

# COVID-19 mRNA “Vaccine” Harms

A Real-World Evidence (RWE) Compilation

*Compiled by*

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*et al.*

A research addendum to  
*TOXIC SHOT: Facing the Dangers of the COVID “Vaccines”*

## COVID-19 mRNA “vaccine” harms: a real-world evidence (RWE) compilation

Compiled by Martin Wucher, MSC Dent Sc (eq DDS), Byram Bridle, PhD, Steven Hatfill, MD, Jessica Rose, PhD, Peter McCullough, MD MPH, Harvey Risch, MD PhD, Kelly Victory, MD, Matt Bain, MD, James Thorp, MD, et al.

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✔ = peer-reviewed

This compilation originated with the authors’ contributions to *TOXIC SHOT: Facing the Dangers of the COVID “Vaccines”* (Foreword by Sen. Ron Johnson)

- I. **Spike protein pathogenicity research library (✔547/557)** p. 4  
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, including over 500 peer-reviewed scientific papers collected in section (a). A second sub-section (b) on p. 59 organizes the research into 35 subject categories.
- II. **Spike protein and “vaccine” mRNA biodistribution studies (✔64/72)** p. 138  
In addition to the pathogenic characteristics of the spike protein antigen, over 60 peer-reviewed studies have demonstrated that both the “vaccine” mRNA encoding for the spike protein antigen and the spike protein itself can leave the injection site to penetrate distant tissues, causing systemic harms.
- III. **Spike protein and “vaccine” mRNA persistence studies (✔41/43)** p. 152  
Dozens of peer-reviewed studies confirm that “vaccine” mRNA and the resulting spike protein antigen 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 17 months for spike protein (Ota N et al.).
- IV. **Lipid nanoparticle toxicity and allergenicity studies (✔92/92)** p. 160  
Over 90 peer-reviewed papers show that 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). Research also suggests much higher anaphylaxis rates following “vaccination” than indicated in official figures.

- V. **COVID-19 “vaccine” immune imprinting library (✓148/156)** p. 181  
Immune imprinting, dubbed “[original antigenic sin](#)” by Thomas Francis Jr., occurs when memory B lymphocytes produced in response to an initial viral infection dominate subsequent responses to related viruses. Over 140 peer-reviewed papers suggest that COVID “vaccines” imprinted the immune systems of recipients through exposure to the “wild type” spike protein from the original Wuhan strain, shaping their response to subsequent variants in potentially harmful ways.
- VI. **SARS-CoV2 “vaccine” and viral variant research library (✓83/85)** p. 220  
In addition to the pathogenicity, distribution, and long persistence of the “vaccine” spike protein, this collection of over 80 peer-reviewed papers suggests that by failing to prevent infection or transmission, the “vaccines” applied strong selective pressure to the fast-mutating SARS-CoV2 virus, quickly giving rise to “vaccine”-resistant variants.
- VII. **COVID “vaccine” cancer, genotoxicity, and DNA contamination risks (✓117/122)** p. 241  
Scientific evidence suggests that the mRNA “vaccines” as well as the adenoviral vector shots (J&J, AstraZeneca) and various inactivated “vaccines” (CoronaVac) can damage DNA and trigger or accelerate the growth of cancers. Research has also revealed contamination of mRNA “vaccines” with residual DNA, a byproduct of the manufacturing process which may be incorporated into cellular DNA during DNA damage repair, permanently altering the human genome.
- VIII. **APPENDIX. Summary and overview of [TOXIC SHOT: Facing the Dangers of the COVID “Vaccines”](#)** p. 274  
This scientific bombshell shatters official propaganda about the COVID-19 “vaccines,” highlighting their risks for healthy people as well as their failure to stop the pandemic. Chapter after chapter presents damning proof of the myriad harms associated with the “vaccines,” drawing on abundant scientific research to explain why the experimental shots are so dangerous. A call to battle, *TOXIC SHOT* leaves no doubt that the COVID-19 “vaccines” must be withdrawn from the market immediately.

**For readers seeking more information:** React19, a global organization advocating for individuals with “vaccine” injuries and their loved ones, has collected over 3,750 published papers documenting “vaccine” injuries available here: <https://react19.org/science>. The Malone Institute maintains a database of over 770 papers documenting COVID “vaccine” harms available here: <https://maloneinstitute.org/reference-project>. DailyClout presents a comprehensive analysis of “vaccine” harms drawing on Pfizer’s own clinical trial data in [The Pfizer Papers: Pfizer’s Crimes Against Humanity](#) (Skyhorse, 2024).

## I. COVID-19 spike protein pathogenicity research library

Compiled by Dr. Martin Wucher, MSC Dent Sc (eq DDS), et al. Last updated November 18, 2025.

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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, independent of the rest of the virus.

The following (a) Alphabetical List collects (**547/557 peer-reviewed ✔**) scientific studies confirming that the spike protein is highly pathogenic on its own. Most *in vitro* and *in vivo* studies cited here used “vaccine”-derived spike protein, recombinant spike protein, or spike protein in pseudoviral vectors, and still produced pathological effects not reliant on the SARS-CoV2 viral machinery. Data presented here directly contradict claims that the “vaccine”-derived spike protein is harmless because it is locked in a “prefusion” conformation: in fact, the “vaccine”-derived spike retains a wide range of bioactivity, including the ability to interact with ACE2 as well as a multitude of other receptors, pathways and systems.

The second section, (b) Categories, p. 59, organizes the research into broad categories including affected tissues and organ systems, mechanisms, and evidence from clinical pathology. Because these areas overlap, many articles appear more than once in the second section.

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).

### (a) ALPHABETICAL LIST (547/557 peer-reviewed ✔)

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4. Adewoye A et al., "Amyloidogenic SARS-CoV-2 Spike Protein-Derived Peptides Form Oligomers and Selectively Damage Lipid Membranes," *Biochemistry* 2025, 64, 16: 3610-3622. doi: [10.1021/acs.biochem.5c00290](https://doi.org/10.1021/acs.biochem.5c00290) ✓
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## II. Spike protein and “vaccine” mRNA biodistribution studies

*Compiled by Dr. Martin Wucher, MSC Dent Sc (eq DDS), et al. Last updated November 18, 2025.*

✔ = peer-reviewed

Biodistribution studies show that both the “vaccine” mRNA encoding for the spike protein antigen and the spike protein itself can leave the injection site to penetrate distant tissues, causing systemic harms to a variety of organs and organ systems, including the placenta. The following research collection presents **(64/72 peer-reviewed ✔)** studies 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, stomach, placenta, umbilical cord, breast milk, lymph nodes, thymus, kidneys, spleen, bladder, small and large intestine, spinal cord, eyes, adrenal glands, uterus, 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 collection includes studies of biodistribution after intravenous injection because many “vaccines” were likely delivered intravenously due to poor administration technique [46, 57]. However, abundant evidence collected here shows that even following intramuscular administration, “vaccine” components are quickly distributed throughout the body via the rich vascular supply of the deltoid muscle [17, 19, 26, 31, 52, 67]. This evidence includes the “vaccine” manufacturers’ own preclinical studies submitted to regulatory agencies for official authorization [2, 20, 21, 38, 45, 47].

A chart below summarizes the findings of dozens of studies collected in this section II, showing which “vaccine” components and products were examined (mRNA, LNP, and/or spike protein) and key tissues and organs affected; studies of biodistribution following intravenous or subcutaneous administration are highlighted in yellow. Taken together with evidence of the spike protein’s pathogenicity, 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.

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).

# COVID "Vaccine" Biodistribution

■ = I.V./SubQ

Authors (study #)

COVID “Vaccine”  
Biodistribution

= I.V./SubQ

	mRNA	LNP	spike	blood	lymph node	spleen	liver	brain	heart	kidneys	adrenal glands	skin	eyes	thymus	bone	bone marrow	ovaries	testes	lung	breast milk	placenta	fetus	stomach	small intestine	large intestine (- colon)	uterus	bladder	spinal cord	
Abe et al. (1)	✓	✓	✓			✓																							
Australian Govt. (2)		✓				✓	✓				✓						✓												
Bansal et al. (3)			✓	✓																									
Baumeier et al. (4)			✓						✓																				
Blizard et al. (5)	✓	✓	✓		✓	✓	✓																						
Boros et al. (6)	✓		✓						✓																				
Brogna et al. (8)			✓	✓																									
Broudic et al. (10)	✓				✓	✓	✓	✓		✓	✓		✓			✓	✓	✓	✓										
Burkhardt (11)			✓			✓	✓	✓	✓			✓							✓										
Castruita et al. (13)	✓			✓																									
Chen et al. (14)	✓		✓				✓														✓	✓							
Ci et al. (15)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				✓	✓	✓		✓		
Di et al. (19)		✓			✓	✓	✓																						
EMA (20)	✓	✓				✓		✓	✓	✓							✓	✓											
EMA (21)	✓							✓	✓				✓				✓	✓	✓										
Fertig et al. (23)	✓			✓																									
Ferraresso et al. (24)			✓	✓		✓	✓	✓	✓	✓							✓		✓				✓	✓	✓	✓	✓		
Hanna et al. (25)	✓																			✓									
Hassett et al. (26)	✓		✓	✓	✓	✓	✓																						
Judicial Watch (28)		✓				✓	✓				✓						✓												
Kammala et al. (29)			✓																		✓								
Kawano et al. (30)			✓						✓																				
Kent et al. (31)	✓	✓		✓	✓																								
Krauson et al. (32)	✓				✓				✓																				
Kwon et al. (33)		✓		✓	✓	✓	✓	✓						✓			✓	✓	✓										
Li et al. (35)			✓					✓																					
Li et al. (36)			✓		✓	✓	✓												✓										
Lin et al. (37)	✓		✓	✓																	✓								
Ma et al. (39)	✓			✓	✓	✓	✓	✓	✓	✓	✓		✓				✓	✓	✓										
Magro et al. (41)			✓									✓																	
Martin-Navarro et al. (43)	✓						✓																						
UK MHPRA (45)		✓					✓																						
Japan MoHLFW (47)		✓					✓	✓	✓	✓			✓		✓	✓			✓					✓			✓		
Mörz (48)			✓					✓	✓																				
Nyein et al. (49)			✓				✓																						
Ogata et al. (50)			✓	✓																									
Ota et al. (51)			✓					✓																					
Parrett et al. (52)		✓					✓																						
Pateev et al. (53)		✓			✓	✓	✓												✓										
Rzymiski et al. (57)	✓		✓					✓																					
Sandelius et al. (58)	✓	✓	✓			✓	✓			✓		✓																	
Sano et al. (59)			✓									✓																	
Sano et al. (60)			✓									✓																	
Schreckenberger et al. (62)			✓						✓																				
Szebeni & Koller (67)			✓	✓			✓	✓	✓	✓									✓									✓	
Yamamoto et al. (69)			✓									✓																	
Yonker (71)			✓	✓																									
Zhong et al. (72)	✓																			✓	✓	✓							
#	20	14	29	14	12	15	22	12	16	8	5	6	5	2	1	3	9	6	11	2	4	2	2	2	3	1	2	1	1

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    - “mRNA-LNP vaccines, and their components, have been observed systemically in humans. Following mRNA-LNP vaccination, widespread immune activation can be attributed, at least partly, to even low amounts of systemic LNP and constituent components. Specifically, the presence of Spike antigen in human organs has been implicated in vaccine reactogenicity, with natural killer (NK) cell cytotoxicity associated with myocarditis, potentially from xenoprotein in cellular membranes. Spike antigen and analyte induction can sometimes contribute to aberrant lymphocyte responses, amplifying inflammation and exacerbating human cytokinopathy following mRNA-LNP vaccination.”
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  - “During vaccination by the intramuscular route, the liposome can, due to its chemical properties, cross the capillary barrier and disseminate itself in all the tissues. By this route, the liposome reaches the general circulation, without having to pass through the portal system and the liver. Absorption will be more or less complete and more or less rapid depending on the physicochemical properties of the liposome: injected into the arm, it does not remain locally, if it is not targeting, and diffuses very quickly (between 15 min and 4 h maximum throughout the body) and can, therefore, be incorporated into any cell of any organ.”
  
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19. Di J et al., “Biodistribution and Non-linear Gene Expression of mRNA LNPs Affected by Delivery Route and Particle Size,” *Pharm Res* 2022, 39: 105-114. doi: [10.1007/s11095-022-03166-5](https://doi.org/10.1007/s11095-022-03166-5) ✓
  - Liver, spleen, muscle, and inguinal lymph nodes

20. European Medicines Agency, *Assessment Report*, available online: [www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report\\_en.pdf](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.”
21. European Medicines Agency, *COVID-19 Vaccine Moderna*, available online: [www.ema.europa.eu/en/documents/assessment-report/spikevax-previously-covid-19-vaccine-moderna-epar-public-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/assessment-report/spikevax-previously-covid-19-vaccine-moderna-epar-public-assessment-report_en.pdf)
  - Vaccine mRNAs are detectable in brain, heart, lungs, eyes, gonads.
22. Ferraresso F et al., “Protein is expressed in all major organs after intravenous infusion of mRNA-lipid nanoparticles in swine,” *Mol. ther., Methods clin. dev.* 2024, 32, 3: 101314. doi: [10.1016/j.omtm.2024.101314](https://doi.org/10.1016/j.omtm.2024.101314) ✓
  - “In this study, we found that exogenous protein expression occurred in all major organs when swine were injected intravenously with a relatively low dose of mRNA encapsulated in a clinically relevant LNP formulation. Exogenous protein was detected in the liver, spleen, lung, heart, uterus, colon, stomach, kidney, small intestine, and brain of the swine without inducing CARPA. Furthermore, protein expression was detected in the bone marrow, including megakaryocytes, hematopoietic stem cells, and granulocytes, and in circulating white blood cells and platelets.”
23. Fertig TE et al., “Beyond the injection site: identifying the cellular targets of mRNA vaccines,” *J Cell Ident* 2024, 3, 1. doi: [10.47570/joci.2024.004](https://doi.org/10.47570/joci.2024.004) ✓
  - Overview of studies showing wide distribution throughout the body.
24. Fertig TE et al., “Vaccine mRNA Can Be Detected in Blood at 15 Days Post Vaccination,” *Biomedicines* 2022, 10, 7: 1538. doi: [10.3390/biomedicines10071538](https://doi.org/10.3390/biomedicines10071538) ✓
  - Plasma
25. Hanna N et al. “Biodistribution of mRNA COVID-19 vaccines in human breast milk,” *eBioMedicine* 2023, 96, 104800. doi: [10.1016/j.ebiom.2023.104800](https://doi.org/10.1016/j.ebiom.2023.104800) ✓
  - “Of 13 lactating women receiving the vaccine (20 exposures), trace mRNA amounts were detected in 10 exposures up to 45 h post-vaccination. “
26. Hassett KJ et al., “mRNA vaccine trafficking and resulting protein expression after intramuscular administration,” *Mol. Ther. Nucleic Acids* 2024, 35, 1: 102083. doi: [10.1016/j.omtn.2023.102083](https://doi.org/10.1016/j.omtn.2023.102083) ✓
  - Plasma, lymph nodes, liver, spleen

27. Hulscher N et al., "Autopsy findings in cases of fatal COVID-19 vaccine-induced myocarditis," *ESC Heart Failure* 2024. doi: [10.1002/ehf2.14680](https://doi.org/10.1002/ehf2.14680) ✓
  - "COVID-19 vaccine Spike protein is produced in the body for an uncontrolled duration and in unknown quantity resulting in deleterious effects, especially on the heart, explaining the cardiovascular deaths seen in our study without evidence of other organ system involvement."
  
28. Judicial Watch, "JW v HHS FDA Pfizer BioNTech Vaccine prod 3 02418," March 21, 2022, available online: [www.judicialwatch.org/documents/jw-v-hhs-fda-pfizer-biontech-vaccine-prod-3-02418/](https://www.judicialwatch.org/documents/jw-v-hhs-fda-pfizer-biontech-vaccine-prod-3-02418/)
  - LNP biodistribution to liver, spleen, adrenal glands, ovaries. "Outside the injection site, low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose."
  
29. Kammala AK et al., "In vitro mRNA-S maternal vaccination induced altered immune regulation at the maternal-fetal interface," *Am. J. Reprod. Immunol.* 2024, 91, 5: e13861. doi: [10.1111/aji.13861](https://doi.org/10.1111/aji.13861) ✓
  - "... our study indicates that mRNA-S-based maternal vaccination during pregnancy may influence the maternal-fetal interface's COVID-19 interaction and immune regulation. Further investigation is warranted to assess safety and implications."
  
30. Kawano H et al., "Fulminant Myocarditis 24 Days after Coronavirus Disease Messenger Ribonucleic Acid Vaccination," *Intern. Med.* 2022, 61, 15: 2319-2325. doi: [10.2169/internalmedicine.9800-22](https://doi.org/10.2169/internalmedicine.9800-22) ✓
  - "... positive immunostaining for severe acute respiratory syndrome coronavirus 2 spike protein and C4d in the myocardium."
  
31. Kent SJ et al., "Blood Distribution of SARS-CoV-2 Lipid Nanoparticle mRNA Vaccine in Humans," *ACS Nano* 2024, 18, 39: 27077-27089. doi: [10.1021/acsnano.4c11652](https://doi.org/10.1021/acsnano.4c11652) ✓
  - "The similar kinetics of intact mRNA and the ionizable lipid in blood and the slow degradation of the mRNA suggest that mRNA lipid nanoparticles remain intact and travel from injection sites or lymph nodes into the bloodstream within 4 h postvaccination. The rapid dissemination of mRNA lipid nanoparticles in blood found in our study is consistent with the recent findings on the detection of mRNA in breast milk at 3–45 h postvaccination."
  
32. 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: [10.1038/s41541-023-00742-7](https://doi.org/10.1038/s41541-023-00742-7) ✓
  - Axillary lymph nodes, myocardium

33. Kwon MH et al., "The Pharmacokinetics of mRNA Vaccine Carrier using Carbon-14," *J. Radiopharm. Mol. Probes* 2024, 10, 1: 73-81. doi: [10.22643/JRMP.2024.10.1.73](https://doi.org/10.22643/JRMP.2024.10.1.73) ✓
  - Serum, lymph nodes, muscle, spleen, liver, testis, ovary, thymus, lung, brain
  
34. Lehmann KJ, "SARS-CoV-2-Spike Interactions with the Renin-Angiotensin-Aldosterone System – Consequences of Adverse Reactions of Vaccination," *J Biol Today's World* 2023, 12/4: 001-013. doi: [10.31219/osf.io/27g5h](https://doi.org/10.31219/osf.io/27g5h) ✓
  - "The presented analysis provides a substantial body of evidence for the causal involvement of Ang II/activated RAAS in eliciting adverse reactions after application of spike-inducing vaccine. As an example, some serious organ disturbances or adverse reactions, in which the connection with an activated RAAS is obvious (cardiovascular and blood coagulation disorders, disorders of the nervous and muscular system, inflammatory reactions, auto-immunological, vascular and renal disorders), are presented and discussed..."
  
35. Li C. et al., "Intravenous Injection of Coronavirus Disease 2019 (COVID-19) mRNA Vaccine Can Induce Acute Myopericarditis in Mouse Model," *Clin. Infect. Dis.* 2022, 74, 11: 1933-1950. doi: [10.1093/cid/ciab707](https://doi.org/10.1093/cid/ciab707) ✓
  - "Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike antigen expression by immunostaining was occasionally found in infiltrating immune cells of the heart or injection site, in cardiomyocytes and intracardiac vascular endothelial cells, but not skeletal myocytes."
  
36. Li C et al., "Mechanisms of innate and adaptive immunity to the Pfizer-BioNTech BNT162b2 vaccine," *Nature Immunol.* 2022, 23: 543-555. doi: [10.1038/s41590-022-01163-9](https://doi.org/10.1038/s41590-022-01163-9) ✓
  - Spleen, muscle, liver, lung and non-dLNs
  
37. Lin X et al., "Transplacental transmission of the COVID-19 vaccine messenger RNA: evidence from placental, maternal, and cord blood analyses postvaccination," *Am J Obstet Gynecol* 2024, 92, 4: e13934. doi: [10.1111/aji.13934](https://doi.org/10.1111/aji.13934) ✓
  - "The vaccine mRNA was detected in the 2 placentas evaluated using quantitative ddPCR and ISH... Using WES, the spike protein expression was detected in the placenta of patient 2, but not in patient 1... Furthermore, the vaccine mRNA was detected in the umbilical cord and maternal blood of patient 1 using ddPCR."
  
38. Luo Y et al., "SARS-Cov-2 spike induces intestinal barrier dysfunction through the interaction between CEACAM5 and Galectin-9," *Front. Immunol.* 2024, 15. doi: [10.3389/fimmu.2024.1303356](https://doi.org/10.3389/fimmu.2024.1303356) ✓

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- Plasma, lymph nodes, liver, adrenal glands, spleen, ovaries, brain, lung, eye, testes, kidney
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- “... 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.”
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42. Magro C et al., “Disruption of the blood-brain barrier is correlated with spike endocytosis by ACE2 + endothelia in the CNS microvasculature in fatal COVID-19. Scientific commentary on ‘Detection of blood-brain barrier disruption in brains of patients with COVID-19, but no evidence of brain penetration by SARS-CoV-2’,” *Acta Neuropathol.* 2024, 147, 1: 47. doi: [10.1007/s00401-023-02681-y](#) ✓
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- “... our results suggest that lipid nanoparticles bearing mRNA molecules encoding SARS-CoV-2 proteins can reach hepatocytes under certain circumstances and deliver mRNA in high quantities that could be used by the translational machinery of the cells to produce spike.”
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- Liver
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- bladder, bone, bone marrow, brain, eyes, heart, kidneys, large intestine, liver, lung
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- “Only spike protein but no nucleocapsid protein could be detected within the foci of inflammation in both the brain and the heart, particularly in the endothelial cells of small blood vessels.”
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- “Here we provide evidence that circulating SARS-CoV-2 proteins are present in the plasma of participants vaccinated with the mRNA-1273 vaccine.”

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  - Brain vasculature
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  - “Off-target transfection of the liver can also be a problem when injecting LNP-mRNA by non-IV routes, since LNPs are documented to leak into the bloodstream and reach the liver regardless of their original site of injection. For example, as much as 21.5% of the LNPs of COVID-19 mRNA-LNP vaccines injected via the IM route were found in the liver in preclinical studies.”
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  - “Intravenous injection led to the detection of fluorescent proteins in the liver, spleen, lungs, and lymph nodes.”
54. Petrovszki D et al., “Penetration of the SARS-CoV-2 Spike Protein across the Blood-Brain Barrier, as Revealed by a Combination of a Human Cell Culture Model System and Optical Biosensing,” *Biomedicines* 2022, 10, 1: 188. doi: [10.3390/biomedicines10010188](https://doi.org/10.3390/biomedicines10010188) ✓
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  - “As shown in vivo in mice, intravenous injection of the BNT162b2 vaccine (BioNTech/Pfizer, Germany/USA) resulted in histopathological changes characteristic for myopericarditis... the amount of mRNA encoding SARS-CoV-2 spike protein and its subsequent myocardial expression was significantly higher



in heart tissue when compared to the animals receiving the intramuscular injection.”

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  - Skin, spleen, liver, kidney
59. 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, 9: 1208-1212. doi: [10.1111/1346-8138.16816](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.”
60. Sano S et al., “SARS-CoV-2 spike protein found in the acrosyringium and eccrine gland of repetitive miliaria-like lesions in a woman following mRNA vaccination,” *J. Dermatol.* 2024, 51, 9: e293-e295. doi: [10.1111/1346-8138.17204](https://doi.org/10.1111/1346-8138.17204) ✓
  - Cutaneous
61. Sattar S Et al., “Nuclear translocation of spike mRNA and protein is a novel feature of SARS-CoV-2,” 2023 *Front. Microbiol.* 2023, 14 (Virology). doi: [10.3389/fmicb.2023.1073789](https://doi.org/10.3389/fmicb.2023.1073789) ✓
  - “Although the S protein is a surface transmembrane type 1 glycoprotein, it has been predicted to be translocated into the nucleus due to the novel nuclear localization signal (NLS) ‘PRRARSV,’ which is absent from the S protein of other coronaviruses. Indeed, S proteins translocate into the nucleus in SARS-CoV-2-infected cells. S mRNAs also translocate into the nucleus. S mRNA colocalizes with S protein, aiding the nuclear translocation of S mRNA.”
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  - “After 48 h, expression of the encoded spike protein was detected in ventricular cardiomyocytes for both mRNAs... mRNA-1273 induced arrhythmic as well as completely irregular contractions associated with irregular as well as localized calcium transients, which provide indications of significant dysfunction of the

cardiac ryanodine receptor (RyR2)... BNT162b2 increased cardiomyocyte contraction via significantly increased protein kinase A (PKA) activity..."

63. Shirasawa T, "Imaging Diagnosis of and Treatment for Spike Protein-Induced Thrombosis after COVID-19 mRNA Vaccination," *MJCR* 2025, 10, 1. doi: [10.30654/MJCR.10195](https://doi.org/10.30654/MJCR.10195) ✓
  - Spike protein in carotid arteries
64. Stern B et al., "SARS-CoV-2 spike protein induces endothelial dysfunction in 3D engineered vascular networks," *J. Biomed. Mater. Res. A*. 2023, 112, 4: 524-533. doi: [10.1002/jbm.a.37543](https://doi.org/10.1002/jbm.a.37543) ✓
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  - "... S1, S1RBD, and S2 subunits exhibit pro-inflammatory effects, resulting in increased BBB permeability via damage to tight junctions (TJs)..."
66. Suprewicz L et al., "Recombinant human plasma gelsolin reverses increased permeability of the blood-brain barrier induced by the spike protein of the SARS-CoV-2 virus," *J Neuroinflamm.* 2022, 19, 1: 282. doi: [10.1186/s12974-022-02642-4](https://doi.org/10.1186/s12974-022-02642-4) ✓
67. Szebeni J and A Koller, "Multisystem Endothelial Inflammation: A Key Driver of Adverse Events Following mRNA-Containing COVID-19 Vaccines," *Vaccines (Basel)* 2025, 13, 8: 855. doi: [10.3390/vaccines13080855](https://doi.org/10.3390/vaccines13080855) ✓
  - Spike protein distribution via blood to heart, brain, spinal cord, peripheral nervous system, lung, kidney, liver. "Accordingly, the localization and systemic spread of the spike protein is strongly determined by the special structures and function of microcirculation of various organs... The differences in the development of AEs may be due to the differences in the microcirculatory networks of various organs... A calculation at 15 min post-injection suggests that approximately 500 to 7000 mRNA-LNP may potentially interact with each endothelial cell in the body... The key implication of these metrics is that vaccine-induced endothelial transfection, activation, and consequent inflammation could potentially affect any segment of the vascular endothelium. Hence, the small volume of vaccine inoculum does not preclude the possibility of off-target distribution of vaccine nanoparticles."
68. Takanashi A et al., "Delivery and Expression of mRNA in the Secondary Lymphoid Organs Drive Immune Responses to Lipid Nanoparticle-mRNA Vaccines after Intramuscular Injection," *Mol. Pharmaceutics* 2023, 20, 8: 3876–3885. doi: [10.1021/acs.molpharmaceut.2c01024](https://doi.org/10.1021/acs.molpharmaceut.2c01024) ✓

- “Our results suggest that the mRNA delivery and transfection of secondary lymphatic organs, not LNP adjuvancy or RNA expression in muscle, are the main drivers for adaptive immune response in mice.”
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    - Spike expressed in vesicular keratinocytes and endothelial cells in the dermis.
  70. Yeo KT et al., “Neutralizing Activity and SARS-CoV-2 Vaccine mRNA Persistence in Serum and Breastmilk After BNT162b2 Vaccination in Lactating Women,” *Front. Immunol.* 2022, 12 (Nutritional Immunology). doi: [10.3389/fimmu.2021.783975](https://doi.org/10.3389/fimmu.2021.783975) ✓
    - “Transient, low intact vaccine mRNA levels was detected in 20/74 (27%) serum samples from 21 mothers, and 5/309 (2%) breastmilk samples from 4 mothers within 1 weeks of vaccine dose.”
  71. Yonker LM et al., “Circulating Spike Protein Detected in Post–COVID-19 mRNA Vaccine Myocarditis,” *Circulation* 2023, 147, 11. doi: [10.1161/CIRCULATIONAHA.122.061025](https://doi.org/10.1161/CIRCULATIONAHA.122.061025) ✓
    - Plasma
  72. Zhong C et al., “COVID-19 Vaccine mRNA Biodistribution: Maternal and Fetal Exposure Risks,” *Am. J. Reprod. Immunol.* 2024, 92, 4: e13934. doi: [10.1111/aji.13934](https://doi.org/10.1111/aji.13934) ✓
    - Placenta, fetus, breast milk

### III. Spike protein and vaccine mRNA persistence studies

Compiled by Dr. Martin Wucher, MSC Dent Sc (eq DDS), et al. Last updated November 18, 2025.

✔ = peer-reviewed

Dozens of studies collected here (**41/43 peer-reviewed** ✔) 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 17 months for spike protein (Ota N et al.). Numerous studies have also shown that viral-derived spike proteins can also persist well over a year in individuals recovered from SARS CoV2 infection or with “long COVID,” with spike protein detected up to two years after infection in one case (Fraser ME et al.). Long-lasting viral-derived spike proteins have frequently been detected *in the absence of viable virus*, as reflected in negative PCR tests and RNA assays, providing more evidence that 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).

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  - “The findings of this study indicated that COVID-19 vaccination resulted in an increase in cytokine levels, which signifies the persistence of the humoral immune response to messenger RNA (mRNA) vaccines. This effect may be attributed to the persistent production of spike protein and highly inflammatory nature of mRNA-lipid nanoparticle.”
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  - Circulating exosomes with spike protein detected four months after vaccination.
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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.”
4. Brogna C et al., “Detection of recombinant Spike protein in the blood of individuals vaccinated against SARS-CoV-2: Possible molecular mechanisms,” *Proteonomics Clin App*. 2023, 17, 6. doi: [10.1002/prca.202300048](https://doi.org/10.1002/prca.202300048) ✓
    - “The minimum and maximum time at which PP-Spike was detected after vaccination was 69 and 187 days, respectively.”
  5. Castruita JAS et al., “SARS-CoV-2 spike mRNA vaccine sequences circulate in blood up to 28 days after COVID-19 vaccination,” *APMIS* 2023, 131: 128–132. doi: [10.1111/apm.13294](https://doi.org/10.1111/apm.13294) ✓
  6. Cheung CCL et al., “Residual SARS-CoV-2 viral antigens detected in GI and hepatic tissues from five recovered patients with COVID-19,” *Gut* 2022, 71, 1: 226–9. doi: [10.1136/gutjnl-2021-324280](https://doi.org/10.1136/gutjnl-2021-324280) ✓
    - Persistence of residual SARS-CoV-2 antigens up to 180 days in the colon, appendix, ileum, haemorrhoid, liver, gallbladder and lymph nodes; unable to detect viral RNA in many patients’ tissues.
  7. Colmenero I et al., “SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases,” *Br J Dermatol*. 2020, 183: 729–737. doi: [10.1111/bjd.19327](https://doi.org/10.1111/bjd.19327) ✓
    - Spike protein detected in lesions up to 30 days after onset of acute infection. SARS-CoV-2 PCR from nasopharyngeal and oropharyngeal swabs was negative in all cases tested (six of six).
  8. 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: [10.1002/jmv.28568](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.”
  9. Crespo-Barrios J, “Vaxtherapy, a Multiphase Therapeutic Protocol Approach for Longvax, the COVID-19 Vaccine-Induced Disease: Spike Persistence as the Core Culprit and Its Downstream Effects,” *Diseases* 2025, 13, 7: 204. doi: [10.3390/diseases13070204](https://doi.org/10.3390/diseases13070204) ✓

- “Evidence for spike persistence has been accumulating since 2021. S1 fragments have been detected inside CD16+ monocytes for up to 15 months, sustaining a low-grade inflammatory milieu that mirrors post-acute COVID-19 sequelae... Longvax is typified by prolonged ipsilateral axillary lymph node enlargement: imaging series after mRNA or adenoviral vaccination report prevalence rates approaching 33%, with a mean ultrasound resolution time near 102 days and pharmacovigilance cases lasting more than 6 months...”
- European Medicines Agency, *Assessment Report*, available online: [www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report\\_en.pdf](http://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...”
  - Fehrer A et al., “Serum Spike Protein Persistence Post COVID Is Not Associated with ME/CFS,” *J. Clin. Med.* 2025, 14(4), 1086; [10.3390/jcm14041086](https://doi.org/10.3390/jcm14041086) ✓
    - “Spike protein was detected in the serum of 11% of recovered controls, 2% of PCS patients, and 14% of ME/CFS patients between 4 and 31 months after SARS-CoV-2 infection...” No measurement of viral RNA was performed.
  - Fertig TE et al., “Vaccine mRNA Can Be Detected in Blood at 15 Days Post Vaccination,” *Biomedicines* 2022, 10, 7: 1538. doi: [10.3390/biomedicines10071538](https://doi.org/10.3390/biomedicines10071538) ✓
  - Finsterer J et al., “A Case Report: Long Post-COVID Vaccination Syndrome During the Eleven Months After the Third Moderna Dose,” *Cureus* 2022, 14, 12: e32433. doi: [10.7759/cureus.32433](https://doi.org/10.7759/cureus.32433) ✓
    - Antibodies to spike protein, but not nucleocapsid protein, detected for 11 months after vaccination, associated with lasting neurological symptoms; table summarizes dozens of cases of post-“vaccination” syndrome, some lasting months or “permanently.”
  - Gaebler C et al., “Evolution of antibody immunity to SARS-CoV-2,” *Nature* 2021, 591: 639-644. doi: [10.1038/s41586-021-03207-w](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.”

15. 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](https://doi.org/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.”
16. 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: [10.1111/tid.14281](https://doi.org/10.1111/tid.14281) ✓
  - Spike protein detectable in 3/16 (19%) participants 14 days after vaccination.
17. Kawano H et al., “Fulminant Myocarditis 24 Days after Coronavirus Disease Messenger Ribonucleic Acid Vaccination,” *Intern. Med.* 2022, 61, 15: 2319-2325. doi: [10.2169/internalmedicine.9800-22](https://doi.org/10.2169/internalmedicine.9800-22) ✓
  - “... positive immunostaining for severe acute respiratory syndrome coronavirus 2 spike protein and C4d in the myocardium.”
18. Kent SJ et al., “Blood Distribution of SARS-CoV-2 Lipid Nanoparticle mRNA Vaccine in Humans,” *ACS Nano* 2024, 18, 39: 27077-27089. doi: [10.1021/acsnano.4c11652](https://doi.org/10.1021/acsnano.4c11652) ✓
  - “The vaccine mRNA was detectable and quantifiable up to 14–15 days postvaccination in 37% of subjects.”
19. 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: [10.1038/s41541-023-00742-7](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.”
20. Li C et al., “Mechanisms of innate and adaptive immunity to the Pfizer-BioNTech BNT162b2 vaccine,” *Nature Immunol.* 2022, 23: 543-555. doi: [10.1038/s41590-022-01163-9](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.”
21. Ma L et al., “6.3. FDA-Approved mRNA Vaccines: Interpretation of Preclinical Pharmacokinetic (PK) Data,” in *Drug Metabolism and Pharmacokinetics: Frontiers, Strategies, and Applications*, ed. L Shen et al., Wiley & Sons, Hoboken, 2025. ISBN: [978-1-394-30013-6](https://doi.org/978-1-394-30013-6)



- “Notably, mRNA may have a persistent distribution at the injection site, lymph nodes, and spleen for 2–3 weeks, with a slow elimination rate.”
22. 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: [10.3390/vaccines10071135](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.”
23. 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: [10.1016/j.jpeds.2021.11.058](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.”
24. Mörz M, “A Case Report: Multifocal Necrotizing Encephalitis and Myocarditis after BNT162b2 mRNA Vaccination against COVID-19,” *Vaccines* 2022, 10, 10: 1651. doi: [10.3390/vaccines10101651](https://doi.org/10.3390/vaccines10101651) ✓
- Vaccine-induced spike detected on autopsy three weeks after last injection.
25. 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: [10.1093/cid/ciab465](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.”
26. Ota N et al., “Expression of SARS-CoV-2 spike protein in cerebral Arteries: Implications for hemorrhagic stroke Post-mRNA vaccination,” *J. Clin. Neurosci.* 2025, 136: 111223. doi: [10.1016/j.jocn.2025.111223](https://doi.org/10.1016/j.jocn.2025.111223) ✓
- Spike protein expression detected in 43.8% of vaccinated subjects, lasting up to 17 months.
27. Parcial ALN et al., “SARS-CoV-2 Is Persistent in Placenta and Causes Macroscopic, Histopathological, and Ultrastructural Changes,” *Viruses* 2022, 14, 9: 1885. doi: [10.3390/v14091885](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...”

28. Pateev I et al., “Biodistribution of RNA Vaccines and of Their Products: Evidence from Human and Animal Studies,” *Biomedicines* 2024, 12, 1: 59. doi: [10.3390/biomedicines12010059](https://doi.org/10.3390/biomedicines12010059) ✓
  - (Röltgen 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.”
  - (Brojna C et al.) “It is noteworthy that in this study, spike protein was still detected in human blood on the 187th day after vaccination.”
29. Patterson BK et al., “Detection of S1 spike protein in CD16+ monocytes up to 245 days in SARS-CoV-2-negative post-COVID-19 vaccine syndrome (PCVS) individuals,” *Hum Vaccin Immunother.* 2025, 21, 1: 2494934. doi: [10.1080/21645515.2025.2494934](https://doi.org/10.1080/21645515.2025.2494934) ✓
30. 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: [10.3389/fimmu.2021.746021](https://doi.org/10.3389/fimmu.2021.746021) ✓
  - Intact viral RNA undetectable in monocytes.
31. 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](https://doi.org/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.”
32. 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: [10.1002/ana.26350](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.
33. 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](https://doi.org/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”
34. 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](https://doi.org/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.”
  35. 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: [10.1111/1346-8138.16816](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.”
  36. 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: [10.1002/jmv.28364](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 controls.
  37. 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: [10.1093/cid/ciac722](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.”
  38. 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 (Infectious Diseases – Surveillance). doi: [10.3389/fmed.2022.1003103](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.”

39. 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: [10.1111/cpr.13091](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.”
40. 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: [10.1002/cia2.12278](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.”
41. Yeo KT et al., “Neutralizing Activity and SARS-CoV-2 Vaccine mRNA Persistence in Serum and Breastmilk After BNT162b2 Vaccination in Lactating Women,” *Front. Immunol.* 2022, 12 (Nutritional Immunology). doi: [10.3389/fimmu.2021.783975](https://doi.org/10.3389/fimmu.2021.783975) ✓
  - “Transient, low intact vaccine mRNA levels was detected in 20/74 (27%) serum samples from 21 mothers, and 5/309 (2%) breastmilk samples from 4 mothers within 1 weeks of vaccine dose.”
42. Yong SJ et al., “Post-COVID-19 Vaccination (or Long Vax) Syndrome: Putative Manifestation, Pathophysiology, and Therapeutic Options,” *Rev. Med. Virol.* 2025, 35, 5: e70070. doi: [10.1002/rmv.70070](https://doi.org/10.1002/rmv.70070) ✓
  - “Our review noted that PCVS typically manifests within days to weeks post-vaccination, with symptoms lasting months to years.”
43. 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: [10.1053/j.gastro.2022.04.037](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.”

#### IV. Lipid nanoparticle toxicity and allergenicity studies

Compiled by Dr. Byram Bridle, PhD, et al. Last updated November 18, 2025.

✔ = peer-reviewed

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, abundant evidence confirms 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 **(92/92 peer-reviewed ✔)** 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 research annotated here also suggests a far higher incidence of anaphylaxis due to mRNA injections than official estimates of 2.5 cases per million doses for Moderna and 11.1 cases per million for Pfizer. Actual reported rates range as high as 1/229 doses (Lidström AK et al), 1/416 (Nachtigall I et al.), 1/919 (Al-Zaidan M et al.), 1/2,280 (Warren CM et al.), 1/4,049 (Blumenthal KG et al.), 1/4,897 (Hashimoto T et al.), and 1/13,882 (Somiya A et al.). Several articles also explore the possibility that adverse events may be due to higher concentrations of LNPs or differing mRNA-LNP ratios in specific “vaccine” lots due to manufacturing variability (Igyarto BZ and Z Qin, Moghimi SM).

It should be emphasized that scientists already knew repeated administration of lipid nanoparticles was toxic before the development of the COVID “vaccines.” Indeed, in the years before the pandemic, lipid nanoparticles were ruled out for medical applications requiring repeat dosing, such as chemotherapy, because the risk was judged excessive – yet billions of people have now been given multiple doses of lipid nanoparticle-encased modRNA shots.

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 (92/92 peer-reviewed ✔)**

1. Ahmed M et al., “Role of NLRP3 inflammasome in nanoparticle adjuvant-mediated immune response,” *Biomater. Sci.* 2025, 13: 2164-2178. doi: [10.1039/D4BM00439F](https://doi.org/10.1039/D4BM00439F) ✔
  - “Reactive oxygen species (ROS) are essential for cells to respond to stress through signal transduction. If the production of ROS continues to increase, the

cellular antioxidant system will become underpowered, resulting in oxidative stress, cell damage, and maybe even cell death. Nanoparticles generating ROS have been shown to induce NLRP3 activation.”

2. 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: [10.1007/s00204-024-03912-1](https://doi.org/10.1007/s00204-024-03912-1) ✓
  - “Histopathological analysis revealed severe inflammation and necrosis at the injection site, decreased erythroid cells in bone marrow, cortical atrophy of the thymus, and increased spleen cellularity... These findings highlight the potential toxicological risks associated with mRNA vaccines, emphasizing the necessity to carefully consider administration routes and dosage regimens in vaccine safety evaluations, particularly given the presence of bone marrow and immune organ toxicity, which, though eventually reversible, remains a serious concern.”
3. Al-Zaidan M et al., “Adverse events of COVID-19 vaccines: Insights from primary health care centers in Qatar,” *Qatar Journal of Public Health* 2025, 1, 4. doi: [10.5339/qjph.2025.4](https://doi.org/10.5339/qjph.2025.4) ✓
  - “The Moderna vaccine had an anaphylaxis rate of 0.2% (n = 4) after the third dose, while Pfizer’s third dose showed a higher rate of 0.3% (n = 14), and Pfizer Pediatric had an even higher rate of 0.9% (n = 2) after the first dose.” Combined rates for Moderna showed 6 cases for a total of 12,497 doses (first, second and third doses) or 1/2,083, while Pfizer showed a total of 17/15,619 doses, or 1/919.
4. Araste F et al., “Potential and risks of nanotechnology applications in COVID-19-related strategies for pandemic control,” *J. Nanopart. Res.* 2023, 25, 229. doi: [10.1007/s11051-023-05867-3](https://doi.org/10.1007/s11051-023-05867-3) ✓
  - “Initially, PEG molecules were thought to be safe and biologically inert, but nowadays PEG and PEG-like polymers are not considered to be as safe as initially thought. An immune response mediated by anti-PEG IgG antibodies may develop in allergic individuals, particularly females... In the presence of reactive oxygen species, anti-PEG antibodies detrimentally affect the respiratory chain and signal transduction pathways, and also disrupt cell membranes. In vivo, oxidation of PEG, especially of the PEG low-molecular polymer chains, produces toxic molecules, i.e., glycolic acid and hydroxy acid metabolites. PEGylated nanoparticles cause pseudoallergic reactions such as complement-activation-related pseudo allergy (CARPA) and toxic or immunogenic responses, particularly with booster doses.”
5. Awaya T et al., “Cytokine Storms and Anaphylaxis Following COVID-19 mRNA-LNP Vaccination: Mechanisms and Therapeutic Approaches,” *Diseases* 2024, 12, 10: 231. doi: [10.3390/diseases12100231](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.”
6. 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: [10.3390/ijms25073595](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.”
  7. 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: [10.1093/eurheartj/ehad655.3291](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...”
  8. Bates SM et al., “The kinetics of endosomal disruption reveal differences in lipid nanoparticle induced cellular toxicity,” *J. Contr. Release* 2025, 386, 10: 114047. doi: [10.1016/j.jconrel.2025.114047](https://doi.org/10.1016/j.jconrel.2025.114047) ✓
    - “LNP cytotoxicity is driven by lipid components, independent of the mRNA cargo. LNP cytotoxicity is influenced independently by both lipid chemistry and endosomal disruption kinetics.”
  9. Bigini P et al., “The role and impact of polyethylene glycol on anaphylactic reactions to COVID-19 nano-vaccines,” *Nat. Nanotechnol.* 2021, 16: 1169–1171. doi: [10.1038/s41565-021-01001-3](https://doi.org/10.1038/s41565-021-01001-3) ✓
    - “... the conjugation of PEG to nanoparticles may lead to hypersensitivity reactions mainly involving the activation of the complement system, through a mechanism called complement activation-related pseudoallergy (CARPA). In the case of COVID-19 vaccines, CARPA can be activated even if the pre-existing anti-PEG antibodies have low affinity for PEG.”
  10. Bitounis D et al., “Strategies to reduce the risks of mRNA drug and vaccine toxicity,” *Nat. Rev. Drug Discov.* 2024, 23: 281–300. doi: [10.1038/s41573-023-00859-3](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.”
  11. Blumenthal KG et al., “Acute Allergic Reactions to mRNA COVID-19 Vaccines,” *JAMA* 2021, 325, 15:1562–1565. doi: [10.1001/jama.2021.3976](https://doi.org/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).”
12. Borgsteede SD et al. “Other excipients than PEG might cause serious hypersensitivity reactions in COVID-19 vaccines,” *Allergy* 2021, 76: 1941–2. doi: [10.1111/all.14774](https://doi.org/10.1111/all.14774) ✓
    - 1,2-Distearoyl-sn-glycero-3-phosphocholine, tromethamine, tromethamine hydrochloride, polysorbate 80, and disodium edetate dihydrate are considered as potential causes of HSRs.
  13. 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: [10.1111/all.14711](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.”
  14. 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](https://doi.org/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.”
  15. Calzetta L et al., “The BNT162b2 mRNA COVID-19 Vaccine Increases the Contractile Sensitivity to Histamine and Parasympathetic Activation in a Human Ex Vivo Model of Severe Eosinophilic Asthma,” *Vaccines* 2023, 11, 2: 282. doi: [10.3390/vaccines11020282](https://doi.org/10.3390/vaccines11020282) ✓
    - “BNT162b2 increases the contractile sensitivity to histamine and parasympathetic activation in hyperresponsive airways, a detrimental effect not related to the active component but to some excipient. A possible candidate for the bronchospasm elicited by BNT162b2 could be the polyethylene glycol/macrogol used to produce LNP.”
  16. 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: [10.3390/ijms22020820](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."
17. Carreño 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: [10.1016/j.vaccine.2022.08.024](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."
  18. 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: [10.3390/pharmaceutics16121521](https://doi.org/10.3390/pharmaceutics16121521) ✓
    - "Other PEG-lipids immunologically induced adverse effects can be accelerated blood clearance ('ABC phenomenon') observed upon repeated administration, and a hypersensitivity reaction non-IgE-mediated pseudo-allergy, referred to as CARPA (complement activation-related pseudo-allergy), caused by the activation of the complement system, which significantly reduces the efficacy and safety of PEGylated nanocarriers."
  19. 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: [10.1021/acsnano.1c05922](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."
  20. 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: [10.1021/acsnano.2c12193](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."
  21. 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](https://doi.org/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).”
22. Dézsi L et al., “A naturally hypersensitive porcine model may help understand the mechanism of COVID-19 mRNA vaccine-induced rare (pseudo) allergic reactions: Complement activation as a possible contributing factor,” *Geroscience* 2022, 44: 597–618. doi: [10.1007/s11357-021-00495-y](https://doi.org/10.1007/s11357-021-00495-y) ✓
    - “These reactions resemble complement (C) activation-related pseudoallergy (CARPA) to i.v. administered liposomes, for which pigs provide a naturally oversensitive model. Using this model, we injected i.v. the human vaccination dose (HVD) of BNT162b2 (Comirnaty, CMT) or its 2-fold (2x) or 5-fold (5x) amounts and measured the hemodynamic changes and other parameters of CARPA. We observed in 6 of 14 pigs transient pulmonary hypertension along with thromboxane A2 release into the blood and other hemodynamic and blood cell changes, including hypertension, granulocytosis, lymphopenia, and thrombocytopenia.”
  23. 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: [10.1111/eci.14296](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.”
  24. Eberlein B et al., “Allergy to PEG (polyethylene glycol) – sensitivity of basophil activation test with COVID-19 mRNA-vaccine BNT162B2,” *Hum Vaccin Immunother.* 2024, 20, 1. doi: [10.1080/21645515.2024.2312600](https://doi.org/10.1080/21645515.2024.2312600) ✓
    - “Basophil activation was significantly higher in PEG allergic patients compared to controls at the higher concentrations used.”
  25. Forster JF (III) et al., “mRNA-carrying lipid nanoparticles that induce lysosomal rupture activate NLRP3 inflammasome and reduce mRNA transfection efficiency,” *Biomater. Sci.* 2022, 10: 5566–5582. doi: [10.1039/D2BM00883A](https://doi.org/10.1039/D2BM00883A) ✓
    - “Ionizable cationic lipids and cholesterol impact endosomal rupture capabilities and lead to NLRP3 inflammasome activation.”
  26. Fu X, “Current landscape and challenges in adjuvant and antigen delivery systems for vaccine,” *Vaccine: X* 2025, 27: 100735. doi: [10.1016/j.jvacx.2025.100735](https://doi.org/10.1016/j.jvacx.2025.100735) ✓

- “LNPs, while central to the success of mRNA vaccines, have also been reported to cause dose-dependent reactogenicity, including fever, chills, and elevated inflammatory cytokines. Collectively, these findings illustrate that adjuvant-delivery systems, although highly effective, may induce both local and systemic adverse reactions that need to be carefully balanced against their immunostimulatory benefits.”
27. 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: [10.1016/j.jcis.2024.08.146](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.”
  28. Garces M et al., “Current understanding of nanoparticle toxicity mechanisms and interactions with biological systems,” *New J. Chem.* 2021, 45: 14328-14344. doi: [10.1039/D1NJ01415C](https://doi.org/10.1039/D1NJ01415C) ✓
    - “Both in vivo and in vitro studies have shown that NPs are closely associated with toxicity by increasing intracellular reactive oxygen species (ROS) levels, and/or the levels of pro-inflammatory mediators.”
  29. Guo C et al., “The interplay between PEGylated nanoparticles and blood immune system,” *Adv Drug Deliv Rev.* 2023, 200: 114004. doi: [10.1016/j.addr.2023.115044](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.”
  30. Haroon HB et al., “Activation of the complement system by nanoparticles and strategies for complement inhibition,” *Eur. J. Pharm. Biopharm.* 2023, 193: 227-240. doi: [10.1016/j.ejpb.2023.11.006](https://doi.org/10.1016/j.ejpb.2023.11.006) ✓
    - “Particulate drug carriers and nanopharmaceuticals typically present architectures and surface patterns that trigger complement system in different ways, resulting in both beneficial and adverse responses depending on the extent of complement activation and regulation as well as pathophysiological circumstances.”
  31. Hashimoto T et al., “High anaphylaxis rates following vaccination with the Pfizer BNT162b2 mRNA vaccine against COVID-19 in Japanese healthcare workers: a secondary analysis of initial post-approval safety data,” *J. Travel Med.* 2021, 28, 7: taab090. doi: [10.1093/jtm/taab090](https://doi.org/10.1093/jtm/taab090) ✓

- “The data included 181 184 HCWs who received one or more doses of vaccination by 11 March 2021... 37 cases of anaphylaxis were observed, equating to 204.2 cases per million doses administered.”
32. 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: [10.1016/j.jconrel.2022.09.031](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.”
33. 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](https://doi.org/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.”
34. Igyarto BZ and Z Qin, “The mRNA-LNP vaccines – the good, the bad and the ugly?” *Front. Immunol.* 2024, 15 (Vaccines and Molecular Therapeutics). doi: [10.3389/fimmu.2024.1336906](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.”
35. Jiang SY et al., “Non-immunoglobulin E-mediated allergy associated with Pfizer-BioNTech coronavirus disease 2019 vaccine excipient polyethylene glycol,” *Ann Allergy Asthma Immunol.* 2021, 127, 6: 694-696. doi: [10.1016/j.anai.2021.09.012](https://doi.org/10.1016/j.anai.2021.09.012) ✓
- “Activation of the patient's basophils on exposure to the vaccine excipient PEG implicates PEG as a potential allergen. However, given the low anti-PEG titers, the reaction seems to be non-IgE- and non-IgG-mediated anaphylaxis.”

36. Jo H et al., “Regulating Immune Responses Induced by PEGylated Messenger RNA–Lipid Nanoparticle Vaccine,” *Vaccines* 2025, 13, 1: 14. doi: [10.3390/vaccines13010014](https://doi.org/10.3390/vaccines13010014) ✓
- “Stimulation of RNA sensors such as TLRs can induce cytokine storm, airway infiltration of immune cells, and activation of mast cells. It has been shown that mRNA COVID-19 vaccines can cause allergies... The BNT162b2 COVID-19 vaccine can exacerbate asthma by enhancing sensitivity to histamines in a human ex vivo model. Phospholipase A2IIA activity is correlated with severity of COVID-19 vaccine. The COVID-19 vaccine can increase levels of lysophosphatidic acid (LPA) and platelet activating factor (PAF) by phospholipase A2IIA. It is well known that PAF mediates allergic reactions via the PAF receptor.”
  - “PEGylated mRNA-LNP vaccines can induce the production of anti-PEG IgG, anti-PEG IgM, and anti-PEG IgE. COVID-19 mRNA-LNP vaccines (Comirnaty and Spikevax) can induce hypersensitivity reactions (HSRs) or anaphylaxis by increasing levels of anti-PEG IgG/IgM. Anti-PEG antibodies can be produced without prior exposure to PEGylated nanoparticles.”
37. Ju Y et al., “Anti-PEG Antibodies Boosted in Humans by SARS-CoV-2 Lipid Nanoparticle mRNA Vaccine,” *ACS Nano* 2022, 16, 8: 11769–11780. doi: [10.1021/acsnano.2c04543](https://doi.org/10.1021/acsnano.2c04543) ✓
- “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.”
38. Ju Y et al., “Impact of anti-PEG antibodies induced by SARS-CoV-2 mRNA vaccines,” *Nat. Rev. Immunol.* 2023, 23: 135-135. doi: [10.1038/s41577-022-00825-x](https://doi.org/10.1038/s41577-022-00825-x) ✓
- “In agreement with previous reports, we found pre-existing anti-PEG antibodies at variable levels (ranging in enzyme-linked immunosorbent assay (ELISA) end point titre from 1:12 to 1:3,000) in plasma from 71% of subjects prior to mRNA vaccination. Anti-PEG IgG levels increased a mean of 13–17 fold after the second 100 µg dose of the mRNA-1273 vaccine but to a much lesser extent after the second 30 µg dose of the BNT162b2 vaccine (1.1–1.8 fold). mRNA vaccines are reactogenic, commonly leading to considerable injection site effects and systemic effects, such as fever, myalgia or headache. Higher reactogenicity of mRNA-1273 versus BNT162b2 is observed but the cause of these differences is unclear.”
39. Kim JA et al., “Sex Differences in Adverse Event Reporting Rates Following COVID-19 Vaccination in South Korea During the Pandemic,” *Int. J. Infect. Dis.* 2025. doi: [10.1016/j.ijid.2025.108107](https://doi.org/10.1016/j.ijid.2025.108107) ✓



- Reported “anaphylactoid reaction” at rates of 3.38/100,000 vaccine doses among women and 1.13/100,000 vaccine doses among men; “anaphylactic reaction” at rates of 0.74/100,000 vaccine doses among women and 0.49/100,000 vaccine doses among men. Female combined rate of anaphylactoid + anaphylactic reactions is 1/24,271.
40. 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: [10.1111/all.14794](https://doi.org/10.1111/all.14794) ✓
- “Allergic reactions to such PEGylated lipids are IgE-mediated. However, non-IgE-mediated reactions should also be considered.”
41. 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: [10.3390/ph16081088](https://doi.org/10.3390/ph16081088) ✓
- “... the current data raise important questions revolving around LNP-associated side effects. For instance, the use of a greater mRNA–LNP dose in the mRNA-1273 vaccine and different ionizable lipids used in the formulation are potential explanations for the increased reactogenicity of mRNA-1273 compared with BNT162b formulations in the Moderna and Pfizer-BioNTech COVID-19 vaccines, respectively.”
42. Korzun T et al., “Lipid Nanoparticles Elicit Reactogenicity and Sickness Behavior in Mice Via Toll-Like Receptor 4 and Myeloid Differentiation Protein 88 Axis,” *ACS Nano* 2024, 18, 36: 24842–24859. doi: [10.1021/acsnano.4c05088](https://doi.org/10.1021/acsnano.4c05088) ✓
- “Our comprehensive investigation utilizing gene ablation studies and pharmacological receptor manipulation proves that TLR4 activation by LNPs triggers distinct physiologically meaningful responses in mice. We show that TLR4 and MyD88 are essential for reactogenic signal initiation, pro-inflammatory gene expression, and physiological outcomes like food intake and body weight – robust metrics of sickness behavior in mice.”
43. Kozma GT et al., “Anti-PEG antibodies: Properties, formation, testing and role in adverse immune reactions to PEGylated nano-biopharmaceuticals,” *Adv. Drug Deliv. Rev.* 2020, 154-155: 163-175. doi: [10.1016/j.addr.2020.07.024](https://doi.org/10.1016/j.addr.2020.07.024) ✓
- “Considering the known causal relationships among C [complement] activation, ABC [accelerated blood clearance], HSRs [hypersensitivity reactions], opsonization and immunogenicity, we proposed the possible rise of an immune stimulatory vicious cycle among these effects...”
44. Kozma GT et al., “Role of anti-polyethylene glycol (PEG) antibodies in the allergic reactions to PEG-containing Covid-19 vaccines: Evidence for immunogenicity of PEG,” *Vaccine* 2023, 41, 31: 4561-4570. doi: [10.1016/j.vaccine.2023.06.009](https://doi.org/10.1016/j.vaccine.2023.06.009) ✓



- “The anti-PEG IgG and/or IgM levels in the 15 vaccine reactors (3 anaphylaxis) were significantly higher compared to nonreactors. Serial testing of plasma showed significant correlation between the booster injection-induced rises of anti-S and anti-PEG IgGs, suggesting coupled anti-S and anti-PEG immunogenicity.”
45. Laisuan W, “COVID-19 vaccine anaphylaxis: current evidence and future approaches,” *Front Allergy*. 2021, 2: 801322. doi:[10.3389/falgy.2021.801322](https://doi.org/10.3389/falgy.2021.801322) ✓
- “Polysorbate 80 is widely used as a stabilizing agent in food and pharmacological products, including vaccines. Previous studies have reported that polysorbate 80 can induce local and systemic allergic reactions, including IgE-mediated and non-immune anaphylaxis. Cross-reactivity to PEG has also been reported.”
46. Li Y et al., “Nanoparticle-Binding Immunoglobulins Predict Variable Complement Responses in Healthy and Diseased Cohorts,” *ACS Nano* 2024, 18, 42: 28649–28658. doi: [10.1021/acsnano.4c05087](https://doi.org/10.1021/acsnano.4c05087) ✓
- “... plasma concentrations of anti-PEG IgG and IgM showed a strong positive correlation with the activation by PLD. Particularly, titers of anti-PEG IgM showed the best predictive value for the ‘risk’ of high complement activation by PLD... Nanoparticle-bound immunoglobulins showed the best correlation with complement activation and a strong predictive value, supporting the critical role of immunoglobulins in inciting complement.”
47. Lidström AK et al., “Adverse drug reactions following SARS-CoV-2 vaccination of 3805 healthcare workers cause substantial sick-leave and are correlated to vaccine regimen, age, sex and serological response,” *Vaccine* 2025, 62: 127553. doi: [10.1016/j.vaccine.2025.127553](https://doi.org/10.1016/j.vaccine.2025.127553) ✓
- Among Swedish healthcare workers, anaphylactic reactions reported by 0.4% (11/2,519) after first dose and 0.26% (6/2,239) after second dose.
48. Lim XR et al., “Anaphylatoxin Complement 5a in Pfizer BNT162b2-Induced Immediate-Type Vaccine Hypersensitivity Reactions,” *Vaccines* 2023, 11, 6: 1020. doi: [10.3390/vaccines11061020](https://doi.org/10.3390/vaccines11061020) ✓
- “The majority of patients with immediate-type BNT162b2 vaccine HSR demonstrated raised C5a and Th2-related cytokines but normal tryptase levels during the acute reaction, together with significantly higher levels of IgM antibodies to the BNT162b2 vaccine (IgM 67.2 (median) vs. 23.9 AU/mL,  $p < 0.001$ ) and ICAM-1 when compared to non-reactor controls. No detectable IgE antibodies to the BNT162b2 vaccine were found in these patients... Acute hypersensitivity reactions post BNT162b2 vaccination suggest pseudo-allergic reactions via the activation of anaphylatoxins C5a and are independent of IgE-

mechanisms. Vaccine reactors have significantly higher levels of anti-BNT162b2 IgM although its precise role remains unclear.”

49. Luxi N et al., “Allergic Reactions to COVID-19 Vaccines: Risk Factors, Frequency, Mechanisms and Management,” *BioDrugs* 2022, 36: 443-458. doi: [10.1007/s40259-022-00536-8](https://doi.org/10.1007/s40259-022-00536-8) ✓
  - “PEG is the only excipient in COVID-19 vaccines that has been clearly demonstrated to cause mainly immediate HRs, while the role of trometamol and PS80 as relevant allergens in these vaccines remains more questionable.”
50. Maltezou HC et al., “Anaphylaxis rates following mRNA COVID-19 vaccination in children and adolescents: Analysis of data reported to EudraVigilance,” *Vaccine* 2023, 41, 14: 2382-2386. doi: [10.1016/j.vaccine.2023.02.067](https://doi.org/10.1016/j.vaccine.2023.02.067) ✓
  - “The overall mean anaphylaxis rate was 12.81 [95% confidence interval (CI): 11.49–14.12] per 10<sup>6</sup> mRNA vaccine doses [12.14 (95% CI: 6.37–17.91) per 10<sup>6</sup> doses for mRNA-1273 and 12.84 (95% CI: 11.49–14.19) per 10<sup>6</sup> doses for BNT162b2].”
51. Maugeri M et al., “Linkage between endosomal escape of LNP-mRNA and loading into EVs for transport to other cells,” *Nat Commun* 2019, 10: 4333. doi: [10.1038/s41467-019-12275-6](https://doi.org/10.1038/s41467-019-12275-6) ✓
  - “... the systemic delivery of both EVs and LNPs cause the expression of proinflammatory cytokines in mice...”
52. Moghimi SM, “Allergic reactions and anaphylaxis to LNP-based COVID-19 vaccines,” *Mol. Ther.* 2021, 29, 3: 898-900. doi: [10.1016/j.ymthe.2021.01.030](https://doi.org/10.1016/j.ymthe.2021.01.030) ✓
  - “Limited information is available on LNP size distribution, polydispersity index, particle number, and presence of likely co-existing vesicles and micelles in the Pfizer-BioNTech and Moderna vaccines. Batch-to-batch variations in these parameters could further play a modulatory role in allergic reactions, and these possibilities were previously suggested for liposomes.”
53. Moghimi SM et al., “Perspectives on complement and phagocytic cell responses to nanoparticles: from fundamentals to adverse reactions,” *J Control Rel.* 2023, 356: 115–129. doi: [10.1016/j.jconrel.2023.02.022](https://doi.org/10.1016/j.jconrel.2023.02.022) ✓
  - “Thus, it is plausible that nanomedicine-mediated infusion reactions in humans arises from the presence of either ‘induced’ PIMs and/or a population of other responsive immune cells that reside either in lung vasculature or outside the pulmonary circulation (e.g., spleen, liver, blood).”
54. Moghimi SM and D Simberg, “Pro-inflammatory concerns with lipid nanoparticles,” *Mo. Ther.* 2022, 30, 6: 2109-2110. doi: [10.1016/j.ymthe.2022.04.011](https://doi.org/10.1016/j.ymthe.2022.04.011) ✓

- “Considering the pro-inflammatory nature of the currently available ionizable cationic lipids, notably their undesirable immune cascade initiated through the IL-1 $\beta$  release, and of other cationic lipids, the potential application of LNPs for systemic administration must be viewed cautiously.”
55. Mouri M et al., “Serum polyethylene glycol-specific IgE and IgG in patients with hypersensitivity to COVID-19 mRNA vaccines,” *Allergol Int.* 2022, 71, 4: 512-519. doi: [10.1016/j.alit.2022.05.007](https://doi.org/10.1016/j.alit.2022.05.007) ✓
- “The results suggest that PEG is one of the antigens in the allergy to COVID-19 mRNA vaccines. Cross-reactivity between PEG and PS might be crucial for allergy to the vaccines.”
56. Muhaimin M et al., “The Toxicological Profile of Active Pharmaceutical Ingredients–Containing Nanoparticles: Classification, Mechanistic Pathways, and Health Implications,” *Pharmaceuticals* 2025, 18, 5: 703. doi: [10.3390/ph18050703](https://doi.org/10.3390/ph18050703) ✓
- “Exposure to nanoparticles has been associated with a range of adverse health effects, including respiratory inflammation, oxidative stress, and neurotoxicity. This has raised concerns about public health. These findings underscore the dual nature of NPs as both therapeutic tools and potential health hazards. Therefore, a comprehensive understanding of their biological interactions and toxicity pathways is essential for the development of safer nanoparticles and the establishment of robust regulatory frameworks.”
57. Nachtigall I et al., “Effect of gender, age and vaccine on reactogenicity and incapacity to work after COVID-19 vaccination: a survey among health care workers,” *BMC Infect. Dis.* 2022, 22, 291. doi: [10.1186/s12879-022-07284-8](https://doi.org/10.1186/s12879-022-07284-8) ✓
- Anaphylactic reactions reported in 0.24% of 16,207 vaccinations.
58. Nakayama T et al., “Comparison of cytokine production in mice inoculated with messenger RNA vaccines BNT162b2 and mRNA-1273,” *Microbiol Immunol* 2022, 67, 3: 120-128. doi: [10.1111/1348-0421.13043](https://doi.org/10.1111/1348-0421.13043) ✓
- “The induction of inflammatory cytokines in the mouse model is related to the cause of adverse events in humans, with a higher incidence of adverse events after the second dose.”
59. Ndeupen S et al., “The mRNA-LNP platform's lipid nanoparticle component used in preclinical vaccine studies is highly inflammatory,” *iScience* 2021, 24, 12: 103479. doi: [10.1016/j.isci.2021.103479](https://doi.org/10.1016/j.isci.2021.103479) ✓
- “Intradermal injection of these LNPs alone or in combination with non-coding poly-cytosine mRNA led to rapid and robust innate inflammatory responses, characterized by neutrophil infiltration, activation of diverse inflammatory pathways, and production of various inflammatory cytokines and chemokines.

The same dose of LNP delivered intranasally led to similar inflammatory responses in the lung and resulted in a high mortality rate.”

60. Nguyen HM et al., “mRNA-LNPs induce immune activation and cytokine release in human whole blood assays across diverse health conditions,” *Mol. Ther.* 2025, 33, 6: 2872-2885. doi: [10.1016/j.ymthe.2024.12.019](https://doi.org/10.1016/j.ymthe.2024.12.019) ✓
- “mRNA-LNPs significantly increased CD69 expression on T cells and natural killer cells, and CD80/CD86 on myeloid subsets, in a dose-dependent fashion. Furthermore, mRNA-LNPs elicited a robust release of pro-inflammatory cytokines, including tumor necrosis factor- $\alpha$ , interleukin (IL)-1 $\beta$ , monocyte chemoattractant protein-1, IL-6, and IP-10, indicating a potent immune response. Notably, mRNA-LNPs stimulate early cytokine production prior to triggering immune cell activation, suggesting a temporal and biological relationship. Moreover, mRNA-LNPs induce complement activation via the alternative pathway, as evidenced by increased serum sC5b-9, C3a, and Bb, which can amplify the inflammatory response and potentially impact safety... Until now, there has been no specific regulatory guidance for assessing the immuno-toxicity of RNA-based therapies. Therefore, this is an essential time to start establishing standards for RNA-LNPs safety.”
61. Omo-Lamai S et al., “Limiting endosomal damage sensing reduces inflammation triggered by lipid nanoparticle endosomal escape,” *Nat. Nanotechnol.* 2025, 20: 1285-1297. doi: [10.1038/s41565-025-01974-5](https://doi.org/10.1038/s41565-025-01974-5) ✓
- “Here we show that LNPs’ hallmark feature, endosomal escape, which is necessary for RNA expression, also triggers inflammation by causing endosomal membrane damage. Large, irreparable, endosomal holes are recognized by cytosolic proteins called galectins, which regulate downstream inflammation.”
62. Padin-Gonzalez E et al., “Understanding the role and impact of poly (ethylene glycol) (PEG) on nanoparticle formulation: implications for COVID-19 vaccines,” *Front. Bioeng. Biotechnol.* 2022, 10: 882363. doi: [10.3389/fbioe.2022.882363](https://doi.org/10.3389/fbioe.2022.882363) ✓
- “The classical and lectin pathway is initiated by the recognition of patterns on the NP surface by soluble mediators in the blood, such as antibodies, IgG or IgM, and sugars (mainly N-acetyl glucosamine and mannose), respectively. On the other hand, when the spontaneous hydrolysis of the thioester bond in the protein C3 takes place, the alternative pathway is initiated... The complex proteolytic cascade generates the release of complement proteins such as iC3b, which enhance macrophage recognition, and the anaphylatoxins C3a, C4a and C5a. CARPA is triggered when the released anaphylatoxins interact with receptors in granulocytes, mast cells and monocytes, activating them and causing the release of vasoactive inflammatory mediators, involving tryptase, histamine, platelet-activating factor and other chemical molecules. These mediators interact with receptors in endothelial cells and muscle cells, triggering their activation and, finally, CARPA.”

63. Parhiz H et al., “Added to pre-existing inflammation, mRNA-lipid nanoparticles induce inflammation exacerbation (IE),” *J Control Release* 2022, 344: 50-61. doi: [10.1016/j.jconrel.2021.12.027](https://doi.org/10.1016/j.jconrel.2021.12.027) ✓
  - “... shortly after LPS immune stimulation, modmRNA-LNP enhanced inflammatory cytokine responses, Interleukin-6 (IL-6) in serum and Macrophage Inflammatory Protein 2 (MIP-2) in liver significantly. Our report identifies this phenomenon as inflammation exacerbation (IE), which was proven to be specific to the LNP, acting independent of mRNA cargo, and was demonstrated to be time- and dose-dependent.”
64. Parry PL et al., “‘Spikeopathy’: COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA,” *Biomedicine* 2023, 11, 8: 2287. doi: [10.3390/biomedicines11082287](https://doi.org/10.3390/biomedicines11082287) ✓
  - “The molecular mechanisms involved in nanoparticle toxicity to the reproductive system are not fully understood, but possible mechanisms include oxidative stress, apoptosis, inflammation, and genotoxicity through induction of reactive oxygen species (ROS), causing damage at the molecular and genetic levels which results in cytotoxicity and DNA damage.”
65. Qin Z et al., “Pre-exposure to mRNA-LNP inhibits adaptive immune responses and alters innate immune fitness in an inheritable fashion,” *PLoS Pathog.* 2022, doi: [10.1371/journal.ppat.1010830](https://doi.org/10.1371/journal.ppat.1010830) ✓
  - “The mRNA-LNP-based SARS-CoV-2 vaccine is highly inflammatory, and its synthetic ionizable lipid component responsible for the induction of inflammation has a long in vivo half-life... We found that pre-exposure to mRNA-LNPs or LNP alone led to long-term inhibition of the adaptive immune response.”
66. Radice A et al., “Potential culprits for immediate hypersensitivity reactions to BNT162b2 mRNA COVID-19 vaccine: not just PEG,” *Eur Ann Allergy Clin Immunol* 2021, 53, 5: 240-242. doi: [10.23822/eurannaci.1764-1489.214](https://doi.org/10.23822/eurannaci.1764-1489.214) ✓
  - “Apart from PEG, another component of the LNP, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), should also be considered a potential culprit as it contains a quaternary ammonium (QA) ion.”
67. Rama TA et al., “Hypersensitivity to the Moderna COVID-19 vaccine caused by tromethamine: PEG is not always the culprit excipient,” *J Investig Allergol Clin Immunol.* 2022, 32, 5: 414-415. doi: [10.18176/jiaci.0773](https://doi.org/10.18176/jiaci.0773) ✓
  - “... this case provides further evidence that the excipient, and specifically IgE-mediated hypersensitivity to tromethamine, may be an underlying mechanism for immediate hypersensitivity to mRNA COVID-19 vaccines.”

68. Sampath V et al., “Vaccines and allergic reactions: The past, the current COVID-19 pandemic, and future perspectives,” *Allergy* 2021, 76, 6: 1640-1660. doi: [10.1111/all.14840](https://doi.org/10.1111/all.14840) ✓
- “This suggests that the incidence of anaphylaxis in the mRNA BNT162b2 (11.1 cases per million doses) and mRNA-1273 COVID-19 vaccines (2.5 cases per million doses) may be about 2 to 8.5 times as high as the incidence reported in the 2016 VSD study for all vaccines (1.31 per million doses).”
69. Sellaturay P et al., “Polyethylene glycol (PEG) is a cause of anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine,” *Clin Exp Allergy* 2021, 51, 6: 861-863. doi: [10.1111/cea.13874](https://doi.org/10.1111/cea.13874) ✓
- “Here, we show polyethylene glycol allergy caused one of the first cases of anaphylaxis to the Pfizer/BioNTech COVID-19 vaccine. Allergy skin prick testing with polyethylene glycol triggered anaphylaxis, highlighting the importance of safety procedures during investigation.”
70. Selvaraj G et al., “Are the Allergic Reactions of COVID-19 Vaccines Caused by mRNA Constructs or Nanocarriers? Immunological Insights,” *Interdiscip. Sci.: Comput. Life Sci.* 2021, 13: 344-347. doi: [10.1007/s12539-021-00438-3](https://doi.org/10.1007/s12539-021-00438-3) ✓
- “The results from AllerTOP indicate that the RBD, receptor-binding motif, binding to human ACE2B (437–508), and two fusion peptides could be a probable allergen, while the results from both tools point to the receptor-binding motif of the spike protein to the host receptor ACE2B as a very probable allergen (Table 1). These results suggest that spike protein-based medication possibly induces an allergic reaction in the host system, likely due to the amino acid residues 437–508 sequence.”
71. Shah MM et al., “Elucidating allergic reaction mechanisms in response to SARS-CoV-2 mRNA vaccination in adults,” *Allergy* 2024 79, 9: 2502-2523. doi: [10.1111/all.16231](https://doi.org/10.1111/all.16231) ✓
- “Vaccine-mediated complement activation correlated with anti-polyethylene glycol (PEG) IgG (but not IgM) levels while anti-PEG IgE was undetectable in all subjects. Depletion of total IgG suppressed complement activation in select individuals.”
72. Sharma N et al., “Nanoparticles toxicity: an overview of its mechanism and plausible mitigation strategies,” *J. Drug. Target.* 2024, 32, 5: 457-469. doi: [10.1080/1061186X.2024.2316785](https://doi.org/10.1080/1061186X.2024.2316785) ✓
- “While their physical and chemical properties are impressive, there is growing concern about the toxicological potential of nanoparticles and possible adverse health effects as enhanced exposure of biological systems to nanoparticles may result in toxic effects leading to serious contraindications. Toxicity associated with nanoparticles (nanotoxicity) may include the undesired response of several



physiological mechanisms including the distressing of cells by external and internal interaction with nanoparticles.”

73. Shi D et al., “To PEGylate or not to PEGylate: Immunological properties of nanomedicine’s most popular component, polyethylene glycol and its alternatives,” *Adv. Drug Deliv. Rev.* 2022, 180: 114079. doi: [10.1016/j.addr.2021.114079](https://doi.org/10.1016/j.addr.2021.114079) ✓
- “First, phagocytic cells of the immune system are at the forefront of clearance of PEG and PEGylated materials; therefore, toxicity to these cells may influence body’s general defense against infections and damaged or transformed host’s cells. Second, generation of the specific immune response to PEG in the form of antibodies contributes to hypersensitivity reactions (HSRs) to PEG and PEGylated products. Such HSRs include true allergy (IgE mediated, type I hypersensitivity), anaphylactoid reactions (complement-mediated immediate type hypersensitivity or complement-mediated pseudoallergy, CARPA), type II and type III hypersensitivity (IgM and IgG-mediated) reactions. Third, neutralization and cross-reactivity of such antibodies may contribute to HSRs and altered PK of other products containing PEG or other structures similar to PEG.”
74. Simberg D et al., “PEGylation technology: addressing concerns, moving forward,” *Drug Deliv.* 2025, 32, 1: 2494775. doi: [10.1080/10717544.2025.2494775](https://doi.org/10.1080/10717544.2025.2494775) ✓
- “While PEGylated medicines are safe in the majority of patients, there are growing concerns about the emergence of anti-PEG antibodies and their impact on the therapeutic efficacy of PEGylated medicines as well as broader immune responses, particularly in complement activation and hypersensitivity reactions.”
75. Somiya M et al., “Sex differences in the incidence of anaphylaxis to LNP-mRNA COVID-19 vaccines,” *Vaccine* 2021, 39, 25): 3313–3314. doi: [10.1016/j.vaccine.2021.04.066](https://doi.org/10.1016/j.vaccine.2021.04.066) ✓
- “On February 17, 2021, Japan started vaccinating healthcare workers with the Pfizer-BioNTech lipid nanoparticle (LNP)-mRNA COVID-19 vaccine. Among total 79 anaphylaxis cases, 70 cases have been reported in women (89.9%) after 1,096,698 doses of the vaccine until April 4, 2021... Another report confirmed the female predominance of anaphylaxis cases in over 60,000 doses of LNP-mRNA vaccinations; 15 (94%) of the 16 confirmed cases were women... One possible explanation for the sex imbalance is that sensitization to PEG is more common in women due to the relatively frequent exposure to PEG-containing products, such as cutaneous exposure to cosmetics or the use of medications such as contraceptive injections.”
76. Song J et al., “Implications of Anaphylaxis Following mRNA-LNP Vaccines: It Is Urgent to Eliminate PEG and Find Alternatives,” *Pharmaceutics* 2025, 17, 6, 798. doi: [10.3390/pharmaceutics17060798](https://doi.org/10.3390/pharmaceutics17060798) ✓



- “In light of the increasing prevalence of anti-PEG antibodies in the population and the need to avoid secondary injuries, this review article... suggests avoiding the use of PEG excipients when designing PEGylated drugs or PEG-modified nano-formulations and provides references for strategies such as utilizing PEG-free or alternative excipients.”
77. Szebeni J et al., “Applying lessons learned from nanomedicines to understand rare hypersensitivity reactions to mRNA-based SARS-CoV-2 vaccines,” *Nat. Nanotechnol.* 2022, 17: 337–346. doi: [10.1038/s41565-022-01071-x](https://doi.org/10.1038/s41565-022-01071-x) ✓
- “In summary, all the components of LNP–mRNA vaccines... have various immunostimulatory effects... collectively required for vaccine efficacy. The same components, however, also contribute to HSR and other IMAEs...”
78. Tahtinen S and I Mellman, “IL-1-mediated inflammation induced by different RNA vaccines is context-specific,” *Nature Immunol.* 2022, 23, 4: 485-486. doi: [10.1038/s41590-022-01177-3](https://doi.org/10.1038/s41590-022-01177-3) ✓
- “Systemic inflammatory responses generated by lipid-formulated RNA vaccines are driven by differential induction of pro- and anti-inflammatory interleukin-1 (IL-1) family members in mice and humans... We discovered that the RNA-LPX vaccine induces the release of the cytokine IL-1. IL-1 initiates an innate immune cascade that results in systemic cytokine release and the adverse events that limit vaccine dosing in humans.”
79. Tahtinen S et al., “IL-1 and IL-1ra are key regulators of the inflammatory response to RNA vaccines,” *Nat. Immunol.* 2022, 23: 532-542. doi: [10.1038/s41590-022-01160-y](https://doi.org/10.1038/s41590-022-01160-y) ✓
- “In human immune cells, RNA vaccines induce production of IL-1 cytokines, predominantly IL-1 $\beta$ , which is dependent on both the RNA and lipid formulation. IL-1 in turn triggers the induction of the broad spectrum of pro-inflammatory cytokines (including IL-6).”
80. Tenchov R et al, “PEGylated Lipid Nanoparticle Formulations: Immunological Safety and Efficiency Perspective,” *Bioconj. Chem.* 2023, 34, 6: 941-960. doi: [10.1021/acs.bioconjchem.3c00174](https://doi.org/10.1021/acs.bioconjchem.3c00174) ✓
- “A search in the CAS Content Collection identified nearly 900 documents, including ~150 patents, related to the PEG–lipids immunologically induced adverse effects such as anti-PEG antibodies generation, accelerated blood clearance, and complement activation-related pseudoallergies.”
81. Tinari S, “The EMA covid-19 data leak, and what it tells us about mRNA instability,” *BMJ* 2021, 372: n672. doi: [10.1136/bmj.n627](https://doi.org/10.1136/bmj.n627) ✓
- “JW Ulm, a gene therapy specialist who has published on tissue targeting of therapeutic vectors, raised concerns about the biodistribution of LNPs: ‘At

- present, relatively little has been reported on the tissue localisation of the LNPs used to encase the SARS-CoV-2 spike protein-encoding messenger RNA, and it is vital to have more specific information on precisely where the liposomal nanoparticles are going after injection.’ It is an unknown that Ulm worries could have implications for vaccine safety.”
82. Tran TT and SR Roffler, “Interactions between nanoparticle corona proteins and the immune system,” *Curr Opin Biotechnol.* 2023, 84: 103010. doi: [10.1016/j.copbio.2023.103010](https://doi.org/10.1016/j.copbio.2023.103010) ✓
    - “Intravenous administration of pegylated liposomal formulations containing Toll-like receptor agonists to mice on days 0, 4, and 8 resulted in hypersensitivity reaction symptoms...”
  83. Troelnikov A et al., “Basophil reactivity to BNT162b2 is mediated by PEGylated lipid nanoparticles in patients with PEG allergy,” *J Allergy Clin Immunol.* 2021, 148, 1: 91-95. doi: [10.1016/j.jaci.2021.04.032](https://doi.org/10.1016/j.jaci.2021.04.032) ✓
    - “Our findings implicate PEG, as covalently modified and arranged on the vaccine lipid nanoparticle, as a potential trigger of anaphylaxis in response to BNT162b2, and highlight shortcomings of current skin testing protocols for allergy to PEGylated liposomal drugs.”
  84. Tsilingiris D et al., “Potential implications of lipid nanoparticles in the pathogenesis of myocarditis associated with the use of mRNA vaccines against SARS-CoV-2,” *Metabol. Open* 2022, 13: 100159. doi: [10.1016/j.metop.2021.100159](https://doi.org/10.1016/j.metop.2021.100159) ✓
    - “The recent observation of a similar adverse event [myocarditis] in a recipient of the non-mRNA, peptide-based NVX-CoV2373 in the frame of a phase III clinical trial with 7020 participants in the active treatment arm raises the question whether the lipid nanoparticle sheath, which is a common structural component of these platforms could be implicated in the pathogenesis of vaccine-induced myocarditis.”
  85. Wang H et al., “Polyethylene glycol (PEG)-associated immune responses triggered by clinically relevant lipid nanoparticles in rats,” *npj Vaccines* 2023, 8: 169. doi: [10.1038/s41541-023-00766-z](https://doi.org/10.1038/s41541-023-00766-z) ✓
    - “... ‘antigen-antibody’ complexes may induce severe side effects including hypersensitivity reactions, although the underlying mechanisms have not been fully clarified... Overall, these data provided strong evidence for the dose- and time-dependent induction of anti-PEG IgM.”
  86. Wang J et al., “Recent Advances in Lipid Nanoparticles and Their Safety Concerns for mRNA Delivery,” *Vaccines* 2024, 12, 10: 1148. doi: [10.3390/vaccines12101148](https://doi.org/10.3390/vaccines12101148) ✓
    - “... as the immunological activation in response to mRNA-LNP treatment increases, the body’s defense capability may also rise, but there is a high

possibility of the mRNA-LNP complexes causing adverse effects, including allergies and autoimmune diseases.”

87. Warren CM et al. “Assessment of Allergic and Anaphylactic Reactions to mRNA COVID-19 Vaccines With Confirmatory Testing in a US Regional Health System,” *JAMA Netw Open* 2021, 4, 9: e2125524. doi: [10.1001/jamanetworkopen.2021.25524](https://doi.org/10.1001/jamanetworkopen.2021.25524) ✓
- “These findings suggest that non-IgE-mediated allergic reactions to PEG may be responsible for many documented cases of allergy to mRNA vaccines.”
88. Xuan L et al., “Nanoparticles-Induced Potential Toxicity on Human Health: Applications, Toxicity Mechanisms, and Evaluation Models,” *MedComm* 2023, 4, 4: e327. doi: [10.1002/mco2.327](https://doi.org/10.1002/mco2.327) ✓
- “We describe in detail the effects of NPs on various systems, including respiratory, nervous, endocrine, immune, and reproductive systems, and the carcinogenicity of NPs. Furthermore, we unravel the underlying mechanisms of NPs including ROS accumulation, mitochondrial damage, inflammatory reaction, apoptosis, DNA damage, cell cycle, and epigenetic regulation.”
89. Yang M et al., “Effects of PEG antibodies on in vivo performance of LNP-mRNA vaccines,” *Int J Pharm.* 2024, 650: 123695. doi: [10.1016/j.ijpharm.2023.123695](https://doi.org/10.1016/j.ijpharm.2023.123695) ✓
- “PEG antibodies binding on the LNP vaccine increased probability of complement activation in animal as well as in human serum and led to lethal side effect in large dosage via intravenous injection of mice. Our data suggested that PEG antibodies in human was a risky factor of LNP-based vaccines for biosafety concerns but not efficacy.”
90. Yu Z et al., “Reactive Oxygen Species-Related Nanoparticle Toxicity in the Biomedical Field,” *Nanoscale Res. Lett.* 2020, 15, 115. doi: [10.1186/s11671-020-03344-7](https://doi.org/10.1186/s11671-020-03344-7) ✓
- “However, concerns about the potential toxicological effects of nanoparticles remain, as they have a higher tendency to generate excessive amounts of reactive oxygen species (ROS). Due to the strong oxidation potential, the excess ROS induced by nanoparticles can result in the damage of biomolecules and organelle structures and lead to protein oxidative carbonylation, lipid peroxidation, DNA/RNA breakage, and membrane structure destruction, which further cause necrosis, apoptosis, or even mutagenesis... The generation of ROS induced by NPs resulted in the accumulation of DNA damage, which drives the development of mutagenicity, oncogenesis, multidrug resistance, aging, and immune escape.”
91. Yuan Z et al., “Impact of physicochemical properties on biological effects of lipid nanoparticles: Are they completely safe,” *Sci Total Environ.* 2024, 927: 172240. doi: [10.1016/j.scitotenv.2024.172240](https://doi.org/10.1016/j.scitotenv.2024.172240) ✓

- “The physicochemical properties of LNPs, like size, surface hydrophobicity, surface charge, surface modification and lipid composition, determine the interaction of LNPs with macromolecules and organelles to a large extent, resulting in negative effects on cells, especially cytotoxicity and genotoxicity, and cell death.”

92. Zhou ZH et al ., “Anti-PEG IgE in anaphylaxis associated with polyethylene glycol,” *J Allergy Clin Immunol Pract* 2021, 9, 4: 1731-1733.e3. doi: [10.1016/j.jaip.2020.11.011](https://doi.org/10.1016/j.jaip.2020.11.011)



- “... all the anaphylaxis case samples and none of the control samples were clearly positive for anti-PEG IgE.”

## V. COVID “vaccine” immune imprinting library

*Compiled by Dr. Steven Hatfill, MD, et al. Last updated November 18, 2025.*

✔ = peer-reviewed

Immune imprinting, dubbed “[original antigenic sin](#)” by Thomas Francis Jr., occurs when memory B lymphocytes produced in response to an initial viral infection dominate subsequent responses to related viruses, producing antibodies geared to the original exposure. Long-term immune memory has many advantages, but immune imprinting can be harmful if it interferes with immune response to later infections.

The following collection of (**148/156 peer-reviewed ✔**) papers suggests that COVID “vaccines” imprinted the immune systems of recipients through exposure to the “wild type” spike protein from the original Wuhan strain, shaping their response to subsequent variants in potentially harmful ways. Immune imprinting impaired responses to new variants by skewing B cell production of antibodies toward the “ancestral” spike protein at the expense of new antibodies specifically tailored to the variants’ heavily mutated spike. Additionally, by imprinting a single antigen – the spike protein – on recipients’ immune systems, the “vaccines” prevented them from forming antibodies to other, less mutation-prone parts of the virus, such as proteins from the virus nucleocapsid (Ahmed MIM et al., Delgado JF et al., Paula NM et al., Smith CP et al., Yao D et al.). Further findings point to “deep immunological imprinting” or “hybrid immune damping,” in which “vaccination” combined with infection alters later immune response unpredictably (Aguilar-Bretones M et al., Gao B et al., Hornsby H et al., Ju B et al., Reynolds CJ et al., Wang Q et al.).

Some authors suggest that immune imprinting can be overcome by simply administering more “vaccines.” However, these suggestions are based on the false assumption that the “vaccines” have no other costs. In view of the ample evidence of “vaccine” harms as well as their clear failure to impart real mucosal immunity to a respiratory virus, any calls for additional “vaccination” must be dismissed as insupportable.

This collection originated with Dr. Steven Hatfill’s contribution to [TOXIC SHOT: Facing the Dangers of the COVID “Vaccines”](#) (Chapter 5: Debunking CDC’s Bad Science).

### **ANNOTATED REFERENCES (148/156 peer-reviewed ✔)**

1. Addetia A et al., “Neutralization, effector function and immune imprinting of Omicron variants,” *Nature* 2023, 621: 592-601. doi: [10.1038/s41586-023-06487-6](https://doi.org/10.1038/s41586-023-06487-6) ✔
  - “Omicron breakthrough infections of Wu-vaccinated subjects primarily recall cross-reactive MBCs specific for epitopes shared by multiple SARS-CoV-2 variants rather than priming naive B cells that recognize Omicron RBD-specific epitopes. We observed an unexpectedly small number of MBCs specific for

- Omicron RBDs (and not cross-reacting with the Wu RBD) even after two exposures to Omicron S antigens, including after Wu/BA.5 or Wu/BA.1 bivalent mRNA vaccination.”
2. Aguilar-Bretones M et al., “Impact of antigenic evolution and original antigenic sin on SARS-CoV-2 immunity,” *J Clin Invest.* 2023, 133, 1: e162192. doi: [10.1172/JCI162192](https://doi.org/10.1172/JCI162192) ✓
    - “... vaccinated individuals infected with the Alpha or Delta variant have a relatively decreased response to variant-specific epitopes compared with unvaccinated individuals, which is indicative of OAS... In addition, more traits of immune imprinting have recently been identified in hybrid-immune individuals who were infected with Wuhan-1 strain before vaccination, in whom enhancement of VOC cross-reactive antibody titers and T cells by Omicron infection was nullified, a phenomenon termed hybrid immune damping.”
  3. Ahmed MIM et al., “Enhanced Spike-specific, but attenuated Nucleocapsid-specific T cell responses upon SARS-CoV-2 breakthrough versus non-breakthrough infections,” *Front. Immunol.* 2022, 13 (Vaccines and Molecular Therapeutics). doi: [10.3389/fimmu.2022.1026473](https://doi.org/10.3389/fimmu.2022.1026473) ✓
    - “Subjects with vaccine breakthrough infection had significantly higher CD4 and CD8 T cell responses targeting the vaccine-encoded Spike during the first and third/fourth week after PCR diagnosis compared to non-vaccinated controls, respectively. In contrast, CD4 T cells targeting the non-vaccine encoded Nucleocapsid antigen were of significantly lower magnitude in BTI as compared to non-BTI. Hence, previous vaccination was linked to enhanced T cell responses targeting the vaccine-encoded Spike antigen, while responses against the non-vaccine encoded Nucleocapsid antigen were significantly attenuated.”
  4. Alsoussi WB et al., “SARS-CoV-2 Omicron boosting induces de novo B cell response in humans,” *Nature* 2023, 617, 7961: 592-598. doi: [10.1038/s41586-023-06025-4](https://doi.org/10.1038/s41586-023-06025-4) ✓
    - “mRNA-1273 and mRNA-1273.213 both elicited robust germinal centre responses and maturation of the MBC and BMPC responses, but we did not isolate any antibodies specifically targeting S proteins from the variant strains encoded by the mRNA-1273.213 vaccine that did not cross-react to the original WA1/2020 S protein. Thus, the B cell response after boosting with the mRNA-1273.213 vaccine was imprinted by the primary vaccination series with mRNA-1273, which encodes the ancestral S protein.”
  5. Altmann DM et al., “COVID-19 vaccination: The road ahead,” *Science* 2022, 375, 6586: 1127-1132. doi: [10.1126/science.abn1755](https://doi.org/10.1126/science.abn1755) ✓
    - “In terms of immune imprinting (‘original antigenic sin’), the data show that different repertoires emerge, with associated implications for variable quality and quantity of neutralization of current or future VOC. For example, our

comparative analysis of differential VOC neutralization patterns in vaccinees shows the development of imprinted differences between those who had a prior infection with either the ancestral or Alpha virus. Faced with these diverse scenarios, the question is whether to keep developing boosters carrying prototypic Wuhan Hu-1 spike sequence or focus on being reactive to regionally predominant VOCs. The iteration of this that pools VOC sequences into multivalent vaccines has appeal, although the immune imprinting data argue the potential for unforeseen, differential response patterns dependent on prior history and subsequent SARS-CoV-2 exposure. There is a danger that, even with ‘plug and play’ platforms and rapid pipelines, this entails a future of playing catchup against oncoming VOCs for diminishing and unpredictable returns in protective immunity.”

6. Amano M et al., “Restoration of Neutralization Activity Against Omicron BA.2 and BA.5 in Older Adults and Individuals With Risk Factors Following the Fourth Dose of Severe Acute Respiratory Syndrome Coronavirus 2 BNT162b2 Vaccine,” *J. Infect. Dis.* 2023, 227, 1: 161-163. doi: [10.1093/infdis/jiac393](https://doi.org/10.1093/infdis/jiac393) ✓
  - “The present data, that a fourth vaccine dose restores protection but does not further enhance the humoral response, may be related to ‘original antigenic sin,’ wherein high-affinity memory B cells inhibit the recruitment of naive B cells against subsequent antigenic stimuli, in particular, against new stimuli. Thus, it is likely that despite the fourth dose, breakthrough infections continue to occur.”
7. Arunachalam PS et al. “Systems vaccinology of the BNT162b2 mRNA vaccine in humans,” *Nature* 2021, 596: 410-416. doi: [10.1038/s41586-021-03791-x](https://doi.org/10.1038/s41586-021-03791-x) ✓
  - “BNT162b2 vaccination also induced a neutralizing antibody response against the B.1.351 variant of concern, albeit at a tenfold-lower magnitude than against the wild-type WA1/2020 (WA1) strain.”
8. Atari N et al., “Omicron BA.2.75 variant is efficiently neutralised following BA.1 and BA.5 breakthrough infection in vaccinated individuals, Israel, June to September 2022,” *Eurosurveillance* 2022, 27, 44: 2200785. doi: [10.2807/1560-7917.ES.2022.27.44.2200785](https://doi.org/10.2807/1560-7917.ES.2022.27.44.2200785) ✓
  - “The neutralisation efficiency in HCW who were infected with BA.1/BA.5 and had previously been vaccinated with three doses of Comirnaty vaccine was significantly higher for all of Omicron variants (unpaired T-test, p value > 0.0008) than in vaccinated but SARS-CoV-2-naïve HCW.”
9. Aydililo T et al., “Immunological imprinting of the antibody response in COVID-19 patients,” *Nat. Commun.* 2021, 12: 3781. doi: [10.1038/s41467-021-23977-1](https://doi.org/10.1038/s41467-021-23977-1) ✓
  - “Our findings thus provide evidence of immunological imprinting by previous seasonal coronavirus infections that can potentially modulate the antibody profile to SARS-CoV-2 infection... A similar scenario to our studies in infected people could be proposed for the vaccines, with some differences due to the



- nature of the stimulus itself. Back-boost of cross-reactive antibody responses might lead to less protective antibodies directed against non-neutralizing conserved epitopes between the S antigen of the vaccine and the S proteins of seasonal human betacoronaviruses.”
10. Bachmann MF et al., “The impact of viral evolution on vaccine development for SARS-CoV-2,” *Curr. Opin. Immunol.* 2025, 96: 102612. doi: [10.1016/j.coi.2025.102612](https://doi.org/10.1016/j.coi.2025.102612) ✓
    - “Immune imprinting’ was proposed for immunity to SARS-CoV-2 variants based on observations that new viral variant(s) primarily boost antibodies induced by previous infections or vaccines, rather than generating new antibody species for the new variant(s). In previously infected or vaccinated individuals, it was demonstrated that anti-SARS-CoV-2 antibodies detected after boosting stemmed from memory B cells rather than from B cells newly recruited from the naïve B-cell pool by the booster vaccine. Such findings are compatible with immune imprinting... An interesting consequence would be that, if immune imprinting is critical in the setting of SARS-CoV-2 infection or vaccination, then currently employed vaccines should not target earlier RBD variants, but only the current ones, and these vaccines may need to be administered several times and/or at relatively high doses to overcome earlier immune imprinting.”
  11. Baerends EAM et al., “Omicron Variant-Specific Serological Imprinting Following BA.1 or BA.4/5 Bivalent Vaccination and Previous SARS-CoV-2 Infection: A Cohort Study,” *Clin. Infect. Dis.* 2023, 77, 11: 1511-1520. doi: [10.1093/cid/ciad402](https://doi.org/10.1093/cid/ciad402) ✓
    - “Vaccination and previous infection leave a clear serological imprint that is focused on the variant-specific antigen.”
  12. Bayarri-Olmos R et al., “Unraveling the impact of SARS-CoV-2 mutations on immunity: insights from innate immune recognition to antibody and T cell responses,” *Front Immunol.* 2024, 15 (Viral Immunology). doi: [10.3389/fimmu.2024.1412873](https://doi.org/10.3389/fimmu.2024.1412873) ✓
    - “Of note, we observed no significant difference in T cell reactivity against the Delta and Omicron spike MP in those with an Omicron infection, nor in T cell reactivity against the Omicron spike in the different donor groups, suggesting that immune imprinting from vaccination may have dampened the induction of Omicron-specific T cells after infection... Taken together, these findings suggest that deployment of Omicron-based vaccines, or other highly divergent SARS-CoV-2 strains, in immune-naïve individuals may induce poorly cross-reactive antibody responses, while Omicron boosters in vaccinees may be of limited use due to the imprinted responses from the ancestral strain-based vaccines.”
  13. Belik M et al., “Long-term COVID-19 vaccine- and Omicron infection-induced humoral and cell-mediated immunity,” *Front. Immunol.* 2024, 15 (Viral Immunology). doi: [10.3389/fimmu.2024.1494432](https://doi.org/10.3389/fimmu.2024.1494432) ✓

- “Interestingly, the bivalent vaccine induced equally high neutralizing antibodies against D614G as the monovalent vaccine, and repeated vaccinations with the original Wuhan-type monovalent vaccine or booster vaccination with a bivalent BA.1 or BA.4/5 vaccine did not broaden the specificity of neutralizing antibodies against XBB.1.5. These results indicate that the vaccines elicit antibody responses based on immune imprinting and the repeated Omicron exposure does not override ancestral SARS-CoV-2 immune imprinting.”
14. Blanco J et al., “Rethinking Optimal Immunogens to Face SARS-CoV-2 Evolution Through Vaccination,” *Influenza Other Respir Viruses* 2025, 19, 1: e70076. doi: [10.1111/irv.70076](https://doi.org/10.1111/irv.70076) ✓
    - “In this repeated vaccination context, antibody repertoire diversification was evidenced, although immune imprinting after booster doses or reinfection was also demonstrated and identified as a major determinant of immunological responses to repeated antigen exposures.”
  15. Blankson JN, “Bivalent COVID-19 Vaccines: Can the Original Antigenic Sin Be Forgiven?” *J. Infect. Dis.* 2023, 11, 1: 1221-1223. doi: [10.1093/infdis/jiad073](https://doi.org/10.1093/infdis/jiad073) ✓
    - “... the lack of a more potent response to BA.5 following bivalent vaccination in some cases may reflect the fact that we are looking at a primary immune response. If that is the case, then there is a chance that subsequent exposure to BA.5 spike protein, either by vaccination or natural infection, will lead to an improved response. Unfortunately, by the time 2 bivalent booster shots are given to a significant part of the population—an unlikely prospect given the limited uptake of the bivalent vaccine and the vaccine weariness of the US population—the variant in question will probably no longer be the dominant variant in circulation.”
  16. Boynton JR and DM Altmann, “Imprinted hybrid immunity against XBB reinfection,” *Lancet Infect Dis.* 2023, 23, 7: 764-765. doi: [10.1016/S1473-3099\(23\)00138-X](https://doi.org/10.1016/S1473-3099(23)00138-X) ✓
    - “If we now appreciate that even hybrid immunity to SARS-CoV-2 infection is (differentially, depending on previous immune experience) poorly durable and annual debates on booster strategy are required, how should we move forward? The dataset from Singapore reminds us that suggesting the booster strategy will simply involve tweaking vaccines annually, as for influenza, seriously underestimates the complexity of the current challenge. The long-term strategy will require considerable effort towards the development of both next-generation vaccines (targeting neutralising epitopes that are truly conserved and disadvantageous for viral mutations) and vaccine platforms that provide durable, local protection in the nasal mucosa, thereby blocking viral transmission.”
  17. Brazer N et al., “Differential immunity induced by Omicron sublineages in naïve and vaccine breakthrough infections,” *Sci. Rep.* 2025, 23718. doi: [10.1038/s41598-025-07702-2](https://doi.org/10.1038/s41598-025-07702-2) ✓

- “Our results suggest that immunological imprinting resulting from prior exposure to SARS-CoV-2 (‘original antigenic sin’), whether via natural infection or vaccination, may have impaired neutralizing antibody responses to the later Omicron sublineages. The poorer elicited immunogenicity and increased capacity for antibody evasion of these sublineages explain in part their persistence and ongoing global circulation.”
18. Brown E and HT Essigmann, “Original Antigenic Sin: the Downside of Immunological Memory and Implications for COVID-19,” *mSphere* 2021, 6, 2. doi: [10.1128/msphere.00056-21](https://doi.org/10.1128/msphere.00056-21) ✓
    - “The impact of OAS on the elicitation of protective immunity should not be ignored in vaccine development. Selection of a vaccine candidate or candidates that are too similar to antigens already ‘seen’ by the population at large could result in three distinct outcomes: (i) a “back-boost” or enhanced protective immunity resulting from a second round of GCRs in response to shared antigens between primary and secondary exposures, (ii) boosting of a nonprotective antibody response, or (iii) in the context of a multicomponent vaccine formulation, the masking of a protective response against some vaccine components if other antigens in the formulation have been previously “seen” by the population as observed with Gardasil 9.”
  19. Cao Y et al., “BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection,” *Nature* 2022, 608, 593-602. doi: [10.1038/s41586-022-04980-y](https://doi.org/10.1038/s41586-022-04980-y) ✓
    - “Of note, BA.2.12.1 and BA.4/BA.5 display increased evasion of neutralizing antibodies compared with BA.2 against plasma from triple-vaccinated individuals or from individuals who developed a BA.1 infection after vaccination... BA.1 infection after vaccination predominantly recalls humoral immune memory directed against ancestral... SARS-CoV-2 spike protein.”
  20. Cao Y et al., “Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution,” *Nature* 2023, 614: 521–529. doi: [10.1038/s41586-022-05644-7](https://doi.org/10.1038/s41586-022-05644-7) ✓
    - “In this work, we showed that due to immune imprinting, our humoral immune repertoire is not effectively diversified by infection with new Omicron variants. The immune pressure on the RBD becomes increasingly concentrated and promotes convergent evolution, explaining the observed sudden acceleration of SARS-CoV-2 RBD evolution and the convergence pattern. Although this study only examines inactivated vaccines, immune imprinting is also observed in those receiving mRNA vaccines.”
  21. Carreño JM et al., “Bivalent COVID-19 booster vaccines and the absence of BA.5-specific antibodies,” *Lancet Microbe* 2023, 4, 8: E569. doi: [10.1016/S2666-5247\(23\)00118-0](https://doi.org/10.1016/S2666-5247(23)00118-0) ✓

- “Pre-booster and post-booster RBD antibody avidity was lower against BA.5 RBD than wild-type RBD, which prompted us to look for BA.5 specific antibodies. Wild-type RBD depleted serum samples had undetectable reactivity to wild-type RBD—as expected—and to BA.5 RBD, suggesting that a single exposure to BA.5 antigens by the administration of bivalent vaccine boosters does not elicit robust concentrations of BA.5 specific serum antibodies.”
22. Carreño JM et al., “XBB.1.5 monovalent vaccine induces lasting cross-reactive responses to SARS-CoV-2 variants such as HV.1 and JN.1, as well as SARS-CoV-1, but elicits limited XBB.1.5 specific antibodies,” *mBio* 2025, 16, 4. doi: [10.1128/mbio.03607-24](https://doi.org/10.1128/mbio.03607-24) ✓
  - “However, antibody depletion experiments showed that most of the response was cross-reactive to the ancestral spike, and only low levels of XBB.1.5-specific antibodies to the spike or the receptor-binding domain were detected... Overall, our data suggest that the XBB.1.5 monovalent vaccine predominantly elicits a cross-reactive response imprinted by viral spike antigens encountered early during the pandemic.”
  23. Cerqueira-Silva T et al., “Effectiveness of monovalent and bivalent COVID-19 vaccines,” *Lancet Infect Dis.* 2023, 23, 11: 1208-1209. doi: [10.1016/S1473-3099\(23\)00379-1](https://doi.org/10.1016/S1473-3099(23)00379-1)
  - “A possible explanation for the lack of increased protection against infection with bivalent vaccines is immune imprinting against the wild-type variant of SARS-CoV-2. This could impair the production of neutralising antibodies against omicron variants after immunological stimulation with a mix of wild-type and omicron antigens (ie, bivalent vaccines) because production of antibodies against antigens that the immune system had previously been exposed to would be prioritized.”
  24. Chalkias S et al., “A Bivalent Omicron-Containing Booster Vaccine against Covid-19,” *N Eng J Med* 2022, 387: 1279-1291. doi: [10.1056/NEJMoa2208343](https://doi.org/10.1056/NEJMoa2208343) ✓
  - “In the primary analysis set of participants without evidence of previous SARS-CoV-2 infection, the observed geometric mean titers of neutralizing antibodies against ancestral SARS-CoV-2 (D614G) were 5977.3 (95% confidence interval [CI], 5321.9 to 6713.3) and 5649.3 (95% CI, 5056.8 to 6311.2) and against omicron were 2372.4 (95% CI, 2070.6 to 2718.2) and 1473.5 (95% CI, 1270.8 to 1708.4) 28 days after the mRNA-1273.214 and mRNA-1273 boosters, respectively.”
  25. Chemaitelly H et al., “2332. COVID-19 Primary Series and Booster Vaccination and Potential for Immune Imprinting,” *Open Forum Infect. Dis.* 2023, 10 (Issue Supplement\_2): ofad500.1954. doi: [10.1093/ofid/ofad500.1954](https://doi.org/10.1093/ofid/ofad500.1954) ✓

- “History of primary-series vaccination enhanced immune protection against omicron reinfection, but history of booster vaccination compromised protection against omicron reinfection.”
26. Chemaitelly H et al., “Long-term COVID-19 booster effectiveness by infection history and clinical vulnerability and immune imprinting: a retrospective population-based cohort study,” *Lancet Infect Dis.* 2023, 23, 7: 816-827. doi: [10.1016/S1473-3099\(23\)00058-0](https://doi.org/10.1016/S1473-3099(23)00058-0) ✓
    - “Protection against omicron infection waned after the booster, and eventually suggested a possibility for negative immune imprinting.”
  27. Chen JJ et al., “Neutralization against XBB.1 and XBB.1.5 after omicron subvariants breakthrough infection or reinfection,” *Lancet Reg Health West Pac.* 2023, 33: 100759. doi: [10.1016/j.lanwpc.2023.100759](https://doi.org/10.1016/j.lanwpc.2023.100759)
    - “In all six groups, neutralization titers were lower against all omicron subvariants than against the D614G strain; the level of neutralizing antibodies was lowest against the XBB.1, followed by XBB.1.5... In addition, significantly enhanced neutralizing activity against all omicron subvariants was observed after BA.5.2 reinfection.”
  28. Chen SY et al., “The Effectiveness of Bivalent COVID-19 Vaccination: A Preliminary Report,” *Life* 2023, 13, 10: 2094. doi: [10.3390/life13102094](https://doi.org/10.3390/life13102094) ✓
    - “Therefore, the human immune system elicits more robust immunity against the initial strain following a booster with an MV or BV. This ‘first love phenomenon’ may explain why the induced immunogenicity against BA.5 is not promising in people who receive a BA.5-containing booster. Our study also demonstrates much higher levels of immunogenicity against ancestral strains than new additional variant strains across enrolled studies.”
  29. Cho A et al., “Anti-SARS-CoV-2 receptor-binding domain antibody evolution after mRNA vaccination,” *Nature* 2021, 600: 517-522. doi: [10.1038/s41586-021-04060-7](https://doi.org/10.1038/s41586-021-04060-7) ✓
    - “Between prime and boost, memory B cells produce antibodies that evolve increased neutralizing activity, but there is no further increase in potency or breadth thereafter. Instead, memory B cells that emerge five months after vaccination of naive individuals express antibodies that are similar to those that dominate the initial response.”
  30. Collier ARY et al. “Immunogenicity of BA.5 Bivalent mRNA Vaccine Boosters,” *N Engl J Med* 2023, 388, 6: 565-567. doi: [10.1056/NEJMc2213948](https://doi.org/10.1056/NEJMc2213948) ✓
    - “Our data indicate that both monovalent and bivalent mRNA boosters markedly increased antibody responses but did not substantially augment T-cell responses. Neutralizing antibody titers against the ancestral strain of SARS-CoV-

- 2 were higher than titers against BA.5 after both monovalent and bivalent boosting... Our findings suggest that immune imprinting by previous antigenic exposure may pose a greater challenge than is currently appreciated for inducing robust immunity against SARS-CoV-2 variants.”
31. Corbett KS et al., “Protection against SARS-CoV-2 Beta variant in mRNA-1273 vaccine–boosted nonhuman primates,” *Science* 2021, 374, 6573: 1343-1353. doi: [10.1126/science.abl8912](https://doi.org/10.1126/science.abl8912) ✓
    - “The relative frequency of B cells specific for WA-1,  $\beta$ , or both did not change after boost with either the homologous or heterologous mRNA, suggesting that priming with mRNA-1273 imprinted the B cell repertoire.”
  32. Cui T et al., “Dynamic immune landscape in vaccinated-BA.5-XBB.1.9.1 reinfections revealed a 5-month protection-duration against XBB infection and a shift in immune imprinting,” *eBioMedicine* 2024, 99: 104903. doi: [10.1016/j.ebiom.2023.104903](https://doi.org/10.1016/j.ebiom.2023.104903) ✓
    - “... XBB.1.9.1 reinfection results in immune imprinting shifting from WT antigen induced by previous vaccination to the new XBB.1.9.1 antigen.”
  33. da Silva ES et al., “Vaccine- and Breakthrough Infection-Elicited Pre-Omicron Immunity More Effectively Neutralizes Omicron BA.1, BA.2, BA.4 and BA.5 Than Pre-Omicron Infection Alone,” *Curr Issues Mol Biol.* 2023, 45, 2: 1741-1761. doi: [10.3390/cimb45020112](https://doi.org/10.3390/cimb45020112) ✓
    - “... immune imprinting by first generation vaccines may restrict, but not abolish, cross-neutralization.”
  34. Dadonite B et al., “SARS-CoV-2 neutralizing antibody specificities differ dramatically between recently infected infants and immune-imprinted individuals,” *J. Virol.* 2025, 99, 4. doi: [10.1128/jvi.00109-25](https://doi.org/10.1128/jvi.00109-25) ✓
    - “While the serum neutralizing activity of the imprinted individuals primarily targets the spike receptor-binding domain (RBD), the serum neutralizing activity of infants infected with only XBB\* mostly targets the spike N-terminal domain.”
  35. Davis-Gardner ME et al., “Neutralization against BA.2.75.2, BQ.1.1, and XBB from mRNA Bivalent Booster,” *N Engl J Med* 2022, 388, 2: 183-185. doi: [10.1056/NEJMc2214293](https://doi.org/10.1056/NEJMc2214293) ✓
    - “The results in both of these cohorts correspond with neutralization titers against BA.1 and BA.5 that were 5 to 9 times as low as that against WA1/2020 and neutralization titers against BA.2.75.2, BQ.1.1, and XBB that were 23 to 63 times as low as that against WA1/2020.”
  36. Degryse J et al., “Antigenic Imprinting Dominates Humoral Responses to New Variants of SARS-CoV-2 in a Hamster Model of COVID-19,” *Microorganisms* 2024, 12, 12: 2591. doi: [10.3390/microorganisms12122591](https://doi.org/10.3390/microorganisms12122591) ✓



- “Our results show that both Comirnaty® XBB.1.5 and YF-S0\* induce robust, however, poorly cross-reactive, neutralizing antibody (nAb) responses. In either case, total antibody and nAb levels increased following infection. Intriguingly, the specificity of these boosted nAbs did not match the respective challenge virus, but was skewed towards the primary antigen used for immunization, suggesting a marked impact of antigenic imprinting, confirmed by antigenic cartography... our findings strongly suggest that antigenic imprinting by previous encounter (in this case, by vaccination) dominates the subsequent humoral response to new SARS-CoV-2 variants.”
37. Delgado JF et al., “SARS-CoV-2 Spike Protein Vaccine-Induced Immune Imprinting Reduces Nucleocapsid Protein Antibody Response in SARS-CoV-2 Infection,” *J. Immunol. Res.* 2022. doi: [10.1155/2022/8287087](https://doi.org/10.1155/2022/8287087) ✓
    - “SARS-CoV-2 primary infection in vaccinated healthcare workers (HCWs) produced significantly lower titers of anti-N antibodies than that in nonvaccinated HCWs: 5.7 (IQR 2.3-15.2) versus 12.2 (IQR 4.2-32.0), respectively (p = 0.005). Therefore, spike protein vaccine-induced immune imprinting (original antigenic sin) reduces N protein antibody response.”
  38. Dowell AC et al., “Immunological imprinting of humoral immunity to SARS-CoV-2 in children,” *Nat. Commun.* 2023, 14: 3845. doi: [10.1038/s41467-023-39575-2](https://doi.org/10.1038/s41467-023-39575-2) ✓
    - “Prior pre-Omicron SARS-CoV-2 virus infection or vaccination primes for robust antibody responses following Omicron infection but these remain primarily focussed against ancestral variants.”
  39. Edara VV et al., “mRNA-1273 and BNT162b2 mRNA vaccines have reduced neutralizing activity against the SARS-CoV-2 omicron variant,” *Cell Rep Med.* 2022, 3, 2: 100529. doi: [10.1016/j.xcrm.2022.100529](https://doi.org/10.1016/j.xcrm.2022.100529) ✓
    - “Six months after the initial two-vaccine doses, sera from naive vaccinated subjects show no neutralizing activity against omicron. In contrast, COVID-19-recovered individuals 6 months after receiving the primary series of vaccinations show a 22-fold reduction, with the majority of the subjects retaining neutralizing antibody responses.”
  40. Einhauser S et al., “Longitudinal effects of SARS-CoV-2 breakthrough infection on imprinting of neutralizing antibody responses,” *eBioMedicine* 2024, 110: 105438. doi: [10.1016/j.ebiom.2024.105438](https://doi.org/10.1016/j.ebiom.2024.105438) ✓
    - “Notably, the longitudinal analysis reveals an initial augmentation of the vaccine-primed nAb response upon infection, followed by a progressive expansion of neutralization capacity towards the infecting SARS-CoV-2 variant. Long-term observation reveals a subsequent contraction and inclination towards dominant wild-type (WT) immunity post-breakthrough infection.”



41. Emmelot ME et al., "SARS-CoV-2 Omicron BA.4/BA.5 Mutations in Spike Leading to T Cell Escape in Recently Vaccinated Individuals," *Viruses* 2023, 15, 1: 101. doi: [10.3390/v15010101](https://doi.org/10.3390/v15010101) ✓
- "In summary, our study shows that several BA.4/BA.5 mutations in the spike protein lead to a reduced responsiveness of epitope-specific T cells in subjects that received two doses of a mRNA vaccine based on the ancestral WT spike sequence. Other currently circulating Omicron sublineages, such as BA.2.75, BA.4.6, BQ.1.1 and XBB, share many of these spike mutations, making our findings also relevant for the impact of the T cell response on these emerging Omicron variants."
42. Erice A et al., "Immune Imprinting, Non-Durable Hybrid Immunity, and Hybrid Immune Damping Following SARS-CoV-2 Primary Vaccination with BNT162b2 and Boosting with mRNA-1273," *Vaccines* 2025, 13, 3: 310. doi: [10.3390/vaccines13030310](https://doi.org/10.3390/vaccines13030310) ✓
- "These findings suggest a modulating effect of previous SARS-CoV-2 infection on the humoral immune response to mRNA vaccination, a non-durable hybrid immunity following mRNA vaccination in previously infected subjects, and attenuation of the humoral immune response (immune damping) after repeated exposure to SARS-CoV-2 antigens through mRNA vaccination and/or infection."
43. Erice A et al., "Long-Term Analyses of SARS-CoV-2 Humoral and T Cell Responses and Breakthrough SARS-CoV-2 Infections after Two Doses of BNT162b2 Followed by mRNA-1273 and Bivalent Omicron-Adapted BNT162b2 Vaccines: A Prospective Study over 2 Years in Non-Immunocompromised Individuals," *Vaccines* 2023, 11, 12: 1835. doi: [10.3390/vaccines11121835](https://doi.org/10.3390/vaccines11121835) ✓
- "In healthy adults who received two doses of BNT162b2 followed by a booster of mRNA-273 and the bivalent Omicron-adapted BNT162b2 over a 26-month period, the evolution of anti-RBD antibodies suggests modulation of the immune response through immune imprinting."
44. Faraone JN and SL Liu, "Immune imprinting as a barrier to effective COVID-19 vaccines," *Cell Rep Med.* 2023, 4, 11: 101291. doi: [10.1016/j.xcrm.2023.101291](https://doi.org/10.1016/j.xcrm.2023.101291) ✓
- "Imprinting from three doses of monovalent vaccine can be alleviated by BA.5 or BQ-lineage breakthrough infection but not by a bivalent booster."
45. Faraone JN et al., "Immune evasion and membrane fusion of SARS-CoV-2 XBB subvariants EG.5.1 and XBB.2.3," *Emerg Microbes Infect* 2023, 12, 2: 2270069. doi: [10.1080/22221751.2023.2270069](https://doi.org/10.1080/22221751.2023.2270069) ✓
- "Bivalent vaccination-induced antibodies neutralized ancestral D614G efficiently, but to a much less extent, two new EG.5.1 and XBB.2.3 variants. In fact, the enhanced neutralization escape of EG.5.1 appeared to be driven by its key defining mutation XBB.1.5-F456L."

46. Fernandez-Ciriza L et al., “COVID-19 Vaccine Booster Dose Fails to Enhance Antibody Response to Omicron Variant in Reinfected Healthcare Workers,” *Viruses* 2025, 17, 1: 78. doi: [10.3390/v17010078](https://doi.org/10.3390/v17010078) ✓
- “The specific sequence of vaccination and infection during the initial Wuhan Hu-1 wave followed by the Omicron wave introduces a new concept: ‘hybrid immune damping.’ This ‘damping’ of booster dose may be due to pre-existing immunological memory, which may limit ‘de novo’ reactivity to non-conserved epitopes (phenomenon of antibody feedback). Consequently, antigen elimination will be stimulated reducing the support to B-cell immune response. In line with this, it has been described that the response against the ancestral variant (wild-type) remains predominant after reinfection with a new variant. This is closely linked to ‘immune imprinting’, as it causes post-vaccination infections (breakthrough infections) with non-ancestral variants to recall cross-reactive memory B cells elicited by wild-type-based vaccines, but rarely produce variant-specific B cells.”
47. Fossum E et al., “Low Levels of Neutralizing Antibodies Against SARS-CoV-2 KP.3.1.1 and XEC in Serum From Seniors in May 2024,” *Influenza Other Respir Viruses* 2025, 19, 5: e70102. doi: [10.1111/irv.70102](https://doi.org/10.1111/irv.70102) ✓
- “The significant reduction in neutralizing antibody titer from B.1 and XBB.1.5 to KP.3.1.1 and XEC does, however, indicate that the seniors had reduced protection against infection with current strains in the summer of 2024. Our results also indicate that prior immunization with the XBB.1.5 monovalent booster in the fall of 2023 was unlikely to protect against infection with the KP.3.1.1 and XEC strains in the fall/winter of 2024, which is in accordance with a study showing limited protection from infection > 12 weeks after administration of the XBB.1.5 vaccine.”
48. Fujita S et al., “Impact of Imprinted Immunity Induced by mRNA Vaccination in an Experimental Animal Model,” *J Infect Dis.* 2023, 228, 8: 1060-1065. doi: [10.1093/infdis/jiad230](https://doi.org/10.1093/infdis/jiad230) ✓
- “The concept of ‘imprinted immunity’ suggests that individuals vaccinated with ancestral virus-based vaccines may not develop effective immunity against newly emerging Omicron subvariants, such as BQ.1.1 and XBB.1. In this study, we investigated this possibility using hamsters. Although natural infection induced effective antiviral immunity, breakthrough infections in hamsters with BQ.1.1 and XBB.1 Omicron subvariants after receiving the 3-dose mRNA-lipid nanoparticle vaccine resulted in only faintly induced humoral immunity, supporting the possibility of imprinted immunity.”
49. Gagne M et al., “mRNA-1273 or mRNA-Omicron boost in vaccinated macaques elicits similar B cell expansion, neutralizing responses, and protection from Omicron,” *Cell* 2022, 185, 9: P1556-1571.E18. doi: [10.1016/j.cell.2022.03.038](https://doi.org/10.1016/j.cell.2022.03.038) ✓

- “The observation that boosting with either mRNA-1273 or mRNA-Omicron resulted in the expansion of a similarly high frequency of cross-reactive B cells likely stems from the recall of prior immune memory after a related antigenic encounter. This principle has been termed original antigenic sin, imprinting, and back boosting... As we have now shown in two different NHP studies, boosting animals with either mRNA-Beta or mRNA-Omicron has not yet been shown to provide any significant advantage over mRNA-1273 in recalling high titer neutralizing antibodies across all variants tested in the short term and protecting from virus replication after challenge. These considerations may apply to the large numbers of individuals with prior immunity from vaccination or infection with current and previous variants.”
50. Gao B et al., “Repeated vaccination of inactivated SARS-CoV-2 vaccine dampens neutralizing antibodies against Omicron variants in breakthrough infection,” *Cell Res.* 2023, 33: 258-261. doi: [10.1038/s41422-023-00781-8](https://doi.org/10.1038/s41422-023-00781-8) ✓
- “Strikingly, we found that although nAb titers against SARS-CoV-2 were comparable between the 2-dose and the 3-dose groups of patients with BA.2 breakthrough infection, nAb titers against the Omicron BA.2, BA.4 and BA.5 variants were significantly lower in the 3-dose group. Our data suggest that repeated vaccination with inactivated virus vaccine back-boosts previous memory and dampens the immune response to a new antigenically related but distinct viral strain. Such vaccination-induced immune imprint could reflect the ‘original antigenic sin’ doctrine...”
51. Garcia-Beltran WF et al., “Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity,” *Cell* 2021, 184, 9: P2372-2383.E9. doi: [10.1016/j.cell.2021.03.013](https://doi.org/10.1016/j.cell.2021.03.013) ✓
- “Strikingly, neutralization of all three South African B.1.351 strains was substantially decreased for both two-dose vaccines (v1: 34.5-fold for BNT162b2 and 27.7-fold for mRNA-1273; v2: 41.2-fold for BNT162b2 and 20.8-fold for mRNA-1273; v3: 42.4-fold for BNT162b2 and 19.2-fold for mRNA-1273;  $p < 0.0001$  for all comparisons). These strains contain the same three RBD mutations as P.1 except for an asparagine versus threonine substitution at K417 (K417N) and several additional mutations in non-RBD regions... Notably, 36.7% (11/30) recipients of two-dose BNT162b2 and 42.9% (15/35) recipients of two-dose mRNA-1273 vaccines did not have detectable neutralization of at least one of the B.1.351 variants.”
52. Germanio CD et al., “Spike and nucleocapsid antibody dynamics following SARS-CoV-2 infection and vaccination: Implications for sourcing COVID-19 convalescent plasma from routinely collected blood donations,” *Transfusion* 2024, 64, 11: 2063-2074. doi: [10.1111/trf.18017](https://doi.org/10.1111/trf.18017) ✓
- “In our study, seroreactivity for variant-specific bAb (MSD) and nAb (RVPN) assays to omicron variant S proteins was lower than the other variants in all the

- donor groups, including among VI cases during the omicron wave. Since all these donors were vaccinated during 2020–2021 when Moderna, Pfizer-BioNTech, or Janssen monovalent vaccines based on the ancestral virus S RNA/protein were administered, this phenomenon may be a result of ‘immune imprinting’. Studies have shown that the first encounter with SARS-CoV-2 S protein, by either vaccination or infection, establishes immunologic memory to the corresponding S antigenic determinants, which impacts capacity for responses to SARS-CoV-2 variant S antigens during subsequent infections.”
53. Gong X et al., “Repeated Omicron infection dampens immune imprinting from previous vaccination and induces broad neutralizing antibodies against Omicron sub-variants,” *J. Infect.* 2024, 89, 2: 106208. doi: [10.1016/j.jinf.2024.106208](https://doi.org/10.1016/j.jinf.2024.106208) ✓
    - “Neutralizing potency against the corresponding infected variant is significantly hampered along with the doses of vaccination during first infection... Breakthrough infection with BA.1 predominantly recalls humoral immune memory against the WT SARS-CoV-2 spike protein and elicited non-neutralizing antibodies, and repeated vaccination of inactivated SARS-CoV-2 vaccine dampens neutralizing antibodies against Omicron variants...”
  54. Gruell H et al., “mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2 Omicron variant,” *Nat. Med.* 2022, 28: 477-480. doi: [10.1038/s41591-021-01676-0](https://doi.org/10.1038/s41591-021-01676-0) ✓
    - “We report a near-complete lack of neutralizing activity against Omicron in polyclonal sera from individuals vaccinated with two doses of the BNT162b2 COVID-19 vaccine and from convalescent individuals, as well as resistance to different monoclonal antibodies in clinical use. However, mRNA booster immunizations in vaccinated and convalescent individuals resulted in a significant increase of serum neutralizing activity against Omicron.”
  55. Haralambieva IH et al., “Restricted Omicron-specific cross-variant memory B-cell immunity after a 3rd dose/booster of monovalent Wuhan-Hu-1-containing COVID-19 mRNA vaccine,” *Vaccine* 2024, 42, 4: 912-917. doi: [10.1016/j.vaccine.2024.01.032](https://doi.org/10.1016/j.vaccine.2024.01.032) ✓
    - “... we observed significantly lower frequencies of MBCs reactive to the receptor-binding domain/RBD, the N-terminal domain/NTD, and the S1 of Omicron/BA.1, compared to Wuhan and Delta, even after a 3rd vaccine dose/booster. Our study is a proof of concept that MBC cross-reactivity to variants with greater sequence divergence from the vaccine strain may be overestimated and suggests that these variants may exhibit immune escape with reduced recognition by circulating pre-existing MBCs upon infection.”
  56. Hoffman M et al., “Effect of hybrid immunity and bivalent booster vaccination on omicron sublineage neutralization,” *Lancet Infect Dis.* 2023, 23, 1: 25-28. doi: [10.1016/S1473-3099\(22\)00792-7](https://doi.org/10.1016/S1473-3099(22)00792-7)

- “Collectively, our results show that the emerging omicron sublineages BQ.1.1 and particularly BA.2.75.2 efficiently evade neutralisation independent of the immunisation history. Although monovalent and bivalent vaccine boosters both induce high neutralising activity and increase neutralisation breadth, BA.2.75.2-specific and BQ.1.1-specific neutralisation activity remained relatively low. This finding is in keeping with the concept of immune imprinting by initial immunisation with vaccines targeting the ancestral SARS-CoV-2 B.1 lineage. Furthermore, the observation that neutralisation of BA.2.75.2pp and BQ.1.1pp was most efficient in the cohort that had a breakthrough infection during the BA.1 and BA.2 wave and later received a bivalent booster vaccination, but was still less efficient than neutralisation of B.1pp, implies that affinity maturation of antibodies and two-time stimulation with different omicron antigens might still not be sufficient to overcome immune imprinting.”
57. Hoffman M et al., “Profound neutralization evasion and augmented host cell entry are hallmarks of the fast-spreading SARS-CoV-2 lineage XBB.1.5,” *Cel Mol Immunol* 2023, 20, 419-422. doi: [10.1038/s41423-023-00988-0](https://doi.org/10.1038/s41423-023-00988-0) ✓
- “Finally, we investigated the neutralization sensitivity of XBB.1.5pp to antibodies induced by vaccination with or without breakthrough infection (BTI). For this, we utilized plasma from triple-vaccinated individuals that experienced a BTI during the BA.5 wave in Germany, and plasma from quadruple-vaccinated individuals that received a monovalent or bivalent mRNA-vaccine booster as fourth vaccination. All tested plasma showed high neutralizing activity against B.1pp, while neutralizing activity against BA.4-5pp and BQ.1.1pp was moderately (BA.4-5pp: 2.3–7.2-fold reduced compared to B.1pp) or strongly (BQ.1.1pp: 6.4–19.9-fold reduced compared to B.1pp) reduced, as expected. In line with published results, neutralizing activity against XBB.1pp was even further reduced compared to BA.4-5pp and BQ.1.1pp (XBB.1pp: 22.5–38.2-fold reduced compared to B.1pp), and neutralizing activity against XBB.1.5pp was comparable to that of XBB.1pp (XBB.1pp: 23.7–35.9-fold reduced compared to B.1pp).”
58. Hornsby H et al., “Omicron infection following vaccination enhances a broad spectrum of immune responses dependent on infection history,” *Nat. Commun.* 2023, 14: 56. doi: [10.1038/s41467-023-40592-4](https://doi.org/10.1038/s41467-023-40592-4) ✓
- “These ‘previously-infected’ individuals have higher spike-specific serum antibody and T-cell responses after each vaccine dose compared to infection-naïve vaccinees. Hybrid immunity generated by post-vaccination infections may be quantitatively and qualitatively different from responses seen in individuals who experienced SARS-CoV-2 infection before receiving a vaccination course. This may be due to differences in the priming SARS-CoV-2 exposure or lower antigenic exposure during the attenuated disease course of omicron viruses; although it is difficult to tease apart the contributions of viral phenotype change from those of pre-existing immunity.”

59. Jia T et al., “Expanded immune imprinting and neutralization spectrum by hybrid immunization following breakthrough infections with SARS-CoV-2 variants after three-dose vaccination,” *J. Infect.* 2024, 89, 6: 106362. doi: [10.1016/j.jinf.2024.106362](https://doi.org/10.1016/j.jinf.2024.106362) ✓
  - “Following Omicron breakthrough infections, the levels of nAbs against WT and pre-Omicron VOCs were higher due to immune imprinting established by WT-based vaccination, in comparison to nAbs against Omicron variants.”
60. Jian F et al., “Evolving antibody response to SARS-CoV-2 antigenic shift from XBB to JN.1,” *Nature* 2025, 637: 921-929. doi: [10.1038/s41586-024-08315-x](https://doi.org/10.1038/s41586-024-08315-x) ✓
  - “Recent research has demonstrated exceptionally strong immune imprinting in individuals vaccinated with mRNA vaccines, as these individuals fail to mount an Omicron-specific antibody response even following several Omicron exposures.”
61. Johnston TS et al., “Immunological imprinting shapes the specificity of human antibody responses against SARS-CoV-2 variants,” *Immunity* 2024, 57, 4: P912-925.E4. doi: [10.1016/j.immuni.2024.02.017](https://doi.org/10.1016/j.immuni.2024.02.017) ✓
  - “We determined the specificity and functionality of antibody and B cell responses following exposure to BA.5 and XBB variants in individuals who received ancestral SARS-CoV-2 mRNA vaccines. BA.5 exposures elicited antibody responses that targeted epitopes conserved between the BA.5 and ancestral spike. XBB exposures also elicited antibody responses that primarily targeted epitopes conserved between the XBB.1.5 and ancestral spike.”
62. Ju B et al., “Antigenic sin of wild-type SARS-CoV-2 vaccine shapes poor cross-neutralization of BA.4/5/2.75 subvariants in BA.2 breakthrough infections,” *Nat. Commun.* 2022, 13: 7120. doi: [10.1038/s41467-022-34400-8](https://doi.org/10.1038/s41467-022-34400-8) ✓
  - “Compared with the neutralizing antibody titers against BA.2, marked reductions are observed against BA.2.75 in both 2-dose and 3-dose vaccine groups. In addition, although BA.2 breakthrough infections induce a certain cross-neutralization capacity against later Omicron subvariants, the original antigenic sin phenomenon largely limits the improvement of variant-specific antibody response. These findings suggest that BA.2 breakthrough infections seem unable to provide sufficient antibody protection against later subvariants such as BA.2.75 in the current immunization background with wild-type vaccines.”
63. Ju B et al., “Striking antibody evasion of SARS-CoV-2 Omicron sub-lineages BQ.1.1, XBB.1 and CH.1.1,” *Natl. Sci. Rev.* 2023, 10, 8: nwad148. doi: [10.1093/nsr/nwad148](https://doi.org/10.1093/nsr/nwad148) ✓
  - “Overall, due to the original antigenic sin (or so-called immune imprinting) of the initial WT vaccination, these plasma samples from BA.4 or BA.5 breakthrough



infected individuals acquired weaker neutralization against subsequent Omicron sub-lineages, such as BQ.1.1, XBB.1 and CH.1.1.”

64. Kaku CI et al., “Evolution of antibody immunity following Omicron BA.1 breakthrough infection,” *Nat. Commun.* 2023, 14: 2751. doi: [10.1038/s41467-023-38345-4](https://doi.org/10.1038/s41467-023-38345-4) ✓
- “While the acute B cell response following BA.1 breakthrough infection was dominated by vaccine-induced cross-reactive clones that exhibited preferential WT binding and neutralization, antibodies isolated from the same donors 5 to 6 months post-infection accumulated additional somatic mutations and displayed enhanced BA.1 recognition at the expense of WT binding... De novo BA.1-specific B cell responses only comprised a small fraction of the total RBD-directed response at both time points studied.”
65. Kaku CI et al., “Recall of preexisting cross-reactive B cell memory after Omicron BA.1 breakthrough infection,” *Sci. Immunol.* 2022, 7, 73. doi: [10.1126/sciimmunol.abq3511](https://doi.org/10.1126/sciimmunol.abq3511) ✓
- “BA.1 breakthrough infection donors exhibited similar (within twofold) serum IgG binding titers to BA.1 and WT S and RBD. In contrast, uninfected/mRNA-vaccinated donors displayed a two- to fourfold and four- to ninefold reduced serum IgG binding to full-length BA.1 S and BA.1 RBD, respectively...”
66. Kalkeri R et al., “Anti-spike IgG4 and Fc effector responses: The impact of SARS-CoV-2 vaccine platform–specific priming and immune imprinting,” *J. Infect.* 2025, 91, 2: 106543. doi: [10.1016/j.jinf.2025.106543](https://doi.org/10.1016/j.jinf.2025.106543) ✓
- “Immune imprinting of anti-S IgG4 and nAbs, and Fc effector function imprinting after mRNA priming was observed. This effect was partially overcome by updated XBB.1.5 protein subunit vaccination, but not by ancestral vaccine strains.”
67. Kaplonek P et al., “Hybrid immunity expands the functional humoral footprint of both mRNA and vector-based SARS-CoV-2 vaccines,” *Cell Rep Med.* 2023, 4, 5: 101048. doi: [10.1016/j.xcrm.2023.101048](https://doi.org/10.1016/j.xcrm.2023.101048) ✓
- “However, hybrid immunity shows a unique augmentation of S2-domain-specific functional immunity that was poorly induced for the vaccination only. These data highlight the importance of natural infection in breaking the immunodominance away from the evolutionarily unstable S1 domain and potentially affording enhanced cross-variant protection by targeting the more highly conserved S2 domain of SARS-CoV-2.”
68. Kim W, “Germinal Center Response to mRNA Vaccination and Impact of Immunological Imprinting on Subsequent Vaccination,” *Immune Netw.* 2024, 24, 4: e28. doi: [10.4110/in.2024.24.e28](https://doi.org/10.4110/in.2024.24.e28) ✓



- “The immunological imprinting induced by ancestral spike-based vaccination was also reflected in serological responses, which are outcomes of B cell responses to subsequent exposures. Individuals who have received two doses of primary vaccination and encountered omicron infection still exhibit low levels of omicron-specific Ab responses.”
69. King SM et al., “First Impressions Matter: Immune Imprinting and Antibody Cross-Reactivity in Influenza and SARS-CoV-2,” *Pathogens* 2023, 12, 2: 169. doi: [10.3390/pathogens12020169](https://doi.org/10.3390/pathogens12020169) ✓
- “This issue may already be playing out with the SARS-CoV-2 bivalent vaccines produced by Pfizer-BNT and Moderna. The first bivalent boosters contained mRNA designed to elicit immunity against the original WA1/2020 SARS-CoV-2 strain, present in the previous monovalent boosters, as well as the then newly emergent BA.1 strain. The results of these were disappointing, with only modest increases in anti-BA.1 neutralizing antibodies. As BA.1 was no longer circulating in the United States, the United States Food and Drug Administration approved new bivalent boosters directed against the now dominant circulating variants BA.4 and BA.5. Results emerging from very recent studies suggest limited boosts in antibody levels with modest protection against target strains, with minimal increases in BA.4 and BA.5 protection from the WA1/2020 and BA.1 boosters. These results are thought to be due to immune imprinting from multiple rounds of the prior WU1/2020 monovalent vaccine series.”
70. Koutsakos M and AH Ellebedy, “Immunological imprinting: Understanding COVID-19,” *Immunity* 2023, 56, 5: 909-913. doi: [10.1016/j.immuni.2023.04.012](https://doi.org/10.1016/j.immuni.2023.04.012) ✓
- “... individuals primed with Hu-1-like spike and then infected with a variant like Delta or Omicron maintain higher antibodies against the Hu-1-like antigen than the infecting variant (antigenic seniority).”
71. Kurhade C et al., “Low neutralization of SARS-CoV-2 Omicron BA.2.75.2, BQ.1.1 and XBB.1 by parental mRNA vaccine or a BA.5 bivalent booster,” *Nat. Med.* 2023, 29: 344-347. doi: [10.1038/s41591-022-02162-x](https://doi.org/10.1038/s41591-022-02162-x) ✓
- “The results showed that a BA.5 bivalent booster elicited a high neutralizing titer against BA.4/5 measured at 14–32 days after boost; however, the BA.5 bivalent booster did not produce robust neutralization against the newly emerged BA.2.75.2, BQ.1.1 or XBB.1. Previous infection substantially enhanced the magnitude and breadth of BA.5 bivalent booster-elicited neutralization.”
72. Lasrado N et al., “Waning immunity and IgG4 responses following bivalent mRNA boosting,” *Sci. Adv.* 2024, 10, 8. doi: [10.1126/sciadv.adj9945](https://doi.org/10.1126/sciadv.adj9945) ✓
- “Here, we show limited durability of neutralizing antibody (NAb) responses against XBB variants and isotype switching to immunoglobulin G4 (IgG4) responses following bivalent mRNA boosting. Bivalent mRNA boosting elicited

- modest XBB.1-, XBB.1.5-, and XBB.1.16-specific NAbs that waned rapidly within 3 months. In contrast, bivalent mRNA boosting induced more robust and sustained NAbs against the ancestral WA1/2020 strain, suggesting immune imprinting.”
73. Lee WS et al., “Durable reprogramming of neutralizing antibody responses following Omicron breakthrough infection,” *Sci. Adv.* 2023, 9, 29. doi: [10.1126/sciadv.adg5301](https://doi.org/10.1126/sciadv.adg5301) ✓
    - “We show that only cross-reactive memory B cells were expanded by breakthrough infection, and the resulting antibody response was dominated by antibodies cross-reactive with ancestral spike, indicating that limited de novo responses were generated against neo-epitopes within BA.1 or BA.2 spike. In line with recent studies, our results are suggestive of immune imprinting, with no evident increase in BA.1 or BA.2 monospecific B cells even up to 4 to 7 months after infection... While the isolation of receptor binding domain (RBD)–specific monoclonal antibodies (mAbs) specific for the BA.1 RBD that do not cross-react with ancestral RBD has been reported, these comprised only a small fraction (median, 4%) of the response to RBD, confirming that neo-epitopes are poorly recognized during breakthrough infection. Immune imprinting is not constrained to breakthrough infections, as monovalent Omicron BA.1 or bivalent Beta/Delta mRNA vaccines also predominantly boost preexisting cross-reactive responses.”
  74. Li Y et al., “Repeated Omicron Infections Overcome T Cell Immune Imprinting to Original SARS-CoV-2,” *J. Med. Virol.* 2025, 97, 2: e70264. doi: [10.1002/jmv.70264](https://doi.org/10.1002/jmv.70264) ✓
    - “Therefore, similar to humoral immunity vaccination with the original SARS-CoV-2 strain-derived vaccines induces T cell immune imprinting when undergoing Omicron subvariants breakthrough infection.”
  75. Liang CY et al., “Imprinting of serum neutralizing antibodies by Wuhan-1 mRNA vaccines,” *Nature* 2024, 630: 950-960. doi: [10.1038/s41586-024-07539-1](https://doi.org/10.1038/s41586-024-07539-1) ✓
    - “Because serum neutralizing responses against Omicron strains and other sabercoronaviruses were abrogated after pre-clearing with Wuhan-1 spike protein, antibodies induced by XBB.1.5 boosting in humans focus on conserved epitopes targeted by the antecedent mRNA-1273 primary series.”
  76. Liu S et al., “Sera from breakthrough infections with SARS-CoV-2 BA.5 or BF.7 showed lower neutralization activity against XBB.1.5 and CH.1.1,” *Emerg Microb Infect* 2023, 12, 2: 2225638. doi: [10.1080/22221751.2023.2225638](https://doi.org/10.1080/22221751.2023.2225638) ✓
    - “The level of neutralizing antibody against the wild strain is the highest which may be attributed to the imprinted original immune responses against the prototype vaccine strain. “
  77. Lustig Y et al., “Neutralising capacity against Delta (B.1.617.2) and other variants of concern following Comirnaty (BNT162b2, BioNTech/Pfizer) vaccination in health

care workers, Israel,” *Eurosurveillance* 2021, 26, 26. doi: [10.2807/1560-7917.ES.2021.26.26.2100557](https://doi.org/10.2807/1560-7917.ES.2021.26.26.2100557) ✓

- “Serum samples neutralised the original, Delta-S1 and Delta-S2 virus isolates with geometric mean titres (GMT) of 247, 107 and 123, respectively, demonstrating a twofold reduction in neutralising titres compared with the original virus in vaccinated individuals.”

78. Madhi SA et al., “Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant,” *N Engl J Med* 2021, 384, 20: 1885-1898. doi: [10.1056/NEJMoa2102214](https://doi.org/10.1056/NEJMoa2102214) ✓

- “Six of 13 vaccine recipients (46%) without evidence of previous SARS-CoV-2 infection showed no neutralization activity against an RBD triple-mutant pseudovirus (containing K417N, E484K, and N501Y variants), and 11 of the 13 (85%) had no neutralization activity against B.1.351 pseudovirus. Geometric mean titers dropped from 297 against the original virus to 85 against the RBD-only mutant and 74 against the B.1.351 variant.”

79. Maltseva M et al., “Immune imprinting: The persisting influence of the first antigenic encounter with rapidly evolving viruses,” *Hum Vaccin Immunother* 2024, 20, 1: 2384192. doi: [10.1080/21645515.2024.2384192](https://doi.org/10.1080/21645515.2024.2384192) ✓

- “Breakthrough infections with the Alpha or Delta variants resulted in a greater increase in antibody titers against the ancestral strain compared to the VOC strain in individuals vaccinated with three doses of ancestral mRNA-LNP, highlighting the effects of immune imprinting... Efforts to enhance vaccine efficacy by updating vaccines have led to improved VOC neutralization. However, individuals previously vaccinated with the ancestral mRNA vaccines showed dominant recall antibody responses following monovalent Beta or Delta boosters, or bivalent ancestral and Beta/Delta boosters... Omicron breakthrough infections pre-dominantly promoted recall responses, leading to reduced neutralization of Omicron variants.”

80. Marcotte H et al., “Limited cross-variant neutralization after primary Omicron infection: consideration for a variant-containing booster,” *Signal Transduct Target Ther* 2022, 7: 294. doi: [10.1038/s41392-022-01146-0](https://doi.org/10.1038/s41392-022-01146-0) ✓

- “The plasma of individuals receiving three doses of mRNA vaccines or a combination of inactivated and mRNA vaccines were shown to neutralize BA.1 but with titers 32-fold lower compared to the wild-type strain. Furthermore, two recent studies showed that sera from individuals who received three doses of vaccines (Pfizer, AstraZeneca, or CoronaVac) and from vaccinated individuals with BA.1 breakthrough infection have a reduced ability to neutralize BA.4, BA.5, and BA.2.12.1 compared with BA.1 and BA.2 due to RBD mutations involving L452R and F486V (BA.4/5) and L452Q (BA.2.12.1). They found that BA.1 Omicron breakthrough infections mainly reactivate WT-induced memory B cells, reducing

the diversity of antibodies, and possibly facilitating the emergence of new mutants.”

81. Martín-Pérez C et al., “Post-vaccination IgG4 and IgG2 class switch associates with increased risk of SARS-CoV-2 infections,” *J. Infect.* 2025, 90, 4: 106473. doi: [10.1016/j.jinf.2025.106473](https://doi.org/10.1016/j.jinf.2025.106473) ✓
  - “IgG4 and IgG2 levels increase markedly after the third mRNA dose against SARS-CoV-2. Elevated IgG4 levels after booster vaccination associate with an increased risk of infections. Increased non-cytophilic to cytophilic antibody ratio correlates with reduced functionality.”
82. Marzi R et al., “Maturation of SARS-CoV-2 Spike-specific memory B cells drives resilience to viral escape,” *iScience* 2023, 26, 1: 105726. doi: [10.1016/j.isci.2022.105726](https://doi.org/10.1016/j.isci.2022.105726) ✓
  - “Whereas MBCs of infected individuals targeted both prefusion and postfusion Spike (S), most vaccine-elicited MBCs were specific for prefusion S, consistent with the use of prefusion-stabilized S in mRNA vaccines.”
83. Medits I et al., “Different Neutralization Profiles After Primary SARS-CoV-2 Omicron BA.1 and BA.2 Infections,” *Front. Immunol.* 2022, 13 (Vaccines and Molecular Therapeutics). doi: [10.3389/fimmu.2022.946318](https://doi.org/10.3389/fimmu.2022.946318) ✓
  - “Serum neutralization of Omicron BA.1 and BA.2 variants was detectable after three-dose mRNA vaccinations, but with reduced titers. Vaccination-breakthrough infections with either Omicron BA.1 or BA.2, however, generated equal cross-neutralizing antibody levels against all SARS-CoV-2 variants tested.”
84. Milne G et al., “Does infection with or vaccination against SARS-CoV-2 lead to lasting immunity?” *Lancet Respir Med* 2021, 9, 12: 1450-1466. doi: [10.1016/S2213-2600\(21\)00407-0](https://doi.org/10.1016/S2213-2600(21)00407-0)
  - “Upon natural infection, the T-cell-mediated response appears to be targeted across a larger variety of epitopes than the humoral response, and hence might be more durable to genetic changes in key immunogenic viral epitopes. Nonetheless, the neutralising antibody response also comprises a key aspect of protection against reinfection... Compared with the immune response to natural infection, vaccination elicits a response of greater magnitude and higher specificity, largely focused on the RBD. Increasing evidence of reduced neutralisation and vaccine effectiveness against emerging variants, alongside emerging data on breakthrough infections, suggests that vaccines will need to be updated in the short-to-medium term.”
85. Montiel-Ruiz M et al., “Immune imprinting and antibody profiles to SARS-CoV-2 in urban and rural Ghana,” *Cell* 2025, 28, 5: 112511. doi: [10.1016/j.isci.2025.112511](https://doi.org/10.1016/j.isci.2025.112511) ✓

- “Vaccinated and urban individuals exhibited significantly greater Spike-pseudotyped virus neutralization than nonvaccinated and rural individuals. Notably, plasma antibodies preferentially bound Wuhan-Hu-1 over Omicron Spike variants. Our findings indicate significant prior and ongoing SARS-CoV-2 transmission as well as immunological imprinting by Wuhan-Hu-1-like SARS-CoV-2 in Ghana.”
86. Moreno A et al., “Divergence of variant antibodies following SARS-CoV-2 booster vaccines in myeloma and impact of hybrid immunity,” *npj Vaccines* 2024, 9: 201. doi: [10.1038/s41541-024-00999-6](https://doi.org/10.1038/s41541-024-00999-6) ✓
- “It has been suggested that immune imprinting provided by prior infection or SARS-CoV-2 vaccination negatively impacts vaccine immunogenicity of booster immunizations. Consistent with this, we observed preferential boosting of nAb against the ancestral WA1 strain following booster immunization.”
87. Mueksche F et al., “Increased memory B cell potency and breadth after a SARS-CoV-2 mRNA boost,” *Nature* 2022, 607: 128-134. doi: [10.1038/s41586-022-04778-y](https://doi.org/10.1038/s41586-022-04778-y) ✓
- “Consistent with prior reports, the third vaccine dose significantly boosted geometric mean NT50 values by 16-fold, 12-fold and 37-fold for the Beta, Delta and Omicron BA.1 variants, respectively. The level of activity against the Beta and Delta variants was not significantly different from that against Wuhan-Hu-1, whereas the activity against Omicron BA.1 was 16-fold lower than that against Wuhan-Hu-1 ( $P = 0.58$ ,  $P = 0.24$  and  $P = 0.0013$ , respectively)... given the correlation between neutralizing antibody levels and protection from Wuhan-Hu-1 infection, the reduced activity against Omicron BA.1 in recipients of a third dose of vaccine probably explains why vaccinated individuals remained particularly susceptible to infection by this variant.”
88. Muik A et al., “Immunity against conserved epitopes dominates after two consecutive exposures to SARS-CoV-2 Omicron BA.1,” *Cell Rep.* 2024, 43, 8: 114567. doi: [10.1016/j.celrep.2024.114567](https://doi.org/10.1016/j.celrep.2024.114567) ✓
- “Upon exposure to the highly altered Omicron spike glycoprotein, pre-immunized individuals predominantly mount recall responses of Wuhan-Hu-1 (wild-type)-imprinted memory B ( $B_{MEM}$ ) cells mostly targeting conserved non-neutralizing epitopes, leading to diminished Omicron neutralization. We investigated the impact of imprinting in individuals double/triple vaccinated with a wild-type-strain-based mRNA vaccine who, thereafter, had two consecutive exposures to Omicron BA.1 spike (breakthrough infection followed by BA.1-adapted vaccine). We found that depletion of conserved epitope-recognizing antibodies using a wild-type spike bait results in strongly diminished BA.1 neutralization. Furthermore, spike-specific  $B_{MEM}$  cells recognizing conserved epitopes are much more prevalent than BA.1-specific  $B_{MEM}$  cells. Our observations suggest that imprinted  $B_{MEM}$  cell recall responses limit the

- induction of strain-specific responses even after two consecutive BA.1 spike exposures. Vaccine adaptation strategies need to consider that prior SARS-CoV-2 infections and vaccinations may cause persistent immune imprinting.”
89. Muik A et al., “Progressive loss of conserved spike protein neutralizing antibody sites in Omicron sublineages is balanced by preserved T cell immunity,” *Cell Rep.* 2023, 42, 8: 112888. doi: [10.1016/j.celrep.2023.112888](https://doi.org/10.1016/j.celrep.2023.112888) ✓
    - “We report that Omicron BA.4/BA.5 breakthrough infection of individuals immunized with SARS-CoV-2 wild-type-strain-based mRNA vaccines results in a boost of Omicron BA.4.6, BF.7, BQ.1.1, and BA.2.75 neutralization but does not efficiently boost BA.2.75.2, XBB, or XBB.1.5 neutralization. In silico analyses showed that the Omicron spike glycoprotein lost most neutralizing B cell epitopes, especially in sublineages BA.2.75.2, XBB, and XBB.1.5.”
  90. Mykytyn AZ et al., “Antigenic mapping of emerging SARS-CoV-2 omicron variants BM.1.1.1, BQ.1.1, and XBB.1,” *Lancet Microbe* 2023, 4, 5: E294-295. doi: [10.1016/S2666-5247\(22\)00384-6](https://doi.org/10.1016/S2666-5247(22)00384-6) ✓
    - “Our data reveal substantial cross-neutralisation of BA.5 antiserum samples against BQ.1.1 but little cross-neutralisation against XBB.1 and BM.1.1.1. Despite the antigenic similarities between BA.5 and BQ.1.1, thus far there is little evidence for increased neutralisation of BQ.1.1 by BA.5 bivalent vaccines, potentially due to immunological imprinting.”
  91. Norton NJ et al., “Characteristics of Vaccine- and Infection-Induced Systemic IgA Anti-SARS-CoV-2 Spike Responses,” *Vaccines* 2023, 11, 9: 1462. doi: [10.3390/vaccines11091462](https://doi.org/10.3390/vaccines11091462) ✓
    - “As with circulating IgG responses, vaccination with an ancestral SARS-CoV-2 S antigen imposed immunological imprinting on IgA responses with preferred recognition of ancestral SARS-CoV-2 S protein over Omicron SARS-CoV-2 S protein persisting following Omicron breakthrough infection.”
  92. Paciello I et al., “Antigenic sin and multiple breakthrough infections drive converging evolution of COVID-19 neutralizing responses,” *Cell Rep.* 2024, 43, 9: 114645. doi: [10.1016/j.celrep.2024.114645](https://doi.org/10.1016/j.celrep.2024.114645) ✓
    - “In line with recent studies, our data revealed that while the initial antibody response was different in vaccinated or infected people, breakthrough infections by a distantly related virus such as Omicron induced the expansion of previously unseen germ lines and, most important, rescued the B cell primed by the original antigenic sin.”
  93. Pape KA et al., “High-affinity memory B cells induced by SARS-CoV-2 infection produce more plasmablasts and atypical memory B cells than those primed by mRNA vaccines,” *Cell Rep.* 2021, 37, 2: 109823. doi: [10.1016/j.celrep.2021.109823](https://doi.org/10.1016/j.celrep.2021.109823) ✓



- “However, infection-induced primary MBCs have better antigen-binding capacity and generate more plasmablasts and secondary MBCs of the classical and atypical subsets than do vaccine-induced primary MBCs. Our results suggest that infection-induced primary MBCs have undergone more affinity maturation than vaccine-induced primary MBCs and produce more robust secondary responses.”
94. Park YJ et al., “Imprinted antibody responses against SARS-CoV-2 Omicron sublineages,” *Science* 2022, 387, 6620: 619-627. doi: [10.1126/science.adc9127](https://doi.org/10.1126/science.adc9127) ✓
    - “Park et al. found that either a vaccination booster or a breakthrough infection elicits neutralization activity against the Omicron variants, but only a breakthrough infection induces an antibody response in the nasal mucosa, which might give better protection against transmission.”
  95. Paula NM et al., “Symptomatology and IgG Levels before and after SARS-CoV-2 Omicron Breakthrough Infections in Vaccinated Individuals,” *Vaccines* 2024, 12, 10: 1149. doi: [10.3390/vaccines12101149](https://doi.org/10.3390/vaccines12101149) ✓
    - “The anti-N and anti-S IgG titers followed the expected pattern, with anti-S titers raised after a vaccination event, whereas both anti-S and anti-N levels increased after an infection event... [P]reexisting anti-S IgG levels correlate poorly with symptomatology during infections caused by Omicron variants. There was also no correlation between the COVID-19 symptoms and anti-S IgG titers after the infections. Quite surprisingly, COVID-19 symptoms correlated with anti-N IgG levels detected after the infection (Spearman  $r = -0.55$ ,  $p = 0.03$ ). Thus, individuals with lower anti-N IgG levels after infection were the ones who experienced the most intense COVID-19 symptoms. This observation suggests that human anti-N IgG antibodies may play an important role in resolution of the disease.”
  96. Pepkowitz SH et al., “Prior vaccination has changed the composition of the COVID-19 convalescent plasma inventory,” *Transfusion* 2022, 62, 10: 2153-2154. doi: [10.1111/trf.17089](https://doi.org/10.1111/trf.17089) ✓
    - “The lower IgG anti-nucleocapsid antibody, lower IgM anti-spike antibody, and higher IgG anti- RBD antibody present in post-breakthrough COVID-19 CCP are likely due to extensive affinity maturation and a decreased presence of IgM memory-cells post-vaccination and to a component of ‘original antigenic sin’ in which the immune system is focused on producing those anti-spike antibodies previously developed in response to prior vaccination, while relatively ignoring additional newly presented viral immunogens.”
  97. Pérez-Alós L et al., “Previous immunity shapes immune responses to SARS-CoV-2 booster vaccination and Omicron breakthrough infection risk,” *Nat. Commun.* 2023, 14: 5624. doi: [10.1038/s41467-023-41342-2](https://doi.org/10.1038/s41467-023-41342-2) ✓



- “Our study shows that both humoral and cellular responses following vaccination were generally higher after SARS-CoV-2 infection compared to infection-naïve. Notably, viral exposure before vaccination was crucial to achieving a robust IgA response. Individuals with lower IgG, IgA, and neutralizing antibody responses postvaccination had a significantly higher risk of reinfection and future Omicron infections.”
98. Petras M and IV Lesna, “SARS-CoV-2 vaccination in the context of original antigenic sin,” *Hum Vaccin Immunother.* 2022, 18, 1: 1949953. doi: [10.1080/21645515.2021.1949953](https://doi.org/10.1080/21645515.2021.1949953) ✓
- “Given the above, it is most appropriate – when scheduling booster vaccination or even re-vaccination – to carefully monitor the seroresponse of those vaccinated since a reduced immune response to new SARS-CoV-2 variants at the expense of an enhanced response to original variants could in fact result in inadequate protection of those vaccinated against the current virus variants. Hence, the extremely high levels of specific anti-SARS-CoV-2 antibodies achieved by vaccination, which – as indicated by the most recent data – tend to persist for months post-vaccination, should serve as a warning sign. In addition, it is not yet obvious if the robust vaccination-induced response of T cells can compensate for original antigenic sin to afford a sufficient level of protection against the new SARS-CoV-2 variants.”
99. Piubelli C et al., “Subjects who developed SARS-CoV-2 specific IgM after vaccination show a longer humoral immunity and a lower frequency of infection,” *eBioMedicine* 2023, 89: 104471. doi: [10.1016/j.ebiom.2023.104471](https://doi.org/10.1016/j.ebiom.2023.104471) ✓
- “Taken together these data, including ours, draw attention on the so-called ‘original immunological sin’, whereby an immune response conditioned by prior immunity against other hCoVs could result in a non-specific SARS-CoV-2 humoral immunity after vaccination, impairing the immune protection.”
100. Planas D et al., “Distinct evolution of SARS-CoV-2 Omicron XBB and BA.2.86/JN.1 lineages combining increased fitness and antibody evasion,” *Nat. Commun.* 2024, 15: 2254. doi: [10.1038/s41467-024-46490-7](https://doi.org/10.1038/s41467-024-46490-7) ✓
- “Neutralizing antibody (NAb) responses from vaccinees and BA.1/BA.2-infected individuals are markedly lower compared to BA.1, without major differences between variants.”
101. Powers JP et al., “Divergent pathogenetic outcomes in BALB/c mice following Omicron subvariant infection,” *Virus Res.* 2024, 341: 199319. doi: [10.1016/j.virusres.2024.199319](https://doi.org/10.1016/j.virusres.2024.199319) ✓
- “Using a live-virus nLuc neutralization assays and sera from mice vaccinated with an alum adjuvanted Wuhan S2P protein vaccine, we observed a significance decrease in neutralizing antibody titer against the three Omicron

- nLuc viruses as compared to SARS-CoV-2 D614G. Antibodies retained the most activity against BQ.1.1 nLuc, reflecting the reduced numbers of amino acid changes as compared with XBB.1 and XBB.1.5. Further reductions were observed with XBB.1 and XBB.1.5 with only 3 and 2 serum samples neutralizing above the limit of detection, respectively.”
102. Pušnik J et al., “Effect of XBB.1.5-adapted booster vaccination on the imprinting of SARS-CoV-2 immunity,” *npj Vaccines* 2024, 9: 231. doi: [10.1038/s41541-024-01023-7](https://doi.org/10.1038/s41541-024-01023-7) ✓
    - “Taken together our data support the previously observed imprinting by the original wild-type-based SARS-CoV-2 vaccines but also suggest that vaccination with XBB.1.5-adapted vaccine might help to withdraw antigenic imprinting in some individuals.”
  103. Pušnik J et al., “Vaccination impairs de novo immune response to omicron breakthrough infection, a precondition for the original antigenic sin,” *Nat. Commun.* 2024, 15: 3102. doi: [10.1038/s41467-024-47451-w](https://doi.org/10.1038/s41467-024-47451-w) ✓
    - “Our data demonstrate a robust humoral response in thrice-vaccinated individuals following omicron breakthrough which is a recall of vaccine-induced memory. The humoral and memory B cell responses against the altered regions of the omicron surface proteins are impaired.”
  104. Qu P et al., “Enhanced neutralization resistance of SARS-CoV-2 Omicron subvariants BQ.1, BQ.1.1, BA.4.6, BF.7, and BA.2.75.2,” *Cell Host Microb.* 2023, 31, 1: P9-17.E3. doi: [10.1016/j.chom.2022.11.012](https://doi.org/10.1016/j.chom.2022.11.012) ✓
    - “We also found that BA.4/5-wave patient sera exhibited weaker neutralization of BA.4/5 than of BA.2, which could be related to prior exposure to SARS-CoV-2 variant antigen biasing patient neutralizing antibody response to BA.4/5 infection.”
  105. Quandt J et al., “Omicron BA.1 breakthrough infection drives cross-variant neutralization and memory B cell formation against conserved epitopes,” *Sci. Immunol.* 2022, 7, 75. doi: [10.1126/sciimmunol.abq2427](https://doi.org/10.1126/sciimmunol.abq2427) ✓
    - “We report that Omicron BA.1 breakthrough infection in BNT162b2-vaccinated individuals resulted in strong neutralizing activity against Omicron BA.1, BA.2, and previous SARS-CoV-2 VOCs but not against the Omicron sublineages BA.4 and BA.5. BA.1 breakthrough infection induced a robust recall response, primarily expanding memory B (BMEM) cells against epitopes shared broadly among variants, rather than inducing BA.1-specific B cells... our data also suggest that the immunity in the early stage of Omicron BA.1 infection in vaccinated individuals is based on recognition of conserved epitopes and is narrowly focused on a small number of neutralizing sites that are not altered in Omicron BA.1 and BA.2. Such a narrow immune response bears a high risk that those few epitopes may be lost by acquisition of further alterations in the course

of the ongoing evolution of Omicron and may result in immune escape, as is being experienced with sublineages BA.2.12.1, BA.4, and BA.5.”

106. Regev-Yochay G et al., “Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron,” *N Eng J Med* 2022, 386, 14: 1377-1380. doi: [10.1056/NEJMc2202542](https://doi.org/10.1056/NEJMc2202542) ✓
- “Furthermore, we observed low vaccine efficacy against infections in health care workers, as well as relatively high viral loads suggesting that those who were infected were infectious. Thus, a fourth vaccination of healthy young health care workers may have only marginal benefits.”
107. Reynolds CJ et al., “Heterologous infection and vaccination shapes immunity against SARS-CoV-2 variants,” *Science* 2021, 375, 6577: 183-192. doi: [10.1126/science.abm0811](https://doi.org/10.1126/science.abm0811) ✓
- “Vaccine responses after infection were found to be less effective if the infection involved heterologous spike from a variant virus. Unfortunately, the N501Y spike mutation, found in many variants, seems to induce the regulatory T cell transcription factor FOXP3, indicating that the virus could subvert effective T cell function. Changes to antibody binding between variants also means that serology data using the Wuhan Hu-1 S1 receptor-binding domain sequence may not be a reliable measure of protection.”
108. Reynolds CJ et al., “Immune boosting by B.1.1.529 (Omicron) depends on previous SARS-CoV-2 exposure,” *Science* 2022, 377, 6603. doi: [10.1126/science.abq1841](https://doi.org/10.1126/science.abq1841) ✓
- “...imprinted patterns such as the specific combination of vaccination with infection during the first ancestral Wuhan Hu-1 wave followed by the B.1.1.529 (Omicron) wave require an additional term: ‘hybrid immune damping’... Notably, although B1.1.529 (Omicron) infection in triple-vaccinated previously uninfected individuals could indeed boost antibody, T cell, and MBC responses against other VOCs, responses to Omicron itself were reduced. This relatively poor immunogenicity against itself may help to explain why frequent B.1.1.529 (Omicron) reinfections with short time intervals between infections are proving a novel feature in this wave. It also concurs with observations that mRNA vaccination carrying the B.1.1.529 (Omicron) spike sequence (Omicron third-dose after ancestral sequence prime and boost) offers no protective advantage.”
109. Reynolds CJ et al., “Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose,” *Science* 2021, 372, 6549: 1418-1423. doi: [10.1126/science.abh1282](https://doi.org/10.1126/science.abh1282) ✓
- “Genotyping indicated that a genetic component underlies heterogeneity in immune responses to vaccine and to natural infection. After vaccination, naïve individuals developed antibody responses similar to those seen in naturally infected persons, but T cell responses were more limited and sometimes absent.”

110. Rodda LB et al., “Imprinted SARS-CoV-2-specific memory lymphocytes define hybrid immunity,” *Cell* 2022, 185, 9: P1588-1601.E14. doi: [10.1016/j.cell.2022.03.018](https://doi.org/10.1016/j.cell.2022.03.018) ✓
  - “SARS-CoV-2 infection prior to vaccination elicits a robust CD4+ T Th1/IFN- $\gamma$  response. Infection-induced Th1/IFN- $\gamma$  signature is not reproduced by three vaccinations.”
111. 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: P1025-1040.E14. doi: [10.1016/j.cell.2022.01.018](https://doi.org/10.1016/j.cell.2022.01.018) ✓
  - “Viral variant infection elicits variant-specific antibodies, but prior mRNA vaccination imprints serological responses toward Wuhan-Hu-1 rather than variant antigens.”
112. Rössler A et al., “Neutralization Profile after Recovery from SARS-CoV-2 Omicron Infection,” *N Engl J Med* 2022, 386, 18: 1764-1766. doi: [10.1056/NEJMc2201607](https://doi.org/10.1056/NEJMc2201607) ✓
  - “We found that neutralizing antibody titers against all the variants were high among vaccinated persons after omicron BA.1 breakthrough infection and among vaccinated or unvaccinated persons who had had previous infection with the wild-type, alpha, or delta variant before infection with the omicron BA.1 variant. Mean neutralizing antibody titers against the omicron BA.1 variant were lower than those against the other variants among previously vaccinated persons but were similar to those against the other variants among unvaccinated persons who had had infection with the wild-type, alpha, or delta variant before infection with the omicron BA.1 variant.”
113. Saade C et al., “BA.1 breakthrough infection elicits distinct antibody and memory B cell responses in vaccinated-only versus hybrid immunity individuals,” *iScience* 2025 28, 4: 111962. doi: [10.1016/j.isci.2025.111962](https://doi.org/10.1016/j.isci.2025.111962) ✓
  - “Regarding the humoral response against the N protein, an antigen not present in most vaccines, the effect of a breakthrough infection was significant in individuals with established hybrid immunity, compared to those with vaccination-induced immunity... These results would suggest that a single exposure to antigens other than the S protein, such as N, might not be sufficient to induce a robust immune response in previously vaccinated individuals.”
114. Sanchez-Senda B et al., “Neutralizing antibodies against SARS-CoV-2 variants of concern elicited by the Comirnaty COVID-19 vaccine in nursing home residents,” *Sci. Rep.* 2022, 12, 3788. doi: [10.1038/s41598-022-07849-2](https://doi.org/10.1038/s41598-022-07849-2)
  - “In summary, herein we show that neutralizing activity of sera against SARS-CoV-2 variants carrying critical escape mutations in the S gene is decreased relative to the ancestral strain in both qualitative and quantitative terms in nursing home residents recently vaccinated with the Comirnaty COVID-19 vaccine, most

- notably in those who were SARS-CoV-2 naïve prior to vaccination. Nevertheless, the fold reduction in NtAb activity in this population group was not significantly different from that seen in vaccinated younger controls.”
115. Selva KJ et al., “Preexisting immunity restricts mucosal antibody recognition of SARS-CoV-2 and Fc profiles during breakthrough infections,” *JCI Insight* 2023, 8, 18: e172470. doi: [10.1172/jci.insight.172470](https://doi.org/10.1172/jci.insight.172470) ✓
    - “IgG and FcγR engagement, but not IgA, responses to breakthrough COVID-19 variants were dampened and narrowed by increased preexisting vaccine-induced immunity against the ancestral strain.”
  116. Servellita V et al., “Neutralizing immunity in vaccine breakthrough infections from the SARS-CoV-2 Omicron and Delta variants,” *Cell* 2022, 185, 9: P1539-1548.E5. doi: [10.1016/j.cell.2022.03.019](https://doi.org/10.1016/j.cell.2022.03.019) ✓
    - “Among immunocompetent, unboosted patients, Delta breakthrough infections induced 10.8-fold higher titers against WT compared with Omicron (p = 0.037)... Following either Delta or Omicron breakthrough infection, limited variant-specific cross-neutralizing immunity was observed. These results suggest that Omicron breakthrough infections are less immunogenic than Delta, thus providing reduced protection against reinfection or infection from future variants.”
  117. Shen X et al., “SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral spike vaccines,” *Cell Host Microbe* 2021, 29, 4: P529-539.E3. doi: [10.1016/j.chom.2021.03.00](https://doi.org/10.1016/j.chom.2021.03.00) ✓
    - “The B.1.1.7 variant was neutralized by all vaccine sera, although with modestly diminished susceptibility compared to the D614G variant. A modest decrease in neutralization susceptibility was also seen with convalescent sera, although not to the same extent seen with vaccine sera.”
  118. Shrestha NK et al., “Effectiveness of the 2023–2024 Formulation of the COVID-19 Messenger RNA Vaccine,” *Clin. Infect. Dis.* 2024, 79, 2: 405-411. doi: [10.1093/cid/ciae132](https://doi.org/10.1093/cid/ciae132) ✓
    - “Risk of COVID-19 was lower among those previously infected with an XBB or more recent lineage and increased with the number of vaccine doses previously received.”
  119. Smith CP et al., “The Trajectory of Antibody Responses One Year Following SARS-CoV-2 Infection among Indigenous Individuals in the Southwest United States,” *Viruses* 2024, 16, 10: 1573. doi: [10.3390/v16101573](https://doi.org/10.3390/v16101573) ✓
    - “The peak antibody concentrations and resulting time to seroreversion were the highest for those with a prior history of vaccination and infection and the lowest for those with a prior history of vaccination but not infection. This is consistent with prior findings showing a blunted anti-N response to infection in people who

have been vaccinated and a faster time to seroreversion for anti-N compared to anti-S antibodies, likely resulting from vaccine-induced immune imprinting against the S protein, leading to decreased dissemination of the virus and partial inhibition of the immune response to the N protein.”

120. Sokol A et al., “SARS-CoV-2 Omicron BA.1 breakthrough infection drives late remodeling of the memory B cell repertoire in vaccinated individuals,” *Immunity* 2023, 56, 9: P2137-2151.E7. doi: [10.1016/j.immuni.2023.07.007](https://doi.org/10.1016/j.immuni.2023.07.007) ✓
  - “Here, we show that this imprinting was not limited to the early extrafollicular response but persisted over time, with very few BA.1-restricted naive B cell clones recruited in de novo GCs. High-affinity serum antibodies elicited during the primary response have recently been demonstrated to reduce the recruitment of naive B cells to GCs during secondary responses.”
121. Solforosi L et al., “Booster with Ad26.COV2.S or Omicron-adapted vaccine enhanced immunity and efficacy against SARS-CoV-2 Omicron in macaques,” *Nat. Commun.* 2023, 14, 1944. doi: [10.1038/s41467-023-37715-2](https://doi.org/10.1038/s41467-023-37715-2) ✓
  - “Based on the observation that the booster immunization mostly recalled cross-reactive S WA1/2020 and S Omicron BA.1 B cells, we speculate that de novo induction of neutralizing antibodies targeting key new epitopes in Omicron S is impaired in boosted animals, at least shortly after vaccination, likely mediated by an imprinting effect of the primary Ad26.COV2.S vaccination.”
122. Sonnleitner ST et al., “Decoding the transcriptome from bulk RNA of infection-naïve versus imprinted patients with SARS-CoV-2 Omicron B.1.1.529,” *Microbiol. Spectr.* 2025, 13, 8. doi: [10.1128/spectrum.02914-24](https://doi.org/10.1128/spectrum.02914-24) ✓
  - “We differentiated between infection-naïve individuals (Group A), individuals imprinted by prior SARS-CoV-2 infection (Group B), and individuals first imprinted by vaccination (Group C)... Our findings revealed significant transcriptomic differences between the study groups. Infection-naïve individuals exhibited the highest number of differentially expressed genes (1,526 DEGs), compared to 27 in previously infected individuals and only seven in vaccinated individuals... The most striking finding was that infection-naïve individuals exhibited a markedly stronger immune activation than both previously infected and vaccinated individuals, particularly in the expression of interferon-stimulated genes (ISGs). While previously infected and vaccinated individuals shared some transcriptional similarities, vaccinated individuals displayed a distinct transcriptional profile characterized by a pronounced downregulation of pathways related to DNA metabolism and cellular replication. These findings suggest that immune imprinting, particularly through vaccination, leads to an attenuated transcriptional response during acute infection with a reduced activation of innate immune pathways.”



123. Stamatos L et al., “mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection,” *Science* 2021, 372, 6549: 1413-1418. doi: [10.1126/science.abg9175](https://doi.org/10.1126/science.abg9175) ✓
  - “Vaccination elevated postinfection serum-neutralizing capacity approximately 1000-fold against Wuhan-Hu-1 and other strains, and serum neutralization against the variant B.1.351 was enhanced. Although responses were relatively muted against the variant, they still showed characteristic memory responses.”
124. Stankov MV et al., “Humoral and cellular immune responses following BNT162b2 XBB.1.5 vaccination,” *Lancet Infect Dis.* 2024, 24, 1: E1-E3. doi: [10.1016/S1473-3099\(23\)00690-4](https://doi.org/10.1016/S1473-3099(23)00690-4)
  - “... these data suggest cross-reactive MBC dominance even after multiple exposures to omicron spikes and underscore persistent immune imprinting.”
125. Suntronwong N et al., “Age associated SARS-CoV-2 immune responses provide insights into population immunity over four years since the COVID-19 pandemic,” *Sci. Rep.* 2025, 15: 23183. doi: [10.1038/s41598-025-05737-z](https://doi.org/10.1038/s41598-025-05737-z) ✓
  - “Among children aged 6 months–11 years, unvaccinated individuals exhibited significantly higher neutralizing activity against JN.1 than WT, whereas vaccinated children displayed comparable titers against both. Moreover, significantly higher neutralizing activity against WT was observed in adolescents (12–17 years) who received two or three vaccine doses and in adults (18–59 years) who received three doses compared to JN.1, indicating the WT-imprinted immunity in vaccinated individuals. In contrast, no significant differences in neutralizing antibody titers between WT and JN.1 were observed in adults (18–59 years) who received two or four doses and elderly participants (≥ 60 years), regardless of the number of vaccine doses. These findings suggest that infections with later SARS-CoV-2 variants enhance cross-reactive neutralization against early strains in unvaccinated individuals and mitigate WT-imprinted immunity in vaccinated individuals.”
126. Suntronwong N et al., “Neutralization of omicron subvariants and antigenic cartography following multiple COVID 19 vaccinations and repeated omicron non JN.1 or JN.1 infections,” *Sci. Rep.* 2025, 15, 1454. doi: [10.1038/s41598-024-84138-0](https://doi.org/10.1038/s41598-024-84138-0) ✓
  - “Neutralizing antibodies exhibited a narrow breadth against BA.5 and BA.2.75 and failed to neutralize BQ.1.1 and XBB lineages after three to five doses of the ancestral monovalent vaccine. Hybrid immunity elicited higher neutralizing titers than vaccination alone, but titers remained relatively low. A single omicron PVI elicited lower neutralization titers to all variants compared to wild-type (WT), indicating immunological imprinting.”
127. Szekely J et al., “Breakthrough SARS-CoV-2 Omicron Variant in Individuals Primed with Heterologous Vaccines Enhances Inhibition Performance of Neutralizing



Antibody to BA.2 Parental Lineage,” *Vaccines* 2023, 11, 7: 1230.

doi: [10.3390/vaccines11071230](https://doi.org/10.3390/vaccines11071230) ✓

- “Negative results for neutralizing antibody against both Omicron variants were observed in persons with antibody levels to wild-type ranging from 12.78–4679.94 BAU/mL. This observation indicates that the level of IgG antibody to wild-type does not correlate with the presence of effective neutralizing antibodies to Omicron variants.”

128. Tan CW et al., “Comparative neutralisation profile of SARS-CoV-2 omicron subvariants BA.2.75 and BA.5,” *Lancet Microbe* 2022, 3, 13: E898.

doi: [10.1016/S2666-5247\(22\)00220-8](https://doi.org/10.1016/S2666-5247(22)00220-8)

- “Despite an overall improvement in neutralising antibody titres following mRNA booster vaccination or an omicron breakthrough infection, there was a significant loss of neutralising antibody potency against omicron subvariants compared with ancestral SARS-CoV-2, with BA.5 being the most effective subvariant at escaping neutralising antibodies. Relative to geometric mean pVNT50s against BA.2, titres against BA.2.75 were 1·1 to 1·4 times lower and those against BA.5 were 2·2 to 3·8 times lower in individuals who had received three doses of mRNA vaccine or recovered from an omicron breakthrough infection.”

129. Tan CW et al., “Distinctive serotypes of SARS-related coronaviruses defined by convalescent sera from unvaccinated individuals,” *hLife* 2023, 1, 1: 26-34. doi:

[10.1016/j.hlife.2023.07.002](https://doi.org/10.1016/j.hlife.2023.07.002) ✓

- “Unlike viruses such as measles and polioviruses that have little to no change in their sensitivity to vaccine-induced immunity for decades, the high structure plasticity of the coronavirus spike protein and the vast diversity of animal coronaviruses make the complete eradication an impossible task with current vaccines. Antigenic maps of vaccinated sera showed a greater extent of antigenic differences between the circulating Omicron variants and SARS-CoV-2, implying that pre-existing SARS-CoV-2 immunity is insufficient to prevent current and future infections. In addition, because of the original antigenic sin, breakthrough infections do not increase NAb epitope diversity but instead further promote the RBD to evolve convergently.”

130. Tarke A et al., “SARS-CoV-2 breakthrough infections enhance T cell response magnitude, breadth, and epitope repertoire,” *Cell Rep Med.* 2024, 5, 6: 101583. doi:

[10.1016/j.xcrm.2024.101583](https://doi.org/10.1016/j.xcrm.2024.101583) ✓

- “In conclusion, BMem responses after a variant BTI showed considerable imprinting by the ancestral sequence in the vaccines, consistent with other reports.”

131. Tavasolian F et al., “HLA, Immune Response, and Susceptibility to COVID-19,” *Front. Immunol.* 2021, 11 (Viral Immunology). doi: [10.3389/fimmu.2020.601886](https://doi.org/10.3389/fimmu.2020.601886) ✓

- “Thus, an inadequate immune response to the mutated virus due to the OAS may generate a significant number of sub-neutralizing cross-reactive antibodies that enhance inflammation and may paradoxically promote virus entry into host cells. The intracellular presence of the pathogen activates a pyroptosis mechanism with the subsequent release of danger-associated molecular patterns (DAMPs) to trigger additional inflammatory cells, which in response release a great number of cytokines; which may be the basis of the ‘cytokine storm’ identified in severe cases of COVID-19.”
132. Tian S et al., “Neutralization against emerging Omicron subvariants after SARS-CoV-2 reinfection,” *J Infect* 2023, 87, 6: 598-601. doi: [10.1016/j.jinf.2023.09.013](https://doi.org/10.1016/j.jinf.2023.09.013) ✓
- “XBB subvariants escape the immunity induced by primary infection or reinfection. SARS-CoV-2 reinfection can alleviate WT-vaccination-induced immune imprinting. G339H, G446S, N460K, and F486S/P mutations are essential for immune escape.”
133. Torresi J and MA Edeling, “Immune imprinting of SARS-CoV-2 responses: changing first immune impressions,” *mSphere* 2024. doi: [10.1128/msphere.00758-23](https://doi.org/10.1128/msphere.00758-23) ✓
- “Although infection with viral variants produces variant-specific antibody responses, prior vaccination with WuH-1 S containing COVID-19 mRNA vaccines has been shown to imprint antibody responses toward the ancestral virus rather than to variant antigens. So prior mRNA vaccination with a WuH-1 vaccine followed by Alpha or Delta infection results in stronger antibody response toward WuH-1 virus and decreased antibody responses to viral variant epitopes compared to unvaccinated individuals infected with these variant viruses. In contrast, individuals infected with Alpha or Delta variants and with no history of vaccination develop antibodies with stronger binding to Alpha or Delta variant receptor binding domain (RBDs) compared to WuH-1 RBD.”
134. Tortorici MA et al., “Persistent immune imprinting occurs after vaccination with the COVID-19 XBB.1.5 mRNA booster in humans,” *Immunity* 2024, 57, 4: P904-911.E4. doi: [10.1016/j.immuni.2024.02.016](https://doi.org/10.1016/j.immuni.2024.02.016) ✓
- “Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) Omicron breakthrough infections and bivalent COVID-19 vaccination primarily recall cross-reactive memory B cells induced by prior Wuhan-Hu-1 spike mRNA vaccination rather than priming Omicron-specific naive B cells... The finding that administration of an XBB.1.5 S booster elicited higher plasma neutralizing activity against Wuhan-Hu-1/D614G S VSV (vaccine mismatched) relative to XBB.1.5 S VSV (vaccine matched) at both time points examined is a serological indication of immune imprinting... These data suggest that XBB.1.5 S vaccination boosts cross-reactive plasma antibody titers previously elicited by Wuhan-Hu-1 S exposure, which are also binding to and neutralizing XBB.1.5 and other variants instead of inducing *de novo* antibody responses against XBB.1.5 S.”

135. Tseng HF et al., “Effectiveness of mRNA-1273 vaccination against SARS-CoV-2 omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, and BA.5,” *Nat. Commun.* 2023, 14, 189. doi: [10.1038/s41467-023-35815-7](https://doi.org/10.1038/s41467-023-35815-7) ✓
  - “Similarly, four-dose VE against infection with BA.2, BA.2.12.1, BA.4, and BA.5 was moderate, and was only approximately 35% against BA.5. The four-dose VE against these subvariants was short-lived, disappearing beyond 90 days after the fourth dose... Taken together, these findings appear to be consistent with those of a recent study that found that the primary benefit of booster vaccines is augmentation of neutralizing antibodies without a strong effect on cellular immunity beyond that already induced by the primary vaccination series.”
136. Uraki R et al., “Humoral immune evasion of the omicron subvariants BQ.1.1 and XBB,” *Lancet Infect Dis.* 2023, 23, 1: 30-32. doi: [10.1016/S1473-3099\(22\)00816-7](https://doi.org/10.1016/S1473-3099(22)00816-7)
  - “The FRNT50 geometric mean titres against BQ.1.1 and XBB were 21·1-fold and 21·6-fold lower, respectively, than those against the ancestral strain (SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo). In addition, the geometric mean titres against BQ.1.1 and XBB were 1·7-fold and 2·6-fold lower, respectively, than those against BA.5 and BA.2. Similar results were obtained with samples from individuals who received four doses of mRNA vaccine; the FRNT50 geometric mean titres against BQ.1.1 and XBB were 43·3-fold and 51·6-fold lower, respectively, than those against the ancestral strain, and were 3·7-fold and 6·2-fold lower than those against BA.5 and BA.2, respectively. In contrast, most of the samples from vaccinees with BA.2 breakthrough infection neutralised BQ.1.1 and XBB; however, the FRNT50 geometric mean titres against BQ.1.1 and XBB were 35·2-fold and 61·7-fold lower, respectively, than those against the ancestral strain, and were 4·9-fold and 15·1-fold lower than those against BA.5 and BA.2, respectively.”
137. Voss WN et al., “Hybrid immunity to SARS-CoV-2 arises from serological recall of IgG antibodies distinctly imprinted by infection or vaccination,” *Cell Rep Med.* 2024, 5, 8: 101668. doi: [10.1016/j.xcrm.2024.101668](https://doi.org/10.1016/j.xcrm.2024.101668) ✓
  - “Infection primarily triggers S2/N-terminal domain (NTD)-reactive antibodies, whereas vaccination mainly induces anti-receptor-binding domain (RBD) antibodies. This imprint persists after secondary exposures wherein >60% of ensuing hybrid immunity derives from the original IgG pool.”
138. Walls AC et al., “SARS-CoV-2 breakthrough infections elicit potent, broad, and durable neutralizing antibody responses,” *Cell* 2022, 185, 5: P872-880.E3. doi: [10.1016/j.cell.2022.01.011](https://doi.org/10.1016/j.cell.2022.01.011) ✓
  - “Here, we demonstrate that breakthrough infections induce serum-binding and -neutralizing antibody responses that are markedly more potent, durable, and resilient to spike mutations observed in variants than those in subjects who received only 2 doses of vaccine.”

139. Wang K et al., “Memory B cell repertoire from triple vaccinees against diverse SARS-CoV-2 variants,” *Nature* 2022, 603: 919-925. doi: [10.1038/s41586-022-04466-x](https://doi.org/10.1038/s41586-022-04466-x) ✓
  - “Here we examined whether sera from individuals who received two or three doses of inactivated SARS-CoV-2 vaccine could neutralize authentic Omicron. The seroconversion rates of neutralizing antibodies were 3.3% (2 out of 60) and 95% (57 out of 60) for individuals who had received 2 and 3 doses of vaccine, respectively. For recipients of three vaccine doses, the geometric mean neutralization antibody titre for Omicron was 16.5-fold lower than for the ancestral virus (254).”
140. Wang M et al., “Original Antigenic Sin on Antibody Response in SARS-CoV-2 Infection,” *Infect. Dis. Immun.* 2024, 4, 3: 132-137. doi: [10.1097/ID9.0000000000000125](https://doi.org/10.1097/ID9.0000000000000125) ✓
  - “OAS is a barrier to the generation of variant-specific antibodies against the current vaccines against rapidly evolving SARS-CoV-2. New vaccine strategies that promote nAb responses to mutated RBD epitopes and avoid boosting imprinted B cell immune responses are required in the future.”
141. Wang Q et al., “Deep immunological imprinting due to the ancestral spike in the current bivalent COVID-19 vaccine,” *Cell Rep Med.* 2023, 4, 11: 101258. doi: [10.1016/j.xcrm.2023.101258](https://doi.org/10.1016/j.xcrm.2023.101258) ✓
  - “Monovalent and BA.5 bivalent mRNA vaccine boosters induced similar antibody responses. BA.5 breakthrough infections yielded higher neutralizing activity than vaccine boosters. The ancestral spike in BA.5 bivalent vaccines caused deep immunological imprinting. Bivalent boosters did not yield superior antibody responses due to immune imprinting.”
142. Wang Z et al., “Ancestral SARS-CoV-2 immune imprinting persists on RBD but not NTD after sequential Omicron infections,” *iScience*, 2025, 28, 1: 111557. doi: [10.1016/j.isci.2024.111557](https://doi.org/10.1016/j.isci.2024.111557) ✓
  - “Plasma neutralizing antibody titers against ancestral SARS-CoV-2 and variants indicate that immune imprinting is not consistently induced by inactivated or recombinant protein vaccines. However, once robustly induced, immune imprinting is not countered by successive Omicron challenges.”
143. Weber T et al., “Enhanced SARS-CoV-2 humoral immunity following breakthrough infection builds upon the preexisting memory B cell pool,” *Sci. Immunol.* 2023, 8, 89. doi: [10.1126/sciimmunol.adk5845](https://doi.org/10.1126/sciimmunol.adk5845) ✓
  - “However, the SARS-CoV-2-specific memory B cell pool was significantly expanded only in individuals with a breakthrough infection after third dose. This was due to selection of pre-existing Omicron-neutralizing memory B cells that potently neutralized a broad range of variants that arose after initial vaccination. These findings demonstrate that SARS-CoV-2 immunity is imprinted during early antigen exposure and adapts to new variants.”

144. Wei D et al., “Sequential reinfection with Omicron variants elicits broader neutralizing antibody profiles in booster vaccinees and reduces the duration of viral shedding,” *J Med Virol* 2023, 95, 10: e29151. doi: [10.1002/jmv.29151](https://doi.org/10.1002/jmv.29151) ✓
- “Sequential reinfection with Omicron variants elicits broader and high-titer variant-specific neutralizing antibody profiles against Omicron variants. It could also dampen the hyperactivation of WT-specific neutralization induced by previous WT-based vaccination.”
145. Wheatley AK et al., “Immune imprinting and SARS-CoV-2 vaccine design,” *Trend Immunol.* 2021, 42, 11: 956-959. doi: [10.1016/j.it.2021.09.001](https://doi.org/10.1016/j.it.2021.09.001) ✓
- “We hypothesize that updated vaccines against SARS-CoV-2 variants might primarily boost ‘imprinted’ immune responses to conserved regions of the Spike protein to the detriment of new neutralizing responses to antigenically altered sites within new variants.”
146. Wrynla XH et al., “Immune imprinting and vaccine interval determine antibody responses to monovalent XBB.1.5 COVID-19 vaccination,” *Commun. Med.* 2025, 5: 182. doi: [10.1038/s43856-025-00898-4](https://doi.org/10.1038/s43856-025-00898-4) ✓
- “Our findings indicate that immune imprinting continues to affect humoral immunity elicited by the XBB.1.5 vaccine.”
147. Yamamoto S et al., “Omicron BA.1 neutralizing antibody response following Delta breakthrough infection compared with booster vaccination of BNT162b2,” *BMC Infect. Dis.* 2023, 23, 282. doi: [10.1186/s12879-023-08272-2](https://doi.org/10.1186/s12879-023-08272-2) ✓
- “Breakthrough infection cases showed marked increases in NAb titers against Wild-type (4.1-fold) and Delta (5.5-fold), and 64% had detectable NAb against Omicron BA.1 at follow-up, although the NAb against Omicron after breakthrough infection was 6.7- and 5.2-fold lower than Wild-type and Delta, respectively. The increase was apparent only in symptomatic cases and as high as in the third vaccine recipients...”
148. Yang Y et al., “Comparative neutralization profiles of naive and breakthrough infections with Delta, Omicron BA.1 and BA.2 variants of SARS-CoV-2,” *Signal Transduct Target Ther* 2022, 7: 316. doi: [10.1038/s41392-022-01166-w](https://doi.org/10.1038/s41392-022-01166-w) ✓
- “Our results for the naive and breakthrough infections with Delta and BA.1 variants showed that limited cross-neutralizing responses were induced, especially for the currently dominant BA.4/5 variant. This is consistent with previous findings that vaccination with BA.1 specific mRNA vaccine alone or infection with BA.1 provided poor cross-protection, and that BA.4/5 variant could significantly escape the immune response induced by BA.1 breakthrough infection. These observations might result from that BA.1 breakthrough infection

predominantly recalls humoral immune memory against the WT SARS-CoV-2 spike protein...”

149. Yao D et al., “Antibody Responses in SARS-CoV-2-Exposed and/or Vaccinated Individuals Target Conserved Epitopes from Multiple CoV-2 Antigens,” *Int. J. Mol. Sci.* 2024, 25, 18: 9814. doi: [10.3390/ijms25189814](https://doi.org/10.3390/ijms25189814) ✓
- “The majority of the current vaccine efforts against SARS-CoV-2 are limited by targeting the S-protein; however, it is important to consider N and M proteins as potential targets that will allow us to establish cross-reactive responses. Our results demonstrate that mRNA-vaccinated, AstraZeneca-vaccinated, and unvaccinated donors generate N- and M-specific IgG antibody titers. However, within the vaccinated groups, those with known COVID-19 infections showed significantly higher N-specific IgG titer.”
150. Yisimayi A et al. “Repeated Omicron exposures override ancestral SARS-CoV-2 immune imprinting,” *Nature* 2024, 625: 148-156. doi: [10.1038/s41586-023-06753-7](https://doi.org/10.1038/s41586-023-06753-7) ✓
- “... immune imprinting induced by vaccination based on the ancestral (hereafter referred to as WT) strain would compromise the antibody response to Omicron-based boosters... in humans, repeated Omicron infections could alleviate WT vaccination-induced immune imprinting and generate broad neutralization responses in both plasma and nasal mucosa.”
151. Yuan F and MH Bluth, “Novel Strategies for Developing Next-Generation Vaccines to Combat Infectious Viral Diseases,” *Vaccines* 2025, 13, 9: 979. doi: [10.3390/vaccines13090979](https://doi.org/10.3390/vaccines13090979) ✓
- “We have seen from COVID-19 vaccinations that boosting with a heterologous spike protein did not induce broader neutralizing antibodies against the variant; instead, the produced antibodies mostly targeted the parental strain of SARS-CoV-2. Immune imprinting, also called ‘original antigenic sin’, refers to the phenomenon where prior infections and vaccinations alter future patterns of antibody response when boosted or infected with a divergent variant strain. During booster immunizations, immune imprinting is influenced by the competitive dynamics between memory B cells and naïve B cells. Memory B cells, having higher-affinity receptors from prior exposure, expand rapidly and dominate the response, which can limit the activation of naïve B cells and shape the specificity and breadth of the resulting antibody response. Omicron breakthrough infections or boosting with Omicron antigens elicit strong anti-spike IgG responses against the Wuhan-hu-1 strain, while there is low neutralizing activity against the Omicron lineages, indicating imprinted immunity. The COVID-19 bivalent vaccine covering BA.4/BA.5 strains elicits markedly lower neutralizing antibodies against BA.2.75.2, BQ.1.1, and XBB variants than against the Wuhan-hu-1 strain. The drifted variants share multiple epitopes in the immunodominant head region, and boosting with variants recalls



- the memory B cells targeting conserved epitopes, resulting in robust induction of non-neutralizing antibodies against the variant, while the critical neutralizing epitopes of the variant only activate the naïve B cell repertoire.”
152. Zelm MCV, “Immune memory to SARS-CoV-2 Omicron BA.1 breakthrough infections: To change the vaccine or not?” *Sci. Immunol.* 2022, 7, 74. doi: [10.1126/sciimmunol.abq5901](https://doi.org/10.1126/sciimmunol.abq5901) ✓
    - “Analysis of memory B cell responses to Spike antigen after Omicron BA.1 breakthrough infections suggests that ‘original antigenic sin’ is in play.”
  153. Zhang L et al., “Neutralisation sensitivity of SARS-CoV-2 lineages EG.5.1 and XBB.2.3,” *Lancet Infect Dis.* 2023, 23, 10: e391 - e392. doi: [10.1016/S1473-3099\(23\)00547-9](https://doi.org/10.1016/S1473-3099(23)00547-9) ✓
    - “Finally, we investigated neutralisation by plasma from quadruple vaccinated people collected 2 months (cohort one) or 4–8 (cohort two) months after vaccination, or from people who were vaccinated three to four times with breakthrough infection (cohort three). Particles bearing XBB S proteins were generally less well neutralised as compared with B.1pp (15–194-fold reduction). No major differences were observed between neutralisation of XBB.1.5pp, XBB.1.16pp, and XBB.2.3pp. However, it is noteworthy that EG.5.1pp evaded neutralisation by plasma collected for cohorts one and three with higher efficiency than XBB.2.3pp, XBB.1.5pp, and XBB.1.16pp.”
  154. Zhou Z et al., “Immune Imprinting and Implications for COVID-19,” *Vaccines* 2023, 11, 4: 875. doi: [10.3390/vaccines11040875](https://doi.org/10.3390/vaccines11040875) ✓
    - “It is plausible that imprinted memory B cells induced by the original mRNA vaccine dominate the response to the booster vaccine. Thus, based on the small-scale preclinical study, at least in the short term, boosting with Omicron-mRNA vaccine has not yet presented big advantage over the original mRNA vaccine regarding the induction of protective NAbS against variant as well as control of viral replication after challenge, and immune imprinting seemingly involved in damping the B cell response to variant epitopes.”
  155. Zhu A et al., “Antigenic characterization of SARS-CoV-2 Omicron subvariants XBB.1.5, BQ.1, BQ.1.1, BF.7 and BA.2.75.2,” *Signal Transduct Target Ther* 2023 8: 125. doi: [10.1038/s41392-023-01391-x](https://doi.org/10.1038/s41392-023-01391-x) ✓
    - “Similar trends were observed for both vaccine- and infection-induced plasma, regardless of the vaccination status, enhanced neutralization resistance of SARS-CoV-2 Omicron subvariants BF.7, BQ.1, BQ.1.1, BA.2.75.2, XBB and XBB.1.5 was observed when compared with their parent BA.2 and BA.4/5. Multiple vaccination strategies... failed to elicit high neutralizing antibody titer against the newly emerged Omicron subvariant...”



156. Zuo F et al., “Heterologous inactivated virus/mRNA vaccination response to BF.7, BQ.1.1, and XBB.1,” *Lancet Reg Health West Pac.* 2023, 33: 100762.  
doi: [10.1016/j.lanwpc.2023.100762](https://doi.org/10.1016/j.lanwpc.2023.100762)
- “Due to humoral immune imprinting... the bivalent vaccine booster and hybrid immunity may not provide sufficient protection against emerging Omicron subvariants.”

## VI. SARS-CoV2 “vaccine” and viral variant research library

*Compiled by Dr. Steven Hatfill, MD, et al. Last updated November 18, 2025.*

✓ = peer-reviewed

In addition to the pathogenicity, distribution, and long persistence of the “vaccine”-produced spike protein, research also links COVID “vaccination” to the evolution of vaccine-resistant viral variants. The following collection of **(83/85 peer-reviewed ✓)** papers shows that by failing to prevent infection or transmission, “vaccines” applied strong selective pressure to the fast-mutating SARS-CoV2 virus, quickly giving rise to “vaccine”-resistant variants. Many authors specifically identify their inability to induce sterilizing or near-sterilizing immunity at mucosal surfaces, where infection occurs, as an integral flaw enabling the emergence of variants. It is noteworthy that variants emerged in temporal and geographic proximity to “vaccine” clinical trials or mass “vaccination”:

1. The Alpha variant was first identified in the county of Kent in [southeast England](#) in November 2020. Phase I/II clinical trials for AstraZeneca’s AZD1222 (ChAdOx1 nCoV-19) adenovector “vaccine” enrolled over 1,000 subjects in [southern England](#) in April 2020, and thousands more in the phase III trial, May-December 2020.
2. The Delta variant was first identified in [Maharashtra](#) state, India, in October 2020. Phase II/III clinical trials for the Covidshield adenovector “vaccine” based on AstraZeneca’s AZD1222 enrolled 1,600 subjects at 14 hospital centers, including eight in [Maharashtra](#) state, from July-October 2020.
3. The Omicron variant was first identified in [Gauteng](#), South Africa, in November 2021, following an intense [provincial “vaccination” campaign](#) from August-October.

Any suggestion that variants can be addressed by simply administering more, updated “vaccines” is insupportable in view of the abundant evidence of “vaccine” harms collected here and elsewhere. Public health officials have already conceded that “chasing variants” is futile due to the injections’ inability to prevent infection or transmission. In January 2023, Dr. Peter Marks, then director of FDA’s Center for Biologics Evaluation and Research, [wrote](#): “Continuing along the current path of... variant-specific vaccine boosters is inadequate as a long-term strategy for addressing COVID-19... Simply updating the existing vaccine constructs with new variant sequences or even making trivalent or quadrivalent vaccines... is not likely to provide the depth and breadth of protection needed to interrupt viral transmission...” FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) member Dr. Paul Offit [told Time](#): “The experience of the past year has taught us that chasing these Omicron variants with a bivalent vaccine is a losing game.”

This compilation originated with Dr. Hatfill’s contribution to [TOXIC SHOT: Facing the Dangers of the COVID “Vaccines”](#) (Chapter 5: Debunking CDC’s Bad Science)

## ANNOTATED REFERENCES (83/85 peer-reviewed ✓)

1. Ahmed MN et al., “The impact of pre-existing immunity on the emergence of within-host immune-escape mutations in Omicron lineages,” *J. Gen. Virol.* 2025, 106, 5. doi: [10.1099/jgv.0.002108](https://doi.org/10.1099/jgv.0.002108) ✓
  - “Non-lineage mutations (39, 33 and 25 in BA.2\*, BA.4\* and BA.5\* lineages, respectively) were detected, some showing higher incidence in vaccinated individuals. Six mutations detected at sub-consensus levels at antigenic sites suggest increased immune pressure on the spike protein in vaccinated individuals. Four high-prevalence antigenic mutations, absent from global GISAID sequences, were identified. Although within-host diversity did not significantly differ between vaccination statuses, detected mutations suggest that vaccine-induced immunity may influence within-host mutation patterns.”
2. Al-Khatib HA et al., “Comparative analysis of within-host diversity among vaccinated COVID-19 patients infected with different SARS-CoV-2 variants,” *iScience*, 2022, 25, 11: 105438. doi: [10.1016/j.isci.2022.105438](https://doi.org/10.1016/j.isci.2022.105438) ✓
  - “Overall, the relatively higher intra-host diversity among vaccinated individuals and the detection of immune-escape mutations, despite being rare, suggest a potential vaccine-induced immune pressure in vaccinated individuals.”
3. Atlani-Duault L et al., “Immune evasion means we need a new COVID-19 social contract,” *Lancet Public Health* 2021, 6, 4: E199-E200. doi: [10.1016/S2468-2667\(21\)00036-0](https://doi.org/10.1016/S2468-2667(21)00036-0)
  - “... the dynamics of natural or vaccinal collective immunity in the regions where these variants emerged might have placed substantial pressure on the viral ecosystem, facilitating the emergence of a variant with enhanced transmissibility... This virological game changer has numerous consequences, not only for vaccines and treatment, but also for prevention and control strategies. The fervently awaited end of this global health crisis might be continually postponed, as new variants emerge and immune evasion reduces vaccination effectiveness in the short and medium term. Hence, it is time to abandon fear-based approaches based on seemingly haphazard stop-start generalised confinement as the main response to the pandemic; approaches which expect citizens to wait patiently until intensive care units are re-enforced, full vaccination is achieved, and herd immunity is reached.”
4. Berkhout B and E Herrera-Carrillo, “SARS-CoV-2 Evolution: On the Sudden Appearance of the Omicron Variant,” *J. Virol.* 2022, 96, 7. doi: [10.1128/jvi.00090-22](https://doi.org/10.1128/jvi.00090-22) ✓
  - “The most compelling evidence for this scenario of regular Darwinian evolution actually comes from inspection of the genetic changes, which reveals a profound preference for mutations that change the amino acid composition of the spike protein: 30 nonsilent changes versus 1 silent mutation.”

5. Brand M and Can Kesmir, “Evolution of SARS-CoV-2-specific CD4+ T cell epitopes,” *Immunogenet.* 2023, 75: 283-293. doi: [10.1007/s00251-023-01295-8](https://doi.org/10.1007/s00251-023-01295-8) ✓
  - “In this study, we aim to study spike (CD4+) T cell epitopes in silico and investigate the effect of vaccine selection pressure on epitope conservation and mutations in VOCs... we demonstrated in silico that selection induced by vaccination worldwide has marginal effects on SARS-CoV-2 spike-specific CD4 T cell responses, while this might be not at all the case for B cell responses. Therefore, it might be worthwhile to consider inclusion of other less mutating SARS-CoV-2 proteins such as ORF3, NSP3, and the N protein in a future vaccine.”
6. Brandolini M et al., “Omicron Sub-Lineage BA.5 and Recombinant XBB Evasion from Antibody Neutralisation in BNT162b2 Vaccine Recipients,” *Microorganisms* 2023, 11, 1: 191. doi: [10.3390/microorganisms11010191](https://doi.org/10.3390/microorganisms11010191) ✓
  - “These evolutionary characteristics have prompted intensively debated questions and speculations, primarily regarding how vaccines will contribute to the emergence of new variants. Moreover, as many vaccines are based on the ancestral Spike protein gene sequence, they elicit a relatively ‘narrow-spectrum’ immune response, which can be easily and rapidly eroded by viral evolution. In fact, there is emerging evidence that the high mutation rate of the S gene constitutes a breeding ground for immune escape mechanisms, reducing the neutralising potential of antibodies produced in vaccinated subjects.”
7. Bushman M et al., “Population impact of SARS-CoV-2 variants with enhanced transmissibility and/or partial immune escape,” *Cell* 2021, 184, 26: P6229-6242.E18. doi: [10.1016/j.cell.2021.11.026](https://doi.org/10.1016/j.cell.2021.11.026) ✓
  - “Here, we use a mathematical model to simulate the dynamics of wild-type and variant strains of SARS-CoV-2 in the context of vaccine rollout and nonpharmaceutical interventions. We show that variants with enhanced transmissibility frequently increase epidemic severity, whereas those with partial immune escape either fail to spread widely or primarily cause reinfections and breakthrough infections. However, when these phenotypes are combined, a variant can continue spreading even as immunity builds up in the population, limiting the impact of vaccination and exacerbating the epidemic.”
8. Cao Y et al., “Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution,” *Nature* 2023, 614: 521–529. doi: [10.1038/s41586-022-05644-7](https://doi.org/10.1038/s41586-022-05644-7) ✓
  - “In this work, we showed that due to immune imprinting, our humoral immune repertoire is not effectively diversified by infection with new Omicron variants. The immune pressure on the RBD becomes increasingly concentrated and promotes convergent evolution, explaining the observed sudden acceleration of SARS-CoV-2 RBD evolution and the convergence pattern. Although this study

only examines inactivated vaccines, immune imprinting is also observed in those receiving mRNA vaccines.”

9. Carabelli AM et al., “SARS-CoV-2 variant biology: immune escape, transmission and fitness,” *Nat Rev Microbiol* 2023, 21, 162–177. doi: [10.1038/s41579-022-00841-7](https://doi.org/10.1038/s41579-022-00841-7) ✓
  - “The increased virus fitness associated with VOCs is the result of a complex interplay of virus biology in the context of changing human immunity due to both vaccination and prior infection.”
10. Case JB et al., “SARS-CoV-2: The Interplay Between Evolution and Host Immunity,” *Annu. Rev. Immunol.* 2025, 43: 29-55. doi: [10.1146/annurev-immunol-083122-043054](https://doi.org/10.1146/annurev-immunol-083122-043054) ✓
  - “Evidence suggests that SARS-CoV-2 evolution initially selected variants with increased transmissibility but currently is driven by immune escape... Since 2022, subvariants descending from BA.2 have exhibited convergent evolution to escape from parental vaccines. Initially, to combat this, bivalent boosters incorporating Omicron variants were developed for the mRNA and recombinant protein subunit vaccines. However, effectiveness against symptomatic infection by subsequent Omicron strains was relatively low... Current vaccination approaches, which elicit systemic immunity through intramuscular administration, may allow infection and transmission cycles to continue due to the relatively low levels of mucosal immunity that are induced. As a result, SARS-CoV-2 evolution, and the emergence of variants with increased fitness, will likely continue until therapeutic or vaccine-induced sterilizing immunity can be achieved.”
11. Chaguza C et al., “Rapid emergence of SARS-CoV-2 Omicron variant is associated with an infection advantage over Delta in vaccinated persons,” *Clin. Transl. Rep.* 2022, 3, 5: P325-334.E4. doi: [10.1016/j.medj.2022.03.010](https://doi.org/10.1016/j.medj.2022.03.010) ✓
  - “As population immunity to SARS-CoV-2 increases through infections and vaccination, selection for variants that are partially resistant to the immune response, in particular neutralizing antibodies, should also increase... We hypothesized that the rapid emergence and spread of the SARS-CoV-2 Omicron variant was partly due to its increased ability to evade immunity from prior infection and/or vaccination. Using a study population seeking outpatient testing when Omicron and Delta were overall relatively equal among infections, we found that Omicron has a relatively higher propensity to cause infections in COVID-19-vaccinated persons.”
12. Chang MR et al., “Analysis of a SARS-CoV-2 convalescent cohort identified a common strategy for escape of vaccine-induced anti-RBD antibodies by Beta and Omicron variants,” *eBioMedicine* 2022, 80: 104025. doi: [10.1016/j.ebiom.2022.104025](https://doi.org/10.1016/j.ebiom.2022.104025) ✓

- “Structural analysis of the Beta and Omicron RBDs reveal a shared immune escape strategy involving residues K417-E484-N501 that is exploited by these variants of concern... Through mutations of the K417-E484-N501 triad, SARS-CoV-2 has evolved to evade neutralization by the class I/II anti-RBD antibody fraction of hybrid immunity plasma as the polyclonal antibody response post-vaccination shows limitations in the ability to solve the structural requirements to bind the mutant RBDs.”
13. Cocherie T et al., “Epidemiology and Characteristics of SARS-CoV-2 Variants of Concern: The Impacts of the Spike Mutations,” *Microorganisms* 2023, 11, 1: 30. doi: [10.3390/microorganisms11010030](https://doi.org/10.3390/microorganisms11010030) ✓
    - “Following the spread of lineage B.1, new lineages emerged in a context of selection pressure related to the extension of vaccination and post-infectious immunization. These lineages have each selected specific sets of mutations, in an asynchronous and geographically isolated manner, which supports the hypothesis of a convergent antigenic evolution, reinforced by the discovery of some of their mutations in independent lineages.”
  14. Collier DA et al., “Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies,” *Nature* 2021, 593: 136–141. doi: [10.1038/s41586-021-03412-7](https://doi.org/10.1038/s41586-021-03412-7) ✓
    - “Taken together, the presence of multiple escape mutations in the NTD is supportive of the hypothesis that this region of the spike, in addition to the RBM, is also under immune pressure... Our data suggest that vaccine escape by the virus of current spike-directed vaccines designed against the Wuhan-1 strain will be inevitable...”
  15. Day T et al., “Pathogen evolution during vaccination campaigns,” *PLoS Biol* 2022, 20, 9: e3001804. doi: [10.1371/journal.pbio.3001804](https://doi.org/10.1371/journal.pbio.3001804) ✓
    - “...vaccine-driven evolution has tended to occur in other pathogens when either the benefits of prophylaxis are small (e.g., the vaccine does not sufficiently suppress pathogen replication below transmissible levels) or when they target a small number of pathogen epitopes. Data increasingly suggest that at least the first of these is true for SARS-CoV-2 and currently deployed vaccines.”
  16. Dijokaite-Guraliuc A et al., “Rapid escape of new SARS-CoV-2 Omicron variants from BA.2-directed antibody responses,” *Cell Rep.* 2023, 42, 2: 112271. doi: [10.1016/j.celrep.2023.112271](https://doi.org/10.1016/j.celrep.2023.112271) ✓
    - “Overall, in line with the observations on the set of mAbs described above, there were large reductions in neutralization titers against most BA.2 sub-lineages, particularly BA.2.75.2, BA.2.3.20, BQ.1, and XBB, suggesting that they have been selected to escape pre-existing immunity to vaccines or earlier waves of SARS-CoV-2 infection... It is likely that evolution of SARS-CoV-2 Omicron is now primarily driven by extreme pressure to escape antibody responses in

- vaccinated and/or naturally infected individuals, with compensatory mutations to maintain or increase ACE2 affinity.”
17. Du P et al., “Defining the serotypes of SARS-CoV-2 subvariants up to December, 2024,” *Lancet* 2025, 6, 8: 101124. doi: [10.1016/j.lanmic.2025.101124](https://doi.org/10.1016/j.lanmic.2025.101124) ✓
    - “However, the substantial reduction in cross-reactivity between KP.2/KP.3 and previous serotypes underscores the existence of the continuous antigenic drift that will lead to new serotypes in the future. Although XBB.1.5 monovalent vaccines maintain effectiveness against JN.1, their effectiveness might be reduced because of the ongoing evolution of serotype VI subvariants under the immune pressure of XBB-based vaccines.”
  18. Duerr R et al., “Dominance of Alpha and Iota variants in SARS-CoV-2 vaccine breakthrough infections in New York City,” *J Clin Invest* 2021, 131, 18: e152702. doi: [10.1172/JCI152702](https://doi.org/10.1172/JCI152702) ✓
    - “Despite the overall effectiveness of vaccination, our full spike mutation analysis revealed a broad set of spike mutations (n = 23) to be elevated in the vaccine breakthrough group. The analysis indicates that adaptive selection is in progress that may subsequently come into full effect.”
  19. Duerr R et al., “Selective adaptation of SARS-CoV-2 Omicron under booster vaccine pressure: a multicentre observational study,” *eBioMedicine* 2023, 97: 104843. doi: [10.1016/j.ebiom.2023.104843](https://doi.org/10.1016/j.ebiom.2023.104843) ✓
    - “Booster shots are required to cope with gaps in immunity. Their discriminative immune pressure contributes to their effectiveness but also requires monitoring of selective viral adaptation processes. Omicron BA.2 and BA.5 had a selective advantage under booster vaccination pressure, contributing to the evolution of BA.2 and BA.5 sublineages and recombinant forms that predominate in 2023.”
  20. Fang FF and Pei-Yong Shi, “Omicron: a drug developer’s perspective,” *Emerg. Microbes & Infect.* 2022, 11, 1. doi: [10.1080/22221751.2021.2023330](https://doi.org/10.1080/22221751.2021.2023330) ✓
    - “Omicron has revealed to us that SARS-CoV-2 has the potential to go beyond the protective threshold provided by vaccines and antibodies. Playing catchup to SARS-CoV-2 selects for more resistant and transmissible variants and may not be successful in the long run.”
  21. Federico M, “Biological and Immune Responses to Current Anti-SARS-CoV-2 mRNA Vaccines beyond Anti-Spike Antibody Production,” *J. Immunol. Res.* 2022. doi: [10.1155/2022/4028577](https://doi.org/10.1155/2022/4028577) ✓
    - “Virus replication in the context of suboptimal antiviral action of vaccine-induced antibodies can lead to emergence of resistant virus quasiespecies. In the SARS-CoV-2 case, this process could have contributed to the selection of VoCs, whose rapid emergence paralleled mass vaccination. This phenomenon can affect the anticipated outcomes from additional vaccine cycles. In fact, it is well



- known that repeated vaccinations against pathogen evolving mutants like SARS-CoV-2 have the risk to meet with the phenomenon referred to as ‘original antigenic sin.’”
22. Focosi D et al., “Convergent Evolution in SARS-CoV-2 Spike Creates a Variant Soup from Which New COVID-19 Waves Emerge,” *Int. J. Mol. Sci.* 2023, 24, 3: 2264. doi: [10.3390/ijms24032264](https://doi.org/10.3390/ijms24032264) ✓
    - “The most likely reason for this convergence is the selective pressure exerted by previous infection- or vaccine-elicited immunity... The combined action of increasing cumulative viral loads in the ‘human culture medium’ and such selective pressures has led to an unprecedented increase in viral diversification in 2022.”
  23. Garcia-Beltran WF et al., “Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity,” *Cell* 2021, 184, 9: p2372-2383.e9. doi: [10.1016/j.cell.2021.03.013](https://doi.org/10.1016/j.cell.2021.03.013) ✓
    - “... we found that B.1.351 variants exhibited remarkable resistance to neutralization, largely due to three mutations in RBD but with measurable contribution from non-RBD mutations. The magnitude of the effect is such that B.1.351 strains escaped neutralizing vaccine responses as effectively as distantly related coronaviruses.”
  24. Gayvert K et al., “Evolutionary trajectory of SARS-CoV-2 genome shifts during widespread vaccination and emergence of Omicron variant,” *npj Viruses* 2023, 1: 5. doi: [10.1038/s44298-023-00007-z](https://doi.org/10.1038/s44298-023-00007-z) ✓
    - “Our analysis revealed that during the first year of the pandemic (2020 to 2021), the SARS-CoV-2 genome was subject to strong conservation... However, we observed a sharp increase in the diversification of the RBD during 2021 (8.1% of sites under diversifying pressure up to 2022), indicating selective pressures that promote the accumulation of mutations. This period coincided with broad viral infection and adoption of vaccination worldwide, and we observed the acquisition of mutations that later defined the Omicron lineages in independent SARS-CoV-2 strains...”
  25. Ghmire D et al., “Structural Plasticity and Immune Evasion of SARS-CoV-2 Spike Variants,” *Viruses* 2022, 14, 6: 1255. doi: [10.3390/v14061255](https://doi.org/10.3390/v14061255) ✓
    - “SARS-CoV-2 viruses are under increased selection pressure from the vaccines, therapeutic approaches, and the host immune system. Whole-genome sequencing technology has allowed identifying the emergence of different SARS-CoV-2 variants... These variants are more transmissible and possibly more pathogenic and immune-evasive. They carry accumulated mutations in the S protein. The resulting amino acid substitutions in S can impact the binding capacity to hACE2 and antibody recognition, therefore imposing constant challenges in current vaccine and therapeutic regimes.”

26. Gobeil SMC et al., “Effect of natural mutations of SARS-CoV-2 on spike structure, conformation, and antigenicity,” *Science* 2021, 373, 6555. doi: [10.1126/science.abi6226](https://doi.org/10.1126/science.abi6226) ✓
- “Although many of the currently circulating variants of interest/concern likely arose from some combination of genetic drift, host adaptation, and immune evasion, the virus will increasingly experience pressure from vaccine-elicited antibody responses.”
27. Gupta S et al., “Analysis of SARS-CoV-2 genome evolutionary patterns,” *Microbiol. Spectr.* 2024, 12, 2. doi: [10.1128/spectrum.02654-23](https://doi.org/10.1128/spectrum.02654-23) ✓
- “In this study, SARS-CoV-2 genome sequences were collected from seven countries in the period January 2020–December 2022. The sequences were classified into three phases, namely, pre-vaccination, post-vaccination, and recent period. Comparison was performed between these phases based on parameters like mutation rates, selection pressure (dN/dS ratio), and transition to transversion ratios (Ti/Tv). Similar comparisons were performed among SARS-CoV-2 variants. Statistical significance was tested using Graphpad unpaired t-test. The analysis showed an increase in the percent genomic mutation rates post-vaccination and in recent periods across all countries from the pre-vaccination sequences. Mutation rates were highest in NSP3, S, N, and NSP12b before and increased further after vaccination. NSP4 showed the largest change in mutation rates after vaccination. The dN/dS ratios showed purifying selection that shifted toward neutral selection after vaccination.”
28. Habib MT et al., “Natural selection shapes the evolution of SARS-CoV-2 Omicron in Bangladesh,” *Front. Genet.* 2023, 14 (Computational Genomics). doi: [10.3389/fgene.2023.1220906](https://doi.org/10.3389/fgene.2023.1220906) ✓
- “We found evidence of adaptive evolution within the spike (S) gene of SARS-CoV-2 Omicron isolated from Bangladesh. In total, 22 codon sites of the S gene displayed a signature of positive selection... Moreover, the lack of selection pressure on the S gene representing SARS-CoV-2 Delta from Bangladesh indicates a possible correlation between vaccination and adaptive evolution.”
29. Hamburg M and GA Poland, “The time is now for committed and comprehensive action to attain more broadly protective coronavirus vaccines: The coronavirus vaccines R&D roadmap,” *Vaccine* 2023, 41, 16: 2645-2647. doi: [10.1016/j.vaccine.2023.02.053](https://doi.org/10.1016/j.vaccine.2023.02.053) ✓
- “... we continue to face continued circulation and evolution of SARS-CoV-2 viruses that mutate to evade immune responses among hosts who have partial or waning vaccine coverage, further exacerbating the situation.”
30. Han W et al., “Predicting the antigenic evolution of SARS-COV-2 with deep learning,” *Nat Comm* 2023, 14: 3478. doi: [10.1038/s41467-023-39199-6](https://doi.org/10.1038/s41467-023-39199-6) ✓

- “We hypothesized that under high immune pressure, the virus would tend to escape the antibody neutralization over a short-term time scale, and therefore the forecasting problem transforms into a search problem: starting from an initial sequence, it searches for a variant sequence within some edit distance range that has an improved antibody escape potential without losing much ACE2-binding ability... These findings verify our assumptions: under the immune selection pressure, the virus evolves in the direction of immune escape, and our model can capture the antibody escape potential of the viral variants.”
31. Harvey WT et al., “SARS-CoV-2 variants, spike mutations and immune escape,” *Nat Rev Microbiol* 2021, 19: 409–424. doi: [10.1038/s41579-021-00573-0](https://doi.org/10.1038/s41579-021-00573-0) ✓
    - “Given that therapeutics (vaccines and antibody-based therapies) target mainly the SARS-CoV-2 spike protein, the selection pressures that favour the emergence of new variants carrying immune escape mutations generated in chronic infection will be similar to those selecting for mutations that allow reinfections within the wider population.”
  32. He P et al., “SARS-CoV-2 Delta and Omicron variants evade population antibody response by mutations in a single spike epitope,” *Nat. Microbiol.* 2022, 7: 1635–1649. doi: [10.1038/s41564-022-01235-4](https://doi.org/10.1038/s41564-022-01235-4) ✓
    - “Owing to immune pressure induced by natural infection and vaccination, numerous SARS-CoV-2 variants have emerged, these variants encoding spike proteins with substituted amino acids that function to evade antibody neutralization... Here we identify an important role for VH1-69 HCDR2 in anti-SARS-CoV-2 immunity... These mutation ‘hot spots’ should be continuously monitored and future studies should address the potential pathogenic consequences of VH1-69 antibody evasion by SARS-CoV-2.”
  33. Jacob JJ et al., “Evolutionary Tracking of SARS-CoV-2 Genetic Variants Highlights an Intricate Balance of Stabilizing and Destabilizing Mutations,” *mBio* 2021, 12, 4. doi: [10.1128/mbio.01188-21](https://doi.org/10.1128/mbio.01188-21) ✓
    - “As all three candidate vaccines encode RBD or the part of spike protein as antigens, the viral population is expected to try and escape by altering the positioning of the respective antigens under vaccine-induced selection pressure.”
  34. Jankowiak M et al., “Inferring selection effects in SARS-CoV-2 with Bayesian Viral Allele Selection,” *PLoS Genet.* 2022, doi: [10.1371/journal.pgen.1010540](https://doi.org/10.1371/journal.pgen.1010540) ✓
    - “... we conduct an analysis that allows for vaccination-dependent selection effects and find tantalizing evidence that S:N501Y exhibits vaccination-dependent differential fitness... The elevated contribution of S-gene mutations (notably in the RBD) over non-S-gene mutations starting around November 2021 is apparent. Collectively these two results suggest that immune escape has become an increasingly prominent factor in SARS-CoV-2 evolution over time,

likely a result of rising rates of convalescent and vaccine-induced immunity to Spike.”

35. Jena D et al., “Impact of vaccination on SARS-CoV-2 evolution and immune escape variants,” *Vaccine* 2024, 42, 21: [10.1016/j.vaccine.2024.07.054](https://doi.org/10.1016/j.vaccine.2024.07.054) ✓
  - “Our comparative analysis revealed a significant higher incidence of intra-host single nucleotides variants (iSNVs) in vaccinated cases compared to unvaccinated ones (p value<0.0001). Furthermore, we have found that specific mutational processes, including APOBEC (C > T) mediated and ADAR1 (A > G) mediated mutations, were found more prevalent in vaccinated cases. Vaccinated cases exhibited higher accumulation of nonsynonymous mutation than unvaccinated cases... Our findings suggest that vaccine plays an important role in the evolution of the virus genome.”
36. Jian F et al., “Viral evolution prediction identifies broadly neutralizing antibodies to existing and prospective SARS-CoV-2 variants,” *Nat. Microbiol.* 2025, 10: 2003-2017. doi: [10.1038/s41564-025-02030-7](https://doi.org/10.1038/s41564-025-02030-7) ✓
  - “Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to rapidly evolve to evade immunity induced by natural infection and vaccination, resulting in highly evasive variant lineages such as XBB.1.5 and JN.1. These variants are continuously accumulating mutations at key receptor-binding domain (RBD) antigenic sites, such as L455, F456 and A475, which may substantially alter their antigenicity and further escape neutralizing antibodies (NAbs) elicited by repeated vaccination and infection.”
37. Kennedy DA and AF Read, “Monitor for COVID-19 vaccine resistance evolution during clinical trials,” *PLoS Biol.* 2020, 18, 11: e3001000. doi: [10.1371/journal.pbio.3001000](https://doi.org/10.1371/journal.pbio.3001000) ✓
  - “To avoid being caught off guard by the evolution of vaccine resistance, standard samples from clinical trials can be repurposed to assess the risk of resistance evolution even before a vaccine is licensed.”
38. Konishi T, “Mutations in SARS-CoV-2 are on the increase against the acquired immunity,” *PLoS One* 2022, 17, 7: e0271305. doi: [10.1371/journal.pone.0271305](https://doi.org/10.1371/journal.pone.0271305) ✓
  - “In Omicron, there was a high density of S mutations suggesting that there was selection pressure to avoid the acquired immunity imparted by monovalent vaccines... These findings suggest that the early mRNA vaccine has lost its effectiveness. Accordingly, the sixth peak in Japan is becoming extremely high without subsiding, which can be due to dependency of the government only on the vaccines.”
39. Koyoma T et al., “Evasion of Vaccine-Induced Humoral Immunity by Emerging Sub-Variants of SARS-CoV-2,” *Future Microbiol.* 2022, 17, 6: 417-424. doi: [10.2217/fmb-2022-0025](https://doi.org/10.2217/fmb-2022-0025) ✓

- “... the selection pressure exerted by vaccines might pave the way for other escape mutants in the near future.”
40. Kumar N et al., “Bayesian Molecular Dating Analyses Combined with Mutational Profiling Suggest an Independent Origin and Evolution of SARS-CoV-2 Omicron BA.1 and BA.2 Sub-Lineages,” *Viruses* 2022, 14, 12: 2764. doi: [10.3390/v14122764](https://doi.org/10.3390/v14122764) ✓
- “Nonetheless, in the event of the emergence of multiple new mutations in the Omicron’s spike protein, which are quite distinct in the BA.1 and BA.2 sub-lineages, as well as their estimated separate most recent common ancestor, it may be more plausible to conclude that a combination of RBD- and NTD-directed classes of antibody therapeutics at sub-optimal doses in COVID-19 patients or optimal doses in an immunocompromised patient or waned vaccine-induced immunity may have provided a conducive environment to accumulate multiple mutations in Omicron’s spike protein.”
41. Kumar SW et al., “Vaccine-elicited immune pressure and SARS-CoV-2 mutational dynamics in breakthrough infections,” *Gene Rep.* 2024, 35: 101899. doi: [10.1016/j.genrep.2024.101899](https://doi.org/10.1016/j.genrep.2024.101899) ✓
- “Vaccinated individuals exhibit significantly higher mutation rates, including immune escape mutations... Selection pressure may drive viral mutations for enhanced immune evasion.”
42. Lewnard JA et al., “Increased vaccine sensitivity of an emerging SARS-CoV-2 variant,” *Nat Commun* 2023, 14: 3854. doi: [10.1038/s41467-023-39567-2](https://doi.org/10.1038/s41467-023-39567-2) ✓
- “Immunological and evolutionary factors driving this apparent bifurcation in evasion of vaccine-derived and infection-derived responses for XBB/XBB.1.5 merit further investigation. Notably, vaccinations available in the US (mRNA-1273, BNT162b2, Ad.26.COV2.S, and NVX-CoV2373) target only the SARS-CoV-2 spike antigen. In contrast, infection with SARS-CoV-2 induces responses against an array of SARS-CoV-2 antigens, some of which may be independently associated with protection.”
43. Li X, “Omicron: Call for updated vaccines,” *J. Med. Virol.* 2022, 94, 4: 1261-1263. doi: [10.1002/jmv.27530](https://doi.org/10.1002/jmv.27530) ✓
- “The Omicron SARS-CoV-2 variant was potentially generated from a chronically infected COVID-19 patient vaccinated with an messenger RNA (mRNA)- or non-mRNA-based vaccine, offering the opportunity for the virus to evolve and mutate to evade the body's immune response. To understand the significance of this SARS-CoV-2 variant and what it means for the global response to the pandemic, vaccinologists should systematically evaluate the role of mRNA- and non-mRNA-based vaccines in the generation of novel SARS-CoV-2 variants, including variants of concerns (VOCs) and interest (VOIs), that occur via breakthrough vaccine-elicited immunity.”

44. Lobinska G et al., “Evolution of resistance to COVID-19 vaccination with dynamic social distancing,” *Nat. Hum. Behav.* 2022, 6, 193-206. doi: [10.1038/s41562-021-01281-8](https://doi.org/10.1038/s41562-021-01281-8) ✓
- “What policy would minimize the chance of emergence of vaccine-resistant strains? On one hand, policymakers can vary the extent of social distancing imposed and the regimes of vaccine administration. The critical biological parameters, on the other hand, include the infectivity of the various strains and the rate of mutation of the virus that may ultimately lead to the emergence of a resistant strain. Here we introduce a mathematical approach that examines various combinations of these parameters.”
45. Lomoio U et al., “SARS-CoV-2 protein structure and sequence mutations: Evolutionary analysis and effects on virus variants,” *PLoS One* 2023, 18, 7: e0283400. doi: [10.1371/journal.pone.0283400](https://doi.org/10.1371/journal.pone.0283400) ✓
- “We explore patterns of changes in a temporal dimension and compare the cumulative distribution of vaccination with the characteristics of the variant. Although we cannot infer any causality regarding vaccination driving the evolution, we should note that the presence of vaccinations in a timeline is located in the middle of the first variants of SARS-CoV-2 and Omicron. Considering also the clinical characteristics of Omicron in terms of vaccine escape and neutralization of immune response, we can assume that the effect of all Omicron changes may be related to the structural changes also revealed by the above-reported measures.”
46. López-Cortés GI et al., “The Spike Protein of SARS-CoV-2 Is Adapting Because of Selective Pressures,” *Vaccines* 2022, 10, 6: 864. doi: [10.3390/vaccines10060864](https://doi.org/10.3390/vaccines10060864) ✓
- “Our results hint that selective pressures are induced by mass vaccination throughout the world and by the persistence of recurrent infections in immunosuppressed individuals, who did not eliminate the infection and ended up facilitating the selection of viruses whose characteristics are different from the previous VOCs, less pathogenic but with higher transmissibility.”
47. Lugano D et al., “Characterization of SARS-CoV-2 intrahost genetic evolution in vaccinated and non-vaccinated patients from the Kenyan population,” *J. Virol.* 2025, 99, 6. doi: [10.1128/jvi.00482-25](https://doi.org/10.1128/jvi.00482-25) ✓
- “Interestingly, we observed that between the transmission waves, some of the most prominent changes were seen during Delta, IW4, and Omicron variants. This was of interest, as it coincided with the timeline in which vaccination started in Kenya.”
48. Luo R et al., “SARS-CoV-2 biology and variants: anticipation of viral evolution and what needs to be done,” *Environ Microbiol* 2021, 23, 5: 2339-2363. doi: [10.1111/1462-2920.15487](https://doi.org/10.1111/1462-2920.15487) ✓



- “Part of the consideration in determining containment measures is the rationale that vaccination will soon stop transmission and allow a return to normality. However, vaccines themselves represent a selection pressure for evolution of vaccine-resistant variants, so the coupling of a policy of permitting high levels of transmission/virus multiplication during vaccine roll-out with the expectation that vaccines will deal with the pandemic, is unrealistic.”
49. Magazine N et al., “Mutations and Evolution of the SARS-CoV-2 Spike Protein,” *Viruses* 2022, 14, 3): 640. doi: [10.3390/v14030640](https://doi.org/10.3390/v14030640) ✓
- “Taken together with the fact that many of these mutations occur within the Omicron variant (which appeared only after vaccinations became widely distributed), it is possible that resistance to neutralizing antibodies (particularly those found in postvaccinated sera) targeting the NTD play a large role in the positive selection for SARS-CoV-2... Mutations within the S protein of the circulating variants of SARS-CoV-2 are increasing at a significant rate and are likely to occur more often as selective pressures from host immunity gained in previous infections and/or vaccinations continue to drive rapid evolution.”
50. Mahroum N et al., “Vaccine-induced strain replacement: theory and real-life implications,” *Future Microbiol.* 2024, 19, 11: 1017-1026. doi: [10.1080/17460913.2024.2345003](https://doi.org/10.1080/17460913.2024.2345003) ✓
- “... increasing fitness of nonvaccine strains and metabolic shifts in the subtypes have been described. Classical examples include pneumococcal infections and viral diseases, such as the human papilloma virus... The recent SARS-CoV-2 virus responsible for the COVID-19 pandemic has been correlated to the vaccine-induced pathogen strain replacement.”
51. Martin DP et al., “Selection Analysis Identifies Clusters of Unusual Mutational Changes in Omicron Lineage BA.1 That Likely Impact Spike Function,” *Mol Biol Evol* 2022, 39, 4: msac061. doi: [10.1093/molbev/msac061](https://doi.org/10.1093/molbev/msac061) ✓
- “Given the evident epidemic growth advantages of Omicron overall previously known SARS-CoV-2 lineages, it is crucial to determine both how such complex and highly adaptive mutation constellations were assembled within the Omicron S-gene, and why, despite unprecedented global genomic surveillance efforts, the early stages of this assembly process went completely undetected.”
52. McLeod DV and S Gandon, “Effects of epistasis and recombination between vaccine-escape and virulence alleles on the dynamics of pathogen adaptation,” *Nat Ecol Evol* 2022, 6: 786–793. doi: [10.1038/s41559-022-01709-y](https://doi.org/10.1038/s41559-022-01709-y) ✓
- “We show that vaccines blocking infection, reducing transmission and/or increasing clearance generate positive epistasis between the vaccine-escape and virulence alleles, favouring strains that carry both mutations, whereas vaccines reducing virulence mortality generate negative epistasis, favouring strains that carry either mutation but not both.”



53. Meganck RM et al., "SARS-CoV-2 variant of concern fitness and adaptation in primary human airway epithelia," *Cell Rep.* 2024, 43, 4: 114076. doi: [10.1016/j.celrep.2024.114076](https://doi.org/10.1016/j.celrep.2024.114076) ✓
- "... the Omicron variant emerged in November of 2021, at which point ~4 billion people are believed to have been vaccinated and more were likely to have been previously infected. The greater level of population immunity likely constituted a selective pressure on the virus. The newly emerged Omicron BA.1 strains contained a greater proportion of viral mutations located in the spike protein, the major antigenic target of SARS-CoV-2 adaptive immune responses, as compared to previous variants."
54. Messali S et al., "Emergence of S gene-based quasispecies explains an optimal adaptation of Omicron BA.5 subvariant in the immunocompetent vaccinated human host," *J Med Virol.* 2023, 95, 1: e28167. doi: [10.1002/jmv.28167](https://doi.org/10.1002/jmv.28167) ✓
- "The low frequency of quasispecies observed in BA.2.3- and BA.5-infected patients supports the hypothesis that these omicron sub-lineages are adapted to vaccine-elicited immune responses."
55. Mussò N et al., "SARS-CoV-2's high rate of genetic mutation under immune selective pressure: from oropharyngeal B.1.1.7 to intrapulmonary B.1.533 in a vaccinated patient," *Int. J. Infect. Dis.* 2022, 118: 169-172. doi: [10.1016/j.ijid.2022.02.044](https://doi.org/10.1016/j.ijid.2022.02.044) ✓
- "The immune reaction was a combination of vaccine and immune response after infection with SARS-CoV-2, but the presence of antibodies did not lead to the disruption of the viral RNA before this could cause pulmonary infection; on the contrary, it accelerated the normal process of 'intra-host specific rearrangement,' as shown by the presence of a new intra-pulmonary lineage characterized by 5 worldwide low-expressed SNPs..."
56. Nabel KA et al., "Structural basis for continued antibody evasion by the SARS-CoV-2 receptor binding domain," *Science* 2021, 375, 6578. doi: [10.1126/science.abc6251](https://doi.org/10.1126/science.abc6251) ✓
- "As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replicates under selective pressure from natural and vaccine-induced immunity, variants of concern (VOCs) continue to emerge. Through adaptive evolution, these variants acquire mutations in the spike protein receptor binding domain (RBD) that binds the cellular receptor angiotensin-converting enzyme 2 (ACE2)... We find that accumulation of large numbers of RBD mutations is facilitated by structural plasticity at the RBD-ACE2 interface and further erodes the activity of therapeutic antibodies and serum from vaccine recipients. Furthermore, acquisition of an N-linked glycan on the SARS-CoV-2 RBD is an additional neutralization escape pathway that should be closely monitored during viral antigenic drift."

57. Oliviera JR et al., “Immunodominant antibody responses directed to SARS-CoV-2 hotspot mutation sites and risk of immune escape,” *Front. Immunol.* 2023, 13 (Viral Immunology). doi: [10.3389/fimmu.2022.1010105](https://doi.org/10.3389/fimmu.2022.1010105) ✓
- “Our results showed that amongst convalescents a more focused response, with fewer peptides being recognized, was associated with higher neutralization titers. We reason that immune pressure following vaccination contributed to epitope spreading and likely surge of omicron that presents several mutations at RBD and the capacity of escaping antibody neutralization.”
58. Ovchinnikov V and M Karplus, “Phenomenological Modeling of Antibody Response from Vaccine Strain Composition,” *Antibodies (Basel)* 2025, 14, 1: 6. doi: [10.3390/antib14010006](https://doi.org/10.3390/antib14010006) ✓
- “However, mutations in the coronavirus spike protein, compounded by high transmission rates and selective evolutionary pressure, exerted by vaccine-induced antibodies, caused the emergence of viral ‘escape’ variants, against which the antibodies induced by the standard prime-boost vaccination regimen had much reduced efficacy, e.g., 67–70% against, e.g., the Omicron variant. Such levels of efficacy are lower than the 80% requirement for herd immunity based on a conservative  $R_0$  estimate of 5.”
59. Patel M et al., “SARS-CoV-2 Alchemy: Understanding the dynamics of age, vaccination, and geography in the evolution of SARS-CoV-2 in India,” *PLOS Negl. Trop. Dis.* 2025. doi: [10.1371/journal.pntd.0012918](https://doi.org/10.1371/journal.pntd.0012918) ✓
- “The analysis also revealed a significant surge in unique substitutions across all age groups during the vaccination period, with substitution rates remaining elevated even after widespread vaccination, compared to pre-vaccination levels. This trend supports the virus’s adaptive response to heightened immune pressures from vaccination, as observed through the increased prevalence of substitutions in important regions of SARS-CoV-2 genome like ORF1ab and Spike, potentially contributing to immune escape and transmissibility.”
60. Peng S et al., “Evolving fitness and immune escape: a retrospective analysis of SARS-CoV-2 spike protein (2020-2024) using protein language model,” *Front. Immunol.* 2025, 16 (Viral Immunology). doi: [10.3389/fimmu.2025.1576414](https://doi.org/10.3389/fimmu.2025.1576414) ✓
- “In summary, comparison with the null model demonstrates that the increases in Fitness and IEI of SARS-CoV-2 S protein sequences are the result of selective evolution rather than random effects from neutral mutations. The distribution of real sequences significantly deviates from the null model expectations, particularly in data-rich regions such as globally and North America, indicating that selective pressures (e.g., immune pressure and environmental factors) have shaped the virus’s evolutionary trajectory... Furthermore, the universality of immune selection pressure, such as the immune escape properties of JN.1, aligns with findings that immune-driven evolution is a global phenomenon, further supporting the global relevance of our conclusions... Notably, despite

- increasing global vaccination coverage, the virus's IEI continues to rise. This highlights the high adaptability of SARS-CoV-2 under immune pressure and its capacity to accumulate new mutations to evade immune responses.”
61. Planas D et al., “Distinct evolution of SARS-CoV-2 Omicron XBB and BA.2.86/JN.1 lineages combining increased fitness and antibody evasion,” *Nat. Commun.* 2024, 15: 2254. doi: [10.1038/s41467-024-46490-7](https://doi.org/10.1038/s41467-024-46490-7) ✓
    - “The variants are closely related and carry an additional and limited set of mutations in the spike corresponding to a stepwise accumulation of changes. Convergent evolution may have been associated with this process... This convergent evolution is likely due to a similar selective pressure exerted by imprinted or hybrid immunity triggered by Omicron infection and/or vaccination.”
  62. Rolland M and PB Gilbert, “Sieve analysis to understand how SARS-CoV-2 diversity can impact vaccine protection,” *PLoS Pathog.* 2021, 17, 3: e1009406. doi: [10.1371/journal.ppat.1009406](https://doi.org/10.1371/journal.ppat.1009406) ✓
    - “The recent spread of outlier variants emphasizes the need to rapidly track the impact of vaccine-induced pressure on SARS-CoV-2 evolution... The variants B.1.1.7 (originally identified in the UK), B.1.351 (originally identified in South Africa), and P.1 (originally identified in Brazil) have more mutations than what was expected at this time in the pandemic, and a large fraction of these mutations are in the Spike, indicating likely selection pressure behind their emergence... . The selective pressure exerted by the vaccine together with limited vaccine coverage in the population has the potential to open ecological niches where rare variants with potentially unfavorable resistance profiles could outcompete circulating viruses.”
  63. Rouzine IM and G Rozhnova, “Evolutionary implications of SARS-CoV-2 vaccination for the future design of vaccination strategies,” *Commun. Med* 2023, 3, 86. doi: [10.1038/s43856-023-00320-x](https://doi.org/10.1038/s43856-023-00320-x) ✓
    - “Mass vaccination, as we show below, might increase this pressure and accelerate SARS-CoV-2 evolution in spike epitopes compared to natural infection.”
  64. Ruan W et al., “SARS-CoV-2 serotyping based on spike antigenicity and its implications for host immune evasion,” *EBioMedicine* 2025, 114: 105634. doi: [10.1016/j.ebiom.2025.105634](https://doi.org/10.1016/j.ebiom.2025.105634) ✓
    - “As SARS-CoV-2 continues to spread and evolve, new variants/sub-variants emerge, raising concerns about vaccine-induced immune escape. Here, we conducted a systematic analysis of the serology and immunogenicity of major circulating variants/sub-variants of SARS-CoV-2 since the outbreak.”
  65. Sanyaolu A et al., “SARS-CoV-2 Omicron variant (B.1.1.529): A concern with immune escape,” *World J Virol* 2022, 11, 3:137–143. doi: [10.5501/wjv.v11.i3.137](https://doi.org/10.5501/wjv.v11.i3.137) ✓

- “Finally, it has been proposed that natural selection can arise as a result of mutations that increase viral infectivity, antibody resistance, and vaccine breakthrough. Evolutionary descent of the Omicron lineages showed that mutations arose under selection pressure due to antibodies elicited by infection, vaccination, or both, in the human population on a large scale.”
66. Servellita V et al., “Predominance of antibody-resistant SARS-CoV-2 variants in vaccine breakthrough cases from the San Francisco Bay Area, California,” *Nat Microbiol* 2022, 7, 277-288. doi: [10.1038/s41564-021-01041-4](https://doi.org/10.1038/s41564-021-01041-4) ✓
- “The predominance of immune-evading variants among post-vaccination cases indicates possible selective pressure for antibody-resistant escape variants circulating locally over time in the vaccinated population.”
67. Tan CW et al., “SARS-CoV-2 Omicron variant emerged under immune selection,” *Nat Microbiol* 2022, 7: 1756–1761. doi: [10.1038/s41564-022-01246-1](https://doi.org/10.1038/s41564-022-01246-1) ✓
- “Using the same serum panels, we demonstrated even more potent NAb escape of mRNA vaccine-induced neutralizing antibodies by Omicron subvariants BA.2.11 and BA.5 with the additional L452R mutation and L452R/F486V/R493Q mutations, respectively... We propose that the SARS-CoV-2 Omicron variant emerged under immune selection imposed during 2 years of virus transmission in humans.”
68. Tang X et al., “Adaptive Evolution of the Spike Protein in Coronaviruses,” *Mol. Biol. Evol.* 2023, 40, 4: msad089. doi: [10.1093/molbev/msad089](https://doi.org/10.1093/molbev/msad089) ✓
- “... the widespread use of vaccines may impose strong selective pressure on the full-length S protein or RBD of SARS-CoV-2, potentially accelerating the emergence and spread of new variants with mutations that confer immune escape. Here, we show that the S gene, particularly the S1 region, has undergone substantial positive selection in both SARS-CoV-2 and other coronaviruses. Although S1-NTD exhibits positive selection in all four coronavirus genera, positive selection was primarily detected in S1-CTD (RBD) in the ongoing evolution of SARS-CoV-2, possibly owing to the change in host settings and the widespread natural infection and SARS-CoV-2 vaccination in humans.”
69. Tuekprakhon A et al., “Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum,” *Cell* 2022, 185, 14: P2422-2433.E13. doi: [10.1016/j.cell.2022.06.005](https://doi.org/10.1016/j.cell.2022.06.005) ✓
- “Although mutations in the VoC are spread throughout S, there are particular hotspots in the NTD and RBD, exactly where potent neutralizing antibodies bind, and they are likely being driven by escape from the antibody response following natural infection or vaccination.”
70. van Dorp CH et al., “Estimating the strength of selection for new SARS-CoV-2 variants,” *Nat Commun* 2021, 12: 7239. doi: [10.1038/s41467-021-27369-3](https://doi.org/10.1038/s41467-021-27369-3) ✓

- “... the gradual rollout of vaccination programs globally is changing the immunological landscape, possibly leading to the emergence of escape strains that are partially or fully resistant to existing vaccines... Integrating molecular epidemiology surveillance into SARS-CoV-2 pipelines is essential for not only monitoring the emergence of new strains, but for establishing an early warning system to monitor for escape mutations in the era of vaccine rollout.”
71. van Dorp L et al., “How Does Large-Scale Genomic Analysis Shape Our Understanding of COVID Variants in Real Time?” *Cell Syst.* 2021, 12, 2: 109-111. doi: [10.1016/j.cels.2021.01.004](https://doi.org/10.1016/j.cels.2021.01.004) ✓
- “With studies of endemic coronaviruses suggesting some propensity for antigenic evolution, and with the new selective pressure of mass vaccination, in all likelihood there will be more lineages to flag. Assessment of the factors underlying the success of such lineages will be vital to the pandemic response moving forward.”
72. Vandana D et al., “Emerging SARS-CoV-2 Omicron Sub-Variants JN.1 and NB.1.8.1: Genomic Evolution, Implications, and Public Health Perspectives for a variant under monitoring (VuM),” *ESMED MRA* 2025, 13, 9. doi: [10.18103/mra.v13i9.6815](https://doi.org/10.18103/mra.v13i9.6815) ✓
- “Both JN.1 and NB.1.8.1 continue the trend of SARS-CoV-2 evolution favouring increased transmission and immune escape with relatively mild clinical outcomes. Their emergence in populations with high levels of vaccine coverage and prior infection highlights the virus’s adaptation to immune pressures.”
73. Vanden Bossche G, floor letter to the Oregon State Legislature, “The Science behind the Catastrophic Consequences of Thoughtless Human Intervention in the Covid-19 Pandemic,” March 13, 2021, available online: <https://olis.oregonlegislature.gov/liz/2021R1/Downloads/FloorLetter/3166>
- “Why are the Covid-19 vaccines likely to enhance viral infectiousness? It’s because they are prophylactic vaccines – designed to build immunity in individuals before they get exposed to the pathogen/virus. They are not suitable at all for administration to people during a pandemic... Exerting high immune pressure without preventing viral replication and transmission is a recipe for selective viral immune escape.”
74. van Egeren D et al., “Risk of rapid evolutionary escape from biomedical interventions targeting SARS-CoV-2 spike protein,” *PLoS One* 2021, 16, 4: e0250780. doi: [10.1371/journal.pone.0250780](https://doi.org/10.1371/journal.pone.0250780) ✓
- “Our modeling suggests that SARS-CoV-2 mutants with one or two mildly deleterious mutations are expected to exist in high numbers due to neutral genetic variation, and consequently resistance to vaccines or other prophylactics that rely on one or two antibodies for protection can develop quickly -and repeatedly- under positive selection.”

75. Wang Q et al., “Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants,” *Cell* 2023, 186, 2: P279-286.E8. doi: [10.1016/j.cell.2022.12.018](https://doi.org/10.1016/j.cell.2022.12.018) ✓
- “Together, our findings indicate that BQ and XBB subvariants present serious threats to current COVID-19 vaccines, render inactive all authorized antibodies, and may have gained dominance in the population because of their advantage in evading antibodies.”
76. Wang R et al., “Emerging Vaccine-Breakthrough SARS-CoV-2 Variants,” *ACS Infect. Dis.* 2022, 8, 3: 546–556. doi: [10.1021/acsinfecdis.1c00557](https://doi.org/10.1021/acsinfecdis.1c00557) ✓
- “We show that prevailing variants can be quantitatively explained by infectivity-strengthening and vaccine-escape (co-)mutations on the spike protein RBD due to natural selection and/or vaccination-induced evolutionary pressure. We illustrate that infectivity strengthening mutations were the main mechanism for viral evolution, while vaccine-escape mutations become a dominating viral evolutionary mechanism among highly vaccinated populations... We foresee an urgent need to develop new virus combating strategies.”
77. Wang R et al., “Mechanisms of SARS-CoV-2 Evolution Revealing Vaccine-Resistant Mutations in Europe and America,” *J. Phys. Chem. Lett.* 2021, 12, 49: 11850–11857. doi: [10.1021/acs.jpcllett.1c03380](https://doi.org/10.1021/acs.jpcllett.1c03380) ✓
- “By tracking the evolutionary trajectories of vaccine-resistant mutations in more than 2.2 million SARS-CoV-2 genomes, we reveal that the occurrence and frequency of vaccine-resistant mutations correlate strongly with the vaccination rates in Europe and America.”
78. Wang Z et al., “mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants,” *Nature* 2021, 592: 616–622. doi: [10.1038/s41586-021-03324-6](https://doi.org/10.1038/s41586-021-03324-6) ✓
- “Nevertheless, emergence of these particular variants is consistent with the dominance of the class-1 and -2 antibody response in infected or vaccinated individuals. We speculate that these mutations emerged in response to immune selection in individuals with nonsterilizing immunity.”
79. Willett BJ et al., “SARS-CoV-2 Omicron is an immune escape variant with an altered cell entry pathway,” *Nat. Microbiol.* 2022, 7: 1161-1179. doi: [10.1038/s41564-022-01143-7](https://doi.org/10.1038/s41564-022-01143-7) ✓
- “Immune evasion by Omicron may have contributed to the extremely high transmission rates in countries with high vaccination rates or natural immunity... These experiments indicate a fundamental change in the biology of Omicron (BA.1 and BA.2) spike. It has a reduced ability to form syncytia, most probably linked to changes in spike pre-processing at the S1/S2 boundary. Omicron spike is also optimized to preferential entry via the endosome, resulting in alterations in cellular tropism. This biological about-face may underpin the evident changes in Omicron transmission and pathogenesis.”



80. Yang Z et al., "SARS-CoV-2 Variants Increase Kinetic Stability of Open Spike Conformations as an Evolutionary Strategy," *mBio* 2022, 13, 1. doi: [10.1128/mbio.03227-21](https://doi.org/10.1128/mbio.03227-21) ✓
- "Under the selection pressure imposed by adaptation to the human host and increasing vaccinations and convalescent patients, SARS-CoV-2 is evolving and has adopted numerous mutations on S variants. These promote virus spreading and immune evasion, partially by increasing the propensity of S to adopt receptor-binding competent open conformations."
81. Zayou L et al., "Dynamics of spike-specific neutralizing antibodies across five-year emerging SARS-CoV-2 variants of concern reveal conserved epitopes that protect against severe COVID-19," *Front. Immunol.* 2025, 16 (Vaccines and Molecular Therapeutics). doi: [10.3389/fimmu.2025.1503954](https://doi.org/10.3389/fimmu.2025.1503954) ✓
- "The world will enter its sixth year of a persistent COVID-19 pandemic, fueled by the continuous emergence of heavily Spike-mutated and highly contagious SARS-CoV-2 variants and sub-variants that continue to: (i) escape immunity induced by the current Spike-alone-based vaccines; (ii) disrupt the efficacy of the COVID-19 booster paradigm; and (iii) outpace the development of variant-adapted bivalent Spike-alone vaccines."
82. Zhang L et al., "SARS-CoV-2 BA.2.86 enters lung cells and evades neutralizing antibodies with high efficiency," *Cell* 2024, 187, 3: P596-608.E17. doi: [10.1016/j.cell.2023.12.025](https://doi.org/10.1016/j.cell.2023.12.025) ✓
- "The origin of the BA.2.86 lineage remains elusive at present and it cannot be excluded that the virus emerged due to evasion of vaccine-induced antibody responses."
83. Zhang Y et al., "Vaccination Shapes Within-Host SARS-CoV-2 Diversity of Omicron BA.2.2 Breakthrough Infection," *J. Infect. Dis.* 2024, 229, 6: 1711-1721. doi: [10.1093/infdis/jiad572](https://doi.org/10.1093/infdis/jiad572) ✓
- "The enrichment of mutations in the spike protein gene indicates selection pressure exerted by vaccination on the evolution of SARS-CoV-2."
84. Zhao H et al., "VOC-alarm: mutation-based prediction of SARS-CoV-2 variants of concern," *Bioinform.* 2022, 38, 14: 3549-3556. doi: [10.1093/bioinformatics/btac370](https://doi.org/10.1093/bioinformatics/btac370) ✓
- "We compared the paces of the evolution that caused the speedy mutation of the VOCs in Stages I, III, V and VII (predicted for Omicron). From Alpha to Delta, the pace of evolution was significantly decreased... which might be related to the fast rollouts of vaccines in late 2020 and early 2021. However, from Delta to Delta plus and Omicron, the pace of evolution has been significantly increased... This might be associated with the adaptiveness of the new VOCs to the selective pressures caused by vaccines."



85. Zhou D et al., “Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera,” *Cell* 2021, 184, 9: p2348-2361.e6. doi: [10.1016/j.cell.2021.02.037](https://doi.org/10.1016/j.cell.2021.02.037) ✓

- “The ACE2-binding surface is to some extent the Achilles heel of the virus as it can be blocked by some neutralizing antibodies; however, since it is so small, it also threatens immune escape, as small changes can throw off neutralizing antibodies, thereby reducing the ability of natural or vaccine-acquired immunity to contain viral replication. Selective pressure for changes in the ACE2 interaction surface can thus have two entirely separate drivers. First, as SARS-CoV-2 has recently crossed a zoonotic barrier, it may be expected that evolution of the ACE2 interaction surface may occur to increase affinity to ACE2 and thereby increase viral transmissibility. And second, conversely, changes to the ACE2 interaction surface may also reduce the protection afforded by previous infection or vaccination, potentially leading to escape from pre-existing immunity induced by natural infection or vaccines.”

## VII. COVID “vaccine” cancer, genotoxicity and DNA contamination risks

*Compiled by Steven Hatfill, MD, and Jessica Rose, PhD. Last updated November 18, 2025.*

✔ = peer-reviewed

No carcinogenicity or genotoxicity studies were performed on the mRNA COVID “vaccines” according to their manufacturers (see inserts: [Pfizer U.S.](#), [Pfizer Australia](#), [Pfizer Europe](#), [Moderna Europe](#)), meaning potential risks for cancer and damage to human DNA are unknown. However, real-world evidence suggests that the mRNA “vaccines” as well as the adenoviral vector shots (e.g. J&J, AstraZeneca) and various inactivated “vaccines” (e.g. CoronaVac) can damage DNA and trigger or accelerate the growth of cancers. Research has also revealed [contamination](#) of mRNA “vaccines” with DNA fragments as a byproduct of the manufacturing process. This foreign DNA may be incorporated into cellular DNA during repair of DNA damage caused by the shots, thereby altering the human genome.

This collection of (117/122 peer-reviewed ✔) studies is comprised of three sections:

**A. COVID “vaccine”-related cancer case reports and cohort studies (48/48 peer-reviewed ✔) p. 242**

Case reports point to possible connections between COVID “vaccination” and various cancers, including lymphoma, sarcoma, leukemia, myeloma, breast cancer, and melanoma.

**B. COVID “vaccine” & spike protein oncogenesis (19/20 peer-reviewed ✔) p. 253**

Research annotated here presents potential causal mechanisms connecting mRNA, spike proteins and lipid nanoparticles to new or accelerated cancers.

**C. DNA damage, contamination & integration risks (50/54 peer-reviewed ✔) p. 259**

Research annotated here shows that COVID “vaccines” can damage human DNA by various means, including creation of reactive oxygen species (ROS) and oxidative stress induced by the spike protein and nanoparticles. The ensuing DNA damage repair process can integrate foreign contaminant DNA – now shown to be present in lipid nanoparticles as a byproduct of the “vaccine” manufacturing process – into human cellular DNA.

This compilation originated with Dr. Hatfill’s and Dr. Rose’s contributions to [TOXIC SHOT: Facing the Dangers of the COVID “Vaccines”](#).

**A. COVID “vaccine”-related cancer case reports and cohort studies (ANNOTATED REFERENCES, 48/48 peer-reviewed ✓)**

Case reports and cohort studies point to connections between COVID “vaccination” and various cancers, including lymphoma, sarcoma, leukemia, myeloma, breast cancer, and melanoma. The high proportion of “vaccine”-related lymphomas likely reflects the fact that these malignancies can develop quickly and often arise at the injection site, allowing clinicians to draw a causal connection with relative confidence. However, the potential underlying causes (see subsection C) may also contribute to development of other types of cancer over longer timeframes, requiring long-term post-“vaccination” cancer surveillance.

1. Abdurrahman Y et al., “Primary Cutaneous Adenoid Cystic Carcinoma in a Rare Location With an Immune Response to a BNT162b2 Vaccine,” *JBJS Case Connector* 2024, 14, 2: e23.00499. doi: [10.2106/JBJS.CC.23.00499](https://doi.org/10.2106/JBJS.CC.23.00499) ✓
  - “... a rare case of primary cutaneous adenoid cystic carcinoma (PCACC) localized in the subcutaneous tissue of the scapular region that grew after BNT162b2 corona virus disease of 2019 (COVID-19) vaccination... may be explained by CD4 and CD8 cell infiltration. The BNT162b2 mRNA vaccine has been associated with a multisystem inflammatory syndrome (MIS-V). A comparable immune reaction could potentially enhance tumor growth rate.”
2. Abue M et al., “Repeated COVID-19 Vaccination as a Poor Prognostic Factor in Pancreatic Cancer: A Retrospective, Single-Center Cohort Study,” *Cancers* 2025, 17, 12: 2006. doi: [10.3390/cancers17122006](https://doi.org/10.3390/cancers17122006) ✓
  - “Repeated COVID-19 vaccination is known to increase spike-specific immunoglobulin G4 (IgG4), and there are concerns regarding its impact on cancer immunity. This study aimed to investigate the relationship between repeated COVID-19 vaccination and prognosis in patients with pancreatic cancer (PC). The study findings were that repeated COVID-19 booster vaccinations are associated with poorer overall survival in patients with PC. Notably, our analysis reveals that high levels of IgG4, induced by vaccination, correlate with a detrimental prognosis in these patients.”
3. Akkus E et al., “Types and Rates of COVID-19 Vaccination in Patients With Newly Diagnosed Microsatellite Stable and Instable Non-Metastatic Colon Cancer,” *Cureus* 16, 6: e61780. doi: [10.7759/cureus.61780](https://doi.org/10.7759/cureus.61780) ✓
  - “Microsatellite instable (deficient mismatch repair, dMMR) colon cancer is associated with hypermutability and immune infiltration-activation. COVID-19 vaccines stimulate immune-inflammation response. This study aimed to investigate the types and rates of COVID-19 vaccines in patients with newly diagnosed colon cancer and compare it according to the microsatellite status. Methods The study was a single-center case-control study. Patients diagnosed with colon cancer at least three months after the last COVID-19 vaccine

- (BNT162b2, CoronaVac) dose were included... The BNT162b2 vaccine was significantly associated with dMMR status (OR: 6.39, 95% CI: 1.55-26.26,  $p=0.01$ ). The dMMR+BNT162b2 group had higher median C-reactive protein (CRP) level ( $p=0.01$ ), erythrocyte sedimentation rate ( $p=0.05$ ), and lower lymphocyte/CRP ratio ( $p=0.04$ ) than the MSS+CoronaVac group. Conclusion Immune infiltration in dMMR colon cancer may interact with COVID-19 vaccine-induced immune activation. Long-term clinical and preclinical studies are needed to confirm these findings.”
4. Ang SY et al., “pH-positive B-cell acute lymphoblastic leukemia occurring after receipt of bivalent SARS-CoV-2 mRNA vaccine booster: A case report,” *Medicina* 2023, 59, 3: 627. doi: [10.3390/medicina59030627](https://doi.org/10.3390/medicina59030627) ✓
    - “... Ph-positive B-cell acute lymphoblastic leukemia (ALL) occurring after a bivalent mRNA COVID-19 vaccine inoculation. The otherwise healthy 43-year-old female patient had a total of six spike antigen exposures in the past 1.5 years... we propose that anti-spike protein immune responses could be a trigger for leukemia.”
  5. Avallone G et al. “Real-world data on primary cutaneous lymphoproliferative disorders following SARS-CoV-2 vaccination: a multicentre experience from tertiary referral hospitals,” *J Eur Acad Dermatol Venereol.* 2023; 37, 4: e451-e455. doi: [10.1111/jdv.18806](https://doi.org/10.1111/jdv.18806) ✓
    - “In this regard, we report a retrospective review of patients attending seven Italian tertiary referral centres between January 2021 and July 2022... The relationship between PCLDs and SARS-CoV2 vaccination appears multifaceted and the exact pathogenic mechanisms, if any, are not understood... The overproduction of CD4+ and CD8+ lymphocytes, expressing CD30 after being triggered by the vaccine, might be held responsible for the disease recurrence.”
  6. Bae E et al., “Development of High-Grade Sarcoma After Second Dose of Moderna Vaccine,” *Cureus* 2023. doi: [10.7759/cureus.37612](https://doi.org/10.7759/cureus.37612) ✓
    - “... an elderly female who received the Moderna mRNA-1273 COVID-19 vaccine and developed a high-grade sarcoma at the site of the injection. Currently, it is unclear whether there is a true association between the vaccines and malignancy or inflammatory response exacerbating underlying malignancy.”
  7. Bresler SC et al., “Two cases of challenging cutaneous lymphoid infiltrates presenting in the context of COVID-19 vaccination: a reactive lymphomatoid papulosis-like eruption and a bona fide lymphoma,” *J Cutan Pathol.* 2023, 50, 3: 213–219. doi: [10.1111/cup.14371](https://doi.org/10.1111/cup.14371) ✓
    - “These cases suggest that immune stimulation following exposure to SARS-Cov-2 protein(s) in vaccine or infection may facilitate the development of a lymphoma or lymphoproliferative disorder in susceptible individuals.”

8. Brumfiel CM et al., "Recurrence of primary cutaneous CD30-positive lymphoproliferative disorder following COVID-19 vaccination," *Leuk. Lymphoma* 2021, 62, 2554–2555. doi: [10.1080/10428194.2021.1924371](https://doi.org/10.1080/10428194.2021.1924371) ✓
  - "Here, we report a case of a new axillary lymphoid tumor developing after COVID-19 vaccination. A 79-year-old male presented with a 3-centimeter ulcerated tumor with surrounding erythema in the left axilla. The lesion appeared two days following initial vaccination with the Pfizer-BioNTech COVID-19 vaccine in the ipsilateral arm... A diagnosis of COVID-19 Vaccine Pfizer-BioNTech-induced recurrence of CD30-positive lymphoproliferative disorder was made."
9. Cavanna L et al., "Non-Hodgkin Lymphoma Developed Shortly after mRNA COVID-19 Vaccination: Report of a Case and Review of the Literature," *Medicina* 2023, 59, 1: 157. doi: [10.3390/medicina59010157](https://doi.org/10.3390/medicina59010157) ✓
  - "We report on a 66-year-old man who presented with a right axillary lymphadenopathy approximately 10 days after receiving the third dose of the BNT162b2 vaccine... A total body computerized tomography (CT) scan, positron emission tomography (PET) and bone-marrow biopsy showed a stage-II non-Hodgkin lymphoma (NHL)... The revision of the literature revealed eight additional cases of NHL developed shortly after COVID-vaccination."
10. De la Torre-Gomar FJ et al., "Primary Cutaneous CD4 Small/Medium T-Cell Lymphoproliferative Disorder Following COVID-19 Vaccination-What Do We Know about Lymphoproliferative Disorders and Cutaneous Lymphomas after COVID-19 Vaccination? A Report of an Atypical Case and a Review of the Literature," *Life (Basel)* 2024, 14, 3: 386. doi: [10.3390/life14030386](https://doi.org/10.3390/life14030386) ✓
  - "Reviewing the literature, albeit infrequently, we can find cases of the recurrence and new onset of lymphoproliferative processes and cutaneous lymphomas following the COVID-19 vaccine... The prevailing hypothesis suggests that the predominant cutaneous reactions to SARS-CoV-2 vaccines may stem from T-cell-mediated immune activation responses to vaccine components, notably messenger RNA (mRNA)."
11. Dupoirieux L, "Aggressive cutaneous lymphoma: A possible link with the mRNA COVID-19 vaccine," *Our Dermatol Online* 2025, 16, 2: 151-153. doi: [10.7241/ourd.20252.6](https://doi.org/10.7241/ourd.20252.6) ✓
  - "Herein, we present a case of malignant transformation of mycosis fungoides into a cutaneous lymphoma on the right arm. This lesion was remarkable by its evolution having nearly doubled its surface in fifteen days. Moreover, the patient also experienced a severe post-operative infection that may suggest an immune depression induced by the COVID-19 vaccine. In the discussion, we analyze the data that may impute this rapidly growing lymphoma to the COVID-19 vaccines. In our recent practice, we have observed several atypical skin tumors that we had not encountered before, and thus, the relationship with COVID-19 vaccines

must be considered... These T-cell lymphomas have been observed in patients having one to three doses of the Comirnaty® mRNA vaccine with an onset of the lesion varying from 1–15 days to 6 months, respectively. Worsening of a pre-existent comorbidity after COVID-19 vaccination must also be taken in consideration and has been described with inflammatory cutaneous disease (psoriasis), yet more alarming is the recurrence of a tumoral pathology.”

12. Embaby A et al., “Diffuse Large B-Cell Lymphoma Developed Shortly After mRNA COVID-19 Vaccination in a Patient with Sickle Cell Disease: A Chicken-and-Egg Problem,” *Bratislava Medical J* 2025, 126, 8. doi: [10.1007/s44411-025-00174-w](https://doi.org/10.1007/s44411-025-00174-w) ✓
  - “A 26-year-old male with SCD, SS-genotype, who presented with cervical, axillary lymphadenopathy and lower neck mass with compressive symptoms approximately 6-week after encountering COVID-19 infection that was preceded by receiving a single dose of BNT162b2, COVID-19 mRNA vaccine... A potential causal relationship or an incidental simple association are possible scenarios.”
13. Erdogdu B et al., “Hematopoietic Adverse Events Associated with BNT162b2 mRNA Covid-19 Vaccine,” *Int. J. Hematol. Oncol.* 2022, 1, 32. doi: [10.4999/uhod.226097](https://doi.org/10.4999/uhod.226097) ✓
  - Case reports including new and recurring leukemias following vaccination.
14. Etesami I et al., “Drug- and Vaccine-Induced Cutaneous T-Cell Lymphoma: A Systematic Review of the Literature,” *J. Skin Cancer* 2025. doi: [10.1155/jskc/3103865](https://doi.org/10.1155/jskc/3103865) ✓
  - “It is important recognizing CTCL as a possible, although rare, adverse effect of certain drugs and vaccines, and taking a history of vaccinations, especially COVID-19 vaccines, and immunosuppressive drugs such as fingolimod, TNF- $\alpha$  inhibitors, and methotrexate.”
15. Farhat M et al., “A Case of Rapid Transformation of a Nail Matrix Nevi to Melanoma After Messenger RNA COVID19 Vaccine: A Cause or a Coincidence?” *Cureus* 2024, 16, 12: e76312. doi: [10.7759/cureus.76312](https://doi.org/10.7759/cureus.76312) ✓
  - “Our case illustrates a malignant transformation of an apparently benign longitudinal melanonychia following the administration of three doses of mRNA COVID-19 vaccines... Finally, this report also illustrates the possible role of the COVID-19 messenger RNA vaccine in cancer development and/or progression.”
16. Goldman S et al., “Rapid progression of angioimmunoblastic T cell lymphoma following BNT162b2 mRNA vaccine booster shot: a case report,” *Front Med.* 2021, 8 (Pathology): 798095. doi: [10.3389/fmed.2021.798095](https://doi.org/10.3389/fmed.2021.798095) ✓
  - “Since nucleoside-modified mRNA vaccines strongly activate T follicular helper cells, it is important to explore the possible impact of approved SARS-CoV-2 mRNA vaccines on neoplasms affecting this cell type. Herein, we report and discuss unexpected rapid progression of lymphomatous lesions after

administration of a BNT162b2 mRNA vaccine booster in a man recently diagnosed with AITL.”

17. Gordon ER et al., “Cutaneous lymphoproliferative disorders after COVID-19 vaccination: clinical presentation, histopathology, and outcomes,” *Leuk. Lymphoma* 2024, 65, 1: 48-54. doi: [10.1080/10428194.2023.2270766](https://doi.org/10.1080/10428194.2023.2270766) ✓
  - “Approximately 84% of cases demonstrated CD30+ positivity in their skin biopsies, suggesting that an antigenic trigger may lead to a type IV adaptive immune response, with clonal expansion of CD30+ T-cells and subsequent oncogenic mutational hits eventuating in transient LPDs.”
18. Gordon ER et al., “Exploring cutaneous lymphoproliferative disorders in the wake of COVID-19 vaccination,” *Skin Health Dis.* 2024, 4, 3: e367. doi: [10.1002/ski2.367](https://doi.org/10.1002/ski2.367) ✓
  - “Fifty cases of biopsy-proven LPDs arising after COVID-19 vaccination were found: 37 from medical literature, 11 from VAERS and two from our institution... LPDs after COVID-19 vaccination appear in the context of the same vaccines (proportionally to their global market shares), share clinical and pathological findings, and have indolent, self-limited character.”
19. Hitzenbichler F et al. “Infection image: Reoccurrence of Kaposi sarcoma after SARS-CoV-2 mRNA vaccination in an HIV-infected patient,” *Infection* 2023, 52, 1: 283–284. doi: [10.1007/s15010-023-02121-9](https://doi.org/10.1007/s15010-023-02121-9) ✓
  - “A 48-year-old male Caucasian patient was diagnosed with HIV infection and Kaposi’s sarcoma (KS) on his right foot sole and lower leg in 2008 (CDC classification C2). Antiretroviral combination therapy was started and both KS lesions showed spontaneous remission within six months. In May 2021 he received the first dose of the SARS-CoV-2 vaccine mRNA-1273 without any adverse effects. HIV viral load was undetectable and CD4 count was 1080/μl (40%) when he presented for his scheduled appointment in May 2021. In June 2021 a second dose of mRNA-1273 was given and approximately one week later he noticed two small flat, dark lesions on the sole of his right foot. In December 2021 he received a SARS-CoV-2 booster dose (BNT162b2). Approximately one week later one of the lesions on his sole progressed to an ulcerative tumor... Our patient’s case with HHV-8 reactivation and the development/reoccurrence of KS lesions in association with a three-dose series of SARS-CoV-2 mRNA vaccination suggests HHV-8 reactivation and KS reoccurrence as an adverse event of mRNA vaccination.”
20. Hobayan CG and CG Chung, “Indolent Cutaneous Lymphoma With Gamma/Delta Expression After COVID-19 Vaccination,” *JAAD Case Reports* 2023, 32, 74-76. doi: [10.1016/j.jdcrr.2022.12.001](https://doi.org/10.1016/j.jdcrr.2022.12.001) ✓
  - “A 79-year-old male received the Moderna COVID-19 vaccine booster in the left upper arm. Three days later, he developed an ulcer at the vaccine site that progressed with surrounding erythema... TCR gene rearrangement studies were



consistent with a clonal T-cell population. These findings were consistent with primary cutaneous gamma/delta T-cell lymphoma (PCGDTCL)... Our patient's presentation is unusual as it arose at the site of a COVID-19 vaccination several days after vaccination... It is unknown if the COVID-19 vaccine directly contributed to his presentation or disease course."

21. Hsieh CY et al., "Nodal T-Follicular Helper Cell Lymphoma, Angioimmunoblastic-Type, Diagnosed in a Patient with Psoriasis Following COVID-19 Vaccination under Adalimumab Treatment: A Causal Association?" *Indian J. Dermatol.* 2024, 69, 3: 264-267. doi: [10.4103/ijd.ijd\\_93\\_23](https://doi.org/10.4103/ijd.ijd_93_23) ✓
  - "We report a case of a patient with psoriasis under adalimumab developing nodal T-follicular helper cell lymphoma, angioimmunoblastic-type following the mRNA-1273 COVID-19 vaccine. We suspect that adalimumab, methotrexate, Epstein-Barr virus (EBV) reactivation, previous reactive lymphoid hyperplasia and psoriasis per se predispose our patient to a lymphoma-prone condition, and the two doses of the mRNA vaccine act as the last straw."
22. Khatri JK et al., "Diagnosis of Angioimmunoblastic T Cell Lymphoma After Receiving First Dose of Pfizer/BioNTech (BNT162b2) Vaccine: A Case Report," *J Investig Med High Impact Case Rep.* 2024, 12: 23247096241231645. doi: [10.1177/23247096241231645](https://doi.org/10.1177/23247096241231645) ✓
  - "Our case demonstrates a plausible correlation between the diagnosis of AITL following mRNA vaccination due to the malignant transformation of the TFH cells in patients who have a predisposing mutation of RHOA-17v."
23. Kreher MA et al., "Subcutaneous Panniculitis-Like T-Cell Lymphoma After COVID-19 Vaccination," *JAAD Case Reports*, 2022, 28: 18-20. doi: [10.1016/j.jdcr.2022.08.006](https://doi.org/10.1016/j.jdcr.2022.08.006) ✓
  - "We describe a young woman who developed SPTCL at the injection site of a recent COVID-19 vaccination... Although causation cannot be established in this single case, this case supports the understanding that certain immunologic triggers, such as a modified adenovirus vaccine, may contribute to the development or exacerbation of SPTCL."
24. Kyriakopoulos AM et al., "Bell's palsy or an aggressive infiltrating basaloid carcinoma post-mRNA vaccination for COVID-19? A case report and review of the literature," *EXCLI J.* 2023, 22: 992-1011. doi: [10.17179/excli2023-6145](https://doi.org/10.17179/excli2023-6145) ✓
  - "We report on an aggressive, infiltrating, metastatic, and ultimately lethal basaloid type of carcinoma arising shortly after an mRNA vaccination for COVID-19... In this study we describe all aspects of this case and discuss possible causal links between the rapid emergence of this metastatic cancer and mRNA vaccination. We place this within the context of multiple immune impairments potentially related to the mRNA injections that would be expected to potentiate more aggressive presentation and progression of cancer. The type of malignancy

- we describe suggests a population risk for occurrence of a large variety of relatively common basaloid phenotype cancer cells, which may have the potential for metastatic disease.”
25. Li YH et al., “Kaposi Sarcoma as a Possible Cutaneous Adverse Effect of ChAdOx1 nCov-19 Vaccine: A Case Report,” *Vaccines* 2024, 12, 10: 1168. doi: [10.3390/vaccines12101168](https://doi.org/10.3390/vaccines12101168) ✓
    - “This study reports a case of classic cutaneous KS in a 79-year-old male following the first dose of the ChAdOx1 nCov-19 vaccine, without prior SARS-CoV-2 infection... Further large-scale studies are warranted to elucidate the relationship between COVID-19 vaccines and latent virus reactivation, ensuring comprehensive safety assessments and informed public health decisions.”
  26. Martellucci CA et al., “COVID-19 vaccination, all-cause mortality, and hospitalization for cancer: 30-month cohort study in an Italian province,” *EXCLI J* 2025, 24: 690-707. doi: [10.17179/excli2025-8400](https://doi.org/10.17179/excli2025-8400) ✓
    - “Compared with the unvaccinated, those receiving  $\geq 1$  dose showed a significantly lower likelihood of all-cause death, and a slightly higher likelihood of hospitalization for cancer (HR: 1.23; 95% CI: 1.11-1.37). The latter association was significant only among the subjects with no previous SARS-CoV-2 infection, and was reversed when the minimum time between vaccination and cancer hospitalization was set to 12 months. The subjects who received SARS-CoV-2 vaccination showed a substantial reduction in all-cause mortality, and a risk of cancer hospitalization that varied by infection status, cancer site, and the minimum lag-time after vaccination.”
  27. Martínez-Ortega JI et al., “Sporadic Kaposi Sarcoma Following a COVID-19 Vaccine: Mere Coincidence or Something More?” *Cureus* 2024, 16, 2: e53925. doi: [10.7759/cureus.53925](https://doi.org/10.7759/cureus.53925) ✓
    - “Studies have shown that spike proteins of SARS-CoV-2 can reactivate the lytic phase of KSHV. The ChAdOx1 nCoV-19 vaccine contains DNA eDNA-encoding proteins. If these spike proteins encounter HHV8-infected cells, it could potentially trigger the reactivation of the virus, leading to the lytic phase.”
  28. Mizutani M et al., “Two cases of axillary lymphadenopathy diagnosed as diffuse large B-cell lymphoma developed shortly after BNT162b2 COVID-19 vaccination,” *J Eur Acad Dermatology Venereol.* 2022, 36, 8: e613–e615. doi: [10.1111/jdv.18136](https://doi.org/10.1111/jdv.18136) ✓
    - “We describe two patients with diffuse large B-cell lymphoma (DLBCL), which developed as axillary lymphadenopathy after BNT162b2 COVID-19 vaccination... BNT162b2 vaccines have been reported to induce a cytokine signature featuring IL-15, IFN- $\gamma$ , CXCL10 and IL-6. On the contrary, the elevation of these cytokines was observed in the sera of patients with pretreated DLBCL, suggesting some roles of these cytokines in the growth or survival of DLBCL. Thus, it might be

conceivable that pre-existing or subclinical DLBCL may rapidly grow in a specific condition induced by BNT162b2 vaccination.”

29. Montoya VG et al., “SARSCOV-2 vaccine associated with primary cutaneous peripheral T cell lymphoma,” *Eur J Cancer*. 2022, 173: S32–S33. doi: [10.1016/S0959-8049\(22\)00617-7](https://doi.org/10.1016/S0959-8049(22)00617-7) ✓
  - “In cutaneous lymphomas, we found two reported cases of mycosis fungoides that were exacerbated after immunization. In this case, we show the association of the appearance and exacerbation of a primary cutaneous peripheral T lymphoma with the inactivated SARSCoV2 viral vaccine.”
30. Obodo OI et al., “Lymphoid Neoplasms and COVID-19 Vaccination,” *Oncol. Adv*. 2025, 3, 4: e00005. doi: [10.14218/OnA.2025.00005](https://doi.org/10.14218/OnA.2025.00005) ✓
  - “The vaccination history of patients presenting with clinical manifestations suggestive of a lymphoid malignancy should be thoroughly investigated, while ruling out other possible differentials such as a benign, self-limiting inflammatory process.”
31. Olszweska B et al., “Rapid Progression of Cutaneous Lymphoma Following mRNA COVID-19 Vaccination: A Case Report and Pathogenetic Insights,” *Vaccines* 2025, 13, 7: 678. doi: [10.3390/vaccines13070678](https://doi.org/10.3390/vaccines13070678) ✓
  - “Accumulated evidence suggests a link between CL occurrence and immunization with an mRNA vaccine. The proposed hypothesis revolves around shared signaling pathways that are enhanced by SARS-CoV-2 mRNA vaccines, thus driving the pathogenesis of MF. We want to raise clinicians’ attention to the rare side effects of COVID-19 vaccines and emphasize the need for thorough monitoring of patients with altered immunity in the course of various lymphoproliferative disorders.”
32. Panou E et al., “Recurrence of cutaneous T-cell lymphoma post viral vector COVID-19 vaccination,” *J Eur Acad Dermatol Venereol*. 2022, 36, 2: e91–3. doi: [10.1111/jdv.17736](https://doi.org/10.1111/jdv.17736) ✓
  - “We present two CTCL cases which were in remission for many years and the immunization with viral vector COVID-19 vaccine (Vaxzevria, Oxford/AstraZeneca, Cambridge, England) induced them to reappear.”
33. Sano S, “A case of metastatic breast carcinoma to the skin expressing SARS-CoV-2 spike protein possibly derived from mRNA vaccine,” *J. Dermatol. Sci*. 2025. doi: [10.1016/j.jdermsci.2025.09.007](https://doi.org/10.1016/j.jdermsci.2025.09.007) ✓
  - “Here we report on a case of breast cancer skin metastasis that manifested acutely after mRNA vaccination of the 6th dose of BNT162b2... The presence of spike protein but not nucleocapsid protein expression in cancer cells is a novel finding... strongly suggesting a potential link between mRNA vaccines and cancer progression/metastasis.”

34. Sekizawa A et al., "Rapid progression of marginal zone B-cell lymphoma after COVID-19 vaccination (BNT162b2): a case report," *Front. Med.* 2022, 9: 963393. doi: [10.3389/fmed.2022.963393](https://doi.org/10.3389/fmed.2022.963393) ✓
- "Although the precise mechanisms for T-cell lymphomas induced by the mRNA COVID-19 vaccines are still unknown, mRNA COVID-19 vaccines may have the capability to overstimulate the immune system as well as trigger autoimmune responses. In our case, the same mechanism by which T-cell lymphomas are induced by the COVID-19 vaccine could be considered for the pathogenesis of MZL. mRNA COVID-19 vaccines are reported to induce T follicular helper cells with a Th1 functional profile, which is associated with selective generation of neutralizing antibodies, and stimulate germinal center B-cells, long-lived plasma cells, and memory B-cells."
35. Shirzad-Yazdi N et al., "Is there a Possible Association between Multiple Myeloma Relapse and Coronavirus Disease 2019 Vaccination? A Case Report," *J. Res. Pharm Pract.* 2024, 13, 1: 27-32. doi: [10.4103/jrpp.jrpp\\_21\\_24](https://doi.org/10.4103/jrpp.jrpp_21_24) ✓
- "Here, we report a case of a possible association between relapse of MM and COVID-19 vaccination with Sinopharm®, an inactivated virus vaccine, in a patient with MM who has remained in complete remission for about 4 years."
36. Sprenger F et al., "Prevertebral Inflammatory Myofibroblastic Tumor Following COVID Vaccine Booster Dose," *Indian J Otolaryngol Head Neck Surg* 2023, 75: 2390-2393. doi: [10.1007/s12070-023-03718-0](https://doi.org/10.1007/s12070-023-03718-0) ✓
- "Computerized tomography (CT) revealed a heterogeneous and infiltrating paravertebral mass at the level of T2 and T3 vertebral bodies, with bone destruction in contact with the esophagus, trachea, and right lung... The exact cause, however, was not confirmed, but due to its relation to antigen aggression and viral infections we could not rule out vaccination-related etiology."
37. Stephan C et al., "Primary cutaneous marginal zone lymphoproliferative disorder following COVID-19 vaccination," *J Cutan Pathol.* 2024, 51, 3: 193-197. doi: [10.1111/cup.14550](https://doi.org/10.1111/cup.14550) ✓
- "We report a case of primary cutaneous marginal zone lymphoproliferative disorder (PCMZLPD) secondary to COVID-19 vaccination... The temporal association with the Moderna vaccination and the occurrence of the lesion at the inoculation site indicate a COVID-19 vaccination-induced PCMZLPD."
38. Tachita T et al., "Newly diagnosed extranodal NK/T-cell lymphoma, nasal type, at the injected left arm after BNT162b2 mRNA COVID-19 vaccination," *Int J Hematol.* 2023, 118, 4: 503-507. doi: [10.1007/s12185-023-03607-w](https://doi.org/10.1007/s12185-023-03607-w) ✓
- "A 73-year-old male presented with a lump in the left arm, which was the site where he received the BNT162b2 mRNA vaccine 3 months prior... It seems that

latent Epstein-Barr virus (EBV)-infected NK/T cells were reactivated by vaccination and contributed to the onset of ENKL.”

39. Tanaka A et al., “Epstein-Barr virus-associated lymphoproliferative disorders after BNT162b2 mRNA COVID-19 vaccination,” *Rinsho Ketsueki* 2023, 64, 4: 277-282. doi: [10.11406/rinketsu.64.277](https://doi.org/10.11406/rinketsu.64.277) ✓
  - “Flow cytometry and RT-PCR revealed that the EBV genome was localized in NK cells, suggesting the diagnosis of EBV-NK-LPD. We administered prednisolone, intravenous immunoglobulin, and etoposide, but the EBV-DNA load failed to decrease, and he died 2 months later.”
40. Tang WR et al., “A Case Report of Posttransplant Lymphoproliferative Disorder after AstraZeneca Coronavirus Disease 2019 Vaccine in a Heart Transplant Recipient,” *Transplant Proc* 2021, 54, 6: 1575-1578. doi: [10.1016/j.transproceed.2021.09.006](https://doi.org/10.1016/j.transproceed.2021.09.006) ✓
  - “We report a case of heart transplant recipient who presented with a rapidly growing Epstein-Barr virus (EBV)-positive, diffuse large B-cell lymphoma 7 days after receiving the first dose of the ChAdOx1 nCoV-19 vaccine... This observation indicates a potential risk of EBV reactivation after coronavirus disease 2019 (COVID-19) vaccination, which might lead to or aggravate the presentation of posttransplant lymphoproliferative disorder in transplantation patients.”
41. Ueda Y et al., “Fatal hemophagocytic lymphohistiocytosis with intravascular large B-cell lymphoma following coronavirus disease 2019 vaccination in a patient with systemic lupus erythematosus: an intertwined case,” *Immunol Med* 2024, 47, 3: 192-199. doi: [10.1080/25785826.2024.2338594](https://doi.org/10.1080/25785826.2024.2338594) ✓
  - “We report a case of neuropsychiatric symptoms and refractory HLH in a woman with systemic lupus erythematosus (SLE) after receiving her COVID-19 vaccine treated with belimumab, later found to have intravascular large B-cell lymphoma (IVLBCL) at autopsy... Despite treatment, the patient died on day 75; autopsy report findings suggested IVLBCL as the underlying cause of HLH... we speculate that the COVID-19 vaccination and her autoimmune condition may have expedited IVLBCL development.”
42. Ukishima S et al., “Subcutaneous panniculitis-like T-cell lymphoma post-mRNA-1273 COVID-19 vaccination,” *Clin. Case Rep.* 2023, 11, 4: e7143. doi: [10.1002/ccr3.7143](https://doi.org/10.1002/ccr3.7143) ✓
  - “... subcutaneous panniculitis-like T-cell lymphoma (SPTCL) diagnosed by skin biopsy in a patient who presented with fever and erythema nodosum in the umbilicum following mRNA-1273 COVID-19 vaccination. COVID-19 vaccines may cause SPTCL and skin biopsy may help in the diagnosis...”
43. Veeraballi S et al., “A Case of Chronic Myelomonocytic Leukemia Unmasked After Receiving J&J COVID-19 Vaccine,” *Cureus* 2022, 14, 6: e26070. doi: [10.7759/cureus.26070](https://doi.org/10.7759/cureus.26070) ✓

- “Our case suggests the possibility of developing CMML associated with limited scleroderma after receiving the J&J COVID vaccine.”
44. Verrienti M et al., “Pituitary and COVID-19 vaccination: a systematic review,” *Pituitary* 2024, 27, 970–985. doi: [10.1007/s11102-024-01402-2](https://doi.org/10.1007/s11102-024-01402-2) ✓
- “... precipitating adrenal crisis was registered in 7 patients and pituitary tumor enlargement in 1 patient after receiving COVID-19 vaccination... Despite the rarity of these events, our research findings suggest an association between COVID-19 vaccination and the subsequent development of pituitary diseases.”
45. Wang Z et al., “The first autopsy case of Epstein-Barr virus-positive marginal zone lymphoma that deteriorated after COVID-19 vaccination,” *Pathol Int.* 2024, 74, 2: 87-92. doi: [10.1111/pin.13398](https://doi.org/10.1111/pin.13398) ✓
- “This is the first autopsy case of Epstein-Barr virus-positive marginal zone lymphoma (EBV + MZL) with other iatrogenic immunodeficiency-associated lymphoproliferative disorders (LPD) (methotrexate [MTX]-associated LPD) that deteriorated after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine.”
46. White E et al., “Unilateral conjunctival Classic Kaposi Sarcoma following a COVID 19 booster,” *Am. J. Ophthalmol. Case Rep.* 2024, 34, 101986. doi: [10.1016/j.ajoc.2023.101986](https://doi.org/10.1016/j.ajoc.2023.101986) ✓
- “We present a case of Classic Kaposi’s sarcoma in a functionally monocular patient following a COVID19 vaccine booster and provide compelling evidence that suggests the booster was a relevant co-factor...”
47. Yanagida E et al., “The case of T-ALL presenting with NK phenotype after COVID-19 vaccination,” *Pathol Res Pract.* 2023, 242: 154310. doi: [10.1016/j.prp.2023.154310](https://doi.org/10.1016/j.prp.2023.154310) ✓
- “Hematological malignancy was suspected due to the presence of atypical lymphoid cells with an elevated IL-2R in laboratory data... TCRβ rearrangement led to the final diagnosis of T-cell lymphoblastic leukemia (T-ALL)... The causal relationship between COVID-19 vaccination and carcinogenesis is not clear, and more cases need to be studied in order to elucidate the relationship between the two factors.”
48. Zamfir MA et al., “Hematologic malignancies diagnosed in the context of the mRNA COVID-19 vaccination campaign: a report of two cases,” *Medicina (B Aires)*, 2022, 58, 7: 874. doi: [10.3390/medicina58070874](https://doi.org/10.3390/medicina58070874) ✓
- “The aim of our paper is to present two cases of hematological malignancies: diffuse large B-cell non-Hodgkin lymphoma and T/NK-cell lymphoma, diagnosed shortly after the administration of the mRNA COVID-19 vaccine.”



## B. COVID “vaccine” & spike protein oncogenesis (ANNOTATED REFERENCES, 19/20 peer-reviewed ✓)

Research annotated here presents potential causal mechanisms connecting COVID “vaccination” to new or accelerated cancers, including immune suppression, DNA damage, chronic inflammation, downregulation of ACE2, autoimmune reactions, mutations in tumor-suppressing genes and blockade of tumor-suppressing proteins, liver metabolic dysfunction, and the presence of N1-methyl-pseudouridine in mRNA “vaccines.”

In support of these connections, authors discuss “vaccine” production of reactive oxygen species ([ROS](#)) and oxidative stress, as well as recombinant spike protein interactions with common cellular signaling pathways and genes associated with cancer. These factors include extracellular signal-related kinases 1/2 ([ERK1/2](#)), vascular endothelial growth factor ([VEGF](#)), nuclear factor-κB ([NF-κB](#)), mitogen-activated protein kinase ([MAPK](#)), and tumor suppressor genes [p53](#) and [BRCA](#), among others. The presence in the “vaccines” of SV40 enhancer, a cancer-promoting gene, is [confirmed](#).

1. Acevedo-Whitehouse K and R Bruno, “Potential health risks of mRNA-based vaccine therapy: A hypothesis,” *Med. Hypotheses* 2023, 171: 111015. doi: [10.1016/j.mehy.2023.111015](https://doi.org/10.1016/j.mehy.2023.111015) ✓
  - “The cytosolic accumulation of the *nms*-mRNA and the reverse transcribed cDNA molecules activates RNA and DNA sensory pathways. Their concurrent activation initiates a synchronized innate response against non-self [nucleic acids](#), prompting type-I interferon and pro-inflammatory cytokine production which, if unregulated, leads to autoinflammatory and autoimmune conditions, while activated TEs increase the risk of insertional mutagenesis of the reverse transcribed molecules, which can disrupt coding regions, enhance the risk of mutations in tumour suppressor genes, and lead to sustained DNA damage. Susceptible individuals would then expectedly have an increased risk of DNA damage, chronic autoinflammation, autoimmunity and cancer.”
2. Angues RV and Bustos YP, “SARS-CoV-2 Vaccination and the Multi-Hit Hypothesis of Oncogenesis,” *Cureus* 2023, 15, 12: e50703. doi: [10.7759/cureus.50703](https://doi.org/10.7759/cureus.50703) ✓
  - “After reviewing the available literature, we are particularly concerned that certain COVID-19 vaccines may generate a pro-tumorigenic milieu (i.e., a specific environment that could lead to neoplastic transformation) that predisposes some (stable) oncologic patients and survivors to cancer progression, recurrence, and/or metastasis. This hypothesis is based on biological plausibility and fulfillment of the multi-hit hypothesis of oncogenesis (i.e., induction of lymphopenia and inflammation, downregulation of angiotensin-converting enzyme 2 (ACE2) expression, activation of oncogenic cascades, sequestration of tumor suppressor proteins, dysregulation of the



- RNA-G quadruplex-protein binding system, alteration of type I interferon responses, unsilencing of retrotransposable elements, etc.) together with growing evidence and safety reports filed to Vaccine Adverse Effects Report System (VAERS) suggesting that some cancer patients experienced disease exacerbation or recurrence following COVID-19 vaccination.”
3. Erdogdu B et al., “Hepatic Metabolic Dysregulation as a Potential Amplifier of Leukemogenesis Following mRNA Vaccination: A Novel Mechanistic Hypothesis,” *Medicina* 2025, 61, 9: 1687. doi: [10.3390/medicina61091687](https://doi.org/10.3390/medicina61091687) ✓
    - “We propose that mRNA vaccines, through their preferential hepatic tropism via lipid nanoparticles (LNPs), may transiently dysregulate hepatic metabolism in susceptible individuals, creating metabolic perturbations that amplify pre-existing leukemogenic vulnerabilities...”
  4. Erdogdu B et al., “Metabolomic Profiling of Leukemic Hematopoiesis: Effects of BNT162b2 mRNA COVID-19 Vaccine Administration,” *Cur Mol Med* 2025. doi: [10.2174/0115665240361878250601074746](https://doi.org/10.2174/0115665240361878250601074746) ✓
    - “This preliminary study identified altered metabolic pathways in leukemia bone marrow and suggests metabolomic differences associated with BNT162b2 vaccination. While the findings do not support a causal link between mRNA vaccination and leukemia development, they highlight the need for further studies to understand vaccine-induced metabolic modulation in hematological contexts.”
  5. Jaiswal A et al., “Oncogenic potential of SARS-CoV-2—targeting hallmarks of cancer pathways,” *Cell Commun. Signal.* 2024, 22, 447. doi: [10.1186/s12964-024-01818-0](https://doi.org/10.1186/s12964-024-01818-0) ✓
    - “Based on existing literature, a study suggested that the spike protein of the virus can stimulate Eph receptors, leading to the activation of pathways such as PI3K/AKT/ERK. Any perturbation within these pathways, whether caused by the activation or overexpression of extracellular signaling molecules or mutations in RTKs, has the potential to strongly drive oncogenesis... Docking analysis has further shown comparable binding affinity between the viral spike protein and EGFR/VEGFR in glioma cells, similar to angiotensin converting enzyme 2 (ACE2). Given that EGFR and VEGFR are commonly expressed in many tumor types, including glioma cells, this interaction suggests that the virus could activate EGFR and its downstream signaling, potentially exacerbating oncogenic pathways. Interestingly, various bioinformatic and in vitro studies have confirmed increased EGFR signaling and its downstream pathways, such as AKT and ERK1/2, in SARS-CoV-2 infected cells mediated by the spike RBD domain... Increased expression of oxidative markers is known to lead to ROS production, which plays a role in various stages of tumorigenesis. Therefore, it is plausible that the Spike protein, through its impact on oxidative markers and ROS expression, may contribute to DNA damage and oncogenesis... Additionally,

- another study also provided evidence supporting the role of spike protein in activating NF- $\kappa$ B and MAPK pathways as well as cytokine production in A549 lung cancer cells. Moreover, spike protein persistence in the blood post-acute COVID-19 raises concerns about long-term complications, as continual presence can perpetuate chronic inflammation, a key driver of tumor growth.”
6. Kim MJ et al., “The SARS-CoV-2 spike protein induces lung cancer migration and invasion in a TLR2-dependent manner,” *Cancer Commun* (London) 2023, 44, 2: 273–277. doi: [10.1002/cac2.12485](https://doi.org/10.1002/cac2.12485) ✓
    - “Upon treatment with the SARS-CoV-2 S protein, Pam3CSK4 (an agonist of TLR1/2), or FSL-1 (an agonist of TLR2/6), migration and invasion abilities of A549 and H1299 lung cancer cells were significantly enhanced compared to those upon treatment with vehicle control.”
  7. McKernan K, “DNA contamination in the mRNA vaccines. Decentralizing Peer Review,” presentation slides, October 2025, [PDF](#).
    - “The 10 ng limit is based on naked DNA. It never considered LNP protected DNA. Naked DNA has a 10 minute half life in the blood. LNP half life not know but assumed to be days to weeks... 50-500 billion SV40 Enhancers in every dose. This paper [Šenigi] demonstrates these recruit mutagenic enzymes and you don’t need Large Tumor Antigen for this to occur.”
  8. Olszewska B et al., “Rare COVID-19 vaccine side effects got lost in the shuffle. Primary cutaneous lymphomas following COVID-19 vaccination: a systematic review,” *Front. Med.* 2024, 11. doi: [10.3389/fmed.2024.1325478](https://doi.org/10.3389/fmed.2024.1325478) ✓
    - “The available literature suggests an association between the occurrence and exacerbation of CLs with immune stimulation following COVID-19 vaccination. We hypothesize that post-vaccine CLs result from an interplay between cytokines and disrupted signaling pathways triggered by vaccine components, concurrently playing a pivotal role in the pathomechanism of CLs.”
  9. Orient JM, “Negative Evidence: COVID-19 Vaccines and Cancer,” *J. Am. Phys. Surg.* 2023, 28, 1. <https://jpands.org/vol28no1/orient.pdf> ✓
    - “For all therapeutic agents except for COVID-19 vaccines, the approval process emphasized pre- and post-marketing surveillance aimed at detection of even the slightest carcinogenic properties of drugs and vaccines. This prudent paradigm was abandoned with introduction of COVID-19 vaccine.”
  10. Palakkott AR et al., “The SARS-CoV-2 Spike Protein Activates the Epidermal Growth Factor Receptor-Mediated Signaling,” *Vaccines* 2023, 11, 4: 768. doi: [10.3390/vaccines11040768](https://doi.org/10.3390/vaccines11040768) ✓
    - “The treatment of cells for 5 min with Spike (2.5  $\mu$ g/mL) promoted a strong phosphorylation of EGFR, AKT, and ERK1/2, which was either similar (EGFR and ERK1/2) or even higher (AKT) to that promoted by stimulation with the maximal

- dose of EGF (5 µg/mL). On the other hand, RBD (5 µg/mL) under a similar condition showed almost no effect on EGFR phosphorylation while it significantly induced AKT and ERK1/2 phosphorylation... Such spike 1 protein-engaged signaling pathways play a role in cancer cell survival that may explain the increased risk of COVID-19 infectivity reported in cancer patients.”
11. Raszek M et al., “Exploring the possible link between the spike protein immunoglobulin G4 antibodies and cancer progression,” *Explor Immunol.* 2024, 4: 267–284. doi: [10.37349/ei.2024.00140](https://doi.org/10.37349/ei.2024.00140) ✓
    - “Repeated inoculation with messenger RNA (mRNA) vaccines elicits immunoglobulin G4 (IgG4) antibody production. Such an increase in the concentration of specific and non-specific IgG4 antibodies allows the growth of some types of cancer by blocking the activation of effector immune cells. This work proposes the hypothesis that cancer growth may be indirectly promoted by increased concentrations of non-specific IgG4 antibodies by the following mechanisms: 1) IgG4 antibodies can bind to anti-tumor IgG1 antibodies and block their interaction with receptors located on effector cells, thus preventing the destruction of cancer cells, 2) IgG4 can interact with fragment crystallizable gamma receptor IIb (FcγRIIb) inhibitory receptors, thus reducing effector functions of innate immune cells, and 3) targeting of specific epitopes by IgG4 could be oncogenic by inducing the production of a microenvironment that can promote cancer development.”
  12. Rubio-Casillas A et al., “Review: N1-methyl-pseudouridine (m1Ψ): Friend or foe of cancer?” *Int J Biol Macromol.* 2024, 267, 1: 131427. doi: [10.1016/j.ijbiomac.2024.131427](https://doi.org/10.1016/j.ijbiomac.2024.131427) ✓
    - “Evidence is provided that adding 100 % of N1-methyl-pseudouridine (m1Ψ) to the mRNA vaccine in a melanoma model stimulated cancer growth and metastasis, while non-modified mRNA vaccines induced opposite results, thus suggesting that COVID-19 mRNA vaccines could aid cancer development. Based on this compelling evidence, we suggest that future clinical trials for cancers or infectious diseases should not use mRNA vaccines with a 100% m1Ψ modification, but rather ones with the lower percentage of m1Ψ modification to avoid immune suppression.”
  13. Šenigi F et al., “The SV40 virus enhancer functions as a somatic hypermutation-targeting element with potential tumorigenic activity,” *Tumour Virus Res.* 2024, 18: 200293. doi: [10.1016/j.tvr.2024.200293](https://doi.org/10.1016/j.tvr.2024.200293) ✓
    - “We demonstrate that the SV40 enhancer has strong somatic hypermutation targeting activity in several cell types and that AID-induced mutations accumulate in SV40 LT in B cells and kidney cells and cause truncated LT expression in B cells. Our results argue that the ability of the SV40 enhancer to target somatic hypermutation to LT is a potential source of LT truncation events

that could contribute to tumorigenesis in various cell types, thereby linking SV40 infection with malignant development through a novel mutagenic pathway.”

14. Simioni C et al., “Effects of SARS-COV-2 on molecules involved in vascularization and autophagy in placenta tissues,” *J. Mol. Histol.* 2024, 55, 753-764. doi: [10.1007/s10735-024-10228-y](https://doi.org/10.1007/s10735-024-10228-y) ✓
  - “Inflammation is a powerful inducer of the proangiogenic marker VEGF. In fact, our results show a positive association between virus SPIKE protein and VEGF detection.”
  
15. Simioni C et al., “Increase of VEGF and Fibronectin expression and ultrastructural alterations of intercellular junctions in a swab negative patient after SARS-COV-2 infection,” *Virol. J.* 2025, 22, 82. doi: [10.1186/s12985-025-02701-1](https://doi.org/10.1186/s12985-025-02701-1) ✓
  - “VEGF immunohistochemical expression was higher in the ulcer than in the control ileum sample and the non-ulcerated ileum areas and co-expressed with the SPIKE protein... The presence of the viral protein was also associated with an increase of VEGF and Fibronectin.”
  
16. Singh N and AB Singh, “S2 Subunit of SARS-nCoV-2 Interacts with Tumor Suppressor Protein p53 and BRCA: An in Silico Study,” *Transl. Oncol.* 2020, 13, 10: 100814. doi: [10.1016/j.tranon.2020.100814](https://doi.org/10.1016/j.tranon.2020.100814) ✓
  - “Here, we have investigated the interaction of S2 subunit to tumor suppressor and cell cycle-related proteins. HADDOCK 2.2 software was used to analyze the interaction and found that S2 subunit of SARS-nCov-2 strongly interacts with p53 and BRCA-1/2 proteins. p53 and BRCA are the well-known tumor suppressor proteins, that regulate downstream genes in response to numerous cellular stress and are frequently mutated in human cancer. Interestingly we found p53, BRCA-1 and BRCA-2 interact with heptic repeat-2 region of S2 subunit through C-terminal domain... This short bioinformatic analysis is a first time report and significant since COVID-19 is more fatal in people with underlying conditions specially lung diseases, diabetes and cancer.”
  
17. Stati G et al., “Concern about the Effectiveness of mRNA Vaccination Technology and Its Long-Term Safety: Potential Interference on miRNA Machinery,” *Int. J. Mol. Sci.* 2023, 24, 2: 1404. [10.3390/ijms24021404](https://doi.org/10.3390/ijms24021404) ✓
  - “The interaction between the vaccine and the host cell is finely regulated by miRNA machinery, a complex network that oversees a wide range of biological processes. The dysregulation of miRNA machinery has been associated with the development of clinical complications during COVID-19 infection and, moreover, to several human pathologies, among which is cancer disease.”
  
18. Talotta R, “Impaired VEGF-A-Mediated Neurovascular Crosstalk Induced by SARS-CoV-2 Spike Protein: A Potential Hypothesis Explaining Long COVID-19 Symptoms

and COVID-19 Vaccine Side Effects?” *Microorganisms* 2022, 10, 12: 2452. doi: [10.3390/microorganisms10122452](https://doi.org/10.3390/microorganisms10122452) ✓

- “In humans, the NRP-1/VEGF-A complex has been extensively studied in cancer, due to its role in tumor progression and invasiveness. Regardless of tumor type, malignant cells overexpress NRP-1 and are thus more sensitive to the mitogenic effects of VEGF and other mediators.”

19. Zeng FM et al., “SARS-CoV-2 spike spurs intestinal inflammation via VEGF production in enterocytes,” *EMBO Mol Med.* 2022, 14: e14844. doi: [10.15252/emmm.202114844](https://doi.org/10.15252/emmm.202114844) ✓

- “Mechanistically, SARS-CoV-2 spike promoted VEGF production through activating the Ras-Raf-MEK-ERK signaling in enterocytes, but not in endothelium, and inducing permeability and inflammation.”

20. Zhang S and WS El-Deiry, “Transfected SARS-CoV-2 Spike DNA for Mammalian Cell Expression Inhibits P53 Activation of p21(WAF1), TRAIL Death Receptor DR5 and MDM2 Proteins in Cancer Cells and Increases Cancer Cell Viability After Chemotherapy Exposure,” *Oncotarget* 2024, 15, 1: 275–284. doi: [10.18632/oncotarget.28582](https://doi.org/10.18632/oncotarget.28582) ✓

- “Further observations on  $\gamma$ -H2AX expression in spike-expressing cells treated with cisplatin may indicate altered DNA damage sensing in the DNA damage response pathway. The preliminary observations reported here warrant further studies to unravel the impact of SARS-CoV-2 and its various encoded proteins including spike on pathways of tumorigenesis and response to cancer therapeutics. More efforts should be directed at studying the effects of the SARS-CoV-2 spike and other viral proteins on host DNA damage sensing, response and repair mechanisms.”

### C. DNA damage, contamination and integration risks (ANNOTATED REFERENCES, 50/54 peer-reviewed ✓)

The following research collection shows that COVID “vaccines” can damage human DNA by various means, including creation of reactive oxygen species (ROS) and oxidative stress induced by the spike protein and nanoparticles, leading to activation of the [cGAS-STING](#) pathway, an innate immune signal for DNA damage. Recombinant spike proteins have been shown to facilitate the formation of micronuclei through cell fusion (syncytium), also connected with DNA damage and cGAS-STING activation, raising the possibility that “vaccine”-derived spike proteins may do the same (Lazebnik Y, Santana LAM et al., Sfera A et al.).

DNA damage repair creates an [opportunity](#) for the [integration](#) of [foreign plasmid DNA](#) into [cellular DNA](#). Moreover, research presented here confirms the [contamination](#) of “vaccines” with residual DNA as a manufacturing byproduct. Taken together these facts suggest that DNA damage repair after “vaccination” may result in integration of contaminant DNA from the “vaccines” into the human genome.

Additionally, the presence of the cancer-promoting SV40 enhancer gene in the mRNA “vaccines” is once again confirmed by research presented here. Finally, studies summarized here document ribosomal frameshifting as well as “vaccine” interference in epigenetic mechanisms, potentially resulting in off-target protein production and disruption of ordinary cellular processes.

1. Ahmed M et al., “Role of NLRP3 inflammasome in nanoparticle adjuvant-mediated immune response,” *Biomater. Sci.* 2025, 13: 2164-2178. doi: [10.1039/D4BM00439F](#) ✓
  - “Reactive oxygen species (ROS) are essential for cells to respond to stress through signal transduction. If the production of ROS continues to increase, the cellular antioxidant system will become underpowered, resulting in oxidative stress, cell damage, and maybe even cell death. Nanoparticles generating ROS have been shown to induce NLRP3 activation.”
2. Aldén M 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](#) ✓
  - “Our results indicate a fast up-take of BNT162b2 into human liver cell line Huh7, leading to changes in LINE-1 expression and distribution. We also show that BNT162b2 mRNA is reverse transcribed intracellularly into DNA in as fast as 6 h upon BNT162b2 exposure.”
3. Aochi S et al., “IgG4-related Disease Emerging after COVID-19 mRNA Vaccination,” *Intern Med.* 2023, 62, 10: 1547–1551. doi: [10.2169/internalmedicine.1125-22](#) ✓



- “After vaccination, coupled with effective anti-SARS-CoV-2-neutralizing antibody production, healthy individuals experience an acute increase in type I interferon (IFN) expression by peripheral blood mononuclear cells and the accumulation of DNA damage.”
4. Banoun H, “mRNA: Vaccine or Gene Therapy? The Safety Regulatory Issues,” *Int. J. Mol. Sci.* 2023, 24, 13: 10514. doi: [10.3390/ijms241310514](https://doi.org/10.3390/ijms241310514) ✓
    - “The mode of action of COVID-19 mRNA vaccines should classify them as gene therapy products (GTPs), but they have been excluded by regulatory agencies. Some of the tests they have undergone as vaccines have produced non-compliant results in terms of purity, quality and batch homogeneity... Long-term expression, integration into the genome, transmission to the germline, passage into sperm, embryo/fetal and perinatal toxicity, genotoxicity and tumorigenicity should be studied in light of the adverse events reported in pharmacovigilance databases. The potential horizontal transmission (i.e., shedding) should also have been assessed. In-depth vaccinovigilance should be carried out. We would expect these controls to be required for future mRNA vaccines developed outside the context of a pandemic.”
  5. Barhoumi T et al., “SARS-CoV-2 coronavirus Spike protein-induced apoptosis, inflammatory, and oxidative stress responses in THP-1-like-macrophages: potential role of angiotensin-converting enzyme inhibitor (perindopril),” *Front Immunol.* 2021, 12: 728896. doi: [10.3389/fimmu.2021.728896](https://doi.org/10.3389/fimmu.2021.728896) ✓
    - “A purified spike (S) glycoprotein of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) coronavirus was used to study its effects on THP-1 macrophages, peripheral blood mononuclear cells (PBMCs), and HUVEC cells... We observed an increase in apoptosis, ROS generation, MCP-1, and intracellular calcium expression in the THP-1 macrophages.”
  6. Beaudoin CA et al., “Are there hidden genes in DNA/RNA vaccines?” *Immune Front.* 2022, 8, 13: 801915. doi: [10.3389/fimmu.2022.801915](https://doi.org/10.3389/fimmu.2022.801915) ✓
    - “Vaccination campaigns have reported high vaccination rates and protection, but numerous unintended effects, ranging from muscle pain to death, have led to concerns about the safety of RNA/DNA vaccines. In parallel to these studies, several open reading frames (ORFs) have been found to be overlapping SARS-CoV-2 accessory genes, two of which, ORF2b and ORF-Sh, overlap the spike protein sequence. Thus, the presence of these, and potentially other ORFs on SARS-CoV-2 DNA/RNA vaccines, could lead to the translation of undesired proteins during vaccination.”
  7. Buckhaults P, “The Pfizer mRNA Vaccine Is Contaminated with the Plasmid DNA Vector That Was Used as the Template for In Vitro Transcription Reaction. Presentation to the Senate of South Carolina.” Testimony transcript, September 12, 2023, available online (PDF):



[www.scstatehouse.gov/CommitteeInfo/SenateMedicalAffairsCommittee/PandemicPreparedness/Phillip-Buckhaults-SC-Senate-09122023-final.pdf](http://www.scstatehouse.gov/CommitteeInfo/SenateMedicalAffairsCommittee/PandemicPreparedness/Phillip-Buckhaults-SC-Senate-09122023-final.pdf)

- “This DNA could be the cause of some of the rare but serious side effects like death from cardiac arrest. The DNA can and likely will integrate into the genomes of transfected cells. There is a very real hazard for genome modification of long-lived somatic cells, which could cause sustained autoimmune attack toward that tissue. There is also a theoretical risk of future cancer, depending on the piece of DNA and site of integration.”
8. Chang YS et al., “Network Analysis of Dysregulated Immune Response to COVID-19 mRNA Vaccination in Hemodialysis Patients,” *Vaccines* 2024, 12, 10: 1146. doi: [10.3390/vaccines12101146](https://doi.org/10.3390/vaccines12101146) ✓
    - “There is a wealth of evidence demonstrating TLR-induced alterations of the epigenetic landscape, leading to both increased and decreased expression of TLR-induced genes. For example, in macrophages, LPS signaling through TLR4 alters chromatin accessibility at TLR-responsive inflammatory genes including IL-6. In support of a mediating role of type 1 IFN in the TLR dysfunction leading to the impaired maturation and activation of DCs, type I IFN has also been shown to catalyze the methylation of promoters of NF-kB-responsive genes. Additionally, oxidative stress has been shown to alter DNA methylation profiles, including in peripheral blood. In fact, oxidative damage to a methyl-CpG site in a methyl-binding protein recognition sequence has been shown to substantially reduce the binding affinity of MECP2.”
  9. Chen Y et al., “New-onset autoimmune phenomena post-COVID-19 vaccination,” *Immunology* 2022, 165, 4: 386-401. doi: [10.1111/imm.13443](https://doi.org/10.1111/imm.13443) ✓
    - “Post-vaccination healthy individuals exhibit acute increases in type I IFN expression, oxidative stress and DNA damage accumulation in blood mononuclear cells, coupled with effective anti-SARS-CoV-2-neutralizing antibody production.”
  10. Cimolai N, “Do RNA vaccines obviate the need for genotoxicity studies?” *Mutagenesis*, 2020, 35, 6: 509–510. doi: [10.1093/mutage/geaa028](https://doi.org/10.1093/mutage/geaa028) ✓
    - “Until any such hypothetical concerns are tested or observed from vaccination or natural infection, regulatory safety assessments of RNA vaccines should include genotoxicity studies... it is yet surprising that there is a dearth of such data published widely in the scientific and medical communities.”
  11. Demongeot J and C Fougere, “mRNA COVID-19 Vaccines—Facts and Hypotheses on Fragmentation and Encapsulation,” *Vaccines* 2023, 11, 1: 40. doi: [10.3390/vaccines11010040](https://doi.org/10.3390/vaccines11010040) ✓
    - “Results: by using data coming from genetic and epidemiologic databases, we show the theoretical possibility of fragmentation of this mRNA into small RNA

sequences capable of inhibiting important bio-syntheses such as the production of beta-globin.”

12. Doerfler S, “Adenoviral Vector DNA- and SARS-CoV-2 mRNA-Based Covid-19 Vaccines: Possible Integration into the Human Genome—Are Adenoviral Genes Expressed in Vector-based Vaccines?” *Virus Res.* 2021, 302: 198466. doi: [10.1016/j.virusres.2021.198466](https://doi.org/10.1016/j.virusres.2021.198466) ✓
  - “Adenovirus vector-based vaccines can lead to the integration of adenovirus DNA at unknown frequency and with unpredictable epigenetic consequences. It is conceivable that epigenetic effects might be noticed only years after vaccination. The adenoviral genes still present in the adenovirus vector DNA might become trans-activated by cellular factors and lead to individually varying immune memory reactions that are experienced by vaccinees as transient post-vaccination symptoms.”
13. Domaset-Lošo T, “mRNA Vaccines: Why Is the Biology of Retroposition Ignored?” *Genes* 2022, 13, 5: 719. doi: [10.3390/genes13050719](https://doi.org/10.3390/genes13050719) ✓
  - “Current engineering strategies and declared future directions for the improvement of mRNA vaccines do not consider the possibility of vaccine mRNA genome integration via L1 retroelements native to human cells. This is at odds with the knowledge base on the biology of L1-mediated retroposition and its role in the genetics, development and evolution of humans. Why this risk is overlooked is even more obscure given that mRNA retroposition is a biomedically recognized phenomenon outside vaccinology.”
14. 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: [10.1111/eci.14296](https://doi.org/10.1111/eci.14296) ✓
  - “LNPs also stimulate ROS generation, which induces cytotoxicity and affects intracellular signalling pathways. ROS acts as a second messenger in many intracellular signalling cascades. It can lead to cellular macromolecular damage, such as DNA fragmentation, membrane lipid breakdown, protein denaturation and mitochondrial dysfunction, significantly affecting cell metabolism and signalling, resulting in deleterious effects on cell viability, proliferation and cell death. The general belief is that the excessive ROS levels produced by NPs are the main reason for their cytotoxicity... Furthermore, Pfizer and Moderna use N1-methyl-pseudouridine-modified mRNA to minimize inherent mRNA immunogenicity; however, internalization of foreign mRNA into the cytosol is detected by intracellular RNA sensors, such as endosomal TLR and cytoplasmic nucleic acid sensors. Binding of mRNA to these host defence receptors will activate innate immune pathways, leading to the expression of hundreds of genes... Antisense RNA can interact directly or indirectly with DNA methyltransferase, interfering with DNA methylation and gene transcription. Therefore, synthetic mRNA can eventually lead to epigenetic and/or genomic

modifications in dividing and nondividing cells. It can lead to modifications of the chromatin structure, chromosomal integration of retrotranscribed synthetic mRNA, genotoxicity and oncogenesis following mRNA vaccine uptake. Synthetic mRNA has been shown to activate the expression of endogenous transposable elements, undergo reverse transcription and enter the cell nucleus... Free plasmid DNA also induces the production of pro-inflammatory cytokines, where the immune response is significantly enhanced when lipid-DNA complexes are used... The exact ratio of linear fragmented DNA versus intact circular plasmid DNA is unknown. However, there is a risk of genome integration, since double-stranded DNA contamination of the sequence encoding the GVG Sp will not require LINE-1 for reverse transcription.”

15. Gimenez S et al., “Monocytic reactive oxygen species–induced T-cell apoptosis impairs cellular immune response to SARS-CoV-2 mRNA vaccine,” *J Allergy Clin Immunol* 2025, 155, 5: 1635-1646. doi: [10.1016/j.jaci.2025.01.003](https://doi.org/10.1016/j.jaci.2025.01.003) ✓
  - “In most vaccinees, we observed that the presence of circulating RBD peaked on day 14 and was linked to an increase in AngII plasma levels with a peak on day 28. This increase correlated with the ability of monocytes to produce ROS and to induce ROS-mediated DNA damage in neighboring cells, including PBMCs...”
16. Greenberger JS et al., “SARS-CoV-2 Spike Protein Induces Oxidative Stress and Senescence in Mouse and Human Lung,” *In Vivo* 2024, 38, 4: 1546-1556. doi: [10.21873/invivo.13605](https://doi.org/10.21873/invivo.13605) ✓
  - “SARS-CoV-2 spike protein induced reactive oxygen species, DNA double-strand breaks, transforming growth factor- $\beta$  signaling pathways, and senescence...”
17. Heil M, “Self-DNA driven inflammation in COVID-19 and after mRNA-based vaccination: lessons for non-COVID-19 pathologies,” *Front. Immunol.* 2023, 14 (Molecular Innate Immunity). doi: [10.3389/fimmu.2023.1259879](https://doi.org/10.3389/fimmu.2023.1259879) ✓
  - “... similar mechanisms to those driven by gp41 can explain how inflammatory self-DNA contributes to some of most frequent adverse events after vaccination with the BNT162b2 mRNA (Pfizer/BioNTech) or the mRNA-1273 (Moderna) vaccine, i.e., myocarditis, herpes zoster, rheumatoid arthritis, autoimmune nephritis or hepatitis, new-onset systemic lupus erythematosus, and flare-ups of psoriasis or lupus.”
18. Kämmerer U et al., “BioNTech RNA-Based COVID-19 Injections Contain Large Amounts Of Residual DNA Including An SV40 Promoter/Enhancer Sequence,” *Science, Public Health Policy and the Law*, 2024, 5: <https://publichealthpolicyjournal.com/biontech-rna-based-covid-19-injections-contain-large-amounts-of-residual-dna-including-an-sv40-promoter-enhancer-sequence/> ✓
  - “We further analyzed RNA and DNA contents of these vials and identified large amounts of DNA after RNase A digestion in all lots with concentrations ranging

from 32.7 ng to 43.4 ng per clinical dose. This far exceeds the maximal acceptable concentration of 10 ng per clinical dose that has been set by international regulatory authorities. Gene analyses with selected PCR primer pairs proved that residual DNA represents not only fragments of the DNA matrices coding for the spike gene, but of all genes from the plasmid including the SV40 promoter/enhancer and the antibiotic resistance gene. Conclusion: Our results raise grave concerns regarding the safety of the BNT162b2 vaccine and call for an immediate halt of all RNA biologicals unless these concerns can be dispelled.”

19. Kankaya S et al., “Glutathione-related antioxidant defence, DNA damage, and DNA repair in patients suffering from post-COVID conditions,” *Mutagenesis* 2023, 38, 4: 216-226. doi: [10.1093/mutage/gead021](https://doi.org/10.1093/mutage/gead021) ✓
  - “In the control group, GSH level and post-repair DNA damage were higher in the vaccinated individuals. In conclusion, oxidative stress formed due to the immune response against SARS-COV-2 may impair DNA repair mechanisms.”
20. König B and JO Kirchner, “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](https://doi.org/10.3390/mps7030041) ✓
  - “In fact, the manufacturer of the mRNA vaccine Comirnaty (BioNTech/Pfizer) only measures DNA impurities in the active substance by means of a quantitative polymerase chain reaction (qPCR), whose DNA target sequence is less than just 1% of the originally added DNA template. This means that no direct DNA quantification takes place, and compliance with the limit value for DNA contamination is only estimated from the qPCR data using mathematical extrapolation methods. However, it is also possible to dissolve the lipid nanoparticles with a detergent to directly measure DNA contamination in the final product by using fluorescence spectroscopic methods. Experimental testing of this approach confirms that reliable values can be obtained in this way.”
21. Lazebnik Y, “Cell fusion as a link between the SARS-CoV-2 spike protein, COVID-19 complications, and vaccine side effects,” *Oncotarget* 2021, 12, 25: 2476-2488. doi: [10.18632/oncotarget.28088](https://doi.org/10.18632/oncotarget.28088) ✓
  - “Given that spike expressed by SARS-CoV-2 fuses cells in COVID-19 patients, that spike expressed by viral vectors or by transfection fuses human cells in the dish, and that spike fuses cells even if expressed in undetectable amounts, it is reasonable to presume, until proven otherwise, that spike does fuse some cells in the injected individuals.”
22. Lee JH et al., “COVID-19 Molecular Pathophysiology: Acetylation of Repurposing Drugs,” *Int. J. Mol. Sci.* 2022, 23, 21: 13260. doi: [10.3390/ijms232113260](https://doi.org/10.3390/ijms232113260) ✓

- “A SARS-CoV-2 infection could induce syncytia formation within cells expressing ACE2 and the SARS-CoV-2 spike protein, producing micronuclei at an average rate of approximately four per syncytium (>93%). These micronuclei are expressed with a high activation level for the DNA damage response and cGAS–STING signaling. These signaling pathways are associated with cellular catastrophe and aberrant immune activation at the cellular and molecular levels.”
23. Li C et al., “Mechanisms of innate and adaptive immunity to the Pfizer-BioNTech BNT162b2 vaccine,” *Nat. Immunol.* 2022, 23: 543-555. doi: [10.1038/s41590-022-01163-9](https://doi.org/10.1038/s41590-022-01163-9) ✓
- “... BNT162b2 induced damage-associated molecular pattern signals, including double-stranded DNA and HMGB1 peaking at 24 h after immunization...”
24. Liu X et al., “SARS-CoV-2 spike protein-induced cell fusion activates the cGAS-STING pathway and the interferon response,” *Sci Signal.* 2022, 15, 729: eabg8744. doi: [10.1126/scisignal.abg8744](https://doi.org/10.1126/scisignal.abg8744) ✓
- “The fused cells exhibited DNA damage and micronuclei, which colocalized with the cytosolic DNA sensor cGAS, and that led to the activation of the adaptor protein STING and stimulated the expression of genes encoding type I IFNs and of IFN-stimulated genes.”
25. Lucchesi S et al., “Transcriptomic analysis after SARS-CoV-2 mRNA vaccination reveals a specific gene signature in low-responder hemodialysis patients,” *Front Immunol.* 2025, 16: 1508659. doi: [10.3389/fimmu.2025.1508659](https://doi.org/10.3389/fimmu.2025.1508659) ✓
- “HDP-low represented 45% of the HDP cohort and were characterized by alterations in genes associated with pre-existing chronic inflammation, cell cycle, EPO-related pathways, reduced expression of B cell-related genes at baseline, and genes potentially correlated with renal disease, while further differences emerged in genes involved in B cell regulation and survival at day 7.”
26. Lymperaki E et al., “A Preliminary Study about the Role of Reactive Oxygen Species and Inflammatory Process after COVID-19 Vaccination and COVID-19 Disease,” *Clin. Pract.* 2022, 12, 4: 599-608. doi: [10.3390/clinpract12040063](https://doi.org/10.3390/clinpract12040063) ✓
- “Our preliminary data after the first stage of analysis (ROS level measurement in a small mRNA-vaccinated group) support the hypothesis that ROS levels are affected by vaccination and may result in a proportional response to antibody production, which prompted us to further investigate the relationship between ROS and antibody production (second stage). Our study was driven by the question of whether ROS could be used as a biomarker of efficient antibody development after vaccination. The first dose of mRNA vaccination resulted in an increase in ROS levels, which remained high until before the second dose, although antibody levels were low after the first dose and increase before the

second dose. After the second dose ROS levels seemed to be lower and stabilized, and antibody levels also stabilized.”

27. Mardomi A et al., “Genotoxicity: A Neglected but Potentially Critical Aspect of Adenoviral COVID-19 Vaccines,” *Future Virol.* 2023, 18, 15: 971-973. doi: [10.2217/fvl-2023-0013](https://doi.org/10.2217/fvl-2023-0013) ✓
  - “Although adenoviral vectors are known for transient gene expression, their expression has been documented for up to 7 years and there is evidence that adenoviral vectors are capable of genome integration in a random manner.”
28. McKernan K, “DNA contamination in the mRNA vaccines. Decentralizing Peer Review,” presentation slides, October 2025, [PDF](#).
  - “The 10 ng limit is based on naked DNA. It never considered LNP protected DNA. Naked DNA has a 10 minute half life in the blood. LNP half life not know but assumed to be days to weeks... 50-500 billion SV40 Enhancers in every dose. This paper [Šenigi] demonstrates these recruit mutagenic enzymes and you don’t need Large Tumor Antigen for this to occur.”
29. McKernan K et al., “Sequencing of bivalent Moderna and Pfizer mRNA vaccines reveals nanogram to microgram quantities of expression vector dsDNA per dose,” 2023, OSF preprint. doi: [10.31219/osf.io/b9t7m](https://doi.org/10.31219/osf.io/b9t7m)
  - “Several methods were deployed to assess the nucleic acid composition of four expired vials of the Moderna and Pfizer bivalent mRNA vaccines. Two vials from each vendor were evaluated with Illumina sequencing, qPCR, RT-qPCR, Qubit™ 3 fluorometry and Agilent Tape Station™ electrophoresis. Multiple assays support DNA contamination that exceeds the European Medicines Agency (EMA) 330ng/mg requirement and the FDAs 10ng/dose requirements. These data may impact the surveillance of vaccine mRNA in breast milk or plasma as RT-qPCR assays targeting the vaccine mRNA cannot discern DNA from RNA without RNase or DNase nuclease treatments. Likewise, studies evaluating the reverse transcriptase activity of LINE-1 and vaccine mRNA will need to account for the high levels of DNA contamination in the vaccines. The exact ratio of linear fragmented DNA versus intact circular plasmid DNA is still being investigated. Quantitative PCR assays used to track the DNA contamination are described.”
30. Meyer K et al., “SARS-CoV-2 Spike Protein Induces Paracrine Senescence and Leukocyte Adhesion in Endothelial Cells,” *J. Virol.* 2021, 95, e0079421. doi: [10.3390/v13112209](https://doi.org/10.3390/v13112209) ✓
  - “Here, we measured intracellular ROS and observed an approximately 3-fold increase in ROS in A549 spike-transfected cells compared to levels in empty plasmid-transfected control cells. Increased production of intracellular ROS contributes to DNA damage, leading to cellular senescence. We observed an increase in the DNA damage response marker  $\gamma$ -H2AX in cells transfected with the viral spike gene.  $\gamma$ -H2AX was found to be localized to the nucleus in viral



- spike-transfected A549 cells. Our results indicated that SARS-CoV-2 spike protein expression induces a senescent state in spike-transfected A549 cells that is associated with the DNA damage response and increased ROS generation.”
31. Mosavie M et al., “Changes in Phenotypic and Molecular Features of Naïve and Central Memory T Helper Cell Subsets following SARS-CoV-2 Vaccination,” *Vaccines* 2024, 12, 9: 1040. doi: [10.3390/vaccines12091040](https://doi.org/10.3390/vaccines12091040) ✓
    - “Compared with the unvaccinated, the vaccinated had higher HLA-DR expression in CD4+ T subsets, a greater number of differentially expressed genes (DEGs) that overlapped with key differentially accessible regions (DARs) along the chromatin linked to inflammasome activation, translation, regulation (of apoptosis, inflammation), and significant changes in clonal architecture beyond SARS-CoV-2 specificity... These genes play roles in apoptosis regulation, inflammasome regulation, antiviral response regulation, associated with autoimmune diseases and inflammation, translation regulation, and chromatin remodeling. They are also involved in tissue injury repair, antibacterial function, tumor promotion, and *ADAM19* is linked to the regulation of human dendritic cells, respectively.”
  32. Mulrone TE et al., “N1-methylpseudouridylation of mRNA causes +1 ribosomal frameshifting,” *Nature* 2024, 625: 189-194. doi: [10.1038/s41586-023-06800-3](https://doi.org/10.1038/s41586-023-06800-3) ✓
    - “Here we demonstrate that incorporation of N1-methylpseudouridine into mRNA results in +1 ribosomal frameshifting in vitro and that cellular immunity in mice and humans to +1 frameshifted products from BNT162b2 vaccine mRNA translation occurs after vaccination... these data highlight potential off-target effects for future mRNA-based therapeutics and demonstrate the requirement for sequence optimization.”
  33. Ntouros PA et al., “Effective DNA damage response after acute but not chronic immune challenge: SARS-CoV-2 vaccine versus Systemic Lupus Erythematosus,” *Clin. Immunol.* 2021, 229: 108765. doi: [10.1016/j.clim.2021.108765](https://doi.org/10.1016/j.clim.2021.108765) ✓
    - “By studying vaccinations against Influenza and SARS-CoV-2 (mRNA-based) we found acute increases of type-I interferon-inducible gene expression, oxidative stress and DNA damage accumulation in blood mononuclear cells of 9 healthy controls, coupled with effective anti-SARS-CoV-2 neutralizing antibody production in all. Increased DNA damage after SARS-CoV-2 vaccine, partly due to increased oxidative stress, was transient, whereas the inherent DNA repair capacity was found intact.”
  34. Ntouros PA et al., “Oxidative stress and endogenous DNA damage in blood mononuclear cells may predict anti-SARS-CoV-2 antibody titers after vaccination in older adults,” *Biochim. Biophys. Acta Mol. Basis Dis.* 2022, 1868: 166393. doi: [10.1016/j.bbadis.2022.166393](https://doi.org/10.1016/j.bbadis.2022.166393) ✓



- “Humoral vaccination response correlates inversely with pre-existing oxidative stress and DNA damage. Reduced vaccination response in the elderly is affected by increased oxidative stress and DNA damage... Particularly, the induction of oxidative stress may lead to the formation of oxidative DNA damage which then triggers the activation of the DNA damage response (DDR) network.”
35. Papanikolaou C et al., “Delineating the SARS-CoV-2 induced interplay between the host immune system and the DNA damage response network,” *Vaccines* 2022, 10: 1746. doi: [10.3390/vaccines10101764](https://doi.org/10.3390/vaccines10101764) ✓
- “They found that 24 h after SARS-CoV-2 vaccination (Comirnaty, Pfizer-BioNTech), peripheral blood mononuclear cells (PBMCs) of healthy individuals showed a transient increase of type I IFN, combined with elevated oxidative stress and accumulation of DNA damage; vaccination did not influence the DNA repair capacity of PBMCs. All these parameters resumed regular levels a few days later. Collectively, these data show that SARS-CoV-2 vaccination, as an acute immune stimulant, successfully triggers the DDR network. Moreover, the cytokine profile of the vaccinated individuals reveals a distinct interleukin 15, interferon gamma and IP10/CXCL10 signature, which correlates with effective immune activation.”
36. Parry PL et al., “‘Spikeopathy’: COVID-19 Spike Protein Is Pathogenic, from Both Virus and Vaccine mRNA,” *Biomedicine* 2023, 11, 8: 2287. doi: [10.3390/biomedicines11082287](https://doi.org/10.3390/biomedicines11082287) ✓
- “The molecular mechanisms involved in nanoparticle toxicity to the reproductive system are not fully understood, but possible mechanisms include oxidative stress, apoptosis, inflammation, and genotoxicity through induction of reactive oxygen species (ROS), causing damage at the molecular and genetic levels which results in cytotoxicity and DNA damage.”
37. Raoult D, “Confirmation of the presence of vaccine DNA in the Pfizer anti-COVID-19 vaccine,” HAL preprint, 2024. <https://hal.science/hal-04778576v1>
- “Three studies reported the presence of DNA in significant amounts in Pfizer mRNA vaccines. We aimed to confirm the presence of this residual DNA. Vaccine plasmid DNA quantification using the Qubit fluorometer on a vaccine vial showed it was 216 ng/dose on average and approximately 24 times greater, reaching 5,160 ng/dose on average, after treatment with Triton-X-100. In addition, we obtained by next-generation sequencing the sequence of the complete plasmid DNA vaccine matrix (7,824 base pairs) with high coverage (98.3%) and sequencing depths (mean, 4,181-4,389 reads), indicating the presence of the plasmid DNA in high copy number. These results call for an assessment of the copy number and nature of DNA in mRNA vaccines at a larger scale and in multiple batches, notably regarding the putative risk of DNA integration after delivery into cells.”

38. Ren H et al., “Micronucleus production, activation of DNA damage response and cGAS-STING signaling in syncytia induced by SARS-CoV-2 infection,” *Biol. Direct.* 2021, 16, 20. doi: [10.1186/s13062-021-00305-7](https://doi.org/10.1186/s13062-021-00305-7) ✓
- “Since cGAS was a known cytoplasmic DNA sensor that signals to upregulate interferon (IFN) expression to activate the anti-virus response, we hypothesize that the micronuclei formed in the syncytial cytosol might be recognized by cGAS to activate IFN response. In line with this idea, immunostaining indicated a strong localization of cGAS on the micronuclei formed in syncytia induced by either spike transfection and SARS-CoV-2 infection... Consistent with the typical subcellular localization pattern of cGAS and IRF3, the expression of IFN (IFNB1) and its downstream target genes (IFIT2, CCL5, CXCL10) were all significantly upregulated in cells forming syncytia upon spike expression as compared with control cells in agreement with the activation of cGAS-STING signaling, the upregulated expression of IFN and its target genes took place concomitantly with increased expression and phosphorylation of cGAS, STING and IRF3 proteins as detected by Western blot.”
39. Ritskes-Hoitinga M et al., “The Promises of Speeding Up: Changes in Requirements for Animal Studies and Alternatives during COVID-19 Vaccine Approval–A Case Study,” *Animals* 2022, 12, 13: 1735. doi: [10.3390/ani12131735](https://doi.org/10.3390/ani12131735) ✓
- “We could identify no toxicokinetic studies performed in the pre-clinical phase, consistent with WHO guidelines on the non-clinical evaluation of vaccines. No genotoxicity and carcinogenicity studies were performed, as all components of the vaccine constructs are lipids and RNA and are, as such, not expected to have genotoxic, carcinogenic, or tumorigenic potential. No separate studies have been performed to determine local tolerance or generate data on prenatal and postnatal development, including maternal function, dosing or further evaluating offspring, which is why, initially, the vaccine was not recommended for pregnant women. Vaccines are generally thought to hardly pass through the placenta, but we need more research into the risks of vaccinations during pregnancy (interviewees 10 and 11, regulatory agency representatives). No data on reproductive toxicity was provided during authorisation either, as it was not deemed necessary at the time of approval.”
40. Roncati L et al., “pDNA Impurities in mRNA Vaccines,” *Microorganisms* 2025, 13, 9: 1975. doi: [10.3390/microorganisms13091975](https://doi.org/10.3390/microorganisms13091975) ✓
- “Although mRNA technology is remarkable and designed to be safe and effective at the same time, news of the presence of DNA impurities in mRNA vaccine vials has caused a stir. These impurities, in fact, derive from the pDNA used as a template in the production of the vaccine itself. Some researchers argue that they were at concentrations permitted by the WHO and regulatory authorities (<10 ng/dose) others claim that they were well above the maximum limit even after the purification process.”

41. Santana LAM et al., "Cytogenetic Alterations Observed in Exfoliative Cells of the Tongue and Oral Mucosa of SARS-CoV-2-Vaccinated Patients: Report of Two Cases and a Brief Literature Review," *Rev. Soc. Bras. Med. Trop.* 2025, 58. doi: [10.1590/0037-8682-0008-2025](https://doi.org/10.1590/0037-8682-0008-2025) ✓
- "Mutagenesis is associated with the occurrence of micronuclei, and their presence is an important biomarker for the assessment of genomic instability, and consequently, carcinogenesis. On the other hand, cytotoxicity represents the risk of cell death, being characterized by the presence of alterations like karyolysis and karyorrhexis. In our study, the main cytogenetic alterations observed were micronuclei formation, karyolysis, binucleation, and pyknosis..."
42. Sattar S et al., "Nuclear translocation of spike mRNA and protein is a novel feature of SARS-CoV-2," *Front. Microbiol.* 2023, 14 (Virology). doi: [10.3389/fmicb.2023.1073789](https://doi.org/10.3389/fmicb.2023.1073789) ✓
- "Although the S protein is a surface transmembrane type 1 glycoprotein, it has been predicted to be translocated into the nucleus due to the novel nuclear localization signal (NLS) 'PRRARSV,' which is absent from the S protein of other coronaviruses. Indeed, S proteins translocate into the nucleus in SARS-CoV-2-infected cells. S mRNAs also translocate into the nucleus. S mRNA colocalizes with S protein, aiding the nuclear translocation of S mRNA."
43. Šenigi F et al., "The SV40 virus enhancer functions as a somatic hypermutation-targeting element with potential tumorigenic activity," *Tumour Virus Res.* 2024, 18: 200293. doi: [10.1016/j.tvr.2024.200293](https://doi.org/10.1016/j.tvr.2024.200293)
- "Our results argue that the ability of the SV40 enhancer to target somatic hypermutation to LT is a potential source of LT truncation events that could contribute to tumorigenesis in various cell types, thereby linking SV40 infection with malignant development through a novel mutagenic pathway."
44. Sfera A et al., "COVID-19 mRNA Vaccines and Pathological Cell-Cell Fusion: An Unintended Consequence," *JIRID* 2022, 2, 1: 1-9. [www.acadwize.com/open-access/covid-19-mrna-vaccines-and-pathological-cell-cell-fusion-an-unintended-consequence-438.pdf](https://www.acadwize.com/open-access/covid-19-mrna-vaccines-and-pathological-cell-cell-fusion-an-unintended-consequence-438.pdf) ✓
- "[Syncytia] may explain the rare postvaccination events associated with cell-cell fusion, including giant cell myocarditis, giant cell arteritis, and CreutzfeldtJakob Disease, recorded in Vaccine Adverse Event Reporting System (VAERS) database..."
45. Speicher DJ et al., "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](https://doi.org/10.1080/08916934.2025.2551517) ✓
- "Manufacturing nucleoside-modified mRNA (modRNA) for commercial COVID-19 vaccines relies on RNA polymerase transcription of a plasmid DNA template."

Previous studies identified high levels of plasmid DNA in vials of modRNA vaccines, suggesting that the removal of residual DNA template is problematic. Therefore, we quantified the DNA load in a limited number of Pfizer-BioNTech and Moderna COVID-19 modRNA vaccine vials using two independent methods... Total DNA ranged 371-1,548 ng/dose and 1,130-6,280 ng/dose in Pfizer and Moderna products, respectively. Specific DNA of multiple plasmid DNA targets ranged 0.22-7.28 ng/dose for Pfizer, and 0.01-0.78 ng/dose for Moderna. The SV40 promoter-enhancer-*ori* (0.25-23.72 ng/dose) was only detected in Pfizer vials. Oxford Nanopore sequencing of one vial found mean and maximum DNA fragment lengths of 214 bp and 3.5 kb, respectively. These data demonstrate the presence of  $1.23 \times 10^8$  to  $1.60 \times 10^{11}$  plasmid DNA fragments per dose encapsulated in lipid nanoparticles. Using fluorometry, total DNA in all vials tested exceeded the regulatory limit for residual DNA set by the US Food & Drug Administration (FDA) and the World Health Organization (WHO) by 36-153-fold for Pfizer and 112-627-fold for Moderna after accounting for nonspecific binding to modRNA.”

46. Szebeni J, “Unique Features and Collateral Immune Effects of mRNA-LNP COVID-19 Vaccines: Plausible Mechanisms of Adverse Events and Complications,” *Pharmaceutics* 2025, 17, 10: 1327. doi: [10.3390/pharmaceutics17101327](https://doi.org/10.3390/pharmaceutics17101327) ✓

- “The accumulation of chemically stabilized SP mRNA in the cytoplasm of APCs, or any other mRNA-LNP-transfected cells, increases the risk of reverse transcription, whereby the mRNA is copied into complementary DNA (cDNA) by reverse transcriptase enzymes. The resulting free-floating DNA in the nucleus or cytoplasm, called episomes, can be integrated into the genome by other enzymes in a process known as insertional mutagenesis. Several mechanisms can mediate insertional mutagenesis, involving transposons, integrases, and DNA repair enzymes, such as topoisomerases. Transposons possess endonuclease activity, allowing them to move within the double helix and induce various sequence alterations, including the insertion of reverse-transcribed mRNA fragments. This mechanism, carried out by ‘LINE-1 retrotransposons’ has been implicated in the integration of reverse-transcribed SARS-CoV-2 DNA into cultured human cells, which was subsequently re-transcribed into viral mRNA, providing a plausible explanation for persistently positive PCR tests in some long-COVID patients. Such ‘neo-gene’ formation may occur if the reverse-transcribed sequence remains intact and is coupled with promoter activity, potentially leading to permanent genomic alteration. In the case of the SP, this could theoretically result in chronic autoimmunity or toxicity. Additionally, topoisomerase-mediated error repair may integrate plasmid sequences during the unwinding and re-ligation of DNA... A newly described potential pathway of mRNA-driven insertional mutagenesis involves human DNA polymerase theta (Polθ, EC 2.7.7.7), a low-fidelity polymerase in mammalian cells mainly engaged in RNA-templated DNA repair. Studies demonstrated that Polθ can use RNA templates to synthesize cDNA and promote its integration into DNA, thus, if

spike cDNA or its fragments accumulate in the nucleus, Polθ could insert them into the genome, at least theoretically.”

47. Talotta R, “COVID-19 mRNA vaccines as hypothetical epigenetic players: Results from an in silico analysis, considerations and perspectives,” *Vaccine* 2023, 41, 35: 5182-5194. doi: [10.1016/j.vaccine.2023.07.007](https://doi.org/10.1016/j.vaccine.2023.07.007) ✓
  - “This pivotal in silico analysis shows that SARS-CoV-2 S gene and the BNT162b2 mRNA vaccine exhibit Watson-Crick nucleotide complementarity with human coding or noncoding genes. Although they do not share the same complementarity pattern, both may disrupt epigenetic mechanisms in target cells, potentially leading to long-term complications.”
48. Theuerkauf SA et al., “Quantitative assays reveal cell fusion at minimal levels of SARS-CoV-2 spike protein and fusion from without,” *iScience* 2021, 24, 3: 102170. doi: [10.1016/j.isci.2021.102170](https://doi.org/10.1016/j.isci.2021.102170) ✓
  - “As a main antigenic determinant, S protein is in focus of various therapeutic strategies. Besides particle-cell fusion, S mediates fusion between infected and uninfected cells resulting in syncytia formation... The data indicate that syncytia formation as pathological consequence during coronavirus disease 2019 (COVID-19) can proceed at low levels of S protein and may not be effectively prevented by antibodies.”
49. Wang J et al., “SARS-CoV-2 Spike Protein S1 Domain Accelerates α-Synuclein Phosphorylation and Aggregation in Cellular Models of Synucleinopathy,” *Mol Neurobiol.* 2024, 61, 4:2446-2458. doi: [10.1007/s12035-023-03726-9](https://doi.org/10.1007/s12035-023-03726-9) ✓
  - “Here we found that the S1 domain interacts with α-syn and promotes α-syn aggregation. The S1 domain induces mitochondrial dysfunction, oxidative stress, and cytotoxicity. “
50. Xuan L et al., “Nanoparticles-Induced Potential Toxicity on Human Health: Applications, Toxicity Mechanisms, and Evaluation Models,” *MedComm* 2023, 4, 4: e327. doi: [10.1002/mco2.327](https://doi.org/10.1002/mco2.327) ✓
  - “We describe in detail the effects of NPs on various systems, including respiratory, nervous, endocrine, immune, and reproductive systems, and the carcinogenicity of NPs. Furthermore, we unravel the underlying mechanisms of NPs including ROS accumulation, mitochondrial damage, inflammatory reaction, apoptosis, DNA damage, cell cycle, and epigenetic regulation.”
51. Yamaguchi T et al., “Points-to-consider: the mRNA vaccine reflection paper,” *Transl. reg. sci.* 2024, 6, 1: 20-27. doi: [10.33611/trs.2023-007](https://doi.org/10.33611/trs.2023-007) ✓
  - “The mRNA in mRNA vaccines is usually encapsulated in lipid nanoparticles (LNPs), and formulation technology is used to ensure that the mRNA is actively taken up by the cells. Therefore, when mRNA vaccines are administered, DNA contaminating the target mRNA as an impurity is actively delivered into the cells

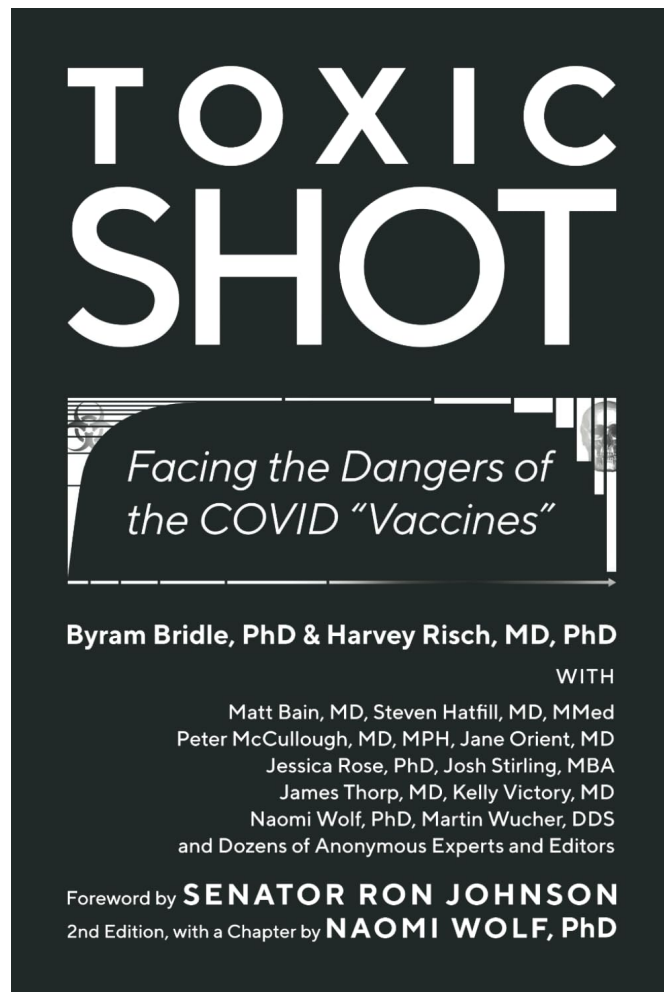
together with the mRNA. Therefore, it is necessary to determine whether the conventional WHO concept of DNA persistence is sufficient. It is necessary to explain the reason (s) for the persistence of DNA, including not only the amount of residual DNA but also its strand length.”

52. Youn JY et al., “Therapeutic application of estrogen for COVID-19: Attenuation of SARS-CoV-2 spike protein and IL-6 stimulated, ACE2-dependent NOX2 activation, ROS production and MCP-1 upregulation in endothelial cells,” *Redox Biol.* 2021, 46: 102099. doi: [10.1016/j.redox.2021.102099](https://doi.org/10.1016/j.redox.2021.102099) ✓
  - “Excessive ROS production by S protein induces ROS dependent cellular signaling including induction of cytokines and chemokines (e.g. IL-6 and MCP-1), all of which contribute to vascular inflammation. IL-6 also induces ROS production in a NOX2 dependent manner, aggravating endothelial oxidative stress, which in turn sustains endothelial dysfunction and vascular inflammation.”
53. Yu Z et al., “Reactive Oxygen Species-Related Nanoparticle Toxicity in the Biomedical Field,” *Nanoscale Res. Lett.* 2020, 15, 115. doi: [10.1186/s11671-020-03344-7](https://doi.org/10.1186/s11671-020-03344-7) ✓
  - “Due to the strong oxidation potential, the excess ROS induced by nanoparticles can result in the damage of biomolecules and organelle structures and lead to protein oxidative carbonylation, lipid peroxidation, DNA/RNA breakage, and membrane structure destruction, which further cause necrosis, apoptosis, or even mutagenesis... The generation of ROS induced by NPs resulted in the accumulation of DNA damage, which drives the development of mutagenicity, oncogenesis, multidrug resistance, aging, and immune escape.”
54. Zhao X et al., “ATM/ATR-Mediated DNA Damage Response Facilitates SARS-CoV-2 Spike Protein-Induced Syncytium Formation,” *J Med Virol.* 2025, 97, 1: e70137. doi: [10.1002/jmv.70137](https://doi.org/10.1002/jmv.70137) ✓
  - “... we investigated the effect of SARS-CoV-2 spike protein on the fusion of homologous and heterologous cells expressing ACE2 in vitro models, focusing on the protein levels of ATR and ATM, the major kinases responding to DNA damage, and their substrates CHK1 and CHK2. We found that both homologous and heterologous cell fusion activated the ATR-CHK1 and ATM-CHK2 signaling axis and induced the aggregation of γH2AX, 53BP1 and RAD51 in syncytia. In addition, siRNA or inhibitors of ATM and ATR suppressed syncytia formation by decreasing the level of S protein.”



## VIII. APPENDIX. Summary and overview of *TOXIC SHOT: Facing the Dangers of the COVID “Vaccines”*

This scientific bombshell shatters official propaganda about the COVID-19 “vaccines,” highlighting their risks for healthy people as well as their failure to stop the pandemic.



America’s health is under threat, but not from COVID-19 or any other “novel” disease. In a tragic irony, it’s the experimental mRNA “vaccines” themselves that are the real menace to our country’s long-term wellbeing. The COVID-19 “vaccines” were hailed as a “scientific miracle,” but in reality, they are nothing short of a global biomedical catastrophe. Rushed to market after clinical trials with no oversight, our government can no longer hide the terrifying fact that these unsafe injections, which fail to qualify as real vaccines by any measure, have sown death and disability around the world. From 2021–2023, the United States alone suffered 600,000 unexplained excess deaths not associated with COVID-19, while official data reveals over two million Americans became newly disabled over the same period. These shocking figures are mirrored by similar trends from abroad, reflecting the global scale of the mRNA “vaccine” catastrophe.

Government officials and academic “experts” claim to be stumped by the these “mysterious” trends, but the cause is plain to see, as shown in *TOXIC SHOT*. In chapter after chapter, brave scientific dissidents present damning proof of the myriad risks posed by the “vaccines,” drawing on abundant scientific research as they explain why the experimental shots are so dangerous. This evidence includes research showing the mechanisms behind potentially fatal side effects such as myocarditis, blood clots, and paralysis, as well as critical harms to fertility and pregnancy, among other dangers.

A call to battle, this book leaves no doubt that the COVID-19 “vaccines” must be withdrawn from the market immediately. It also equips readers with critical scientific information to



enable them to confront public officials, and finally force them to admit the devastating truth.

### **Chapter 1: The COVID-19 modRNA Shots Are Not Real Vaccines**

Dr. Byram Bridle highlights crucial distinctions between real vaccines and the experimental COVID-19 shots, which fail to qualify as true vaccines on multiple counts. The most important is their failure to stop infection or transmission—the central purpose of real vaccines and the rationale presented by public health authorities to justify mass “vaccination.”

### **Chapter 2: A Government Prototype Rushed to Market without Adequate Testing**

Dr. Harvey Risch examines the “vaccine” testing and manufacturing agreements signed by Pfizer and Moderna with the Pentagon in the spring of 2020, showing how their unusual terms appear to have freed the “vaccine”-makers from responsibility to conduct clinical trials with official oversight. The chapter then reviews some of FDA’s previous regulatory lapses, and their disastrous impact on public health.

### **Chapter 3: Introduction to *The Pfizer Papers: Pfizer’s Crimes Against Humanity***

Dr. Naomi Wolf, founder and CEO of DailyClout, gives a preview of the shocking findings from their groundbreaking, crowd-sourced analysis of COVID “vaccine” dangers, based on internal documents which the FDA tried to keep secret for 75 years, but was later forced to divulge under a court order. These damning data, drawn from Pfizer’s own clinical trial and post-marketing safety tracking, are presented in full in the DailyClout book, [\*The Pfizer Papers: Pfizer’s Crimes Against Humanity\*](#) (Skyhorse, Fall 2024).

### **Chapter 4: The Spike Protein Is Harmful by Itself**

Dr. Martin Wucher focuses on one of FDA’s most serious lapses: neglecting to study the spike protein encoded by the modRNA shots. Originally part of the outer coat of the COVID-19 virus, where it functions as a “key” to “unlock” (infect) cells, spike proteins are also produced in large amounts by the modRNA products, triggering a short-lived immune response in the form of antibodies. However, FDA failed to consider the possibility the spike protein might be harmful by itself. Dr. Wucher explores the growing body of evidence that the spike protein is highly pathogenic, causing harms on its own, independent of the rest of the COVID-19 virus—requiring immediate withdrawal of the shots.

### **Chapter 5: Debunking CDC’s Bad Science**

FDA’s failure to ensure adequate testing was compounded by the Centers for Disease Control and Prevention (CDC), whose public health policies appear intended to obscure, rather than clarify, the key issues of “vaccine” efficacy and safety. Following a comprehensive accounting of the agency’s scientific and regulatory failures from 2020 to 2023, Dr. Steven Hatfill shows that CDC and its Big Tech partners used advanced data-mining technology from the Census Bureau to monitor and censor the daily communications of Americans who were trying to share dissenting views about COVID-19—

abrogating their right to free speech in a constitutional betrayal of the people it was meant to serve.

### **Chapter 6: Safety Signals from the Vaccine Adverse Event Reporting System (VAERS)**

FDA, Department of Health and Human Services (HHS), and CDC created and implemented VAERS in 1990 to receive reports of adverse events associated with, and potentially caused by, biological products such as vaccines. Dr. Jessica Rose uses VAERS data to demonstrate that—despite the admitted limitations of the system—the sheer numbers, range, and rates of occurrence of adverse events associated with the COVID-19 injectable products—including deaths—are wholly unprecedented, demanding the immediate withdrawal of the COVID-19 injectable products.

### **Chapter 7: Immunological Harms of the modRNA “Vaccines”**

Returning to the issue of “vaccine” damage to immune function, Dr. Bridle presents public health data clearly pointing to immune harms, including an apparent increase in likelihood of infection among the “vaccinated.” Dr. Bridle reviews some likely mechanisms of immune harm from the modRNA products, before presenting yet more evidence that public health authorities have been actively suppressing negative information about this critical issue.

### **Chapter 8: Cardiac and Cardiovascular Damage from the modRNA “Vaccines”**

Dr. Peter McCullough takes a closer look at the true incidence and severity of two of the most serious complications of the modRNA “vaccines”: myocarditis (inflammation of the heart muscle) and blood clots. After presenting evidence that public health authorities are underestimating their true prevalence, Dr. McCullough outlines short-, mid-, and long-term health consequences, including sudden death from heart failure—especially among young men.

### **Chapter 9: Neurological Injuries from the modRNA “Vaccines”**

After explaining how his own initial enthusiasm for COVID-19 “vaccination” led to treating neurological injuries from the modRNA “vaccines,” Dr. Matt Bain reviews over a dozen categories of common neurological injury likely resulting from modRNA “vaccination”: acute transverse myelitis, acute disseminated encephalomyelitis, stroke, small-fiber neuropathy, Guillain-Barré syndrome, Bell’s palsy, and myasthenia gravis, among others. Dr. Bain concludes with an overview of some promising treatments for “vaccine” injuries.

### **Chapter 10: Cancer Risks of the modRNA “Vaccines”**

Dr. Jane Orient emphasizes that any discussion of potential cancer risks must start with the fact that cancer is both poorly understood and extraordinarily complex in terms of underlying factors, triggers, and timing. Noting widespread social media reports of sudden, fast-developing cancers after “vaccination,” Dr. Orient acknowledges plausible hypotheses about potential causal mechanisms. However, she reiterates that, because of the huge scale of the problem, the very long time frame, and the many unknowns, the highest priority must be a concerted, well-resourced national post-“vaccination” cancer surveillance

effort, as well as urgent study of the causal mechanisms behind “vaccination”-related cancers.

### **Chapter 11: COVID-19 “Vaccine” Effects on Women of Reproductive Age and Pregnancy**

Dr. James Thorp reviewed ultrasound images from 27,000 pregnant women from 2020 to 2023, putting him in a unique position to directly observe the physiological impact of the modRNA “vaccines” on the health of pregnant women and their fetuses. His chapter reviews the well-documented adverse effects of the COVID-19 experimental gene therapies on women’s fertility, fetal viability and pregnancy, live births, and maternal health, and also exposes deliberate deceptions in the campaign to persuade the public that the modRNA shots were safe, effective, and necessary in pregnancy.

### **Chapter 12: Risks to Children**

Dr. Kelly Victory addresses one of the central issues in the COVID-19 “vaccine” debate: the necessity and safety of “vaccination” in children. Taking the foundational ethical principles of medicine as her touchstone—with particular focus on the need for healthcare professionals to be transparent in presenting cost-benefit risk analyses to the parents of young children—Dr. Victory debunks all rationales offered for childhood “vaccination” and highlights even higher rates of certain adverse events among children.

### **Chapter 13: “Vaccine” Mortality Insights from Autopsy Reports**

Drs. McCullough and Risch and their collaborators explore possible causal links between the COVID-19 “vaccines” and deaths, using autopsy and postmortem data. Clustering of harms in certain organ systems, close resemblance to post-“vaccination” deaths reported through pharmaco-vigilance systems, and consistency with likely mechanisms of harm described elsewhere, all strongly suggest that COVID-19 “vaccines” were the main or contributing cause of death in most cases. Circulating spike protein, produced uncontrollably throughout the body by the experimental shots, is likely the main mechanism of harm.

### **Chapter 14: “All Hands on Deck”—The Catastrophe of US Longevity and What We Can Do about It**

Veteran insurance executive and entrepreneur Josh Stirling analyzes official data to reveal shocking, unexplained increases in death and disability among working-age Americans, from 2021 onward. From 2021 to 2023, Stirling notes around 600,000 excess deaths not due to COVID-19, as well as over two million newly disabled Americans, concentrated in demographic groups typically at low risk of disability. Pointing to a systemic cause, Stirling proposes large-scale screening with cheap, easily performed blood tests, to identify members of the population who have been exposed to known pathogenic agents.