

Accordingly, modalities for broadly neutralizing influenza A virus infections, in particular with improved potency, are needed.

SUMMARY

5 In one aspect, the present disclosure relates to an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) comprising a complementarity determining region (CDR)H1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3, wherein: (i) the CDRH1 comprises or consists of the amino acid sequence of any one of SEQ ID NOs.: 32, 3, or 15, or a functional variant thereof comprising one, two, or three acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or (ii) the CDRH2 comprises or consists of the amino acid sequence of any one of SEQ ID NOs.: 35, 4, 29, 16, and 42, or a functional variant thereof comprising one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or (iii) the CDRH3 comprises or consists of the amino acid sequence of SEQ ID NO.: 5 or 17, or a functional variant thereof comprising one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or (iv) the CDRL1 comprises or consists of the amino acid sequence of SEQ ID NO.: 9 or 21, or a functional variant thereof comprising one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or (v) the CDRL2 optionally comprises or consists of the amino acid sequence of SEQ ID NO.: 10 or 22, or a functional variant thereof comprising one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or (vi) the CDRL3 comprises or consists of the amino acid sequence of SEQ ID NO.: 11 or 23, or a functional variant thereof comprising having one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid, wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).

30 In another aspect, the present disclosure relates to an antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein: (i) the VH comprises a CDRH1, a CDRH2, and a CDRH3 according to the VH amino acid sequence set forth in any one of SEQ ID NOs.: 37, 2, 26, 28, 31, 34, 14, 39 and 41; and (ii) the VL comprises a CDRL1, a CDRL2, and a CDRL3 according to the VL amino acid sequence set forth in SEQ ID NO.:20 or 8, wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).

35 In another aspect, the present disclosure relates to an isolated polynucleotide encoding the antibody or antigen-binding fragment as disclosed herein, or encoding a VH, a heavy chain, a VL, and/or a light chain of the antibody or the antigen-binding fragment.

40 In another aspect, the present disclosure relates to a recombinant vector comprising the polynucleotide as disclosed herein.

45 In yet another aspect, the present disclosure relates to a host cell comprising the polynucleotide as disclosed herein and/or the vector as disclosed herein, wherein the polynucleotide is heterologous to the host cell and wherein the host cell is capable of expressing the encoded antibody or antigen-binding fragment.

In another aspect, the present disclosure relates to an isolated human B cell comprising the polynucleotide and/or the vector as disclosed herein, wherein polynucleotide is heterologous to the human B cell and/or wherein the human B cell is immortalized.

In yet another aspect, the present disclosure relates to a composition comprising: (i) the antibody or antigen-binding fragment as disclosed herein; (ii) the polynucleotide as disclosed herein; (iii) the recombinant vector as disclosed herein; (iv) the host cell as disclosed herein; and/or (v) the human B cell as disclosed herein, and a pharmaceutically acceptable excipient, carrier, or diluent.

In yet another aspect, the present disclosure relates to a composition comprising the polynucleotide or the vector as disclosed herein encapsulated in a carrier molecule, wherein the carrier molecule optionally comprises a lipid, a lipid-derived delivery vehicle, such as a liposome, a solid lipid nanoparticle, an oily suspension, a submicron lipid emulsion, a lipid microbubble, an inverse lipid micelle, a cochlear liposome, a lipid microtubule, a lipid microcylinder, lipid nanoparticle (LNP), or a nanoscale platform.

In yet another aspect, the present disclosure relates to a method of making an antibody or antigen-binding fragment as disclosed herein, comprising culturing the host cell or the human B cell as disclosed here in for a time and under conditions sufficient for the host cell or human B cell to express the antibody or antigen-binding fragment, wherein, optionally, the method further comprises isolating the antibody or antigen-binding fragment.

In another aspect, the present disclosure relates to the antibody or antigen-binding fragment, the polynucleotide, the recombinant vector, the host cell, the human B cell, and/or the composition as disclosed herein, for use therapy.

In yet another aspect, the present disclosure relates to a use of the antibody or antigen-binding fragment, the polynucleotide, the recombinant vector of claim 38, the host cell, the human B cell, and/or the composition as disclosed herein in the preparation of a medicament for the treatment of an influenza virus infection, optionally a influenza A virus infection, in a subject.

In yet another aspect, the present disclosure relates to a method for in vitro diagnosis of an influenza A virus infection, the method comprising: (i) contacting a sample from a subject with an antibody or antigen-binding fragment as disclosed herein; and (ii) detecting a complex comprising an antigen and the antibody, or comprising an antigen and the antigen-binding fragment.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a workflow for anti-"HA" (hemagglutinin) stem monoclonal antibody discovery, described in further detail in Example 1.

Figure 2 shows binding of monoclonal antibodies "FHF11" (also referred-to herein as "FHF11-WT"; VH: SEQ ID NO.:2; VL: SEQ ID NO.:8) and "FHF12" (VH: SEQ ID NO.:14; VL: SEQ ID NO.:20) to influenza A virus (IAV)-derived hemagglutinins (HA)s, as determined by flow cytometry using HA-expressing mammalian target cells. A comparator antibody "FM08" (VH: SEQ ID NO.:43; VL: SEQ ID NO.:44) was also tested.

Figures 3A and 3B show binding of FHF11 and FHF12 to group I IAV-derived H1, H2, H5, and H9 (Figure 3A) and group II IAV-derived H3 (Figure 3B) measured by ELISA, reported as Log EC50 (ng/ml). Binding by a comparator antibody, FM08, was also measured.

5 **Figure 4** shows binding of FHF11 and FHF12 to HA from an H1N1 Swine Eurasian avian-like (EA) strain, A/Swine/Jiangsu/J004/2018 expressed on mammalian cells, was measured by flow cytometry. Binding was measured at antibody concentrations of 50 µg/ml, 10 µg/ml, 2 µg/ml, and 0.4 µg/ml. Mock staining is shown as a negative control. Binding by a comparator antibody, FM08, was also measured.

10 **Figure 5** shows lack of polyreactivity of FHF11 and FHF12, as tested against human epithelial type 2 (HEP-2) cells. A polyreactive comparator, "FI6v3.11.18", was included as a positive control, and anti-paramyxovirus antibody "MPE8" was included as a negative control.

15 **Figures 6A and 6B** show *in vitro* neutralization of H1N1 and H3N2 IAV pseudovirus by FHF11 and FHF12. Figure 6A shows neutralization of H1N1 A/California//07/2009. Figure 6B shows neutralization of H3N2 A/Aichi/2/68. Data for comparator antibodies FM08 and FY1 is also shown.

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CLAIMS

What is claimed is:

1. An antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) comprising a complementarity determining region (CDR)H1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3, wherein:

(i) the CDRH1 comprises or consists of the amino acid sequence of any one of SEQ ID NOs.: 32, 3, or 15, or a functional variant thereof comprising one, two, or three acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or

(ii) the CDRH2 comprises or consists of the amino acid sequence of any one of SEQ ID NOs.: 35, 4, 29, 16, and 42, or a functional variant thereof comprising one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or

(iii) the CDRH3 comprises or consists of the amino acid sequence of SEQ ID NO.: 5 or 17, or a functional variant thereof comprising one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or

(iv) the CDRL1 comprises or consists of the amino acid sequence of SEQ ID NO.: 9 or 21, or a functional variant thereof comprising one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or

(v) the CDRL2 optionally comprises or consists of the amino acid sequence of SEQ ID NO.: 10 or 22, or a functional variant thereof comprising one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid; and/or

(vi) the CDRL3 comprises or consists of the amino acid sequence of SEQ ID NO.: 11 or 23, or a functional variant thereof comprising having one, two, or three amino acid substitutions, one or more of which substitutions is optionally a conservative substitution and/or is a substitution to a germline-encoded amino acid, wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).

2. The antibody or antigen-binding fragment of claim 1, wherein (1) the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA on a cell surface of a host cell and/or on a virion-, and/or

~~3. The antibody or antigen-binding fragment of claim 1 or 2, which (2)~~ wherein the antibody or antigen-binding fragment is capable of neutralizing an IAV infection in an *in vitro* model of infection and/or in an *in vivo* animal model of infection and/or in a human, wherein, optionally, the *in vitro* model of infection comprises a target cell and a pseudovirus or a target cell and a live virus.

~~43.~~ The antibody or antigen-binding fragment of ~~any one of claims 1-3~~ 1 or 2, comprising CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences of SEQ ID NOs.:

- (i) 32, 35, 5, and 9-11, respectively;
- (ii) 3, 29, 5 and 9-11, respectively;
- (iii) 32, 4, 5 and 9-11, respectively;
- (iv) 3, 35, 5 and 9-11, respectively;
- (v) 3-5 and 9-11, respectively;
- (vi) 15-17 and 21-23, respectively; or
- (vii) 15, 42, 17 and 21-23, respectively.

54. The antibody or antigen-binding fragment of ~~any one of claims 1-3~~ **1 or 2**, comprising CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 amino acid sequences of SEQ ID NOs.:

- (i) 3, 29, 5 and 9-11, respectively;
- (ii) 3, 35, 17 and 9-11, respectively; or
- (iii) 32, 35, 17, and 9-11, respectively.

65. The antibody or antigen-binding fragment of any one of claims 1-**54**, wherein:

- (i) the VH comprises or consists of an amino acid sequence having at least 80% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more) identity to the amino acid sequence of any one of SEQ ID NOs.: 37, 2, 26, 28, 31, 34, 14, 39 and 41, wherein sequence variation with reference to SEQ ID NO.: 37, 2, 26, 28, 31, 34, 14, 39 or 41, respectively, is optionally comprised in one or more framework region and/or sequence variation comprises one or more substitution to a germline-encoded amino acid; and/or
- (ii) the VL comprises or consists of an amino acid sequence having at least 80% (*e.g.*, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more) identity to the amino acid sequence of any one of SEQ ID NOs.: 8 or 20, wherein sequence variation with respect to SEQ ID NO.:8 or 20, respectively, is optionally comprised in one or more framework regions and/or sequence variation comprises one or more substitution to a germline-encoded amino acid.

76. The antibody or antigen-binding fragment of any one of claims 1-**65**, wherein:

- (i) the VH comprises or consists of an amino acid sequence having at least 80% identity to the amino acid sequence of any one of SEQ ID NOs.: 37, 2, 26, 28, 31, 34, 14, 39 and 41, and the VL comprises or consists of an amino acid sequence having at least 80% identity to the amino acid sequence of SEQ ID NO.:8; or
- (ii) the VH comprises or consists of an amino acid sequence having at least 80% identity to the amino acid sequence of any one of SEQ ID NOs.: 37, 2, 26, 28, 31,

34, 14, 39 and 41, and the VL comprises or consists of an amino acid sequence having at least 80% identity to the amino acid sequence of SEQ ID NO.:20.

~~87.~~ The antibody or antigen-binding fragment of any one of claims 1-~~76~~, wherein the VH and the VL comprise or consist of the amino acid sequences according to SEQ ID NOs.:

- (i) 37 and 8, respectively;
- (ii) 26 and 8, respectively;
- (iii) 28 and 8, respectively;
- (iv) 31 and 8, respectively;
- (v) 34 and 8, respectively;
- (vi) 2 and 8, respectively;
- (vii) 14 and 20, respectively;
- (viii) 39 and 20, respectively; ~~or~~
- (ix) 41 and 20, respectively; ~~or~~

~~9. — The antibody or antigen-binding fragment of any one of claims 1-7, wherein the VH and the VL comprise or consist of the amino acid sequences according to SEQ ID NOs.:~~

- ~~(ix)~~ 2 and 20, respectively;
- ~~(ixi)~~ 26 and 20, respectively;
- ~~(ixii)~~ 28 and 20, respectively;
- ~~(ixiii)~~ 31 and 20, respectively;
- ~~(ixiv)~~ 34 and 20, respectively;
- ~~(ixv)~~ 37 and 20, respectively;
- ~~(ixvi)~~ 14 and 8, respectively;
- ~~(ixvii)~~ 39 and 8, respectively; or
- ~~(ixviii)~~ 41 and 8, respectively.

~~10. — An antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a~~

~~light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3, wherein the CDRH1, CDRH2, and CDRH3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 32, 35, and 5, respectively, and the CDRL1, CDRL2, and CDRL3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 9-11, respectively,~~

~~wherein the antibody or antigen binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).~~

~~11. — An antibody, or antigen binding fragment thereof, comprising a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3, wherein the CDRH1, CDRH2, and CDRH3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 3, 29, and 5, respectively, and the CDRL1, CDRL2, and CDRL3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 9-11, respectively,~~

~~wherein the antibody or antigen binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).~~

~~12. — An antibody, or antigen binding fragment thereof, comprising a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3, wherein the CDRH1, CDRH2, and CDRH3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 32, 4, and 5, respectively, and the CDRL1, CDRL2, and CDRL3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 9-11, respectively,~~

~~wherein the antibody or antigen binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).~~

~~13. — An antibody, or antigen binding fragment thereof, comprising a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3,~~

~~wherein the CDRH1, CDRH2, and CDRH3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 3, 35, and 5, respectively, and the CDRL1, CDRL2, and CDRL3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 9-11, respectively;~~

~~wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).~~

~~14. — An antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3, wherein the CDRH1, CDRH2, and CDRH3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 3-5, respectively, and the CDRL1, CDRL2, and CDRL3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 9-11, respectively;~~

~~wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).~~

~~15. — An antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3, wherein the CDRH1, CDRH2, and CDRH3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 15-17, respectively, and the CDRL1, CDRL2, and CDRL3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 21-23, respectively;~~

~~wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).~~

~~16. — An antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) comprising a CDRH1, a CDRH2, and a CDRH3, and a light chain variable domain (VL) comprising a CDRL1, a CDRL2, and a CDRL3, wherein the CDRH1, CDRH2, and CDRH3 comprise or consist of the amino acid sequences set forth in SEQ ID NOs.: 15, 42, and 17, respectively, and the CDRL1,~~

~~CDRL2, and CDRL3 comprise or consist of the amino acid sequences of SEQ ID NOs.: 21-23, respectively,~~

~~wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).~~

~~178.~~ ~~An~~The antibody, or antigen-binding fragment ~~thereof~~ of any one of claims 1-7, comprising:

(1) a heavy chain variable domain (VH) comprising the amino acid sequence of SEQ ID NO.:53, the amino acid sequence of any one of SEQ ID NOs.:4, 29, and 35, and the amino acid sequence of any one of SEQ ID NOs.:5 and 17; and

(2) a light chain variable domain (VL) comprising the amino acid sequences of SEQ ID NOs.:9-11;

~~wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).~~

~~189.~~ An antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein:

(i) the VH comprises a CDRH1, a CDRH2, and a CDRH3 according to the VH amino acid sequence set forth in any one of SEQ ID NOs.: 37, 2, 26, 28, 31, 34, 14, 39 and 41; and

(ii) the VL comprises a CDRL1, a CDRL2, and a CDRL3 according to the VL amino acid sequence set forth in SEQ ID NO.:20 or 8,

wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).

~~19. — An antibody, or antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein:~~

~~(i) — the VH comprises a CDRH1, a CDRH2, and a CDRH3 according to the VH amino acid sequence set forth in any one of SEQ ID NOs.: 37, 2, 26, 28, 31, 34, 14, 39 and 41; and~~

(ii) ~~the VL comprises a CDRL1, a CDRL2, and a CDRL3 according to the VL amino acid sequence set forth in SEQ ID NO.:8,~~

~~wherein the antibody or antigen-binding fragment is capable of binding to an influenza A virus (IAV) hemagglutinin (HA).~~

~~20~~10. The antibody or antigen-binding fragment of claim ~~18 or 19~~ 9, wherein the CDRs are according to:

~~(i)~~ (i) the IMGT numbering system;

~~21. The antibody or antigen-binding fragment of claim 18 or 19, wherein the CDRs are according to~~ (ii) the Kabat numbering system;

~~22. The antibody or antigen-binding fragment of claim 18 or 19, wherein the CDRs are according to~~ (iii) the Chothia numbering system;

~~23. The antibody or antigen-binding fragment of claim 18 or 19, wherein the CDRs are according to~~ (iv) the AHo numbering system;

~~24. The antibody or antigen-binding fragment of claim 18 or 19, wherein the CDRs are according to~~ (v) the North numbering system; or

~~25. The antibody or antigen-binding fragment of claim 18 or 19, wherein the CDRs are according to~~ (vi) the Martin numbering system.

~~26~~11. The antibody or antigen-binding fragment of any one of claims 1-~~25~~ 10, wherein the VH is encoded by or derived from *VH6-1*, *DH3-3*, and *JH6*, and/or the VL is encoded by or derived from *VK3-20* and *JK3*.

~~27. An anti-influenza hemagglutinin (HA) antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence of SEQ ID NO.: 37 and the VL comprises or consists of the amino acid sequence of SEQ ID NO.: 8.~~

~~28. An anti-influenza hemagglutinin (HA) antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain~~

~~variable domain (VL), wherein the VH comprises or consists of the amino acid sequence of SEQ ID NO.: 26 and the VL comprises or consists of the amino acid sequence of SEQ ID NO.: 8.~~

29. — ~~An anti-influenza hemagglutinin (HA) antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence of SEQ ID NO.: 28 and the VL comprises or consists of the amino acid sequence of SEQ ID NO.: 8.~~

30. — ~~An anti-influenza hemagglutinin (HA) antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence of SEQ ID NO.: 31 and the VL comprises or consists of the amino acid sequence of SEQ ID NO.: 8.~~

31. — ~~An anti-influenza hemagglutinin (HA) antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence of SEQ ID NO.: 34 and the VL comprises or consists of the amino acid sequence of SEQ ID NO.: 8.~~

32. — ~~An anti-influenza hemagglutinin (HA) antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence of SEQ ID NO.: 2 and the VL comprises or consists of the amino acid sequence of SEQ ID NO.: 8.~~

33. — ~~An anti-influenza hemagglutinin (HA) antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid~~

~~sequence of SEQ ID NO.: 14 and the VL comprises or consists of the amino acid sequence of SEQ ID NO.: 20.~~

~~34. — An anti-influenza hemagglutinin (HA) antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence of SEQ ID NO.: 39 and the VL comprises or consists of the amino acid sequence of SEQ ID NO.: 20.~~

~~35. — An anti-influenza hemagglutinin (HA) antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable domain (VH) and a light chain variable domain (VL), wherein the VH comprises or consists of the amino acid sequence of SEQ ID NO.: 41 and the VL comprises or consists of the amino acid sequence of SEQ ID NO.: 20.~~

~~36~~12. The antibody or antigen-binding fragment of any one of claims 1-~~35~~11, wherein the antibody or antigen-binding fragment is capable of preventing and/or attenuating an infection by:

- (i) a H1N1 IAV, wherein, optionally, the H1N1 IAV comprises A/PR8/34; and/or
- (ii) a H3N2 IAV, wherein, optionally, the H3N2 IAV comprises A/Hong Kong/68.

~~37~~13. The antibody or antigen-binding fragment of any one of claims 1-~~36~~12, wherein:

(1) the antibody or antigen-binding fragment is capable of preventing or reducing weight loss in a subject having an IAV infection, optionally for (i) up to 15 days, or (ii) for 15 or more days, following administration of an effective amount of the antibody or antigen-binding fragment, wherein preventing or reducing weight loss is with reference to an untreated reference subject having the IAV infection-~~i~~

~~38. — The antibody or antigen-binding fragment of any one of claims 1-37,~~
~~wherein (2)~~ the antibody or antigen-binding fragment is capable of preventing a loss
in body weight of greater than 10% in a subject having an IAV infection, wherein a loss
in body weight is determined by reference to the subject's body weight just prior to or
in an early stage of the IAV infection;

~~39. — The antibody or antigen-binding fragment of any one of claims 1-38,~~
~~wherein (3)~~ the antibody or antigen-binding fragment is capable of extending
survival of a subject having an IAV infection, as compared to survival of an untreated
reference subject having the IAV infection; and/or

~~40. — The antibody or antigen-binding fragment of any one of claims 1-39,~~
~~wherein (4)~~ the antibody or antigen-binding fragment has an *in vivo* half-life in a
mouse (*e.g.*, a tg32 mouse):

(i) in a range of: from about 7 days to about 12.2 days, from about 8 days to
about 11 days, from about 8.5 days to about 10.5 days, or from about 9 days to about
10.5 days;

(ii) of between 8 days and 11 days, or between 8.5 days and 10.5 days, or
between 9 days and 10 days;

(iii) of 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5,
9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7, 10.8, 10.9, 11.0, 11.1,
11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, or 12.2 days;

(iv) in a range of from about 9.5 days to about 12.5 days, from about 10 days
to 11.5 days;

(v) of from 10 days to 11 days, or from 10.5 days to 11 days;

(vi) between 10 days and 11.5 days, or between 10.5 days and 11 days, or
between 10 days and 11 days; and/or

(vii) of 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4, 10.5, 10.6, 10.7,
10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9, 12.0, 12.1, 12.2,
12.3, 12.4, or 12.5 days.

~~41~~14. The antibody or antigen-binding fragment of any one of claims 1-~~40~~13, which specifically binds to the HA and does not bind to, or does not specifically bind to, a non-HA target.

~~42~~15. The antibody or antigen-binding fragment of any one of claims 1-~~41~~14, which is capable of binding to any one or more of the following IAV subtypes: H1, H2, H3, H4, H5, H8, H9, H10, H11, H12, H13, H14, H15, H17, and H18.

~~43~~16. The antibody or antigen-binding fragment of any one of claims 1-~~42~~15, wherein the antibody or antigen-binding fragment is capable of preventing or attenuating an IAV infection a subject.

~~44~~17. The antibody or antigen-binding fragment of any one of claims 1-~~43~~16, which is capable of:

~~(1)~~ neutralizing infection by:

(i) a H1N1 IAV, wherein, optionally, the H1N1 IAV comprises any one or more of: A/California/07/2009, A/PR/8/34, and A/Solomon Islands/3/06; and

(ii) a H3N2 IAV, wherein, optionally, the H3N2 IAV comprises any one or more of: A/Aichi/2/68, A/Brisbane/10/07, and A/Hong Kong/68-; ~~and/or~~

~~45. The antibody or antigen-binding fragment of any one of claims 1-44, which is capable of:~~
~~(2)~~

(iii) neutralizing a H1N1 IAV infection, optionally by A/California/07/2009, with an IC₅₀ in a range of from about 10³ ng/mL to about 10⁴ ng/mL, optionally in a range of from 2,000 ng/mL to 6,000 ng/mL (e.g., 2,000, 2,500, 3,000, 3,500, 4,000, 4,500, 5,000, 5,500, or 6,000 ng/mL); and/or

(iv) neutralizing a H3N2 IAV infection, optionally by A/Aichi/2/68, with an IC₅₀ in a range of from 10³ ng/mL to 10⁴ ng/mL, optionally in a range of from 3,000 ng/mL to 10,000 ng/mL-; ~~and/or~~

~~46. The antibody or antigen-binding fragment of any one of claims 1-45, which is capable of:~~
~~(3)~~ neutralizing infection by:

(i) a Group 1 IAV, wherein, optionally, the Group 1 IAV comprises or is a H5 IAV, wherein, further optionally, the H5 IAV comprises or is H5/VN/11/94 pp; and

(ii) a Group 2 IAV, wherein, optionally, the Group 2 IAV comprises or is a H7 IAV, wherein, further optionally, the H7 IAV comprises or is H7/IT/99 pp,

wherein, optionally, neutralization of infection is as determined using a virus pseudotyped with the IAV; and/or

~~47. The antibody or antigen-binding fragment of claim 46, which is capable of:~~ (4)

(iii) neutralizing an infection by a Group 1 IAV, optionally H5/VN/11/94, with an IC50 in a range of from about 1 ng/mL to about 8ng/mL (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, or 8 ng/nL); and

(iv) neutralizing an infection by a Group 2 IAV, optionally H7/IT/99 pp, with an IC50 in a range of from about 10 ng/mL to about 200 ng/mL.

~~48~~18. The antibody or antigen-binding fragment of any one of claims 1-~~47~~17, which is capable of: (1) activating a human FcγRIIIa, which is optionally a F158 allele; and/or

~~49. The antibody or antigen-binding fragment of any one of claims 1-48, which is capable of~~ (2) activating a human a human FcγRIIa, which is optionally a H131 allele.

~~50~~19. The antibody or antigen-binding fragment of claim ~~48~~or 4918, wherein activation is as determined using a host cell (optionally a Jurkat cell) comprising: (i) (a) the human FcγRIIIa (optionally a F158 allele), and/or (b) the human FcγRIIa (optionally a H131 allele); and (ii) a NFAT expression control sequence operably linked to a sequence encoding a reporter, such as a luciferase reporter,

following incubation (*e.g.*, of 20 hours) of the antibody or antigen-binding fragment with a target cell (*e.g.*, a A549 cell) infected with an IAV; wherein, optionally,

~~51. The antibody or antigen-binding fragment of claim 50, wherein~~ activation is as determined following incubation of the antibody or antigen-binding fragment with:

(1) the target cell infected with a H1N1 IAV, wherein, optionally, the H1N1 IAV is A/PR/8/34, and wherein, optionally, the infection has a multiplicity of infection (MOI) of 6; and/or

(2) the target cell infected with a H3N2 IAV, wherein, optionally, the H3N2 IAV is A/Aichi/2/68, and wherein, optionally, the infection has a multiplicity of infection (MOI) of 18.

~~52~~20. The antibody or antigen-binding fragment of any one of claims 1-~~51~~19, which is capable of:

(1) neutralizing infection by a H5 pseudovirus with a IC₅₀ of less than 4.5 ng/mL, 4.0 ng/mL or less, 3.0 ng/mL or less, 2.5 ng/mL or less, 2.0 ng/mL or less, 1.5 ng/mL or less, 1.0 ng/mL or less, 0.9 ng/mL or less, 0.8 ng/mL or less, 0.7 ng/mL or less, 0.6 ng/mL or less, 0.5 ng/mL or less, 0.4 ng/mL or less, 0.3 ng/mL or less, or 0.2 ng/mL or less; and/or

~~53. The antibody or antigen-binding fragment of any one of claims 1-52, which is capable of~~ (2) neutralizing infection by a H5 pseudovirus with an IC₅₀ in a range of: from about 0.2 ng/mL to about 4.5 ng/mL, or from about 0.2 ng/mL to about 4.0 ng/mL, or from about 0.2 ng/mL to about 3.5 ng/mL, or from about 0.2 ng/mL to about 3.0 ng/mL, or from about 0.2 ng/mL to about 2.5 ng/mL, or from about 0.2 ng/mL to about 2.0 ng/mL, or from about 0.2 ng/mL to about 1.5 ng/mL, or from about 0.2 ng/mL to about 1.0 ng/mL, or from about 0.2 ng/mL to about 0.5 ng/mL, or from about 0.5 ng/mL to about 4.5 ng/mL, or from about 0.5 ng/mL to about 4.0 ng/mL, or from about 0.5 ng/mL to about 3.5 ng/mL, or from about 0.5 ng/mL to about 3.0 ng/mL, or from about 0.5 ng/mL to about 2.5 ng/mL, or from about 0.5 ng/mL to about 2.0 ng/mL, or from about 0.5 ng/mL to about 1.5 ng/mL, or from about 0.5 ng/mL to about 1.0 ng/mL, or from about 1.0 ng/mL to about 4.5 ng/mL, or from about 1.0 ng/mL to about 4.0 ng/mL, or from about 1.0 ng/mL to about 3.5 ng/mL, or from about 1.0 ng/mL to about 3.0 ng/mL, or from about 1.0 ng/mL to about 2.5 ng/mL, or from about 1.0 ng/mL to about 2.0 ng/mL, or from about 1.0 ng/mL to about 1.5 ng/mL, or from about 1.5 ng/mL to about 4.5 ng/mL, or from about 1.5 ng/mL to about 4.0 ng/mL, or from about 1.5 ng/mL to about 3.5 ng/mL, or from about 1.5 ng/mL to about 3.0 ng/mL,

or from about 1.5 ng/mL to about 2.5 ng/mL, or from about 1.5 ng/mL to about 2.0 ng/mL, or from about 2.0 ng/mL to about 4.5 ng/mL, or from about 2.0 ng/mL to about 4.0 ng/mL, or from about 2.0 ng/mL to about 3.5 ng/mL, or from about 2.0 ng/mL to about 3.0 ng/mL, or from about 2.0 ng/mL to about 2.5 ng/mL, or from about 2.5 ng/mL to about 4.5 ng/mL, or from about 2.5 ng/mL to about 4.0 ng/mL, or from about 2.5 ng/mL to about 3.5 ng/mL, or from about 2.5 ng/mL to about 3.0 ng/mL, or from about 3.0 ng/mL to about 4.5 ng/mL, or from about 3.0 ng/mL to about 4.0 ng/mL, or from about 3.0 ng/mL to about 3.5 ng/mL, or from about 3.5 ng/mL to about 4.5 ng/mL, or from about 3.5 ng/mL to about 4.0 ng/mL, or from about 4.0 ng/mL to about 4.5 ng/mL; and/or

~~54. — The antibody or antigen-binding fragment of any one of claims 1–53, which is capable of (3) _____~~ neutralizing infection by a H5 pseudovirus with a IC₅₀ of about 0.6 ng/mL, about 0.5 ng/mL, about 0.4 ng/mL, about 0.3 ng/mL, or about 0.2 ng/mL; and/or

~~55. — The antibody or antigen-binding fragment of any one of claims 1–54, which is capable of (4) _____~~ neutralizing infection by a H5 pseudovirus with a IC₅₀ of 0.7 ng/mL or less, 0.6 ng/mL or less, 0.5 ng/mL or less, 0.4 ng/mL or less, 0.3 ng/mL or less, or 0.20 ng/mL or less; and/or

~~56. — The antibody or antigen-binding fragment of any one of claims 1–55, which is capable of (5) _____~~ neutralizing infection by:

(i) a H1N1 IAV with a IC₅₀ in a range of from about 850 ng/mL to about 4,500 ng/mL, and/or with a IC₉₀ in a range of from about 1,000 ng/mL to about 5,400 ng/mL; and/or

(ii) a H3N2 IAV with a IC₅₀ in a range of from about 300 ng/mL to about 2,800 ng/mL, and/or with a IC₉₀ in a range of from about 350 ng/mL to about 7,600 ng/mL; and/or

~~57. — The antibody or antigen-binding fragment of any one of claims 1–56, which is capable of (6) _____~~ neutralizing infection by:

(i) a H1N1 IAV with a IC₅₀ in a range of from about 880 ng/mL to about 1,120 ng/mL, and/or with a IC₉₀ in a range of from about 1,050 ng/mL to about 1,680 ng/mL;

- (ii) a H3N2 IAV with a IC50 in a range of from about 300 ng/mL to about 2,100 ng/mL and/or with a IC90 in a range of from about 350 ng/mL to about 2,700 ng/mL;
- (iii) a H1N1 IAV with a IC50 in a range of from about 1,100 ng/mL to about 2,700 ng/mL, and/or with a IC90 in a range of from about 1,040 ng/mL to about 4,540 ng/mL;
- (iv) a H3N2 IAV with a IC50 in a range of from about 500 ng/mL to about 2,420 ng/mL and/or with a IC90 in a range of from about 680 ng/mL to about 4,570 ng/mL;
- (v) a H1N1 IAV with a IC50 in a range of from about 1,030 ng/mL to about 1,680 ng/mL, and/or with a IC90 in a range of from about 1,780 ng/mL to about 4,760 ng/mL;
- (vi) a H3N2 IAV with a IC50 in a range of from about 440 ng/mL to about 2,540 ng/mL and/or with a IC90 in a range of from about 450 ng/mL to about 4,250 ng/mL;
- (vii) a H1N1 IAV with a IC50 in a range of from about 1,950 ng/mL to about 2,000 ng/mL, and/or with a IC90 in a range of from about 2,420 ng/mL to about 5,400 ng/mL; and/or
- (viii) a H3N2 IAV with a IC50 in a range of from about 880 ng/mL to about 2,820 ng/mL and/or with a IC90 in a range of from about 1,170 ng/mL to about 7,630 ng/mL; ~~and/or~~

~~58. The antibody or antigen-binding fragment of any one of claims 1-57,~~
~~which is capable of~~ (7) neutralizing infection by:

- (i) a H1N1 A/PR/8/34 IAV with a IC50 in a range of from about 850 ng/mL to about 2000 ng/mL (*e.g.*, about 880 ng/mL, about 1,000 ng/mL, about 1100 ng/mL, about 2,000 ng/mL), and/or with a IC90 in a range of from about 1050 ng/mL to about 2,400 ng/mL (*e.g.*, about 1,050 ng/mL, about 1850 ng/mL, about 1,780 ng/mL, about 2,400 ng/mL);
- (ii) a H1N1 A/Solomon Islands/3/06 IAV with a IC50 in a range of from about 1,100 ng/mL to about 2,700 ng/mL (*e.g.*, about 1,100 ng/mL, about 1,680 ng/mL, about 1950 ng/mL, about 2,700 ng/mL) and/or with a IC90 in a range of from about

1680 ng/mL to about 5,400 ng/mL (e.g., about 1680 ng/mL, about 4,500 ng/mL, about 4700 ng/mL, about 5,400 ng/mL);

(iii) a H3N2 A/Aichi/2/68 IAV with a IC50 in a range of from about 2,100 ng/mL to about 2,900 ng/mL (e.g., about 2,100 ng/mL, about 2,400 ng/mL, about 2,500 ng/mL, about 2,800 ng/mL) and/or with a IC90 in a range of from about 2,700 ng/mL to about 7,600 ng/mL (e.g., about 2,700 ng/mL, about 4,200, about 4,500 ng/mL, about 7,600 ng/mL);

(iv) a H3N2 A/Brisbane/10/07 IAV with a IC50 in a range of from about 300 ng/mL to about 880 ng/mL (e.g., about 300 ng/mL, about 440 ng/mL, about 500 ng/mL, about 880 ng/mL) and/or with a IC90 in a range of from about 350 ng/mL to about 1,200 ng/mL (e.g., about 350 ng/mL, about 450 ng/mL, about 680 ng/mL, about 1,200 ng/mL);

(v) a H1N1 A/CAL/09 IAV with a IC50 in a range of from about 3,100 ng/mL to about 4,500 ng/mL (e.g., about 3,100 ng/mL, about 3,600 ng/mL, about 4,300 ng/mL, about 4,500 ng/mL) and/or with a IC90 in a range of from about 350 ng/mL to about 1,200 ng/mL (e.g., about 350 ng/mL, about 450 ng/mL, about 680 ng/mL, about 1,200 ng/mL); and/or

(vi) a H3N2 A/HK/68 IAV with a IC50 in a range of from about 2,000 ng/mL to about 3,000 ng/mL (e.g., about 2,000 ng/mL, about 2,100 ng/mL, about 2,200 ng/mL, about 2,300 ng/mL, about 2,400 ng/mL, about 2,500 ng/mL, about 2,600 ng/mL, about 2,700 ng/mL, about 2,800 ng/mL, about 2,900 ng/mL, about 3,000 ng/mL), preferably in a range of from about 2,100 ng/mL to about 2,500 ng/mL; and/or

~~59. —The antibody or antigen-binding fragment of any one of claims 1–58,~~
~~which is capable of~~ (8) neutralizing infection by:

(i) a H1N1 A/PR/8/34 IAV with a IC50 in a range of: from about 860 to about 920 ng/mL, from about 1,000 to about 1,060 ng/mL, from about 1,080 ng/mL to about 1,140 ng/mL, or from about 1,970 ng/mL to about 2,030 ng/mL, and/or with a IC90 in a range of: from about 1,015 ng/ml to about 1,075 ng/mL, from about 1,750 ng/mL to about 1,810 ng/mL, from about 1,750 ng/mL to about 1,830 ng/mL, or from about 2,390 ng/mL to about 2,450 ng/mL;

(ii) a H1N1 A/Solomon Islands/3/06 IAV with a IC50 in a range of from about 1,100 ng/mL to about 2,700 ng/mL (*e.g.*, about 1,100 ng/mL, about 1,680 ng/mL, about 1950 ng/mL, about 2,700 ng/mL) and/or with a IC90 in a range of from about 1680 ng/mL to about 5,400 ng/mL (*e.g.*, about 1680 ng/mL, about 4,500 ng/mL, about 4700 ng/mL, about 5,400 ng/mL);

(iii) a H3N2 A/Aichi/2/68 IAV with a IC50 in a range of from about 2,100 ng/mL to about 2,900 ng/mL (*e.g.*, about 2,100 ng/mL, about 2,400 ng/mL, about 2,800 ng/mL) and/or with a IC90 in a range of from about 2,700 ng/mL to about 7,600 ng/mL (*e.g.*, about 2,700 ng/mL, about 4,200, about 4,500 ng/mL, about 7,600 ng/mL); and/or

(iv) a H3N3 A/Brisbane/10/07 IAV with a IC50 in a range of from about 300 ng/mL to about 880 ng/mL (*e.g.*, about 300 ng/mL, about 440 ng/mL, about 500 ng/mL, about 88 ng/mL) and/or with a IC90 in a range of from about 350 ng/mL to about 1,200 ng/mL (*e.g.*, about 350 ng/mL, about 450 ng/mL, about 680 ng/mL, about 1,200 ng/mL).

~~60~~21. The antibody or antigen-binding fragment of any one of claims 1-~~59~~20, which is capable of binding to any one or more of the following H3N2 IAV subtypes: A/Babol/36/2005; A/Hong Kong/CUHK31987/2011; A/Texas/50/2012; A/Wisconsin/67/2005; A/Netherlands/178/1995; A/Johannesburg/33/1994; A/Guangdong-Luohu/1256/2009; A/California/7/2004; A/Hanoi/EL134/2008; A/Wuhan/359/1995; A/Victoria/210/2009; A/Philippines/472/2002; A/Hanoi/EL201/2009; A/Victoria/210/2009; A/Missouri/09/2014; A/Perth/16/2009; A/Wyoming/03/2003; A/Moscow/10/1999; A/Sydney/5/1997; A/Nanchang/933/1995; A/Beijing/32/92; A/Aichi/2/1968; A/Brisbane/10/2007; and A/Switzerland/9715293/2013.

~~61~~22. The antibody or antigen-binding fragment of claim ~~60~~21, which is capable of binding to the one or more H3N2 IAV subtype(s) with a logEC50 (ng/mL) in a range of: from about 0.1 to about 6, from about 0.1 to about 5.5, from about 1 to about 5, from about 0.1 to about 4.5, from about 0.1 to about 4.0, from about 0.1 to about 3.5, from about 0.1 to about 3, from about 0.1 to about 2.5, from about 0.1 to about 2.0,

from 0.1 to about 1.5, from 0.1 to about 1.0, or of about 1.9, about 1.8, about 1.7, about 1.6, about 1.5, about 1.4, about 1.3, about 1.2, about 1.1, about 1.0, about 0.9, about 0.8, about 0.7, about 0.6, about 0.5, about 0.4, about 0.3, about 0.2, or about 0.1 ng/mL, wherein the binding is as determined by ELISA.

~~62~~23. The antibody or antigen-binding fragment of any one of claims 1-~~61~~22, (1) which is capable of binding to one or more of (i)-(iv):

(i) a H1 HA, which optionally comprises any one or more of:
A/England/195/2009; A/Brisbane/59/2007; A/Solomon Islands/3/2006; A/New Caledonia/20/99; A/Texas/36/1991; A/Taiwan/01/1986; A/New Jersey/8/1976; A/Albany/12/1951; A/Fort Monmouth/1/1947; A/New York/1/1918; A/Puerto Rico/8/34; and A/California/07/2009;

(ii) a H2 HA, optionally comprising A/Japan/305/1957;

(iii) a H5 HA, optionally comprising A/Vietnam/1194/2004; and

(iv) a H9 HA, optionally comprising A/Hong Kong/1073/99-; and/or

~~63.~~ The antibody or antigen-binding fragment of any one of claims 1-~~62~~,(2) which which binds to H5 HA and/or to H7 HA with a KD of less than 1.0E-12 M, less than 1.0E-11 M, less than 1.0E-10 M, less than 1.0E-9 M, less than 1.0E-8 M, or less than 1.0E-7 M, or of 1.0E-8M or less, of 1.0E-9M or less, of 1.0E-10 or less, of 1.0E-11 or less, or 1.0E-12 or less (*e.g.*, as determined by Bio-Layer Interferometry (BLI)).

~~64.~~ The antibody or antigen-binding fragment of claim 62, which is capable of binding to one or more of (i)-(iv) with a logEC50 (ng/mL) in a range: from about 0.05 to about 1.5, from about 0.05 to about 1.4, from about 0.05 to about 1.3, from about 0.05 to about 1.2, from about 0.05 to about 1.1, from about 0.05 to about 1.0, from about 0.05 to about 0.9, from about 0.05 to about 0.8, from about 0.05 to about 0.7, from about 0.05 to about 0.6, from about 0.05 to about 0.5, from about 0.1 to about 1, or about 1.3, about 1.2, about 1.1, about 1.0, about 0.9, about 0.8, about 0.7, about 0.6, about 0.5, about 0.4, about 0.3, about 0.2, about 0.1, or about 0.05,

~~wherein the binding is as determined by ELISA.~~

~~65~~24. The antibody or antigen-binding fragment of any one of claims 1-~~64~~23, which is a IgG, IgA, IgM, IgE, or IgD isotype.

~~66~~25. The antibody or antigen-binding fragment of any one of claims 1-~~65~~24, which is an IgG isotype selected from IgG1, IgG2, IgG3, and IgG4.

~~67~~26. The antibody or antigen-binding fragment of any one of claims 1-~~66~~25, which is human, humanized, or chimeric.

~~68~~27. The antibody or antigen-binding fragment of any one of claims 1-~~67~~26, wherein the antibody, or the antigen-binding fragment, comprises a human antibody, a monoclonal antibody, a purified antibody, a single chain antibody, a Fab, a Fab', a F(ab')₂, or a Fv, such as a scFv.

~~69~~28. The antibody or antigen-binding fragment of any one of claims 1-~~68~~27, wherein the antibody or antigen-binding fragment is a multi-specific antibody or antigen binding fragment-wherein, optionally,

~~70. — The antibody or antigen-binding fragment of claim 69, wherein the~~
antibody or antigen binding fragment is a bispecific antibody or antigen-binding fragment.

~~71~~29. The antibody or antigen-binding fragment of any one of claims 1-~~70~~28, further comprising a Fc polypeptide or a fragment thereof, wherein, optionally, the Fc polypeptide or fragment thereof is an IgG1 isotype.

~~72~~30. The antibody or antigen-binding fragment of claim ~~71~~29, wherein the Fc polypeptide or fragment thereof comprises:

(i) a mutation that extends *in vivo* half-life of the antibody or antigen-binding fragment, as compared to the antibody or antigen-binding fragment comprising

a reference (e.g., native of a same isotype) Fc polypeptide or fragment thereof that does not comprise the mutation; and/or

(ii) a mutation that increases binding affinity to a human FcγR (e.g., a FcγRIIa and/or a FcγRIIIa), as compared to a reference Fc polypeptide that does not comprise the mutation; wherein, optionally,

~~73. The antibody or antigen-binding fragment of claim 72, wherein (1)~~ the mutation that extends *in vivo* half-life of the antibody or antigen-binding fragment comprises: M428L; N434S; N434H; N434A; N434S; M252Y; S254T; T256E; T250Q; P257I; Q311I; D376V; T307A; E380A; or any combination thereof,

wherein Fc amino acid numbering is according to the EU numbering system; and/or

~~74. The antibody or antigen-binding fragment of claim 72 or 73, wherein (2)~~ the mutation that extends *in vivo* half-life of the antibody or antigen-binding fragment comprises:

- (i) M428L/N434S;
- (ii) M252Y/S254T/T256E;
- (iii) T250Q/M428L;
- (iv) P257I/Q311I;
- (v) P257I/N434H;
- (vi) D376V/N434H;
- (vii) T307A/E380A/N434A; or
- (viii) any combination of (i)-(vii); and/or

~~75. The antibody or antigen-binding fragment of any one of claims 72-74,~~ wherein (3) the mutation that extends *in vivo* half-life comprises M428L/N434S; and/or

~~76. The antibody or antigen-binding fragment of any one of claims 72-75,~~ wherein (4) the mutation that enhances binding to a FcγR comprises S239D; I332E; A330L; G236A; or any combination thereof,

wherein Fc amino acid numbering is according to the EU numbering system; and/or

~~77. The antibody or antigen-binding fragment of any one of claims 72-76,~~
wherein (6) the mutation that enhances binding to a FcγR comprises:

- (i) S239D/I332E;
- (ii) S239D/A330L/I332E;
- (iii) G236A/S239D/I332E; or
- (iv) G236A/A330L/I332E, optionally not comprising S239D, further optionally comprising a S at position 239.

~~78~~31. The antibody or antigen-binding fragment of any one of claims 1-~~77~~30, wherein the antibody or antigen-binding fragment:

- (i) comprises a mutation that alters glycosylation, wherein the mutation that alters glycosylation comprises N297A, N297Q, or N297G; and/or
- (ii) is aglycosylated and/or is afucosylated.

~~79~~32. The antibody or antigen-binding fragment of any one of claims 1-~~78~~31, comprising (1) a CH1-CH3 that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:47 or 49, and/or (2)

~~80. The antibody or antigen-binding fragment of any one of claims 1-79,~~
comprising a CL that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:48.

~~81~~33. ~~An~~The antibody, or ~~an~~antigen-binding fragment thereof, of any one of claims 1-32, wherein the antibody or antigen binding fragment comprises~~ing~~ two heavy chains and two light chains, wherein:

- (i) each of the two heavy chains comprises or consists of (1) a heavy chain variable domain (VH), wherein the VH comprises or consists of the amino acid sequence of SEQ ID NO.: 37, and (2) a CH1-CH3 that comprises or consists of the amino acid sequence set forth in SEQ ID NO.:47 or 49; and
- (ii) each of the two light chains comprises or consists of (1) a light chain variable domain (VL), wherein the VL comprises or consists of the amino acid

sequence of SEQ ID NO.:8, and (2) a CL that comprises or consists of the amino acid sequence of SEQ ID NO.:48.

~~82~~34. An isolated polynucleotide encoding the antibody or antigen-binding fragment of any one of claims 1-~~81~~33, or encoding a VH, a heavy chain, a VL, and/or a light chain of the antibody or the antigen-binding fragment.

~~83~~35. The polynucleotide of claim ~~82~~34, wherein (1) the polynucleotide comprises deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), wherein the RNA optionally comprises messenger RNA (mRNA)-, and/or (2)

~~84. — The polynucleotide of claim 82 or 83, comprising the polynucleotide~~
comprises a modified nucleoside, a cap-1 structure, a cap-2 structure, or any combination thereof-, wherein, optionally,

~~85. — The polynucleotide of claim 84, wherein~~ the polynucleotide comprises a pseudouridine, a N6-methyladenosine, a 5-methylcytidine, a 2-thiouridine, or any combination thereof-, wherein, further optionally,

~~86. — The polynucleotide of claim 85, wherein~~ the pseudouridine comprises N1-methylpseudouridine.

~~87. — The polynucleotide of any one of claims 82-86, which is codon-optimized for expression in a host cell.~~

~~88. — The polynucleotide of claim 87, wherein the host cell comprises a human cell.~~

~~89~~36. The polynucleotide of ~~any one of claims 82-88~~ claim 34 or 35, comprising a polynucleotide having at least 50% (e.g., 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more) identity to the polynucleotide sequence according to any one or more of SEQ ID NOs.: 1, 6, 7, 12, 25, 27, 30, 33, 36, 13, 18, 19, 24, 38, and 40.

~~90~~37. The polynucleotide of any one of claims ~~82-89~~ 34-36, comprising:

- (i) a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:6 and a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:12;
- (ii) a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:25 and a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:12;
- (iii) a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:27 and a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:12;
- (iv) a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:30 and a polynucleotide having at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:12;
- (v) a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:33 and a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:12;
- (vi) a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:36 and a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:12;
- (vii) a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:18 and a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:24;

(viii) a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:38 and a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:24; or

(ix) a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:40 and a polynucleotide having at least 75% identity to, or comprising or consisting of, the polynucleotide sequence of SEQ ID NO.:24.

9138. A recombinant vector comprising the polynucleotide of any one of claims ~~82-90~~ 34-37.

9239. A host cell comprising the polynucleotide of any one of claims ~~82-90~~ 34-37 and/or the vector of claim 9138, wherein the polynucleotide is heterologous to the host cell and wherein the host cell is capable of expressing the encoded antibody or antigen-binding fragment.

9340. An isolated human B cell comprising the polynucleotide of any one of claims ~~82-90~~ 34-37 and/or the vector of claim 9138, wherein polynucleotide is heterologous to the human B cell and/or wherein the human B cell is immortalized.

9441. A composition comprising:

- (i) the antibody or antigen-binding fragment of any one of claims 1-~~81~~33;
 - (ii) the polynucleotide of any one of claims ~~82-90~~ 34-37;
 - (iii) the recombinant vector of claim 9138;
 - (iv) the host cell of claim 9239; and/or
 - (v) the human B cell of claim 9340,
- and a pharmaceutically acceptable excipient, carrier, or diluent.

~~95. — The composition of claim 94, comprising a first antibody or antigen-binding fragment and a second antibody or antigen-binding fragment, wherein each of the first antibody or antigen-binding fragment and the second antibody or antigen-binding fragment are different and are each independently according any one of claims 1-81.~~

~~96~~42. A composition comprising the polynucleotide of any one of claims ~~82-90~~34-37 or the vector of claim ~~91~~38 encapsulated in a carrier molecule, wherein the carrier molecule optionally comprises a lipid, a lipid-derived delivery vehicle, such as a liposome, a solid lipid nanoparticle, an oily suspension, a submicron lipid emulsion, a lipid microbubble, an inverse lipid micelle, a cochlear liposome, a lipid microtubule, a lipid microcylinder, lipid nanoparticle (LNP), or a nanoscale platform.

~~97~~43. A method of making an antibody or antigen-binding fragment of any one of claims 1-~~81~~33, comprising culturing the host cell of claim ~~39~~92 or the human B cell of claim ~~40~~93 for a time and under conditions sufficient for the host cell or human B cell to express the antibody or antigen-binding fragment, wherein, optionally, the method further comprises

~~98. — The method of claim 97, further comprising~~ isolating the antibody or antigen-binding fragment.

~~99. — A method of treating or preventing an influenza A virus infection in a subject, the method comprising administering to the subject an effective amount of:~~

- ~~(i) — the antibody or antigen-binding fragment of any one of claims 1-81;~~
- ~~(ii) — the polynucleotide of any one of claims 82-90;~~
- ~~(iii) — the recombinant vector of claim 91;~~
- ~~(iv) — the host cell of claim 92;~~
- ~~(v) — the human B cell of claim 93; and/or~~
- ~~(vi) — the composition of any one of claims 94-96.~~

~~100.—A method of treating or preventing an influenza infection in a human subject, the method comprising administering to the subject the polynucleotide of any one of claims 82-90, the recombinant vector of claim 91, or the composition of claim 96, wherein the polynucleotide comprises mRNA.~~

~~101.—The method of claim 100, wherein the influenza infection comprises an IAV infection.~~

~~102.—The method of any one of claims 99-101, comprising administering a single dose of the antibody or antigen-binding fragment, polypeptide, polynucleotide, recombinant vector, host cell, or composition to the subject.~~

~~103.—The method of any one of claims 99-102, comprising administering two or more doses of the antibody or antigen-binding fragment, polypeptide, polynucleotide, recombinant vector, host cell, or composition to the subject.~~

~~104.—The method of any one of claims 99-103, comprising administering a dose of the antibody or antigen-binding fragment, polypeptide, polynucleotide, recombinant vector, host cell, or composition to the subject once during a year, optionally in advance of or during an influenza season.~~

~~105.—The method of any one of claims 99-103, comprising administering a dose of the antibody or antigen-binding fragment, polypeptide, polynucleotide, recombinant vector, host cell, or composition to the subject two or more times during a year; e.g. about once every 6 months.~~

~~106.—The method of any one of claims 99-105, comprising administering the antibody or antigen-binding fragment, polypeptide, polynucleotide, recombinant vector, host cell, or composition intramuscularly, subcutaneously, or intravenously.~~

~~107. The method of any one of claims 99-106, wherein the treatment and/or prevention comprises post-exposure prophylaxis.~~

~~108. The method of any one of claims 99-107, wherein the subject has received, is receiving, or will receive an antiviral agent.~~

~~109. The method of claim 108, wherein the antiviral agent comprises a neuraminidase inhibitor, an influenza polymerase inhibitor, or both.~~

~~110. The method of claim 108 or 109, wherein the antiviral agent comprises oseltamivir, zanamivir, baloxavir, or any combination thereof.~~

~~111~~44. The antibody or antigen-binding fragment of any one of claims 1-~~81~~33, the polynucleotide of any one of claims ~~82-90~~34-37, the recombinant vector of claim ~~91~~38, the host cell of claim ~~92~~39, the human B cell of claim ~~93~~40, and/or the composition of ~~any one of claims 94-96~~ claim 41 or 42, for use ~~therapy~~in a method of treating or preventing an influenza A virus infection in a subject.

~~112~~45. Use of ~~T~~the antibody or antigen-binding fragment of any one of claims 1-~~81~~33, the polynucleotide of any one of claims ~~82-90~~34-37, the recombinant vector of claim ~~91~~38, the host cell of claim ~~92~~39, the human B cell of claim ~~93~~40, and/or the composition of ~~any one of claims 94-96~~ claim 41 or 42, ~~for use~~ in the preparation of a medicament for the treatment of an influenza virus infection, optionally a influenza A virus infection, in a subject.

~~113~~46. A method for *in vitro* diagnosis of an influenza A virus infection, the method comprising:

(i) contacting a sample from a subject with an antibody or antigen-binding fragment of any one of claims 1-~~8~~33; and

(ii) detecting a complex comprising an antigen and the antibody, or comprising an antigen and the antigen-binding fragment.