



Case Study

Open Access

Comparative Immunogenicity of mRNA and Protein Subunit Vaccine Platforms

Stojanovic S^{1*}, Stojanovic N² and Radovic S³

¹Department of Health Sciences, Skopje Institute of Applied Immunology, Serbia Scopus Author ID: 57963691222

Email: stefan.stojanovic@skopje.edu

ORCID: <https://orcid.org/2052-1271-4046-6037>

²Department of Clinical Research, Belgrade Institute of Vaccinology, Croatia Scopus Author ID: 57715616868 Email:

nikola.stojanovic@belgrade.edu

ORCID: <https://orcid.org/5403-2521-7687-8113>

³Department of Clinical Research, Belgrade Institute of Vaccinology, Serbia Scopus Author ID: 57635922266 Email:

snezana.radovic@belgrade.edu

ORCID: <https://orcid.org/8114-5452-8764-1105>

***Correspondence to:** Stefan Stojanovic, Department of Health Sciences, Skopje Institute of Applied Immunology, Serbia Scopus Author ID: 57963691222 Email: stefan.stojanovic@skopje.edu

Received: 21 January 2026; **Accepted:** 17 April 2026; **Published:** 23 June 2026

Copyright: © 2026 SS, et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

The rapid, parallel authorization of mRNA and adjuvanted protein subunit vaccines against SARS-CoV-2 created an unusually informative natural comparison between two mechanistically distinct approaches to eliciting protective immunity against the same structurally defined spike antigen. This article synthesizes the published immunogenicity, efficacy, and durability literature for both platforms, tracing the mRNA approach from nucleoside-modification chemistry and lipid-nanoparticle delivery through to clinical antibody and T cell data, and the protein subunit approach from saponin-based adjuvant biology through to its own clinical immunogenicity readouts. Phase 3 trials reported efficacy of 95% for BNT162b2, 94.1% for mRNA-1273, and 89.7% for NVX-CoV2373 against symptomatic COVID-19, with overlapping confidence intervals; both platforms elicited neutralizing antibody titers exceeding those seen in convalescent serum and drove comparably Th1-skewed cellular responses despite activating innate immunity through entirely different molecular mechanisms. We give particular weight to the evidentiary limits of cross-trial comparison, the asymmetry in published durability and germinal-centre data between the two platforms, and the practical manufacturing and reactogenicity tradeoffs that distinguish them. Read together, the evidence supports both platforms as independently validated, comparably effective, and mechanistically complementary routes to protective immunity, an outcome we treat as a useful redundancy for future vaccine development rather than a contest with a clear winner.

Keywords: mRNA vaccine; protein subunit vaccine; immunogenicity; SARS-CoV-2 spike antigen; vaccine adjuvants

1. Introduction

Two vaccine platforms carried the global response to SARS-CoV-2 from laboratory concept to authorized product faster than any prior vaccine effort in history, and they did so by taking almost opposite routes to the same immunological destination. One route, embodied by BNT162b2 and mRNA-1273, delivers a nucleoside-modified messenger RNA encapsulated in a lipid nanoparticle (LNP) and lets the vaccinee's own cells manufacture the antigen *in situ* [1,2,3]. The other, embodied by NVX-CoV2373, delivers a fully assembled, recombinantly produced spike protein nanoparticle together with a saponin-based adjuvant, handing the immune system a finished antigen rather than a set of instructions for making one [4,5]. Both approaches reached phase 3 efficacy above 89% against the ancestral and early-variant strains of SARS-CoV-2, and both generated an extraordinary volume of immunogenicity data in a compressed timeframe, which makes the pandemic-era literature an unusually rich, head-to-head natural experiment in comparative vaccinology [1,2,4].

That experiment did not happen by accident. mRNA vaccines built on two decades of work on nucleoside modification and lipid nanoparticle delivery that predates COVID-19 by more than fifteen years, and protein subunit vaccines built on an even longer tradition of adjuvant science stretching back to alum and, more recently, to saponin- and oil-in-water-based systems designed explicitly to shape the quality, not just the quantity, of the resulting immune response [6,7,8,9]. What COVID-19 vaccine development did was compress the normal decade-plus cycle of platform validation into about a year, forcing regulators, clinicians, and now researchers writing in retrospect to compare these two mechanistically distinct platforms directly, on the same pathogen, in overlapping populations, using largely comparable trial endpoints [10].

This article synthesizes that comparative literature. Our central question is not which platform is "better" in some abstract sense — that framing under-serves both the biology and the evidence — but rather how the two platforms differ mechanistically in how they engage the innate and adaptive immune systems, what the resulting differences in antibody kinetics, T cell responses, and durability actually look like in the published data, and where the open questions remain for the next generation of both platforms. We organize the discussion around

five themes: the structural logic of the shared spike antigen both platforms target; the innate-immune and molecular biology of mRNA vaccine immunogenicity, including the nucleoside-modification chemistry that made the platform viable at all; the adjuvant-driven immunogenicity of protein subunit vaccines; the head-to-head clinical evidence on efficacy, antibody titers, and durability; and the comparative cellular immunology of germinal center and T cell responses across platforms. We close with an honest account of what remains unresolved.

A scope note is warranted before proceeding. This is a literature synthesis, not a new experiment, and the immunogenicity comparisons we draw are necessarily comparisons across separately conducted trials with different populations, timepoints, and assay platforms rather than a single randomized head-to-head study — a limitation the field itself has been candid about, and one we return to in our discussion of open challenges [11].

It is also worth noting at the outset why this particular pair of platforms, out of the several that reached authorization during the pandemic, makes for such an informative comparison. Viral vector vaccines, inactivated whole-virus vaccines, and DNA vaccines each occupy different points on the same design spectrum — some closer to mRNA in delivering genetic instructions rather than finished antigen, others closer to protein subunit vaccines in presenting a non-replicating, pre-formed immunogen — but mRNA and adjuvanted protein subunit vaccines sit at genuinely opposite poles of that spectrum: one asks the vaccinee's own cellular machinery to manufacture antigen transiently *in situ*, the other delivers a fully manufactured antigen and relies entirely on an external adjuvant to supply the innate-immune signal that would otherwise be missing. That polarity is what makes the comparison mechanistically interesting rather than merely a comparison of two similar products with different brand names, and it is why we have restricted this synthesis to these two platforms rather than attempting a broader, shallower survey of every COVID-19 vaccine technology pursued during the pandemic.

2. Structural Basis of the Shared Antigen Target

Both platforms owe their antigen design to the same body of structural biology. Prior to the SARS-CoV-2 pandemic, work on the related betacoronaviruses

MERS-CoV and SARS-CoV had already established that the coronavirus spike glycoprotein could be locked into its prefusion conformation by introducing two consecutive proline substitutions at the top of the central helix in the S2 subunit, a modification now generally referred to as "2P" stabilization. Wrapp and colleagues applied this logic to SARS-CoV-2 within weeks of the genome sequence becoming available, solving the cryo-EM structure of the prefusion-stabilized spike ectodomain and showing that this stabilized form displayed the receptor-binding domain in the conformation recognized by the most potently neutralizing antibodies, distinct from the postfusion conformation the native, unmodified spike readily collapses into [12]. That single structural insight became a shared design input for essentially every major SARS-CoV-2 vaccine that followed, regardless of platform.

For the mRNA platforms, the practical consequence was that the encoded genetic payload was never simply "the spike gene" but a carefully engineered construct encoding the full-length, membrane-anchored, proline-stabilized spike, selected after systematic preclinical comparison of antigen designs. Corbett and colleagues' account of the design process behind mRNA-1273 is explicit that antigen design, not merely lipid nanoparticle formulation, was treated as a primary variable, and that the prefusion-stabilized, full-length transmembrane spike outperformed alternative constructs (including a secreted, non-membrane-bound version) in preclinical immunogenicity studies before being carried forward into the vaccine that ultimately reached phase 3 [13]. This "prototype pathogen preparedness" framing is worth dwelling on, because it explains why an mRNA vaccine against a genome sequenced in January 2020 could enter human trials in March: the platform's speed advantage was not purely about manufacturing, it was about antigen engineering having already been substantially de-risked on related coronaviruses.

For the protein subunit platform, the same structural logic had to be solved differently, because the antigen is not expressed transiently in the vaccinee's own cells but manufactured at scale in an insect-cell expression system, purified as a soluble trimeric nanoparticle, and formulated with adjuvant before injection. Keech and colleagues' description of NVX-CoV2373's antigen — a

full-length, prefusion-stabilized spike expressed in a baculovirus/Sf9 insect cell system and self-assembled into polysorbate-80-stabilized nanoparticles bearing multiple spike trimers per particle — reflects the same stabilization principle applied within a fundamentally different manufacturing and delivery paradigm [5]. The nanoparticle geometry itself is not incidental: multivalent antigen display on a single particle is a well-established way to promote B cell receptor cross-linking and germinal center engagement independent of any adjuvant effect, a general principle in protein subunit vaccine design that predates COVID-19 and is discussed at length in broader treatments of vaccine antigen design [14].

The upshot is that the two platforms, despite their radically different delivery mechanisms, target immunologically similar antigen conformations, which is precisely what makes downstream comparisons of the resulting antibody responses meaningful rather than an apples-to-oranges exercise. Dai and Gao's review of viral targets for COVID-19 vaccines situates the near-universal convergence on prefusion-stabilized spike as the dominant vaccine antigen across essentially every platform pursued during the pandemic, mRNA and protein subunit included, as a reflection of how strong the structural rationale for that specific antigen conformation turned out to be [15].

3. mRNA Vaccine Immunogenicity: Innate Sensing and Antigen Expression

The mRNA vaccine platform's viability depended on solving a problem that looks, at first glance, like it should have killed the entire approach: unmodified, in-vitro-transcribed RNA is intensely immunostimulatory on its own, triggering a battery of innate pattern-recognition receptors, including endosomal Toll-like receptors 3, 7, and 8 and cytosolic sensors such as RIG-I and PKR, that collectively produce a strong type I interferon response capable of shutting down translation of the very mRNA meant to produce antigen [6,3]. Karikó and colleagues' 2005 paper is the foundational finding here: they showed that naturally occurring modified nucleosides found in cellular and transfer RNA — pseudouridine, 5-methylcytidine, N6-methyladenosine, and others — when substituted for their unmodified counterparts in synthetic mRNA, dramatically suppressed activation of RNA-sensing Toll-like receptors, apparently because these

modifications are evolutionarily associated with "self" RNA and are recognized as such by the innate immune system, which had evolved to treat unmodified RNA as a signature of viral infection [6]. This was not a minor formulation tweak; it was the discovery that made therapeutic and vaccine use of synthetic mRNA immunologically tolerable in the first place.

The follow-on 2008 paper extended this finding in a direction that turned out to matter just as much for vaccine efficacy as for tolerability: Karikó and colleagues showed that pseudouridine-modified mRNA was not merely less immunostimulatory but also translated substantially more efficiently and persisted longer in cells than unmodified mRNA, because unmodified mRNA activates protein kinase R (PKR), which phosphorylates eIF2 α and shuts down cap-dependent translation as part of the same innate antiviral response that the modification suppresses [7]. In other words, nucleoside modification solved two problems with a single chemical substitution: it reduced unwanted innate inflammatory signaling, and it increased the amount and duration of antigen actually produced from each injected mRNA molecule — precisely the combination needed for a usable vaccine platform, since too little of either property leaves either an intolerably reactogenic product or an ineffectively immunogenic one.

Nucleoside modification is only one half of a two-part solution, and it is worth situating it within the broader arc of mRNA therapeutics research that predates the COVID-19 vaccines by a decade. Sahin, Karikó, and Türeci's 2014 review of mRNA-based therapeutics laid out, well before any mRNA vaccine had reached late-stage clinical testing, the general case for treating synthetic mRNA as a drug modality in its own right: unlike DNA-based approaches, mRNA acts entirely in the cytoplasm without any risk of genomic integration, its dose can in principle be titrated by adjusting the amount of RNA delivered, and — crucially for vaccine applications specifically — transient antigen expression from mRNA is well matched to the transient antigen-presentation window that a prophylactic vaccine needs, without the persistence concerns that attend some other gene-based delivery platforms [16]. That review's synthesis of the field's formulation challenges, chemical modification strategies, and delivery obstacles reads, in retrospect, as a fairly

accurate roadmap of exactly the problems the COVID-19 mRNA vaccine programs had to solve in order to succeed, and it is a useful reminder that the platform's 2020 debut was the product of a long, largely unglamorous research program rather than a technology invented for the pandemic.

Nucleoside modification alone does not make an mRNA vaccine; the mRNA still has to survive extracellular and endosomal degradation, escape the endosome, and reach the cytoplasmic translation machinery of a cell, typically at the injection site or in draining lymph node antigen-presenting cells. This is the job of the lipid nanoparticle. Hassett and colleagues' systematic characterization of LNP formulations for intramuscular mRNA vaccine delivery describes the four-component design that has become close to a platform standard: an ionizable cationic lipid that complexes with the negatively charged mRNA and facilitates endosomal escape at low pH, a PEGylated lipid that controls particle size and circulation time, a structural phospholipid, and cholesterol for membrane stability, and they show that the specific choice and ratio of these components substantially affects both the magnitude of the resulting antibody response and, independently, the reactogenicity profile at the injection site [17]. This formulation work is easy to treat as mere delivery-vehicle engineering, but the immunogenicity data make clear it is doing real immunological work: the LNP itself has adjuvant-like properties, and its ionizable lipid component has been shown in multiple mRNA vaccine formulations to contribute directly to the innate immune activation that helps prime the adaptive response, meaning the LNP is not a passive carrier but an active immunological component of the vaccine [3].

The clinical consequence of this molecular design is visible from the very earliest human trials. Jackson and colleagues' phase 1 report on mRNA-1273 documented dose-dependent binding and neutralizing antibody responses after just two doses in healthy adults, with titers at the higher dose levels exceeding those typically seen in convalescent serum from symptomatic COVID-19 patients, alongside a reactogenicity profile — transient local pain, fatigue, myalgia — broadly consistent with the innate immune engagement the nucleoside-modification and LNP literature would predict [18]. Mulligan and colleagues' parallel phase 1/2 report on BNT162b1, the RBD-encoding predecessor

construct to the full-length spike-encoding BNT162b2 that ultimately advanced to phase 3, similarly documented robust dose-dependent immunogenicity within weeks of first dosing, reinforcing that the platform's core molecular design translated into rapid, substantial human immune responses well before the phase 3 efficacy readout confirmed clinical protection [19].

4. Protein Subunit Vaccine Immunogenicity: Adjuvants and the Humoral Response

Protein subunit vaccines solve the innate-sensing problem that so occupied mRNA vaccine development in a completely different way: rather than engineering the antigen-encoding molecule to minimize unwanted innate activation, they engineer a separate adjuvant component specifically to provide the innate immune stimulation that a purified, non-replicating protein antigen otherwise lacks on its own. Coffman, Sher, and Seder's synthesis of adjuvant immunology frames this as the central design problem of the entire protein-and-adjuvant vaccine tradition: purified protein antigens are, almost by definition, poor at triggering the pattern-recognition receptor signaling that the innate immune system uses to license a strong, durable adaptive response, so an effective adjuvant has to supply that signal deliberately, and the choice of adjuvant shapes not just the magnitude but the qualitative character (antibody isotype distribution, Th1 versus Th2 polarization, CD8 T cell engagement) of the resulting immune response [8].

NVX-CoV2373 uses Matrix-M, a saponin-based adjuvant derived from Quillaja saponaria bark extract formulated into cholesterol- and phospholipid-containing immune-stimulating complexes. Keech and colleagues' phase 1/2 data provide the clearest published quantification of what this adjuvant contributes: in their trial, the two-dose, 5- μ g adjuvanted regimen produced a geometric mean anti-spike IgG response of 63,160 ELISA units and a geometric mean neutralizing antibody titer of 3,906, compared with geometric mean responses of 8,344 ELISA units and 983 in convalescent serum from mostly symptomatic COVID-19 patients — roughly 7.6-fold higher binding antibody levels and roughly 4-fold higher neutralizing titers than natural infection produced in the same assay system [5]. This is a genuinely striking result for a non-replicating protein subunit vaccine, and it is difficult to attribute to the

antigen alone, since unadjuvanted arms in the same trial and in related saponin-adjuvant studies consistently show substantially lower immunogenicity; the adjuvant is doing a large share of the immunological work.

Table 1: Selected immunogenicity and efficacy figures reported for the two platforms across the primary trials synthesized in this article. [1,2,4,5,21,20].

Vaccine (platform)	Source	Endpoint	Reported value
BNT162b2 (mRNA)	Polack et al. [1]	Phase 3 efficacy vs. symptomatic COVID-19	95% (95% CrI, 90.3-97.6)
mRNA-1273 (mRNA)	Baden et al. [2]	Phase 3 efficacy vs. symptomatic COVID-19	94.1% (95% CI, 89.3-96.8)
NVX-CoV2373 (protein subunit)	Heath et al. [4]	Phase 3 efficacy vs. symptomatic COVID-19	89.7% (95% CI, 80.2-94.6)
NVX-CoV2373 (protein subunit)	Keech et al. [5]	Anti-spike IgG GMT vs. convalescent serum	63,160 EU vs. 8,344 EU (~7.6x higher)
NVX-CoV2373 (protein subunit)	Keech et al. [5]	Neutralizing antibody GMT vs. convalescent serum	3,906 vs. 983 (~4.0x higher)
BNT162b2 (mRNA)	Turner et al. [21]	Germinal centre B cell/Tfh response persistence	Detectable at least 12 weeks post-vaccination
mRNA-1273 (mRNA)	Widge et al. [20]	Binding/neutralizing antibody persistence	Detectable in all participants through day 90

Pulendran, Arunachalam, and O'Hagan's broader review of adjuvant science helps explain the mechanistic basis for why a saponin-based system like Matrix-M produces this magnitude of effect: saponin adjuvants promote antigen uptake and cross-presentation by dendritic cells, engage inflammasome and other innate signaling pathways distinct from the RNA-sensing pathways relevant to mRNA vaccines, and have been shown across multiple adjuvant platforms to promote strong T follicular helper cell responses, which in turn drive the germinal center reaction responsible for high-affinity, class-switched antibody production [9]. This is a genuinely different innate-immune entry point than the RNA-sensing and LNP-mediated activation relevant to mRNA vaccines, even though both, in the end, feed into a broadly similar downstream germinal center and antibody-maturation process. Heath and colleagues' phase 3 report on NVX-CoV2373 translated this strong immunogenicity signal into clinical efficacy of 89.7% (95% CI, 80.2 to 94.6) against symptomatic COVID-19, with efficacy against the B.1.1.7 variant of 86.3% and against non-B.1.1.7 variants of 96.4% in the same trial's post hoc variant analysis [4].

It is worth being precise about what the adjuvant does

not obviously solve. Protein subunit vaccines still require, in essentially every published formulation, a two-dose regimen with several weeks between doses to reach peak immunogenicity, a schedule broadly comparable in timing to the mRNA platforms rather than dramatically faster or slower, and the manufacturing pipeline — insect-cell expression, purification, and nanoparticle assembly, followed by separate adjuvant formulation — is a more classically biotech-scale, less rapidly reconfigurable process than in-vitro transcription of a new mRNA sequence, a distinction that mattered enormously for how quickly each platform's manufacturers could pivot to variant-updated formulations during the pandemic [10,14].

5. Head-to-Head Evidence: Efficacy, Antibody Titers, and Durability

Laid side by side, the phase 3 efficacy figures from the pivotal trials of each platform are close enough to be genuinely comparable and far enough apart to be worth taking seriously as a real, if modest, difference: BNT162b2 showed 95% efficacy (95% credible interval, 90.3 to 97.6) based on 8 vaccine-group cases versus 162 placebo-group cases among participants whose illness onset occurred at least 7 days after the second dose [1]; mRNA-1273 showed 94.1% efficacy (95% CI, 89.3 to 96.8) against symptomatic Covid-19 with onset at least 14 days after the second dose [2]; and NVX-CoV2373 showed 89.7% efficacy (95% CI, 80.2 to 94.6) against symptomatic infection at least 7 days after the second dose [4]. All three trials were conducted in broadly overlapping timeframes against broadly overlapping circulating viral lineages, which is precisely what makes this comparison unusually clean relative to most cross-platform vaccine efficacy comparisons in the wider vaccinology literature, where trials against different pathogens or in different eras are rarely comparable at all [11].

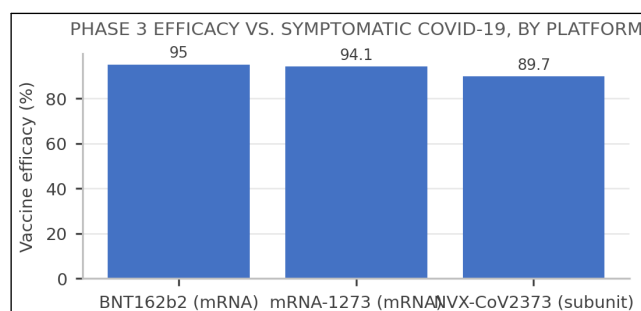


Figure 1: Phase 3 vaccine efficacy against symptomatic COVID-19 reported for the pivotal trials of each platform -- BNT162b2 and mRNA-1273 (mRNA) versus NVX-CoV2373 (adjuvanted protein subunit) -- assessed at least 7-14 days after the final dose in broadly overlapping trial periods [1,2,4].

The gap between the two mRNA vaccines and the protein subunit vaccine — roughly 5 to 6 percentage points of point-estimate efficacy, with overlapping confidence intervals — is small enough that no single trial should be read as establishing one platform's clinical superiority over the other; the confidence intervals of all three studies overlap substantially, and cross-trial comparisons of point efficacy estimates are always confounded by differences in case ascertainment, circulating variant mix, follow-up duration, and population characteristics between trials that were not designed to be compared to one another [11]. What the underlying immunogenicity data do support more confidently is that both platforms are each individually capable of eliciting neutralizing antibody responses well above the levels typically observed in convalescent serum from natural infection — a bar that, by the mid-pandemic period, had become something close to a working benchmark for "sufficiently immunogenic" across the field, since natural infection was known to confer meaningful, if imperfect and variably durable, protection [5,18].

Durability is where the comparative picture becomes genuinely more interesting than the initial efficacy readouts suggest, because efficacy trials by design capture protection over a relatively short follow-up window, while durability requires longer observation. Widge and colleagues' follow-up report on mRNA-1273 recipients found that binding and neutralizing antibody responses, while declining somewhat from their peak, remained detectable in all evaluated participants through 90 days after the second dose, providing some of the earliest published durability data for the mRNA platform beyond the initial phase 1 immunogenicity window [20]. Turner and colleagues went considerably further on the cellular side of durability, directly

sampling draining lymph node germinal centers in BNT162b2 recipients and showing that antigen-specific germinal center B cell and T follicular helper cell responses persisted for at least 12 weeks after vaccination — direct histological evidence, rather than inference from circulating antibody titers alone, that mRNA vaccination drives a genuinely sustained germinal center reaction rather than a transient antibody spike that rapidly decays [21]. Comparable direct germinal center sampling data are, to our knowledge, considerably sparser in the published protein subunit vaccine literature, which is itself a notable asymmetry in the comparative evidence base rather than necessarily a biological difference between the platforms.

A further point worth making explicit is how much of this comparative confidence rests on the fact that all three pivotal trials used broadly similar primary endpoints — virologically confirmed, symptomatic COVID-19 with onset at least 7 to 14 days after the final dose — assessed by independent, blinded adjudication committees, and all three were powered as formal efficacy trials rather than immunogenicity-bridging studies. This shared trial architecture is itself a product of the regulatory environment the pandemic created, in which harmonized guidance from major regulators effectively standardized what a pivotal COVID-19 vaccine efficacy trial had to look like, and it is precisely this standardization that makes the cross-platform comparison in this section more defensible than most retrospective cross-trial vaccine comparisons attempted in the broader vaccinology literature, where trial design heterogeneity is often severe enough to make efficacy comparisons close to uninterpretable [14,11]. That said, standardized primary endpoints do not eliminate the confounds inherent to comparing separately conducted trials, and the point stands that a single randomized head-to-head trial, were one ever conducted, would carry more evidentiary weight than any synthesis of the existing separate trials possibly could.

6. Cellular Immunity Across Platforms

Antibody titers, however useful as a headline comparison metric, are only part of the immunogenicity picture, and the T cell response each platform elicits has increasingly been recognized as immunologically important in its own right, particularly for cross-variant protection against severe disease when neutralizing

antibody titers against a drifted variant have declined. Sahin and colleagues' detailed immunogenicity study of BNT162b2 recipients found that vaccination induced not just high neutralizing antibody titers but robust CD4+ and CD8+ T cell responses recognizing multiple spike epitopes, with a T helper 1 (Th1)-skewed cytokine profile — a polarization generally considered favorable, since a Th2-skewed response to a respiratory virus antigen has historically been associated, in other vaccine contexts, with a risk of vaccine-associated enhanced respiratory disease that developers were explicitly monitoring for throughout SARS-CoV-2 vaccine development [22].

The protein subunit literature reports a structurally similar picture using a mechanistically different route to get there. The Matrix-M adjuvant used in NVX-CoV2373 was itself selected and studied for years before COVID-19 specifically because saponin-based adjuvants of this family reliably promote Th1-skewed, rather than Th2-skewed, cellular responses when paired with protein antigens — an adjuvant-selection choice that reflects exactly the kind of qualitative-response engineering Coffman, Sher, and Seder describe as the central purpose of rational adjuvant design, and one that Pulendran, Arunachalam, and O'Hagan's broader review identifies as a recurring design goal across the modern adjuvant literature well beyond this one product [8,9]. That both platforms converged on Th1-skewed cellular responses despite reaching that endpoint through entirely different innate-sensing mechanisms — RNA-sensing pathways and LNP-mediated signaling for the mRNA platform, saponin-driven innate activation for the adjuvanted subunit platform — is one of the more interesting convergences in the comparative literature, and it argues that Th1 polarization was less an accident of either specific platform's chemistry than a design target both platforms were independently optimized to hit, guided by the same accumulated adjuvant and vaccinology theory [14].

Where the platforms are harder to compare directly is in the fine-grained kinetics and breadth of the T cell response — how quickly it develops, how broadly it targets different spike epitopes, and how well it is maintained against antigenically drifted variants — because the assay platforms, epitope panels, and sampling timepoints used across the mRNA and protein subunit trial literatures have not, in general, been

harmonized across studies in the way the antibody titer and efficacy endpoints largely have been. This is a genuine gap in the comparative evidence base rather than a settled finding that one platform's T cell response is superior, and it is one of the clearer places where future work with harmonized, prospectively designed head-to-head comparisons would add real value beyond what retrospective synthesis of separately conducted trials can establish.

7. Open Challenges

Several gaps recur across the comparative literature synthesized here and deserve to be named plainly. First, and most fundamentally, essentially none of the immunogenicity and efficacy comparisons discussed above come from a single, prospectively randomized head-to-head trial directly comparing an mRNA and a protein subunit vaccine in the same population, at the same time, using identical assay platforms; every comparison, including our own, is necessarily a cross-trial synthesis subject to the confounding that entails, a limitation the field has been reasonably candid about even as it continues to draw comparative conclusions from the available data [11]. Second, durability data, while encouraging for both platforms over the observation windows published so far, remain considerably shorter than the multi-year durability data available for many long-established vaccine platforms, and the rate of antibody and cellular response decline beyond the roughly 90-day to 6-month windows captured in the papers reviewed here is less well characterized, particularly for the protein subunit platform where the published direct-sampling germinal center data are sparser than for mRNA vaccines [20,21].

Third, the mechanistic literature on how the LNP component of mRNA vaccines and the saponin adjuvant of protein subunit vaccines each independently drive innate immune activation is, in both cases, still incomplete relative to how well the platforms' clinical performance is characterized; Pardi and colleagues' review is candid that the precise contribution of the LNP itself, independent of the encoded mRNA, to the overall innate and adaptive response remains only partially resolved even for the platform's most-studied formulations [3]. Fourth, reactogenicity and tolerability comparisons across platforms, while extensively reported within each individual trial, have not been systematically harmonized across the mRNA and protein

subunit literatures using comparable solicited-symptom instruments and severity grading, making rigorous cross-platform tolerability comparisons harder to draw with confidence than the efficacy comparisons this article has focused on.

Fifth, and more forward-looking: both platforms' manufacturing and update pathways for future variant-adapted or next-pathogen formulations differ substantially in speed and flexibility, with the mRNA platform's in-vitro transcription process generally regarded as faster to reconfigure for a new antigen sequence than the protein subunit platform's cell-culture expression and purification pipeline, a practical distinction that matters enormously for pandemic preparedness even though it is not, strictly speaking, an immunogenicity question at all [10,13]. We do not think any of these gaps undermine the basic finding that both platforms are genuinely, comparably immunogenic against their shared spike antigen target; they are, instead, the honest state of a still-maturing comparative evidence base, and readers drawing platform-selection conclusions for future vaccine development should weigh them accordingly.

8. Conclusion

The comparative literature on mRNA and protein subunit COVID-19 vaccines supports a fairly specific set of claims. Both platforms, despite reaching the same prefusion-stabilized spike antigen target through fundamentally different molecular strategies — in-cell antigen expression driven by nucleoside-modified, LNP-encapsulated mRNA on one side, adjuvant-driven immune engagement of a pre-manufactured recombinant nanoparticle antigen on the other — achieved genuinely high phase 3 efficacy against symptomatic COVID-19, in the 90 to 95% range, in trials conducted over broadly overlapping periods against broadly overlapping circulating variants [1,2,4]. Both generated neutralizing and binding antibody responses substantially exceeding those seen in natural infection, and both drove Th1-skewed cellular responses despite activating the innate immune system through entirely distinct molecular mechanisms — RNA sensing and lipid nanoparticle signaling for the mRNA platform, saponin-adjuvant-driven innate activation for the protein subunit platform [5,22,8].

The differences that do emerge from the comparative literature are, so far, differences of degree and of

evidentiary completeness rather than differences suggesting one platform is categorically superior to the other. The small gap in point-estimate phase 3 efficacy between the mRNA and protein subunit trials sits within overlapping confidence intervals and cross-trial confounds that the field itself acknowledges limit any strong ranking claim [11]. What is better established is a set of platform-specific tradeoffs worth stating directly: the mRNA platform's manufacturing flexibility for rapid antigen updates versus the protein subunit platform's longer track record with adjuvant technology and, in some populations, a differentiated reactogenicity profile; the mRNA platform's richer published direct-sampling germinal center durability data versus comparatively sparser equivalent data for the adjuvanted subunit platform [21,13]. Read together, the strongest conclusion the current evidence supports is that nucleoside-modified mRNA and adjuvanted protein subunit vaccines represent two independently validated, mechanistically distinct, and comparably effective routes to eliciting strong humoral and cellular immunity against the same structurally defined antigen target — a genuinely useful redundancy for future vaccine development rather than a competition with a clear winner, and one that deserves continued, harmonized, prospective comparative study rather than further retrospective cross-trial synthesis alone.

9. References

- Polack, F.P., Thomas, S.J., Kitchin, N., et al. (2020) Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine*, 383(27): 2603-2615. DOI: [10.1056/NEJMoa2034577](https://doi.org/10.1056/NEJMoa2034577)
- Baden, L.R., El Sahly, H.M., Essink, B., et al. (2021) Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine*, 384(5): 403-416. DOI: [10.1056/NEJMoa2035389](https://doi.org/10.1056/NEJMoa2035389)
- Pardi, N., Hogan, M.J., Porter, F.W., Weissman, D. (2018) mRNA Vaccines - A New Era in Vaccinology. *Nature Reviews Drug Discovery*, 17(4): 261-279. DOI: [10.1038/nrd.2017.243](https://doi.org/10.1038/nrd.2017.243)
- Heath, P.T., Galiza, E.P., Baxter, D.N., et al. (2021) Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *New England Journal of Medicine*, 385(13): 1172-1183. DOI: [10.1056/NEJMoa2107659](https://doi.org/10.1056/NEJMoa2107659)
- Keech, C., Albert, G., Cho, I., et al. (2020) Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. *New England Journal of Medicine*, 383(24): 2320-2332. DOI: [10.1056/NEJMoa2026920](https://doi.org/10.1056/NEJMoa2026920)
- Karikó, K., Buckstein, M., Ni, H., Weissman, D. (2005) Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA. *Immunity*, 23(2): 165-175. DOI: [10.1016/j.immuni.2005.06.008](https://doi.org/10.1016/j.immuni.2005.06.008)
- Karikó, K., Muramatsu, H., Welsh, F.A., Ludwig, J., Kato, H., Akira, S., Weissman, D. (2008) Incorporation of Pseudouridine Into mRNA Yields Superior Nonimmunogenic Vector With Increased Translational Capacity and Biological Stability. *Molecular Therapy*, 16(11): 1833-1840. DOI: [10.1038/mt.2008.200](https://doi.org/10.1038/mt.2008.200)
- Coffman, R.L., Sher, A., Seder, R.A. (2010) Vaccine Adjuvants: Putting Innate Immunity to Work. *Immunity*, 33(4): 492-503. DOI: [10.1016/j.immuni.2010.10.002](https://doi.org/10.1016/j.immuni.2010.10.002)
- Pulendran, B., Arunachalam, P.S., O'Hagan, D.T. (2021) Emerging Concepts in the Science of Vaccine Adjuvants. *Nature Reviews Drug Discovery*, 20(6): 454-475. DOI: [10.1038/s41573-021-00163-y](https://doi.org/10.1038/s41573-021-00163-y)
- Krammer, F. (2020) SARS-CoV-2 Vaccines in Development. *Nature*, 586: 516-527. DOI: [10.1038/s41586-020-2798-3](https://doi.org/10.1038/s41586-020-2798-3)
- Tregoning, J.S., Flight, K.E., Higham, S.L., Wang, Z., Pierce, B.F. (2021) Progress of the COVID-19 Vaccine Effort: Viruses, Vaccines and Variants versus Efficacy, Effectiveness and Escape. *Nature Reviews Immunology*, 21(10): 626-636. DOI: [10.1038/s41577-021-00592-1](https://doi.org/10.1038/s41577-021-00592-1)
- Wrapp, D., Wang, N., Corbett, K.S., et al. (2020) Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation. *Science*, 367(6483): 1260-1263. DOI: [10.1126/science.abb2507](https://doi.org/10.1126/science.abb2507)
- Corbett, K.S., Edwards, D.K., Leist, S.R., et al. (2020) SARS-CoV-2 mRNA Vaccine Design Enabled by Prototype Pathogen Preparedness. *Nature*, 586: 567-571. DOI: [10.1038/s41586-020-2622-0](https://doi.org/10.1038/s41586-020-2622-0)
- Pollard, A.J., Bijker, E.M. (2021) A Guide to Vaccinology: From Basic Principles to New Developments. *Nature Reviews Immunology*, 21(2): 83-100. DOI: [10.1038/s41577-020-00479-7](https://doi.org/10.1038/s41577-020-00479-7)
- Dai, L., Gao, G.F. (2020) Viral Targets for Vaccines Against COVID-19. *Nature Reviews Immunology*, 21(2): 73-82. DOI: [10.1038/s41577-020-00480-0](https://doi.org/10.1038/s41577-020-00480-0)
- Sahin, U., Karikó, K., Türeci, Ö. (2014) mRNA-Based Therapeutics - Developing a New Class of Drugs. *Nature Reviews Drug Discovery*, 13(10): 759-780. DOI: [10.1038/nrd4278](https://doi.org/10.1038/nrd4278)
- Hassett, K.J., Benenato, K.E., Jacquinet, E., et al. (2019) Optimization of Lipid Nanoparticles for Intramuscular Administration of mRNA Vaccines. *Molecular Therapy* -

Nucleic Acids, 15: 1-11. DOI: [10.1016/j.omtn.2019.01.013](https://doi.org/10.1016/j.omtn.2019.01.013)

18. Jackson, L.A., Anderson, E.J., Roupael, N.G., et al. (2020) An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *New England Journal of Medicine*, 383(20): 1920-1931. DOI: [10.1056/NEJMoa2022483](https://doi.org/10.1056/NEJMoa2022483)
19. Mulligan, M.J., Lyke, K.E., Kitchin, N., et al. (2020) Phase I/II Study of COVID-19 RNA Vaccine BNT162b1 in Adults. *Nature*, 586: 589-593. DOI: [10.1038/s41586-020-2639-4](https://doi.org/10.1038/s41586-020-2639-4)
20. Widge, A.T., Roupael, N.G., Jackson, L.A., et al. (2021) Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. *New England Journal of Medicine*, 384(1): 80-82. DOI: [10.1056/NEJMc2032195](https://doi.org/10.1056/NEJMc2032195)
21. Turner, J.S., O'Halloran, J.A., Kalaidina, E., et al. (2021) SARS-CoV-2 mRNA Vaccines Induce Persistent Human Germinal Centre Responses. *Nature*, 596(7870): 109-113. DOI: [10.1038/s41586-021-03738-2](https://doi.org/10.1038/s41586-021-03738-2)
22. Sahin, U., Muik, A., Vogler, I., et al. (2021) BNT162b2 Vaccine Induces Neutralizing Antibodies and Poly-Specific T Cells in Humans. *Nature*, 595(7868): 572-577. DOI: [10.1038/s41586-021-03653-6](https://doi.org/10.1038/s41586-021-03653-6)

10. Declarations

Funding

This literature synthesis received no specific grant or funding from agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors have no competing interests to declare relevant to the content of this article.

Data Availability Statement

No new data were generated for this article, which is a synthesis of previously published literature; readers should consult the cited sources for the underlying trial data and code availability statements.

Ethical Approval

Not applicable. As a literature synthesis, this article did not involve human participants, animal subjects, or the collection or analysis of primary data.

Citation: Stojanovic S, Stojanovic N, Radovic S. "Comparative Immunogenicity of mRNA and Protein Subunit Vaccine Platforms." *J Vaccines Immunopathol* (2026): 001-010 doi: [10.5281/zenodo.22849476](https://doi.org/10.5281/zenodo.22849476)