Workgroup Safety Uncertainties of mRNA COVID Vaccines

Wafik El-Deiry, MD, PhD, FACP
Director, Legorreta Cancer Center
Associate Dean, Oncologic Sciences
Warren Alpert Medical School, Brown University

Charlotte Kuperwasser, PhD
Director, Tufts Convergence Laboratory of Biomedical, Physical, and Engineering Sciences
Professor Developmental, Molecular & Chemical Biology, Tufts University School of Medicine

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Summary of Workgroup Activities for TORs

1. Immune Changes
2. Biodistribution
3. Frameshifting
4. Impurities

Immune Changes

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COVID vaccination, especially multiple doses, can lead to the following immune responses:

- IgG4 class switching [1]
- Production of anti-idiotype antibodies [2,3]
- Low long-term IgG Fc galactosylation and sialylation levels [4]
- Persistent cytokine changes [5,6]
- Reduction in circulating memory and effector CD4 T cells, and increases in TNFα+ CD8 T cells [7]
- Risk of more persistent and/or recurring infections [8-10]

1) Irrgang et al. *Sci Immunol* (2023)
2) Murphy et al . N Engl J Med (2022).
3) Bellucci et al. Front Immunol. 2024
4) Buhre, et al. *Front Immunol* (2023)
5) Alghamdi et al. *Immun Inflamm Dis* (2025)
6) Cabău et al. *Vaccines* (2024)
7) Bhattacharjee et al. & Iwasaki A *medRxiv* (2025)
8) Noé, A. *et al. Front Immunol* (2023).
9) Yamamoto, M. et al. *J Cut Immun and Allergy* (2022)
10) Park, H et al. *Science Trans Med* (2025).

Covid vaccine safety issues

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Immune Summary

- The persistence, clinical significance, and potential long-term consequences of these immune changes is uncertain.

- More research is needed to understand vaccine non-specific effects on innate and adaptive immunity and its ability to reprogram innate and adaptive immune cells.

Biodistribution

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Pfizer- Comirnaty

FDA Summary Basis for Regulatory Action (SBRA)

Used a **luciferase reporter mRNA** (instead of spike mRNA) in mice and rats, delivered in the same lipid nanoparticles (LNPs). Also tested biodistribution/metabolism of Pfizer's two novel lipids (ALC-0315 and ALC-0159):

IM injection in mice:

High levels detected in:

- Injection site
- Liver

Biodistribution

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Moderna- SPIKEVAX
FDA Summary Basis for Regulatory Action (SBRA)

States **no biodistribution study was performed with mRNA-1273**; instead, FDA reviewed a biodistribution study of **a different mRNA vaccine** made with the same SM-102 LNP, considered those results *supportive* for Spikevax.

High levels in:
- Draining lymph nodes
- Spleen
- Eye
- Liver

- Low levels detected in many tissues including:
  - Heart, lung, testis, brain
- In brain, ~2–4% of plasma levels (so *trace crossing* of the blood–brain barrier).

Biodistribution

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Vaccine mRNA in humans

Site	Persistence After Vaccination	Reference(s)
Axillary lymph node	Up to **30 days**	Krauson et al. *NPJ Vaccines* (2023)
Heart (myocardium/cardiac ventricles)	Up to **30 days**	1. Yonker et al., *Circulation* (2023) 2. Boros et al, *Pharmacol Res Perspect* (2024) 3. Krauson et al. *NPJ Vaccines* (2023)
Blood	**~15 days** to **23 months**	1. Patterson et al, *Hum Vaccin Immunother* (2025) 2. Ogata et al, *Clin Infect Dis* (2022) 3. Fertig et al, *Biomedicines* (2022) 4. Bhattacharjee et al. *medRxiv* (2025) 5. Brogna et al. *Proteomics Clin Appl (*2023)
CNS (skull/meninges/ Cerebral arteries	**Up to ~17 months**	1. Ota et al. *J Clin Neurosci* (2025) 2. Luis et al *Brain Behav Immun Health* (2021)
Breast milk	**45 hours**	Hanna et al. *JAMA Pediatr* (2022)

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Biodistribution Summary

- Neither Moderna or Pfizer biodistribution studies used commercial product for testing.
- Neither Moderna or Pfizer biodistribution data showed confinement to site of injection. Distribution included draining lymph nodes, liver, spleen, heart, brain, lungs, and blood. It was noted that it could cross the BBB.
- Covid vaccine mRNA has been detected in multiple tissues in humans including lymph nodes, heart, CNS, blood, and others.
- Covid vaccine mRNA has been reported to persist for up to 706 days.

Frameshifting

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Off-target protein production

- Therapeutic/in vitro-transcribed (IVT) mRNAs often contain modified nucleotides (ribonucleotides), such as N^1-methylpseudouridine to help reduce innate immune activation and increase stability.
- Nucleoside-modified mRNA is synthetic and not a natural mRNA.
- This modification instructs cells to produce off-target proteins due to ribosomal slipping [1,2].

1) Mulroney, T. E.. *Nature* 625, 189-194 (2024).
2) Boros, L. G. *et al.*. *Pharmacol Res Perspect* (2024).

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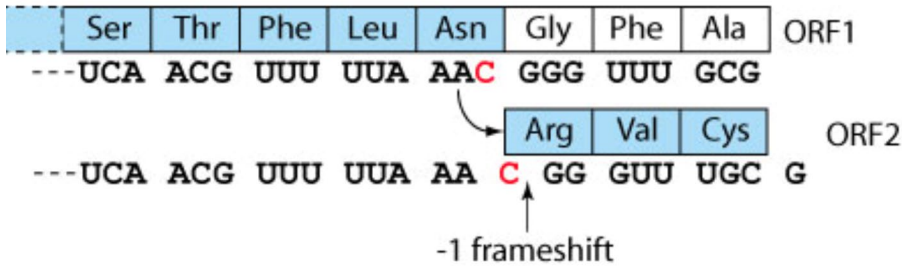
Frameshifting

- There is evidence that these unintended/off-target proteins generate an immune (T cell) response in humans [1]
- Immunogenic or toxic properties of the non-spike proteins is unknown.
- The health consequences of prolonged and persistent non-spike protein production have not been studied



1) Mulroney, T. E.. *Nature* 625, 189-194 (2024).

Impurities

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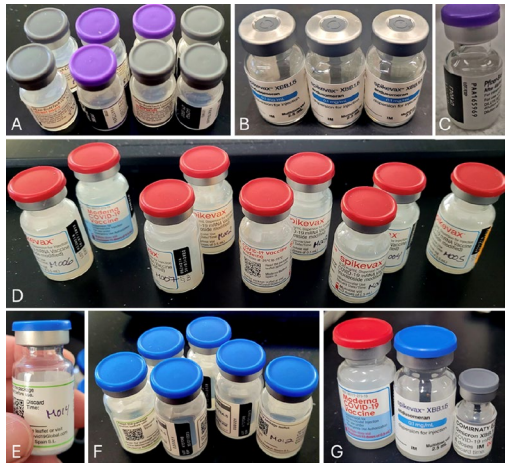
Sources during manufacturing

1. Incomplete Digestion (DNAse)

2. Separation Challenges

DNA impurities in vaccines have been reported in the following:

1. Speicher, D. J., et al .(2025).
2. McKernan, K. (2023).
3. Raoult, D. (2024).
4. Kaiser, S., et al (2025).
5. Kämmerer, et al (2024).
6. Buckhaults, P. (2023).
7. König, B. (2024).
8. Wang et al (2024).

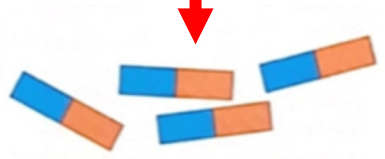


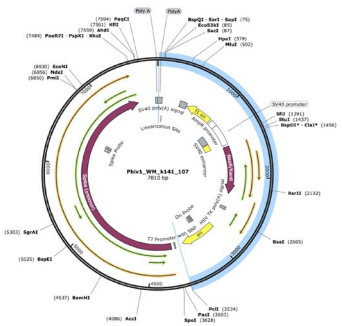
Unexpected impurities

Pfizer

Pfizer
Moderna

SV40 promoter-enhancer-ori





Differences between Pfizer vs Moderna

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	Pfizer/Comirnaty	Moderna/Spikevax
Vector used for generating the DNA template	Bacterial plasmid that contains mammalian-cell expression elements, including **SV40 promoter/enhancer** sequences.	Bacterial plasmid
Foreign DNA material of concern	**SV40 promoter/enhancer-ori**	Full nucleotide sequences have not been published
DNA fragment sizes & quantity	Mean ~214 bp, maximum ~3.5 kb **~ 371-1,548 ng per dose***	Similar fragmented distribution, but maximum size smaller, consistent with smaller plasmid backbone. ~ **1,130-6,280 ng per dose***
Clinical trial vs marketed product	Clinical trials used a clean PCR product template. Commercial product uses plasmid. **No clinical trial was conducted on marketed product**.	Same product on market as clinical trial

***FDA limit of 10 ng set for naked DNA, not DNA in presence of LNP that carries DNA into cells and their nuclei.**

Covid vaccine safety issues

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Impurities

- Pfizer vaccine: Exceeds limits[1] by ~36-153-fold and SV40 promoter/enhancer sequences detected[2].
- Moderna: Exceeds limits[1] by ~112-627-fold and small sizes could enable more integration events[2].
- No safety considerations or guidelines for LNP enveloped DNA impurities have been established by regulatory agencies.
- Concerns due to known DNA integration and gene activation/disruption by SV40 promoter/enhancer sequences.

1) Regulatory limit guidelines (WHO/FDA/ EMA)
2) Speicher, D. J. et al. *Autoimmunity* (2025)

COVID Vaccine Safety Issues: Impurities

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- Cancers have been reported in mRNA vaccinated individuals in temporal association to immunization including (38 case reports and study of 96 cases of PDAC outcomes vs IgG4):
  - High grade sarcoma at injection site (case report).
  - Kaposi's sarcoma (cutaneous and conjunctival reported; 2 cases).
  - Non-Hodgkin's Lymphoma (8 cases reported in one publication).
  - Primary Cutaneous Lymphomas (14 cases).
  - Marginal Zone B-cell Lymphoma (case report).
  - Glioblastoma (2 case reports).
  - Gastric and intestinal polyposis (2 case reports).
  - IgG4 correlates with poor survival outcomes in PDAC (96 cases).
  - Axillary Lymphangioma (case report).
  - Multiple Keratoacanthomas (skin cancer; case report).
  - Ph+ B-cell ALL (leukemia; case report).
  - T-cell ALL (leukemia; case report).
  - CMML (leukemia; case report).
  - Multiple Myeloma relapse (case report).
  - Cardiac Myxoma (2 case reports).

COVID Vaccine Safety Issues: Impurities

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Gaps in Knowledge

- Extent of DNA contamination in current lots; plasmid biodistribution.
- Genomic integration in tissues or tumors in vaccinated patients; mechanisms.
- Prevalence of adverse outcomes from impurities versus extent of contamination.
- Multiple vaccinations and Spike persistence.
- Cancer mechanisms.
- Variations in host susceptibilities to adverse outcomes.

COVID Vaccine Summary & Recommendations

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COVID-19 vaccine safety concerns stem from unexpected biological activities of mRNA gene therapy platforms, raising questions about potential pathogenic mechanisms and HRP.

- Proactive and modernized safety surveillance programs including:
  - Blood- and tissue-based monitoring
  - Epidemiologic studies
  - AI-driven analyses using reliable, standardized datasets
- Expanded autopsy programs to clarify causality in serious outcomes

- Programs that systematically evaluate COVID-19 vaccine safety
- FDA approval policies calibrated to gene therapy–like risks; DNA limits
- Stronger pharmaceutical accountability
- CDC guidelines ensuring transparent risk disclosure, mitigation strategies, and robust informed consent