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 and its subvariant LP.8.1.1 have become dominant worldwide, particularly so in North America. Other variants, such as the LF.7 subvariant LF.7.2.1, have emerged with a growth advantage in Asia. To characterize the antigenicity of LP.8.1, LP.8.1.1, LF.7, LF.7.2.1, and another variant under monitoring, MC.10.1, we tested serum samples from 20 individuals who recently received KP.2 MV in neutralization assays against JN.1, KP.2, KP.3, KP.3.1.1, XEC, LP.8.1, LP.8.1.1, LF.7, LF.7.2.1, or MC.10.1 pseudoviruses. Serum neutralizing antibody titers against LP.8.1, LP.8.1.1, LF.7, LF.7.2.1, and MC.10.1 were comparable to those against KP.3.1.1 and XEC, indicating that LP.8.1.1 and other recently dominant subvariants are antigenically similar to their 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 variant emerging.

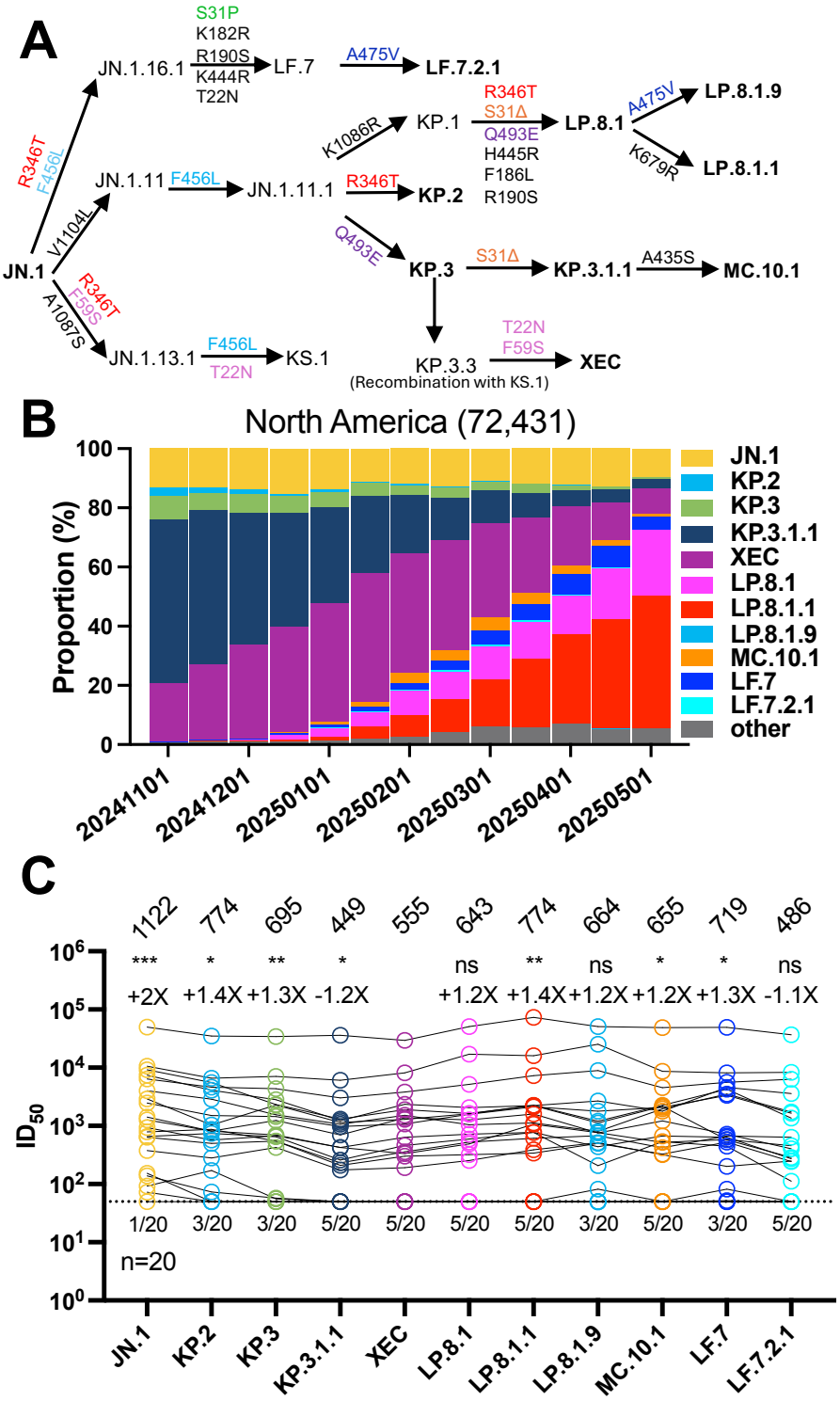
Main Text

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. KP.2-based monovalent COVID-19 mRNA vaccines (KP.2 MV) were approved in 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 that 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 ones that emerged later and became dominant, such as KP.3.1.1 and XEC[1]. Recent work showed that KP.2 MV have substantial vaccine efficacy against KP.3.1.1 and XEC, with estimates of up to 75% in protecting against hospitalization in those 65 years of age or older[2]. A progeny virus, LP.8.1, emerged in early 2025 and it and its descendant LP.8.1.1 became dominant worldwide in the ensuing months (Figs. 1A, 1B, S1A). Today, the LP.8.1 sublineage accounts for >70% of new SARS-CoV-2 infections in North America, based on viral sequences deposited (Fig. 1B). LP.8.1 possesses 5 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, as well as K1086R in the S2 region (Figs. 1A, S1B). LP.8.1.1 bears an additional K679R mutation near the Furin cleavage site (Fig. S1B). Another JN.1 progeny, LF.7, emerged in Asia, featuring 7 additional spike mutations beyond JN.1, including T22N, S31P, K182R, R190S, R346T, K444R, and F456L. LF.7.2.1, a descendant of LF.7 bearing a further A475V mutation, quickly outcompeted LF.7. However, LF.7.2.1 is not as dominant in North America (Fig. 1B). Another variant under monitoring, MC.10.1, includes A435S in addition to the other spike mutations found in KP.3.1.1 (Fig. 1A). MC.10.1 was gradually increasing in early 2025 but is no longer growing in any location (Figs. 1A, 1B). Due to the many spike mutations and recent dominance of these variants, an understanding of their antigenic properties, particularly of LP.8.1.1, 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. To assess the antigenicity of LP.8.1.1 and other recent subvariants, we performed pseudovirus neutralization assays using serum samples from 20 KP.2 MV recipients in the US obtained at approximately 1 month post boost (Tables S1, S2). We found that neutralizing titers against LP.8.1, LP.8.1.1, MC.10.1, LF.7, and LF.7.2.1 (geometric means 643, 774, 655, 719, 486, respectively) were at least equivalently high to those against XEC (geometric mean 555) in the serum of 20 US-based participants who received KP.2 MV (Fig. 1C). In a subset of these participants, we then checked for durability of neutralizing antibody titers. Since LP.8.1.1 is antigenically similar to LP.8.1 in the serum of KP.2 MV recipients, we focused on titers against LP.8.1. Serum neutralizing antibody titers against KP.3.1.1, XEC, and LP.8.1 were similar in range as well as in their respective geometric mean titers at 1 month post boost and at 4 months post boost (Fig. S1C). The estimated 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, LP.8.1.1, MC.10.1, LF.7, and LF.7.2.1 are antigenically similar to KP.3.1.1 and XEC after KP.2 MV. Our finding of antigenic similarity of LP.8.1 is concordant with other published results using sera obtained from China, Japan, and Germany, in populations with different exposure and vaccination histories than those in North America [3–5]. We also show that KP.2 MV recipients have titers against

LP.8.1.1 that are at least as high as against LP.8.1. This conclusion, in turn, raises the specter that current COVID-19 boosters may not currently need reformulation. 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 the production of a new formulation of COVID-19 booster shots for 2025, barring the emergence of another distinct SARS-CoV-2 variant in the meantime.

Figure Legend

Figure 1: Evolution and serum neutralization of recently dominant SARS-CoV-2 JN.1 subvariants. **A**: Spike mutations present in recently dominant JN.1 subvariants. **B**: Relative frequencies of SARS-CoV-2 variants in North America from 11/01/2024 to 05/01/2025. Data from GISAID. **C**: Serum neutralizing titers (ID_{50}) against VSV-based pseudoviruses bearing spike proteins of JN.1, KP.2, KP.3, KP.3.1.1, XEC, LP.8.1, LP.8.1.1, LP.8.1.9, MC.10.1, LF.7, or LF.7.2.1, for samples from recipients of KP.2 MV boosters at ~1 month 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. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. Numbers under the dotted lines denote numbers of serum samples that were under the limit of detection ($ID_{50} < 50$).


A
JN.1
JN.1.16.1
S31P
K182R
R190S
K444R
T22N
LF.7
A475V
LF.7.2.1
R346T
F456L
V1104L
JN.1.11
F456L
JN.1.11.1
R346T
KP.2
K1086R
KP.1
R346T
S31Δ
Q493E
H445R
F186L
R190S
LP.8.1
A475V
LP.8.1.9
K679R
LP.8.1.1
Q493E
KP.3
S31Δ
KP.3.1.1
A435S
MC.10.1
R346T
F59S
A1087S
JN.1.13.1
F456L
T22N
KS.1
KP.3.3
(Recombination with KS.1)
T22N
F59S
XEC
B
North America (72,431)
Proportion (%)
100
80
60
40
20
0
20241101
20241201
20250101
20250201
20250301
20250401
20250501
JN.1
KP.2
KP.3
KP.3.1.1
XEC
LP.8.1
LP.8.1.1
LP.8.1.9
MC.10.1
LF.7
LF.7.2.1
other
C
1122
774
695
449
555
643
774
664
655
719
486
***
*
**
*
ns
**
ns
*
*
ns
+2X
+1.4X
+1.3X
-1.2X
+1.2X
+1.4X
+1.2X
+1.2X
+1.3X
-1.1X
ID50
10^6
10^5
10^4
10^3
10^2
10^1
10^0
1/20
3/20
3/20
5/20
5/20
5/20
5/20
3/20
5/20
3/20
5/20
n=20
JN.1
KP.2
KP.3
KP.3.1.1
XEC
LP.8.1
LP.8.1.1
LP.8.1.9
MC.10.1
LF.7
LF.7.2.1

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