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; and

(d) one or more machine learning influenza virus HAs 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 HAs 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, wherein the one or more machine learning influenza virus HAs comprise a first machine learning influenza virus HA, wherein the first machine learning influenza virus HA is an H3 HA, and wherein the first machine learning influenza H3 HA and the second influenza H3 HA generate an antibody response that is different from each other as measured by binding titers or neutralizing titers.

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 one of claims 1-3, wherein the molecular sequence is an amino acid sequence or a nucleic acid sequence.

5. The immunogenic composition according to any one of claims 1-4, 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 one of claims 1-4, 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 one of claims 1-6, wherein the one or more machine learning influenza virus HA are recombinant influenza virus HA.

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

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

10. The immunogenic composition according to any one of claims 1-9, wherein the first machine learning influenza H3 HA is from a different clade than the second influenza H3 HA.

11. The immunogenic composition according to any one of claims 1-10, wherein the first machine learning influenza H3 HA enhances or broadens a protective immune response induced by the second influenza H3 HA.

12. The immunogenic composition according to any one of claims 1-11, wherein the first machine learning influenza virus H3 HA is from the 3C.2A clade or the 3C.3A clade.

13. The immunogenic composition according to any one of claims 1-12, wherein the one or more machine learning influenza virus HAs comprise a second machine learning influenza virus HA.

14. The immunogenic composition according to claim 13, wherein the second machine learning 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 second machine learning influenza virus HA.

15. The immunogenic composition according to claim 14, wherein the second machine learning influenza virus H1 HA and the first influenza H1 HA generate an antibody response that is different from each other as measured by binding titers or neutralizing titers, or wherein the second machine learning influenza H1 HA enhances a protective immune response induced by the first influenza virus H1 HA, or wherein the second machine learning influenza virus H1 HA broadens a protective immune response induced by the first influenza virus H1 HA, or wherein the second machine learning influenza virus H1 HA is from a different clade than the first influenza virus H1 HA, or wherein the second machine learning influenza H1 HA is from a same clade as the first influenza virus H1 HA.

16. The immunogenic composition according to any one of claims 13-15, wherein the one or more machine learning influenza virus HAs comprise a third machine learning 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 third machine learning influenza virus HA.

17. The immunogenic composition according to any one of claims 13-16, wherein the one or more machine learning influenza virus HAs comprise a fourth machine learning 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 fourth machine learning influenza virus HA.

18. The immunogenic composition according to any one of claims 1-17, wherein the machine learning model is trained to predict a biological response, wherein the biological response comprises a hemagglutinin inhibition assay (HAI), antibody forensics (AF), or neutralization assay.

19. The immunogenic composition according to any one of claims 1-18, wherein each of the first, second, and third influenza virus HA is a recombinant influenza virus HA.

20. The immunogenic composition according to any one of claims 1-18, wherein each of the first, second, and third influenza virus HA is present in an inactivated influenza virus.

21. The immunogenic composition according to any one of claims 1-18, comprising the first, second, and third influenza virus HA as ribonucleic acid molecules.

22. The immunogenic composition according to any one of claims 7-19, wherein each of the recombinant influenza virus HA is produced by a baculovirus expression system in cultured insect cells.

23. The immunogenic composition according to any one of claims 1-22, 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.

24. The immunogenic composition according to claim 23, wherein the H3N2 influenza virus strain is a future standard of care strain and the first machine learning influenza H3 HA is identified or designed using the machine learning model based on the future standard of care strain.

25. The immunogenic composition according to any one of claims 1-24, wherein the composition further comprises an adjuvant.

26. The immunogenic composition according to claim 25, wherein the adjuvant comprises a squalene-in-water adjuvant or a liposome-based adjuvant.

27. The immunogenic composition according to claim 26, wherein the squalene-in-water adjuvant comprises AF03.

28. The immunogenic composition according to claim 26, wherein the liposome-based adjuvant comprises SPA14.

29. The immunogenic composition according to any one of claims 1-28, wherein each ribonucleic acid molecule comprises one or more modified nucleotides.

30. The immunogenic composition according to any one of claims 1-29, wherein the composition is formulated for intramuscular injection.

31. The immunogenic composition according to any one of claims 1-30, 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.

32. The immunogenic composition according to any one of claims 1-31, wherein each of the first, second, and third standard of care influenza virus is a future standard of care strain.

33. Use of the immunogenic composition of any one of claims 1-32 in the manufacture of a medicament for immunizing a subject against influenza virus.

34. The use of claim 33, wherein the immunogenic composition prevents influenza virus infection in the subject.

35. The use of claim 33 or 34, wherein the immunogenic composition raises a protective immune response in the subject.

36. The use of claim 35, wherein the protective immune response comprises an HA antibody response.

37. The use of any one of claims 33-36, wherein the subject is human.

38. The use of any one of claims 33-37, wherein the immunogenic composition is to be administered intramuscularly, intradermally, subcutaneously, intravenously, intranasally, by inhalation, or intraperitoneally.

39. The use of any one of claims 33-38, wherein the immunogenic composition treats or prevents disease caused by either or both a seasonal and a pandemic influenza strain.

40. The use of any one of claims 33-39, 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.

41. Use of the immunogenic composition of any one of claims 1-32 in the manufacture of a medicament for reducing one or more symptoms of influenza virus infection in a subject.

42. The use of any one of claims 33-41 wherein the immunogenic composition is to be administered to the subject in two doses with an interval of 2-6 weeks, optionally 4 weeks.

43. A vaccine composition comprising the immunogenic composition according to any one of claims 1-32.

44. The use of any one of claims 33-42, wherein the immunogenic composition is a vaccine composition.

45. The immunogenic composition of any one of claims 1-32, wherein the ribonucleic acid molecule is an artificial ribonucleic acid molecule, such as an artificial mRNA.

46. A method of manufacturing a multivalent influenza vaccine composition, the method comprising:

receiving, by a system of one or more computers, data defining a plurality of wild-type influenza hemagglutinin amino acid sequences;

generating, using a machine-learning model, a plurality of candidate influenza hemagglutinin sequences;

ranking or scoring the candidate influenza hemagglutinin sequences based on predicted performance against one or more target influenza sequences;

selecting at least one candidate influenza hemagglutinin sequence based on the ranking or scoring;

generating an influenza hemagglutinin amino acid sequence from the selected candidate influenza hemagglutinin sequence; and

manufacturing a multivalent influenza vaccine composition comprising at least one of: a protein defined by the generated influenza hemagglutinin amino acid sequence, a nucleic acid capable of producing the protein, or a delivery vehicle capable of producing the protein,

wherein the multivalent influenza vaccine composition further comprises influenza hemagglutinins from at least three standard-of-care influenza virus strains, or nucleic acids encoding the influenza hemagglutinins from the at least three standard-of-care influenza virus strains.