duarte-Salles, T.; Suchard, M. A.; Ryan, P. B.; Hripcsak, G.; Prieto-Alhambra, D., Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study. BMJ 2021, 373, n1435.

139. Inokuma, Y.; Kneller, R., Imprecision in vaccine adverse event reporting and a methodological analysis of reporting systems to improve pharmacovigilance and public health. Eur J Clin Pharmacol 2023, 79, (7), 989-1002.

140. World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Participants.

141. World Medical Association Declaration of Geneva. https://www.wma.net/what-we-do/medical-ethics/declaration-of-geneva/ Accessed on: 2025-03-24.

142. Kämmerer, U.; Schulz, V.; Steger, K., BioNTech RNA-Based COVID-19 Injections Contain Large Amounts Of Residual DNA Including An SV40 Promoter/Enhancer Sequence. Science, Public Health Policy and the Law. 2024, v5.2019-2024.

143. Raoult, D., Confirmation of the presence of vaccine DNA in the Pfizer anti-COVID-19 vaccine. HAL science ouverte 2024.

144. Wang, T. J.; Kim, A.; Kim, K., A rapid detection method of replication-competent plasmid DNA from COVID-19 mRNA vaccines for quality control. Journal of High School Science 2024, 8, 427-39.

145. Speicher, D. J.; Rose, J.; Gutschi, L. M.; Wiseman, D. M.; McKernan, K., DNA Fragments Detected in Monovalent and Bivalent Pfizer/biontech and Moderna Modrna COVID-19 Vaccines from Ontario, Canada: Exploratory Dose Response Relationship with Serious Adverse Events. OST Preprint 2023.

146. McKernan, K.; Helbert, Y.; Kane, L. T.; McLaughlin, S., Sequencing of bivalent Moderna and Pfizer mRNA vaccines reveals nanogram to microgram quantities of expression vector dsDNA per dose. OST Preprint 2023.

147. Konig, B.; Kirchner, J. O., Methodological Considerations Regarding the Quantification of DNA Impurities in the COVID-19 mRNA Vaccine Comirnaty((R)). Methods Protoc 2024, 7, (3).

148. Sandy Run News USC Professor Dr. Phillip Buckhaults, SC Senate Hearing, September 12, 2023. https://youtu.be/C7Qs166xR28?si=mlCnp2YiaWAoJQ1T Access Date (2025-03-24),

149. Pekova, S., Quantitative Multiplex Real-Time PCR analysis of Moderna (Spikevax) and Pfizer (BNT162b2) vaccines. In Republic, G. O. o. t. S., Ed. 2025.

150. Yang, H., Establishing acceptable limits of residual DNA. PDA J Pharm Sci Technol 2013, 67, (2), 155-63.

151. Hou, X.; Zaks, T.; Langer, R.; Dong, Y., Lipid nanoparticles for mRNA delivery. Nat Rev Mater 2021, 6, (12), 1078-94.

152. Kaiser, S.; Kaiser, S.; Reis, J.; Marschalek, R., Quantification of objective concentrations of DNA impurities in mRNA vaccines. Vaccine 2025, 55, 127022.

153. Kariko, K.; Muramatsu, H.; Welsh, F. A.; Ludwig, J.; Kato, H.; Akira, S.; Weissman, D., Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability. Mol Ther 2008, 16, (11), 1833-40.

154. Mulroney, T. E.; Pöyry, T.; Yam-Puc, J. C.; Rust, M.; Harvey, R. F.; Kalmar, L.; Horner, E.; Booth, L.; Ferreira, A. P.; Stoneley, M.; Sawarkar, R.; Mentzer, A. J.; Lilley, K. S.; Smales, C. M.; von der Haar, T.; Turtle, L.; Dunachie, S.; Klenerman, P.; Thaventhiran, J. E. D.; Willis, A. E., N1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting. Nature 2023.

155. Monroe, J.; Eyler, D. E.; Mitchell, L.; Deb, I.; Bojanowski, A.; Srinivas, P.; Dunham, C. M.; Roy, B.; Frank, A. T.; Koutmou, K. S., N1-Methylpseudouridine and pseudouridine modifications modulate mRNA decoding during translation. Nat Commun 2024, 15, (1), 8119.

156. Boros, L. G.; Kyriakopoulos, A. M.; Brogna, C.; Piscopo, M.; McCullough, P. A.; Seneff, S., Long-lasting, biochemically modified mRNA, and its frameshifted recombinant spike proteins in human tissues and circulation after COVID-19 vaccination. Pharmacol Res Perspect 2024, 12, (3), e1218.

157. Tsutani, K., Withdrawn drugs: Various side effects. Farumashia 2007, 43, (11).

158. Tsutani, K., [Various Aspects of Drug Withdrawal]. Jpn J Clin Pharmacol Ther 2009, 40, (1).

159. Nishimura, T.; Tada, H.; Fukushima, M., Lessons from gefitinib-induced interstitial lung disease: Pharmacovigilance for erlotinib in Japan. International Journal of Risk and Safety in Medicine 2009, 21, (3), 161-67.

160. Fukushima, M., The overdose of drugs in Japan. Nature 1989, 342, (6252), 850-1.

161. Takahashi, H., [The history of adverse drug reactions, relief for these health damage and safety measures in Japan]. Yakushigaku Zasshi 2009, 44, (2), 64-70.

162. Doi, O., Sorivudine Incident. Pharmaceutical and Medical Device Regulatory Science 2010, 41, (12), 958-59.

163. The Hope Accord. https://thehopeaccord.org/ Access Date (2025-2-20).

164. Margolis, J. Proposed bill would ban administration of mRNA vaccines in Montana. https://nbcmontana.com/newsletter-daily/proposed-bill-would-ban-administration-of-mrna-vaccines-in-montana (2025-03-24),

165. Kmetz, G., HB 371: Ban mRNA vaccinations in Montana for humans. In 2025.

166. U.S. Food & Drug Administration Recalls Background and Definitions. https://www.fda.gov/safety/industry-guidance-recalls/recalls-background-and-definitions

167. U.S. Food & Drug Administration, Regulatory Procedures Manual Chapter 7: RECALL

PROCEDURES VERSION 10. In 2021.

168. e-Stat Portal Site of Official Statistics of Japan. https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450011&tstat=000001028897&cycle=1&tclass1=000001053058&tclass2=000001053059&cycle_facet=tclass1&tclass3val=0 (2025-04-22).

169. Ministry of Health, Labour and Welfare, Japan. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/yobou-sesshu/syukeihou_00005.html

170. Ministry of Health, Labour and Welfare, Japan. https://covid19.mhlw.go.jp/extensions/public/index.html

171. Summary of results of population estimates. https://www.stat.go.jp/data/jinsui/2.html#monthly

Revisions

This updated version corrects two minor errors in the originally published article:
(1) a clarification in Figure 2, noting that Japan's cumulative vaccination rate exceeded 140%, indicating multiple booster doses per capita; and
(2) a correction in Table 2 (general pharmaceutical products) specifying that nonclinical studies must include at least two animal species—one rodent and one non-rodent other than rabbits.

These corrections do not alter the scientific content or conclusions of the paper. Original publication can be accessed at UedaEtAl_SciencePublicHealthPolicyAndTheLaw_v8.2019-2025.Aug_2025_.pdf

*Correspondence: junueda@asahikawa-med.ac.jp
1. Department of Advanced Medical Science, Asahikawa Medical University, Asahikawa, Hokkaido, 078-8510, Japan.
2. Matsubara Clinic, Department of Primary Health Care, Kochi, 785-0773, Japan.
3. Translational Research & Health Data Science, Learning Health Society Institute, Nagoya, 450-0003, Japan.
4. MCL Corporation, Jimukino-Ueda bldg. 603, 21 Sakaimachi Gojo-Takakurakado, Shimogyo-Ku, Kyoto 600-8191, Japan.
5. Kitaris Co., Ltd., Iwakura, Aichi, 482-0003, Japan.
6. Shima Law Office, Fujimi, Saitama, 354-0035, Japan.
7. Medical Corporation Soreiyu-Kai, Takarazuka, Hyogo, 665-0841, Japan.