On average 41,400 people died each year in the United States between 1979 and 2001 from influenza.

SUMMARY

The disclosure is based, at least in part, on the discovery of human anti-HA antibodies comprising functional and structural properties disclosed herein, e.g., antibodies that bind a conserved region or epitope on influenza virus and uses thereof.

Accordingly, the disclosure features binding agents, e.g., antibody molecules, or preparations, or isolated preparations thereof, that bind hemagglutinin (HA) from influenza viruses. In an embodiment, a binding agent, e.g., an antibody molecule, is broad spectrum, and binds more than one HA, e.g., an HA from one or both of Group 1 or Group 2 strains of influenza A viruses and/or one or more strains of influenza B viruses. Therefore, in some embodiments, a binding agent, e.g., an antibody molecule, featured in the disclosure can treat or prevent infection by a Group 1 influenza virus and a Group 2 influenza virus. In other embodiments, a binding agent, e.g., an antibody molecule, featured in the disclosure can treat or prevent infection by an influenza A virus and an influenza B virus. The binding agents, e.g, antibody molecules, share sufficient structural similarity with antibodies or variable regions disclosed herein such that they possess functional attributes of the antibodies disclosed herein. In embodiments the structural similarity can be in terms of three dimensional structure or linear amino acid sequence or both.

In an aspect, the disclosure features an isolated antibody molecule comprising: (a) a heavy chain immunoglobulin variable region segment comprising: a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68); a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69); and a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and (b) a light chain immunoglobulin variable region segment comprising a CDR1 comprising the sequence Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145); a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

In another aspect, the disclosure features the use of the antibody molecule featured in the disclosure for the manufacture of a medicament for preventing or treating an influenza virus infection in a human subject.

In one ~~aspect~~embodiment, the disclosure features an anti-hemagglutinin (anti-HA) binding agent, e.g., a specific binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising one or more or all of the following properties:

(a) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004;

sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from light chain disclosed herein.

In one aspeetembodiment, an anti-HA antibody molecule featured in the disclosure, or preparation, or isolated preparation thereof, comprises

(a) a heavy chain immunoglobulin variable domain comprising a sequence at least 60, 70, 80, 85, 87, 90, 95, 97, 98, or 99, e.g., 90%, homologous, to a heavy chain consensus sequence provided herein, e.g., the heavy chain consensus sequence provided in Fig. 2 or Fig 13, e.g., the heavy chain consensus sequence provided in Fig. 2, SEQ ID NO:161; and

(b) a light chain immunoglobulin variable domain comprising a sequence at least 60, 70, 80, 85, 87, 90, 95, 97, 98, or 99, e.g., 95%, homologous, to a light chain consensus sequence provided herein, e.g., the light chain consensus sequence provided in Fig. 3 or Fig 14, e.g., the light chain consensus sequence provided in Fig. 3, SEQ ID NO:62.

For example, in one embodiment, the anti-HA antibody molecule featured in the disclosure comprises one or both of:

(a) a heavy chain immunoglobulin variable domain comprising the sequence of SEQ ID NO:161, or a sequence at least 87% identical to SEQ ID NO:161; and

(b) a light chain immunoglobulin variable domain comprising the sequence SEQ ID NO:62, or a sequence at least 95% identical to SEQ ID NO:62.

In another embodiment the antibody molecule comprises:

(a) a heavy chain immunoglobulin variable domain comprising the sequence of SEQ ID NO:161, or a sequence at least 87% identical to SEQ ID NO:161; and

(b) a light chain immunoglobulin variable domain comprising the sequence SEQ ID NO:62, or a sequence at least 95% identical to SEQ ID NO:62, wherein said antibody molecule:

(i) fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza virus (e.g., an

In an embodiment the antibody molecule comprises one or both of:

a) one or more framework regions (FRs) from heavy chain consensus sequence disclosed herein. e.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from heavy chain consensus sequence disclosed herein; and

b) one or more framework regions (FRs) from light chain consensus sequence disclosed herein. e.g., the antibody molecule comprises one or more or all of FR1, FR2, FR3, or FR4, or sequences that differ individually, or collectively, by no more than 1, 2, 3, 4, of 5 amino acid residues, e.g., conservative residues, from light chain consensus disclosed herein.

In an embodiment the binding agent, e.g., an antibody molecule, specifically binds the HA antigen.

In another ~~aspect~~embodiment, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of Ab 044.

In an embodiment, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

(SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

ii) a light chain variable region segment comprising:

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an embodiment, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329 ; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an embodiment the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an embodiment the molecule has properties c, cc, d, and dd.

In another ~~aspect~~embodiment, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of Ab 069.

In an embodiment, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an embodiment, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329 ; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an embodiment the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an embodiment the molecule has properties c, cc, d, and dd.

In an embodiment the molecule has properties c, cc, d, and dd.

In another ~~aspect~~embodiment, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of Ab 032.

In an embodiment, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an embodiment, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an embodiment the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an embodiment the molecule has properties c, cc, d, and dd.

In another ~~aspect~~embodiment, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of Ab 031.

In an embodiment, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising:

i) a heavy chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G

(SEQ ID NO:69); and

1 mg/kg; (k) it binds with high affinity to a hemagglutinin (HA) of an influenza B virus, e.g., B/Wisconsin/1/2010; (l) it treats or prevents infection by an influenza B virus, e.g., B/Wisconsin/1/2010; (m) it is effective for prevention or treatment of infection, e.g., in humans or mice, with an influenza B virus, e.g., B/Wisconsin/1/2010 when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg; (n) the concentration of antibody molecule required for 50% neutralization of influenza A virus is less than 10 μg/mL; (o) the concentration of antibody molecule required for 50% neutralization of influenza B virus, e.g., B/Wisconsin/1/2010, is less than 10 μg/mL; (p) it prevents or minimizes secondary infection (e.g., secondary bacterial infection) or effects thereof on a subject; (q) it is effective for preventing or minimizing secondary infection (e.g., secondary bacterial infection) or effects thereof on a subject when administered at 50 mg/kg, 25 mg/kg, 10 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2 mg/kg, or 1 mg/kg; (r) it binds an epitope which comprises or consists of the hemagglutinin trimer interface; and (s) it binds an epitope other than that bound by a reference anti-HA antibody molecule, e.g., Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, e.g., when tested by a method disclosed herein, e.g., by competition in an ELISA assay.

In another ~~aspect~~embodiment, the disclosure features an antibody molecule comprising: (a) a heavy chain immunoglobulin variable region segment comprising SEQ ID NO:24 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom); and (b) a light chain variable region segment comprising SEQ ID NO:45 (or a sequence that differs by no more than 1, 2, 3, 4 or 5 amino acids, e.g., conservative amino acids, therefrom). In some embodiments, the antibody molecule comprises one or more or all of the following properties: (i) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 10, 9, 8, 7, 6, or 5 rounds of serial infections in cell culture with a mixture of the antibody molecule and an influenza a virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004; and (ii) it produces fewer escape mutants than does a

aa) H1 HA1 residues H31, N279, and S292;

bb) H1 HA2 residue G12;

cc) H1 HA1 residues T319, R322, and I324 ; or

dd) H1 HA2 residues A7, E11, I18, D19, G20, W21, Q38, K39, T41, Q42, N43, I45, I48, T49, V52, N53, I56, and E57.

In an embodiment, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an embodiment the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an embodiment the molecule has properties c, cc, d, and dd.

In another ~~aspect~~embodiment, the disclosure features, a binding agent, e.g., an antibody molecule, or preparation, or isolated preparation thereof, comprising a structural or functional property of one or both a heavy chain variable region and a light chain variable region disclosed herein.

In an embodiment, the antibody molecule competes with a reference antibody molecule, e.g., an antibody molecule described herein, for binding to a substrate, e.g., an HA. The reference antibody molecule can be:

a) an antibody molecule comprising the heavy and light CDRs from :

a heavy chain variable region from Table 3, Table 4A, Table 4B, Fig.2, Fig 13, or Fig. 17; and

In an embodiment, the antibody molecule has a K_D for H1 of equal to or less than 10^{-6}, wherein said K_D is increased by no more than 2, or 5 fold, by a mutation or mutations in any of:

cc) H1 HA1 residues Q328 and S329; or

dd) H1 HA2 residues G1, L2, F3, G4, and D46;

In an embodiment the antibody molecule has one, two, three or all of the following properties:

a and aa;

b and bb;

c and cc;

d and dd.

In an embodiment the molecule has properties c, cc, d, and dd.

In one ~~aspect~~embodiment, the disclosure features an anti-hemagglutinin (anti-HA) binding agent, e.g., antibody molecule, or preparation, or isolated preparation thereof, comprising:

(a) a heavy chain immunoglobulin variable region segment comprising one or more or all of a

CDR1 comprising the sequence G-F-T-F-[S/T]-[S/T]-Y-[A/G]-M-H (SEQ ID NO:1), or a sequence that differs from SEQ ID NO:1 by no more than 1 or 2 residues;

a CDR2 comprising the sequence V-[I/V/L]-S-[Y/F]-D-G-[S/N]-[Y/N]-[K/R]-Y-Y-A-D-S-V-Q-G (SEQ ID NO:2) or a sequence that differs from SEQ ID NO:2 by no more than 1 or 2 residues; and

a CDR3 comprising the sequence D-[S/T]-[R/K/Q]-L-R-[S/T]-L-L-Y-F-E-W-L-S-[Q/S]-G-[Y/L/V]-[F/L]-[N/D]-[P/Y] (SEQ ID NO:3), or a sequence that differs from SEQ ID NO:3 by no more than 1 or 2 residues; and

(b) a light chain variable region segment comprising one or more or all of a CDR1 comprising the sequence [K/R]-S-S-Q-[S/T]-[V/L/I]-[T/S]-[Y/F/W]-[N/S/D]-Y-K-N-Y-L-A (SEQ ID NO:4) or a sequence that differs from SEQ ID NO:4 by no more than 1 or 2 residues, or comprising the sequence [K/R]-S-S-Q-[S/T]-

In one ~~aspect~~embodiment, the disclosure features an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment featured in the disclosure.

In another ~~aspect~~embodiment, the disclosure features an isolated nucleic acid molecule that comprises a nucleotide sequence encoding a light chain immunoglobulin variable region segment featured in the disclosure.

In yet another ~~aspect~~embodiment, the disclosure features an isolated nucleic acid molecule that comprises a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment featured in the disclosure and a light chain immunoglobulin variable region segment featured in the disclosure.

In yet another ~~aspect~~embodiment, the disclosure features a recombinant vector, such as an expression vector, that comprises a nucleic acid molecule that comprises a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment or nucleotide sequence that encodes a light chain immunoglobulin variable region segment featured in the disclosure.

In one ~~aspect~~embodiment, the disclosure features a recombinant vector, such as an expression vector, that comprises a nucleotide sequence that encodes a heavy chain immunoglobulin variable region segment and a nucleotide sequence that encodes a light chain immunoglobulin variable region segment featured in the disclosure.

In one embodiment, the nucleic acid molecules in the recombinant vector include a nucleotide sequence encoding (a) a heavy chain immunoglobulin variable region segment comprising the amino acid sequence of: S-Y-A-M-H (SEQ ID NO:68) in CDR1; V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69) in CDR2; and D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70) in CDR3; and (b) a light chain immunoglobulin variable region segment comprising the amino acid sequence of: Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145) in CDR1;

W-G-S-Y-L-E-S (SEQ ID NO:72) in CDR2; and Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73) in CDR3.

In one ~~aspect~~embodiment, the disclosure features a cell containing a recombinant vector featured in the disclosure, such as a recombinant vector comprising a nucleic acid sequence that encodes a heavy chain immunoglobulin variable region, or a recombinant vector comprising a nucleic acid sequence that encodes a light chain immunoglobulin variable region. In one embodiment, the cell contains a recombinant vector comprising a nucleic acid sequence that encodes a heavy chain immunoglobulin variable region, and a recombinant vector comprising a nucleic acid sequence that encodes a light chain immunoglobulin variable region. In yet another embodiment, the cell contains a recombinant vector comprising a nucleic acid sequence that encodes a heavy chain immunoglobulin variable region, and a nucleic acid sequence that encodes a light chain immunoglobulin variable region.

In one ~~aspect~~embodiment, the disclosure features a method of making an antibody molecule featured in the ~~invention~~disclosure, such as by providing a host cell comprising a nucleic acid sequence expressing a heavy chain segment and a nucleic acid sequence expressing a light chain segment, and expressing the nucleic acids in the host cell.

In one embodiment, the nucleic acid sequence expressing the heavy chain segment and the nucleic acid sequence expressing the light chain segment are on the same recombinant expression vector. In another embodiment, the nucleic acid sequence expressing the heavy chain segment and the nucleic acid sequence expressing the light chain segment are on separate recombinant expression vectors.

In one aspect, the disclosure features a pharmaceutical composition containing an antibody molecule featured in the disclosure, and a pharmaceutically acceptable carrier.

In another ~~aspect~~embodiment, the disclosure features a method of treating or preventing infection with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or

In an embodiment the binding agent, e.g., an antibody molecule, is administered prior to known exposure to influenza, or to particular influenza substypes or strains.

In an embodiment the binding agent, e.g., an antibody molecule, is administered prior to manifestation of effects or symptoms of influenza infection, or to one or more particular effects manifestation of effects or symptoms of influenza infection.

In an embodiment the binding agent, e.g., an antibody molecule, is administered after known exposure to influenza, or to particular influenza substypes or strains.

In an embodiment the binding agent, e.g., an antibody molecule, is administered after manifestation of effects or symptoms of influenza infection, or after observation of one or more particular effects manifestation of effects or symptoms of influenza infection.

In an embodiment the binding agent, e.g., an antibody molecule, is administered in response to, or to treat or prevent, a manifestation of an effect or a symptom of influenza infection, e.g., inflammation, fever, nausea, weight loss, loss of appetite, rapid breathing, increase heart rate, high blood pressure, body aches, muscle pain, eye pain, fatigue, malaise, dry cough, runny nose, and/or sore throat.

In an embodiment, the method further comprises, testing the human subject for the influenza virus, e.g., with a method disclosed herein. In embodiments, the administration is responsive to a positive test for influenza.

In yet another ~~aspect~~embodiment, the disclosure features a method of treating a subject, e.g., a human subject, infected with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005

or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010) by administering a binding agent, e.g., an antibody molecule, featured in the disclosure. For example, the influenza A virus is an H1, H5, H9, H3 or H7 strain, such as an H1N1 strain, an H3N2 strain, or an H5N1 strain of influenza A virus.

In one embodiment, a binding agent, e.g., an anti-HA antibody, described herein is administered instead of a vaccine for prevention of influenza. In another embodiment, the binding agent, e.g., anti-HA antibody molecule, is administered in combination with (simultaneously or sequentially with) a vaccine for prevention of the flu.

In yet another ~~aspect~~embodiment, the disclosure features a method of detecting influenza (e.g., influenza A or influenza B) virions in a biological sample, such as by contacting the sample with a binding agent, e.g., an antibody molecule, featured in the disclosure, and then detecting the binding of the antibody molecule to the sample. In one embodiment, the method of detecting the influenza virus (e.g., influenza A or influenza B virus) is performed in vitro.

In one ~~aspect~~embodiment, the disclosure features a method of (a) providing a sample from a patient; (b) contacting the sample with a binding agent, e.g., an antibody molecule, featured in the disclosure, and (c) determining whether the binding agent, e.g., an antibody molecule, featured in the disclosure binds a polypeptide in the sample, where if the binding agent, e.g., an antibody molecule, binds a polypeptide in the sample, then the patient is determined to be infected with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., e.g., B/Wisconsin/1/2010). In one embodiment, the patient is determined to be infected with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010), and the patient is further administered a binding agent, e.g., an antibody molecule, disclosed

herein, e.g., the binding agent, e.g., an antibody molecule, with which the test was performed.

In another ~~aspect~~embodiment, the ~~invention~~ disclosure features, a method of inducing immunity to one or more influenza strains, or preventing, delaying or reducing infection with an influenza strain, or symptom thereof, in a vertebrate, e.g., a human. The method comprises administering to the vertebrate, e.g., a human, a broad range vaccine, or broad range immunogen, described herein.

In an embodiment the broad range vaccine, or broad range immunogen, induces an immune response against, or confers protection against, one or more influenza strains.

In an embodiment the broad range vaccine, or broad range immunogen, induces an immune response against, or confers protection against, two influenza strains.

In an embodiment the broad range vaccine, or broad range immunogen, induces an immune response against, or confers protection against, two Group 1 influenza strains.

In an embodiment the broad range vaccine induces, or broad range immunogen, an immune response against, or confers protection against, at least one Group 1 strain, and a second strain from Group 1, Group2 or an influenza B strain.

In one embodiment, the influenza A virus is an H1, H5, H9, H3 or H7 strain, such as an H1N1 strain, an H3N2 strain, or an H5N1 strain of influenza A virus.

In an embodiment the administration results in, or correlates with, one or more of : a reduction in the chance of an infection, a reduction in the incidence or severity of a symptom or manifestation of an influenza infection, or the delay or onset of a symptom or manifestation of an influenza infection.

In an embodiment the broad range vaccine, or broad range immunogen, is administered after known exposure to influenza, or to particular influenza substypes or strains.

In an embodiment the broad range vaccine is administered after manifestation of effects or symptoms of influenza infection, or after observation of one or more particular effects manifestation of effects or symptoms of influenza infection.

In an embodiment the broad range vaccine, or broad range immunogen, is administered in response to, or to treat or prevent, a manifestation of an effect or a symptom of influenza infection, e.g., inflammation, fever, nausea, weight loss, loss of appetite, rapid breathing, increase heart rate, high blood pressure, body aches, muscle pain, eye pain, fatigue, malaise, dry cough, runny nose, and/or sore throat.

In an embodiment, the method further comprises, testing the human subject for the influenza virus, e.g., with a method disclosed herein. In embodiments, the administration is responsive to a positive test for influenza.

In yet another ~~aspect~~embodiment, the disclosure features a method of treating a subject, e.g., a human subject, infected with an influenza virus (e.g., an influenza A virus, e.g., a Group 1 strain, e.g., an H1N1 strain, e.g., A/South Carolina/1/1918, A/Puerto Rico/08/1934, or A/California/04/2009, or an H5N1 strain, e.g., A/Indonesia/5/2005 or A/Vietnam/1203/2004, or an influenza B virus, e.g., B/Wisconsin/1/2010) by administering a broad range vaccine featured in the disclosure. For example, the influenza A virus is an H1, H5, H9, H3 or H7 strain, such as an H1N1 strain, an H3N2 strain, or an H5N1 strain of influenza A virus.

In another embodiment~~aspect~~, the ~~invention~~ disclosure features, a method of reducing the severity of influenza in a population. The method includes administering a broad range vaccine, or broad range immunogen, to sufficient individuals in the population to prevent or decrease the chance of influenza virus transmission to another individual in the population.

In another embodimentaspect, the invention disclosure features, a kit comprising one or more containers having disposed therein a broad range immunogen, a nucleic acid encoding the broad range epitope, or a broad range vaccine described herein. In an embodiment the kit includes a container having adjuvant disposed therein. In an embodiment the kit comprises a delivery device, e.g., an injection device or inhaler. In an embodiment the broad range epitope described herein, or a nucleic acid encoding the broad range epitope or broad reange vaccine, is disposed in a delivery device.

In an embodiment the kit comprises a delivery device, e.g., an injection device or inhaler. In an embodiment the vaccine is disposed in a delivery device.

In another aspect, the disclosure features a kit comprising the antibody molecule featured in the disclosure; and a pharmaceutically acceptable delivery vehicle or buffer, a delivery device, or both.

In another aspectembodiment, the invention disclosure features, a composition, e.g., a vaccine, comprising a broad range epitope described herein, packaged in a hermetically sealed container such as an ampoule. In an embodiment, the composition a liquid. In an embodiment, the composition is liquid a dry sterilized lyophilized powder or water free concentrate.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more embodiments featured in the disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages featured in the disclosure will be apparent from the description and drawings, and from the claims.

We Claim:

1. An antibody molecule comprising:

(a) a heavy chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence **S**-Y-**A**-M-H (SEQ ID NO:68) (or a sequence that differs by no more than, 1, 2, or 3 amino acids therefrom, optionally provided that, both of **S** and **A** are unchanged);

a CDR2 comprising the sequence V-**V**-S-Y-D-**G**-**N**-Y-K-Y-Y-A-D-S-V-**Q**-G (SEQ ID NO:69) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that **V**, or, both **N** and **Q**, or all three of **V**, **N**, and **Q** are unchanged);

a CDR3 comprising the sequence D-S-**R**-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-**N-P** (SEQ ID NO:70) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that **R** is unchanged); and

(b) a light chain variable region segment comprising:

a CDR1 comprising the sequence:

Q-S-**I**-T-**F**-**D**-Y-K-N-Y-L-A (SEQ ID NO:145) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that **I** or **D** is unchanged);

a CDR2 comprising the sequence W-**G**-S-**Y-L**-E-S (SEQ ID NO:72) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5amino acids therefrom, optionally provided that, at least 1, 2 or 3 of the highlighted residues are unchanged);

a CDR3 comprising the sequence Q-Q-**H**-Y-R-T-P-P-**S** (SEQ ID NO:73) (or a sequence that differs by no more than, 1, 2, 3, 4, or 5 amino acids therefrom, optionally provided that **S** is unchanged),

provided that:

a CDR of one or both the light or heavy chain includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR, (i.e., while other residues in that CDR might be changed, the highlighted residue or combination of residues, are unchanged).

2. The antibody molecule of claim 1, wherein:

a CDR of the light and a CDR of the heavy chain each includes one of the highlighted residues, or one of the highlighted combinations of residues, for that CDR.

3. The antibody molecule of claim 1, comprising:

(a) a heavy chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69);

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

(b) a light chain variable region segment comprising

a CDR1 comprising the sequence Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

4. The antibody molecule of claim 1, wherein, said antibody has one or more or all of the following properties:

(i) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 5 rounds of serial infections in cell culture with a mixture of the antibody and an influenza A virus; and

(ii) it produces fewer escape mutants than does a reference anti-HA antibody selected from Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, when tested by the method described in (i).

5. The antibody molecule of claim 1, wherein:

a) the heavy chain immunoglobulin variable region segment further comprises one or more or all of:

an FR1 comprising the sequence Q-V-Q-L-L-E-T-G-G-G-L-V-K-P-G-Q-S-L-K-L-S-C-A-A-S-G-F-T-F-T (SEQ ID NO:74);

an FR2 comprising the sequence W-V-R-Q-P-P-G-K-G-L-E-W-V-A (SEQ ID NO:75);

an FR3 comprising the sequence R-F-T-I-S-R-D-N-S-K-N-T-L-Y-L-Q-M-N-S-L-R-A-E-D-T-A-V-Y-Y-C-A-K (SEQ ID NO:76); and

an FR4 comprising the sequence W-G-Q-G-T-T-L-T-V-S-S (SEQ ID NO:77); and

b) the light chain immunoglobulin variable region segment comprises one or more or all of:

an FR1 comprising the sequence D-I-Q-M-T-Q-S-P-S-S-L-S-A-S-V-G-D-R-V-T-I-T-C-R-S-S (SEQ ID NO:78);

an FR2 comprising the sequence W-Y-Q-Q-K-P-G-K-A-P-K-L-L-I-Y (SEQ ID NO:79);

an FR3 comprising the sequence G-V-P-S-R-F-S-G-S-G-S-G-T-D-F-T-L-T-I-S-S-L-Q-P-E-D-F-A-T-Y-Y-C (SEQ ID NO:80); and

an FR4 comprising the sequence F-G-Q-G-T-K-V-E-I-K (SEQ ID NO:81).

6. The antibody molecule of claim 1, comprising:

a) a heavy chain immunoglobulin variable region segment comprising VH25 SEQ ID NO: 25; and

b) a light chain variable region segment comprising VL52 SEQ ID NO:52.

7. The antibody molecule of claim1 , wherein the antibody molecule has one or more or all of the following properties:

(a) it fails to produce any escape mutants as determined by the failure of a viral titer to recover following at least 5 rounds of serial infections in cell culture with a mixture of the antibody and an influenza A virus;

(b) it produces fewer escape mutants than does a reference anti-HA antibody selected from Ab 67-11, FI6, FI28, C179, F10, CR9114, or CR6261, when tested by the method described in (a);

(c) it binds with high affinity to a hemagglutinin (HA) of at least 1 influenza subtypes of Group 1 and at least 1 influenza subtypes of Group 2;

(d) it prevents infection by at least 1 influenza subtypes of Group 1, and by at least 1 influenza subtypes of Group 2;

(e) it inhibits fusogenic activity of the targeted HA;

(f) it treats or prevents infection by a Group 1 virus, wherein the virus is an H1, H5, or H9 virus; and treats or prevents infection by a Group 2 virus, wherein the virus is an H3 or H7 virus;

(g) it treats or prevents infection by influenza A strains H1N1 and H3N2; and

(j) it binds an epitope which includes or consists of the hemagglutinin trimer interface.

8. The antibody molecule of claim 1, wherein the antibody molecule is a single chain antibody (scFv), a $F(ab')_2$ fragment, a Fab fragment, or an Fd fragment.

9. The antibody molecule of claim 1, wherein the antibody molecule is an IgG1 antibody.

10. The antibody molecule of claim 1, comprising an epitope that has one, two, three, four, five, or all of, the following properties a-f:

a) it includes one, two, or all of, H3 HA1 residues N38, I278, and D291;

b) it includes H3 HA2 residue N12;

c) it does not include one, two or all of, H3 HA1 residues Q327, T328, and R329;

d) it does not include one, two, three, four, or all of, H3 HA2 residues G1, L2, F3, G4, and D46;

e) it includes one, two, or all of, H3 HA1 residues T318, R321, and V323; or

f) it includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or all of, H3 HA2 residues A7, E11, I18, D19, G20, W21, L38, K39, T41, Q42, A43, I45, I48, N49, L52, N53, I56,and E57.

11. The antibody molecule of claim 10, comprising properties: c; and d.

12. The antibody molecule of claim 10, which binds an epitope that does not include one or both of:

cc) one or both of H1 HA1 residues Q328 and S329; and

dd) one, two, three, four, or all of, H1 HA2 residues G1, L2, F3, G4, and D46;

13. The antibody molecule of claim 10, comprising properties: a or b; and c or d.

14. An antibody molecule that competes for binding with the antibody of claim 1, provided that, the antibody's epitope:

a) does not include one, two or all of, H3 HA1 residues Q327, T328, and R329; and

b) does not include one, two, three, four, or all of, H3 HA2 residues G1, L2, F3, G4, and D46.

15. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a heavy chain immunoglobulin variable region of claim 1.

16. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a light chain immunoglobulin variable region of claim 1.

17. A recombinant vector comprising one or both of the nucleic acid molecule of claim 15 and the nucleic acid molecule of claim 16.

18. A cell comprising the vector of claim 17.

19. A method of making the antibody molecule of claim 1, comprising providing a host cell of claim 16 and expressing the nucleic acids in the host cell, thereby making the antibody molecule.

20. A method of preventing or treating an infection with an influenza virus in a human subject comprising administering an antibody molecule of claim 1.

21. The method of claim 20, wherein the human subject is at high risk of exposure to influenza virus.

22. The method of claim 20, wherein the human subject is immunocompromised, 65 years or older, 6 months to 18 years old, or has a chronic medical condition.

23. The method of claim 20, further comprising administering a second agent.

24. The method of claim 23, wherein the second agent is a vaccine.

25. The method of claim 23, wherein the second agent is an anti-viral agent,

26. The method of claim 23, wherein the second agent is a neuraminidase inhibitor or nucleoside analog.

27. The method of claim 23, wherein the second agent is selected from zidovudine, gangcyclovir, vidarabine, idoxuridine, trifluridine, foscarnet, acyclovir, ribavirin, amantadine, remantidine, saquinavir, indinavir, ritonavir, alpha-interferons

and other interferons, zanamivir (Relenza®), oseltamivir (Tamiflu®), laninamivir, peramivir, and rimantadine.

28. The method of claim 23, wherein the second agent is an anti-HA antibody

29. The method of claim 28, wherein the antibody is selected from Ab 67-11, FI6, FI28, C179, F10, CR9114 or CR6261.

30. The method of claim 28, wherein the antibody is selected from Ab 069, Ab 032, and Ab 031.

31. The method of claim 20, wherein the influenza is influenza A.

32. The method of claims 31, wherein the influenza A virus is an H1, H5, H9, H3 or H7 strain.

33. A method of inducing immunity to one or more influenza strains in a human subject comprising:

administering to the human subject, a broad range vaccine.

34. The method of claim 33, wherein said method comprises preventing, delaying or reducing infection with an influenza strain, or symptom thereof,

35. The method of claim 33, wherein the broad range vaccine induces an immune response against two influenza strains.

36. The method of claim 33, wherein the broad range vaccine induces an immune response against two Group 1 influenza strains.

37. The method of claim 33, wherein the broad range vaccine induces an immune response against a Group 1 strain, and a second strain from Group 1, Group2

or an influenza B strain.

38. The method of claim 33, wherein the broad range vaccine is administered in combination with a second agent.

39. The method of claim 38, wherein the second agent is an anti-viral agent,

40. The method of claim 38, wherein the second agent is a neuraminidase inhibitor or nucleoside analog.

41. The method of claim 38, wherein the second agent is an anti-HA antibody

42. A method of detecting an influenza virus in a biological sample, comprising contacting the sample with an antibody molecule of claim 1, and detecting the binding of the antibody molecule to the sample, thereby detecting the influenza virus in the sample.

43. A method comprising:

(a) providing a sample from a patient,

(b) contacting the sample with an antibody molecule of claim 1, and

(c) determining whether the antibody molecule of claim 1 binds a polypeptide in the sample, wherein

if the antibody molecule binds a polypeptide in the sample, then the patient is determined to be infected with influenza.

44. The method of claim 43, wherein the patient is determined to be infected with influenza A or B, and the patient is further administered an antibody molecule of claim 1.

45. A pharmaceutical composition comprising an antibody molecule of claim 1 and a pharmaceutically acceptable carrier.

46. A broad range vaccine.

47. A isolated broad range immunogen.

48. A kit comprising one or more of: a container having disposed therein an antibody molecule of claim 1; a pharmaceutically acceptable delivery vehicle or buffer; and a delivery device, optinally having the antibody molecule of claim 1 disposed therein.

49. A kit comprising one or more of: one or more containers having disposed therein a broad range vaccine; a container having adjuvant disposed therein; and a delivery device, optinally having a broad range vaccine disposed therein.

We Claim:

1. An isolated antibody molecule comprising:

(a) a heavy chain immunoglobulin variable region segment comprising:

a CDR1 comprising the sequence S-Y-A-M-H (SEQ ID NO:68);

a CDR2 comprising the sequence V-V-S-Y-D-G-N-Y-K-Y-Y-A-D-S-V-Q-G (SEQ ID NO:69); and

a CDR3 comprising the sequence D-S-R-L-R-S-L-L-Y-F-E-W-L-S-Q-G-Y-F-N-P (SEQ ID NO:70); and

(b) a light chain immunoglobulin variable region segment comprising

a CDR1 comprising the sequence Q-S-I-T-F-D-Y-K-N-Y-L-A (SEQ ID NO:145);

a CDR2 comprising the sequence W-G-S-Y-L-E-S (SEQ ID NO:72); and

a CDR3 comprising the sequence Q-Q-H-Y-R-T-P-P-S (SEQ ID NO:73).

2. The isolated antibody molecule of claim 1, comprising a heavy chain immunoglobulin variable region segment that comprises SEQ ID NO: 25.

3. The isolated antibody molecule of claim 1 or 2, comprising a light chain immunoglobulin variable region segment that comprises SEQ ID NO: 52.

4. The isolated antibody molecule of any of claims 1-3, comprising a heavy chain immunoglobulin variable region segment that comprises SEQ ID NO: 25 and a light chain immunoglobulin variable region segment that comprises SEQ ID NO: 52.

5. The isolated antibody molecule of any of claims 1-4, comprising a tetramer of two heavy chain immunoglobulin variable region segments, each comprising SEQ ID NO: 25 and two light chain immunoglobulin variable region segments, each comprising SEQ ID NO: 52.

6. The isolated antibody molecule of any of claims 1-5, wherein said antibody molecule comprises a full length antibody.

7. The isolated antibody molecule of any of claims 1-6, wherein said antibody molecule comprises a humanized antibody molecule.

8. The isolated antibody molecule of any of claims 1-7, wherein said antibody molecule comprises two heavy chain immunoglobulin variable regions and two light chain immunoglobulin variable regions.

9. The isolated antibody molecule of any of claims 1-8, wherein said antibody molecule is an IgG antibody.

10. The isolated antibody molecule of any of claims 1-4, wherein said antibody molecule is a single chain antibody (scFv), a $F(ab')_2$ fragment, a Fab fragment, or an Fd fragment.

11. Use of the antibody molecule of any of claims 1-10 for the manufacture of a medicament for preventing or treating an influenza virus infection in a human subject.

12. The use of claim 11, wherein the human subject is at high risk of exposure to influenza virus.

13. The use of claim 11 or 12, wherein the human subject is immunocompromised, 65 years or older, 6 months to 18 years old, or has a chronic medical condition.

14. The use of any of claims 11-13, wherein the subject has or is at risk of having a secondary bacterial infection.

15. The use of any of claims 11-14, for use in combination with a second agent.

16. The use of claim 15, wherein the second agent is selected from the group consisting of a vaccine, an anti-viral agent, a pain reliever, an anti-inflammatory agent, an

antibiotic, a steroidal agent, a second antibody molecule, an adjuvant, a protease, a glycosidase, and a neuraminidase inhibitor.

17. The use of claim 15, wherein the second agent is selected from the group consisting of acyclovir, ribavirin, amantadine, rimantadine, zanamivir, oseltamivir, laninamivir, and peramivir.

18. The use of any of claims 11-17, wherein the influenza virus is an influenza A virus.

19. The use of claim 18, wherein the influenza A virus is a Group 1 strain.

20. The use of claim 18, wherein the influenza A virus is a Group 2 strain.

21. The use of claim 18, wherein the influenza A virus is selected from the group consisting of H1, H3, H5, H7, and H9 strains.

22. The use of claim 18 or 21, wherein the influenza A virus is an H1N1, H3N2, or H5N1 strain.

23. The use of any of claims 11-22, wherein the antibody molecule is administered at a dose of between 1 mg/kg and 50 mg/kg.

24. The use of any of claims 11-23, wherein the antibody molecule is administered at a dose of between 25 mg/kg and 50 mg/kg.

25. The use of any of claims 11-24, wherein the antibody molecule is administered prior to known exposure to the influenza virus infection.

26. The use of any of claims 11-24, wherein the antibody molecule is administered prior to manifestation of an effect or a symptom of the influenza virus infection.

27. The use of any of claims 11-24, wherein the antibody molecule is administered after known exposure to the influenza virus infection.

28. The use of any of claims 11-24, wherein the antibody molecule is administered after manifestation of an effect or a symptom of the influenza virus infection.

29. The use of any of claims 11-28, wherein the human subject is tested for the influenza virus.

30. The use of any of claims 11-29 for the manufacture of a medicament for preventing the influenza virus infection in the human subject.

31. The use of any of claims 11-29 for the manufacture of a medicament for treating the influenza virus infection in the human subject.

32. A pharmaceutical composition comprising the antibody molecule of any of claims 1-10 and a pharmaceutically acceptable carrier.

33. A kit comprising the antibody molecule of any of claims 1-10; and a pharmaceutically acceptable delivery vehicle or buffer, a delivery device, or both.