

COVID-19 mRNA “vaccine” harms research collection

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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 (n=375)**

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 370 peer-reviewed scientific papers collected in section I.

II. **Spike protein and “vaccine” mRNA biodistribution studies (n=61)**

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 penetrate distant tissues, causing systemic harms.

III. **Spike protein and “vaccine” mRNA persistence studies (n=41)**

Over 40 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; viral spike proteins, resulting from natural infection, have been shown to persist even longer, bolstering concerns that the identical “vaccine” spike may also last longer than anticipated.

IV. **Lipid nanoparticle toxicity and allergenicity studies (n=80)**

80 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).

V. **COVID-19 “vaccine” immune imprinting library (n=140)**

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. 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 (n=70)

In addition to the pathogenicity, distribution, and long persistence of the “vaccine” spike protein, this collection of 70 peer-reviewed papers suggests the “vaccines” applied strong selective pressure to the fast-mutating SARS-CoV2 virus, quickly giving rise to “vaccine”-resistant variants.

I. COVID-19 spike protein pathogenicity research library

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Originally part of the outer coat of the SARS-CoV2 virus, where it functions as a “key” to “unlock” (infect) cells, spike proteins are also produced in large amounts by the mRNA “vaccines,” triggering a short-lived immune response in the form of antibodies. However, a growing body of evidence has shown that the spike protein is harmful by itself, independent of the rest of the virus.

The following (I. Alphabetical List) collects over 370 (**n=375**) peer-reviewed scientific studies confirming that the spike protein is highly pathogenic on its own; most *in vitro* studies cited here used recombinant spike proteins or spike proteins in pseudoviral vectors, and produced pathological effects not reliant on the SARS-CoV2 viral machinery.

The second section (II. Categories) 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).

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II. CATEGORIES

- A. General/Overview (36)**
- B. ACE2 (23)**
- C. Amyloid, prion-like properties (14)**
- D. Autoimmune (14)**
- E. Blood pressure/hypertension (2)**
- F. CD147 (13)**
- G. Cell membrane permeability, barrier dysfunction (16)**
- H. Cerebral, cerebrovascular, neurologic, blood-brain barrier, cognitive (28)**
- I. Clinical pathology (23)**
- J. Clotting, platelets, hemoglobin (35)**
- K. Cytokines, chemokines, interferon, interleukins (36)**
- L. Endothelial (30)**
- M. Gastrointestinal (8)**
- N. Immune dysfunction (8)**
- O. Macrophages, monocytes, neutrophils (32)**
- P. MAPK/NF-kB (10)**
- Q. Mast cells (4)**
- R. Microglia (10)**
- S. Microvascular (8)**
- T. MIS-C, pediatric (8)**
- U. Mitochondria/metabolism (9)**
- V. Myocarditis, cardiac, cardiomyopathy (22)**
- W. NLRP3 (15)**
- X. Ocular, ophthalmic, conjunctival (3)**
- Y. Other cell signaling (20)**
- Z. PASC, post COVID, long COVID (22)**
- AA. Pregnancy, fetal, placenta (7)**
- BB. Pulmonary, respiratory (33)**
- CC. Renin-Angiotensin-Aldosterone System (3)**
- DD. Senescence/aging (3)**
- EE. Stem cells (3)**
- FF. Syncytia/cell fusion (10)**
- GG. Therapeutics (44)**
- HH. Toll-like receptors (TLRs) (15)**

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C. Amyloid, prion-like properties

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II. Spike protein and “vaccine” mRNA biodistribution studies

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Biodistribution studies show that both the “vaccine” mRNA encoding for the spike protein antigen and the spike protein itself can penetrate distant tissues, causing systemic harms to a variety of organs and organ systems, including the placenta. The following research collection presents over 60 peer-reviewed studies (**n=61**) documenting the wide distribution of “vaccine” mRNA and the associated spike protein throughout human beings and animal test subjects.

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

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. 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).

Chart: COVID-19 mRNA “vaccine” biodistribution studies

author/article #	mRNA	LNP	spike	blood	lymph nodes	spleen	liver	brain	heart	kidneys	adrenal glands	skin	eyes	bone	bone marrow	ovaries	testes	lungs	breast milk	placenta	fetus
Australian Govt (1)	✓				✓						✓					✓					
Bansal et al. (2)			✓	✓																	
Baumeier et al (3)			✓						✓												
Blizard et al (4)	✓	✓	✓		✓	✓	✓														
Boros et al. (5)	✓		✓						✓												
Brogna et al. (7)			✓	✓																	
Broudic et al. (8)	✓				✓	✓	✓	✓		✓	✓		✓		✓	✓	✓	✓			
Burkhardt (9)			✓		✓	✓	✓	✓				✓						✓			
Castruita et al. (11)	✓			✓																	
Chen et al. (12)	✓		✓				✓													✓	✓
Di et al. (15)		✓			✓	✓	✓														
EMA (16)	✓	✓				✓		✓	✓	✓											
EMA (17)	✓							✓	✓				✓					✓			
Fertig et al. (19)	✓			✓																	
Hanna et al. (20)			✓																✓		
Hassett et al. (21)	✓		✓	✓	✓	✓	✓														
Judicial Watch (23)		✓		✓	✓	✓					✓					✓					
Kammala et al. (24)			✓																		✓
Kawano et al. (25)			✓						✓												
Kent et al. (26)	✓	✓		✓	✓																
Krauson et al. (27)	✓			✓					✓												
Kwon et al. (28)		✓		✓	✓	✓	✓	✓								✓	✓	✓			
Li et al. (30)			✓							✓											
Li et al. (31)			✓		✓	✓	✓											✓			
Lin et al. (32)	✓		✓	✓																	✓
Ma et al. (34)	✓			✓	✓	✓	✓														
Magro et al. (36)			✓									✓									
Martin-Navarro et al. (38)		✓					✓														
UK MHPRA (40)		✓					✓														
Japan MoHLW (41)		✓					✓	✓		✓			✓	✓	✓			✓			
Mörz et al. (42)			✓					✓	✓												
Nyein et al. (43)			✓				✓														
Ogata et al. (44)			✓	✓																	
Ota et al. (45)			✓					✓													
Pateev et al. (46)		✓			✓	✓	✓											✓			
Sandelius et al. (51)	✓	✓	✓			✓	✓			✓		✓									
Sano et al. (52)			✓										✓								
Sano et al. (53)			✓										✓								
Schreckenber (55)			✓						✓												
Yamamoto et al. (60)			✓									✓									
Yonker et al. (61)			✓	✓																	

14 12 25 12 10 13 16 8 9 5 3 6 3 1 2 4 2 7 1 3 1

Original source: "mRNA 'vaccine' biodistribution, persistence, and adjuvant toxicity library," <https://zenodo.org/records/14559625>
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- “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.”
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- Plasma

III. Spike protein and vaccine mRNA persistence studies

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Dozens of studies collected here (n=41) demonstrate that both “vaccine” mRNA, and the spike protein antigen it encodes, persist in the tissues of human vaccine recipients and animal test subjects far longer than claimed by public health officials: up to eight weeks in the case of mRNA (Röltgen K et al.) and up to six months for spike protein (Brognia C et al.). Numerous studies have also shown that viral spike proteins can persist even longer in individuals recovered from SARS CoV2 infection or with “long COVID,” with spike protein detected 15 months (Patterson BK et al.) to two years (Fraser ME et al.) after infection. Long-lasting viral spike proteins have frequently been detected in the absence of viable virus, as reflected in negative PCR tests and RNA assays, suggesting identical “vaccine” spike proteins may also persist for a year or more.

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

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 - “... with spike antigen still present as late as 60 days post-second dose”

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- “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.”
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weeks post-infection despite no overt exposure to SARS-CoV-2 infected individuals.”

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 - “...our studies showed that spike antigens rose over the first few days of MIS-C symptoms and persisted for more than 10 days, occasionally through 6 months...”
 - “... we measured SARS-CoV-2 RNA from MIS-C stool samples collected several weeks after the initial SARS-CoV-2 infection or exposure. Indeed, a majority of the patients showed detectable viral loads in the stool ranging from 1.5×10^2 to 2.5×10^7 RNA copies/mL, suggesting an ongoing nidus of infection in MIS-C.”
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 - 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

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The anti-SARS CoV2 mRNA injections rely on lipid nanoparticles (LNPs) bonded with polyethylene glycol (PEG) to deliver mRNA coding for the spike protein antigen into human cells. However, a growing body of evidence suggests that the ionizable LNPs used in the experimental mRNA injections are highly inflammatory on their own, while PEG has long been recognized as an allergen with the potential to trigger anaphylaxis (a severe, possibly life-threatening allergic reaction). This annotated research collection presents (**n=80**) scientific papers detailing the potential harms of LNPs, PEG, and other components of the mRNA injections to the human body and setting forth possible or established mechanisms. Some of the research annotated here also suggests a far higher incidence of anaphylaxis due to the mRNA injections than claimed in official estimates, ranging from 1/2,280 doses (Warren CM et al.) to 1/4,049 (Blumenthal KG et al.) and 1/13,882 (Somiya A et al.).

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

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- “In human immune cells, RNA vaccines induce production of IL-1 cytokines, predominantly IL-1 β , 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).”
69. Tenchov R et al, “PEGylated Lipid Nanoparticle Formulations: Immunological Safety and Efficiency Perspective,” *Bioconjug. Chem.* 2023, 34, 6: 941-960. doi: <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.”
70. Tinari S, “The EMA covid-19 data leak, and what it tells us about mRNA instability,” *BMJ* 2021, 372: n672. doi: <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.”
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- “Intravenous administration of pegylated liposomal formulations containing Toll-like receptor agonists to mice on days 0, 4, and 8 resulted in hypersensitivity reaction symptoms...”
72. 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: <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.”
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- “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.”
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- “... ‘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.”
75. 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.”
76. 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.”
77. Xuan L et al., “Nanoparticles-Induced Potential Toxicity on Human Health: Applications, Toxicity Mechanisms, and Evaluation Models,” *MedComm* 2023, 4, 4: e327. doi: <https://doi.org/10.1002/mco2.327>
78. 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.”

79. 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: <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.”

80. 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

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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 peer-reviewed papers (**n=140**) 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.).

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 (N=140)

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 (Sec. Vaccines and Molecular Therapeutics). doi: <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: <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: <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."
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 - "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.”

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 - “Vaccination and previous infection leave a clear serological imprint that is focused on the variant-specific antigen.”
11. 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 (Sec. Viral Immunology). doi: <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.”
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 - “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.”
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 - “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.”
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- “... 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.”
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 - “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.”
 16. Brown E and HT Essigmann, “Original Antigenic Sin: the Downside of Immunological Memory and Implications for COVID-19,” *mSphere* 2021, 6, 2. doi: <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.”
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 - “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.”

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 - “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.”

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 - “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.”

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 - “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.”

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24. 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.”
25. Chen SY et al., “The Effectiveness of Bivalent COVID-19 Vaccination: A Preliminary Report,” *Life* 2023, 13, 10: 2094. doi: <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.”
26. 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.”
27. 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.”
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 - “... immune imprinting by first generation vaccines may restrict, but not abolish, cross-neutralization.”
 31. 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.”
 32. 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.”

33. 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: <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.”
34. 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.”
35. 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.”
36. 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.”
37. 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: <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.”
38. 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.”
39. 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: <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.”
40. 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.”
41. 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: <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.”

42. 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: <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.”
43. 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.”
44. 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: <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...”
45. 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.”
46. 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: <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.”
47. 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 in breakthrough infection.”
48. 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: <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.”

49. 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.”
50. 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.”
51. 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: <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).”

52. 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: <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-naive 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.”
53. 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.”
54. 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.”
55. 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. <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.”

56. 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.”
57. Kaku CI et al., “Evolution of antibody immunity following Omicron BA.1 breakthrough infection,” *Nat. Commun.* 2023, 14: 2751. doi: <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.”
58. 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, relative to WT.”
59. 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.”
60. Kim W, “Germinal Center Response to mRNA Vaccination and Impact of Immunological Imprinting on Subsequent Vaccination,” *Immune Netw.* 2024, 24, 4: e28. doi: <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.”
61. 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: <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.”
62. 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).”
63. 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: <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.”
64. 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 (NAbs) 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.”

65. 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.”
66. 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.”
67. 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.”
68. 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: <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. “

69. 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.”
70. 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: <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.”
71. 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: <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.”
72. 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.”
73. Medits I et al., “Different Neutralization Profiles After Primary SARS-CoV-2 Omicron BA.1 and BA.2 Infections,” *Front. Immunol.* 2022, 13 (Sec. Vaccines and Molecular Therapeutics). doi: <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.”
74. 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.”
75. 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.”
76. 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: <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.”

77. 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.”
78. 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.”
79. 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.”

80. 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.”
81. Norton NJ et al., “Characteristics of Vaccine- and Infection-Induced Systemic IgA Anti-SARS-CoV-2 Spike Responses,” *Vaccines* 2023, 11, 9: 1462. doi: <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.”
82. 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.”
83. 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.”
84. 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.”

85. 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: <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.”
86. Pepkowitz SH et al., “Prior vaccination has changed the composition of the COVID-19 convalescent plasma inventory,” *Transfusion* 2022, 62, 10: 2153-2154. doi: <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.”
87. 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: <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-naive. 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.”
88. Petras M and IV Lesna, “SARS-CoV-2 vaccination in the context of original antigenic sin,” *Hum Vaccin Immunother.* 2022, 18, 1: 1949953. doi: <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.”

89. 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.”
90. 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: <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.”
91. Powers JP et al., “Divergent pathogenetic outcomes in BALB/c mice following Omicron subvariant infection,” *Virus Res.* 2024, 341: 199319. doi: <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.”
92. 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.”

93. 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: <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."
94. 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."
95. 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."
96. 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."
97. 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.”
98. 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.”
99. 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.”
100. 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- γ response. Infection-induced Th1/IFN- γ signature is not reproduced by three vaccinations.”
101. 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.”
102. 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.”
103. 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.”
104. 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.”
105. 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.”

106. 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: <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.”
107. 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: <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.”
108. 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.”
109. Solfrosi L et al., “Booster with Ad26.COVS or Omicron-adapted vaccine enhanced immunity and efficacy against SARS-CoV-2 Omicron in macaques,” *Nat. Commun.* 2023, 14, 1944. doi: <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.COVS vaccination.”
110. Stamatou 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.”

111. 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.”
112. 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: <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.”
113. 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.”
114. Tan CW et al., “Distinctive serotypes of SARS-related coronaviruses defined by convalescent sera from unvaccinated individuals,” *hLife* 2023, 1, 1: 26-34. doi: <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.”

115. 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.”
116. Tavasolian F et al., “HLA, Immune Response, and Susceptibility to COVID-19,” *Front. Immunol*. 2021, 11 (Sec. 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.”
117. 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.”
118. 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.”

119. 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.”
120. 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: <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.”
121. 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.”

122. 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.”
123. 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.”
124. 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).”
125. 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/ID9.000000000000125](https://doi.org/10.1097/ID9.000000000000125)
- “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.”
126. 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.”

127. 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.”
128. 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.”
129. 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.”
130. 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.”
131. 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: <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.”
132. 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: <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...”
133. 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...”
134. 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: <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.”
135. 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.”
136. 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.”
137. 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.”
138. Zhou Z et al., “Immune Imprinting and Implications for COVID-19,” *Vaccines* 2023, 11, 4: 875. doi: <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 NAb 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.”
139. 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: <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...”
140. 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

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In addition to the pathogenicity, distribution, and long persistence of the “vaccine”-produced spike protein, a growing body of research links COVID “vaccination” to the evolution of vaccine-resistant viral variants. The following collection of (**n=70**) peer-reviewed papers suggests the “vaccines” applied strong selective pressure to the fast-mutating SARS-CoV2 virus, quickly giving rise to “vaccine”-resistant 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.

On this note, public health officials have warned that “chasing variants” is likely futile:

- In January 2023, Dr. Peter Marks, 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 (n=70)

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: <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: <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: <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: <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: <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: <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. Chaguzo 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.”
11. 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.”
12. 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: <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.”

13. 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...”
14. Day T et al., “Pathogen evolution during vaccination campaigns,” *PLoS Biol* 2022, 20, 9: e3001804. doi: <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.”
15. 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.”
16. 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.”
17. 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.”

18. 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."

19. 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: <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."

20. 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."

21. 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: <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..."

22. Ghmire D et al., "Structural Plasticity and Immune Evasion of SARS-CoV-2 Spike Variants," *Viruses* 2022, 14, 6: 1255. doi: <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.”

23. 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.”
24. Habib MT et al., “Natural selection shapes the evolution of SARS-CoV-2 Omicron in Bangladesh,” *Front. Genet.* 2023, 14 (Sec. Computational Genomics). doi: <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.”
25. 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: <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.”
26. Han W et al., “Predicting the antigenic evolution of SARS-COV-2 with deep learning,” *Nat Comm* 2023, 14: 3478. doi: <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.”
27. Harvey WT et al., “SARS-CoV-2 variants, spike mutations and immune escape,” *Nat Rev Microbiol* 2021, 19: 409–424. doi: <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.”
28. 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: <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.”
29. 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.”
30. Jena D et al., “Impact of vaccination on SARS-CoV-2 evolution and immune escape variants,” *Vaccine* 2024, 42, 21: <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.”
31. Kennedy DA and AF Read, “Monitor for COVID-19 vaccine resistance evolution during clinical trials,” *PLoS Biol.* 2020, 18, 11: e3001000. doi: <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.”
32. 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.”
33. 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: <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.”
34. 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.”
35. Kumar SW et al., “Vaccine-elicited immune pressure and SARS-CoV-2 mutational dynamics in breakthrough infections,” *Gene Rep.* 2024, 35: 101899. doi: <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.”
36. 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.COVS, 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.”

37. Li X, “Omicron: Call for updated vaccines,” *J. Med. Virol.* 2022, 94, 4: 1261-1263. doi: <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.”
38. 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: <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.”
39. 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.”
40. Magazine N et al., “Mutations and Evolution of the SARS-CoV-2 Spike Protein,” *Viruses* 2022, 14, 3): 640. doi: <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.”

41. 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.”

42. 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: <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.”

43. 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: <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.”

44. 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.”

45. 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.”
46. 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...”
47. 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.abl6251](https://doi.org/10.1126/science.abl6251)
- “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 adaptative 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.”
48. Oliviera JR et al., “Immunodominant antibody responses directed to SARS-CoV-2 hotspot mutation sites and risk of immune escape,” *Front. Immunol.* 2023, 13 (Sec. Viral Immunology). doi: <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.”
49. 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: <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.”
50. 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: <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.”
51. 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: <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.”
52. 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.”
53. 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.”

54. 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: <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.”
55. Tan CW et al., “SARS-CoV-2 Omicron variant emerged under immune selection,” *Nat Microbiol* 2022, 7: 1756–1761. doi: <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.”
56. 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.”
57. 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, <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.”
58. 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.”

59. 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: <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.”
60. 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.”
61. Wang R et al., “Emerging Vaccine-Breakthrough SARS-CoV-2 Variants,” *ACS Infect. Dis.* 2022, 8, 3: 546–556. doi: <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.”
62. 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: <https://doi.org/10.1021/acs.jpcclett.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.”
63. 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.”
64. 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: <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.”
65. Yang Z et al., “SARS-CoV-2 Variants Increase Kinetic Stability of Open Spike Conformations as an Evolutionary Strategy,” *mBio* 2022, 13, 1. doi: <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.”
66. 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 (Sec. Vaccines and Molecular Therapeutics). doi: <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.”
67. 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.”
68. 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.”
69. 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.”

70. 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.”