Title

Do Existing COVID-19 Vaccines Need to Be Updated in 2025?

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Abstract

COVID-19 vaccines have been updated each year since 2022 to improve protection against evolving SARS-CoV-2 variants. However, it is unclear whether a reformulation will be necessary for 2025. KP.2-based monovalent COVID-19 mRNA vaccines (KP.2 MV) were authorized for use in 2024, and they conferred substantial protection against hospitalizations caused by viral variants that emerged and dominated later, such as KP.3.1.1 and XEC. Today, LP.8.1 has become the dominant variant worldwide, particularly so in North America. To characterize the antigenicity of LP.8.1, we tested serial serum samples from 16 individuals who recently received KP.2 MV in neutralization assays against KP.3.1.1, XEC, and LP.8.1 pseudoviruses. Serum neutralizing antibody titers against LP.8.1 were comparable to those against KP.3.1.1 and XEC, indicating that LP.8.1 is antigenically similar to its predecessors. Therefore, the currently authorized KP.2 MV may not need to be updated for 2025, if the vaccine manufacturers could demonstrate comparable immunogenicity for KP.2 MV and LP.8.1-based mRNA vaccines and, of course, in the absence of an antigenically divergent SARS-CoV-2 emerging.

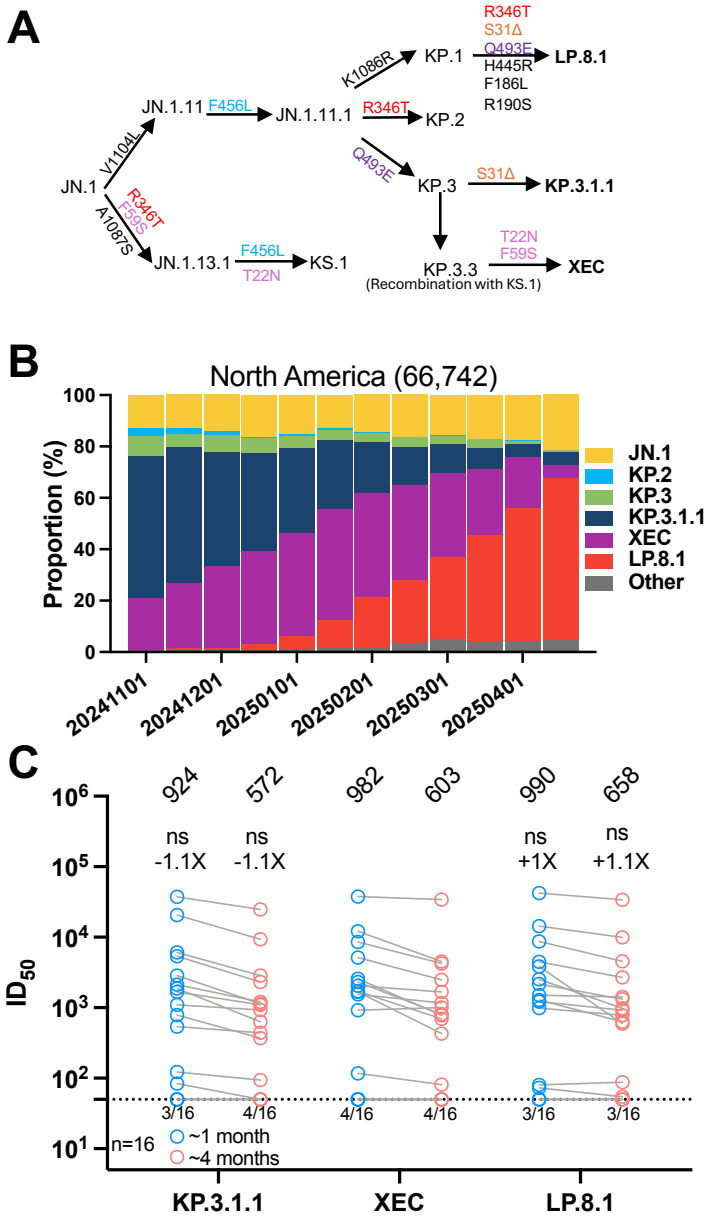
Main Text

COVID-19 vaccines have been updated each year since 2022 to improve protection against evolving SARS-CoV-2 variants[1]. However, it is unclear whether a reformulation will be necessary for 2025[2]. KP.2-based monovalent COVID-19 mRNA vaccines (KP.2 MV) were approved in mid to late 2024 in the US, EU, and UK to improve protection against the antigenically distinct viruses in the JN.1 lineage, including KP.2 and KP.3, which were prevalent at the time of strain selection. Indeed, KP.2 MV robustly boosted neutralizing antibody titers against not only the intended target viruses but also against later dominant subvariants, such as KP.3.1.1 and XEC[1]. Recent work showed that KP.2 MV had substantial vaccine effectiveness during periods dominated by KP.3.1.1 and XEC, with estimates of up to 75% protection from hospitalization in individuals 65 years of age or older[3]. A progeny virus, LP.8.1, emerged in early 2025 and became dominant worldwide in the ensuing months (Figs. 1A, 1B, S1A). Today, viruses in the LP.8.1 sublineage account for >60% of new SARS-CoV-2 infections in North America based on deposited viral sequences (Figs. 1B). LP.8.1 possesses five additional spike mutations compared with KP.3.1.1, including R346T and H445R in the receptor-binding domain, F186L and R190S in the N-terminal domain, and K1086R in the S2 region (Figs. 1A, S1B). Therefore, an understanding of the antigenic properties of LP.8.1 is of great importance to regulatory agencies and vaccine advisory bodies as they consider whether COVID-19 vaccines need to be updated to provide better coverage of this subvariant[4]. To assess LP.8.1 antigenicity, we performed pseudovirus neutralization assays using serum samples from 16 recipients of KP.2 MV in the US (Tables S1, S2) obtained at 1 month and 4 months post vaccine boost. LP.8.1.1 in the LP.8.1 sublineage contains an additional K679R mutation near the furin cleavage site (Fig. S1B), is antigenically similar to LP.8.1 (Fig. S1C); therefore, results presented below for LP.8.1 also represent those for LP.8.1.1. Serum neutralizing antibody titers against KP.3.1.1, XEC, and LP.8.1 were similar in range and in their respective geometric mean titers: 924, 982, and 990 at 1 month post boost and 572, 603, and 658 at 4 months post boost (Fig. 1C). The half-lives for the decay in neutralizing antibodies titers against these subvariants were also comparable, ranging from 66 to 91 days (Fig. S2). These findings show that LP.8.1 is antigenically similar to KP.3.1.1 and XEC following KP.2 MV, as has been noted using sera obtained from China, Japan, and Germany, in populations with different infection and vaccination histories[5–7]. This conclusion, in turn, raises the specter that current COVID-19 boosters may not need reformulation for 2025. But antigenicity does not equal immunogenicity. Vaccine manufacturers could readily compare the immunogenicity of LP.8.1-based vaccines to that of KP.2 MV in both animals and humans. Comparable results from such studies would reinforce the suggestion provided herein that vaccine manufacturers could potentially avoid producing an updated COVID-19 vaccine formulation for 2025, barring the emergence of another antigenically distinct SARS-CoV-2 variant in the meantime.

Figure Legend

***Figure 1**: Evolution, dominance, and antigenicity of SARS-CoV-2 LP.8.1*. **A**: Evolution of the spike proteins of viruses in the JN.1 lineage. **B**: Relative frequencies of SARS-CoV-2 variants from November 2024 to mid-April 2025. Data were derived from GISAID, and "LP.8.1" also included LP.8.1.1 and other members of the LP.8.1 sublineage. **C**: Serum neutralizing titers (ID_{50}) against VSV-based pseudoviruses bearing spike proteins of KP.3.1.1, XEC, or LP.8.1, for samples from recipients of KP.2 MV at ~1 month and ~4 months post booster. The geometric mean ID_{50} titer (GMT) is presented at the top. The fold change in GMT for each virus compared to XEC is also shown immediately above the symbols. Statistical analyses used Wilcoxon matched-pairs signed-rank tests, comparing to XEC. n, sample size; ns, not significant. Numbers under the dotted lines denote numbers of serum samples that were under the limit of detection ($ID_{50} < 50$).

Main Figure


A
JN.1
V1104L
JN.1.11
F456L
JN.1.11.1
K1086R
KP.1
R346T
S31Δ
Q493E
H445R
F186L
R190S
LP.8.1
R346T
KP.2
Q493E
KP.3
S31Δ
KP.3.1.1
R346T
F59S
A1087S
JN.1.13.1
F456L
T22N
KS.1
KP.3.3
(Recombination with KS.1)
T22N
F59S
XEC
B
North America (66,742)
Proportion (%)
100
80
60
40
20
0
20241101
20241201
20250101
20250201
20250301
20250401
JN.1
KP.2
KP.3
KP.3.1.1
XEC
LP.8.1
Other
C
ID50
924
572
982
603
990
658
ns
-1.1X
ns
-1.1X
ns
+1X
ns
+1.1X
3/16
4/16
4/16
4/16
3/16
3/16
n=16
~1 month
~4 months
KP.3.1.1
XEC
LP.8.1

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