

Reanalysis of FDA Clinical Data for mFLUSIVA (mRNA-1010)

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Abstract

Background/objectives: On 5 August 2026, the FDA approved Moderna's mFLUSIVA (mRNA-1010) for adults aged ≥ 50 years, granting Traditional Approval for ages 50–64 years based on clinical efficacy and Accelerated Approval for ages ≥ 65 years based on hemagglutination-inhibition titres. We reassessed the evidentiary basis for licensure on an absolute benefit–risk scale.

Methods: FDA regulatory and clinical-trial data were reanalyzed using absolute risk differences, numbers needed to vaccinate (NNV), numbers needed to harm, unadjusted risk ratios (RRs) with 95% confidence intervals (CIs), and harms incurred per clinical benefit obtained.

Results: Neither pivotal trial included a placebo arm. Every solicited adverse reaction was more frequent with mFLUSIVA than with the standard-dose comparator. Overall solicited adverse reactions occurred in 75.7% of mFLUSIVA recipients versus 46.7% of comparator recipients, and Grade 3 systemic reactions occurred in 5.5% versus 0.9% (RR, 6.15; 95% CI, 4.11–9.20). Unexplained deaths occurred in 23 mFLUSIVA recipients versus 9 com-

parator recipients (RR, 2.55; 95% CI, 1.18–5.52), increasing to 29 mFLUSIVA recipients versus 12 comparator recipients when related fatal-event terms were pooled (RR, 2.42; 95% CI, 1.23–4.73). Only one autopsy was performed across the clinical program, in the comparator arm. Relative vaccine efficacy against RT-PCR-confirmed influenza-like illness was 26.6% (95% CI, 16.7–35.4). The NNV was 137 for one confirmed illness, 1003 for one higher-level-care encounter, and 5017 for one hospitalization. Per hospitalization averted, approximately 1454 additional solicited adverse reactions, 233 additional Grade 3 systemic reactions, and 2 excess unexplained deaths were observed. No influenza-mortality endpoint was specified, collected, or reported.

Conclusion: mFLUSIVA demonstrated minimal absolute clinical benefit while producing substantially greater reactogenicity and a significant unresolved mortality signal. The extreme risk-benefit profile does not support continued licensure of mFLUSIVA and supports reconsideration of its market authorization.

Keywords: mRNA vaccine, mFLUSIVA, regulatory science, influenza, risk-benefit analysis

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Introduction

In August 2026, the FDA authorized Moderna's mFLUSIVA for adults ≥ 50 years. (1,2) The pivotal trials contained no saline placebo control. Within seven days, 75.3% of older adult recipients experienced at least one solicited adverse reaction versus 49.3% with Fluzone High-Dose; Grade-3 systemic reactions were four-fold higher (6.7% vs 1.7%). (1)

mFLUSIVA (mRNA-1010) is a trivalent messenger RNA vaccine. Each 0.38 mL intramuscular dose contains 37.5 μg of nucleoside-modified mRNA, 12.5 μg encoding each of the full-length, mem-

brane-bound hemagglutinin (HA) glycoproteins of influenza A/H1N1, A/H3N2, and B/Victoria, encapsulated in lipid nanoparticles. (1,3) It differs from every influenza vaccine licensed before it in what it delivers. Inactivated, recombinant, and live attenuated influenza vaccines deliver antigen. mFLUSIVA delivers instructions, and the recipient's own cells manufacture the antigen: an unmeasured quantity of membrane-anchored viral fusion glycoprotein, produced for an unmeasured period, in tissues that were never determined. The strains in the licensed 2026–2027 formulation are A/Missouri/11/2025, A/Michigan/105/2025, and B/Pennsylvania/19/2025, none of which was tested in either pivotal trial. (3)

The approval was bifurcated. Adults 50 through 64 years received Traditional Approval based on clinical efficacy from Study P304. Adults 65 years and older, the stratum that accounts for approximately 70% to 85% of U.S. influenza deaths and 50% to 70% of hospitalizations, received Accelerated Approval based on hemagglutination inhibition (HAI) geometric mean titers and seroconversion rates as surrogate endpoints, contingent on a Phase 4 confirmatory trial. (1) The evidentiary record is unusually well documented: FDA published a 91-page briefing document for the June 18, 2026 meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) containing the primary efficacy tables, the integrated safety summary, and the Agency's own enumeration of unresolved issues. (1) The pivotal trial has been published (4) and the product labeling is public. (3)

mFLUSIVA employs the identical LNP-nucleoside-modified mRNA platform used in COVID-19 vaccines. That platform has been shown to deliver residual plasmid DNA, (5–7) to permit reverse transcription of vaccine sequence (8,9) and its integration into the human genome, (10) to persist for years after injection, (11,12) to reprogram the transcriptome, (13,14) to induce ribosomal stalling and +1 frameshifting, (15,16) and to drive proteostatic collapse through endoplasmic reticulum stress. (13,17,18) Annual administration multiplies every liability. (19–23)

What follows is a reanalysis of the Agency's own efficacy and safety data on an absolute scale, so that the benefit and the harm can be read against one another in the same units. That analysis rests wholly on the regulatory record and assumes nothing about mechanism. The molecular behavior of the platform, which bears on what annual redosing means over a lifetime, is taken up afterwards.

Methods

Data sources

The primary data source was the FDA briefing document prepared for the June 18, 2026 meeting of the Vaccines and Related Biological Products Advisory Committee on BLA 125869/0, which contains the efficacy tables, the Integrated Safety Summary, the appendices for Studies P304 and P303 Part C, and the Agency's own benefit-risk framework. (1) Case counts, denominators, and percentages were taken from that document and cross-checked against the published pivotal trial report, (4) the product labeling, (3) and the trial registrations. (24,25) The regulatory chronology was reconstructed from contemporaneous reporting of the February 2026 refusal-to-file letter, its reversal, and the June 2026 Advisory Committee vote. (26–28) No confidential or unpublished data were used, and no primary participant-level data were available to us.

Absolute-scale analysis

The Agency presented benefits as relative vaccine efficacy percentages and harms as raw reactogenicity percentages. These are not commensurable, and no table in the briefing document expressed both on a common scale. We therefore reanalyzed every reported outcome on an absolute risk scale. For benefits we computed the absolute risk difference and the number needed to vaccinate (NNV), defined as the reciprocal of the difference between comparator and mRNA-1010 event proportions, using the per-protocol set for efficacy endpoints. For harms we computed the absolute risk increase and the number needed to harm (NNH), defined as the reciprocal of the difference between mRNA-1010 and comparator proportions, using the solicited safety subset for reactogenicity and the safety set or Integrated Safety Summary for serious events. Unadjusted risk ratios were calculated with 95% confidence intervals by the log method. Benefit analyses were stratified by outcome severity, age group, baseline high-risk status, and influenza strain; harm analyses were stratified by individual solicited symptom, severity grade, and age group. Harm per unit of benefit was calculated as NNV divided by NNH for matched Study P304 comparisons. All calculations were performed by the authors from published counts; where the briefing document reported only percentages, counts were reconstructed from the stated denominators and are identified as such. No quantity reported in the Results is derived from any source outside the regulatory record.

Results

Regulatory history: a reversal without new efficacy data

Moderna submitted BLA 125869/0 on December 5, 2025. (1) In February 2026, FDA's Center for Biologics Evaluation and Research (CBER) issued a refusal-to-file letter, declining to review the application at all. The stated basis was singular: Moderna's use of a licensed standard-dose influenza vaccine as the comparator in the pivotal trial did not represent the best-available standard of care for older adults. CBER raised no concerns regarding safety or efficacy. (26)

The scientific merit of that objection is documented in FDA's own briefing package. For adults 65 years and older, the Advisory Committee on Immunization Practices preferentially recommends high-dose, recombinant, or adjuvanted formulations over standard-dose vaccines to address immunosenescence. ICH E10 guidance directs that the control group in such trials should reflect the relevant standard of care. (1,29) The standard-dose comparator used in P304 was not that standard of care for roughly half the enrolled population.

Approximately one week later, following public disclosure and applicant objection, FDA reversed. Moderna proposed an age-stratified strategy: Traditional Approval for adults 50 through 64 years, and Accelerated Approval for adults 65 years and older paired with a postmarketing study using a high-dose comparator. FDA accepted the amended application with a user-fee goal date of August 5, 2026. (27) In June 2026 the VRBPAC voted unanimously to recommend the product. (28)

Two features of this sequence warrant attention. First, no new efficacy data were generated between the refusal-to-file letter and the acceptance of the amended application. The comparator deficiency that FDA identified in February was not remedied; it was reclassified. Second, the remedy adopted transferred the burden of proof from the pre-licensure to the post-licensure period specifically for the age group in which the original objection applied most forcefully. Adults 65 years and older, for whom the comparator was conceded to be inadequate, were the group moved onto a surrogate endpoint. The population at highest absolute risk of influenza complications is thus the population for which clinical benefit relative to the therapy they would otherwise receive remains unmeasured. An objection the Agency itself raised, and never answered, was disposed of by redrawing the indication around it.

What the efficacy data show

The primary endpoint is a relative measure

Study P304 (NCT06602024) randomized 40,805 adults 50 years of age and older 1:1 to mRNA-1010 trivalent formulation or a licensed standard-dose comparator (Fluarix trivalent in North America, quadrivalent elsewhere) across 301 sites in 11 countries during the 2024–2025 Northern Hemisphere season. (1,24) RT-PCR-confirmed protocol-defined influenza-like illness occurred in 411 of 20,179 per-protocol recipients (2.0%) versus 557 of 20,124 comparator recipients (2.8%), yielding a relative vaccine efficacy (rVE) of 26.6% (95% CI: 16.7, 35.4). (1,4) The trial, designated Fluent, was funded by Blackstone Life Sciences and Moderna. (4)

Efficacy declines in the populations that matter most

In adults 75 years and older, rVE was 25.3% with a 95% confidence interval of –10.4 to 49.5, crossing zero. (1) In participants with at least one high-risk condition, rVE was 22.3% (95% CI: 8.0, 34.3) compared with 32.1% (95% CI: 17.5, 44.2) in participants without. The confidence intervals overlap and the study was not powered for this comparison, so the difference is not statistically established. FDA nonetheless recorded that the direction "suggests that rVE in the healthier study population may overestimate effectiveness in the general U.S. target population." (1)

That concern is quantitatively substantial. High-risk conditions were present in 57.0% of P304 participants against an estimated 78% of U.S. adults aged 35 to 64 years and 93% of adults 65 years and older. (1,30) Among P304 participants 65 years and older, 73.3% were classified as fit rather than vulnerable or frail on the Edmonton Frail Scale, and fewer than 1% were moderately or severely frail. Immunocompromised individuals were excluded outright. (1)

Efficacy against influenza B/Victoria was 29.1% (95% CI: –18.5, 57.5), based on 25 versus 35 cases. (1) Influenza A accounted for 94.0% of confirmed cases, so the single-season estimate is effectively an influenza A estimate. Antigenic match for A/H3N2 was approximately 52% to 56%, and rVE against matched A/H3N2 cases was 30.5% versus 22.2% overall, indicating season-specific dependence. (1)

The 65-and-older indication rests on antibody titers

For adults 65 years and older, effectiveness was inferred from Study P303 Part C (NCT05827978), in which 3,003 participants received mRNA-1010

quadrivalent or Fluzone High-Dose quadrivalent. (1,25) mRNA-1010 met noninferiority and superiority criteria for HAI geometric mean titer ratio and seroconversion rate difference across all four strains, with GMT ratios ranging from 1.1 to 1.3. (1) Four qualifications attach to this inference, each documented by FDA.

First, no correlate of protection has been established for mFLUSIVA; formal correlate-of-risk and correlate-of-protection analyses were ongoing and outside the scope of the briefing document. (1) HAI titer is being used as a surrogate for a clinical benefit whose quantitative relationship to that surrogate is undefined for this product.

Second, the HAI assays used exclusively Madin-Darby Canine Kidney cell-derived virus matched to mRNA-1010 vaccine strains. FDA noted that this design "could systematically favor mFlusiva in comparative immunogenicity assessments" against egg-based comparators, and that the analysis of this effect was ongoing. (1) The surrogate on which the Accelerated Approval rests was measured with an assay FDA acknowledged may be biased toward the product.

Third, licensure was sought for the trivalent formulation, but P303 Part C evaluated the quadrivalent. The bridge is a post hoc, non-randomized comparison across studies conducted in different influenza seasons. (1)

Fourth, the strains in the licensed product (A/Missouri/11/2025, A/Michigan/105/2025, B/Pennsylvania/19/2025) are the 2026–2027 formulation, not the strains tested in either pivotal trial. (3) This is conventional for influenza vaccines and is not itself an objection, but it compounds the reliance on an unvalidated surrogate: the approved product was neither efficacy-tested nor immunogenicity-tested in its licensed composition. Every link in the chain supporting the 65-and-older indication is inferential, and each was accepted without the confirmatory data that would have closed it.

Quantitative risk-benefit analysis

The VRBPAC benefit-risk framework presented benefits as relative efficacy percentages and risks as raw reactogenicity percentages. (1) These are not commensurable quantities, and no table in the briefing document expressed both on a common absolute scale. We construct that comparison here from the primary data.

Absolute benefit

In this study, the overall chance of developing influenza-like illness over the season was 2.4%. Thus, broad application of influenza vaccination is not warranted from a public health perspective, unless safety of immunization is not an issue whatsoever.

Table 1 restates every efficacy outcome reported for Study P304 as an absolute risk difference and a number needed to vaccinate, stratified by outcome severity, age, baseline risk, and infecting strain.

Over a full influenza season with unusually high transmission, in a population healthier than the intended recipients, mFLUSIVA averted four hospitalizations relative to the comparator across 20,179 vaccinated adults. The absolute hospitalization rate was 0.02% versus 0.04%. Absolute benefit was smallest in precisely the strata the product is marketed to protect: NNV rose from 133 in adults 50 through 64 years to 180 in adults 75 years and older, and from 110 in participants with no high-risk condition to 168 in those with at least one. Against influenza B/Victoria the NNV was 1,999. (1) A product that must be given to 5,017 adults to keep one out of hospital, and to nearly 2,000 to prevent one B/Victoria infection, is not delivering a benefit that can absorb an unresolved safety signal.

Absolute harm

Table 2 applies the same treatment to the harm side, giving the absolute risk increase, the number needed to harm, and the risk ratio for each composite reactogenicity category in both pivotal trials.

At the level of individual symptoms in P304, injection-site pain occurred in 65.8% of mRNA-1010 recipients versus 29.8% of comparator recipients, fatigue in 45.1% versus 20.3%, headache in 37.8% versus 18.0%, and myalgia in 35.4% versus 11.6%. (4) Every solicited symptom category was at least twice as frequent in the mRNA-1010 arm. Two Grade 4 solicited systemic reactions occurred in the mRNA-1010 group of P303 Part C, both fever: 104.9°F on Day 2 and 105.0°F on Day 3. None occurred in the Fluzone High-Dose group. (1)

Table 2 reports composite categories. Because the composites average across symptoms of widely differing frequency, they understate the disparities at the level of the individual reaction a recipient actually experiences. **Table 3** gives the symptom-level detail, which the briefing document presents but does not analyze comparatively.

Sixteen of the eighteen individual comparisons in **Table 3** are statistically significant, and the two that are not (Grade 3 nausea or vomiting, Grade 3 swelling) are the two with the fewest events. The disparities widen sharply with severity: at any grade the risk ratios cluster between 2 and 7, while at Grade 3 they range from 5 to 27. Chills illustrate the pattern. Any-grade chills were 5.30 times more frequent with mRNA-1010; chills severe enough to prevent daily activity were 15.41 times more frequent.

The pattern holds in the age group in which the absolute benefit is smallest. Among participants 65 years and older, Grade 3 systemic reactions occurred in 4.6% of mRNA-1010 recipients versus 0.7% of comparator recipients (risk ratio 6.24; 95% CI: 3.31, 11.73), and Grade 3 local reactions in 1.5% versus 0.1% (risk ratio 11.43; 95% CI: 2.70, 48.40). (1) Reactogenicity did not attenuate with age in the manner that immune responses generally do.

Harm incurred per unit of benefit

Placing the two preceding tables on a common denominator gives the exchange rate the Advisory Committee was never shown. **Table 4** reports, for each averted outcome, how many recipients experienced each category of harm.

For every influenza hospitalization prevented relative to a standard-dose vaccine, approximately 233 recipients experienced a Grade 3 systemic adverse reaction, defined as a reaction preventing daily activity, and approximately 1,454 experienced at least one solicited adverse reaction. This comparison was not available to the Advisory Committee in any form. Had it been, the vote would have required members to affirm that 233 reactions preventing daily activity are an acceptable price for one averted hospitalization. No member was asked to affirm anything of the kind.

Expressed as headcount rather than as a ratio, among the 5,017 mFLUSIVA recipients required to avert that one hospitalization, approximately 3,798 experienced a solicited adverse reaction and 278 experienced a Grade 3 systemic reaction; 1,454 and 233 of these respectively are attributable to the switch from a standard-dose vaccine.

A regulator concluding that 233 Grade 3 systemic reactions are an acceptable price for one averted hospitalization should be required to state that conclusion and defend the exchange rate. The briefing document instead described the reactogenicity profile as "acceptable for the intended population" without ever quantifying what was being traded. (1)

An exchange rate that is never computed cannot be defended, and one that is never disclosed cannot be consented to by the recipient.

Mortality: the endpoint the program did not measure

Influenza mortality is the stated justification for this product class. FDA opens its briefing document with the observation that influenza causes 6,300 to 52,000 U.S. deaths annually and that adults 65 years and older account for 70% to 85% of them. (1) However, the regulatory definition of an influenza death does not require clinical adjudication establishing that a positive influenza test was causally related to the death. It is concerning that no influenza-mortality endpoint was specified, collected, or reported anywhere in the mRNA-1010 clinical development program. Deaths appear in the submitted evidence only as all-cause safety events. Neither pivotal trial estimated, and neither was designed to estimate, whether mFLUSIVA prevents a single influenza death.

The number needed to vaccinate to avert one influenza death is therefore not estimable from the submitted evidence, and no figure for it appears in this analysis. A quantity that was never measured cannot be recovered by modeling, and the licensure decision required the measurement.

The program does, by contrast, yield mortality harm estimates. **Table 5** sets these out on the same absolute scale, giving the risk ratio, the excess per million vaccinated, and the number needed to harm for every mortality endpoint the pooled database reports.

First, the only mortality quantity the program permits us to compute directly is a harm quantity. Two of the five measured mortality endpoints have confidence intervals excluding unity, both in the direction of excess deaths in the mRNA-1010 arm, with numbers needed to harm of 2,570 and 2,116. No corresponding benefit quantity exists, because influenza mortality was never an endpoint.

All-cause mortality was somewhat balanced (102 versus 97). That does not, however, answer the question about excess deaths of unknown cause and no autopsy was performed on any decedent in the mRNA-1010 arm. (1) The single diagnostic procedure capable of resolving the question was omitted from every relevant case.

A further comparison follows directly from these figures. The program demonstrated one averted in-

fluenza hospitalization per 5,017 vaccinations, and produced one unexplained death per 2,116 recipients. That is approximately two unexplained deaths for every hospitalization prevented: 1.95 using the preferred term alone, 2.37 pooling related terms. The hospitalization estimate comes from Study P304 against a standard-dose comparator; the mortality estimate comes from the pooled safety database, whose control arm FDA designates "SD/HD" because it combines standard-dose and high-dose recipients. The mismatch is smaller than it appears: P304 supplies 40,703 of the 71,916 pooled participants (56.6%), the only high-dose comparator study is P303 Part C at 2,992 participants (4.2%), and both populations are adults 50 years and older followed for approximately six months. The pooled comparator arm is therefore overwhelmingly standard-dose, but it is not exclusively so, and the ratio should be read with that in mind. The comparison is not an assertion that mFLUSIVA killed two people for every hospitalization it prevented. It is narrower, and still damning: the safety signal this program failed to resolve is roughly twice the magnitude of the clinical benefit it succeeded in demonstrating.

A licensure decision for a product to be administered annually to tens of millions of older adults was taken on an evidence base that never measured the outcome the product exists to prevent, and that was never capable of measuring the mortality effect it was designed to produce. That is not a residual uncertainty suitable for postmarketing surveillance. It is the absence of the determination the licensure decision required. A vaccine licensed to prevent deaths it was never tested against, in a program incapable of detecting the deaths it might cause, has not met the evidentiary standard for marketing authorisation in any meaningful sense.

Cumulative burden under annual administration

Influenza vaccination is annual. Projecting the P304 point estimates across ten seasons for 1,000 recipients, holding rates constant, yields approximately 463 Grade 3 systemic reaction episodes against approximately 2.0 hospitalizations averted. This projection assumes stable efficacy and reactogenicity across repeated doses, which is unverified: reactogenicity on repeat annual mRNA dosing has not been characterized in this program, and no data address whether solicited reaction rates rise, fall, or persist with successive annual exposures. The Discussion sets out why the assumption of stable cumulative risk is the least defensible element of the entire licensure rationale.

Safety signals identified and set aside

FDA identified three numerical imbalances in the Integrated Safety Summary (35,965 mRNA-1010 recipients; 35,951 standard-dose or high-dose comparator recipients; median follow-up 198 days), all three in the direction of more events among mRNA-1010 recipients, and assessed each as unlikely to be causally related. (1)

One further comparison is not presented in this form anywhere in the briefing document. In Study P304 considered alone, serious adverse events over the full study period occurred in 455 of 20,350 mRNA-1010 recipients (2.2%) versus 392 of 20,353 comparator recipients (1.9%), a risk ratio of 1.16 with a 95% confidence interval of 1.02 to 1.33, excluding unity. (1) In the larger pooled database the same comparison (3.1% versus 2.9%) yields a risk ratio of approximately 1.07 with an interval crossing unity. FDA characterized both as balanced. The pivotal efficacy trial, taken on its own, does not support that characterization.

Table 6 collects the non-fatal events that occurred more often in the mRNA-1010 arm of the pooled database, with risk ratios calculated from the reported counts.

Deaths of unspecified cause

Deaths coded to the preferred term "death (unspecified)" were more than twice as frequent among mRNA-1010 recipients: 23 versus 9, a risk ratio of 2.55 (95% CI: 1.18, 5.52). Pooling sudden death, sudden cardiac death, and unspecified fatal events widened the excess to 29 versus 12, a risk ratio of 2.42 (95% CI: 1.23, 4.73). (1) Both intervals exclude unity. In plain terms, participants who received mRNA-1010 were about two and a half times as likely as comparator recipients to die of a cause that was never determined. The absolute numbers are small, 23 deaths among 35,965 recipients against 9 among 35,951, and the interval is wide, so the true magnitude could lie anywhere between a modest excess and a fivefold one. FDA's dismissal rested on four arguments: deaths within 28 days were comparable (3 vs 2); the remaining deaths showed no temporal clustering; all-cause mortality was balanced (102 vs 97); and decedents had extensive comorbidities. (1)

That argument nonetheless has a specific and consequential weakness, which FDA itself stated: "No autopsies were conducted in the mRNA-1010 group deaths." (1) Across the entire pooled program a single autopsy was performed, and it was in the com-

parator arm. (1) The category at issue is deaths of unknown cause. In a pre-licensure program of 71,916 participants supporting an indication for tens of millions of annual recipients, the absence of autopsy in every unexplained death in the intervention arm is a major failure.

One death on Day 2 in Study P303 Part A, in a 76-year-old woman with prior coronary artery bypass graft, atrial fibrillation, and type 2 diabetes, was assessed as vaccine-related by the investigator on temporal grounds. FDA considered underlying cardiac disease more plausible while stating that "a contribution from a vaccine-related inflammatory response cannot be fully excluded." (1)

Urinary tract infection and anemia serious adverse events

UTI SAEs were 38 versus 22 and anemia SAEs 14 versus 8. (1) FDA cited late onset, absence of temporal clustering, established risk factors, and balanced medically attended event rates in P304 (153 vs 158 for UTI; 31 vs 30 for anemia). The residual question is why the serious subset diverged while the total did not, which is not addressed in the briefing document.

Rare events are undetectable by design

FDA stated plainly that the safety database "is insufficient to detect rare adverse events, including myocarditis, Guillain-Barré syndrome (GBS), and other neurological events of interest," and that post-licensure monitoring "will be required." (1) One GBS case occurred in the mRNA-1010 group at Day 134 and none in comparators. For a novel platform in a new indication, with the acknowledged inability to detect rare events, the risk-management response was routine pharmacovigilance. Moderna's Pharmacovigilance Plan "identified no important identified or potential risks and no missing information requiring additional pharmacovigilance beyond routine surveillance," and consequently proposed no additional pharmacovigilance studies. (1) That position did not survive the review. In the final approval package the Applicant committed to a post-marketing study conducting active surveillance for deaths, both unspecified and all-cause, together with myocarditis, pericarditis, myopericarditis, and Guillain-Barre syndrome, and to aggregate assessment of seven adverse events of special interest in periodic safety reports for the first three years. (31,32) The signals the pharmacovigilance plan declared absent are the signals now under mandated surveillance. What the record shows is not that nothing

was missing, but that the applicant proposed to look only after licensure had been granted.

Events the investigators attributed to the vaccine

Across the pooled program, nine mRNA-1010 recipients had at least one serious adverse event assessed as vaccine-related by the treating investigator, against three comparator recipients, and five had an adverse event of special interest so assessed, against two. (1) The five investigator-attributed AESIs in the mRNA-1010 arm were thrombocytopenia at Day 84, facial swelling at Day 2, myopericarditis at Day 95, myocarditis at Day 183, and Bell's palsy at Day 16. FDA and the Applicant disputed the investigator's attribution in most of these cases, generally on grounds of latency or comorbidity.

Two cases warrant naming. In Study P304 a 62-year-old woman experienced syncope on Day 2 with a concurrent temperature of 101.3°F, body aches, chills, and headache. FDA did not dispute this one: the Agency stated that it "agrees with the investigator's assessment that this SAE of syncope is likely related to study vaccine, given the timing of onset postvaccination and the concurrent documented fever and solicited Ars." (1) A serious adverse event was therefore conceded by the Agency to be a probable consequence of vaccination.

The second is the only Cardiac Event Adjudication Committee-confirmed myopericarditis in the mRNA-1010 arm of Study P304. A 64-year-old man with no significant medical history developed progressive dyspnea, orthopnea, and edema, presenting on Day 183 in atrial fibrillation with markedly elevated brain natriuretic peptide. Echocardiography showed severely impaired biventricular systolic function; cardiac magnetic resonance imaging showed late gadolinium enhancement. He was discharged with heart failure with reduced ejection fraction. The adjudication committee confirmed myopericarditis and the investigator assessed the event as vaccine-related; the Applicant and FDA attributed it to a preceding rhinovirus infection and to the long latency. (1)

Cardiac adverse events of special interest mapped to the cardiac disorders system organ class occurred in 10 mRNA-1010 recipients and 6 comparator recipients, with a seventh comparator event of viral pericarditis not mapped to that class. Adjudication-confirmed cases were balanced at four in each group. (1) Investigators at the bedside attributed serious events to the vaccine three times as often in the mRNA-1010 arm, and that the disagreements be-

tween those investigators and the sponsor were resolved in the sponsor's favor in every case but one.

Structural limitations of the evidence base

The following limitations are drawn from the briefing document and are not contested by the Agency: (1)

1. Single season. Efficacy derives from one interim analysis in the 2024–2025 season. The study terminated early because case accrual (968) exceeded target (836). Performance in influenza B-predominant seasons or seasons with greater antigenic mismatch is unassessed.
2. No placebo arm. Both pivotal trials were active-controlled. This is conventional where licensed vaccines exist, but it means absolute vaccine efficacy, absolute reactogenicity attributable to the product, and background rates of the observed SAEs are all unmeasured for this product.
3. Excluded populations. Immunocompromised individuals and the very frail were excluded. These groups bear the highest absolute risk of severe influenza.
4. Non-preferred comparator in the highest-risk stratum, as described in Section 3.1.
5. No concomitant administration data for COVID-19, RSV, or pneumococcal vaccines, all routinely given to this population in the same visit.
6. Low occurrence of influenza-like illness, at 2.4%.
7. Duration of protection. Median follow-up was 181 days in P304. Protection beyond a single season is uncharacterized.
8. Potential assay bias favoring the product in the surrogate endpoint underpinning the 65-and-older indication.
9. No established correlate of protection, with correlate analyses ongoing at the time of the Advisory Committee meeting.
10. Numerically more deaths occurred among mRNA-1010 recipients than comparator recipients.

Each of these was disclosed. Eight acknowledged evidentiary gaps were resolved in favor of approval by deferral to a Phase 4 study whose protocol and timeline were, at the time of the briefing document, still "under review and the subject of ongoing discussions between FDA and the Applicant." (1) Accelerated approval regulations permit reliance on a surrogate endpoint reasonably likely to predict clinical benefit, conditioned on confirmatory study; (33) they do not specify how many independent ev-

identiary gaps may be carried simultaneously into the postmarketing period. Eight is not a residual uncertainty. It is an evidence base that was not assembled.

Taken together, these gaps mean the licensure decision was made without the determinations it required. The reactogenicity in **Tables 2 and 3** is also more than a tolerability cost: on this platform the fever and the myalgia are the outward sign of cellular events that have been studied in detail and that do not end when the symptoms do.

The confirmatory study is not designed to confirm benefit

Accelerated Approval was granted for adults 65 years and older on the condition that a Phase 4 study verify and describe the clinical benefit that the surrogate endpoint was taken to predict. The synopsis of that study appears in the briefing document. (1)

It is a cluster-randomized pragmatic trial of approximately 800,000 adults, enrolled across the 2027–2028 and 2028–2029 seasons, comparing mRNA-1010 with a CDC-preferentially recommended vaccine. Its primary endpoint is laboratory-confirmed medically attended influenza. Its design is noninferiority, with a margin of –15%: the null hypothesis is that relative vaccine efficacy is 15% or more below the comparator, and the study succeeds by rejecting that null. The sample size calculation states that 1,632 endpoint events provide at least 80% power to demonstrate noninferiority "assuming a true rVE of 0%." (1)

The study required to verify the clinical benefit of mFLUSIVA in adults 65 years and older is powered on the explicit assumption that its true benefit over the preferred comparator is zero, and it will be declared successful if the product is shown to be no more than 15% worse. A trial constructed this way cannot verify a clinical benefit, because it does not test for one. It tests for the absence of substantial inferiority.

Three further features compound this. Hospitalization appears only among secondary objectives, and stratified analyses are qualified as being conducted "if feasible", so the outcome that motivates the indication is again not the outcome the study is powered on. A waiver of informed consent is anticipated for all 800,000 participants. And the study timeline is recorded in the briefing document as "Under Review", with an interim analysis permitted to end the study after a single season. (1)

The commitment on which the 65-and-older indica-

tion rests will report its first interim analysis in December 2027 and its final report in May 2030, on an endpoint short of hospitalization. In the interim the product is administered to the population it was licensed for. The condition attached to the Accelerated Approval cannot discharge the obligation it was imposed to discharge, and the Agency accepted it anyway.

The approval letter issued on August 5, 2026 sets the terms. The confirmatory study is designated mRNA-1010-P910, a pragmatic randomized trial of relative vaccine effectiveness against a high-dose comparator in adults 65 years and older, with study initiation on August 31, 2026, three interim reports due at the end of 2027, 2028 and 2029, study completion on July 31, 2029, and a final report on May 31, 2030. (32) The letter states that if the study "fails to verify that clinical benefit is conferred by Influenza Vaccine, mRNA, or is not conducted with due diligence," approval may be withdrawn. (32) The difficulty is that a noninferiority design against an active comparator, with a margin permitting the product to be shown up to 15% less effective than the vaccine these patients are preferentially recommended to receive, is not constructed to verify a clinical benefit. It is constructed to exclude substantial inferiority. Four additional deferred pediatric studies were imposed under the Pediatric Research Equity Act, extending the platform toward children as young as six months, with final reports due between 2029 and 2031. (32)

Discussion

Principal findings

The annual occurrence of influenza in healthy adult populations is very low. Therefore, safety standards for vaccination must be very high. mFLUSIVA demonstrated an extremely unfavorable risk-benefit profile in the very clinical program used to justify its approval. A vaccine licensed in large part to prevent severe influenza outcomes was never tested against influenza death; no influenza-mortality endpoint appears anywhere in its development program. The mortality findings the program did produce instead favored the comparator. Unexplained deaths were more than twice as frequent among mFLUSIVA recipients, occurring at roughly twice the rate of the hospitalizations the vaccine prevented, and the signal can no longer be adequately resolved because only one autopsy was performed across 71,916 participants—and it was in the comparator arm. Serious adverse events were more frequent in the pivotal trial than in its control.

Grade 3 reactions severe enough to prevent daily activity were up to 27 times more frequent and did not attenuate with age. Against this burden, mFLUSIVA prevented only 4 influenza hospitalizations among 20,179 vaccinated adults during a season of unusually high transmission. Even the Phase 4 study required to verify clinical benefit in the age group bearing most influenza mortality is powered on the explicit assumption that true relative benefit is zero.

Study P304 met every statistical endpoint it was designed to meet. But when those results are converted to the absolute scale relevant to a benefit-risk decision, the clinical gain is small. A total of 137 adults had to receive mFLUSIVA rather than a standard-dose vaccine to prevent 1 laboratory-confirmed influenza illness, 1,003 to prevent 1 higher-level-care encounter, and 5,017 to prevent 1 hospitalization. Only 4 hospitalizations were prevented across 20,179 mFLUSIVA recipients during a season of unusually high influenza transmission. (1)

Benefit was smallest where protection was most needed. The NNV increased from 133 among adults aged 50 to 64 years to 180 among those aged ≥ 75 years, and from 110 among participants without high-risk conditions to 168 among those with at least one. The trial population was also healthier than the population for whom the vaccine is licensed: 57% had a high-risk condition compared with approximately 78% to 93% in the corresponding U.S. population, while immunocompromised and very frail individuals were excluded outright. (1,30)

Harm moved decisively in the opposite direction. One additional recipient experienced a solicited adverse reaction for every 3.4 vaccinated, 1 required an antipyretic or analgesic for every 5.2, and 1 experienced a Grade 3 systemic reaction preventing daily activity for every 21.6. Every individual solicited symptom was significantly more frequent with mFLUSIVA than with the comparator. The largest disparities occurred among severe reactions: chills were 5.30-fold more frequent at any grade and 15.41-fold at Grade 3, myalgia 3.05- and 10.79-fold, and fatigue 2.22- and 7.42-fold, respectively. These differences did not diminish with age. Among recipients ≥ 65 years, Grade 3 systemic reactions were 6.24-fold more frequent and Grade 3 local reactions 11.43-fold more frequent than with the comparator. (1,4)

The most consequential evidentiary failure concerns mortality. No influenza-mortality endpoint was

specified in either pivotal trial, so the program provides no direct evidence that mFLUSIVA prevents influenza death. (1) Yet the mortality quantities that can be calculated point toward harm rather than benefit. Unexplained deaths occurred in 23 mRNA-1010 recipients versus 9 comparator recipients (RR, 2.55; 95% CI: 1.18, 5.52), and in 29 versus 12 when related fatal-event terms were pooled (RR, 2.42; 95% CI: 1.23, 4.73); both confidence intervals exclude unity. Only 1 autopsy was performed across the entire 71,916-participant clinical program, and it was in the comparator arm. (1) Anchored to the demonstrated hospitalization benefit, the unresolved mortality imbalance amounted to approximately 2 unexplained deaths for every hospitalization averted. This does not establish that mFLUSIVA caused those deaths, but it establishes something directly relevant to licensure: the program left unresolved a mortality signal roughly twice the magnitude of the principal severe clinical benefit it demonstrated.

Figure 1 makes the extreme risk-benefit imbalance clear: to prevent just one hospitalization, 5,017 people had to receive mFLUSIVA instead of a standard flu shot—resulting in roughly 1,454 additional adverse reactions, 233 severe reactions that prevented normal daily activity, and 2 excess unexplained deaths.

Why this benefit-risk profile is hazardous

For every 1 hospitalization prevented, roughly 233 people were laid up by a reaction that stopped them going about their day, and roughly 1,454 experienced some reaction they would not otherwise have had. At population scale that arithmetic becomes concrete: vaccinate a million older adults and the modal outcome is not a prevented hospitalization but a week of illness that the vaccine itself caused.

The Advisory Committee was shown relative efficacy percentages beside raw reactogenicity percentages, quantities that cannot be compared, and asked to vote. No member was ever asked to affirm that 233 disabling reactions are a fair price for 1 averted hospitalization, because nobody had worked out that this was the price. (1)

The mortality gap is graver. A product class justified almost entirely by the deaths influenza causes was licensed without a single trial designed to find out whether it prevents any. Worse, the evidence base could not have detected the deaths it might cause. With 199 deaths across both arms and no influenza-specific cause of death recorded, the program was never capable of detecting a mortality

effect of the size the product exists to produce, in either direction.

And one signal did surface. Deaths of unspecified cause were significantly more frequent among mFLUSIVA recipients, at more than twice the comparator rate, and at roughly twice the rate of the hospitalizations the vaccine prevented. Whatever is driving that excess, the program produced more of it than it produced benefit. This cannot be checked, because the one procedure (autopsy) that would have settled it was performed once, on the wrong arm. A safety question that could have been answered for the cost of a post-mortem examination has instead been made unanswerable for good. No regulator should accept a mortality signal that the sponsor has rendered permanently uninvestigable.

Set against a benefit of this size, that residue of unresolved risk would already be difficult to justify. It is not, however, the whole of the exposure. mFLUSIVA is not a single injection. It is the first of 25 or 30 that a 55-year-old following the label will receive, delivered on a platform whose behavior inside human cells has been studied since 2021 and found to be considerably more eventful than the phrase "the mRNA degrades within days" suggests. The remainder of this section sets out what that platform has been shown to do.

Residual Plasmid DNA: A Deliverable Contaminant

Independent analyses of commercial COVID-19 mRNA lots have repeatedly detected residual plasmid DNA, including backbone sequences and SV40 promoter-enhancer fragments. (5–7) Quantities measured by fluorometry frequently exceed the nominal 10 ng/dose limit; fragments remain LNP-encapsulated and are efficiently taken up by cells. (5) Because influenza mRNA manufacturing is identical, residual DNA of comparable character is expected in mFLUSIVA and can participate in non-homologous end-joining or LINE-1-mediated insertion under inflammatory conditions. (8,9,20,23)

A multi-laboratory study reported residual DNA below regulatory limits, but it did not eliminate the underlying concern: plasmid-derived sequences still comprised 83.5%–98.1% of sequencing reads, and its lower DNA estimates depended on attributing higher fluorometric measurements to interference from vaccine mRNA. (34–36) The dispute therefore hinges on whether RNase treatment fully removed RNA-derived signal and whether that was adequately verified. When different validated methods produce results that differ by orders of magnitude on the same lots, the assay itself becomes a regula-

tory problem. mFLUSIVA was licensed without a specified orthogonal residual-DNA release method, RNase-verification requirement, or reported residual-DNA analysis in the FDA briefing document. (1)

Figure 2 summarizes the route by which residual template DNA and vaccine mRNA reach the nucleus: lipid nanoparticle uptake, LINE-1 activation, reverse transcription, and chromosomal insertion.

Transcription and Genomic Integration

Nucleoside-modified mRNA can activate endogenous LINE-1 elements, enabling reverse transcription and nuclear entry of vaccine-derived cDNA. (8,9) We previously reported the first peer-reviewed host-vector chimeric integration in a human subject: a previously healthy 31-year-old woman developed rapidly progressive stage-IV bladder cancer within 12 months of a three-dose Moderna series. (10) Circulating tumor DNA revealed a chimeric read at chr19:55,482,637–55,482,674 (GRCh38), outside the AAVS1 safe harbor and within a gene-dense zinc-finger region. The 20-bp sequence matched the spike ORF with probability ~ 1 in 10^{12} . Concurrent multi-omics showed oncogene activation and DNA-repair impairment. (10)

No systematic surveillance exists to determine whether such integration events are rare, recurrent, or cumulative with repeat dosing. That is the regulatory failure. A platform now licensed for indefinite annual administration carries a plausible genomic hazard whose population frequency is simply unknown because regulators have never required the surveillance needed to measure it.

Ribosomal Stalling Dynamics

The same chemical modification that prolongs mRNA half-life, N1-methylpseudouridine ($m^1\Psi$), fundamentally perturbs translational fidelity. Mulroney et al. demonstrated that incorporation of $m^1\Psi$ causes +1 ribosomal frameshifting both in vitro and in vivo, generating frameshifted polypeptides that elicit off-target cellular immunity in vaccinated mice and humans. (15,16)

mFLUSIVA is an N1-methylpseudouridine-modified product. Moderna's influenza vaccine patent claims a vaccine in which "100% of uracil nucleosides in the open reading frame are N1-methylpseudouridine", at a dose of 10 to 100 μg of mRNA polynucleotide, a range that brackets the 37.5 μg trivalent and 50 μg quadrivalent formu-

lations evaluated here. (37) The product runs on the same lipid nanoparticle and nucleoside-modified platform as the manufacturer's COVID-19 vaccine, in which complete $m^1\Psi$ substitution is established. What the FDA briefing document does not do is say so. Across 91 pages it describes the product as encoding full-length membrane-bound HA glycoproteins encapsulated in lipid nanoparticles, with "modified untranslated regions across all influenza strains to extend mRNA durability", and never states the nucleoside composition of the coding sequence. The words pseudouridine, N1-methylpseudouridine, and nucleoside-modified do not appear in it. (1) An Advisory Committee was asked to vote on the safety of a construct whose nucleoside chemistry it was never told.

Mechanistically, $m^1\Psi$ alters base-pairing geometry and stacking interactions within the ribosomal A site, slowing cognate aminoacyl-tRNA accommodation and peptidyl transfer. The resulting ribosome stalling creates a kinetic window for slippage. At "slippery" sequences (typically runs of U or A residues or related motifs), the stalled ribosome can shift +1 nucleotide into an alternative reading frame. (15,16) Once in the +1 frame, the ribosome frequently encounters a premature stop codon, releasing a truncated, out-of-frame polypeptide. These truncated products lack proper folding domains, expose hydrophobic surfaces, and are highly aggregation-prone.

Stalling also promotes ribosome collisions. Collided ribosomes activate quality-control pathways (including ribosome-associated quality control, RQC) and further increase the probability of frameshifting or drop-off. The net result is a continuous supply of aberrant polypeptides that must be handled by cellular protein-quality-control machinery. (15,16,38)

The mechanistic account above, advanced on kinetic grounds, has since been confirmed structurally. Rozman et al. used subcodon-resolution ribosome profiling and cryo-electron microscopy to show that $m^1\Psi$ increases ribosome density, directly slows elongation in defined sequence contexts, and alters interactions within the ribosomal decoding center, independent of innate immune activation or eIF2 α phosphorylation. (38) Monroe et al. independently characterized altered decoding kinetics at $m^1\Psi$ -modified codons. (39) The A-site perturbation described above is therefore no longer inferential, and the stalling that drives it is a direct physical consequence of the modification mFLUSIVA employs.

Frameshifting and Production of Misfolded Proteins

The frameshifted products are not merely non-functional; they constitute a distinct class of proteotoxic species. Because the amino-acid sequence after the shift is entirely different, these polypeptides cannot adopt the native fold of the encoded antigen. They frequently contain hydrophobic stretches that drive aggregation and are recognized by the ER as unfolded or misfolded cargo. (13,15,16) In addition, the intended full-length antigen is itself a large, heavily glycosylated membrane protein whose folding already places substantial burden on the ER. This is as true of hemagglutinin, which mFLUSIVA encodes in full-length membrane-bound form, as of the spike protein in which the phenomenon was originally characterized: both are trimeric class I fusion glycoproteins that fold in the ER, are extensively N-glycosylated, and traffic to the plasma membrane. The simultaneous production of both correct and frameshifted species overwhelms chaperone capacity. (14,17,18) What happens next is not incidental to the platform but is the cell's canonical response to precisely this form of insult, and it is the point at which a transient burden becomes a sustained one.

Figure 3 contrasts the two translational outcomes at a slippery sequence: normal-frame reading, which yields the intended antigen, and +1 slippage, which yields a truncated out-of-frame polypeptide that misfolds and aggregates.

Unfolded Protein Response and Transition to Proteostatic Collapse

Accumulation of misfolded and truncated proteins in the ER lumen activates the unfolded protein response through three parallel sensors: (17,18)

PERK arm. PERK phosphorylates eIF2 α , attenuating global translation while selectively allowing translation of ATF4. ATF4 induces adaptive genes but, under prolonged stress, also induces the proapoptotic transcription factor CHOP.

IRE1 arm. IRE1 oligomerizes and splices XBP1 mRNA, generating the active transcription factor XBP1s. XBP1s up-regulates ER-associated degradation (ERAD) components and chaperones, but chronic IRE1 signaling also drives inflammatory pathways (NF- κ B, JNK) and regulated IRE1-dependent decay (RIDD).

ATF6 arm. ATF6 translocates to the Golgi, where sequential cleavage by S1P/S2P releases the ATF6f

transcription factor that induces BiP/GRP78, GRP94, and other chaperones.

When ER stress is acute and resolvable, the UPR restores homeostasis. When stress is chronic, as occurs with repeated annual dosing of a frameshift-prone mRNA, the adaptive response fails. Sustained PERK-CHOP signaling, chronic IRE1-driven inflammation, proteasome overload, and accumulation of toxic aggregates produce frank proteostatic collapse, cellular toxicity, and tissue dysfunction. (13,14,17,18) Our transcriptomic data from post-mRNA injury cohorts precisely show these signatures: ribosomal stress, proteasome overload, non-sense-mediated decay, and mitochondrial dysfunction. (13)

The Encoded Antigen: Hemagglutinin Is Not an Inert Payload

mFLUSIVA does not encode the SARS-CoV-2 spike protein. It encodes the full-length, membrane-bound hemagglutinin (HA) glycoproteins of influenza A/H1N1, A/H3N2, and B/Victoria, 12.5 μ g of each mRNA, 37.5 μ g in total. (1) Hemagglutinin is not an inert immunogen but one of the best-characterized fusogens in molecular biology.

HA is a trimeric class I fusion glycoprotein. It binds sialic acid, a terminal sugar displayed on the glycoproteins and glycolipids of essentially every human cell type, including erythrocytes, platelets, endothelium, and leukocytes; the protein is named for its capacity to agglutinate red blood cells through exactly this interaction. Following proteolytic cleavage into the disulfide-linked HA1 and HA2 subunits, mildly acidic conditions trigger an irreversible conformational change that exposes the HA2 fusion peptide and drives membrane merger. Cells expressing HA on their plasma membrane fuse with adjacent cells on acidification, forming multinucleated syncytia. This is not an incidental observation but a standard laboratory technique: HA is used precisely because it is a reliable, well-characterized cell-cell fusogen, and transfection of cells with an HA-encoding construct followed by low-pH exposure is a routine syncytium assay. (40,41)

A vaccine that instructs cells to synthesize full-length membrane-bound HA is therefore instructing them to display a functional fusogen and a sialic-acid-binding lectin on their surface. Three consequences follow that were not evaluated in this licensure application. First, HA displayed on a host cell membrane makes that cell a target for antibody-dependent cellular cytotoxicity and for cytotoxic T

lymphocytes, which is the intended immunological mechanism, but the identity, number, and tissue distribution of the transfected cells that are consequently destroyed is unknown, because no biodistribution study of mFLUSIVA in humans was submitted. (1) Second, cleavage of HA into its fusion-competent form is performed by host proteases, and the pH thresholds for HA-mediated fusion lie within the range encountered in endosomal and certain inflamed or ischemic tissue microenvironments. Third, free HA protein is not immunologically neutral: purified hemagglutinin binds and internalizes into human natural killer cells via sialic acids, downregulates the CD3 ζ chain through the lysosomal pathway, and reduces NKp46- and NKp30-mediated cytotoxicity, while influenza virus itself directly infects NK cells and induces apoptosis. (42,43) A protein with demonstrated capacity to suppress natural killer cell function is being expressed endogenously, at unmeasured quantity, for an unmeasured duration, annually, in adults whose innate immune competence is already age-attenuated.

The more directly relevant question is whether HA expression itself stresses the cell that produces it. Frabutt and colleagues showed that host cells sense influenza HA glycoproteins through the ER stress pathway, and that HA expression triggers ER-associated protein degradation as an antiviral response. (44) Slaine and colleagues, screening thiopurines, found that disrupting HA and neuraminidase maturation activated all three UPR sensors, ATF6, IRE1, and PERK, and that a chemical chaperone partially restored glycoprotein processing, placing HA maturation squarely within the ER folding-capacity problem. (45) Most directly on point, heterologous expression of influenza haemagglutinin, that is, HA expressed from an introduced construct rather than delivered by virus, produced early and transient activation of the unfolded protein response, the same experimental configuration an mRNA vaccine creates. (46) Against this, Mazel-Sanchez and colleagues, explicitly contradicting what they described as a panel of previous reports, identified neuraminidase rather than hemagglutinin as the determinant of ER stress during influenza infection. (47) The disagreement is unresolved. What is not in dispute is that HA is a heavily N-glycosylated membrane glycoprotein that folds in the ER under chaperone supervision, that its maturation consumes folding capacity, and that influenza infection induces apoptosis in cultured mammalian cells through pathways in which ER stress participates. (48) The unresolved question is what quantity of

HA, expressed for what duration, in which tissues, crosses from adaptive UPR signaling into the chronic activation described in Section 4.7. That question is answerable by experiment and was not asked.

Inactivated vaccines deliver a fixed, measured dose of exogenous HA that is cleared by ordinary protein catabolism. An mRNA product instructs an unspecified population of the recipient's own cells, in unspecified tissues, to manufacture membrane-anchored HA in unmeasured quantity for an unmeasured period. The FDA briefing document contains no quantification of HA expression, no measurement of its duration, no biodistribution data, and no assessment of whether expressed HA retains fusogenic competence. (1) For a product to be administered annually across the remaining decades of a recipient's life, these are not unreasonable questions. None was asked before licensure, and none will be answered by the confirmatory study that was required instead.

Concurrent mRNA Products in the Same Recipients

mFLUSIVA does not enter this population alone. Moderna's mRESVIA (mRNA-1345) was licensed in May 2024 for adults 60 years and older and subsequently extended to high-risk adults 18 through 59 years, and ACIP recommends a single dose of an RSV vaccine for all adults 75 years and older and for those 60 through 74 years at increased risk. (49,50,51) The recommended recipients of mRESVIA and the licensed recipients of mFLUSIVA are substantially the same people.

The two products are the same technology. mRESVIA delivers 50 μ g of nucleoside-modified mRNA encoding the membrane-anchored RSV fusion glycoprotein stabilized in its prefusion conformation, encapsulated in lipid nanoparticles composed of SM-102, PEG2000-DMG, cholesterol, and DSPC, the identical lipid formulation used in the manufacturer's COVID-19 vaccine. (49) An older adult who receives both products in a single season is instructed to synthesize four foreign membrane glycoproteins: three influenza hemagglutinins and one RSV prefusion F protein, from a combined 87.5 μ g of nucleoside-modified mRNA. All four are class I viral fusion glycoproteins. All four fold in the endoplasmic reticulum, are extensively N-glycosylated, and traffic to the plasma membrane of whichever cells take up the particles. Every liability set out in Sections 4.3 through 4.8 applies to both products, and applies twice to anyone who receives both.

The three products are set out side by side in **Table 7**. What the comparison shows is not a family of related vaccines but one technology pointed at three pathogens. The delivery vehicle is the same four-lipid nanoparticle in each case, the nucleoside chemistry is the same, and every encoded antigen belongs to the same structural class. What differs between the columns is the pathogen, the dose, and the licensed population. Nothing that bears on cumulative platform exposure differs at all.

No study has examined that combination. FDA states in the briefing document that data on concomitant administration with routinely co-administered vaccines, naming COVID-19, RSV, and pneumococcal vaccines, are not available. (1) There is therefore no assessment of combined reactogenicity, no assessment of combined mRNA and lipid nanoparticle burden, no assessment of whether expressing four fusion glycoproteins simultaneously exceeds cellular folding capacity in a way that expressing three does not, and no assessment of cumulative genomic or proteostatic exposure across two products given in the same visit or the same season. Each product was evaluated as though it were the only mRNA product its recipient would ever receive, and the population for which both are recommended was never studied receiving both.

Neither mFLUSIVA nor mRESVIA is indicated for pregnant women. mRNA COVID-19 vaccines, built on the same platform and delivered in the same lipid nanoparticles, were recommended in pregnancy. The technology did not change between those decisions; only the product did. This platform was judged unsuitable for pregnancy when the disease was influenza or RSV, and suitable for pregnancy when the disease was COVID-19. Both positions cannot be correct, and no reasoning reconciling them has been published. A regulatory posture that shifts with the product rather than with the technology is not a safety standard.

Multi-Year Persistence and Cumulative Risk of Annual Dosing

We have previously documented vaccine-derived spike mRNA, residual plasmid DNA, and bioactive spike protein persisting beyond 3.5 years. (11) Complementary studies confirm circulating spike and vaccine mRNA for weeks to months. (53–56) A 2026 systematic review screening 2,470 records and synthesizing 20 studies concluded that the foundational assumptions of rapid decay and localised distribution have not consistently held. (12) Annual influenza mRNA dosing would repeatedly impose ri-

bosomal stalling, frameshifting, ER stress, and potential integration events on cells already carrying residual material, converting transient insults into lifelong genomic and proteostatic burden. (11,19–21)

Every one of these persistence measurements was made on COVID-19 vaccines encoding the SARS-CoV-2 spike protein, because those are the only nucleoside-modified mRNA products that have been in human populations long enough to measure. No equivalent biodistribution or persistence study has been conducted for an mRNA product encoding hemagglutinin, and none was submitted in support of this licensure. (1) The relevant inference is not that hemagglutinin will behave as spike does, but that the delivery platform, the residual template DNA, and the modified nucleotide chemistry are common to both, and that the clearance assumptions which failed for one product have never been tested for the other. Repeated antigen exposure on this platform additionally drives immune imprinting and class switching toward non-inflammatory spike-specific IgG4, (57,58) an effect characterized for spike and unstudied for annually readministered hemagglutinin. The pre-licensure program for mFLUSIVA was designed around single-dose exposure with approximately six months of follow-up. (1) The product is indicated for annual administration for the remainder of a recipient's life: a 55-year-old vaccinated per label will receive on the order of 25 to 30 doses. No element of the submitted evidence addresses cumulative exposure, and the required Phase 4 study is designed to evaluate relative effectiveness in adults 65 and older, not cumulative platform effects. (1)

Anticipated Cardiotoxicity

Myocarditis and pericarditis are the adverse events for which the mRNA platform carries the clearest regulatory precedent, and they are the events this program was least equipped to detect. FDA stated that the safety database "is insufficient to detect rare adverse events, including myocarditis, Guillain-Barre syndrome (GBS), and other neurological events of interest." (1) That statement is quantitatively correct and its magnitude deserves to be made explicit. Detecting a doubling of myocarditis incidence against a background rate of 1 to 2 per 100,000 requires on the order of 2.4 to 4.7 million participants at 80% power. The entire pooled safety database for mFLUSIVA comprised 71,916 participants, between 16-fold and 65-fold short of that requirement. The absence of a detected myocarditis signal in this program is therefore uninformative. It is what a study of this size produces whether or not

the hazard exists.

What the program did produce is consistent with the hazard rather than against it. Cardiac adverse events of special interest mapped to the cardiac disorders system organ class occurred in 10 mRNA-1010 recipients and 6 comparator recipients, and one adjudication-confirmed myopericarditis occurred in a 64-year-old man with no significant medical history who was discharged with heart failure with reduced ejection fraction, assessed as vaccine-related by the treating investigator. (1) FDA has now imposed postmarketing active surveillance for myocarditis, pericarditis, myopericarditis, and Guillain-Barre syndrome, (59,60) which is an acknowledgement that the question was not answered before licensure.

The mechanistic basis for anticipating cardiac injury is established and specific to this platform. Krauson and colleagues identified COVID-19 vaccine mRNA in the hearts of individuals who died within 30 days of vaccination, together with histologically confirmed myocardial injury. (55) Baumeier and colleagues, in an endomyocardial biopsy-proven case series, detected vaccine-encoded spike protein and no nucleocapsid in the myocardium of individuals with vaccine-associated myocarditis, establishing that the antigen itself reaches cardiac tissue and that the finding is not attributable to prior infection. (61) Schreckenber and colleagues showed that mRNA-1273 and BNT162b2 induce cardiotoxic effects on ventricular myocyte function and structure in isolated cardiomyocytes, demonstrating direct toxicity independent of any immune-mediated mechanism. (62) Taken together, these findings establish cardiac tropism of the delivery system, cardiac deposition of the encoded antigen, and direct myocyte toxicity of the product.

None of the three mechanisms above depends on the identity of the encoded antigen. Lipid nanoparticle biodistribution, cardiac uptake, and myocyte-level toxicity are properties of the delivery platform and the nucleoside chemistry, both of which mFLUSIVA shares with the products in which these findings were made. What changes is that hemagglutinin, rather than spike, will be the glycoprotein expressed in cardiac tissue, and hemagglutinin is a sialic-acid-binding lectin and a competent cell-cell fusogen, as set out in Section 4.8.

Real-world data indicate that a cardiac mortality signal from this platform emerges only at population scale. In King County, Washington, a population of approximately 2.3 million with approximately 98% COVID-19 vaccination coverage, excess fatal cardiopulmonary arrests rose from 11 in

2020 to 147 in 2023, and excess cardiopulmonary arrest mortality increased quadratically with vaccination rate. (63) A signal of that kind became apparent in a vaccinated population of roughly 2 million, which is approximately thirty times the size of the entire mFLUSIVA clinical program.

If mFLUSIVA is administered annually at population scale, we expect vaccine-associated myocarditis, myopericarditis, and cardiac arrest to become detectable in passive and active surveillance within one to three seasons, and we expect vaccine-derived mRNA and hemagglutinin antigen to be recoverable from myocardial tissue in decedents who die within thirty days of administration. The tissue studies required to test this were not performed before licensure and are not required by any postmarketing commitment.

Why FDA approval should be reversed

Table 8 sets out seventeen independent grounds for reversal. The first nine arise entirely from FDA's own regulatory record and trial arithmetic, and several are sufficient on their own to warrant withdrawal. The remaining eight establish the additional platform-level hazards being accepted in exchange for an absolute benefit of just one hospitalization averted per 5,017 vaccinations. Every one of these grounds remained unresolved at licensure. The approval was therefore not made despite minor residual uncertainty, but in the face of multiple unresolved failures in efficacy, safety, and platform risk that directly undermine the benefit-risk determination itself.

A regulatory system functioning as designed would have required a trial against the preferred standard of care in adults 65 years and older before licensure in that population, not after. That trial is now a post-marketing commitment, and the product will be administered to an unknown number of older adults during the 2026–2027 season while it is conducted.

The evidence submitted in support of BLA 125869/0 does not establish a favorable benefit-risk relationship for mFLUSIVA in either licensed age group, and on the arithmetic set out in the Results it establishes the opposite: harms two to three orders of magnitude more frequent than the severe outcomes averted, an unresolved and now unresolvable mortality signal, and no measurement whatever of the outcome that motivates the indication. The approval should be reversed, and it should be reversed before the 2026–2027 season rather than after it.

A product whose measured benefit is 1 averted hos-

pitalization per 5,017 recipients is being administered on a platform that generates residual DNA capable of integration, activates LINE-1 reverse transcription, induces ribosomal stalling and +1 frameshifting, and drives chronic UPR activation, annually, for the remainder of each recipient's life. The benefit does not justify accepting even a small probability of those outcomes, and no surveillance system capable of detecting them was required at licensure. A recipient consenting to annual mFLUSIVA is accepting an unquantified cumulative genomic and proteostatic exposure in exchange for a 1-in-5,000 chance of avoiding a hospitalization. No informed person would price that trade as the Agency has.

Limitations

This analysis inherits the limitations of its sources. All efficacy and safety counts derive from the FDA briefing document (1) and have been checked against the Clinical Review Memorandum and approval letter issued on August 5, 2026; (31,32) every figure reported here is unchanged in the final approval package. Our NNV and NNH calculations assume the per-protocol and solicited-safety-subset denominators are appropriate for absolute risk estimation, and the solicited safety subset was approximately 15% of P304 participants. Risk ratios and confidence intervals in **Tables 2** through **6** were calculated by us from published counts and are unadjusted.

Recommendations

The findings above do not describe a product that can be made acceptable through stronger labeling or closer postmarketing surveillance. They describe an approval that should not have been granted because the evidentiary requirements for licensure were not met. The first two recommendations in **Table 9** therefore address the approval itself; the remainder address the regulatory failures that allowed such a decision to occur.

Conclusion

The evidence presented here does not support continued licensure of mFLUSIVA. Its extreme risk-benefit profile supports reconsideration of market authorization in both age groups and suspension of distribution pending a substantially more rigorous demonstration of clinical benefit and long-term safety. The central risk-benefit calculation is pro-

foundly unfavorable. Relative to a standard-dose influenza vaccine, 5,017 adults had to receive mFLUSIVA to avert one influenza hospitalization, while approximately 1,454 additional recipients experienced a solicited adverse reaction and 233 additional recipients experienced a Grade 3 systemic reaction severe enough to prevent daily activity. Benefit was smallest in the oldest and highest-risk recipients, precisely those for whom meaningful protection is most important. Meanwhile, every solicited symptom was more frequent with mFLUSIVA, serious adverse events were significantly more frequent in the pivotal trial considered alone, and deaths of unspecified cause occurred more than twice as frequently among mFLUSIVA recipients. Neither pivotal trial included a placebo arm, so absolute vaccine-attributable harm and background event rates were never established; all observed safety comparisons were made against other influenza vaccines rather than an unvaccinated control.

Most importantly, the clinical development program never measured whether mFLUSIVA prevents influenza death. No influenza-mortality endpoint was specified or collected, yet the only statistically significant mortality findings in the submitted evidence favored the comparator. Those unexplained deaths can no longer be adequately investigated because no autopsy was performed on any affected mFLUSIVA recipient.

These deficiencies are compounded by the proposed lifelong pattern of exposure. mFLUSIVA extends nucleoside-modified mRNA technology to annual administration despite unresolved questions concerning residual DNA, reverse transcription and genomic integration, translational fidelity, protein misfolding, proteostatic stress, biodistribution, persistence, and cumulative effects of repeated dosing. None was adequately characterized for decades of annual exposure. This is not a benefit-risk profile that warrants stronger labeling or routine postmarketing surveillance. It is a benefit-risk profile that fails to justify licensure in the first place.

Ethics Statement

Institutional Review Board approval and informed consent were not required because this study used only previously published literature, publicly available regulatory documents, and publicly accessible trial data. No new human or animal research was conducted, and no identifiable private information was accessed or analyzed.

Conflict of Interest Statement

John Catanzaro is the CEO and a shareholder of Neo7Bioscience.

Data Availability Statement

No new participant-level dataset was generated for this study. All data analyzed or discussed were obtained from publicly available sources, including FDA regulatory documents, published clinical-trial reports, trial registries, product labeling, and the cited scientific literature. The data supporting the

analyses and conclusions are therefore available through the referenced public sources.

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Generative AI statement

Artificial intelligence (AI) tools (ChatGPT) were used to assist in the generation and refinement of figures included in this manuscript.

Table 1. Absolute benefit of mFLUSIVA versus standard-dose comparator by outcome severity, age, baseline risk, and strain. Study P304, per-protocol set.

Endpoint or subgroup	mRNA-1010	Comparator	ARD (pp)	NNV
By outcome severity (all participants)				
RT-PCR-confirmed protocol-defined ILI	411/20,179	557/20,124	0.731	137
Modified CDC-defined ILI	223/20,179	290/20,124	0.336	298
Any healthcare encounter	80/20,179	120/20,124	0.200	500
Higher level of care (hospital/ER/urgent care)	22/20,179	42/20,124	0.100	1,003
Urgent care visit	13/20,179	24/20,124	0.055	1,824
Emergency room visit	6/20,179	12/20,124	0.030	3,345
Hospitalization	4/20,179	8/20,124	0.020	5,017
Death from influenza	not measured	not measured	—	not estimable
By age (protocol-defined ILI)				
50 through 64 years	229/10,542	307/10,501	0.751	133
65 through 74 years	138/7,307	191/7,289	0.732	137
75 years and older	44/2,230	59/2,334	0.555	180
By baseline risk (protocol-defined ILI)				
At least one high-risk condition	241/11,465	309/11,457	0.595	168
No high-risk condition	170/8,714	248/8,667	0.911	110
By strain (protocol-defined ILI)				
Influenza A/H1N1	223/20,179	315/20,124	0.460	217
Influenza A/H3N2	158/20,179	202/20,124	0.221	453
Influenza B/Victoria	25/20,179	35/20,124	0.050	1,999

Legend: ARD=absolute risk difference; NNV=number needed to vaccinate; pp=percentage points.

Case counts from FDA briefing document Table 1, Table 2, Table 3, Appendix B Table 10 and Appendix B Table 14. (1) Absolute risk differences and NNV calculated by the authors. No influenza-mortality endpoint was specified, collected, or reported at any point in the clinical development program; NNV for one influenza death averted is therefore not estimable from the submitted evidence.

Table 2. Absolute reactogenicity burden

Endpoint	mRNA-1010	Comparator	ARI (pp)	NNH	Risk ratio (95% CI)
P304, versus standard dose (n = 3,015 vs 2,997)					
Any solicited adverse reaction	75.7%	46.7%	29.0	3.4	1.62 (1.55, 1.69)
Any solicited local reaction	67.5%	32.1%	35.4	2.8	2.10 (1.99, 2.23)
Any solicited systemic reaction	58.0%	32.4%	25.7	3.9	1.79 (1.69, 1.90)
Grade 3 local reaction	1.7%	0.1%	1.6	64.2	12.67 (4.59, 35.02)
Grade 3 systemic reaction	5.5%	0.9%	4.6	21.6	6.15 (4.11, 9.20)
Antipyretic or analgesic use	28.5%	9.1%	19.4	5.2	3.14 (2.77, 3.57)
P303 Part C, versus Fluzone High-Dose (n = 1,502 vs 1,490)					
Any solicited adverse reaction	75.3%	49.3%	26.0	3.8	1.53 (1.44, 1.62)
Any solicited local reaction	66.1%	38.9%	27.2	3.7	1.70 (1.58, 1.83)
Any solicited systemic reaction	61.3%	32.9%	28.3	3.5	1.86 (1.71, 2.02)
Grade 3 local reaction	2.4%	0.8%	1.6	62.8	2.98 (1.55, 5.70)
Grade 3 systemic reaction	6.9%	1.7%	5.2	19.3	4.08 (2.65, 6.29)

Legend: ARI=absolute risk increase; NNH=number needed to harm; pp=percentage points.

Data from FDA briefing document Appendix B Tables 18 to 20 and Appendix C Tables 11 to 13. (1) Risk ratios and confidence intervals calculated by the authors. The Grade 3 systemic reaction rate in P303 Part C is 6.9% per Appendix C Table 11 and 6.7% per the accompanying narrative text; this discrepancy is internal to the source document.

Table 3. Solicited adverse reactions by individual symptom and severity, Study P304 (mRNA-1010 n = 3,015; standard-dose comparator n = 2,997). Every comparison but one favors the comparator, and all but two are statistically significant.

Reaction	mRNA-1010 % (n)	Comparator % (n)	Risk ratio (95% CI)
Systemic, any grade			
Fever	5.8 (174)	0.9 (26)	6.65 (4.42, 10.01)
Chills	22.8 (688)	4.3 (129)	5.30 (4.42, 6.35)
Antipyretic or analgesic use	28.5 (860)	9.1 (272)	3.14 (2.77, 3.57)
Myalgia	35.4 (1,067)	11.6 (348)	3.05 (2.73, 3.40)
Arthralgia	27.8 (839)	10.6 (317)	2.63 (2.34, 2.96)
Nausea or vomiting	8.6 (259)	3.4 (102)	2.52 (2.02, 3.16)
Fatigue	45.1 (1,360)	20.3 (609)	2.22 (2.05, 2.41)
Headache	37.8 (1,140)	18.0 (538)	2.11 (1.93, 2.30)
Systemic, Grade 3 (prevents daily activity)			
Grade 3 chills	2.1 (62)	0.1 (4)	15.41 (5.61, 42.30)
Grade 3 myalgia	2.5 (76)	0.2 (7)	10.79 (4.98, 23.37)
Grade 3 arthralgia	1.9 (57)	0.2 (6)	9.44 (4.08, 21.87)
Grade 3 fatigue	3.2 (97)	0.4 (13)	7.42 (4.17, 13.20)
Grade 3 any systemic	5.5 (167)	0.9 (27)	6.15 (4.11, 9.20)
Grade 3 headache	2.0 (59)	0.3 (10)	5.86 (3.01, 11.44)
Grade 3 fever	0.6 (17)	0.1 (3)	5.63 (1.65, 19.20)
Grade 3 nausea or vomiting	0.2 (5)	<0.1 (2)	2.49 (0.48, 12.80)
Local, any grade			
Swelling ≥25 mm	5.7 (172)	1.5 (45)	3.80 (2.75, 5.25)
Erythema ≥25 mm	3.9 (117)	1.3 (38)	3.06 (2.13, 4.40)
Axillary swelling or tenderness	17.2 (520)	6.1 (184)	2.81 (2.39, 3.30)
Injection site pain	65.8 (1,985)	29.8 (894)	2.21 (2.08, 2.35)
Local, Grade 3			
Grade 3 injection site pain	0.9 (27)	<0.1 (1)	26.84 (3.65, 197.4)
Grade 3 any local	1.7 (51)	0.1 (4)	12.67 (4.59, 35.02)
Grade 3 axillary swelling/tenderness	0.3 (10)	<0.1 (1)	9.94 (1.27, 77.61)
Grade 3 erythema	0.3 (10)	<0.1 (2)	4.97 (1.09, 22.66)
Grade 3 swelling	0.3 (9)	0.1 (4)	2.24 (0.69, 7.25)

Legend: Counts from FDA briefing document Appendix B Tables 19 and 20. (1) Risk ratios and 95% confidence intervals calculated by the authors and are unadjusted; wide intervals on the Grade 3 local reactions reflect small comparator event counts. Grade 3 for systemic symptoms other than fever is defined by the protocol as a reaction that prevents daily activity. No Grade 4 solicited systemic reactions were reported in Study P304.

Table 4. Harm incurred per unit of benefit obtained. Each cell gives the number of recipients experiencing the column harm for every one recipient spared the row benefit, derived from Tables 1, 2 and 3.

Benefit obtained (one event averted)	Any solicited reaction	Antipyretic or analgesic use	Any Grade 3 systemic reaction	Grade 3 fatigue	Grade 3 myalgia	Grade 3 chills	Any Grade 3 local reaction
RT-PCR-confirmed influenza-like illness	40	27	6	4	3	3	2
Modified CDC-defined ILI	86	58	14	8	7	6	5
Any healthcare encounter	145	97	23	14	11	10	8
Higher-level-care encounter	291	195	47	28	23	19	16
Emergency room visit	969	651	155	93	77	64	52
Influenza hospitalization	1,454	976	233	140	115	96	78

Legend: Calculated as the number needed to vaccinate for the row benefit multiplied by the unrounded absolute risk increase for the column harm, using Study P304 figures throughout. Values are computed from exact event counts rather than from the rounded numbers needed to harm shown in Tables 2 and 3.

Table 5. Mortality in the pooled Phase 3 safety database (mRNA-1010 n = 35,965; comparator n = 35,951; median follow-up 198 days), expressed on an absolute scale.

Mortality endpoint	mRNA-1010	Comparator	Risk ratio (95% CI)	Excess per million	NNH
All-cause death	102	97	1.05 (0.80, 1.39)	+138	7,248
Death, unspecified cause (PT)	23	9	2.55 (1.18, 5.52)	+389	2,570
Unspecified fatal events (pooled PTs)	29	12	2.42 (1.23, 4.73)	+473	2,116
All-cause death within 28 days	13	14	0.93 (0.44, 1.97)	-28	not applicable
Unspecified fatal events within 28 days	3	2	1.50 (0.25, 8.97)	+28	35,993

Legend: PT=MedDRA preferred term; NNH=number needed to harm.

Counts from FDA briefing document Sections 3.2.2 and 3.2.3. (1) Risk ratios, confidence intervals, per-million excesses and NNH calculated by the authors and are unadjusted. Negative values in the excess column denote deaths averted.

Table 6. Non-fatal adverse events reported more frequently among mRNA-1010 recipients than comparator recipients, pooled Phase 3 safety database

Event	mRNA-1010	Comparator	Risk ratio (95% CI)
Serious adverse events, Study P304 alone	455	392	1.16 (1.02, 1.33)
Urinary tract infection SAEs (expanded)	38	22	1.73 (1.02, 2.92)
Anemia SAEs (expanded)	14	8	1.75 (0.73, 4.17)
Investigator-assessed vaccine-related SAEs	9	3	3.00 (0.81, 11.08)
Myocarditis/pericarditis (any time)	10	7	1.43 (0.54, 3.75)
Guillain-Barré syndrome	1	0	not estimable

Legend: SAE=serious adverse event.

Counts from FDA briefing document Sections 3.2.2 and 3.2.3. (1) Risk ratios and confidence intervals calculated by the authors and are unadjusted.

Table 7. The three licensed Moderna mRNA vaccines compared. Compiled from the product labeling and the FDA briefing document. (1,3,49,52)

Attribute	Spikevax (mRNA-1273)	mFLUSIVA (mRNA-1010)	mRESVIA (mRNA-1345)
Target pathogen	SARS-CoV-2	Influenza A and B	Respiratory syncytial virus
Encoded antigen	Spike glycoprotein, pre-fusion-stabilized	Hemagglutinin, full-length membrane-bound	Fusion (F) glycoprotein, prefusion-stabilized
Foreign glycoproteins expressed per dose	1	3 (A/H1N1, A/H3N2, B/Victoria)	1
Antigen structural class	Class I viral fusion glycoprotein	Class I viral fusion glycoprotein	Class I viral fusion glycoprotein
mRNA per dose	50 µg	37.5 µg (12.5 µg per strain)	50 µg
Nucleoside modification	m ¹ Ψ, complete uridine substitution	m ¹ Ψ; not stated in the briefing document	Nucleoside-modified
Lipid nanoparticle	SM-102, PEG2000-DMG, cholesterol, DSPC	Same platform	SM-102, PEG2000-DMG, cholesterol, DSPC
Licensed population	≥6 months	≥50 years	≥60 years; 18–59 years at increased risk
Dosing schedule	Annual, seasonally reformulated	Annual, indefinitely	Single dose
Indicated in pregnancy	Recommended	No	No
Coadministration with the other mRNA products	Not studied	Not studied	Not studied

Legend: m¹Ψ=N1-methylpseudouridine; DSPC=1,2-distearoyl-sn-glycero-3-phosphocholine; PEG2000-DMG=1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000.

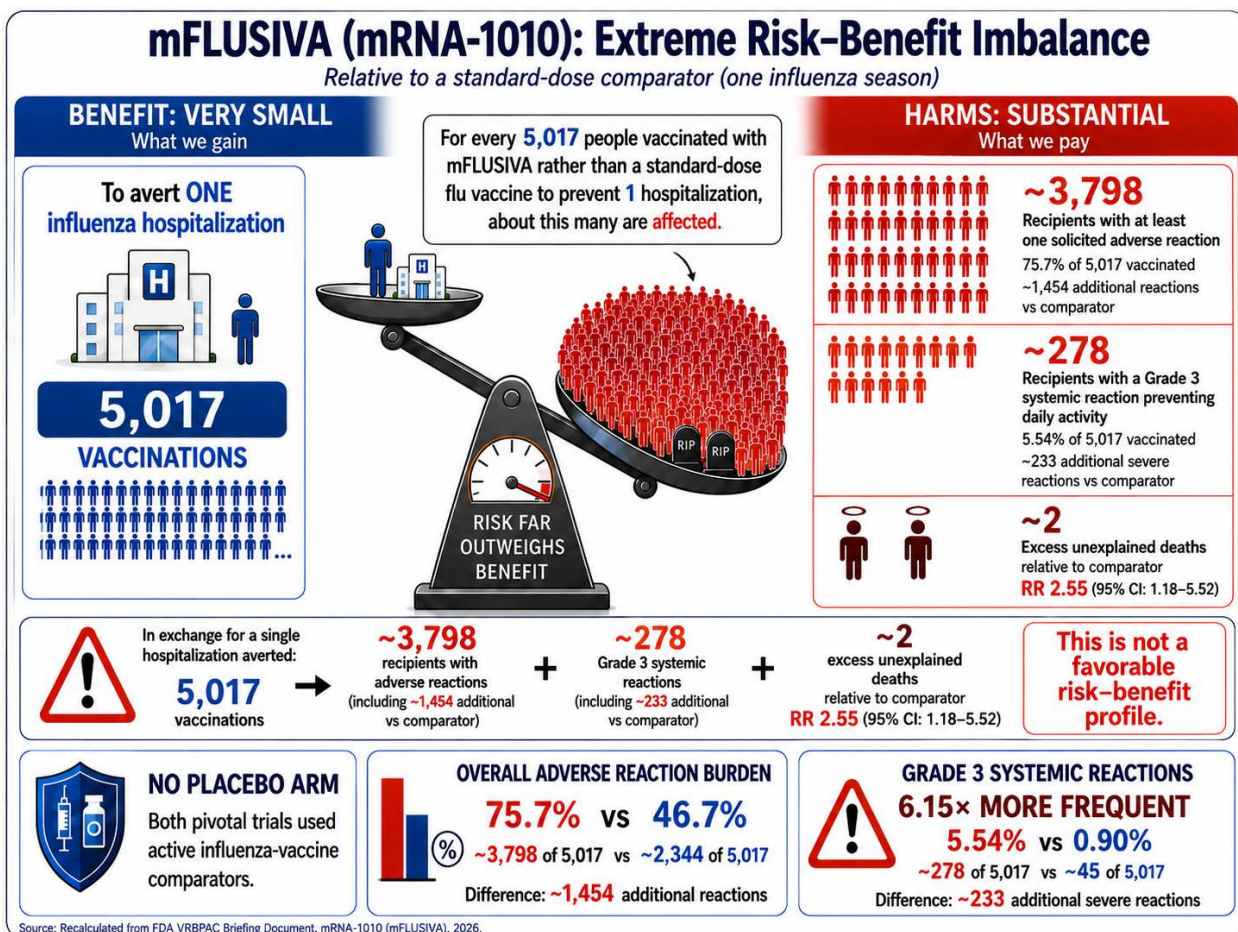
The nucleoside composition of mFLUSIVA is stated nowhere in the briefing document; the entry shown is established for the manufacturer's COVID-19 product and claimed in the manufacturer's influenza vaccine patent. (37) Pregnancy entries describe licensed indication and recommendation status, not a safety determination.

Table 8. Grounds for reversal of the mFLUSIVA approval, in order of evidentiary independence. Grounds 1 through 9 are drawn from the FDA briefing document and the trial arithmetic; grounds 10 through 17 are drawn from the published platform literature.

Ground	Basis
Comparator ruled inadequate, then not	FDA determined in February 2026 that the pivotal comparator was inadequate, then reversed within approximately one week without new efficacy data. The deficiency was reclassified, not remedied. (26,27)
Burden shifted to the highest-risk group	The remedy transferred the unmet evidentiary burden to the post-licensure period specifically for adults 65 years and older, the group for whom the original objection was strongest and the group at highest absolute risk. (1,27)
Absolute benefit is small	NNV 137 for 1 confirmed influenza-like illness, 1,003 for 1 higher-level-care encounter, 5,017 for 1 hospitalization, and smallest in the oldest and highest-risk strata. (1)
Absolute harm is large and pervasive	NNH 3.4 for any solicited reaction and 21.6 for a Grade 3 systemic reaction, yielding approximately 233 Grade 3 systemic reactions per hospitalization averted. Every solicited symptom was significantly more frequent, and reactogenicity did not attenuate with age. (1)
The decisive outcome was never measured	No influenza-mortality endpoint was specified, collected, or reported anywhere in the program. The outcome the product exists to prevent was never measured. (1)
The mortality signal can never be resolved	Deaths of unspecified cause were more than twice as frequent among mRNA-1010 recipients, with a confidence interval excluding unity. One autopsy was performed across 71,916 participants, and it was in the comparator arm. (1)
Eight evidentiary gaps deferred, not closed	Eight structural evidentiary gaps were disclosed and resolved by deferral to a Phase 4 study whose final protocol was submitted four weeks before the Advisory Committee vote and whose results will not be complete until 2030. (1)
The confirmatory study cannot confirm benefit	The Phase 4 study required to verify clinical benefit in adults 65 years and older is a noninferiority trial with a –15% margin, powered on the explicit assumption of a true relative vaccine efficacy of 0%. (1)
The licensed product was never tested	The licensed strain composition was never tested in either pivotal trial, in a product whose 65-and-older indication rests on an unvalidated surrogate measured by a potentially biased assay. (1,3)
Irreversible genomic insertion	Integrated foreign DNA becomes a permanent genomic resident. (10,23)
Ribosomal stalling and frameshifting	m ¹ Ψ systematically generates truncated, aggregation-prone polypeptides. (15,16,38)
Chronic UPR and proteostatic collapse	Repeated ER stress exhausts adaptive capacity and drives inflammation and cell death. (13,17,18)
Cumulative oncogenic and proteotoxic load	Annual dosing compounds genomic instability and proteotoxic stress over decades. (13,19–21)
Reactogenicity as a mechanistic warning	Extreme systemic reactions reflect the cellular stress that promotes stalling, frameshifting, and UPR activation. The magnitude is quantified: 1 Grade 3 systemic reaction per 22 recipients, against 1 hospitalization averted per 5,017. (1,14,15)
Uncharacterized expression of a fusogen	Hemagglutinin is a sialic-acid-binding lectin and a well-characterized cell-cell fusogen. Its expression from mFLUSIVA was not quantified, its duration not measured, its biodistribution not studied, and its fusogenic competence not assessed. (1,40,42)

Unstudied combined exposure	The same older adults are recommended to receive mFLUSIVA and mRESVIA, instructing their cells to produce four foreign class I fusion glycoproteins from 87.5 µg of nucleoside-modified mRNA in a single season, with no study of the combination. (1,49)
Absence of appropriate surveillance	No requirement for long-read genomic analysis, frameshift-product monitoring, or proteostasis assessment accompanied authorization, and the applicant's pharmacovigilance plan identified no important risks and no missing information whatever. (1)
Anticipated cardiotoxicity, undetectable by design	Vaccine mRNA and encoded antigen have been recovered from human myocardium, and mRNA-1273 and BNT162b2 are directly cardiotoxic to isolated ventricular myocytes. Detecting a doubling of myocarditis incidence requires 2.4 to 4.7 million participants; the pooled safety database held 71,916. (1,55,61–63)

Figure 1. Absolute risk-benefit profile of mFLUSIVA relative to a standard-dose influenza vaccine, one season, expressed per 5,017 adults vaccinated



Legend: The denominator is the number needed to vaccinate to avert one influenza hospitalization in Study P304. Counts of affected recipients are obtained by applying the Study P304 solicited-reaction rates to that denominator; values labeled additional are the excess attributable to mFLUSIVA over the comparator arm, and are the quantities on which the benefit-risk comparison rests. The mortality figure derives from the pooled Phase 3 safety database, whose control arm combines standard-dose and high-dose recipients: deaths of unspecified cause occurred in 23 of 35,965 mFLUSIVA recipients against 9 of 35,951 comparator recipients, a risk ratio of 2.55 (95% CI: 1.18, 5.52), equivalent to approximately 2 excess deaths for every hospitalization averted. Neither pivotal trial included a placebo arm, so every comparison shown is against an active influenza vaccine rather than against no vaccination. Derived by the authors from the FDA briefing document. (1)

Figure 2. LNP-mediated delivery of modified mRNA and residual plasmid DNA, LINE-1 activation, reverse transcription, nuclear entry, and chromosomal integration. (8,9,10,23)

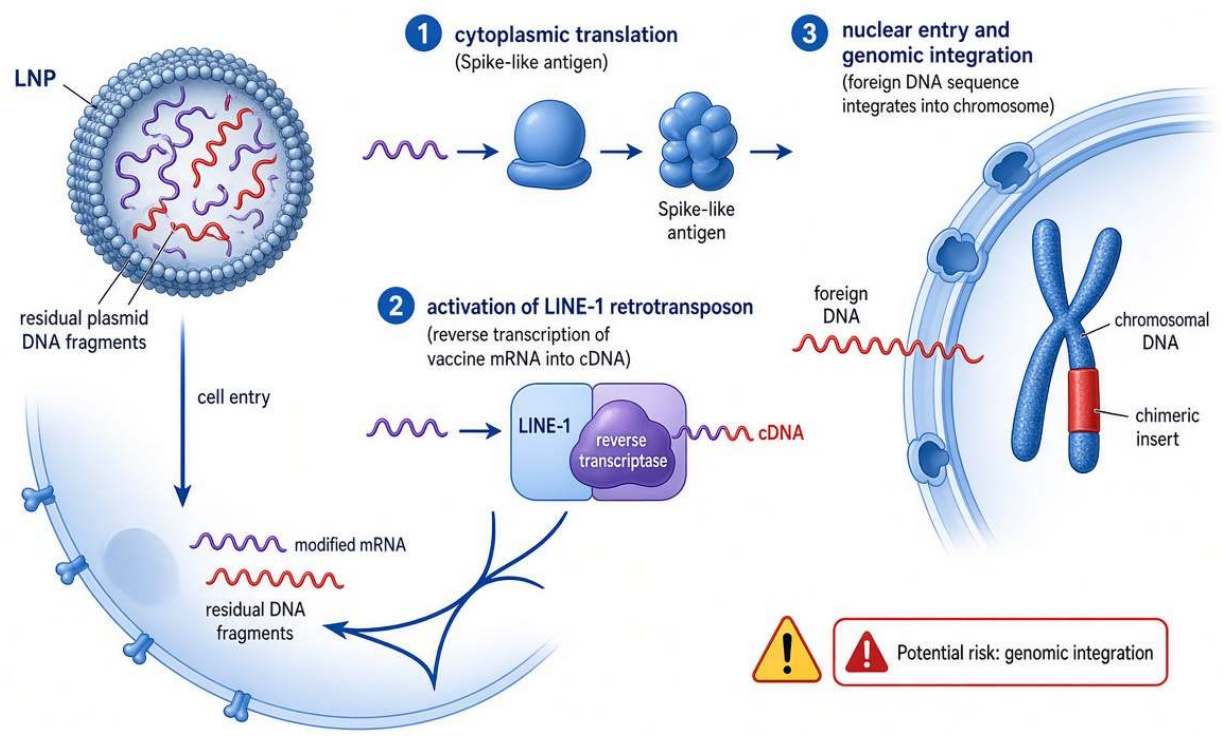
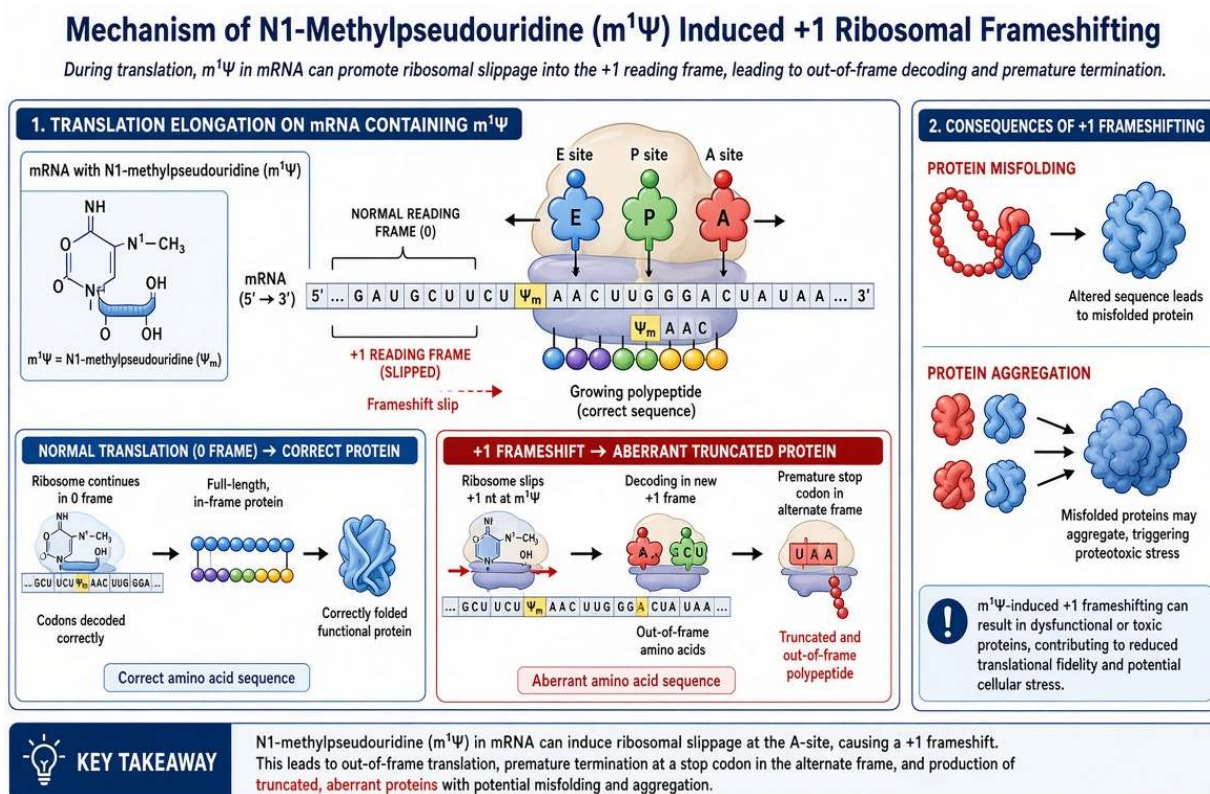


Figure 3. Mechanism of N1-methylpseudouridine-induced +1 ribosomal frameshifting



Legend: Normal-frame translation yields the intended protein; +1 slippage produces truncated, out-of-frame polypeptides prone to misfolding and aggregation. (15,16)

References

1. U.S. Food and Drug Administration. FDA Briefing Document: Influenza Vaccine, mRNA (Proposed Trade Name: mFlusiva), BLA 125869/0, Moderna TX, Inc. Vaccines and Related Biological Products Advisory Committee Meeting, June 18, 2026. Accessed August 16, 2026. <https://www.fda.gov/media/193130/download>
2. Moderna, Inc. Moderna receives US FDA approval for influenza vaccine mFlusiva. News release. August 5, 2026.
3. mFlusiva (Influenza Vaccine, mRNA). Package insert. Moderna, Inc.; 2026.
4. Leroux-Roels I, Huang G, Ferguson M, et al; Fluent Trial Investigators. Efficacy and safety of an mRNA seasonal influenza vaccine in adults. *N Engl J Med*. 2026;394(18):1803–1813. doi:10.1056/NEJMoa2516491
5. Speicher DJ, Rose J, McKernan K. Quantification of residual plasmid DNA and SV40 promoter-enhancer sequences in Pfizer/BioNTech and Moderna modRNA COVID-19 vaccines from Ontario, Canada. *Autoimmunity*. 2025;58(1):2551517. doi:10.1080/08916934.2025.2551517
6. König B, Kirchner JO. Methodological considerations regarding the quantification of DNA impurities in the COVID-19 mRNA vaccine Comirnaty. *Methods Protoc*. 2024;7(3):41. doi:10.3390/mps7030041
7. Therapeutic Goods Administration. Summary report of residual DNA and endotoxin on COVID-19 mRNA vaccines conducted by TGA Laboratories. Australian Government Department of Health and Aged Care; 2024. Accessed August 16, 2026.
8. Aldén M, Olofsson Falla F, Yang D, et al. Intracellular reverse transcription of Pfizer BioNTech COVID-19 mRNA vaccine BNT162b2 in vitro in human liver cell line. *Curr Issues Mol Biol*. 2022;44(3):1115–1126. doi:10.3390/cimb44030073
9. Zhang L, Richards A, Barrasa MI, Hughes SH, Young RA, Jaenisch R. Reverse-transcribed SARS-CoV-2 RNA can integrate into the genome of cultured human cells and can be expressed in patient-derived tissues. *Proc Natl Acad Sci U S A*. 2021;118(21):e2105968118. doi:10.1073/pnas.2105968118
10. Catanzaro JA, Hulscher N, McCullough PA. Genomic integration and molecular dysregulation in aggressive stage IV bladder cancer following COVID-19 mRNA vaccination. *Int J Innov Res Med Sci*. 2025;10(10):380–386. doi:10.23958/ijirms/vol10-i10/2130
11. Hulscher N, Catanzaro JA, McCullough PA, et al. Persistence of vaccine mRNA, plasmid DNA, spike protein, and genomic dysregulation over 3.5 years post-COVID-19 mRNA vaccination. *Med Res Arch*. 2026;14(6). doi:10.18103/mra.2026.0351
12. Selem E, Raszek M, Varon J, Halma M. The persistence of COVID-19 vaccine artifacts in bodily fluids and tissues: a systematic review. *Future J Pharm Sci*. 2026;12(1):16. doi:10.1186/s43094-026-00939-2
13. Von Ranke NL, Zhang W, Anokhin P, Hulscher N, McKernan K, McCullough P, Catanzaro J. Synthetic messenger RNA vaccines and transcriptomic dysregulation: evidence from new-onset adverse events and cancers post-vaccination. *World J Exp Med*. 2025;15(4):113869. doi:10.5493/wjem.v15.i4.113869
14. Seneff S, Nigh G, Kyriakopoulos AM, McCullough PA. Innate immune suppression by SARS-CoV-2 mRNA vaccinations: the role of G-quadruplexes, exosomes, and MicroRNAs. *Food Chem Toxicol*. 2022;164:113008. doi:10.1016/j.fct.2022.113008
15. Mulrone TE, Pöyry T, Yam-Puc JC, et al. N1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting. *Nature*. 2024;625(7993):189–194. doi:10.1038/s41586-023-06800-3
16. Crunkhorn S. Modified mRNA produces frameshifted peptides. *Nat Rev Drug Discov*. 2024;23(2):104. doi:10.1038/d41573-024-00003-9
17. Hetz C, Zhang K, Kaufman RJ. Mechanisms, regulation and functions of the unfolded protein response. *Nat Rev Mol Cell Biol*. 2020;21(8):421–438. doi:10.1038/s41580-020-0250-z
18. Walter P, Ron D. The unfolded protein response: from stress pathway to homeostatic regulation. *Science*. 2011;334(6059):1081–1086. doi:10.1126/science.1209038
19. Cosentino M, Marino F. Understanding the pharmacology of COVID-19 mRNA vaccines: playing dice with the spike? *Int J Mol Sci*. 2022;23(18):10881. doi:10.3390/ijms231810881
20. Acevedo-Whitehouse K, Bruno R. Potential health risks of mRNA-based vaccine therapy: a hypothesis. *Med Hypotheses*. 2023;171:111015. doi:10.1016/j.mehy.2023.111015
21. Parry PI, Lefringhausen A, Turni C, et al.

- ‘Spikeopathy’: COVID-19 spike protein is pathogenic, from both virus and vaccine mRNA. *Biomedicines*. 2023;11(8):2287. doi:10.3390/biomedicines11082287
22. Yamamoto K. Adverse effects of COVID-19 vaccines and measures to prevent them. *Virol J*. 2022;19(1):100. doi:10.1186/s12985-022-01831-0
 23. Domazet-Lošo T. mRNA vaccines: why is the biology of retroposition ignored? *Genes (Basel)*. 2022;13(5):719. doi:10.3390/genes13050719
 24. A Study of mRNA-1010 Compared With a Licensed Influenza Vaccine in Adults ≥ 50 Years of Age (Fluent). ClinicalTrials.gov identifier: NCT06602024. Accessed August 16, 2026. <https://clinicaltrials.gov/study/NCT06602024>
 25. A Study of mRNA-1010 Seasonal Influenza Vaccine in Adults. ClinicalTrials.gov identifier: NCT05827978. Accessed August 16, 2026. <https://clinicaltrials.gov/study/NCT05827978>
 26. Ferruggia K. FDA declines to review Moderna’s mRNA-1010 flu vaccine application, citing comparator concerns. *Pharmacy Times*. February 11, 2026. Accessed August 16, 2026.
 27. Ferruggia K, Yang T. After refusal-to-file, FDA reconsiders Moderna’s mRNA flu vaccine with higher bar for older adults. *Pharmacy Times*. February 18, 2026. Accessed August 16, 2026.
 28. Antrim A. FDA panel unanimously backs Moderna’s mRNA flu vaccine. *Pharmacy Times*. June 19, 2026. Accessed August 16, 2026.
 29. International Council for Harmonisation. ICH E10: Choice of Control Group and Related Issues in Clinical Trials. 2000.
 30. Watson KB, Wiltz JL, Nhim K, Kaufmann RB, Thomas CW, Greenlund KJ. Trends in multiple chronic conditions among US adults, by life stage, Behavioral Risk Factor Surveillance System, 2013–2023. *Prev Chronic Dis*. 2025;22:E15. doi:10.5888/pcd22.240539
 31. U.S. Food and Drug Administration. BLA Clinical Review Memorandum, STN 125869/0, Influenza Vaccine, mRNA (mFlusiva), Moderna TX, Inc. Review completion date August 5, 2026. Accessed August 17, 2026. <https://www.fda.gov/media/194140/download>
 32. U.S. Food and Drug Administration. BLA approval letter and accelerated approval requirements, STN BL 125869/0, Influenza Vaccine, mRNA (MFLUSIVA), Moderna TX, Inc. August 5, 2026. Accessed August 17, 2026. <https://www.fda.gov/media/194121/download>
 33. Accelerated approval of biological products for serious or life-threatening illnesses. 21 CFR §601 Subpart E.
 34. Achs A, Sedlackova T, Predajna L, et al. Systematic analysis of COVID-19 mRNA vaccines using four orthogonal approaches demonstrates no excessive DNA impurities. *npj Vaccines*. 2025;10(1):259. doi:10.1038/s41541-025-01304-9
 35. Kaiser S, Kaiser S, Reis J, Marschalek R. Quantification of objective concentrations of DNA impurities in mRNA vaccines. *Vaccine*. 2025;55:127022. doi:10.1016/j.vaccine.2025.127022
 36. Vieth S, Waibler Z, Schumann GG. Opting for the appropriate methodology for quantification of residual DNA impurities in mRNA vaccines. *Vaccine*. 2025;56:127186. doi:10.1016/j.vaccine.2025.127186
 37. Moderna TX, Inc. Influenza vaccine. US patent 12,409,218.
 38. Rozman B, Broennimann K, Rajan KS, et al. N1-methylpseudouridine directly modulates translation dynamics. *Nature*. 2026;651:533–541. doi:10.1038/s41586-025-09945-5
 39. Monroe J, Eyler DE, Mitchell L, et al. N1-methylpseudouridine and pseudouridine modifications modulate mRNA decoding during translation. *Nat Commun*. 2024;15(1). doi:10.1038/s41467-024-51301-0
 40. Richard JP, Leikina E, Chernomordik LV. Cytoskeleton reorganization in influenza hemagglutinin-initiated syncytium formation. *Biochim Biophys Acta*. 2009;1788(2):450–457. doi:10.1016/j.bbamem.2008.09.010
 41. Markovic I, Leikina E, Zhukovsky M, Zimmerberg J, Chernomordik LV. Synchronized activation and refolding of influenza hemagglutinin in multimeric fusion machines. *J Cell Biol*. 2001;155(5):833–844. doi:10.1083/jcb.200103005
 42. Mao H, Tu W, Liu Y, et al. Inhibition of human natural killer cell activity by influenza virions and hemagglutinin. *J Virol*. 2010;84(9):4148–4157. doi:10.1128/JVI.02340-09
 43. Mao H, Tu W, Qin G, et al. Influenza virus directly infects human natural killer cells and induces cell apoptosis. *J Virol*. 2009;83(18):9215–9222. doi:10.1128/JVI.00805-09
 44. Frabutt DA, Wang B, Riaz S, Schwartz RC, Zheng YH. Innate sensing of influenza A virus hemagglutinin glycoproteins by the host endoplasmic reticulum stress pathway triggers a potent antiviral response via ER-associated protein degradation. *J Virol*. 2018;92(1):e01690-

17. doi:10.1128/JVI.01690-17
45. Slaine PD, Kleer M, Duguay BA, et al. Thiopurines activate an antiviral unfolded protein response that blocks influenza A virus glycoprotein accumulation. *J Virol*. 2021;95(15):e00453-21. doi:10.1128/JVI.00453-21
46. Hamel LP, Comeau MA, Tardif R, et al. Heterologous expression of influenza haemagglutinin leads to early and transient activation of the unfolded protein response in *Nicotiana benthamiana*. *Plant Biotechnol J*. 2024;22(4):1146–1163. doi:10.1111/pbi.14252
47. Mazel-Sanchez B, Iwaszkiewicz J, Bonifacio JPP, et al. Influenza A viruses balance ER stress with host protein synthesis shutoff. *Proc Natl Acad Sci U S A*. 2021;118(36):e2024681118. doi:10.1073/pnas.2024681118
48. Takizawa T, Matsukawa S, Higuchi Y, Nakamura S, Nakanishi Y, Fukuda R. Induction of programmed cell death (apoptosis) by influenza virus infection in tissue culture cells. *J Gen Virol*. 1993;74(Pt 11):2347–2355. doi:10.1099/0022-1317-74-11-2347
49. MRESVIA (Respiratory Syncytial Virus Vaccine). Package insert. Moderna US, Inc.; 2024. Accessed August 16, 2026. <https://www.fda.gov/media/179005/download>
50. Wilson E, Goswami J, Baqui AH, et al. Efficacy and safety of an mRNA-based RSV preF vaccine in older adults. *N Engl J Med*. 2023;389(24):2233–2244. doi:10.1056/NEJMoa2307079
51. Centers for Disease Control and Prevention. ACIP evidence to recommendations for use of Moderna RSV vaccine (mResvia) in all adults aged ≥ 75 years and in adults aged 60–74 years at increased risk of severe RSV disease. Accessed August 16, 2026.
52. SPIKEVAX (COVID-19 Vaccine, mRNA). Package insert. Moderna US, Inc.; 2025. Accessed August 16, 2026.
53. Castruita JAS, Schneider UV, Mollerup S, et al. SARS-CoV-2 spike mRNA vaccine sequences circulate in blood up to 28 days after COVID-19 vaccination. *APMIS*. 2023;131(3):128–132. doi:10.1111/apm.13294
54. Fertig TE, Chitoiu L, Marta DS, et al. Vaccine mRNA can be detected in blood at 15 days post-vaccination. *Biomedicines*. 2022;10(7):1538. doi:10.3390/biomedicines10071538
55. Krauson AJ, Casimero FVC, Siddiquee Z, Stone JR. Duration of SARS-CoV-2 mRNA vaccine persistence and factors associated with cardiac involvement in recently vaccinated patients. *NPJ Vaccines*. 2023;8(1):141. doi:10.1038/s41541-023-00742-7
56. Brogna C, Cristoni S, Marino G, et al. Detection of recombinant spike protein in the blood of individuals vaccinated against SARS-CoV-2. *Proteomics Clin Appl*. 2023;17(6):e2300048. doi:10.1002/prca.202300048
57. Röltgen K, Nielsen SCA, Silva O, et al. Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. *Cell*. 2022;185(6):1025–1040.e14. doi:10.1016/j.cell.2022.01.018
58. Irrgang P, Gerling J, Kocher K, et al. Class switch toward noninflammatory, spike-specific IgG4 antibodies after repeated SARS-CoV-2 mRNA vaccination. *Sci Immunol*. 2023;8(79):eadg0887. doi:10.1126/sciimmunol.adg0887
59. U.S. Food and Drug Administration. BLA Clinical Review Memorandum, STN 125869/0, Influenza Vaccine, mRNA (mFlusiva), Moderna TX, Inc. August 5, 2026. Accessed August 18, 2026. <https://www.fda.gov/media/194140/download>
60. U.S. Food and Drug Administration. BLA approval letter and postmarketing requirements, STN BL 125869/0, Influenza Vaccine, mRNA (MFLUSIVA), Moderna TX, Inc. August 5, 2026. Accessed August 18, 2026. <https://www.fda.gov/media/194121/download>
61. Baumeier C, Aleshcheva G, Harms D, et al. Intramyocardial inflammation after COVID-19 vaccination: an endomyocardial biopsy-proven case series. *Int J Mol Sci*. 2022;23(13):6940. doi:10.3390/ijms23136940
62. Schreckenber R, Woitasky N, Itani N, et al. Cardiac side effects of RNA-based SARS-CoV-2 vaccines: hidden cardiotoxic effects of mRNA-1273 and BNT162b2 on ventricular myocyte function and structure. *Br J Pharmacol*. 2024;181(3):345–361. doi:10.1111/bph.16262
63. Hulscher N, Cook MJ, Stricker RB, McCullough PA. Excess cardiopulmonary arrest and mortality after COVID-19 vaccination in King County, Washington. *J Emerg Med OA*. 2024;2(1):1–11. doi:10.33140/JEMOA.02.01.12