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REVIEW ARTICLE

Evolution, Vaccine Development and World Prevalence of SARS-CoV-2 as of October 31, 2024

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ABSTRACT

Background: SARS-CoV-2 is the etiological agent responsible for the Coronavirus Disease 2019 (COVID-19).

The virus it has a high mutation rate that generates a rapid and constant appearance of new viral variants that have spread rapidly around the world. By improving the virus ability to bind to the ACE2 cell receptor, and icrease the evasion of antibodies, monoclonal antibody treatments or vaccines to combat it, mutations in viral S-protein is to blame for its high rate of spread.

This review intended for to highlight the functional virus classification used by the WHO, PANGO, GISAID and Nextrain, the major findings related to the rate of spread, the S-protein mutations linked to the decrease host immune responses elicited by prior SARS-CoV-2 infections and by the protection induced by vaccination.

Aim: The purpose of the manuscript is to perform a systematic review on the SARS-CoV-2 virus evolution, structural, genomic, pathogenic characteristics, prevalence and COVID-19 vaccine development as of October 31, 2024.

Material and Methods: Original scientific articles published in Medline, Pubmed, Science Direct, Web of Science, Scopus, EBSCO and BioMed Central databases, official health organizations (World Health Organization, U.S. Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control, The Africa Centres for Disease Control and Prevention) electronic publications, and specialized media in the subject, were electronically searched to accomplish the aim of the study. Articles published in any language were included from January 1, 2024, to October 31, 2024, using a variety of keywords in combination. The studies relevant to our review were analyzed and compared.

Results and Discussion: SARS-CoV-2 evolve at least between hosts and within hosts.

Because the continuous evolution at the inter-host level, there are variants that evolve within individual hosts, either as they reproduce generation after generation during a persistent infection, or by recombination between two variants that infect the same host simultaneously.

SARS-CoV-2 variants derived from intrahost evolution or recombination, might not compete well against variants that had been evolving among hosts all along, but there have been several cases where only a few additional mutations made their descendants extremely successful.

These include recombinant XBB lineages such as XBB.1.5, XBB.1.16, EG.5, and EG.5.1, and more recently JN.1*, a descendent of BA.2.86.

Recently the FliRT and FluQE Variants are globally increasing in prevalence, mainly in Japan, Australia, United States and other countries.

The increased prevalence or KP.3.1.1 and XEC variants is observed globally and in USA as of Ocober 26, 2024.

The next COVID-19 vaccine update will focus on JN.1, a variant that has already largely disappeared, which is likely to be replaced by variants with other mutations.

The current COVID-19 vaccines present high but heterogenous levels of protection, with decreasing protective effects for vaccines based on traditional technologies as SARS-CoV-2 variants emerged over time. The actual mRNA vaccines offered substantially higher and more consistent protection.

Conclusions: The evolution of SARS-CoV-2 has developed in the emergence of new mutant strains, some exhibiting enhanced transmissibility, immune evasion capabilities, and reduced vaccine efficacy.

Actually, KP.3.1.1 and XEC are the globally prevalent SARS-CoV-2 variants which exhibit an increase in their binding to human cell receptors but a decreased virulence.

There is no known broad estimate of the duration of protection offered by SARS-CoV-2 vaccines against COVID-19 disease, which varies not only by disease status and type, but also by circulating variants.

Current mRNA vaccines against COVID-19 have shown high effectiveness against severe disease, even after six months of the application of the primary series, improving after a booster dose.

Keywords: SARS-CoV-2, COVID-19, FliRT, FluQE, mRNA vaccines.

Introduction

SARS-COV-2 EVOLUTION

T. Ryan Gregory posted on 18 June 2024 in his tweeter account "We have both continuous and continual SARS-CoV-2 variant evolution happening. What do I mean?"[1]

Pointed that viruses evolve at least two levels: between hosts and within hosts.

Among hosts, the main determinant of viral fitness (i.e., reproductive success and the continued existence of that lineage) is penetration and dissemination into new hosts.

In general terms, traits such as transmissibility and infectiousness are under selection at the level of the host organism (inter-host).

When there is some degree of immunity in the population, characteristics such as immune escape become very relevant to viral fitness.

Because there are large numbers of hosts, SARS-CoV-2 is not seasonal, circulates at fairly high (or very high) levels throughout the year, and is not running out of evolutionary space, evolution at this level is "continuous."

"Continuous" means that it advances almost non-stop at a steady pace with increasingly apt mutations becoming more common over viral generations due to natural selection.

This is how "variant trackers" have managed to predict with impressive accuracy which variants will prevail.

This continuous background, which advances somewhat predictably, is what happens with the lineages that are evolving among the hosts (**Figure 1**).

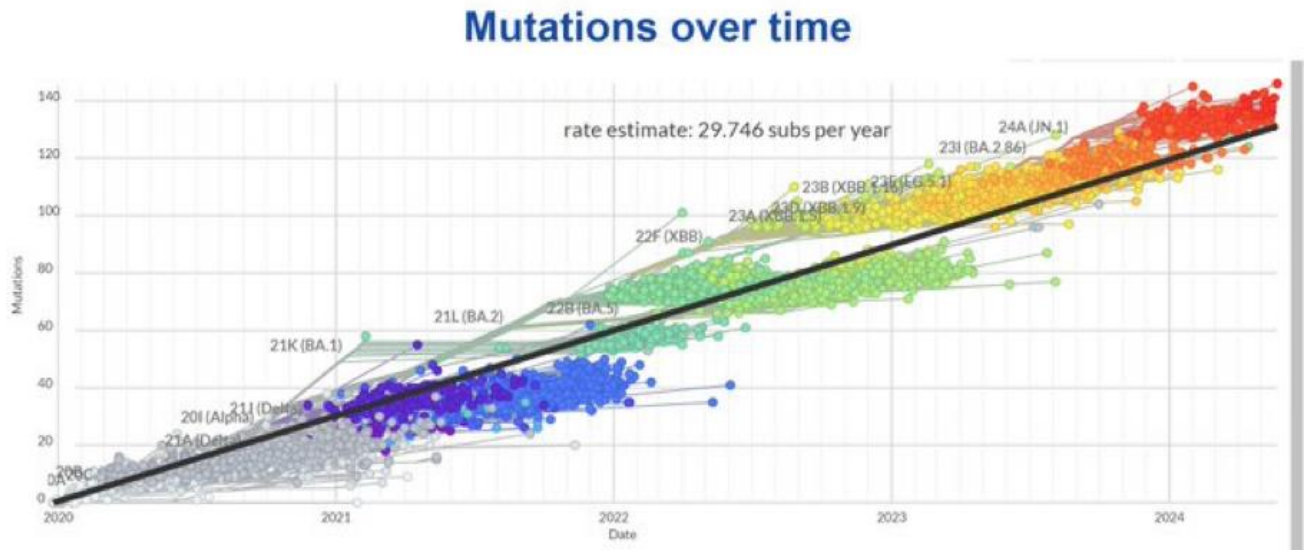
There are SARS-CoV-2 variants that evolve within individual hosts, that reproduce in two ways, generation after generation during a persistent infection, or by recombination between two variants that infect the same host simultaneously.

The virus features that evolve within hosts may be different coming out of it is under selection within them.

Important evolutionary traits are if the virus is able to avoid the immunity of the host, and to infect multiple tissues.

Evolution within the host does not involve the mass transmission that occurs every time a new host becomes infected, experts in evolutionary biology states.

Figure 1. SARS-CoV-2 Evolution Over Time.

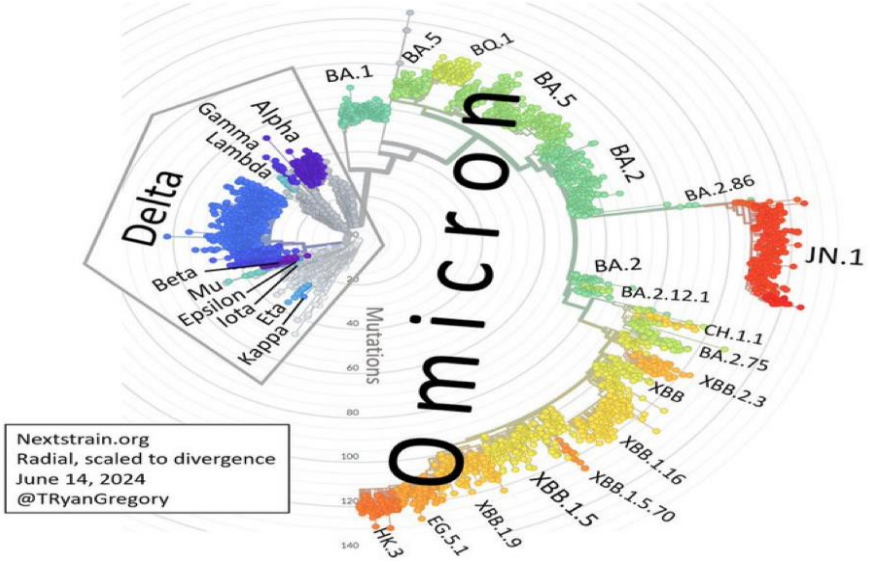


SARS-CoV-2 variants derived from intrahost evolution or recombination, might not compete acceptably against variants that had been evolving among hosts.

However there have been several cases where only a few additional mutations made virus descendants extremely successful.

These likely include Omicron BA.1, XBB lineages, and the BA.2.86 including its descendant JN.1 family (**Figure 2**).

Figure 2. Omicron Variants Divergence.



Omicron BA.1* replaced Delta and XBB replaced the previously dominant BA.2* and BA.5* lineages and currently JN.1* has replaced XBB[2,3].

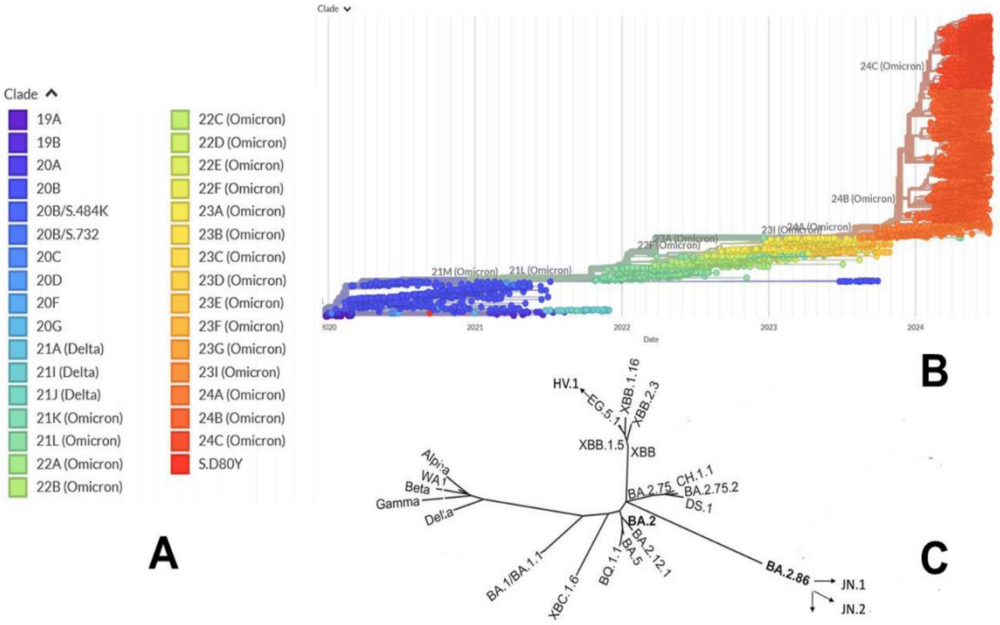
Such variants are very divergent and continuously replace the previous one.

The continuous evolution in new virus lineages involves the slightly predictable accumulation of mutations within lineages.

Mutations occur repeatedly, but intermittently and less predictably.

The effects of continuous evolution can be observed in SARS-CoV-2, specially when S-protein mutations are considered (**Figure 3**)[3].

Figure 3. An Overview of the Phylogenetic Analysis and Divergence of Omicron Variants.

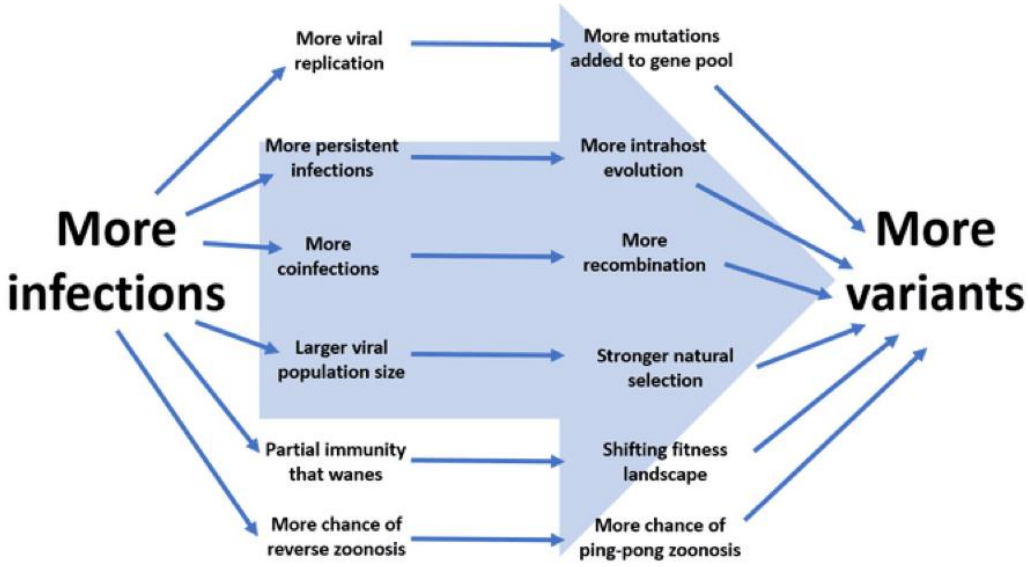


Panels **A**,**B** real-time tracking of evolving pathogen populations (https://nextstrain.org/). Phylogenetic analysis of SARS-CoV-2 clusters showing 7349 of 7349 genomes sampled between Dec 2019 and Jul 2024. BA.2.86 corresponds to Nextstrain clade 23I, JN.1 is clade 24A (BA.2.86 + S:L455S), JN.1.7 is clade 24A (J?N.1 + S:T572I, S:1150D), KP.2 is clade 24B (JN.1 + S:R346TK, D:F456L, S:V1104L) and KP.3 is clade 24C (JN.1 + S:F456L, S:Q493E, S:V110L). (**C**) The graph outlines diversification branches of Omicron mutations, highlighting evolutionary divergences between XBB.1.5 and BA.2.86 sublineages. Evolutionary trajectories of JN.1, JN.2 and JN.3 that originated from the BA.2.86 variant are schematically depicted.

There are a notable increasing in the emergence of each new lineage, followed by smaller and more gradual changes.

It is important to emphasize that the more transmissions there are to new guests, the more continuous the evolution between them will be (Figure 4).

Figure 4. SARS-CoV-2 Infections, Transmissions and Variants.



THE FLIRT AND FLUQE VARIANTS

FLiRT[4]

FLiRT is the acronym used to describe an entire family of SARS-CoV-2 variants.

KP.2, JN.1.7, and any other variants that start with KP or JN are included.

The FLiRT variants appear to have independently obtained the same set of mutations (convergent evolution).

The FLiRT variants appear to have independently obtained the same set of mutations, i.e., by Convergent Evolution.

The mutations that characterize the "FLiRT" variants are F456L + R346T.

F456L and R346T mutations remove S-protein binding sites targeted by SARS-CoV-2 neutralizing antibodies.

These binding sites are also important for the virus to bind to and enter cells.

At the same time, the T572I mutation appears to allow the virus to more tightly bind to cells and ultimately cause an infection[5].

A JN.1 infection should provide a strong protection against the FLiRT variants because they differ by only one or two amino acid changes.

Against JN.1, the vaccine designed around XBB.1.5 does generate some cross-reactive antibodies.

Studies have not been yet done with some of these newer variants, but those are likely to be a little less cross-reactive.

It's also been several months since many people received their last dose of the vaccine, and that immunity wanes over time.

Last year, the vaccines were based on the XBB.1.5 variant, and only a few months later, the JN.1 variant became the dominant variant in the U.S.

Yes, the good news is that

Paxlovid is recommended for high risk individuals, works against variants up to JN.1.

Based on the sequencing of the FLiRT variants, they should be susceptible to Paxlovid, as well as to antiviral drugs like molnupiravir and remdesivir.

The companies that produce these drugs are always testing them against new variants to ensure they continue to be effective.

FluQE[5,6]

FLuQE variants are all those derived from the KP.3 family of SARS-CoV-2 (**Figure 5**).

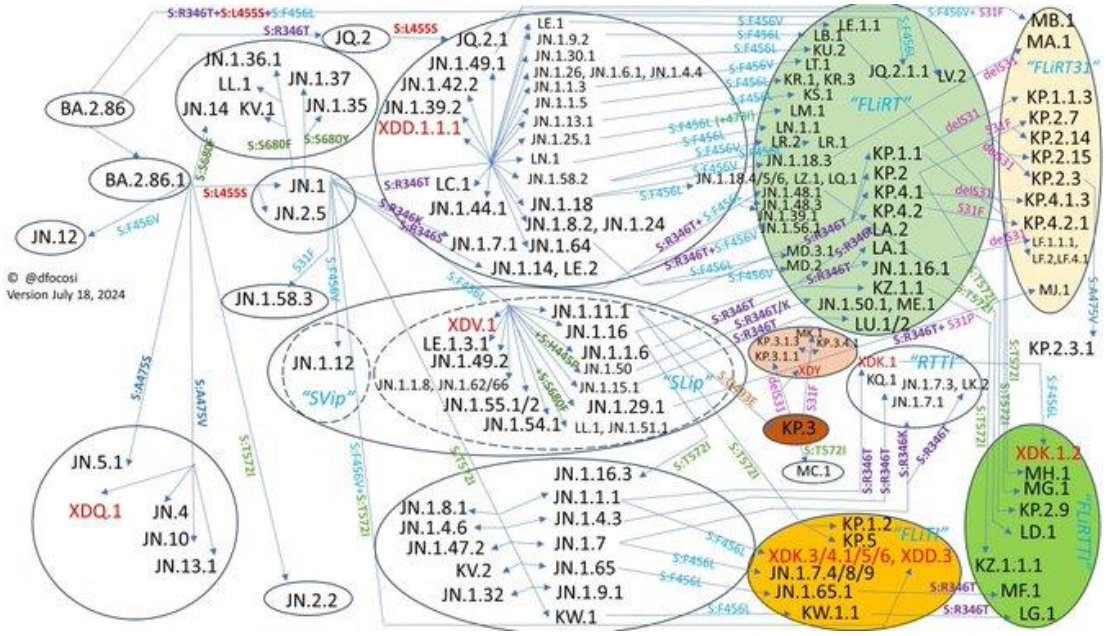
KP.3 (JN.1.11.1.3) features mutations R346T, L455S, F456L, Q493E and V1104L[7].

The F456L and Q493E mutations are collectively referred to as FLuQE.

A series of variants with mutations at L455, F456 and R346 convergent hotspot sites emerged, including the "SLip" variant, which possesses the JN.1 mutation L455S with the additional F456L[8].

The Nextclade update, consulted on June 20, 2024, categorizes all lineages derived from JN.1* that exhibit the S:Q493E mutation into a new group of variants.

Figure 5. Evolution of SARS-CoV-2 Variants[9].



The lineage is refered as "L2 lineage"= JN.1*+FLuQE.

Globally, these have been most successful in Japan (74%) and growing in Australia.

The "FLuQE" variants continue to dominate "FLiRT" and exhibit strong growth in most states across Australia.

The lack of molecular details on structure, dynamics, and binding energetics of the FLiRT and FLuQE variants including primarily JN.1, KP.2, and KP.3 RBD binding with the ACE2 receptor and antibodies, provides a considerable challenge that needs to be addressed to rationalize the experimental data and establish the atomistic basis for the proposed molecular mechanisms.

We employed an integrative computational approach in which structure and conformational ensembles of the JN.1, KP.2, and KP.3 RBD-ACE2 complexes were first predicted using AlphaFold2 (AF2) methods[10,11] using a multiple sequence alignment (MSA) approach[12-14].

The results of the investigation suggested the existence of epistatic interactions between convergent mutational sites at L455, F456, and Q493 positions that enable protection and restoration of ACE2-binding affinity while conferring beneficial immune escape.

The results also showed that Q493E and F456L can act cooperatively through epistatic couplings to reverse the detrimental effect of individual Q493E mutation seen in other genetic backgrounds.

The epistatic interactions between these sites may arise due to the increased side-chain flexibility of the interacting F456L and Q493E on RBD with H34 and K31 on ACE2 within a rather confined RBD-ACE2 interface.

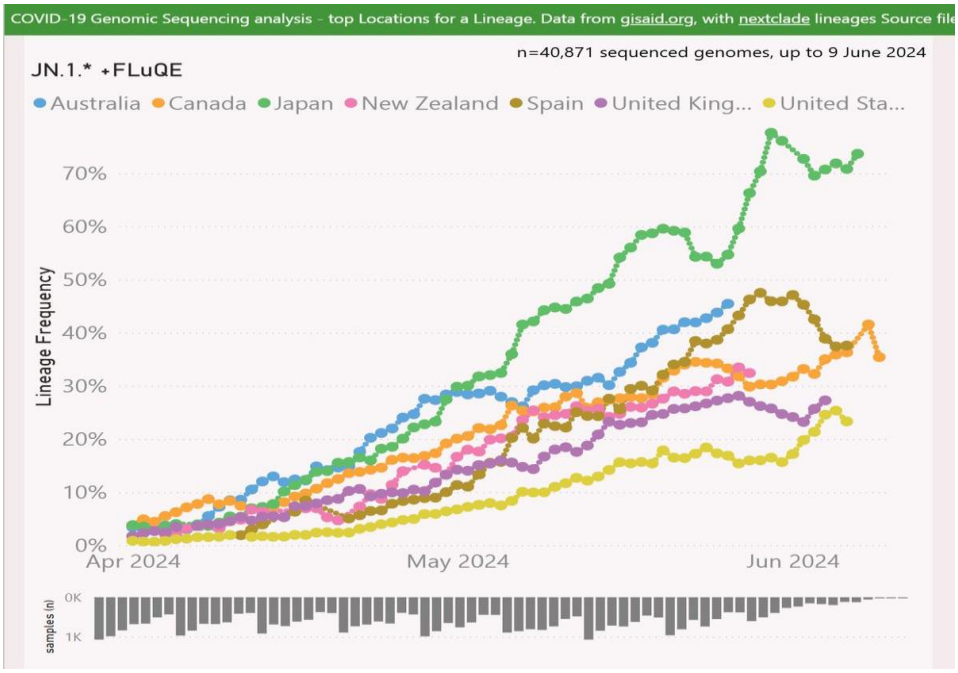
Enhanced flexibility of the binding interface induced by L455S and F456L mutations.

The results demonstrated that JN.1, KP.2, and KP.3 variants harboring the L455SS, F456L, and Q493E mutations can significantly impair the neutralizing activity of RBD class 1 monoclonal antibodies, also revealing that Y453, L455, and F456 emerged as major escape hotspots for these variants.

Mutational profiling in the KP.3 background showed that the Q493E mutation becomes more favorable when combined with KP.3 change L455S and especially F456L.

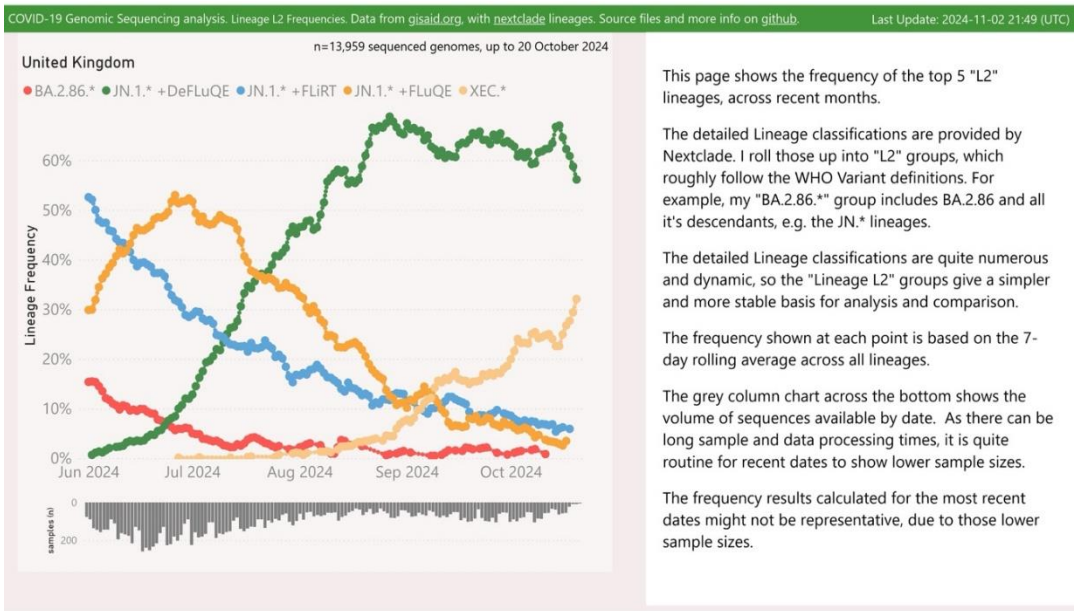
Globally, JN.1* + FluQE continues growing, mainly in Japan and Australia (**Figure 6**)

Figure 6. Globally JN.1* + FluQE Variants Evolution and Growing[15].



FLiRT and FLuQE variants have been overtaken by XEC.*, growing to around 32% (**Figure 7**).

Figure 7. SARS-CoV-2 Variant Prevalence in the United Kingdom[16].

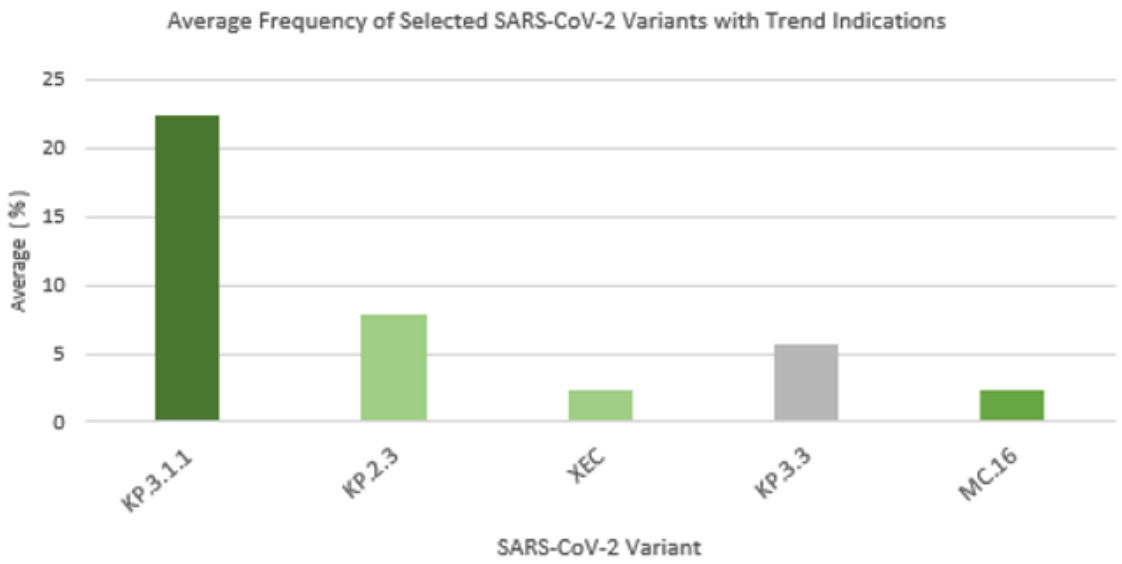


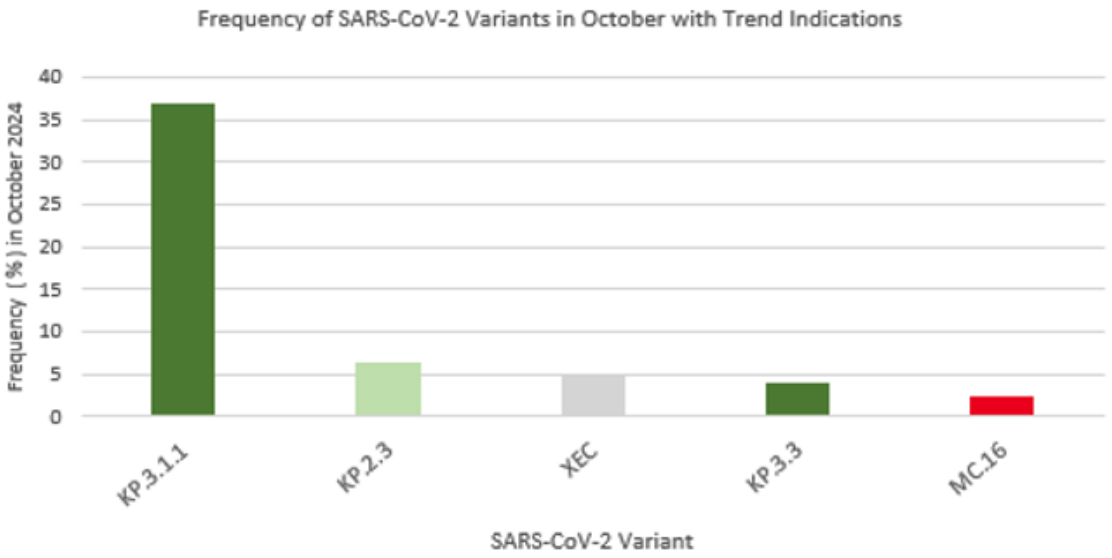
KP.3.1.1 and descendants are globally the SARS-CoV-2 prevalent variants (**Table 1, Figure 8**).

Table 1. SARS-CoV-2 Variants Global Prevalence from June 2024 to October 2024.

SARS-CoV-2 Variant	June 2024	July 2024	August 2024	September 2024	October 2024	Average	Notes
KP.3.1.1	3.03	12.37	22.70	37.50	**36.90**	22.50	Increasing
KP.2.3	5.70	7.85	9.62	9.36	**6.40**	7.78	Increasing but diminish October 2024
XEC			0.20	2.32	**4.70**	2.40	Increasing
KP.3.3	3.06	8.50	7.92	4.82	**3.90**	5.64	Diminishing
MC.16				2.30	**2.30**	2.30	Stable
MC.13				2.20	**2.20**	2.20	Stable
KP.1.1.3	1.67	2.12	2.12	2.12	**1.90**	1.98	Slow decrasing in October 2024
LB.1	3.86	2.20	2.62	2.26	**1.80**	2.54	Decreasing in October 2024
KP.3.1	5.76	8.15	5.87	2.53	**1.70**	4.80	Decreasing
LB.1.3	2.20	1.35	2.05	1.35	**1.60**	1.71	Random but increasing in October 2024
lB.1.7	1.20	0.97	2.25	2.23	**1.40**	1.41	Decreasing in October 2024
MC.11				1.40	**1.40**	1.40	Stable
MC.1		0.02		0.78	**1.30**	0.70	Increasing
KP.2.2	1.90	2.75	2.50	1.68	**1.30**	2.02	Decreasing
MC.9				1.30	**1.30**	1.30	Stable
MC.10				1.20	**1.20**	1.20	Stable
KP.3.3.1		0.50	0.42%	0.93	**1.20**	0.76	Increasing
KP.3.3.3		1.55	1.22%	1.22	**1.10**	1.27	Decreasing
KP.3.2.3	1.40	2.67	2.22	1.17	**1.00**	1.69	Decreasing

Figure 8. SARS-CoV-2 Five Prevalent Variants Frequency from June to October 2024 and in October 2024.

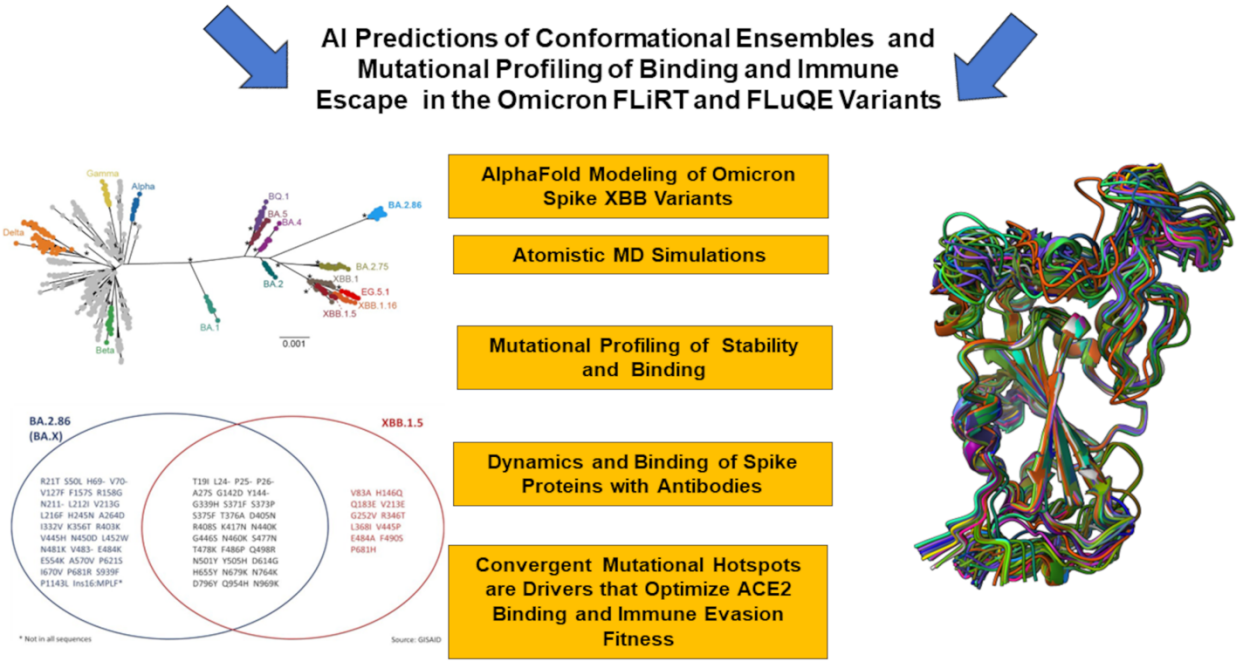




Prepared by Oscar Cobar

Figure 9 shows the predictions of conformational ensembles and mutational profiling of binding and immune escape in the Omicron FliRT and FluQE variants.

Figure 9. AI Predictions of FliRT and FluQE Conformational Ensembles and Immune Scape[17].



COVID-19 VACCINE DEVELOPMENT AGAINST SARS-COV-2 VARIANTS.

On the subject of COVID-19 vaccines, one of the complications is the lack of guidance towards continuous evolution.

The first booster targeted the wild-type plus BA.1 or BA.4/BA.5, and the second targeted XBB.1.5, "the same problem."

The next COVID-19 vaccine update will focus on JN.1, a variant that has already largely disappeared, or its descendant KP.2 (a "FLiRT" variant), which is likely to be replaced soon by variants with other mutations.

Below are statements from leading COVID-19 vaccine manufacturers on the ongoing development of their platforms.

Novavax[18]

Novavax Submits Application to European Medicines Agency for Updated Protein-based 2024-2025 Formula COVID-19 Vaccine.

Novavax's COVID-19 JN.1 vaccine is active against circulating strains of SARS-CoV-2, including KP.2 and KP.3.

GAITHERSBURG, Md., June 24, 2024 /PRNewswire / Novavax, Inc. (Nasdaq: NVAX), a global company advancing protein-based vaccines with its Matrix-M™ adjuvant, today announced that it has applied for a "Type II Variation" of the existing marketing authorization with the European Medicines Agency (EMA) for its COVID-19 vaccine JN.1 (NVX-CoV2705) for people 12 years of age and older.

The application is in line with guidance from the EMA and the World Health Organization to combat the JN.1 lineage this fall.

"Novavax is working closely with the European market to offer, this fall for COVID-19 vaccination, a protein-based alternative to mRNA," said John C. Jacobs, Novavax's President and Chief Executive Officer.

"Our updated COVID-19 vaccine is active against current circulating strains, including KP.2 and KP.3".

To date, non-clinical data have shown that Novavax's JN.1 COVID-19 vaccine induces broad neutralization responses against viruses of the JN.1 lineage, including those containing the F456L and R346T mutations and the "FLiRT" and "FLuQE" variants.

The Novavax vaccine also produces conserved, polyfunctional, Th1-biased CD4+ T cell responses to a variety of variants of the JN.1.2 lineage.

Novavax's JN.1 COVID-19 vaccine targets the "parental strain" of KP.2 and KP.3.2.

Novavax intends to make its vaccine in unit-dose vials available for distribution in the European Union for immediate release immediately upon approval.

Novavax has also filed with the U.S. Food and Drug Administration (FDA) and is working with other regulatory authorities globally on the authorization or approval of its JN.1 COVID-19 vaccine.

NOVAVAX'S COVID-19 VACCINE 2024-2025 FORMULA (NVX-COV2705)

NVX-CoV2705 is an updated version of Novavax's COVID-19 vaccine prototype (NVX-CoV2373) formulated to combat the JN.1 variant of SARS-CoV-2.

It is a protein-based vaccine that is made by creating copies of the S-protein from the surface of SARS-CoV-2.

With Novavax's unique recombinant nanoparticle technology, the non-infectious S-protein serves as an antigen that primes the immune system to recognize the virus, while Novavax's Matrix-M adjuvant enhances and amplifies the immune response.

The vaccine is packaged as a ready-to-use liquid formulation and stored at a temperature between 2°C and 8°C, allowing the use of existing vaccine supply channels and the cold chain.

Matrix-M™ Adjuvant

Novavax's patented saponin-based Matrix-M, when incorporated into vaccines, enhances the immune system's response, making it broader and longer-lasting.

Matrix-M stimulates the entry of antigen-presenting cells into the injection site and improves the amount of antigen in the local lymph nodes.

About Novavax

Novavax, Inc. (Nasdaq: NVAX) promotes improved health by discovering, developing, and commercializing innovative vaccines to help fight serious infectious diseases.

Novavax, a global company headquartered in Gaithersburg, Maryland, USA, offers a differentiated vaccine platform, combining a recombinant protein approach, innovative nanoparticle technology, and the patented Matrix-M adjuvant to enhance the immune system's response.

The company's portfolio includes its COVID-19 vaccine and a combined COVID-19 and influenza vaccine.

In addition, Novavax's adjuvant is included in the R21/Matrix-M malaria vaccine from the University of Oxford and the Serum Institute of India.

Forward-Looking Statements

Statements herein relating to Novavax's future, operational plans and prospects, the immunogenic

response of its vaccine technology against strains of different variants and the scope, timing, outcome of future submissions and regulatory actions, including EMA or FDA recommendations, intent to be ready to deliver a JN.1 protein-based COVID-19 vaccine this fall, are forward-looking statements of the Company.

Novavax cautions that these forward-looking statements are subject to numerous risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements.

These risks and uncertainties include, but are not limited to;

1. SARS-CoV2 S-protein antigenic drift or displacement, challenges that satisfy, alone or in conjunction with partners, various product safety, efficacy and characterization requirements, including those related to process qualification and assay validation, necessary to satisfy applicable regulatory authorities;

2. Difficulty in obtaining raw materials and scarce supplies;

3. Resource constraints, including human capital and manufacturing capacity, in Novavax's ability to follow planned regulatory pathways;

4. Challenges or delays in obtaining regulatory authorization for a COVID-19 vaccine based on the JN.1 protein or for future changes in virus variants;

5. Challenges or delays in clinical trials;

6. Delays or challenges in manufacturing, distribution, or export;

7. Novavax's exclusive reliance on Serum Institute of India Pvt. Ltd. for co-formulation and filling and the impact of any delay or disruption in its operations on the delivery of orders to customers, and;

8. Other risk factors identified in the "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of Novavax's Annual Report on Form 10-K for the year ended December 31, 2023 and subsequent Quarterly Reports on Form 10-Q, as filed with the Securities and Exchange Commission (SEC).

We caution investors to exercise caution in the forward-looking statements contained in this press release.

We encourage you to read our SEC filings, available at www.sec.gov and www.novavax.com, for information about these and other risks and uncertainties.

The forward-looking statements in this press release speak only as of the date hereof and we undertake no obligation to update or revise any of the statements.

Our work is subject to substantial risks and uncertainties, including those mentioned above.

Investors, potential investors, and others should carefully consider these risks and uncertainties.

Pfizer-BioNTech COVID-19 Vaccine[19-21]

COMIRNATY®, also known as Pfizer-BioNTech COVID-19 vaccine, is a messenger RNA (mRNA) based vaccine against coronavirus disease 2019 (COVID-19).

The mRNA instructs the cell to produce proteins of the S antigen (a piece of the spike protein unique to SARS-CoV-2) to stimulate an immune response.

In clinical trials, high vaccine efficacy of generally 90 to 100% was observed against symptomatic SARS-CoV-2 infection with the ancestral strain in persons 16 years and older.

Post-introduction effectiveness studies showed very high protection against hospitalization and death and moderate vaccine impact against transmission.

However, with the emergence of variants of concern since the ancestral strain, lower vaccine effectiveness (VE) has been observed, in particular for mild breakthrough infections and impact on transmission.

Booster doses restore vaccine effectiveness against Delta and Omicron variants, though waning of VE is observed for Omicron even after the booster dose.

Recommended for age 12 years of age and older, without an upper age limit WHO SAGE recommends prioritization of different population groups according to the WHO Prioritization Roadmap.

Recommended schedule Primary Vaccination Series: 2 doses at a recommended interval of 21-28 days: Dose 1: at the start date Dose 2: 21-28 days after first dose.

If the second dose is inadvertently administered earlier than 21 days, the dose does not need to be repeated.

WHO SAGE recommends that the second dose should be provided 4 to 8 weeks after the first dose, preferentially 8 weeks as a longer interval between doses is associated with higher vaccine effectiveness and potentially lower risk of myocarditis/pericarditis.

Recommended schedule Booster Doses: At least six months after completion of primary vaccination series in individuals 18 years of age and older, in accordance with the WHO Prioritization Roadmap.

Using the same product to complete primary and booster schedule is considered standard practice.

However, WHO supports programmatic flexibility and supports use of vectored vaccines and recombinant protein subunit vaccine to complete primary series and/or booster vaccination ("heterologous schedule").

Route and site of administration Intramuscular (i.m.) administration: The preferred site is deltoid muscle, with a dosage of 0.3 mL/dose.

Diluent: For multi-dose vials with purple cap 0.9% sodium chloride solution for injection, unpreserved, in a 10 mL vial for single use or in a 2 mL vial, 1.8 mL diluent is required per 6 dose vaccine vial; for multi-dose vials with gray cap not applicable since already diluted.

Mixing syringe Reuse prevention (RUP) syringe: 3 mL (5 mL RUP syringe acceptable), needle 21G or narrower.

Comirnaty is a vaccine for preventing coronavirus disease 2019 (COVID-19) in people from the age of 6 months.

The originally authorised Comirnaty contains tozinameran, a messenger RNA (mRNA) molecule with instructions for producing a protein from the original strain of SARS-CoV-2, the virus that causes COVID-19.

As SARS-CoV-2 keeps evolving, Comirnaty has been adapted to target the most recent strains of the virus.

This helps maintain protection against COVID-19.

Therefore, Comirnaty is also authorised as four adapted vaccines, with Comirnaty JN.1 and Comirnaty KP.2 being the most recent:

- Comirnaty Original/Omicron BA.4-5 contains tozinameran and famtozinameran, an mRNA molecule with instructions for producing a protein from the Omicron BA.4 and BA.5 subvariants of SARS-CoV-2;
- Comirnaty Omicron XBB.1.5 contains raxtozinameran, an mRNA molecule with instructions for producing a protein from the SARS-CoV-2 Omicron XBB.1.5;
- Comirnaty JN.1 contains bretovameran, an mRNA molecule with instructions for producing a protein from the Omicron JN.1 subvariant of SARS-CoV-2;
- Comirnaty KP.2 contains an mRNA molecule with instructions for producing a protein from the Omicron KP.2 subvariant of SARS-CoV-2.

On August 22, 2024, the Food and Drug Administration amended the emergency use authorization (EUA) of Pfizer-BioNTech COVID-19 Vaccine to include the 2024-2025 formula.

The Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) includes a monovalent (single) component that corresponds to the Omicron variant KP.2 strain of SARS-CoV-2.

The Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) is authorized for all doses administered to individuals 6 months through 11 years of age to prevent COVID-19.

Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) is authorized for use as follows:
Individuals 6 months through 4 years of age:

- Unvaccinated individuals:

Three doses of Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) are administered.

The first two doses are administered three weeks apart.

The third dose is administered at least 8 weeks after the second dose.

- Individuals who have received one previous dose of any Pfizer BioNTech COVID-19 Vaccine that is no longer authorized for use in the United States:

Two doses of Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) are administered.

The first dose of Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula) is administered three weeks after receipt of the previous dose and the second dose is administered at least 8 weeks later.

- Individuals who have received two or more previous doses of any Pfizer BioNTech COVID-19 Vaccine that is no longer authorized for use in the United States:

A single dose of Pfizer-BioNTech COVID 19 Vaccine (2024-2025 Formula) is administered at least 8 weeks after receipt of the last previous dose.

- Individuals 5 years through 11 years of age, regardless of vaccination status:

A single dose of Pfizer-BioNTech COVID-19 Vaccine (2024-2025 Formula).

If previously vaccinated with any COVID-19 vaccine that is no longer authorized for use in the United States, administer at least 2 months after receipt of the last previous dose of any COVID-19 vaccine.

- Immunocompromised individuals 6 months through 11 years of age:

Complete at least a three-dose series with a COVID-19 vaccine with an age appropriate dose and dosing schedule. At least one dose should be with a COVID-19 vaccine (2024-2025 Formula).

COMPARING THE COVID-19 VACCINES: HOW ARE THEY DIFFERENT?[22]

Pfizer-BioNTech

The Pfizer-BioNTech vaccine (brand name: Comirnaty) was granted full Food and Drug Administration (FDA) approval in August 2021 for people ages 16 and older.

Before that, it was the first COVID vaccine to receive FDA Emergency Use Authorization (EUA) back in December 2020, after the company reported that its vaccine was highly effective at preventing symptomatic disease.

This is a messenger RNA (mRNA) vaccine, which uses a relatively new technology.

It must be stored in freezer-level temperatures, which can make it more difficult to distribute than some other vaccines.

Status: Pfizer's vaccine has been updated over time to target new virus variants.

First introduced in December 2020, the original COVID mRNA vaccines from both Pfizer and Moderna protected against the original SARS-CoV-2 virus.

They have been replaced three times since then with shots targeting different iterations of the Omicron strain of the virus.

In 2022, "bivalent" vaccines targeted both the original virus and Omicron variants BA.4 and BA.5; in 2023, a monovalent shot targeted the XBB lineage of the Omicron variant; and in 2024, a new updated shot aims to protect against KP.2, which circulated in the U.S. earlier in the year.

The previous vaccines are no longer in use.

Who can get it:
People 6 months and older.

The CDC has specific recommendations for the following groups, noting that anyone who recently had COVID may need to consider delaying their vaccination by 3 months:

- Children ages 6 months to 4 years need multiple doses (check the CDC website for more specific recommendations), including at least one dose of the 2024-2025 updated vaccine.

- Children ages 5 to 11 years may get one dose of the 2024-2025 updated vaccine.
- People ages 12 and older may get one dose of the 2024-2025 updated vaccine

People 65 years and older, and those who are moderately or severely immunocompromised, may receive a second dose six months after their first dose.

People who are moderately or severely immunocompromised may decide to receive additional doses in consultation with their healthcare provider.

Possible side effects:
Pain, redness, or swelling at the site where the shot was administered, and/or tiredness, headache, muscle pain, chills, fever, or nausea throughout the rest of the body.

If these side effects occur, they should go away in a few days.

A few side effects are serious, but rare. These include anaphylaxis, a severe reaction that is treatable with epinephrine (the drug in EPIPENs®).

FDA warnings:
The FDA added a warning label on the mRNA vaccines regarding serious (but rare) cases of inflammation of the heart muscle (myocarditis) and of the outer lining of the heart (pericarditis) in adolescents and young adults, more often occurring after the second dose of an mRNA vaccine.

The inflammation, in most cases, gets better on its own without treatment.

How it works:
It uses mRNA technology, which is a way of sending instructions to host cells in the body for making copies of a spike protein (like the spikes you see sticking out of the coronavirus in pictures).

Our cells recognize that this protein doesn't belong, and the immune system reacts by activating immune cells and producing antibodies.

This will prompt the body to recognize and attack the real SARS CoV-2 spike protein if you become exposed to the actual virus.

How well it works:
The 2024-2025 updated vaccines were approved based on preclinical studies of their efficacy against circulating strains.

Some people may still become infected even though they have been vaccinated, but the goal of the vaccines now is to prevent severe disease, hospitalization and death.

Research has suggested that people who are infected after vaccination also are less likely to report Long COVID (defined as signs, symptoms, and conditions that continue or develop after acute COVID infection), compared to those who were not vaccinated.

In its recommendations for COVID vaccines, the CDC has cited a study showing the risk of cardiac complications, including myocarditis (an inflammation of the heart muscle), in males 12-17 years old was 1.8–5.6 times higher after a COVID infection compared to after COVID vaccination.

In December 2020, Pfizer-BioNTech's Phase 3 clinical data for its original vaccine showed 95% efficacy for preventing symptomatic COVID.

Later data on real-world effectiveness for adults showed that the protection from the mRNA two-dose primary series waned over time, suggesting that updated vaccines would be needed to bring the immune system back to robust levels.

Additional information is available on the FDA's Pfizer-BioNTech 2024-2025 vaccine fact sheet[23].

Moderna
The FDA granted the Moderna vaccine (brand name: Spikevax) full approval for people 18 and older in January 2022, upgrading the vaccine's EUA, which was granted in December 2020 (a week after Pfizer-BioNTech).

Moderna uses the same mRNA technology as Pfizer-BioNTech and had a similarly high efficacy at preventing symptomatic disease when the companies applied for authorization; it also needs to be stored in freezer-level temperatures.

Status:
Moderna's vaccine has been updated over time to target new virus variants.

First introduced in December 2020, the original COVID mRNA vaccines from both Pfizer and Moderna protected against the original SARS-CoV-2 virus.

They have been replaced three times since then with shots targeting different iterations of the Omicron strain.

In 2022, "bivalent" vaccines targeted both the original virus and Omicron variants BA.4 and BA.5; in 2023, a monovalent shot targeted the XBB lineage of the Omicron variant; and in 2024, a new updated shot aims to protect against KP.2, which circulated in the U.S. earlier in the year.

The previous vaccines are no longer in use.

Who can get it:
People ages 6 months and older.
The CDC has specific recommendations for the following groups, noting that anyone who recently had COVID may need to consider delaying their vaccination by 3 months:

- Children ages 6 months to 4 years need multiple doses (check the CDC website for more specific recommendations), including at least one dose of the 2024-2025 updated vaccine.
- Children ages 5 to 11 years may get one dose of the 2024-2025 updated vaccine.
- People ages 12 and older may get one dose of the 2024-2025 updated vaccine.

People 65 years and older, and those who are moderately or severely immunocompromised, may receive a second dose six months after their first dose.

People who are moderately or severely immunocompromised may decide to receive additional doses in consultation with their healthcare provider.

Possible side effects:
The side effects are similar to Pfizer-BioNTech's vaccine: Pain, redness, or swelling at the site where the shot was administered, and/or tiredness, headache, muscle pain, chills, fever, or nausea throughout the rest of the body.

If any of these side effects occur, they should go away in a few days.

A few side effects are serious, but rare. These include anaphylaxis, a severe reaction that is treatable with epinephrine (the drug in EPIPENs®).

FDA warnings:
The FDA placed a warning label on the Moderna vaccine regarding a "likely association" with reported cases of heart inflammation in young adults.

This inflammation may occur in the heart muscle (myocarditis) or in the outer lining of the heart (pericarditis), it more often occurs after the second dose of an mRNA vaccine.

The inflammation, in most cases, gets better on its own without treatment.

How it works:
Similar to the Pfizer vaccine, this is an mRNA vaccine that sends host cells in the body instructions for making a spike protein that will train the immune system to recognize it.

The immune system will then attack the spike protein the next time it sees one (attached to the actual SARS CoV-2 virus).

How well it works:
The 2024-2025 updated vaccines were approved based on preclinical studies of their efficacy against the latest circulating strains.

Some people may still become infected even though they have been vaccinated, but the goal of the vaccines now is to prevent severe disease, hospitalization, and death.

Research has suggested that people who are infected after vaccination also are less likely to report Long COVID compared to those who were not vaccinated.

In its recommendations for COVID vaccines, the CDC has cited a study showing the risk of cardiac complications, including myocarditis (an inflammation of the heart muscle), in males 12-17 years old was 1.8-5.6 times higher after a COVID infection compared to after COVID vaccination.

Moderna's initial Phase 3 clinical data in December 2020 was similar to Pfizer-BioNTech's, both vaccines showed about 95% efficacy for prevention of COVID.

Later data on real-world effectiveness for adults showed that the protection from the mRNA two-dose primary series wanes over time, but booster doses brought the immune system back to robust levels.

Additional Information is available on the FDA´s Moderna 2024-2025 vaccine fact sheet[24].

Novavax

The Novavax vaccine (brand names: Nuvaxovid and Covovax) was the fourth COVID vaccine to be administered in the U.S (after Johnson & Johnson, which is no longer available).

The Novavax vaccine is the only non-mRNA updated COVID vaccine that has been available in the U.S.

This vaccine is a protein adjuvant that had a 90% efficacy in its clinical trial, performing almost as well as the mRNA vaccines in their early trials.

It is simpler to make than some of the other vaccines and can be stored in a refrigerator, making it easier to distribute.

Status:

The FDA authorized an updated COVID vaccine from Novavax at the end of August for everyone ages 12 and older.

Novavax designed its updated shot to target JN.1, a predecessor of KP.2. Novavax's 2023-2024 vaccine is no longer available in the U.S., since all doses have expired.

Who can get it:

People 12 and older.

People 65 years and older, and those who are moderately or severely immunocompromised may receive a second dose six months after their first dose.

People who are moderately or severely immunocompromised may decide to receive additional doses in consultation with their healthcare provider.

Possible side effects:

Injection site tenderness, fatigue, headache, muscle pain.

There were rare cases of myocarditis and pericarditis (six cases in 40,000 participants) in the clinical trial, and rare severe allergic reactions.

How it works:

Unlike the mRNA and vector vaccines, this is a protein adjuvant (an adjuvant is an ingredient used to strengthen the immune response).

While other vaccines trick the body's cells into creating parts of the virus that can trigger the immune system, the Novavax vaccine takes a different approach.

It contains the spike protein of the coronavirus itself but formulated as a nanoparticle, which cannot cause disease.

When the vaccine is injected, this stimulates the immune system to produce antibodies and T-cell immune responses.

How well it works:

While it's 2024-2025 updated vaccine targets the JN.1 variant, and not KP.2 like Pfizer and Moderna, Novavax has reported that non-clinical data has demonstrated broad cross-neutralizing antibodies against multiple variant strains, including JN.1, KP.2 and KP.3.

Earlier studies of its original vaccine showed it to be 90% effective overall against lab-confirmed, symptomatic infection and 100% effective against moderate and severe disease in Phase 3 trial results published in The New England Journal of Medicine in December 2021.

Additional information is available on the FDA's Novavax 2024-2025 vaccine fact sheet[25].

Where to get a COVID vaccine:

As with previous COVID vaccines, the 2024-2025 updated COVID vaccines are available at participating pharmacies and provider offices.

To find a location near you that carries the vaccine and to schedule an appointment, go to Vaccines.gov.

You can also call 1-800-232-0233 (TTY 1-888-720-7489).

SARS-COV-2 VARIANTS PREVALENCE IN 2024

COVID-19 has had a significant impact on the world since its appearance in 2019.

Although vaccines have been developed and distributed worldwide, SARS-CoV-2, the virus that causes COVID-19, continues to mutate, representing a great challenge for public health systems around the world.

In 2024, the COVID-19 pandemic continues, due to the ability to adapt and evolve into new variants of SARS-CoV-2.

Since the end of March, KP.3 lineage viruses have been rising, and in early June, they overtook KP.2 as the dominant variants.

In May 2024, KP.2 was responsible for 28.2% of COVID-19 cases in the U.S., followed by the JN.1 variant, responsible for 15.7%.

However, since the beginning of June, a new FLiRT variant, named KP.3, has taken the lead and now represents 25 percent of COVID-19 cases in the U.S.

KP.2 still follows as a close second, representing 22.5 percent of cases.

Since August 2024, KP.3.1.1 has overtaken KP.3 and is currently the only major variant increasing in proportion.

As of October 31, 2024, the KP* family, mainly KP.3, predominates around the world.

The KP.3.1.1 variant is the predominant variant to date with more than 40% prevalence worldwide, followed by XEC (KS.1.1 and KP.3.3 recombinant) with about 15%[26].

The KP.3* family is part of the FLiRT group of SARS-CoV-2.

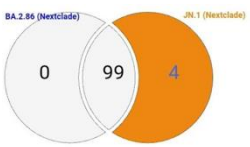
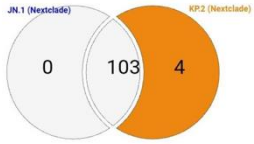
KP.3.1.1, of the Omicron family, is now the predominant SARS-CoV-2 variant circulating globally and in the United States, having overtaken its parent linage KP.3 and previous KP.2 variants.

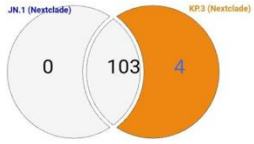
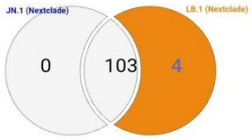
In parallel, the XEC lineage, a recombinant of KS.1.1 and KP.3.3, is on track of becoming the next dominant lineage in Europe and North America[27]. KP.3 variant can spread quickly and its symptoms include a sore throat, runny nose, cough, headaches, fever, congestion, fatigue and muscle aches.

Because new variants contain mutations that can pose a threat to public health, public health organizations are continuously monitoring COVID-19 cases around the world.

WHO is currently tracking multiple variants, including (**Table 2**):

Table 2. Recently SARS-CoV-2 Variants Explained. Adapted from T. Ryan Gregory; June 23, 2024[26].

Variant	What is it?	Status	Relevance	Mutations
JN.1 (Pirola clan)	Descendant of BA.2.86, with an additional mutation in its S Protein. **JN.1 = BA.2.86.1.1.**	Very low prevalence, with a tendency to disappear.	Most of the variants currently circulating are descended from it. It may be the target of the new COVID-19 vaccine.	 **Mutations:** ORF1a:K1973R, ORF1a:R3821K, S:L455S, ORF7b:F19L
KP.2 (Pirola clan, "FLiRT")	A descendant of JN.1 with mutations "FLiRT" (F456L + R346T). **KP.2 = JN.1.11.1.2.**	Dominant in some countries, competing with other	Important mutations. May be targeted for future	 **Mutations:** ORF1a:T2283I, S:R346T, S:F456L, S:V1104L

Variant	What is it?	Status	Relevance	Mutations
		ascending variants such as KP.3 and LB.1.	COVID-19 Vaccine updates.	
KP.3 (Pirola clan, "FLuQE")	A descendant of JN.1 with mutations FLuQE (F456L + Q493E). KP.3 = JN.1.11.1.3.	Rapidly increasing its prevalence in some areas of the planet.	It may overcome KP.2 in prevalence.	 **Mutations:** ORF1a:T2283I, S:F456L, S:Q493E, S:V1104L
LB.1 (Pirola clan, "FLiRT")	A descendant of JN.1 with mutations FLiRT (F456L + R346T). Mutations evolved in FLiRT regardless of KP.2. LB.1 = JN.1.9.2.1.	Increasing its prevalence in some areas of the planet.	Important mutations. Competitive vs. KP.2.	 **Mutations:** S:S31-, S:Q183H, S:R346T, S:F456L

Material and Methods

Original scientific articles published in Medline, Pubmed, Science Direct, Web of Science, Scopus, EBSCO and BioMed Central databases, official health organizations (World Health Organization, U.S. Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control, The Africa Centres for Disease Control and Prevention) electronic publications, and specialized media in the subject, were electronically searched to accomplish the aim of the study.

Articles published in any language were included from January 1, 2024, to October 31, 2024, using a variety of keywords in combination.

The studies relevant to our review were analyzed and compared.

Results and Discussion

SARS-CoV-2 evolve at least between hosts and within hosts.

Because the continuous evolution at the inter-host level, there are variants that evolve within individual hosts, either as they reproduce generation after generation during a persistent infection, or by recombination between two variants that infect the same host simultaneously.

SARS-CoV-2 variants derived from intrahost evolution or recombination, might not compete well against variants that had been evolving among hosts all along, but there have been several cases where only a few additional mutations made their descendants extremely successful.

These include recombinant XBB lineages such as XBB.1.5, XBB.1.16, EG.5, and EG.5.1, and more recently JN.1*, a descendent of BA.2.86.

Recently the FliRT and FluQE Variants are globally increasing in prevalence, mainly in Japan, Australia, United States and other countries.

The increased prevalence or KP.3.1.1 and XEC variants is observed globally and in USA as of Ocober 26, 2024.

Both KP.3.1.1 and XEC were less well neutralised compared with JN.1, denoting elevated immune evasion.

JN.1 booster vaccination improved neutralisation of all SARS-CoV-2 lineages and therefore will likely

increase protection against post-COVID sequelae from infection caused by KP.3.1.1 and XEC.

There are evidence for serum S-protein persistence in individuals after SARS-CoV-2 infection without an association with PCS.

Among individuals aged ≥60 years, mRNA XBB-vaccination provided limited and short-term, protection against COVID-19 hospitalization due to JN.1*, KP.3.1.1,and XEC variants in.

Overall, compared people with no updated vaccination, and those with Pfizer/BioNTech's updated vaccine, the updated Moderna COVID-19 vaccine provided protection that resulted in fewer clinical cases, and was cost-saving at the individual and system levels in high-risk populations.

The next COVID-19 vaccine update will focus on JN.1, a variant that has already largely disappeared, which is likely to be replaced by variants with other mutations.

The current COVID-19 vaccines present high but heterogenous levels of protection, with decreasing protective effects for vaccines based on traditional technologies as SARS-CoV-2 variants emerged over time.

The actual mRNA vaccines offered substantially higher and more consistent protection.

Conclusions

COVID-19 is a complex, multi-organ, and heterogeneous disease with diverse clinical manifestations.

The disease progresses from uncomplicated forms to pneumonia and acute respiratory distress syndrome requiring intensive care.

The evolution of SARS-CoV-2 has developed in the emergence of new mutant strains, some exhibiting enhanced transmissibility, immune evasion capabilities, and reduced vaccine efficacy.

The critical role of NTD mutations in dictating aspects of spike biology impact negatively vaccine efficacy and disease manifestation.

The SARS-CoV-2 immune imprinting has shifted from pre-Omicron toward Omicron variants, depending on the time and/or number of immune stimuli as of infection and/or vaccination.

Actually, KP.3.1.1 and XEC are the globally prevalent SARS-CoV-2 variants which exhibit an increase in their binding to human cell receptors but a decreased virulence.

KP.3.1.1 has become the new globally dominant strain, while XEC is rapidly expanding across Europe and North America.

Both variants carry mutations, S31del of KP.3.1.1 and T22N of XEC, that could introduce new N-linked glycans on the S-protein N-terminal domain (NTD), emphasizing the urgent need to evaluate their potential changes in viral characteristics.

There is no known broad estimate of the duration of protection offered by SARS-CoV-2 vaccines against COVID-19 disease, which varies not only by disease status and type, but also by circulating variants.

Bivalent COVID-19 mRNA Pfizer-BioNTech) and Moderna vaccines protected against symptomatic infection.

Current mRNA vaccines against COVID-19 have shown high effectiveness against severe disease, even after six months of the application of the primary series, improving after a booster dose.

It is crirtical to emphasize the need to stay up to date on recommended COVID-19 vaccination.

The high rates of adverse outcomes in the ICU population are likely due to the severity of the systemic inflammatory response in COVID-19, rather than a direct viral-mediated cardiovascular effect.

Notably, the results of current research increase the probability that viral recurrence and increased prevalence contribute to the development of Post-acute Sequelae of COVID-19 (PASC).

Conflict of Interest:

None.

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