For these reasons, there is a need for additional influenza A virus antibodies and therapies against influenza A virus infection.

It is an object of the ~~present invention~~embodiments disclosed herein to provide additional antibodies specific for multiple influenza A virus subtypes, or functional equivalents of such antibodies and compositions comprising such antibodies. Preferably antibodies are provided that have a high influenza virus neutralizing activity. Furthermore, preferably antibodies are provided which are capable of neutralizing at least two influenza virus subtypes.

The present ~~invention~~disclosure provides such antibodies specific for multiple influenza A virus subtypes. As demonstrated in the Examples, antibodies are provided that are capable of binding at least two influenza A virus subtypes, preferably both group 1 and group 2 influenza A virus subtypes. Furthermore, antibodies are provided that have a high influenza A virus neutralizing capacity.

The ~~invention~~disclosure provides in one ~~embodiment~~ aspect an isolated, synthetic or recombinant antibody or functional part thereof or immunoglobulin chain or functional equivalent thereof, having an *in vitro* H3N2 influenza A virus neutralizing activity with an IC50 value of less than 1 μg/ml, preferably of less than 0.7 μg/ml, more preferably of equal to or less than 0.3 μg/ml, more preferably of less than 0.2 μg/ml, which antibody or functional part or immunoglobulin chain or functional equivalent is capable of specifically binding at least one other influenza A virus subtype. Said H3N2 influenza A virus preferably comprises a H3N2 A/Ned/177/2008, H3N2 HKX-31 or H3N2 A/swine/Neth/St.Oedenrode/96 strain, most preferably a H3N2 A/Ned/177/2008 strain.

H3N2 influenza virus is one of the influenza viruses capable of infecting humans. H3N2 can be transferred from human to other humans. Antibodies capable of neutralizing H3N2 influenza virus are therefore particularly important for application in humans.

In another preferred embodiment the ~~invention~~disclosure provides an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin

chain or functional equivalent thereof, having an *in vitro* H7N1 influenza A virus neutralizing activity with an IC50 value of less than 5.0 μg/ml, preferably of less than 4.0 μg/ml, more preferably of less than 1.0 μg/ml, more preferably equal to or less than about 0.6 μg/ml. Said H7N1 influenza A virus preferably comprises a H7N1 A/ck/Italy/1067/99 strain. In a particularly preferred embodiment said antibody or functional part or immunoglobulin chain or functional equivalent is also capable of specifically binding at least one other influenza A virus subtype, so that protection against multiple strains can be obtained. Although to date, no cases have been reported of transmission of H7N1 from birds to humans, mutations may occur making this virus infectious for humans.

In another preferred embodiment the ~~invention~~disclosure provides an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, having an *in vitro* H7N7 influenza A virus neutralizing activity with an IC50 value of less than 0.5 μg/ml, preferably equal to or less than about 0.4 μg/ml, more preferably equal to or less than about 0.2 μg/ml, most preferably equal to or less than about 0.1 μg/ml. Said H7N7 influenza A virus preferably comprises a H7N7 A/ck/Neth/621557/03 strain. In a particularly preferred embodiment said antibody or functional part or immunoglobulin chain or functional equivalent is also capable of specifically binding at least one other influenza A virus subtype, so that protection against multiple strains can be obtained. H7N7 influenza virus is one of the influenza viruses capable of infecting humans following bird to human transmission. Antibodies capable of neutralizing H7N7 influenza virus are therefore particularly important for application in humans.

In another preferred embodiment the ~~invention~~disclosure provides an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, having an *in vitro* H1N1 influenza A virus neutralizing activity with an IC50 value of less than 5.0 μg/ml, preferably of less than 4.0 μg/ml, more preferably of less than 3.0 μg/ml, more preferably equal to or less than about 2.7 μg/ml. Said H1N1 influenza A virus preferably comprises a H1N1 A/Neth/602/2009 strain or, most preferably, a H1N1 A/Hawaii/31/2007 strain. In a particularly preferred embodiment said antibody or functional part or

immunoglobulin chain or functional equivalent is also capable of specifically binding at least one other influenza A virus subtype, so that protection against multiple strains can be obtained. H1N1 influenza virus is one of the influenza viruses capable of infecting humans following human to human transmission. Antibodies capable of neutralizing H1N1 influenza virus are therefore particularly important for application in humans.

In another preferred embodiment the ~~invention~~disclosure provides an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, having an *in vitro* H5N1 influenza A virus neutralizing activity with an IC50 value of less than 5.0 μg/ml, preferably of less than 4.0 μg/ml, more preferably of less than 3.0 μg/ml, more preferably of less than 2.0 μg/ml, more preferably equal to or less than about 1.3 μg/ml. Said H5N1 influenza A virus preferably comprises a H5N1 A/turkey/Turkey/05 strain. In a particularly preferred embodiment said antibody or functional part or immunoglobulin chain or functional equivalent is also capable of specifically binding at least one other influenza A virus subtype, so that protection against multiple strains can be obtained. H5N1 influenza virus is one of the influenza viruses capable of infecting humans following human to human transmission. Antibodies capable of neutralizing H5N1 influenza virus are therefore particularly important for application in humans.

The disclosure provides in another aspect an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, comprising:
- a heavy chain CDR1 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's:1-5, and/or
- a heavy chain CDR2 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's:6-10, and/or
- a heavy chain CDR3 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's:11-15, and/or
- a light chain CDR1 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's:16-20, and/or
- a light chain CDR2 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's:21-25, and/or

- a light chain CDR3 sequence comprising a sequence which is at least 70% identical to a sequence selected from the group consisting of SEQ ID NO's:26-30.

The disclosure provides in another aspect an isolated, synthetic or recombinant nucleic acid molecule with a length of at least 15 nucleotides, or a functional equivalent thereof, encoding at least one CDR sequence of an antibody or functional part thereof or immunoglobulin chain or functional equivalent as defined herein.

The disclosure provides in another aspect a vector comprising a nucleic acid molecule or functional equivalent as defined herein.

The disclosure provides in another aspect an isolated or recombinant cell comprising a nucleic acid molecule or functional equivalent as defined herein, and/or a vector as defined herein.

The disclosure provides in another aspect a pharmaceutical composition comprising an antibody or functional part or immunoglobulin chain or functional equivalent or a nucleic acid molecule or functional equivalent or a vector as defined herein and a pharmaceutical acceptable carrier, diluent and/or excipient.

The disclosure provides in another aspect an antibody or functional part or immunoglobulin chain or functional equivalent or a nucleic acid molecule or functional equivalent thereof or a vector as defined herein, for use as a medicament and/or prophylactic agent.

The disclosure provides in another aspect an antibody or functional part or immunoglobulin chain or functional equivalent, or a nucleic acid molecule or functional equivalent, or a vector as defined herein, for use as a medicament and/or prophylactic agent for at least in part treating and/or preventing an influenza A virus infection.

The disclosure provides in another aspect a method for producing an antibody or functional part or immunoglobulin chain or functional equivalent as defined herein, comprising providing a cell with a nucleic acid molecule or functional equivalent or a vector as defined herein, and allowing said cell to translate said nucleic acid molecule or functional equivalent or vector, thereby producing said antibody or functional part or immunoglobulin chain or functional equivalent as defined herein, preferably further comprising harvesting, purifying and/or isolating said antibody or functional part or immunoglobulin chain or functional equivalent.

The disclosure provides in another aspect an antibody or functional part or immunoglobulin chain or functional equivalent as defined herein for use in diagnosis of an influenza A virus infection.

The disclosure provides in another aspect a method for determining whether an influenza A virus is present in a sample comprising:
- contacting said sample with an antibody or functional part or immunoglobulin chain or functional equivalent as defined herein,
- allowing said antibody or functional part or immunoglobulin chain or functional equivalent to bind said influenza A virus, if present, and
- determining whether influenza A virus is bound to said antibody or functional part or immunoglobulin chain or functional equivalent, thereby determining whether an influenza A virus is present in said sample.

The disclosure provides in another aspect an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, having an *in vitro* H7N1 influenza A virus neutralizing activity with an IC50 value of less than 5.0 μg/ml, preferably of less than 4.0 μg/ml, more preferably of less than 1.0 μg/ml, more preferably equal to or less than about 0.6 μg/ml.

The disclosure provides in another aspect an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, having an *in vitro* H7N7 influenza A virus neutralizing activity with an IC50 value of less than 0.5 μg/ml, preferably equal to or less than about 0.4 μg/ml, more preferably equal to or less than about 0.2 μg/ml, most preferably equal to or less than about 0.1 μg/ml.

The disclosure provides in another aspect an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, having an *in vitro* H1N1 influenza A virus neutralizing activity with an IC50 value of less than 5.0 μg/ml, preferably of less than 4.0 μg/ml, more preferably of less than 3.0 μg/ml, more preferably equal to or less than about 2.7 μg/ml.

The disclosure provides in another aspect an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, having an *in vitro* H5N1 influenza A virus neutralizing activity with an IC50 value of less than 5.0 μg/ml, preferably of less than 4.0 μg/ml, more preferably of less than 3.0 μg/ml, more preferably of less than 2.0 μg/ml, more preferably equal to or less than about 1.3 μg/ml.

The disclosure provides in another aspect an antibody or functional part or immunoglobulin chain or functional equivalent according to any one of claims 17-20, which is capable of specifically binding at least one other influenza A virus subtype.

The disclosure provides in another aspect a synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent thereof, comprising:

i) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_003 and AT10_004 and AT10_005; and

ii) at least two different heavy chain CDR sequences and at least two different light chain CDR sequences of an antibody selected from the group consisting of AT10_001 and AT10_002 and AT10_003 and AT10_004 and AT10_005,

wherein said antibody selected in i) is different from said antibody selected in ii).

The disclosure provides in another aspect an isolated or recombinant cell or a pharmaceutical composition comprising a multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein.

The disclosure provides in another aspect a synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein for use as a medicament and/or prophylactic agent.

The disclosure provides in another aspect a synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein for use as a medicament and/or prophylactic agent for at least in part treating and/or preventing and/or alleviating the symptoms of an influenza A infection.

The disclosure provides in another aspect a synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein for use in diagnosis of an influenza A infection.

The disclosure provides in another aspect use of a multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein and/or a cell or pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment and/or prevention of an influenza A virus infection.

The disclosure provides in another aspect use of multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein in the manufacture of a medicament for the neutralization of a H1N1 influenza A virus and/or an H3N2 influenza A virus, wherein said H1N1 influenza A virus and/or said H3N2 influenza A virus is to be contacted with a multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein, resulting in neutralization of said virus.

The disclosure provides in another aspect a method for determining whether an influenza A virus is present in a sample comprising:

- contacting said sample with a multimeric antibody, multimeric immunoglobulin or functional equivalent as defined herein,
- allowing said multimeric antibody, multimeric immunoglobulin or functional equivalent to bind said influenza A virus, if present, and
- determining whether influenza A virus is bound to said multimeric antibody, multimeric immunoglobulin or functional equivalent, thereby determining whether an influenza A virus is present in said sample.

The disclosure provides in another aspect an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, capable of interacting with amino acids at positions A38, A40, A41, A42, A291, A292, A293, A318, B18, B19, B20, B21, B38, B41, B42, B45, B46, B48, B49, B52, B53, and B56 of influenza A virus group 1 hemagglutinin (H1/H5).

The disclosure provides in another aspect an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, capable of interacting with amino acids at positions A21, A324, A325, A327, B12, B14, B15, B16, B17, B18, B19, B25, B26, B30, B31, B32, B33, B34, B35, B36, B38, B146, B150, B153, and B154 of influenza A virus group 2 hemagglutinin (H3/H7).

The disclosure provides in another aspect an isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, capable of interacting with amino acids at positions A38, A48, A275, A276, A277, A278, A289, A291, A318, B19, B20, B21, B36, B38, B39, B41, B42, B45, B46, B48, B49, B50, B52, B53, B56, B57, B58, B150 of influenza A virus group 2 hemagglutinin (H3/H7).

A "functional part of an antibody" is defined herein as a part that has at least one shared property as said antibody in kind, not necessarily in amount. Said functional part is capable of binding the same antigen as said antibody, albeit not necessarily to the same extent. A functional part of an antibody preferably comprises a single domain antibody, a single chain antibody, a nanobody, an unibody, a single chain variable fragment (scFv), a Fab fragment or a $F(ab')_2$ fragment.

A functional part of an antibody is also produced by altering an antibody such that at least one property - preferably an antigen-binding property - of the resulting compound is essentially the same in kind, not necessarily in amount. This is done in many ways, for instance through conservative amino acid substitution, whereby an amino acid residue is substituted by another residue with generally

31. A synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 22-28 for use as a medicament and/or prophylactic agent for at least in part treating and/or preventing and/or alleviating the symptoms of an influenza A infection.

32. A synthetic or recombinant multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 22-28 for use in diagnosis of an influenza A infection.

33. Use of a multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 22-28 and/or a cell or pharmaceutical composition according to claim 29 in the manufacture of a medicament for the treatment and/or prevention of ~~A method for at least in part treating and/or preventing~~ an influenza A virus infection~~, comprising administering to an individual in need thereof a therapeutically effective amount of a multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 22-28 and/or a cell or pharmaceutical composition according to claim 29~~.

34. Use of a multimeric immunoglobulin or functional equivalent according to any one of claims 22-28 in the manufacture of a medicament for the neutralization of ~~A method for neutralizing~~ a H1N1 influenza A virus and/or an H3N2 influenza A virus, wherein ~~comprising contacting~~ said H1N1 influenza A virus and/or said H3N2 influenza A virus is to be contacted with a multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 22-28, resulting in neutralization of said virus.

35. A method for determining whether an influenza A virus is present in a sample comprising:
- contacting said sample with a multimeric antibody, multimeric immunoglobulin or functional equivalent according to any one of claims 22-28,
- allowing said multimeric antibody, multimeric immunoglobulin or functional equivalent to bind said influenza A virus, if present, and
- determining whether influenza A virus is bound to said multimeric antibody, multimeric immunoglobulin or functional equivalent, thereby determining whether an influenza A virus is present in said sample.

36. An isolated, synthetic or recombinant antibody or functional part thereof, or immunoglobulin chain or functional equivalent thereof, capable of interacting with