mRNA “vaccine” biodistribution, persistence, and adjuvant toxicity library

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Originally part of the outer coat of the SARS-CoV2 virus, where it functions as a “key” to “unlock” (infect) cells, spike proteins are also produced in large amounts by the mRNA “vaccines,” triggering a short-lived immune response in the form of antibodies. However, a growing body of evidence has shown that the spike protein is harmful by itself (see: “Spike protein pathogenicity research library,” https://zenodo.org/records/14269255). Furthermore, research has demonstrated that:

1) Both the “vaccine” mRNA encoding for the spike protein antigen and the spike protein itself can penetrate distant tissues, causing systemic harms.

2) “Vaccine” mRNA and the spike protein antigen persist in the tissues of human vaccine recipients and animal test subjects far longer than claimed by public health officials, while viral spike proteins have been shown to persist even longer.

3) The ionizable lipid nanoparticles (LNPs) used in the experimental mRNA injections are highly inflammatory on their own, including their polyethylene glycol (PEG) component, an established cause of anaphylaxis (an extreme allergic reaction).

The following research collection presents over 100 peer-reviewed studies (**n=130**) documenting I) the wide distribution and II) persistence of “vaccine” mRNA and the encoded spike protein, as well as III) the potential harms of the LNP delivery system (some studies with overlapping findings appear in more than one category). Taken together with evidence of the spike protein’s pathogenicity (https://zenodo.org/records/14269255), these findings suggest that the mRNA “vaccines” can distribute harmful, long-lasting spike protein uncontrollably throughout the body, causing injuries and death by various means.

Please note that a small number of studies in section I) investigate the ability of viral spike protein resulting from infection to cross important physiological barriers on its own, while some studies in section II) demonstrate the long persistence of viral-derived spike protein in the absence of viable virus, bolstering concerns about the identical “vaccine” spike.

These compilations originated with Dr. Wucher’s and Dr. Bridle’s contributions to *TOXIC SHOT: Facing the Dangers of the COVID "Vaccines."*

I. Spike protein and “vaccine” mRNA biodistribution

Compiled by Dr. Martin Wucher, MSC Dent Sc (eq DDS), Erik Sass, et al.

Biodistribution studies show that both the “vaccine” mRNA encoding for the spike protein antigen and the spike protein itself can penetrate distant tissues, causing systemic harms to a variety of organs and organ systems, including the placenta. The following research collection presents over 50 peer-reviewed studies (**n=54**) documenting the wide distribution of “vaccine” mRNA and the associated spike protein throughout human beings and animal test subjects.

These articles confirm that “vaccine” mRNA and spike protein can reach tissues and organs including the heart, liver, brain, lungs, placenta, umbilical cord, breast milk, lymph nodes, thymus, kidneys, spleen, bladder, large intestine, eyes, adrenal glands, ovaries, testes, bone marrow, skin, lacrimal glands, and appendix. Additionally, a small number of studies demonstrate the viral spike protein’s ability to cross important physiological barriers independently of the rest of the virus, suggesting identical “vaccine”-derived spike protein can do the same.

This compilation originated with Dr. Wucher's contribution to *TOXIC SHOT: Facing the Dangers of the COVID "Vaccines,"* (Chapter 4: The Spike Protein Is Harmful By Itself).

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- "… clinical studies now report that modified SARS-CoV-2 mRNA routinely persist up to a month from injection and can be detected in cardiac and skeletal muscle at sites of inflammation and fibrosis, while the recombinant spike protein may persist a little over half a year in blood."

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    - liver, spleen, muscle, and inguinal lymph nodes

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    - plasma

II. Spike protein and vaccine mRNA persistence research library

Compiled by Dr. Martin Wucher, MSC Dent Sc (eq DDS), Erik Sass, et al.

Dozens of studies collected here (**n=39**) demonstrate that both "vaccine" mRNA, and the spike protein antigen it encodes, persist in the tissues of human vaccine recipients and animal test subjects far longer than claimed by public health officials: up to eight weeks in the case of mRNA (Röltgen K et al.) and up to six months for spike protein (Brogna C et al.). Numerous studies have also shown that viral spike proteins can persist even longer in individuals recovered from SARS CoV2 infection or with "long COVID," with spike protein detected 15 months (Patterson BK et al.) to two years (Fraser ME at al.) after infection. Long-lasting viral spike proteins have frequently been detected in the absence of viable virus, as reflected in negative PCR tests and RNA assays, suggesting identical "vaccine" spike proteins may also persist for a year or more.

This compilation originated with Dr. Wucher's contribution to *TOXIC SHOT: Facing the Dangers of the COVID "Vaccines,"* (Chapter 4: The Spike Protein Is Harmful By Itself).

ANNOTATED REFERENCES (n=39)

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7. Craddock V et al., "Persistent circulation of soluble and extracellular vesicle-linked Spike protein in individuals with postacute sequelae of COVID-19," *J Med. Virol.* 2023, 95, 2: e28568. doi: https://doi.org/10.1002/jmv.28568
    - "… our findings suggest that Spike and/or viral RNA fragments persist in the recovered COVID-19 patients with PASC up to 1 year or longer after acute SARS-CoV-2 infection." Further, "this is the first report to show that part of the circulating Spike is linked to extracellular vesicles without any presence of viral RNA in these vesicles."

8. European Medicines Agency, *Assessment Report,* available online: https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf
    - "Synthetic mRNAs encapsulated in LNPs can reach many organs, such as the spleen, heart, kidneys, lungs and brain. The mRNAs were found in the ovaries and the testicles in small quantities, during the biodistribution studies of this vaccine after 9 days…"

9. Fertig TE et al., "Vaccine mRNA Can Be Detected in Blood at 15 Days Post Vaccination," *Biomedicines* 2022, 10, 7: 1538. doi: https://doi.org/10.3390/biomedicines10071538

10. Fraser ME at al., "SARS-CoV-2 Spike Protein and Viral RNA Persist in the Lung of Patients With Post-COVID Lung Disease (abstract)," *Am J Respir Crit Care Med* 2024, 209: A4193. doi: https://doi.org/10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A4193
    - "Spike protein and RNA persists in BAL from patients with post-COVID lung disease up to two years after acute infection."

11. Gaebler C et al., "Evolution of antibody immunity to SARS-CoV-2," *Nature* 2021, 591: 639-644. doi: https://doi.org/10.1038/s41586-021-03207-w
    - Gastrointestinal tract biopsies suggest spike antigen persisted in the small bowel in 7 of 14 individuals who were asymptomatic at 4 months after infection… Clinically approved nasopharyngeal-swab PCR assays were negative in all 14 individuals at the time of biopsy. However, biopsy samples from 3 of the 14 participants produced PCR amplicons that were sequence-verified as SARS-CoV-2. In addition, viral RNA was detected by in situ hybridization in biopsy samples from the two participants who were tested.

12. George S et al., "Evidence for SARS-CoV-2 Spike Protein in the Urine of COVID-19 Patients," *Kidney360* 2021, 2, 6: 924-936. doi: 10.34067/KID.0002172021
    - "The SARS-CoV-2 spike protein could be detected in urine from day 1 to day 44 post–hospital admission… Of the 23 adults who were Ur-S+, only one individual showed detectable viral RNA in urine."

13. Goh D et al., "Case report: Persistence of residual antigen and RNA of the SARS-CoV-2 virus in tissues of two patients with long COVID," *Front. Immunol.* 2022, 13 (Sec. Viral Immunology). doi: https://doi.org/10.3389/fimmu.2022.939989
    - Persistence of spike protein 426 days after symptom onset; residual viral RNA also detected.

14. Hano S et al., “A case of persistent, confluent maculopapular erythema following a COVID-19 mRNA vaccination is possibly associated with the intralesional spike protein expressed by vascular endothelial cells and eccrine glands in the deep dermis,” *J Dermatol* 2023, 50, 9: 1208-1212. doi: https://doi.org/10.1111/1346-8138.16816
    - “Surprisingly, immunohistochemical staining of the lesion 100 days after the disease onset revealed the COVID-19 spike protein expressed by vascular endothelial cells and eccrine glands in the deep dermis. As she had no episode of COVID-19 infection, it is highly likely that the spike protein was derived from the mRNA vaccine and it might be the cause of the development and persistence of her skin lesions.”

15. Karaba AH et al., “Detectable plasma severe acute respiratory syndrome coronavirus 2 spike antigen is associated with poor antibody response following third messenger RNA vaccination in kidney transplant recipients,” *Transpl Infect Dis* 2024, 26, 3: e14281. doi: https://doi.org/10.1111/tid.14281
    - Spike protein detectable in 3/16 (19%) participants 14 days after vaccination.

16. Kawano H et al., “Fulminant Myocarditis 24 Days after Coronavirus Disease Messenger Ribonucleic Acid Vaccination,” *Intern. Med.* 2022, 61, 15: 2319-2325. doi: https://doi.org/10.2169/internalmedicine.9800-22
    - “... positive immunostaining for severe acute respiratory syndrome coronavirus 2 spike protein and C4d in the myocardium."

17. Kent SJ et al., “Blood Distribution of SARS-CoV-2 Lipid Nanoparticle mRNA Vaccine in Humans,” *ACS Nano* 2024, 18, 39: 27077-27089. doi: https://doi.org/10.1021/acsnano.4c11652
    - “The vaccine mRNA was detectable and quantifiable up to 14–15 days postvaccination in 37% of subjects.”

18. Krauson AM et al., “Duration of SARS-CoV-2 mRNA vaccine persistence and factors associated with cardiac involvement in recently vaccinated patients,” *npj Vaccines,* 8, 141. doi: https://doi.org/10.1038/s41541-023-00742-7
    - “Vaccine was detected in the axillary lymph nodes in the majority of patients dying within 30 days of vaccination... Vaccine was detected in the myocardium in a subset of patients vaccinated within 30 days of death.”

19. Li C et al., “Mechanisms of innate and adaptive immunity to the Pfizer-BioNTech BNT162b2 vaccine,” *Nature Immunol.* 2022, 23: 543-555. doi: https://doi.org/10.1038/s41590-022-01163-9
    - “mRNA could be detected in the spleen, and the spike protein itself was detectable in the serum, for up to 7 d after immunization.”

20. Magen E et al., “Clinical and Molecular Characterization of a Rare Case of BNT162b2 mRNA COVID-19 Vaccine-Associated Myositis,” *Vaccines* 2022, 10, 7: 1135. doi: https://doi.org/10.3390/vaccines10071135
    - “... although the BNT162b2 vaccine mRNA was not properly expressed in blood cells seven days after receipt of the first vaccine dose, it was still expressed in muscle tissue distant from the vaccination site one month after receipt of the first vaccine dose.”

21. Mayordomo-Colunga J et al., “SARS-CoV-2 spike protein in intestinal cells of a patient with coronavirus disease 2019 multisystem inflammatory syndrome,” *J Pediatr.* 2022, 243: 214-18e215. doi: https://doi.org/10.1016/j.jpeds.2021.11.058
    - Spike protein detected 6 weeks after acute infection. “At presentation, the patient tested negative for SARS-CoV-2 by reverse-transcriptase polymerase chain reaction on nasopharyngeal swab but positive for serum SARS-CoV-2 immunoglobulin G.”

22. Mörz M, "A Case Report: Multifocal Necrotizing Encephalitis and Myocarditis after BNT162b2 mRNA Vaccination against COVID-19," Vaccines 2022, 10, 10: 1651. doi: https://doi.org/10.3390/vaccines10101651
    - Vaccine-induced spike detected on autopsy three weeks after last injection.

23. Ogata AF et al., "Circulating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients," *Clin. Infect. Dis.* 2022, 74, 4: 715-728. doi: https://doi.org/10.1093/cid/ciab465
    - "Spike protein was detectable in 3 of 13 participants an average of 15 days after the first injection."

24. Parcial ALN et al., "SARS-CoV-2 Is Persistent in Placenta and Causes Macroscopic, Histopathological, and Ultrastructural Changes," *Viruses* 2022, 14, 9: 1885. doi: https://doi.org/10.3390/v14091885
    - "Three of five placentas presented SARS-CoV-2 RNA detected by RT-PCRq at least two to twenty weeks after primary pregnancy infection symptoms, and SARS-CoV-2 spike protein was detected in all placentas by immunoperoxidase assay."

25. Pateev I et al., "Biodistribution of RNA Vaccines and of Their Products: Evidence from Human and Animal Studies," *Biomedicines* 2024, 12, 1: 59. doi: https://doi.org/10.3390/biomedicines12010059
    - (Roltgen K et al) "The amount of the spike antigen declined significantly at 4 months after the double vaccination but was still detectable."
    - "Immunohistochemical staining for the spike antigen in the lymph nodes of vaccinated patients revealed peak amounts of the spike protein in germinal centers 16 days after dose 2, with the spike antigen still detectable on day 60."
    - (Brogna C et al.) "It is noteworthy that in this study, spike protein was still detected in human blood on the 187th day after vaccination."

26. Patterson BK et al., "Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection," *Front. Immunol.* 2022, 12: 746021. doi: https://doi.org/10.3389/fimmu.2021.746021
    - Intact viral RNA undetectable in monocytes.

27. Peluso MJ et al., "Plasma-based antigen persistence in the post-acute phase of COVID-19," *Lancet* 2024, 24, 6: E345-E347. doi: 10.1016/S1473-3099(24)00211-1
    - "Of 660 pandemic-era specimens tested, 61 (9·2%) specimens from 42 participants (25% of the group), had one or more detectable SARS-CoV-2 antigens. The most commonly detected antigen was spike (n=33, 5·0%), followed by S1 (n=15, 2·3%)…"
    - "… our data provide strong evidence that SARS-CoV-2, in some form or location, persists for up to 14 months following acute SARS-CoV-2 infection."
    - "… our findings provide no direct evidence regarding the persistent presence of replication-competent or even transcriptionally active virus."

28. Peluso MJ et al., "SARS-CoV-2 and mitochondrial proteins in neural-derived exosomes of COVID-19," *Ann Neurol* 2022, 91, 6: 772-781. doi: https://doi.org/10.1002/ana.26350
    - Exosomes containing spike protein were detected in plasma of long COVID patients with neuropsychiatric symptoms at two months.

29. Roden AC et al., "Comparison of In Situ Hybridization, Immunohistochemistry, and Reverse Transcription–Droplet Digital Polymerase Chain Reaction for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Testing in Tissue," *Arch Pathol Lab Med* 2021, 145, 7: 785–796. doi: https://doi.org/10.5858/arpa.2021-0008-SA

- Detected viral protein 46 days after onset of symptoms.
- "All patients from our institution had tested positive for COVID-19 by nasopharyngeal swab within a median of 14.5 days (range, 0–67 days) before death. All patients from our institution but one were tested for COVID-19 again at time of autopsy; 10 of 13 (76.9%) tested positive."

30. Röltgen K 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. doi: 10.1016/j.cell.2022.01.018
    - "mRNA vaccination stimulates robust GCs containing vaccine mRNA and spike antigen up to 8 weeks postvaccination in some cases."
    - "… with spike antigen still present as late as 60 days post-second dose"

31. Rong Z et al., "Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19," *Cell Host Microbe* 2024, 26: S1931-3128(24)00438-4. doi: 10.1016/j.chom.2024.11.007
    - "In a time course experiment, we found the spike protein in the skull marrow, kidney, liver, and lung 3 days post-injection, remaining detectable in the kidney and liver 14 days post-injection."

32. Sano H et al., "A case of persistent, confluent maculopapular erythema following a COVID-19 mRNA vaccination is possibly associated with the intralesional spike protein expressed by vascular endothelial cells and eccrine glands in the deep dermis," *J. Dermatol.* 2023, 50: 1208–1212. doi: https://doi.org/10.1111/1346-8138.16816
    - "Surprisingly, immunohistochemical staining of the lesion 100 days after the disease onset revealed the COVID-19 spike protein expressed by vascular endothelial cells and eccrine glands in the deep dermis. As she had no episode of COVID-19 infection, it is highly likely that the spike protein was derived from the mRNA vaccine and it might be the cause of the development and persistence of her skin lesions."

33. Schultheiss C et al., "Liquid biomarkers of macrophage dysregulation and circulating spike protein illustrate the biological heterogeneity in patients with post-acute sequelae of COVID-19," *J Med Virol* 2023, 95, 1: e28364. doi: https://doi.org/10.1002/jmv.28364
    - Detected SARS-CoV-2 S1 protein in the plasma of approximately 64% of PASC study participants recruited at a median of 8 months (range 1–17 months) after acute COVID-19, but only in approximately 35% of convalescent control patients.

34. Swank Z et al., "Persistent circulating SARS-CoV-2 spike is associated with post-acute COVID-19 sequelae," *Clin. Infect. Dis.* 2022, 76: e487-e490. doi: https://doi.org/10.1093/cid/ciac722
    - "We detect severe acute respiratory syndrome coronavirus 2 spike predominantly in PASC patients up to 12 months after diagnosis… Although the detection of spike in PASC patients months after diagnosis suggests the presence of replicating viral reservoirs, further analyses are needed to confirm this hypothesis."

35. Visvabharathy L et al., "Case report: Treatment of long COVID with a SARS-CoV-2 antiviral and IL-6 blockade in a patient with rheumatoid arthritis and SARS-CoV-2 antigen persistence," *Front. Med.* 2022, 9 (Sec. Infectious Diseases – Surveillance). doi: https://doi.org/10.3389/fmed.2022.1003103
    - "The patient tested RT-PCR– for SARS-CoV-2 at 14 days post-infection and multiple times thereafter but continued to test intermittently antigen+ for 14 weeks post-infection despite no overt exposure to SARS-CoV-2 infected individuals."

36. Wu H et al., "Molecular evidence suggesting the persistence of residual SARS-CoV-2 and immune responses in the placentas of pregnant patients recovered from COVID-19," *Cell Prolif.* 2021, 54, 9: e13091. doi: https://doi.org/10.1111/cpr.13091

- "Our study showed that SARS-CoV-2 nucleic acid (in one patient) and protein (in five patients) were present in the placentas of clinically recovered pregnant patients for more than 3 months after diagnosis."

37. Yamamoto M et al., "Persistent varicella zoster virus infection following mRNA COVID-19 vaccination was associated with the presence of encoded spike protein in the lesion," *J. Cutan. Immunol. Allergy* 2022, 6, 1: 18-23. doi: https://doi.org/10.1002/cia2.12278
    - "multi-dermatomal vesicles, necrotizing vasculitis and superficial thrombophlebitis-like lesions, which lasted as long as 3 months possibly associated with two doses of BNT162b2"

38. Yonker LM et al., "Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier," *J Clin Invest*. 2021, 131, 14: e149633. doi: https://doi.org/10.1172/JCI149633
    - "...our studies showed that spike antigens rose over the first few days of MIS-C symptoms and persisted for more than 10 days, occasionally through 6 months..."
    - "... we measured SARS-CoV-2 RNA from MIS-C stool samples collected several weeks after the initial SARS-CoV-2 infection or exposure. Indeed, a majority of the patients showed detectable viral loads in the stool ranging from 1.5×10^2 to 2.5×10^7 RNA copies/mL, suggesting an ongoing nidus of infection in MIS-C."

39. Zollner A et al., "Postacute COVID-19 is Characterized by Gut Viral Antigen Persistence in Inflammatory Bowel Diseases," *Gastroenterology* 2022, 163, 2: 495-506.e8. doi: https://doi.org/10.1053/j.gastro.2022.04.037
    - Viral spike protein detected 219 days after original positive endoscopy in gut lining of 15 out of 132 subjects.
    - "We were unable to culture SARS-CoV-2 from gut tissue of patients with viral antigen persistence."

III. Lipid nanoparticle toxicity and allergenicity research library

Compiled by Dr. Byram Bridle, PhD, Erik Sass, et al.

The anti-SARS CoV2 mRNA injections rely on lipid nanoparticles (LNPs) bonded with polyethylene glycol (PEG) to deliver mRNA coding for the spike protein antigen into human cells. However, a growing body of evidence suggests that the ionizable LNPs used in the experimental mRNA injections are highly inflammatory on their own, while PEG has long been recognized as an allergen with the potential to trigger anaphylaxis (a severe, possibly life-threatening allergic reaction). This annotated research collection presents over 50 (**n=57**) scientific papers detailing the potential harms of LNPs, PEG, and other components of the mRNA injections to the human body and setting forth possible or established mechanisms. Some of the research annotated here also suggests a far higher incidence of anaphylaxis due to the mRNA injections than claimed in official estimates, ranging from 1/2,280 doses (Warren CM et al.) to 1/4,049 (Blumenthal KG et al.) and 1/13,882 (Somiya A et al.).

This compilation originated with one of Dr. Bridle's contributions to *TOXIC SHOT: Facing the Dangers of the COVID "Vaccines,"* (Chapter 1: The COVID Shots Are Not Real Vaccines).

ANNOTATED REFERENCES (n=57)

1. Ahn JH et al., "Impact of administration routes and dose frequency on the toxicology of SARS-CoV-2 mRNA vaccines in mice model," *Arch Toxicol.* 2024. doi: https://doi.org/10.1007/s00204-024-03912-1
   - "These results suggest that mRNA vaccines may exhibit various potential toxicities, and the toxicological phenotype may vary depending on the LNP composition."

2. Awaya T et al., "Cytokine Storms and Anaphylaxis Following COVID-19 mRNA-LNP Vaccination: Mechanisms and Therapeutic Approaches," *Diseases* 2024, 12, 10: 231. doi: https://doi.org/10.3390/diseases12100231
   - "…during the process of endosomal escape, ionizable lipids disrupt the endosomal membrane to release mRNA, which can, in some cases, lead to the excessive production of inflammatory cytokines."

3. Bakos T et al., "mRNA-LNP COVID-19 Vaccine Lipids Induce Complement Activation and Production of Proinflammatory Cytokines: Mechanisms, Effects of Complement Inhibitors, and Relevance to Adverse Reactions," *Int. J. Mol. Sci.* 2024, 25, 7: 3595. doi: https://doi.org/10.3390/ijms25073595
   - "… the novel findings in the present study include (i) the dominance of alternative pathway activation, (ii) the increased strength of C activation relative to corresponding PEGylated liposomes, and (iii) the absence of C activation by naked mRNAs."

4. Barta BA et al., "The COVID-19 mRNA vaccine Comirnaty induces anaphylactic shock in an anti-PEG hyperimmune large animal model," *Eur. Heart J.* 2023, 44 (supp 2): ehad655.3291. doi: https://doi.org/10.1093/eurheartj/ehad655.3291

- "Consistent with previous studies, our current data show a causal role of anti-PEG Abs in the anaphylaxis to Comirnaty, which involves complement activation…"

5. Bitounis D et al., "Strategies to reduce the risks of mRNA drug and vaccine toxicity," *Nat. Rev. Drug Discov.* 2024, 23: 281-300. doi: https://doi.org/10.1038/s41573-023-00859-3
   - "… cell tropism and tissue distribution of mRNA and lipid nanoparticles can lead to toxicity, and their possible reactogenicity."

6. Blumental KG et al., "Acute Allergic Reactions to mRNA COVID-19 Vaccines," *JAMA* 2021, 325, 15:1562-1565. Doi: 10.1001/jama.2021.3976
   - "… severe reactions consistent with anaphylaxis occurred at a rate of 2.47 per 10 000 vaccinations… The incidence rate of confirmed anaphylaxis in this study is larger than that reported by the Centers for Disease Control and Prevention based on passive spontaneous reporting methods (0.025-0.11 per 10 000 vaccinations)."

7. Cabanillas B et al., "Allergic reactions to the first COVID-19 vaccine: A potential role of polyethylene glycol?" Allergy 2021, 76, 6: 1617-1618. doi: https://doi.org/10.1111/all.14711
   - "Although the trigger of the adverse allergic reactions suffered by the two NHS workers after receiving the vaccine BNT162b2 against COVID-19 has yet to be determined, the potential role of the excipient ALC-0159 containing PEG as a high-risk hidden trigger of dangerous allergic reactions should be carefully considered before advising the administration of BNT162b2 vaccine."

8. Calogiuri G et al., "Polyethylene glycols and polysorbates: Two still neglected ingredients causing true IgE-mediated reactions," *J Allergy Clin Immunol Pract* 2019, 7, 7: 2509-2510. doi: 10.1016/j.jaip.2019.05.058
   - "In the light of increased exposure of PEGs and polysorbates in our environment, a greater incidence of PEG hypersensitivity should be expected in the next years."

9. Camera GL et al., "A Step-by-Step Approach to Improve Clinical Translation of Liposome-Based Nanomaterials, a Focus on Innate Immune and Inflammatory Responses," *Int. J. Mol. Sci.* 2021, 22, 2: 820. doi: https://doi.org/10.3390/ijms22020820
   - "… a large proportion of the selected, commercially available carriers failed to pass the first homogeneity tests, and further products were found to be cytotoxic or interact with the immune system in an undesired way."

10. Carreno JM et al., "mRNA-1273 but not BNT162b2 induces antibodies against polyethylene glycol (PEG) contained in mRNA-based vaccine formulations," *Vaccine* 2022, 40, 42: 6114-6124. doi: https://doi.org/10.1016/j.vaccine.2022.08.024
    - "We detected an increase in the reactivity to mRNA vaccine formulations in mRNA-1273 but not BNT162b2 vaccinees' sera in a prime-boost dependent manner. Furthermore, we observed the same pattern of reactivity against irrelevant lipid nanoparticles."

11. Catenacci L et al., "Effect of Lipid Nanoparticle Physico-Chemical Properties and Composition on Their Interaction with the Immune System," *Pharmaceutics* 2024, 16, 12: 1521. doi: https://doi.org/10.3390/pharmaceutics16121521
    - "COVID-19 mRNA vaccines administered in the deltoid muscle in humans stimulate inflammation and recruitment of neutrophils, monocytes, and dendritic cells…"

12. Chen BM et al., "Polyethylene Glycol Immunogenicity: Theoretical, Clinical, and Practical Aspects of Anti-Polyethylene Glycol Antibodies," *ACS Nano* 2021, 15, 9: 14022–14048. doi: https://doi.org/10.1021/acsnano.1c05922

- "Hypersensitivity reactions including anaphylaxis after infusion of pegylated medicines are well documented in both animal and clinical studies… Pegylated liposomes encapsulating oligonucleotides induce anti-PEG IgM antibodies in mice and cause anaphylactic shock upon a second injection of liposomes."

13. Chen WA et al., "Antibodies against Poly(ethylene glycol) Activate Innate Immune Cells and Induce Hypersensitivity Reactions to PEGylated Nanomedicines," *ACS Nano* 2023, 17, 6: 5757–5772. doi: https://doi.org/10.1021/acsnano.2c12193
    - "We demonstrate that anti-PEG IgG but not IgM antibodies induce hypersensitivity-like symptoms against PLD and other PEGylated nanoparticles and macromolecules in mice that depend primarily on neutrophils, macrophages, and basophils."

14. de Vriez J, "Pfizer's vaccine raises allergy concerns. Polymer in mRNA's "packaging" may cause rare anaphylactic reactions," *Science* 2021, 371, 6524: 10-11. doi: 10.1126/science.371.6524.10
    - "Severe allergy-like reactions in at least 12 people who received the COVID-19 vaccine produced by Pfizer and BioNTech may be due to a compound in the packaging of the messenger RNA (mRNA) that forms the vaccine's main ingredient, scientists say. A similar mRNA vaccine developed by Moderna also contains the compound, polyethylene glycol (PEG)."

15. du Preez HN et al., "COVID-19 vaccine adverse events: Evaluating the pathophysiology with an emphasis on sulfur metabolism and endotheliopathy," *Eur J Clin Invest*. 2024, 54, 10: e14296. doi: https://doi.org/10.1111/eci.14296
    - "We hypothesize that after COVID-19 vaccination, the combination of the genetic-vaccine-generated (GVG) Sp antigen, the genetic material and LNPs, will ultimately contribute to GL [glycocalyx] degradation; mainly through the generation of chronic, skewed or excessive inflammatory responses, and oxidative stress. Therefore, AEs experienced postvaccination results from compromised barrier functions, circulating pro-inflammatory cytokines, reactive oxygen species (ROS), GL fragments, harmful NPs, and soluble GVG Sp and its fragments, all of which cause various cytotoxic effects."

16. Gao Z et al., "Exploring the impact of lipid nanoparticles on protein stability and cellular proteostasis," *J. Colloid Interface Sci.* 2025, 678(A): 656-665. doi: https://doi.org/10.1016/j.jcis.2024.08.146
    - "… LNPs may induce subtle proteome stress by compromising protein stability and proteostasis even without obvious damage to cell viability."

17. Guo C et al., "The interplay between PEGylated nanoparticles and blood immune system," *Adv Drug Deliv Rev.* 2023, 200: 114004. doi: https://doi.org/10.1016/j.addr.2023.115044
    - "Complement activation-related pseudoallergy (CARPA) and accelerated blood clearance (ABC) phenomenon are the most notorious problems. CARPA is a non-IgE-activated hypersensitivity reaction (HSR) that manifests as a hemodynamic disturbance and an inflammatory response that can cause serious consequences or even fatalities."

18. Ibrahim M et al., "Polyethylene glycol (PEG): The nature, immunogenicity, and role in the hypersensitivity of PEGylated products," *J Control Release* 2022, 351: 215-230. doi: https://doi.org/10.1016/j.jconrel.2022.09.031
    - "… the main causes and exact mechanisms of hypersensitivity to mRNA COVID-19 vaccines have not been fully elucidated, but reports of hypersensitivity reactions have focused on the role of the PEG polymer that is used in the preparation of these vaccines… we explain the potential role of PEG in the reports of the immunogenicity and hypersensitivity that has been encountered post-mRNA COVID-19 vaccination."

19. Igyarto BZ et al., "Future considerations for the mRNA-lipid nanoparticle vaccine platform," *Curr Opin Virol.* 2021, 48: 65–72. doi: 10.1016/j.coviro.2021.03.008
    - "… some of the immediate allergic responses observed with the first shot of mRNA-LNP vaccines might be related to pre-existing PEG antibodies. Since these vaccines often require a booster shot, anti-PEG antibody formation is expected after the first shot. Thus, the allergic events are likely to increase upon re-vaccination."
    - "It has been shown that mRNA-LNP vaccines have an altered tissue distribution, dynamics, and uptake in animals that have been pre-exposed to inflammatory agents. These findings suggest that people with pre-existing inflammatory conditions might show altered immune responses to these vaccines and might present with more severe side-effects."

20. Igyarto BZ and Zhen Qin, "The mRNA-LNP vaccines – the good, the bad and the ugly?" *Front. Immunol.* 2024, 15 (Sec. Vaccines and Molecular Therapeutics). doi: https://doi.org/10.3389/fimmu.2024.1336906
    - "… the LNPs' ionizable lipid component of the mRNA-LNP vaccine is highly inflammatory … another potential explanation for the distinct lots triggering different levels of adverse events could be that the amounts of mRNA-LNP or the mRNA : LNP ratio differed between lots."

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    - "We conclude that PEG-specific antibodies can be boosted by LNP mRNA vaccination and that the rise in PEG-specific antibodies is associated with systemic reactogenicity and an increase of PEG particle–leukocyte association in human blood."

22. Klimek L et al., "Allergenic components of the mRNA-1273 vaccine for COVID-19: Possible involvement of polyethylene glycol and IgG-mediated complement activation," *Allergy* 2021, 76, 11: 3307-3313. doi: https://doi.org/10.1111/all.14794
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23. Korzun T et al., "From Bench to Bedside: Implications of Lipid Nanoparticle Carrier Reactogenicity for Advancing Nucleic Acid Therapeutics," *Pharmaceuticals* 2023, 16, 8: 1088. doi: https://doi.org/10.3390/ph16081088
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