CLAIMS

What is claimed is:

1. An immunogenic composition, comprising:

(a) a first influenza virus hemagglutinin (HA) wherein the first influenza virus HA is an H1 HA from a first standard of care influenza virus strain, or a first ribonucleic acid molecule encoding the first influenza virus H1 HA;

(b) a second influenza virus HA wherein the second influenza virus HA is an H3 HA from a second standard of care influenza virus strain, or a second ribonucleic acid molecule encoding the second influenza virus H3 HA;

(c) a third influenza virus HA wherein the third influenza virus HA is from a third standard of care influenza virus strain from the B/Victoria lineage, or a third ribonucleic acid molecule encoding the third influenza virus HA from the B/Victoria lineage;

(d) one or more machine learning influenza virus HA having a molecular sequence identified or designed from a machine learning model, or one or more ribonucleic acid molecules encoding the one or more machine learning influenza virus HA, wherein the one or more machine learning influenza virus HA are selected from an H1 HA, an H3 HA, an HA from a B/Victoria lineage, an HA from a B/Yamagata lineage, or a combination thereof.

2. The immunogenic composition according to claim 1, wherein the ribonucleic acid molecule is an mRNA molecule.

3. The immunogenic composition according to claim 1 or 2, wherein the ribonucleic acid molecule is encapsulated in a lipid-nanoparticle (LNP).

4. The immunogenic composition according to any of the preceding claims, wherein the molecular sequence is an amino acid sequence or a nucleic acid sequence.

5. The immunogenic composition according to any of the preceding claims, wherein the one or more machine learning influenza virus HA comprise a wild type influenza virus HA molecular sequence.

6. The immunogenic composition according to any of the preceding claims, wherein the one or more machine learning influenza virus HA comprise a non-wild type influenza virus HA molecular sequence.

7. The immunogenic composition according to any of the preceding claims, wherein the one or more machine learning influenza virus HA is a recombinant influenza virus HA.

8. The immunogenic composition according to any of claims 1-6, wherein the one or more machine learning influenza virus HA is present in an inactivated influenza virus, optionally a split-inactivated virus.

9. The immunogenic composition according to any of claims 1-6, comprising a ribonucleic acid molecule encoding at least one of the one or more machine learning influenza virus HA.

10. The immunogenic composition according to any of claims 1-9, wherein the one or more machine learning influenza virus HAs is a fourth influenza virus HA, wherein the fourth influenza virus HA is an H3 HA, and wherein the fourth influenza H3 HA is antigenically dissimilar than the second influenza H3 HA or wherein the fourth influenza H3 HA is from a different clade than the second influenza H3 HA.

11. The immunogenic composition according to any of claims 1-9, wherein the one or more machine learning influenza virus HAs is a fourth influenza virus HA, wherein the fourth influenza virus HA is an H3 HA, and wherein the fourth influenza H3 HA enhances or broadens a protective immune response induced by the second influenza H3 HA.

12. The immunogenic composition according to any of claims 1-9, wherein the one or more machine learning influenza virus HAs is a fourth influenza virus HA, wherein the fourth influenza virus HA is an H3 HA, and wherein the fourth influenza H3 HA is antigenically similar to the second influenza H3 HA or wherein the fourth influenza H3 HA is from a same clade as the second influenza H3 HA.

13. The immunogenic composition according to any of claims 1-9, wherein the one or more machine learning influenza virus HA is a fourth influenza virus HA, wherein the fourth influenza virus HA is an H1 HA, and wherein the fourth influenza H1 HA is antigenically

dissimilar than the first influenza H1 HA or wherein the fourth influenza H1 HA is from a different clade than the first influenza H1 HA.

14. The immunogenic composition according to any of claims 1-9, wherein the one or more machine learning influenza virus HA is a fourth influenza virus HA, wherein the fourth influenza virus HA is an H1 HA, and wherein the fourth influenza H1 HA enhances or broadens a protective immune response induced by the first influenza H1 HA.

15. The immunogenic composition according to any of claims 1-9, wherein the one or more machine learning influenza virus HAs is a fourth influenza virus HA, wherein the fourth influenza virus HA is an H1 HA, and wherein the fourth influenza H1 HA is antigenically similar to the first influenza H1 HA wherein the fourth influenza H1 HA is from a same clade as the first influenza H1 HA.

16. The immunogenic composition according to any of claims 1-9, wherein the one or more machine learning influenza virus HAs is a fourth influenza virus HA, wherein the fourth influenza virus HA is an H3 HA from the 3C.2A clade or the 3C.3A clade.

17. The immunogenic composition according to any of claims 1-12, further comprising a fifth influenza virus HA.

18. The immunogenic composition according to claim 17, wherein the fifth influenza virus HA is an H1 HA having a molecular sequence identified or designed from a machine learning model, or a ribonucleic acid molecule encoding the fifth influenza virus HA.

19. The immunogenic composition according to claim 18, wherein the fifth influenza H1 HA is antigenically dissimilar than the first influenza H1 HA, wherein the fifth influenza H1 HA enhances a protective immune response induced by the first influenza H1 HA, wherein the fifth influenza H1 HA broadens a protective immune response induced by the first influenza H1 HA, wherein the fifth influenza H1 HA is from a different clade than the first influenza H1 HA, wherein the fifth influenza H1 HA is from a same clade as the first influenza H1 HA, or wherein the fifth influenza H1 HA is antigenically similar to the first influenza H1 HA.

20. The immunogenic composition according to any one of claims 17-19, further comprising a sixth influenza virus HA from the B/Victoria lineage having a molecular sequence

identified or designed from a machine learning model, or a ribonucleic acid molecule encoding the sixth influenza virus HA.

21. The immunogenic composition according to any of claims 17-20, further comprising seventh influenza virus HA from the B/Yamagata lineage having a molecular sequence identified or designed from a machine learning model, or a ribonucleic acid molecule encoding the seventh influenza virus HA.

22. The immunogenic composition according to any of the preceding claims, wherein the machine learning model is trained to predict a biological response.

23. The immunogenic composition according to claim 22, wherein the biological response is a human, ferret, or mouse biological response.

24. The immunogenic composition according to claim 22 or 23, wherein the biological response comprises a hemagglutinin inhibition assay (HAI), antibody forensics (AF), or neutralization assay.

25. The immunogenic composition according to any one of claims 1-24, wherein each of the first, second, and third influenza virus HA is a recombinant influenza virus HA.

26. The immunogenic composition according to any one of claims 1-24, wherein each of the first, second, and third influenza virus HA is present in an inactivated influenza virus.

27. The immunogenic composition according to any one of claims 1-24, comprising the first, second, and third influenza virus HA as ribonucleic acid molecules.

28. The immunogenic composition according to any one of claims 7-27, wherein each of the recombinant influenza virus HA is produced by a baculovirus expression system in cultured insect cells.

29. The immunogenic composition according to any of the preceding claims, wherein the first influenza virus HA is an H1 HA from an H1N1 influenza virus strain and the second influenza virus HA is an H3 HA from an H3N2 influenza virus strain.

30. The immunogenic composition according to any of the preceding claims, wherein the composition further comprises an adjuvant.

31. The immunogenic composition according to claim 30, wherein the adjuvant comprises a squalene-in-water adjuvant or a liposome-based adjuvant.

32. The immunogenic composition according to claim 31, wherein the squalene-in-water adjuvant comprises AF03.

33. The immunogenic composition according to claim 31, wherein the liposome-based adjuvant comprises SPA14.

34. The immunogenic composition according to any of the preceding claims, wherein each ribonucleic acid molecule comprises one or more modified nucleotides.

35. The immunogenic composition according to any of the preceding claims, wherein the composition is formulated for intramuscular injection.

36. The immunogenic composition according to any of the preceding claims, wherein the ribonucleic acid molecule is encapsulated in an LNP comprising a cationic lipid, a PEGylated lipid, a cholesterol-based lipid, and a helper lipid.

37. Use of the immunogenic composition of any one of claims 1-36 in the manufacture of a medicament for immunizing a subject against influenza virus.

38. The use of claim 37, wherein the immunogenic composition prevents influenza virus infection in the subject.

39. The use of claim 37 or 38, wherein the immunogenic composition raises a protective immune response in the subject.

40. The use of claim 39, wherein the protective immune response comprises an HA antibody response.

41. The use of any one of claims 37-40, wherein the subject is human.

42. The use of any one of claims 37-41, wherein the immunogenic composition is administered intramuscularly, intradermally, subcutaneously, intravenously, intranasally, by inhalation, or intraperitoneally.

43. The use of any one of claims 37-42, wherein the immunogenic composition treats or prevents disease caused by either or both a seasonal and a pandemic influenza strain.

44. The use of any one of claims 37-43, wherein the subject is human and the human is 6 months of age or older, 6 to 35 months of age, at least 2 years of age, at least 3 years of age, less than 18 years of age, at least 18 years of age, at least 60 years of age, at least 65 years of age, at least 6 months of age and less than 18 years of age, at least 3 years of age and less than 18 years of age, or at least 18 years of age and less than 65 years of age.

45. Use of the immunogenic composition of any one of claims 1-36 in the manufacture of a medicament for reducing one or more symptoms of influenza virus infection in a subject.

46. The use of any one of claims 37-45 comprising administering to the subject two doses of the immunogenic composition with an interval of 2-6 weeks, optionally 4 weeks.

47. A vaccine composition comprising the immunogenic composition according to any one of claims 1-36.

48. The use of any one of claims 37-46, wherein the immunogenic composition is a vaccine composition.

49. An immunogenic composition, comprising:

(a) at least three or at least four influenza virus hemagglutinins (HAs) from standard of care influenza virus strains, or at least three or at least 4 ribonucleic acid molecule encoding the influenza virus HAs; and

(b) one or more machine learning influenza virus HA having a molecular sequence identified or designed from a machine learning model, or one or more ribonucleic acid molecules encoding the one or more machine learning influenza virus HA, wherein the one or more machine learning influenza virus HA are selected from an H1 HA, an H3 HA, an HA from a B/Victoria lineage, an HA from a B/Yamagata lineage, or a combination thereof.

50. The immunogenic composition of claim 49, comprising:

(a) a first influenza virus hemagglutinin (HA) wherein the first influenza virus HA is an H1 HA from a first standard of care influenza virus strain, or a first ribonucleic acid molecule encoding the first influenza virus H1 HA;

(b) a second influenza virus HA wherein the second influenza virus HA is an H3 HA from a second standard of care influenza virus strain, or a second ribonucleic acid molecule encoding the second influenza virus H3 HA;

(c) a third influenza virus HA wherein the third influenza virus HA is from a third standard of care influenza virus strain from the B/Victoria lineage, or a third ribonucleic acid molecule encoding the third influenza virus HA from the B/Victoria lineage; and

(d) the one or more machine learning influenza virus HA having a molecular sequence identified or designed from a machine learning model, or one or more ribonucleic acid molecules encoding the one or more machine learning influenza virus HA.

51. The immunogenic composition of any one of claims 1-36, 49, or 50, wherein the ribonucleic acid molecule is an artificial ribonucleic acid molecule, such as an artificial mRNA.