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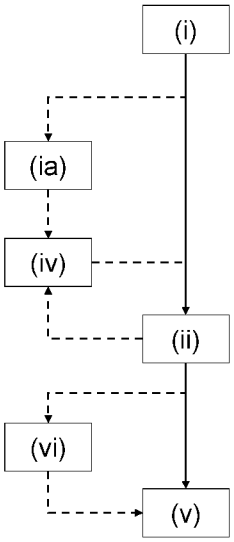

Fig. 4

(57) Abstract: Disclosed herein is a method of assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, comprising: measuring the concentration of Interferon-inducible T-cell Alpha Chemoattractant (ITAC) and the concentration of Macrophage Inflammatory Protein 3 Beta (MIP3B) in a biological sample obtained from the subject; and analysing the concentration of ITAC and the concentration of MIP3B in conjunction with each other, to assess whether the subject is at risk of developing severe symptoms of disease and/or becoming contagious. Also disclosed are related products and methods.

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Methods of assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus

Field of the Disclosure

The present disclosure relates to methods for assessing whether one or more subjects are at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus; especially influenza. The disclosure includes methods of conducting clinical trials or field studies, but more generally, the methods of the disclosure may be used in any healthcare or non-healthcare setting for assessing the risk of an individual patient. For example, the methods of the disclosure may be used to triage patients infected with a respiratory virus to identify those who are at risk of developing severe symptoms of disease and/or becoming contagious and may therefore require early medical intervention. Subjects may have been administered a medicinal product for treatment or prevention of respiratory viral disease, and the methods of the disclosure may therefore be used as a companion analytical product to predict the likely efficacy of the medicinal product. The present disclosure also comprehends related methods, including computer-implemented methods, networks and prognostic kits.

Background of the Disclosure

Acute upper and lower respiratory infections are a major public health problem and a leading cause of morbidity and mortality worldwide. Viruses are the predominant cause of respiratory tract illnesses and include RNA viruses such, for example, as respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, metapneumovirus, rhinovirus (HRV) and coronavirus (Hodinka, *Microbiol. Spectr.*, 2016, 4(4)).

The Centre for Disease Control and Prevention (CDC) estimates that in the 2015-2016 period in the US there were 25 million influenza illnesses, 11 million influenza-associated medical visits, 310,000 influenza-related hospitalisations, and 12,000 pneumonia and influenza deaths (Rolfes *et al.*, *'Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United States'*, CDC, 2016). In 2003, the annual economic burden of influenza in the US alone was estimated to be around 87 billion dollars (Molinari *et al., Vaccine*, 2007, 25(27), 5086–5096). The costs of influenza are clearly substantial and any method to treat or diagnose influenza would be of enormous value.

Influenza infects all age groups and causes a range of outcomes from asymptomatic infection and mild respiratory disease to severe respiratory disease and even death. As such, different subjects exposed to the same influenza virus, which may be a seasonal strain, not necessarily a highly pathogenic strain, may be asymptomatic, mildly symptomatic, subclinical, exhibit acute symptoms,

or require medical attention, or even urgent hospitalisation (Cox *et al., Lancet*, 1999, 354(9186), 1277-1282). Further, the proportion of infections that are asymptomatic or subclinical, and the degree to which these are contagious, as well as the proportion of shedding which occurs prior to onset of symptoms, affect the potential impact of control measures and decisions regarding treatment and the administration of medicinal products (Lau *et al., J Infect Dis.*, 2010, 201(10):1509-16).

There are various reasons why it may be advantageous to assess in advance whether a subject is at risk of developing severe disease (such as symptoms or signs requiring hospitalisation) and/or becoming contagious, after exposure (or possible exposure) to a respiratory virus (such, for example, as influenza).

By way of example, this may enable informed treatment decisions, leading a physician to administer suitable care. In some circumstances, a proportion of the population may have mild (even asymptomatic) infections, especially in response to seasonal strains of virus such as influenza. Treating everyone having an infection, including those subjects assessed not to be at risk of developing severe symptoms of disease and/or becoming contagious, may mean exposing subjects unnecessarily to drugs with side effects. This may be especially undesirable for subject groups that are more susceptible to side effects, such, for example, as may be the case amongst patients who are resident in hospital (particularly patients who may be resident in the hospital for reasons other than viral infection) and/or infants (i.e. younger than one year old); children (i.e. younger than ten years old); elderly subjects (i.e. 65 years old or more); and pregnant women.

By way of a further example, it may help to improve the trial design for investigative medicaments. Current trial designs within human challenge models for assessing investigative treatment drugs and medicinal products for influenza, RSV, coronaviruses, or HRV rely on either:

a. "*Universal dosing*" - universally treating all subjects inoculated with virus on a given day post inoculation (e.g. 24 hrs or 48 hrs post inoculation) irrespective of whether the subjects become infected or not;

b. "*Triggered dosing*" - treating only those subjects having either one or both of the following:

   i. their first (or confirmed) PCR positive respiratory sample (i.e. treating only those who are expected to be infected post-inoculation); and

   ii. initial respiratory symptoms that are indicative of onset of viral infection; or

c. "*Triggered dosing + universal dosing*" (de Vincenzo *et al., N. Engl. J. Med.*, 2014, 371(8):711-22; de Vincenzo *et al., N. Engl. J. Med.*, 2015, 373(21):2048-58) - this uses the principles of triggered dosing for the primary endpoint. However, at a certain day post-inoculation (e.g. Day 5) subjects who still do not have a positive viral sample (or symptoms) are subsequently given the drug regardless.

Subjects who are universally given the drug in this scenario may be included for analysis in two sub-analysis approaches:

i. On their own as a sub-group;

ii. Combined with the triggered sub-group.

In research models such as human challenge models, knowing which subjects will develop significant symptoms in advance would allow dosing of an investigational medicinal product to be triggered only in subjects who would otherwise go on to develop severe symptoms of disease and/or become contagious. A method capable of assessing who is at risk of developing severe symptoms of disease and/or become contagious would allow the identification and selection of subjects for administration of the medicinal product. Benefits of this volunteer selection method for dosing may include:

- An improved ability to detect a clinically relevant reduction in disease, by only evaluating the effects of a medicinal product (or products) in subjects who would have gone on to present with severe symptoms of disease and/or become contagious. This contrasts with trial designs where triggering of treatment might be based on the presence of symptoms, or universal administration of the medicinal product (or products) to all inoculated people. Selecting appropriate subjects for a trial in advance may avoid problems associated with assessing the efficacy of the medicinal product (or products) in populations where the ability to detect a difference is more difficult (i.e. uninfected, asymptomatic infected or people who only have a mild infection with minimal viral loads).
- Fewer people will be exposed to the medicinal product (or products) unnecessarily, thereby:
  i. reducing medicinal product requirements, leading to manufacturing and cost benefits;
  ii. providing a treatment regime with an improved benefit/risk profile by selecting to provide treatment only to subjects who are assessed to be at risk of developing severe symptoms and/or become contagious;
  iii. providing an improved benefit/risk profile for both the medicinal product and the study, by requiring fewer people to be exposed to an investigational medicinal product.

Woods *et al.*, '*A Host Transcriptional Signature for Presymptomatic Detection of Infection in Humans Exposed to Influenza H1N1 or H3N2*' (*PLOS ONE*, 2013, 8(1): e52198) describes the generation of a viral gene signature (or factor) for symptomatic influenza that is reported to be capable of detecting 94% of infected cases. The authors report that the gene signature is detectable as early as 29 hours post-exposure and achieves maximal accuracy on average 43 hours ($p = 0.003$, H1N1) and 38 hours (p-value equals 0.005, H3N2) before peak clinical symptoms.

Muller *et al.*, *'Development of an objective gene expression panel as an alternative to self-reported symptom scores in human influenza challenge trials'* (*J. Transl. Med.* (2017) 15:134) discloses methods for detecting and differentiating between different levels of symptoms of disease in an influenza challenge trial, using a panel of biomarkers to provide a more accurate assessment of symptoms than may be attained by means of (subjective) self-reported symptom scores.

However, there remains a need for methods of assessing as early as possible whether a subject is at risk of developing severe disease (such as symptoms or signs requiring hospitalisation; and/or symptoms or signs comprising, by way of example, one or more of: tachypnoea, hypoxemia, an arterial oxygen saturation of $\leq$ 92% on room air by a transcutaneous method and radiological pulmonary infiltrates) and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, to enable informed treatment decisions, to administer the correct level of care, and/or to improve the trial design for investigative medicaments.

Summary of the Disclosure

In a first aspect of the present disclosure, therefore, there is provided a method of assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, comprising:

(a) measuring the concentration of Interferon-inducible T-cell Alpha Chemoattractant (ITAC) and the concentration of Macrophage Inflammatory Protein 3 Beta (MIP3B) in a biological sample obtained from the subject; and

(b) analysing the concentration of ITAC and the concentration of MIP3B to assess whether the subject is at risk of developing severe symptoms of disease and/or becoming contagious.

Interferon-inducible T-cell Alpha Chemoattractant (ITAC) is a protein also known in the art as C-X-C motif chemokine 11 (CXCL11), being encoded by the CXCL11 gene. Other aliases include H174, IP-9, IP9, SCYB11, SCYB9B, and b-R1. ITAC is a small cytokine belonging to the CXC chemokine family.

The concentration of ITAC circulating in the bloodstream may be elevated, for example, in SARS-COV-2 infection. Without wishing to be bound by theory, it is thought that this may be induced by JAK/STAT and TLR3 via the AKT signalling pathway. Similarly, the concentration of ITAC circulating in the bloodstream may be elevated in Dengue virus infection.

Meanwhile, Macrophage Inflammatory Protein 3 Beta (MIP3B) is a protein also known in the art as EBI1 ligand chemokine (ELC) or Chemokine C-C motif ligand 19 (CCL19), being encoded by the CCL19 gene. It is a small cytokine belonging to the CC chemokine family. MIP3B regulates the induction of T cell activation, immune tolerance, and inflammatory responses during continuous

immune surveillance, homeostasis, and development. The expression of MIP3B is induced in epithelial cells in response to virus (such, for example, as influenza) to assist with immune cell recruitment.

By "measuring the concentration of ITAC" and "measuring the concentration of MIP3B" herein may be meant measuring those respective concentrations by immunoassays in the biological sample. Suitably, the concentration of ITAC may be measured by immunoassay of the biological sample using one or more antibodies specific for ITAC. The concentration of MIP3B may likewise be measured by immunoassay of the biological sample using one or more antibodies specific for MIP3B.

A wide range of suitable immunoassay techniques are available to those skilled in the art, including competitive, non-competitive, homogeneous, heterogeneous, one site and two site assays. In some embodiments, antibodies specific for ITAC or MIP3B, or competing amounts of ITAC or MIP3B respectively, may be labelled in a manner well known to those skilled in the art to enable quantification of the respective concentrations of the analytes. Suitable labels include enzymes, isotopes, DNA probes, fluorogenic reporters and electrochemiluminescent tags. Alternatively, a labeless immunoassay may be used, e.g. surface plasmon resonance (SPR) immunoassay.

Thus, in a second aspect, the present disclosure provides a method of measuring the concentration of ITAC and the concentration of MIP3B in a subject who is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, comprising:

a) obtaining a biological sample from the subject;
b) measuring the concentration of ITAC in the biological sample by immunoassay of the biological sample using one or more antibodies specific for ITAC; and
c) measuring the concentration of MIP3B by immunoassay of the biological sample using one or more antibodies specific for MIP3B.

The subject may be assessed to be at risk of developing severe symptoms of disease and/or becoming contagious based on the concentration of ITAC and the concentration of MIP3B in combination, in accordance with the present disclosure.

In some embodiments, the concentration of ITAC and/or MIP3B in the biological sample may be measured by using an enzyme-linked immunosorbent assay (ELISA) or by a single- or multi-plex bead array assay.

A presently preferred immunoassay is a multiplex bead-based assay characterised as follows: Human Multi-Analyte Profile; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions). Additional details of said assay are provided in *An Overview of*

Assay Quality Systems at Myriad RBM™, QC White Paper, B.T. Welsh and L. Mapes, April 2019, the contents of which are incorporated herein in their entirety.

Those skilled in the art will be familiar with methods for measuring the concentration, or a proxy for the concentration, of a protein in a biological sample. It will be appreciated that values of protein concentration, or values of a proxy for protein concentration, such as fluorescence intensity measured using an immunoassay, are typically expressed in arbitrary units, which may optionally be denoted as "a.u.".

In some embodiments, the biological sample may have been obtained from the subject at least about 30 to about 90 hours after exposure, or possible exposure, to the respiratory virus; preferably about 40 to about 50 hours after exposure, or possible exposure; for example about 45 hours after exposure, or possible exposure, to the respiratory virus. As disclosed herein, it has been found that upregulation of ITAC and MIP3B may begin about 30 hours (for example, about 40 hours, such as about 45 hours) after (deliberate) inoculation with a respiratory virus, and may last for a period of up to several days thereafter, in a person at risk of developing severe symptoms of disease and/or becoming contagious. Accordingly in some embodiments, the biological sample may be obtained about 1 to about 7 days after exposure, or possible exposure, to the respiratory virus, for example about 1 to about 5 days after exposure, or possible exposure, to the respiratory virus. Suitably, in some embodiments, the biological sample may be obtained about 30, 40 or 45 hours or more after exposure, or possible exposure.

In some embodiments, step (b) may include dividing the concentration of ITAC measured in step (a) by a baseline concentration of ITAC to obtain a value for the fold change in the concentration of ITAC; and dividing the concentration of MIP3B measured in step (a) by a baseline concentration of MIP3B to obtain a value for the fold change in the concentration of MIP3B.

By "baseline level" herein is meant a concentration of a protein (ITAC or MIP3B as the case may be) in a biological sample obtained from the subject prior to exposure, or possible exposure, of the subject to the respiratory virus, or a concentration of a protein (ITAC or MIP3B) in a biological sample obtained from one or more uninfected control subjects.

In some embodiments, the analysing step (b) may comprise comparing the measured fold change in the concentration of ITAC with a reference threshold fold change in the concentration of ITAC and comparing the fold change in the concentration of MIP3B with a reference threshold fold change in the concentration of MIP3. When the fold change in the measured concentration of ITAC is above the reference threshold fold change in the concentration of ITAC and the measured fold change in the concentration of MIP3B is above the reference threshold fold change in the

concentration of MIP3B, the subject may be assessed in accordance with the present disclosure to be at risk of developing severe symptoms of disease and/or becoming contagious.

In some embodiments, the reference threshold fold change in the concentration of ITAC and the reference threshold fold change in the concentration of MIP3B may be determined by: measuring the baseline concentration of ITAC and the baseline concentration of MIP3B in biological samples obtained from a group of persons uninfected with the respiratory virus; measuring the concentration of ITAC and the concentration of MIP3B in biological samples obtained from the group of persons after inoculation with the respiratory virus; ascertaining the fold change in the concentration of ITAC and the fold change in the concentration of MIP3B for each person from uninfected to after inoculation; classifying members of the group, after inoculation, according to their risk of developing severe symptoms of disease and/or becoming contagious; and setting the reference threshold fold changes for ITAC and MIP3B, respectively, to be a fold change in the concentration of ITAC and a fold change in the concentration of MIP3B which discriminate between persons at risk and persons not at risk, according to a desired measure of test performance. As used herein (and as normally used in the art) "test performance" may mean the ability of a method to discriminate between subjects having a relevant characteristic (herein, being at risk of developing severe symptoms of disease and/or becoming contagious) and subjects lacking the relevant characteristic. Measures of test performance which are well known to those skilled in the art include sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV). One or more of these measures of test performance may be used in the methods of the present disclosure.

By "inoculation" as used herein may be meant exposure of a subject on purpose to respiratory virus, for example by intranasal inoculation with virus, e.g. via pipette.

Suitably, the biological samples obtained from the group of persons after inoculation with respiratory virus may be obtained about 30 to about 90 hours after inoculation, preferably about 40 to about 50 hours after inoculation; for example about 45 hours after inoculation. It has been found that upregulation of ITAC and MIP3B may begin about 30 hours or about 40 hours after inoculation with a respiratory virus, such, for example, as about 45 hours after inoculation with a respiratory virus, and may last for a period of up to several days thereafter, in a person at risk of developing severe symptoms of disease and/or becoming contagious. Accordingly, in some embodiments, the biological samples may be obtained from the group of subjects about 1 to about 7 days after inoculation, for example about 1 to about 5 days after inoculation. Suitably, in some embodiments, the biological samples may be obtained about 30, 40 or 45 hours or more after inoculation.

In some embodiments, persons may be classified as being at risk of developing severe symptoms of disease and/or becoming contagious if they have a high viral load after inoculation;

typically if their peak viral load after inoculation falls in a top quantile of the group for peak viral load. Those skilled in the art will be familiar with methods for measuring viral load, such, for example, as by qPCR.

Further or alternatively, persons may be classified as being at risk of developing severe symptoms of disease and/or becoming contagious if they display one or more relevant symptoms and/or signs after inoculation; such, for example, as one or more of sneezing, cough, runny nose, stuffy nose and sore throat. Those skilled in the art will be familiar with methods for identifying relevant symptoms and/or signs. For example, persons may be classified as such if they are in the top quantile of the group after inoculation for a peak combined Visual Analogue Score (VAS) or Categorical Score (e.g. a score on a standard categorical five-grade scale, 5GS) for sneezing, cough, runny nose, stuffy nose and sore throat (which may in some embodiments be determined by VAS self-reported score card).

Suitably, in some embodiments, the top quantile may be the top tertile or quartile, but other quantiles may be used depending on how it is desired to define a person who is at risk of severe symptoms of disease and/or becoming contagious for a particular application.

By "after inoculation" in the classification step herein may be meant within a period of assessment post inoculation. By way of example, the period of assessment may be up to 7 or 8 days post inoculation, and in some cases up to 15 or even 28 days, although it will be appreciated that persons will generally display peak viral loads and/or peak symptoms or signs of infection much sooner, typically within 3-5 days, especially those falling in the top quantile. In some embodiments, persons may be classified as being at risk of developing severe symptoms of disease and/or becoming contagious if they have a peak viral load and/or peak symptoms or signs in the top quantile for the group within about 36-84 hours after inoculation.

In some embodiments, the reference threshold fold change in the concentration of ITAC may be about 1.4 to about 2.6; for example about 1 to about 1.6; such, for example, as about 1.2 to about 1.6, as measured using a multiplex bead-based assay. Said multiplex bead-based assay may be characterised as follows: Human Multi-Analyte Profile; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions) and expressed in arbitrary units.

The reference threshold fold change in the concentration of MIP3B may be about 1.2 to about 1.7; for example about 1.2 to about 1.5; such, for example, as about 1.3 to about 1.5, as measured using a multiplex bead-based assay. Said multiplex bead-based assay may be characterised as follows: Human Multi-Analyte Profile; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions) and expressed in arbitrary units.

In some embodiments, the probability that a subject who will go on to develop severe symptoms of disease and/or become contagious has a measured fold change in the concentration of ITAC of greater than the ITAC reference threshold fold change (sensitivity) may be in a range of about 0.3 to about 0.7, for example about 0.4 to about 0.6; such, for example, as about 0.45 to about 0.6.

The probability that a subject who will go on to develop severe symptoms of disease and/or become contagious has a measured fold change in the concentration of MIP3B of greater than the MIP3B reference threshold fold change (sensitivity) may be in a range of about 0.3 to about 0.7; for example about 0.4 to about 0.6; such, for example, as about 0.5 to about 0.6.

In some embodiments, the probability that a subject who will not go on to develop severe symptoms of disease and/or become contagious has a measured fold change in the concentration of ITAC below the ITAC reference threshold fold change (specificity) may be in a range of about 0.6 to about 0.9; for example about 0.65 to about 0.85; such, for example, as about 0.7 to about 0.85.

The probability that a subject who will not go on to develop severe symptoms of disease and/or become contagious has a measured fold change in the concentration of MIP3B below the MIP3B reference threshold fold change (specificity) may be in a range of about 0.6 to about 0.9; for example about 0.65 to about 0.85; such, for example, as about 0.7 to about 0.85.

In accordance with the present disclosure, it has been found that a measured fold change in the concentration of ITAC of greater than the ITAC reference threshold fold change may correspond to a positive predictive value (PPV) in a range of about 0.3 to about 0.5; such, for example, as about 0.4 to about 0.5.

A measured fold change in the concentration of MIP3B of greater than the MIP3B reference threshold fold change may correspond to a positive predictive value (PPV) in a range of about 0.3 to about 0.5; for example, about 0.35 to about 0.45.

The term “positive predictive value” as used here may mean the probability that a measured fold change in the concentration of a protein (ITAC and/or MIP3B) of greater than the reference threshold fold change correctly identifies a subject who is at risk of developing severe symptoms of disease and/or becoming contagious.

Meanwhile, a measured fold change in the concentration of ITAC of less than the ITAC reference threshold fold change may correspond to a negative predictive value (NPV) in a range of about 0.7 to about 0.9; for example, about 0.75 to about 0.85.

A fold change in the measured concentration of MIP3B of less than the MIP3B reference threshold fold change may correspond to a negative predictive value (NPV) in a range of about 0.7 to about 0.9; for example about 0.75 to about 0.9.

The term "negative predictive value" as used here may mean the probability that a fold change in the measured concentration of a protein (ITAC or MIP3B) of less than the reference threshold fold change correctly identifies a subject who is not at risk of developing severe symptoms of disease and/or becoming contagious.

In some embodiments, step (b) of the method of the first aspect of the present disclosure may comprise comparing the measured concentration of ITAC to a reference threshold for the concentration of ITAC; and comparing the measured concentration of MIP3B to a reference threshold for the concentration of MIP3B. When the measured concentration of ITAC and the measured concentration of MIP3B are both above their respective reference thresholds, the subject may be assessed to be at risk of developing severe symptoms of disease and/or becoming contagious.

In some embodiments, the reference threshold concentration of ITAC and the reference threshold concentration of MIP3B may be determined by measuring the concentration of ITAC and the concentration of MIP3B in biological samples obtained from a group of persons after inoculation with respiratory virus; classifying members of the group, after inoculation, according to their risk of developing severe symptoms of disease and/or becoming contagious; and setting the reference threshold concentrations of ITAC and MIP3B, respectively, to be a concentration of ITAC and a concentration of MIP3B which discriminate between persons at risk and persons not at risk, according to a desired measure of test performance.

Suitably, the biological samples obtained from the group of persons after inoculation with respiratory virus may be obtained at time points after inoculation disclosed herein.

In some embodiments, persons may be classified as being at risk of developing severe symptoms of disease and/or becoming contagious if they have a high viral load after inoculation; for example if their peak viral load after inoculation falls in a top quantile of the group for peak viral load. Those skilled in the art will be familiar with methods for measuring viral load, such, for example, as by qPCR.

Further or alternatively, persons may be classified as being at risk of developing severe symptoms of disease and/or becoming contagious if they display one or more relevant symptoms and/or signs after inoculation, such, for example, as one or more of sneezing, cough, runny nose, stuffy nose and sore throat. Those skilled in the art will be familiar with methods for identifying symptoms and/or signs. For example, persons may be classified as such if they are in a top quantile of the group after inoculation for a peak combined Visual Analogue Score (VAS) or Categorical

Score (such, for example, as a score on a standard categorical five-grade scale, 5GS) for sneezing, cough, runny nose, stuffy nose and sore throat (which may in some embodiments be determined by VAS self-reported score card).

Suitably, in some embodiments, the top quantile may be the top tertile or quartile, but other quantiles may be used depending on how it is desired to define a person who is at risk of severe symptoms of disease and/or becoming contagious for a particular application.

In some embodiments, the reference threshold concentration of ITAC may be about 14 to about 40; for example about 19 to about 35; particularly about 19 to about 25, as measured using a multiplex bead-based assay. Said multiplex bead-based assay may be characterised as follows: Human Multi-Analyte Profile; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions) and expressed in arbitrary units.

The reference threshold concentration of MIP3B may be about 250 to about 350; for example about 250 to about 300; particularly about 270 to about 300, as measured using a multiplex bead-based assay. Said multiplex bead-based assay may be characterised as follows: Human Multi-Analyte Profile; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions) and expressed in arbitrary units.

In some embodiments, the probability that a subject who will go on to develop severe symptoms of disease and/or become contagious has a measured concentration of ITAC greater than the reference threshold concentration of ITAC (sensitivity) may be in a range of about 0.4 to about 0.9; for example about 0.4 to about 0.7; particularly about 0.5 to about 0.7.

The probability that a subject who will go on to develop severe symptoms of disease and/or become contagious has a measured concentration of MIP3B greater than the reference threshold concentration of MIP3B (sensitivity) may be in a range of about 0.3 to about 0.8; for example about 0.4 to about 0.65; particularly about 0.45 to about 0.65.

In some embodiments, the probability that a subject who will not go on to develop severe symptoms of disease and/or become contagious has a measured concentration of ITAC below the reference threshold concentration of ITAC (specificity) may be in a range of about 0.6 to about 0.85; for example about 0.65 to about 0.85; particularly about 0.7 to about 0.8.

The probability that a subject who will not go on to develop severe symptoms of disease and/or become contagious has a measured concentration of MIP3B below the reference threshold concentration of MIP3B (specificity) is in a range of about 0.65 to about 0.9; for example about 0.65 to about 0.85; particularly about 0.7 to about 0.85.

In accordance with the present disclosure, it has been found that a measured concentration of ITAC above the reference threshold concentration of ITAC may correspond to a positive predictive value (PPV) in a range of about 0.3 to about 0.5; for example about 0.35 to about 0.5; particularly about 0.4 to about 0.5

A measured concentration of MIP3B above the reference threshold concentration of MIP3B may correspond to a positive predictive value (PPV) in a range of about 0.3 to about 0.6; for example about 0.3 to about 0.5; particularly about 0.4 to about 0.5.

The term "positive predictive value" as used here may mean the probability that a measured concentration of a protein (ITAC or MIP3B) of greater than the reference threshold concentration correctly identifies a subject at risk of developing severe symptoms of disease and/or becoming contagious.

Meanwhile, a measured concentration of ITAC below the reference threshold concentration of ITAC may correspond to a negative predictive value (NPV) in a range of about 0.7 to about 0.9; for example about 0.75 to about 0.9; particularly about 0.8 to about 0.9.

A measured concentration of MIP3B below the reference threshold concentration of MIP3B may correspond to a negative predictive value (NPV) in a range of about 0.7 to about 0.9; for example about 0.75 to about 0.9; particularly about 0.8 to about 0.9.

The term "positive predictive value" as used here may mean the probability that a measured concentration of a protein (ITAC or MIP3B) of less than the reference threshold concentration does in fact identify a subject not at risk of developing severe symptoms of disease and/or becoming contagious (i.e., correctly identifies a subject truly not at risk of developing severe symptoms of disease and/or becoming contagious).

It will be appreciated by those skilled in the art that the prevalence of a relevant characteristic in a group of persons, such, for example, as the prevalence of persons having severe symptoms of disease and/or being contagious, may vary from one group to another. By "prevalence" herein may be meant the frequency of the relevant characteristic, for example expressed as a percentage of the group. This may affect a positive predictive value and/or a negative predictive value of a reference threshold disclosed herein. The "positive predictive value" of a reference threshold disclosed herein (such, for example, as, in various embodiments, a threshold fold change in the concentration of ITAC, a threshold fold change in the concentration of MIP3B, a threshold concentration of ITAC, or a threshold concentration of MIP3B) may accordingly be defined as (sensitivity of threshold x prevalence) / [(sensitivity of threshold x prevalence) + ((1 – specificity of threshold) x (1 – prevalence))]. Meanwhile, the term "negative predictive value" of a reference threshold disclosed herein (such as, in various embodiments, a threshold fold change in the concentration of ITAC, a

threshold fold change in the concentration of MIP3B, a threshold concentration of ITAC, or a threshold concentration of MIP3B) may be defined as (specificity of threshold x (1 – prevalence)) / [(specificity of threshold x (1 – prevalence)) + ((1 – sensitivity of threshold) x prevalence)]. It will further be appreciated that where the prevalence of the relevant characteristic varies, the sensitivity and/or specificity of a reference threshold disclosed herein (such as, in various embodiments, a threshold fold change in the concentration of ITAC, a threshold fold change in the concentration of MIP3B, a threshold concentration of ITAC, or a threshold concentration of MIP3B) may remain invariant.

In some embodiments, the prevalence of persons having severe symptoms of disease and/or being contagious may be in a range of about 10 to about 50 % of the group of persons; for example about 10 to about 30 %; about 15 to about 30 %; or about 20 to about 25 %.

In some embodiments, the subject may be tested two or more times for the concentration of ITAC and the concentration of MIP3B, and the subject may be assessed to be at risk of developing severe symptoms and/or becoming contagious if the result of at least one or more than one of the tests indicates so, optionally wherein successive tests of the two or more tests are separated by a time interval of at least about 12 hours; for example at least about 24 hours; at least about 36 hours; or at least about 48 hours.

In some embodiments, the ITAC and MIP3B reference thresholds above which a positive result is obtained may be different for the two or more tests. The ITAC and MIP3B reference thresholds for at least one test may be configured to minimise false positives. The ITAC and MIP3B reference thresholds for at least another test may be configured to have fewer false negatives than the one test.

In some embodiments, the subject may have had one or more positive diagnostic tests for respiratory viral disease, presents with symptoms of respiratory viral disease, and/or has had prolonged exposure to at least one other person who is infected with a respiratory virus.

In some embodiments, the one or more diagnostic tests for respiratory viral disease may comprise use of reverse transcriptase polymerase chain reaction (RT-PCR) in a diagnostic test for the presence of viral RNA, carried out on a nose and/or throat or upper airway sample, such, for example, as a nasopharyngeal sample, collected from the subject.

Further or alternatively, the one or more diagnostic tests for respiratory viral disease may comprise a lateral flow test for the presence of one or more viral antigens, carried out on a nose and/or throat or upper airway sample, such, for example, as a nasopharyngeal sample, collected from the subject.

In some embodiments, the subject may present with one or more of nasal congestion, sneezing, rhinorrhoea, pyrexia (fever) and cough and sputum production.

In some embodiments, the respiratory virus may be respiratory syncytial virus (RSV), parainfluenza virus (HPIV), metapneumovirus (HMPV), rhinovirus (HRV), coronavirus such, for example, as SARS-CoV (for example, SARS-CoV-1 or SARS-CoV-2), adenovirus (HAdV), enterovirus (EV), bocavirus (HBoV), parechovirus (HPeV) or an influenza virus, such, for example, as a seasonal strain of influenza, such as H3N2. In particular embodiments the respiratory virus may be an influenza virus. In other particular embodiments, the respiratory virus may be an HRV virus.

The methods of the present disclosure may especially be useful for assessing whether a subject, who has been exposed to a seasonal strain of a respiratory virus, is likely to suffer severe symptoms and/or be contagious, because in general a smaller proportion of subjects exhibit symptoms (particularly severe symptoms) when infected with a seasonal strain (e.g. H3N2) as opposed to a highly pathogenic strain (e.g. H1N1) which may give rise to a stronger immediate immune response in most subjects.

In some embodiments, the biological sample may be or may comprise a blood sample. In particular embodiments, the biological sample may be or may comprise a blood serum sample, or a blood plasma sample. Further or alternatively, the biological sample may be or may comprise a sputum sample, nasal wash (lavage) sample, nasopharyngeal sample, nasal aspirate sample, oral swab sample, saliva sample, tissue biopsy sample, peritoneal fluid sample, or pleural fluid sample. The biological sample may be obtained from the subject using any clinically acceptable method.

In some embodiments, the concentration of ITAC and the concentration of MIP3B may be measured by immunoassaying the biological sample, for example by lateral flow assay, enzyme-linked immunosorbent assay (ELISA) or by single-plex or multiplex bead-based assay. Suitable methods for this are known to those skilled in the art. A presently preferred immunoassay is a multiplex bead-based assay characterised as follows: Human Multi-Analyte Profile; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions) and expressed in arbitrary units.

For example, in a lateral flow assay (which may for example be provided in dipstick format, or in a housed cassette) a biological sample may be placed on a sample pad (optionally comprising a filter) configured to deliver the sample (for example, a blood sample, e.g. a whole blood sample or a blood serum sample) in a controlled manner (e.g. by capillary action) to a conjugate pad. The conjugate pad may be loaded with immobilised labelled antibodies specific to a relevant protein (ITAC or MIP3B) and which bind to the relevant protein if it is present in the sample. Suitable antibodies and labels therefor are known to those skilled in the art; for example chromophore-labelled

antibodies which give rise to a coloured line on the conjugate pad (visible to a user, such, for example, as in a viewing window of a dipstick or housed cassette) only when the relevant protein is present. It will be appreciated by those skilled in the art that the intensity of the colour (or other detectable signal, such, for example, as fluorescence or phosphorescence) may vary depending on the quantity of the relevant protein present. From this may be derived the concentration of the relevant protein (ITAC or MIP3B). Suitable imaging techniques for quantification, such, for example, as quantification by colorimeter, are known to those skilled in the art. It will further be appreciated that a lateral flow assay may include two sample pads and two conjugate pads, and thus two lanes of analysis, one for ITAC, and one for MIP3B.

In an enzyme-linked immunosorbent assay (ELISA) direct or indirect capture may be used to quantify a relevant protein or proteins. These modes of capture are well known to those skilled in the art, and depend on the same principles. Briefly, a capture step may be carried out comprising direct or indirect immobilization of a relevant protein on a surface of microplate wells (wells may be made of any suitable material; for example polystyrene). In the next step (which is sometimes denoted in the art as "plate blocking") irrelevant protein, or other molecules, may be added to the assay, in order to cover all unsaturated surface-binding sites. A detection step may then carried out, by incubating antibodies specific to the relevant protein, which bind only to the relevant protein. A quantification step may then be carried out, involving measurement of the signal generated by tags on the antibodies specific to the relevant protein. Suitable tags (such, for example, as fluorescent or phosphorescent chromophores) and methods of measuring their signal are well known to those skilled in the art.

In a bead-based assay, a sample may be added to a mixture of color-coded beads (the beads having been coated with analyte-specific capture antibodies). It will be appreciated that in a single-plex bead-based assay, a sample may be added to beads coated with capture antibodies. The capture antibodies are specific to a (single) protein of interest. Meanwhile, in a multiplex bead-based assay, a sample may be added to a mixture of color-coded beads coated with capture antibodies. The different bead colours may correspond to different capture antibodies, specific to different proteins of interest. In this way, quantification of multiple proteins of interest in a single sample may be accomplished. For example, in accordance with the present disclosure, quantification of the concentrations of ITAC and MIP3B respectively, in the same sample, may be accomplished.

In more detail (with reference to a multiplex bead-based assay) a capture antibody may bind to the relevant protein. Detection antibodies specific to the protein of interest may then be added to the assay. A detection antibody may also bind to the relevant protein, thereby forming a capture antibody-protein-detection antibody "sandwich" bound to the surface of a bead. Suitably, the detection antibodies may be biotinylated, such that when phycoerythrin-conjugated streptavidin is

added to the assay, it binds to the biotinylated detection antibodies. This may enable quantification of the relevant protein by detection of fluorescence; for example by a dual laser detection instrument, wherein a first laser may classify the colour-coded bead to ascertain the protein that is being detected, while a second laser determines the magnitude of the fluorescence intensity of the phycoerythrin-derived signal, which is directly proportionate to the concentration of protein bound and may act as a proxy, expressed in arbitrary units, for the concentration of protein bound to the bead. The concentration of protein bound may be derived from the fluorescence intensity, and may likewise be expressed in arbitrary units. The concentration of a protein, whether in arbitrary units or, for example, in μg/ml, may be obtained by comparing the fluorescence intensity detected in a sample of interest to a standard curve of fluorescence intensity against protein concentration, generated by serial dilution of a sample having a known concentration of the protein, under the same experimental conditions. It will be appreciated that suitable known alternatives to phycoerythrin may be used. Those skilled in the art are familiar with suitable alternatives to phycoerythrin. In some embodiments, the beads may be magnetic, and protein quantification may be accomplished by using a magnet to arrange the beads in a monolayer, while two spectrally distinct light-emitting diodes illuminate the beads. One light-emitting diode identifies the protein that is being detected and, the second light-emitting diode determines the magnitude of the phycoerythrin-derived signal.

Suitably, a multiplex bead-based assay may involve the following steps. The sample of interest may be added to a reaction well containing capture beads, which are microspheres conjugated to capture antibodies and having a unique fluorescent signature specific to the protein of interest (ITAC or MIP3B). The beads are incubated with the sample to allow the proteins of interest to bind to their targets, before other reagents are added. Then, protein-specific biotinylated detection reagents are added to the microsphere mixture, followed by the addition of a fluorescent reporter molecule. Finally, unbound detection reagents are removed in a washing step. Following this, the beads are read using an instrument that uses hydrodynamic focusing to pass the microspheres, one at a time, along a path that is interrogated by two lasers. These identify the unique fluorescent signature of each bead, and measure the fluorescence intensity generated, which is in proportion to the protein concentration in the sample. The median fluorescence intensity (MFI) value of the measured beads is then derived for each protein (ITAC or MIP3B) in the multiplexed assay. It has been found that the use of the median reduces the impact that data outliers (such as bead measurement errors) may have on the results. A standard curve may serve as the basis for calculating protein concentrations from the sample, for example, in μg/ml. Alternatively, values of fluorescence intensity may be reported, or values of protein concentration may be reported, in arbitrary units. To provide the standard curve, serially diluted samples having a known concentration of the protein of interest (ITAC or MIP3B)

are analysed for their fluorescence intensity. The fluorescence intensity detected in the sample of interest may then be compared to the standard curve of concentration against fluorescence intensity.

A preferred multiplex bead-based assay of this kind is characterised as follows: Human Multi-Analyte Profile; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions).

Suitably, the instrument used for "reading" the beads may be of the kind that is commercially available from Luminex, e.g Luminex xMAP, INTELLIFLEX, Luminex 200 (LX200) or FLEXMAP 3D.

In some embodiments, the subject may be administered one or more medicinal products before or after exposure or possible exposure to the respiratory virus.

In some embodiments, the method of the first or second aspect of the present disclosure may comprise administering one or more medicinal products to the subject, if the subject is assessed to be at risk of developing severe symptoms and/or becoming contagious.

In some embodiments, the one or more medicinal products may be selected from one or more antiviral agents and/or one or more immunomodulatory agents.

Suitable medicaments may thus include one or more immunomodulators, such, for example, as those described in WO 2018/007788 or WO 2019/122909 (the contents of each of which are incorporated by reference in their entirety) for example UR-13870 or POLB 001; antiviral agents (such, for example, as oseltamivir); antibiotics; and other drugs. It will be appreciated that where an antiviral agent is referred to herein, the antiviral agent may be any one, or more, of the following or pharmaceutically acceptable salts thereof: amantadine; rimantadine; ribavirin; idoxuridine; trifluridine; vidarabine; acyclovir; ganciclovir; foscarnet; zidovudine; didanosine; zalcitabine; stavudine; famciclovir; valaciclovir; antitussives; mucolytics; expectorants; antipyretics; analgesics and/or nasal decongestants. In particular, the antiviral agent may be a neuraminidase inhibitor, such, for example, as: oseltamivir (which may be in the form of oseltamivir phosphate), zanamivir, peramivir and/or laninamivir. In certain embodiments, the antiviral agent may be molnupiravir.

It will be appreciated that further or alternatively to one or more suitable medicinal products, a subject may be subjected to one or more surgical or non-surgical interventions. For example, the subject may be hospitalised or at least allocated a hospital bed in anticipation of their condition worsening. In some embodiments, the subject may be administered oxygen, such, for example, as by means of a ventilator, or by means of extracorporeal membrane oxygenation.

Viral transmission may occur through the spread of virions (intact whole viral particles) in droplets via coughing, sneezing or even breathing (whereby air is expelled from a person's lungs

through their nose or mouth). An increase in viral load, and thus in viral shedding, may therefore increase the quantity of virions in droplets spread by a given subject, and is likely to increase the contagiousness of the subject. Likewise, any signs of disease that could increase the spread of droplets would also increase the chances of being contagious.

Accordingly, by "contagious" herein may be meant any person who releases virions into the surrounding atmosphere; optionally wherein the person is capable of releasing virions over a period of at least 1, 2, or 3 days. In some cases, the person may continue to shed virus particles for up to 10 days or even longer.

Further or alternatively, a contagious person may be a person who transmits virions to other persons, optionally wherein the person is capable of transmitting virions over a period of at least 1, 2, or 3 days. In some cases, the person may be capable of transmitting virus particles for up to 10 days or even longer.

In some embodiments, a contagious person may release and/or transmit infectious virions by one or more of: coughing, sneezing, and transferring virions from a body surface to an object.

In accordance with the present disclosure, a person may be defined as contagious if they have a high viral load and/or exhibit symptoms or signs which are calculated to spread virions, for example one or more of the following symptoms: sneezing, cough, runny nose, stuffy nose and sore throat.

In some embodiments, the subject may be an infant (i.e. younger than one year old) or elderly (i.e. 65 years old or more) or may be a pregnant woman. It will be appreciated that viral infection can lead to especially severe symptoms and/or contagiousness in children (i.e. younger than ten years old) or infants (i.e. younger than one year old). For example, RSV infection is thought to lead to particularly severe symptoms and/or contagiousness in children or infants of less than two years old.

In some embodiments, a human subject may have one or more underlying comorbidities that predispose the subject to severe symptoms of disease. For example, the subject may be immunocompromised, or may suffer from COPD, severe genetic anaemia, asthma or diabetes, chronic hepatic or renal insufficiency, obesity or a cardiovascular disorder or condition. For example, where the virus is an HRV virus, the subject may suffer from asthma.

In some embodiments, the subject may have been vaccinated against a relevant respiratory virus. Vaccination may lower the probability of infection following exposure to respiratory virus, and/or of a subject developing severe symptoms of disease following such exposure. Nonetheless, subjects who, despite having been vaccinated, may go on to develop severe symptoms of disease and/or become contagious, may be assessed, in methods of the first or second aspect of the present disclosure, as at risk of developing severe symptoms of disease and/or becoming contagious.

In some embodiments, the subject may be serologically naïve, i.e. seronegative for circulating antibodies or T cells to the respiratory virus. By way of example, this may be the case for many subjects in the first 1, 2, 3, 4, 5, or 6 months of a respiratory virus pandemic, when it may be expected that a majority of a local or worldwide population (for example, more than 50, 70, or 90 % of a population) are serologically naïve to the virus.

It will be appreciated that where a majority of a local or worldwide population (for example, more than 50, 70, or 90 % of a population) are serologically naïve, it may be preferable to use medicaments sparingly. By way of example, sparing use of medicaments (such, for example, as antiviral agents, immunomodulators and/or antibiotics, disclosed herein) may be preferable where there are local or worldwide shortages. For such reasons, in determining which subjects to treat, a physician may sometimes find it necessary to be more selective than would be normal practice. In some embodiments, the physician may administer one or more suitable medicaments only to subjects who are assessed to be at risk of developing severe symptoms of disease and/or becoming contagious. Alternatively, only such subjects may be permitted to self-administer the one or more suitable medicaments. Additionally or alternatively, where there is a shortage of hospital facilities, only such subjects may be referred (where they present at a primary care facility, or are visited at home by a physician) to hospital.

In a pandemic, implementation of the method of the first or second aspect of the present disclosure may, in some embodiments, comprehend: post-exposure assessment (or assessment following suspected exposure to virus); assessment when a subject develops symptoms suspected to indicate viral infection; event-triggered assessment, such, for example, as when a subject boards or disembarks a train, plane, ship or other mode of public transport; and/or regular assessment of healthcare workers and certain other staff, for example all staff in a hospital or primary care facility, over a period of time. Successive assessments over a period of time may, for example, be separated by a time interval of at least about 12 hours; for example at least about 24 hours; at least about 36 hours; or at least about 48 hours.

In some embodiments, the subject may be a patient who is resident in a hospital. It will be appreciated that an outbreak of one or more respiratory viruses may sometimes occur amongst patients who may be resident in the hospital for reasons other than viral infection. For example, the subject may be on a ward of patients considered by a physician to be at high risk of morbidity and mortality following viral infection (or one or more secondary infections associated with a primary viral infection) such, for example, as may be found in a hospital high dependency unit, or intensive care unit.

Following exposure, or possible exposure, to a respiratory virus, the risk of the subject (patient) developing severe symptoms of disease and/or becoming contagious may be assessed in accordance with the method of the first or second aspect of the present disclosure, in order to determine whether or not to administer one or more suitable medicaments to the subject. Where the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious, one or more suitable medicaments may be administered to the subject. For example, a physician may administer the one or more suitable medicaments to the subject. Alternatively, the subject may self-administer the one or more suitable medicaments.

In some embodiments, therefore, the method of the first or second aspect of the present disclosure may further comprise administering one or more medicinal products to the subject prophylactically, if the subject is assessed to be at risk of developing severe symptoms and/or becoming contagious.

Suitable medicaments may include one or more immunomodulators; antiviral agents (such, for example, as oseltamivir); antibiotics; and other drugs, such, for example, as those disclosed herein.

Implementation of the method of the first or second aspect of the present disclosure may, in some embodiments, be triggered by: an outbreak in the ward, or in one or more nearby wards; the onset of a period of risk, for example the 'flu season' and/or winter (notably, the 'flu season' and winter may, or may not, overlap); exposure to another subject who is known to be infected with a respiratory virus; and very early symptoms suggesting infection with a respiratory virus. The method may thus provide an advance 'early warning system' to assess the risk of severity and/or contagiousness. A subject (patient) may have regular scheduled assessments over time. For example, a subject may be assessed at regular scheduled intervals during the 'flu season', during winter, and/or when there is or has recently been an outbreak in the hospital, or the surrounding local area. Successive scheduled assessments may be separated by a time interval of at least about 12 hours; for example at least about 24 hours; at least about 36 hours; or at least about 48 hours.

It will be appreciated that a proportion of the population may have mild (even asymptomatic) infections. Treating everyone having an infection, including those subjects assessed not to be at risk of developing severe symptoms of disease and/or becoming contagious, may mean exposing subjects unnecessarily to drugs with side effects. This may be especially undesirable, for example, for subject groups that are more susceptible to side effects, such, for example, as may be the case amongst patients who are resident in hospital (particularly patients who may be resident in the hospital for

reasons other than viral infection) and/or infants (i.e. younger than one year old); children (i.e. younger than ten years old); elderly subjects (i.e. 65 years old or more); and pregnant women.

It will be appreciated that, rather than being a patient who is resident in a hospital, the subject may in some embodiments be a resident of a care home. Care homes may accommodate elderly (i.e. 65 years old or more) and/or frail subjects. In some embodiments, these subjects (residents) may be at high risk of morbidity and mortality as a result of viral infection, or secondary infections associated with a primary viral infection. In some embodiments, one or more underlying comorbidities, for example those mentioned above, may predispose such subjects (residents) to severe viral infection. It will be appreciated that features described in relation to a patient who is resident in a hospital may apply in relation to a resident of a care home and *vice versa*.

In some embodiments, the method of the first or second aspect of the present disclosure may comprise assessing the effect of a given treatment, for example a medicament, on the recovery of a subject from infection with a respiratory virus. It may be preferable to determine whether a subject may develop a (potentially severe) 'rebound' infection, or make a (full) recovery. This may sometimes be especially preferable where the subject is a child (of younger than ten years old); an infant (i.e. younger than one year old); or elderly (i.e. 65 years old or more); or a pregnant woman. It may also sometimes be especially preferable where one or more underlying comorbidities predispose the subject to severe viral infection.

In embodiments where a subject has been treated successfully, for example with a medicament, the assessment may be that the subject is not or is no longer at risk of developing severe symptoms of disease and/or becoming contagious.

In embodiments where treatment has not (yet) succeeded, the assessment may be that the subject remains at risk of developing severe symptoms of disease and/or becoming contagious. This may form the basis for a clinical decision to begin a new treatment, or an escalation of treatment until the assessment is that the subject is not at risk of developing severe symptoms of disease and/or becoming contagious. In some embodiments, therefore, the subject may be treated, for example administered one or more suitable medicaments, for example those disclosed herein, until the assessment is that the subject is no longer at risk of developing severe symptoms of disease and/or becoming contagious. In some embodiments, the subject may be treated with a suitable medicament to which the subject is naïve (i.e. which the subject has not previously received as treatment for the present infection); for example one or more suitable medicaments as disclosed herein, and/or their treatment with one or more suitable medicaments (which the subject has already received, or been receiving, as treatment for the present infection) may be escalated (for example, the frequency of dosing may be increased, and/or the dose may be increased) until the subject is assessed to no longer

be at risk of developing severe symptoms of disease and/or becoming contagious. In some embodiments, a physician may administer the one or more suitable medicaments to the subject. Alternatively, the subject may self-administer the one or more suitable medicaments.

In some embodiments, the subject may have a clinical management plan which is under review by a physician. The physician may be considering whether one or more changes should be made to a clinical management plan of the subject, for example other than adapting medication. In some embodiments, the physician may be considering whether the patient should be monitored more or less frequently over time; and/or whether the patient should enter, remain in, or leave quarantine.

Where the subject is assessed as being at risk of developing severe symptoms of disease and/or becoming contagious, the clinical management plan of the subject may be adapted in accordance with the present disclosure, such that the subject is monitored more frequently, and/or such that the subject remains in, or enters, quarantine.

Where the subject is assessed as not being at risk of developing severe symptoms of disease and/or becoming contagious, the clinical management plan of the subject may be adapted in accordance with the present disclosure, such that the subject is monitored less frequently, and/or such that the subject leaves, or does not enter, quarantine.

In some embodiments, the subject may be a person, such as an outpatient, presenting in a primary care or outpatient facility. A physician in such a facility may use the method of the present disclosure to anticipate progression to severe illness, possibly involving referral to hospital for treatment.

By "having severe symptoms of disease" herein may be meant that a person requires hospitalisation, and optionally referral to a hospital high dependency unit, or even an intensive care unit. This may be, for example, the view of one or more than one physician examining the person. Further, or alternatively, a person may be diagnosed (for example, by examination by one or more than one physician) to have severe symptoms of disease based on one or more of their respiratory rate, blood oxygen level, and chest radiograph (chest X-ray or CXR). As noted above, a person may exhibit severe symptoms of disease even in response to infection with a normally mild, seasonal strain of a respiratory virus, such as influenza H1N1 or H3N2, as opposed to a highly pathogenic strain of the kind which more commonly causes severe disease such as an avian influenza strain such as H5N1.

In some embodiments, severe symptoms of disease may be symptoms or signs indicative of lower respiratory tract disease and/or lower respiratory tract inflammation and/or hypercytokinemia (e.g. lung or systemic). They may comprise one or more of: tachypnoea, hypoxemia, an arterial oxygen saturation of $\leq$ 92% on room air by a transcutaneous method and radiological pulmonary infiltrates.

Further or alternatively, severe symptoms of disease may be distinct from clinically tolerable symptoms and signs such, for example, as nasal congestion, sneezing, rhinorrhoea, pyrexia (fever) and cough and sputum production, from which a patient normally recovers naturally without the need for therapeutic intervention.

However, it will be appreciated that different persons with severe symptoms may present with a wide range of different severe symptoms of disease, and may additionally present with more clinically tolerable symptoms.

In some embodiments, severe symptoms of disease may accordingly comprise tachypnoea (respiratory rate ≥ 30 for ages ≥ 12 years; rate ≥ 40 for ages 6 to 12 years; rate ≥ 45 for ages 3 to 6 years; rate ≥ 50 for ages 1 to 3 years).

In some embodiments, the person may have or show signs of discomfort with breathing or dyspnoea (unable to speak full sentences, appear breathless, using accessory respiratory muscles).

Further, or alternatively, severe symptoms may comprise abnormal levels of fatigue and/or lethargy.

Further or alternatively, severe symptoms of disease may comprise hypoxemia and/or cardiopulmonary insufficiency. In some embodiments, the person may have an arterial oxygen saturation of ≤ 92% on room air by a transcutaneous method. Typically, hypoxemia or cardiopulmonary insufficiency may comprehend one or more of dyspnoea, tachypnoea, cyanosis, low blood pressure (designated as below normal range for age and sex) and tachycardia. In some cases, hypoxemia and/or cardiopulmonary insufficiency may be such, for example, as to require the administration of supplementary oxygen, such, for example, as by means of a ventilator, or by means of extracorporeal membrane oxygenation.

Further, or alternatively, severe symptoms of disease may comprise the presence of radiological pulmonary infiltrate; for example as determined by chest radiograph (chest X-ray or CXR).

Accordingly, in particular embodiments, severe symptoms of disease may comprise tachypnoea, an arterial oxygen saturation of ≤ 92% on room air by a transcutaneous method, and radiological pulmonary infiltrates.

In some embodiments, a person with severe symptoms of disease may have significantly higher absolute neutrophil counts than a person with mild or moderate symptoms of disease. Typically, a person with severe symptoms may have a neutrophil count in the range 2.1-24.5 x 103 /μl (as compared with a person with moderate symptoms, who may have a neutrophil count in the range 0.62-10.88 x 103 /μl or a person with mild symptoms of disease, who may have a neutrophil

count in the range 0.5-6.5 x 10^3 /µl). In some embodiments, the absolute platelet count may be significantly lower in persons with severe symptoms of disease, e.g. 27-250 x 103 /µl (as compared with a person with moderate symptoms, who may have a platelet count in the range 55-345 x 103 /µl or a person with mild symptoms, who may have a platelet count in the range 79-370 x 103 /µl).

A person having severe symptoms of disease may, in some embodiments, have one or more secondary infections (for example, one or more bacterial infections) associated with a primary viral infection.

In some embodiments, implementation of the method of the first or second aspect of the present disclosure may be triggered by: the subject (e.g. an outpatient) being considered by a physician to be at risk of severe infection, for example where the subject (e.g. outpatient) is an infant (i.e. younger than one year old); elderly (i.e. 65 years old or more); a pregnant woman; and/or where the subject has one or more underlying comorbidities predispose the subject to severe viral infection.

In some embodiments, for example by way of precaution, an otherwise healthy subject (e.g. outpatient) may be assessed using the method of the present disclosure. This may comprehend an inclusionary approach to assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus.

In some embodiments, where the subject (e.g. outpatient) is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious, one or more suitable medicaments disclosed herein may be administered to the subject. In some embodiments, a physician may administer one or more suitable medicaments to the subject (e.g. outpatient). Alternatively, the subject may self-administer one or more suitable medicaments.

Additionally or alternatively, in embodiments where the subject (e.g. outpatient) is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious, the subject may be referred to hospital.

In some embodiments, the subject may be military personnel. It will be appreciated that in a military setting, maintaining the health of subjects (personnel) may be especially preferable, to enable proper execution of their duties. As soon as infection or symptoms are suspected, a subject may, in some embodiments, be assessed and optionally treated and/or managed in an appropriate way to limit the impact of infection on the subject and/or their close contacts.

Where the subject (personnel) is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious, one or more suitable medicaments disclosed herein may be administered to the subject. In some embodiments, a physician may administer one or more suitable medicaments to the subject. Alternatively, the subject may self-administer one or more suitable

medicaments. Additionally or alternatively, where the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious, the subject may be referred to hospital.

Implementation of the method of the present disclosure may, in some embodiments, be triggered by: outbreaks in the surrounding local area; the onset of a period of risk, for example the 'flu season' and/or winter; exposure to another subject who is known to be infected with a respiratory virus; and very early symptoms suggesting infection with a respiratory virus.

In some embodiments, a subject (personnel) may have regular scheduled assessments over time. For example, a subject may be assessed at regular scheduled intervals during the 'flu season', during winter, and/or when there is or has recently been an outbreak in the surrounding local area. Successive scheduled assessments may be separated by a time interval of at least about 12 hours; for example at least about 24 hours; at least about 36 hours; or at least about 48 hours. It will be appreciated that the risk of viral infection may be higher in military settings such, for example, as training camps, ships and aircraft, so in these settings the performance of assessments at regular scheduled time intervals may be particularly appropriate.

Identifying subjects assessed to be at risk of developing severe symptoms of disease and/or becoming contagious, and initiating early treatment and/or management, may reduce both the impact of the disease on the subject, and their risk of transmitting it to other persons. It may sometimes be preferable to be able to avoid moving personnel about to develop severe symptoms of disease and/or become contagious into a high risk area (such, for example, as an area with a civilian population, and/or an area of active combat).

It will be appreciated that the assessment of whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, may in some embodiments assist with a decision to quarantine a subject away from other personnel, to reduce the impact of an outbreak, e.g. in training camps or on board ships.

It will also be appreciated that the considerations disclosed herein with reference to military personnel apply in similar environments, for example amongst sports teams, restaurant or other hospitality staff, factory workers, building site staff, and aeroplane or ship crew.

In some embodiments, one or more (for example all) steps of the method of the present disclosure may be carried out at home. In a home environment, subjects may be assessed promptly if they have been exposed, or possibly exposed, to a respiratory virus.

Implementation of one or more steps of the method of the present disclosure in a home environment may, in some embodiments, be triggered by: outbreaks in the surrounding local area; the onset of a period of risk, for example the 'flu season' and/or winter; exposure to another subject who is known to be infected with a respiratory virus; and very early symptoms suggesting infection

with a respiratory virus. A subject may have regular scheduled assessments over time. For example, a subject may be assessed at regular scheduled intervals during the 'flu season', during winter, and/or when there is or has recently been an outbreak in the surrounding local area. Successive assessments may be separated by a time interval of at least about 12 hours; for example at least about 24 hours; at least about 36 hours; or at least about 48 hours.

Subjects for whom at-home assessment may be particularly appropriate include subjects already considered by a physician to be at risk of severe infection and/or contagiousness; for example where the subject has one or more underlying comorbidities, such as those disclosed herein, that predispose the subject to severe viral infection. By way of example, at-home assessment may sometimes be particularly appropriate where the subject is a pregnant woman, or where the subject is elderly (i.e. 65 years old or more); a child (i.e. younger than ten years old); or an infant (of younger than one year old).

For children and infants, notably, the risk of viral infection may cause particular concern for parents or guardians. It may therefore be useful to assess whether a child or infant is at risk of developing severe symptoms of disease and/or becoming contagious by implementing a method disclosed herein, thus identifying a confident threshold of seriousness before the child or infant should be treated with one or more medicaments disclosed herein, and/or referred to hospital.

In some embodiments, one or more (for example all) steps of the method of the present disclosure may be carried out in a home environment for an otherwise-healthy subject. While some viral infections may resolve without treatment, in other instances the condition of a subject may deteriorate, sometimes rapidly. If a risk of deterioration is suspected, at-home assessment may provide additional data to inform a decision on whether to present at a primary care facility, or hospital. By way of example, in embodiments wherein the subject is a health service employee then, having performed the assessment at home, they could seek treatment as soon as possible, and thereby return to work more quickly. This may reduce the impact of absence from work of health service employees or certain other staff during the 'flu season', and/or during winter, when health service employees and certain other staff are in greater demand. For this reason, a subject such as a health service employee may have regular scheduled assessments over time. In some embodiments, a subject may be assessed at regular scheduled intervals during the 'flu season', during winter, and/or when there is or has recently been an outbreak in the surrounding local area. Successive assessments may be separated by a time interval of at least about 12 hours; for example at least about 24 hours; at least about 36 hours; or at least about 48 hours.

Where the members of a household include one or more at-risk member(s) (for example, having one or more underlying comorbidities leading to a predisposition to severe viral infection)

then a household member assessed, by a method disclosed herein, to be at risk of developing severe symptoms of disease and/or becoming contagious, may reduce the likelihood of transmitting the viral infection to the at-risk member(s) by seeking early treatment. In some embodiments, one or more suitable medicaments disclosed herein may be administered to the household member assessed to be at risk of developing severe symptoms of disease and/or becoming contagious. For example, a physician may administer the one or more suitable medicaments. Thus, in some embodiments, the household member may self-administer the one or more suitable medicaments. Additionally or alternatively, where the household member is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious, they may be referred to hospital.

In some embodiments, the method of the first or second aspect of the present disclosure may comprise assessing which participants of a study on viral transmission are at risk of becoming contagious. These subjects (study participants) may be under review for supervised transmission to volunteers, and/or selection for aerosol generation analysis.

In some embodiments, where the subject (study participant) is assessed as being at risk of becoming contagious, the subject may be managed for supervised transmission to volunteers, and/or selected for aerosol generation analysis.

In some embodiments, where the subject is assessed as not being at risk of becoming contagious, the subject (study participant) may not be managed for transmission to volunteers, and/or may therefore not be selected for aerosol generation analysis.

In a third aspect of the present disclosure, therefore, there is provided a method of conducting a clinical trial or field study, comprising:

(a) measuring the concentration of ITAC and the concentration of MIP3B in biological samples obtained from a plurality of subjects;

(b) analysing the measured concentration of ITAC and the measured concentration of MIP3B in each sample in conjunction, to assess whether a respective subject is at risk of developing severe symptoms of disease and/or becoming contagious; and

(c) including or excluding a subject who is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious in the clinical trial or field study or in a subgroup of the clinical trial or field study.

Suitably, the concentration of ITAC in each biological sample may be measured by immunoassay using at least one antibody that is specific for ITAC.

The concentration of MIP3B in each biological sample may be measured by immunoassay using at least one antibody that is specific for MIP3B.

In some embodiments, a subject who is included in the clinical trial or field study, or in the subgroup of the clinical trial or field study, may be administered one or more medicinal products; for example an investigational medicament.

In some embodiments, all subjects included in the clinical trial or field study may be administered one or more medicinal products; for example an investigational medicament. The response of all subjects to the medicinal product may be analysed, and the response of those included in the subgroup may be compared to those of subjects excluded from the subgroup.

Suitably, the methods of the present disclosure may be carried out using one or more computers. For example, a computer may receive input data representing the measured concentration of ITAC and the measured concentration of MIP3B in a biological sample obtained from a subject. The same or a different computer may, for example, process the data to analyse the measured concentrations of ITAC and MIP3B to assess the likelihood that the subject will develop severe symptoms of disease and/or become contagious; or, alternatively, may transmit that data to a further computer for analysis. An output may then be generated by the first or further computer, or by a yet further computer, representing the likelihood of the subject developing severe symptoms of disease and/or becoming contagious.

In a fourth aspect of the present disclosure, therefore, there is provided a computer-implemented method of assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, comprising:

(a) receiving by a computer input data representing the measured concentration of ITAC and the measured concentration of MIP3B in a biological sample obtained from the subject;

(b) processing by a computer the input data to analyse the measured concentrations of ITAC and MIP3B to assess the likelihood that the subject will develop severe symptoms of disease and/or become contagious; and

(c) outputting by a computer output data representing the likelihood of the subject developing severe symptoms of disease and/or becoming contagious.

In some embodiments, said outputting step (c) may comprise displaying the output data on a display in a form which can be understood by a human being or transmitting the output data to a remote computer.

Suitably, the concentration of ITAC in the biological sample obtained from the subject may be measured by immunoassay using at least one antibody that is specific for ITAC.

The concentration of MIP3B in the biological sample may be measured by immunoassay using at least one antibody that is specific for MIP3B.

In a fifth aspect, therefore, the present disclosure provides a computer program comprising instructions which, when carried out by a computer, cause the computer to carry out step (b) of the method of the first, second, third or fourth aspect of the present disclosure.

In a sixth aspect of the present disclosure, there is provided a method of providing data relevant to whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, comprising:

(a) measuring the concentration of ITAC and the concentration of MIP3B in a biological sample obtained from the subject;

(b) receiving the measured concentrations in a computer and encoding the measured concentrations in computer-readable form, and

(c) transmitting the encoded concentrations to a remote computer for evaluation in accordance with a method of the third aspect of the present disclosure.

In a seventh aspect of the present disclosure, there is provided a network comprising:

(a) at least one server;

(b) at least one other computing device; and

(c) a data communications link between the server and the other computing device;

wherein the at least one other device is configured to transmit data to the at least one server, the data representing the measured concentration of ITAC and the measured concentration of MIP3B in a biological sample obtained from a subject; and the at least one server is configured to process the data to analyse the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction, thereby to assess whether the subject is at risk of developing severe symptoms of disease and/or becoming contagious by executing a method of the fourth aspect of the present disclosure.

In some embodiments, the at least one server may be configured to analyse the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction, before relaying a

result to the other device, the result concerning whether the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious.

In some embodiments, the network may further comprise at least one further computing device, wherein the at least one server is configured to process the data to analyse the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction, before relaying a result to the at least one further computing device (the result concerning whether the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious); for example for display by the at least one additional computing device. The at least one additional computing device may be a tablet, laptop, mobile phone, or the like.

In an eighth aspect of the present disclosure, there is provided a kit for assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, the kit comprising two or more reagents allowing quantitation of the concentrations of ITAC and MIP3B.

In some embodiments, the kit may comprise the components of one or more of: two or more enzyme-linked immunosorbent assays as disclosed herein, respectively specific to ITAC and MIP3B; two or more single-plex bead-based assays, as disclosed herein, respectively specific to ITAC and MIP3B; and a multiplex bead-based assay, as disclosed herein, specific to ITAC and MIP3B. Said components may be in separate containers but packaged together.

In some embodiments, the kit may comprise molecular standards and/or positive and/or negative control formulations for the proteins to be screened.

In some embodiments, the kit may comprise buffers, antibodies, wash reagents, and the like, which may be in separate containers but packaged together.

In some embodiments, the kit may comprise instructions for assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus.

In some embodiments, the kit may comprise one or more tools for collecting a biological sample, such, for example, as a blood sample collection tube or nasopharyngeal swab.

Further, it will be appreciated that analysis can be carried out in a variety of physical formats, and the format of the kit will depend on the setting of use. For example, large assays and/or or bead-based assays may be suitable for processing large numbers of biological samples. Alternatively, single sample formats, such, for example, as lateral flow assays (for example, in the format of a

dipstick, or a housed cassette) may be suitable for point of care settings, home settings, and/or testing a small number of biological samples.

It will be appreciated that features described in relation to one aspect of the present disclosure, may be incorporated into any other aspect of the present disclosure, and *vice versa*.

Description of the Drawings

Embodiments of the present disclosure will now be described, by way of example only, with reference to the accompanying drawings, in which:

Figure 1A is a visual analogue scale (VAS) subject self-reported symptom diary card, as used in Example 1 below;

Figures 1B and 1C are plots of the mean fold change (from baseline) in the concentration of ITAC and MIP3B, respectively, over time (from before inoculation, at day -1, to day 3 after inoculation) measured in 47 subjects, 7 of whom are classified, in accordance with the present disclosure, to be at risk of developing severe symptoms of disease and/or becoming contagious, and 40 of whom are classified, in accordance with the present disclosure, to not be at risk of developing severe symptoms of disease and/or becoming contagious;

Figure 2A is a receiver operating characteristic (ROC) curve for the concentration of ITAC in samples obtained 45 hours after inoculation (with no adjustment for baseline);

Figure 2B is a receiver operating characteristic (ROC) curve for the concentration of MIP3B in samples obtained 45 hours after inoculation (with no adjustment for baseline);

Figure 3A is a receiver operating characteristic (ROC) curve for the concentration of ITAC in samples obtained 45 hours after inoculation (as fold change from baseline);

Figure 3B is a receiver operating characteristic (ROC) curve for the concentration of MIP3B in samples obtained 45 hours after inoculation (as fold change from baseline);

Figure 4 is a flow chart showing how a subject may be processed through a typical decision process, as in Example 2 below; and

Figure 5 is a schematic drawing showing a network comprising a device configured to transmit data to a server; optionally, the network further comprises at least one additional device.

Examples

Example 1 –Test thresholds for ITAC and MIP3B

The present example investigates the use of the concentrations of ITAC and MIP3B proteins in humans to assess whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus. The example particularly investigates the impact of varying reference "threshold" concentrations of ITAC and MIP3B (i.e. the concentrations of ITAC and MIP3B, respectively, above which a subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious) both (i) with and (ii) without adjusting for a "baseline" level of expression. In the present example, the "baseline" concentration of a protein (ITAC or MIP3B) is the concentration of that protein in a biological sample obtained from the subject prior to inoculation of the subject with a respiratory virus. It will be appreciated that in other implementations, a baseline concentration of a protein (ITAC or MIP3B) may be the concentration of that protein in a biological sample obtained from an uninfected control subject. Where a change from baseline is measured, the threshold may be a threshold change from baseline.

Table 1 below lists definitions of terms used in determining the utility of a selected threshold concentration of a protein (ITAC or MIP3B). In determining the utility of a threshold, a decision is typically made to maximise either true positives (for example, by maximising PPV) or true negatives (for example, by maximising NPV). Only a perfect test would allow simultaneous maximisation of both of these. It is noted that as the prevalence of a condition of interest varies, PPV and NPV may also vary.

Table 1: Definitions

Term	Definition
Case	A subject who goes on to be severe/contagious
Control	A subject who does not go on to be severe/contagious
True positive	A positive obtained for a case
True negative	A negative obtained for a control
Sensitivity *	Probability that a case receives a positive result
Specificity *	Probability that a control receives a negative result
Positive Predictive Value (PPV) *	Probability that a positive result denotes a case
Negative Predictive Value (NPV) *	Probability that a negative result denotes a control

Accuracy *	(true positives + true negatives)/(cases + controls)

* Measures of test performance.

Procedure

After completing standard influenza human viral challenge screening assessments and meeting standard influenza human viral challenge eligibility criteria, in addition to having no detectable or low levels of pre-existing serological antibodies against GMP challenge virus strain A/Perth/16/2009 H3N2 (hVIVO, Queen Mary Bioenterprises Innovation Centre, 42 New Road, London, E1 2AX, UK) as determined by hemagglutination inhibition assay. 56 subjects entered quarantine 1 to 2 days prior to inoculation. During this time, baseline samples were collected.

Subjects were inoculated intranasally with the GMP challenge virus via pipette. Virus inoculation day was termed "day 0" and the subjects were monitored closely from day 1 to day 8, when they were discharged from quarantine. Subjects returned for a follow-up visit on day 15 (± 1) and a final discharge visit on day 28 (± 3).

Subjects were monitored by completion of Visual Analogue Score (VAS) diary cards three times daily for self-reported symptoms. A copy of a VAS diary card used in the present Example is shown in **Figure 1A** of the accompanying drawings, but it will be understood that the precise layout/format of the scorecard is immaterial, and different presentations may be used to collect the same or similar information. As shown in **Figure 1A**, subjects reported signs and symptoms including: runny nose, stuffy nose, sneezing, sore throat, earache, malaise (tiredness), headache, muscle and/or joint ache, chilliness/feverishness, cough, chest tightness, shortness of breath, and wheeze, assessed on a 100 mm scale of from "not at all bothered" to "severely bothered." A subject's mark along the 100 mm scale was measured to the closest mm by clinic staff (giving a symptom score for each symptom of from 0 to 100).

Analysis for viral shedding was conducted by qRT-PCR from nasopharyngeal swabs (NPS) collected several (e.g. two or three) times daily. NPS sample collection commenced on day 1 post-inoculation, as it is thought that sampling earlier may interfere with the establishment of infection post-inoculation. NPS samples were collected throughout the duration of the quarantine phase and at follow up visits, and were processed by centrifugation, followed by separation of cell pellets from the supernatant. The supernatant was used for qRT-PCR viral load assessments, in accordance with standard procedures in the art and in line with US Food and Drug Administration Good Clinical Practice and Clinical Trials Regulations.

Viral transmission often occurs through the spread of virions (intact whole viral particles) in droplets via coughing, sneezing or even breathing. An increase in viral load, and thus in viral

shedding, may therefore increase the quantity of virions in droplets spread by a given subject, and is likely to increase the contagiousness of a subject. Likewise, any signs of infection that could increase the spread of droplets (e.g. by expulsion of air through the nose or mouth) would also increase the chances of being contagious. In the present example, subjects were defined as being contagious if they entered the top tertile for peak viral load (based on qPCR titre) during the period of the study after inoculation and/or the top tertile for a peak combination of five cold-like symptoms and signs (sneezing, cough, runny nose, stuffy nose and sore throat) during the period of the study after inoculation.

For the purposes of this analysis, subjects were similarly defined as having, or being at risk of developing, severe signs of disease if they entered the top tertile for a peak combination of five self-reported cold-like symptoms (sneezing, cough, runny nose, stuffy nose and sore throat) during the period of the study after inoculation and/or the top tertile for peak viral load (based on qPCR titre) during the period of the study after inoculation.

Of the study participants, 27 individuals were thus classified as contagious/ severe after inoculation, whereas 63 individuals were classified as non-contagious/ non-severe/ uninfected after inoculation.

Serum samples were collected in plastic BD Vacutainer® SST™ collection tubes (Cat. # 367988 or equivalent, available from ThermoFisher Scientific, 168 Third Avenue, Waltham, MA 02451, USA) twice daily. Following collection, the samples were allowed to clot in the collection tubes for a minimum of 30 minutes at room temperature, i.e. 25 °C. Serum was separated from the clot by centrifuging the collection tube for 10 minutes at 1,300 xg at a temperature of 25 °C, within two hours of collection. The serum was aspirated by Pasteur pipette and stored in standard plastic microcentrifuge tubes. All serum samples were frozen on dry ice immediately after collection and processing. Serum was thawed and ITAC and MIP3B concentration was measured using a multiplex bead-based assay (Human Multi-Analyte Profile, MAP; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions)) with values expressed in arbitrary units. Final data were provided in .xls (Microsoft Excel) format. Analysis-ready data were obtained by correcting for batch effects and the following analysis is based upon that processed data.

The data set obtained for each subject thus comprised: (i) a classification as defined herein as to whether they have, or are at risk of developing, severe signs of disease; and/or are, or are at risk of becoming, contagious; (ii) their measured baseline, pre-exposure concentrations of ITAC and MIP3B, respectively; and (iii) their measured concentrations of ITAC and MIP3B, respectively, at regular time intervals following exposure to virus.

As shown in **Figures 1B and 1C**, it was found that the concentrations of ITAC and MIP3B may begin to be elevated shortly after inoculation (such as by about 30 hours after inoculation) in subjects who have, or are at risk of developing, severe signs of disease; and/or are, or are at risk of becoming, contagious. It was found that the concentrations of ITAC and MIP3B may remain high for an extended period of time after inoculation, e.g. for up to six or seven days after inoculation.

The following analysis was carried out on data obtained from samples obtained 45 hours after inoculation.

No adjustment for baseline (absolute values)

Figure 2A shows a receiver operating characteristic (ROC) curve for the measured concentration of ITAC in samples obtained 45 hours after inoculation, with no adjustment for baseline (i.e., based on an assessment of the absolute values for the measured concentration of ITAC). This demonstrates the impact of varying a reference "threshold" concentration of ITAC (i.e. the concentration of ITAC above which a subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious if that subject has a measured concentration of MIP3B above the "threshold" concentration of MIP3B) without adjusting for a "baseline" concentration of ITAC. The ROC curve displays the sensitivity versus (1 –specificity) at different threshold levels for the reference concentration of ITAC.

Meanwhile, **Figure 2B** shows a receiver operating characteristic (ROC) curve for the measured concentration of MIP3B in samples obtained 45 hours after inoculation, with no adjustment for baseline (i.e., based on an assessment of the absolute values for the measured concentration of MIP3B). This demonstrates the impact of varying a reference "threshold" concentration of MIP3B (i.e. the concentration of MIP3B above which a subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious if that subject has a measured concentration of ITAC above the "threshold" concentration of ITAC) without adjusting for a "baseline" concentration of MIP3B. The ROC curve displays the sensitivity versus (1 – specificity) at different threshold levels for the reference concentration of MIP3B.

Those skilled in the art will appreciate that a perfect test, with a sensitivity of 1.0 (no false negatives) and a specificity of 1.0 (no false positives) would have an area under the ROC curve (AUC) of 1.0. A test of no predictive value would have an AUC of 0.5.

The areas under the curve (AUC) of **Figures 2A** and **2B**, respectively, are 0.77 and 0.69, indicating good predictive value for the concentrations of ITAC and MIP3B, in conjunction.

Table 2A below shows the test performance measures arising from the application of various test thresholds (column 1) on the concentration of ITAC at 45 hours after inoculation.

Table 2A: Test performance measures for ITAC (no adjustment for baseline)

Protein Level *	Percentile	Sensitivity	Specificity	Accuracy	PPV	NPV
37.5	80	0.39	0.86	0.75	0.47	0.82
19.0	70	0.61	0.76	0.73	0.44	0.87
14.0	60	0.72	0.69	0.70	0.42	0.89
9.8	50	0.78	0.58	0.62	0.36	0.89
8.1	40	0.89	0.44	0.55	0.33	0.93
7.1	30	0.94	0.34	0.48	0.30	0.95
5.9	20	1.00	0.25	0.43	0.29	1.00
4.6	10	1.00	0.08	0.30	0.25	1.00

* as measured using a multiplex bead-based assay characterised as follows: Human Multi-Analyte Profile; Luminex platform; antibodies provided by Myriad Rules Based Medicine (Q2 Solutions) and expressed in arbitrary units.

Additionally, **Figure 2A** illustrates, by way of example (point **A**) that at 45 hours after inoculation, for ITAC with a threshold of 47.00, the sensitivity is 0.17, the specificity is 0.98, and the accuracy is 0.79.

Table 2B below shows the test performance measures arising from the application of various test thresholds (column 1) on the concentration of MIP3B at 45 hours after inoculation.

Table 2B: Test performance measures for MIP3B (no adjustment for baseline)

Protein Level *	Percentile	Sensitivity	Specificity	Accuracy	PPV	NPV
364	90	0.28	0.95	0.79	0.62	0.81
302	80	0.44	0.88	0.78	0.53	0.84
270	70	0.56	0.76	0.71	0.42	0.85
255	60	0.61	0.64	0.64	0.34	0.84
232	50	0.67	0.54	0.57	0.31	0.84
215	40	0.72	0.42	0.49	0.28	0.83
207	30	0.83	0.34	0.45	0.28	0.87
189	20	0.94	0.22	0.39	0.27	0.93
168	10	0.94	0.10	0.30	0.24	0.86

* as measured using a multiplex bead-based assay characterised as follows: Human Multi-Analyte Profile; Luminex platform; antibodies provided by Myriad Rules Based Medicine (Q2 Solutions) and expressed in arbitrary units.

Additionally, **Figure 2B** illustrates, by way of example (point **B**) that at 45 hours after inoculation, for MIP3B with a threshold of 326.00, the sensitivity is 0.39, the specificity is 0.93, and the accuracy is 0.81.

Change from baseline

Figure 3A shows a receiver operating characteristic (ROC) curve for ITAC concentration in samples obtained 45 hours after inoculation, divided by the concentration of ITAC at baseline (i.e. prior to inoculation of the subject with GMP challenge virus strain A/Perth/16/2009). It is noted that a slight drop in performance is seen as a result of the adjustment for baseline, in that the AUC is decreased from 0.77 in **Figure 2A** to 0.67 in **Figure 3A**.

Figure 3B shows a receiver operating characteristic (ROC) curve for MIP3B concentration in samples obtained 45 hours after inoculation, divided by the measured concentration of MIP3B at baseline (i.e. prior to inoculation of the subject with GMP challenge virus strain A/Perth/16/2009). It is noted that a slight drop in performance is seen as a result of the adjustment for baseline, in that the AUC is decreased from 0.69 in **Figure 2B** to 0.66 in **Figure 3B**.

Table 3A below shows the variation in performance of ITAC concentration when the threshold change in expression level from baseline (column 1) is varied.

Table 3A: Test performance measures for ITAC (fold change from baseline)

Fold Change*	Percentile	Sensitivity	Specificity	Accuracy	PPV	NPV
2.61	90	0.22	0.93	0.77	0.50	0.80
1.60	80	0.39	0.85	0.74	0.44	0.82
1.42	70	0.50	0.75	0.69	0.38	0.83
1.02	60	0.61	0.66	0.65	0.35	0.85
0.90	40	0.78	0.44	0.52	0.30	0.87
0.73	30	0.83	0.34	0.45	0.28	0.87
0.53	20	0.89	0.22	0.38	0.26	0.87
0.22	10	1.00	0.12	0.32	0.26	1.00

* as measured using a multiplex bead-based assay characterised as follows: Human Multi-Analyte Profile; Luminex platform; antibodies provided by Myriad Rules Based Medicine (Q2 Solutions).

As indicated in **Figure 3A**, by way of example (point **C**) at 45 hours after inoculation, for a threshold fold change of 5.00, the sensitivity is 0.17, the specificity is 1.00, and the accuracy is 0.81.

Table 3B below shows the variation in performance of MIP3B concentration when the threshold change in expression level from baseline (column 1) is varied.

Table 3B: Test performance measures for MIP3B (fold change from baseline)

Fold Change*	Percentile	Sensitivity	Specificity	Accuracy	PPV	NPV
1.61	90	0.06	0.88	0.69	0.12	0.75
1.49	80	0.33	0.83	0.71	0.38	0.80
1.29	70	0.56	0.76	0.71	0.42	0.85
1.26	60	0.56	0.64	0.62	0.32	0.83
1.20	50	0.61	0.53	0.55	0.28	0.82
1.13	40	0.83	0.46	0.55	0.32	0.90
1.06	30	0.83	0.34	0.45	0.28	0.87
0.98	20	0.89	0.22	0.38	0.26	0.87
0.93	10	1.00	0.12	0.32	0.26	1.00

* as measured using a multiplex bead-based assay characterised as follows: Human Multi-Analyte Profile; Luminex platform; antibodies provided by Myriad Rules Based Medicine (Q2 Solutions)

Example 2 - Identifying which patients will become severe and/or contagious in a clinical study

In designing a clinical study, it may sometimes be useful to be able to identify pre-emptively study participants who are at risk of developing severe symptoms of disease and/or becoming contagious, thereby allowing selective dosing of these subjects with an investigational or licensed medicament (drug/vaccine) or placebo at the earliest opportunity. This may improve the ability to detect a clinically relevant reduction in disease in response to the medicament by only evaluating the effects of the medicament in individuals who will/would have developed severe symptoms of disease and/or become contagious. This may also reduce unnecessary exposure of subjects to an investigational medicament, which may have unknown and/or unpleasant side effects. This may also reduce the amount of medicament required.

In the present example, subjects are screened for eligibility for the evaluation of efficacy of an investigational medicament in a clinical study. Eligible subjects arrive at the clinic and blood samples and symptom scores are taken at a known time (e.g. in accordance with the procedure of Example 1 above) before subjects are exposed to virus in accordance with the study protocol (e.g. by inoculation, such as inoculation with GMP challenge virus strain A/Perth/16/2009 H3N2, see Example 1). Baseline values for the concentrations of ITAC and MIP3B, respectively, are obtained from the pre-exposure blood samples (e.g. in accordance with the procedure of Example 1).

Blood samples are taken regularly at specific time-points after virus exposure (e.g. twice, three times a day, or more often) alongside symptom scores. Values for the concentrations of ITAC and MIP3B, respectively, are obtained from the blood samples (e.g. in accordance with the procedure

of Example 1). The clinical study operator may refer to the absolute concentrations of ITAC and MIP3B, respectively and at a given time-point, or alternatively the concentrations of ITAC and MIP3B, respectively and at a given time-point, may be divided by the baseline concentrations of ITAC and MIP3B (i.e. a subject's pre-exposure concentrations of ITAC and MIP3B) to provide fold change values in the concentrations of ITAC and MIP3B.

Reference threshold concentrations of ITAC and MIP3B as disclosed herein may be selected to minimise false positives, such, for example, as by maximising PPV; for example by increasing the reference threshold concentrations of ITAC and MIP3B, respectively, above which the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious. Alternatively, the threshold concentrations of ITAC and MIP3B may be selected to minimise false negatives, such, for example, as by maximising NPV; for example by decreasing the threshold concentrations of ITAC and MIP3B, respectively, above which the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious. In a clinical trial, it may sometimes be especially preferred to minimise false positives. It will be appreciated that this may be useful where the investigational medicament has one or more side effects, where its side effects are unknown, and/or where the investigational medicament is expensive and/or in short supply.

Where a subject is assessed as being at risk of developing severe symptoms of disease and/or becoming contagious (by reference to the selected threshold, e.g. a threshold selected to minimise false positives, or to minimise false negatives) this may immediately trigger dosing of the subject with an investigational medicament (drug/vaccine/placebo). Medicaments could include one or more immunomodulators; antiviral agents; antibiotics; and other drugs, as disclosed herein.

Other actions that may be triggered (additionally or as an alternative to dosing with a medicament) include increasing the frequency of observations/ samples/ measurements in those assessed as being at risk of developing severe symptoms of disease and/or becoming contagious, or reducing observations/samples/measurements in those who are assessed not to be at risk of developing severe symptoms of disease and/or becoming contagious.

Using methods of the present disclosure as part of a decision-making procedure in a clinical trial may enable the trial operator to select only those subjects who are assessed to be likely to develop severe symptoms of disease and/or become contagious for inclusion in statistical analysis of the efficacy of an investigational medicament. It will be appreciated that this may be useful where the investigational medicament has one or more side effects, where its side effects are unknown, and/or where the investigational medicament is expensive and/or in short supply. Another benefit is that the analysis of the efficacy of the investigational medicament is likely to be more accurate, since it will (mostly) be used to treat those who develop severe symptoms of disease and/or become contagious,

rather than all subjects (encompassing uninfected subjects and those with mild infections). It will be appreciated that the decision to minimise false positives, or minimise false negatives, may accordingly turn on these considerations.

In some instances, where a subject is assessed as not being at risk of developing severe symptoms of disease and/or becoming contagious, the subject may be dosed in any event at a predetermined time point post exposure or inoculation (e.g. day 4, 5 or 6). Such subjects may then form a further subgroup for analysis.

A typical decision process is summarised with reference to the flowchart of **Figure 4**.

The process commences by **(i)** measuring the level of concentrations of ITAC and MIP3B, respectively, in a first biological sample obtained from a subject.

The process operator may then proceed to **(ii)** input the concentrations of ITAC and MIP3B into an algorithm, which analyses the concentrations of ITAC and MIP3B, in conjunction. The output is entered into a decision tree. The subject is accordingly assigned either to a group 'at risk of developing severe symptoms of disease and/or becoming contagious' or a group 'not at risk'.

Optionally, the operator may **(ia)** reassess the subject's risk, by measuring the concentrations of ITAC and MIP3B, respectively, in a further biological sample (or further biological samples); for example a sample (or samples) obtained at a time interval (or intervals) after the first sample. The time interval (or intervals) may be in a range of about 40 to about 50 hours after inoculation; for example about 45 hours after inoculation. Optionally, the operator may themselves **(iv)** compare the concentrations of ITAC and MIP3B, respectively, in the further biological sample(s) to the concentrations of ITAC and MIP3B in the first biological sample, before proceeding to step **(ii)**.

Where the subject is assigned to the group 'not at risk', steps **(i)** and **(ii)**, and optionally one or both of steps **(ia)** and **(iv)** may optionally be repeated.

Where the subject is assigned to the group 'at risk of developing severe symptoms of disease and/or becoming contagious', then **(v)** a medicament and/or other treatment may be administered to the subject, and/or the subject may be quarantined. Optionally, before proceeding to step **(v)**, **(vi)** the operator may combine the assessment with additional diagnostic/clinical evidence to further assess the risk level of the subject.

Example 3 - Identifying which patients will become severe and/or contagious in a sports team

In a sports team, it may sometimes be useful to be able to identify pre-emptively subjects who are at risk of developing severe symptoms of disease and/or becoming contagious, thereby allowing quarantine of such subjects away from other members of the team, and dosing of these

subjects with one or more suitable medicaments (drug/vaccine) at the earliest opportunity. It will be appreciated that in a sports team, maintaining the health of subjects may be especially preferable in view of the impact of even a minor and/or temporary deterioration in health on sporting performance. As soon as infection or symptoms are suspected, a subject may be assessed in accordance with methods of the present disclosure, and optionally treated and/or managed in an appropriate way to limit the impact of infection on the subject and/or their close contacts (e.g. other members of the team).

In the present example, blood samples and symptom scores are taken from subjects (e.g. in accordance with the procedure of Example 1 above) at a time when subjects are known to not have been exposed to virus. Baseline values for the concentrations of ITAC and MIP3B, respectively, are obtained from these pre-exposure blood samples (e.g. in accordance with the procedure of Example 1).

Blood samples are taken regularly at specific time-points thereafter (e.g. once a day, or more often). Values for the concentrations of ITAC and MIP3B, respectively, are obtained from the blood samples (e.g. in accordance with the procedure of Example 1). A managing physician may refer to the absolute concentrations of ITAC and MIP3B, respectively and at a given time-point, or alternatively the concentrations of ITAC and MIP3B, respectively and at a given time-point, may be divided by the baseline concentrations of ITAC and MIP3B (i.e. a subject's pre-exposure concentrations of ITAC and MIP3B).

Reference threshold concentrations of ITAC and MIP3B as defined in Example 1 above may be selected to minimise false positives, such, for example, as by maximising PPV; for example by increasing the reference threshold concentrations of ITAC and MIP3B, respectively, above which the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious. Alternatively, the threshold concentrations of ITAC and MIP3B may be selected to minimise false negatives, such, for example, as by maximising NPV; for example by decreasing the reference threshold concentrations of ITAC and MIP3B, respectively, above which the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious. In a sports team, it may sometimes be especially preferred to minimise false negatives in view of the impact of incorrectly assessing a subject to not be at risk of developing severe symptoms of disease and/or becoming contagious on the health and thus sporting performance of that subject, and/or on the health and thus sporting performance of the remaining members of the team. It will be appreciated that in a sports team, an inclusionary approach to medicating subjects may be preferable.

Where a subject is assessed as being at risk of developing severe symptoms of disease and/or becoming contagious (by reference to the selected reference thresholds, e.g. thresholds selected to

minimise false negatives) this may immediately trigger dosing of the subject with a medicament (drug/vaccine). Medicaments could include one or more immunomodulators; antiviral agents; antibiotics; and other drugs, as disclosed herein.

Other actions that may be triggered (additionally or as an alternative to dosing with a medicament) include increasing the frequency of observations, taking samples and/or measurements in those assessed as being at risk of developing severe symptoms of disease and/or becoming contagious, or reducing observations/samples/measurements in those who are assessed not to be at risk of developing severe symptoms of disease and/or becoming contagious.

In some instances, where a subject is assessed as not being at risk of developing severe symptoms of disease and/or becoming contagious, the subject may be dosed in any event; for example dosed with a vaccine. This may be preferable where the subject is about to travel to a location having a higher prevalence of viral disease (e.g., when travelling to a sporting event).

It will be appreciated that the considerations of this example apply in similar environments, such, for example, as amongst military personnel, restaurant or other hospitality staff, factory workers, building site staff, and aeroplane or ship crew.

Example 4 – Assessing risk of severe disease/contagiousness in a subject presenting with symptoms and/or signs of infection

An individual subject presents in a primary care facility or hospital with symptoms and/or signs of viral infection, e.g. fever, sneezing, cough, runny nose, stuffy nose and/or sore throat. It may be unknown how much time has elapsed since the subject may have been exposed to a respiratory virus (or whether exposure has occurred at all). The concentrations of ITAC and MIP3B of the individual subject prior to exposure, or possible exposure, of that subject to the respiratory virus may also be unknown.

When the subject arrives at the primary care facility or hospital, blood samples and symptom scores are taken, e.g. in accordance with the procedure of Example 1 above. The concentrations of ITAC and MIP3B are each measured from the blood sample, e.g. in accordance with the procedure of Example 1.

Since the concentrations of ITAC and MIP3B of the individual subject prior to exposure, or possible exposure, of that subject to the respiratory virus are unknown (unless this is in the patient's medical records) it may not be possible to analyse the measured concentrations of ITAC and MIP3B of the individual subject divided, respectively, by measured baseline concentrations of ITAC and MIP3B (the pre-exposure concentrations of ITAC and MIP3B of the same individual subject).

However, it may be possible to analyse the measured concentrations of ITAC and MIP3B of the individual subject divided, respectively, by baseline concentrations of ITAC and MIP3 which are the measured concentrations of ITAC and MIP3B of an uninfected control subject of the same or a similar phenotype (age, gender, BMI, ethnicity, underlying conditions, etc.). One may assess whether the subject is at risk of developing severe symptoms of disease and/or becoming contagious using the absolute value of the measured concentrations of ITAC and MIP3B for the individual subject.

The absolute values (or values divided, respectively, by baseline) of the measured concentrations of ITAC and MIP3B for the individual subject may be assessed against reference threshold absolute values (or values divided, respectively, by baseline) of the concentrations of ITAC and MIP3B as defined in Example 1 above, defining minimum absolute values (or values divided, respectively, by baseline) of the measured concentrations of ITAC and MIP3B required, in conjunction, for the subject to be assessed as being at risk of developing severe symptoms of disease and/or becoming contagious, as described in the following paragraph.

The reference thresholds may, for example, be set to maximise PPV or NPV (see **Tables 2A, 2B, 3A** and **3B** of Example 1). If the thresholds are set to maximise PPV, there may be fewer false positives (i.e. a smaller probability of the subject mistakenly being assessed as at risk of developing severe symptoms of disease and/or becoming contagious). It will be appreciated that this may be useful where it is preferable to avoid treating everyone having an infection, for example if treatment entails exposing subjects to medicaments with harmful side effects, or where suitable medicament(s) is/are expensive, and/or in short supply. If the thresholds are set to maximise NPV, then there may be fewer false negatives (i.e. a smaller probability of the subject mistakenly being assessed as not at risk of developing severe symptoms of disease and/or becoming contagious). This may be useful where it is preferable to identify everyone having an infection, for example if treatment entails exposing subjects to an inexpensive medicament in abundant supply with minimal side effects, and/or where an inclusionary quarantine policy is in place in the local area.

It will be appreciated that the assessment may optionally be supplemented with a different diagnostic test that confirms the individual subject has the relevant respiratory viral infection (e.g. a viral test).

Where the subject is assessed as being at risk of developing severe symptoms of disease and/or becoming contagious, this may trigger dosing of the subject with a suitable medicament (drug/vaccine). Medicaments could include one or more immunomodulators, such as those described in WO 2018/007788 or WO 2019/122909, for example UR-13870, antiviral agents such as oseltamivir, antibiotics, and other drugs, such as those disclosed herein.

The subject may undergo assessment two or more times, and may be considered to be at risk of developing severe symptoms and/or becoming contagious if at least one or more than one of the assessments concludes that the subject is at risk of developing severe symptoms of disease and/or becoming contagious. Optionally, successive assessments of the two or more assessments may be based on blood samples collected at the same time. Optionally, successive assessments of the two or more assessments may be based on blood samples collected at different times, for example separated by a time interval of at least about 12 hours; for example at least about 24 hours; at least about 36 hours; or at least about 48 hours. The reference threshold concentrations of ITAC and MIP3B (where a subject above both thresholds is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious) may be set to be different for the two or more tests; for example, the reference thresholds for at least one test being configured to maximise PPV and the reference thresholds for at least one other test being configured to maximise NPV (see **Tables 2A, 2B, 3A** and **3B** of Example 1).

Other actions that may be triggered alongside or instead of dosing with a medicament include increasing the observations/samples/measurements in a subject assessed to be at risk of developing severe symptoms of disease and/or becoming contagious, or reducing observations/samples/measurements in a subject assessed not to be at risk of developing severe symptoms of disease and/or becoming contagious.

Suitably, the method may be implemented using one or more computers. **Figure 5** shows a network **(N)** used in a computer-implemented method of assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus according to the present disclosure. The network **(N)** comprises at least one server **(S)**, and at least one other computing device **(1)** for example, a desktop computer, laptop, or mobile device such, for example, as a tablet. There is a data communications link **(L)** between server **(S)** and device **(1)**. Link **(L)** typically comprises at least one transmission medium (e.g., the Internet, or a local area network) that carries data traffic between source and destination, data communication equipment, communication protocols and software. Device **(1)** is configured to transmit input data to server **(S)** (which may be remote from device **(1)**, for example in a different country) the input data representing the measured concentrations of ITAC and MIP3B in a biological sample obtained from a subject. Server **(S)** is configured to execute a computer program comprising instructions which cause the server to receive the input data; analyse the input data to assess the likelihood that the subject will develop severe symptoms of disease and/or become contagious, in accordance with Example 1, i.e. perform a comparison with reference threshold concentrations of ITAC and MIP3B, respectively; and output data representing the likelihood of the subject developing severe symptoms of disease and/or becoming contagious (which may be accompanied by an indication of the

specificity, sensitivity, PPV and NPV of the selected thresholds). Server **(S)** may then relay a result to device **(1)**, the result concerning whether the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious. The network further comprises at least one additional device **(2)**. Server **(S)** may be configured to relay the result via link **(L)** to additional device **(2),** for example for display by the at least one additional computing device. The at least one additional computing device may be a tablet, laptop, mobile phone, or the like**.**

Where in the foregoing description, integers or elements are mentioned which have known, obvious or foreseeable equivalents, then such equivalents are herein incorporated as if individually set forth. Reference should be made to the claims for determining the true scope of the present disclosure, which should be construed so as to encompass any such equivalents. It will also be appreciated by the reader that integers or features of the disclosure that are described as preferable, advantageous, convenient or the like are optional and do not limit the scope of the independent claims. Moreover, it is to be understood that such optional integers or features, whilst of possible benefit in some embodiments of the disclosure, may not be desirable, and may therefore be absent, in other embodiments.

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Claims

1. A method of assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, comprising:
    a) measuring the concentration of Interferon-inducible T-cell Alpha Chemoattractant (ITAC) and the concentration of Macrophage Inflammatory Protein 3 Beta (MIP3B) in a biological sample obtained from the subject; and
    b) analysing the concentration of ITAC and the concentration of MIP3B in conjunction with each other, to assess whether the subject is at risk of developing severe symptoms of disease and/or becoming contagious.

2. A method of assessing the concentration of ITAC and the concentration of MIP3B in a subject who is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, the method comprising:
    a) obtaining a biological sample from the subject;
    b) measuring the concentration of ITAC in the biological sample by immunoassay using one or more antibodies specific for ITAC;
    c) measuring the concentration of MIP3B in the biological sample by immunoassay using one or more antibodies specific for MIP3B; and
    d) analysing the measured concentration of ITAC and the measured concentration of MIP3B in conjunction with each other, to determine whether the subject is at risk of developing severe symptoms of disease and/or becoming contagious.

3. A method of conducting a clinical trial or field study, comprising:
    a) measuring the concentration of ITAC and the concentration of MIP3B in biological samples obtained from a plurality of subjects;
    b) analysing the measured concentration of ITAC and the measured concentration of MIP3B in each sample in conjunction with each other, to assess whether a respective subject is at risk of developing severe symptoms of disease and/or becoming contagious; and
    c) including or excluding a subject who is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious in the clinical trial or field study or in a subgroup of the clinical trial or field study.

4. A computer-implemented method of assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, comprising:
    a) receiving by a computer input data representing the measured concentration of ITAC and the concentration of MIP3B in a biological sample obtained from the subject;

b) processing by a computer the input data to analyse the measured concentration of ITAC and the measured concentration of MIP3B in conjunction with each other, to assess the likelihood that the subject will develop severe symptoms of disease and/or become contagious; and

c) outputting by a computer output data representing the likelihood of the subject developing severe symptoms of disease and/or becoming contagious.

5. A method of providing data relevant to whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, comprising:

a) measuring the concentration of ITAC and the concentration of MIP3B in a biological sample obtained from the subject;

b) receiving the measured concentrations in a computer and encoding the measured concentrations in computer-readable form, and

c) transmitting the encoded measured concentrations to a remote computer for evaluation in accordance with a method of claim 3.

6. The method of claim 4, wherein said outputting step (c) comprises displaying the output data on a display in a form which can be understood by a human being or transmitting the output data to a remote computer.

7. The method of any of claims 1 or 3 to 5, wherein (b) analysing the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction, comprises: dividing the measured concentration of ITAC measured in step (a) by a measured baseline concentration of ITAC (which is the concentration of ITAC measured in a biological sample obtained from the subject prior to exposure, or possible exposure, of the subject to the respiratory virus), to obtain a value for the fold change in the measured concentration of ITAC; and dividing the measured concentration of MIP3B measured in step (a) by a measured baseline concentration of MIP3B (which is the measured concentration of MIP3B in a biological sample obtained from the subject prior to exposure, or possible exposure, of the subject to the respiratory virus), to obtain a value for the fold change in the measured concentration of MIP3B; or the method of claim 2, wherein (d) analysing the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction, comprises: dividing the measured concentration of ITAC measured in step (b) by a measured baseline concentration of ITAC (which is the concentration of ITAC measured in a biological sample obtained from the subject prior to exposure, or possible exposure, of the subject to the respiratory virus), to obtain a value for the fold change in the measured concentration of ITAC; and dividing the measured concentration of MIP3B measured in step (c) by a measured baseline concentration of MIP3B (which is the measured concentration of MIP3B in a biological sample obtained from the subject prior to

exposure, or possible exposure, of the subject to the respiratory virus), to obtain a value for the fold change in the measured concentration of MIP3B.

8. The method of any of claims1 or 3 to 5, wherein (b) analysing the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction, comprises: dividing the measured concentration of ITAC measured in step (a) by a measured baseline concentration of ITAC (which is the concentration of ITAC measured in a biological sample obtained from one or more uninfected control subjects) to obtain a value for the fold change in the measured concentration of ITAC; and dividing the measured concentration of MIP3B measured in step (a) by a measured baseline concentration of MIP3B (which is the concentration of MIP3B measured in a biological sample obtained from one or more uninfected control subjects), to obtain a value for the fold measured change in the concentration of MIP3B; or the method of claim 2, wherein (d) analysing the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction, comprises: dividing the measured concentration of ITAC measured in step (b) by a measured baseline concentration of ITAC (which is the concentration of ITAC measured in a biological sample obtained from one or more uninfected control subjects) to obtain a value for the fold change in the measured concentration of ITAC; and dividing the measured concentration of MIP3B measured in step (c) by a measured baseline concentration of MIP3B (which is the concentration of MIP3B measured in a biological sample obtained from one or more uninfected control subjects), to obtain a value for the fold measured change in the concentration of MIP3B.

9. The method of claim 7 or claim 8, wherein the analysing step (b) of any of claims 1 to 3 or 5, or the analysing step (d) of claim 2, further comprises: comparing the fold change in the measured concentration of ITAC with a reference threshold fold change in the concentration of ITAC; and comparing the fold change in the measured concentration of MIP3B with a reference threshold fold change in the concentration of MIP3B; wherein when the fold change in the measured concentration of ITAC is above the reference threshold fold change in the concentration of ITAC, and the fold change in the measured concentration of MIP3B is above the reference threshold fold change in the concentration of MIP3B, the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious.

10. The method of claim 9, wherein the reference threshold fold change in the concentration of ITAC and the reference threshold fold change in the concentration of MIP3B are determined by:

- measuring the baseline concentration of ITAC and the baseline concentration of MIP3B in biological samples obtained from a group of persons uninfected with respiratory virus;
- measuring the concentration of ITAC and the concentration of MIP3B in biological samples obtained from the group of persons after inoculation with respiratory virus;

- ascertaining the fold change in the concentration of ITAC and the fold change in the concentration of MIP3B for each person from uninfected to after inoculation;
- classifying members of the group, after inoculation, according to their risk of developing severe symptoms of disease and/or becoming contagious; and
- setting the reference threshold fold changes for ITAC and MIP3B, respectively, to be a fold change in the concentration of ITAC and a fold change in the concentration of MIP3B which together discriminate between persons at risk and persons not at risk, according to a desired measure of test performance.

11. The method of claim 9 or claim 10, wherein the reference threshold fold change in the concentration of ITAC is about 1 to about 1.6; and the reference threshold fold change in the concentration of MIP3B is about 1.2 to about 1.5, as measured using a multiplex bead-based assay, for example a multiplex bead-based assay characterised as follows: Human Multi-Analyte Profile; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions) and expressed in arbitrary units.

12. The method of claim 11, wherein the probability that a subject who will go on to develop severe symptoms of disease and/or become contagious has a fold change in the measured concentration of ITAC of greater than the ITAC reference threshold fold change (sensitivity) is in a range of about 0.4 to about 0.6; and the probability that a subject who will go on to develop severe symptoms of disease and/or become contagious has a fold change in the measured concentration of MIP3B of greater than the MIP3B reference threshold fold change (sensitivity) is in a range of about 0.3 to about 0.6.

13. The method of claim 11 or claim 12, wherein the probability that a subject who will not go on to develop severe symptoms of disease and/or become contagious has a fold change in the measured concentration of ITAC below the ITAC reference threshold fold change (specificity) is in a range of about 0.65 to about 0.85; and the probability that a subject who will not go on to develop severe symptoms of disease and/or become contagious has a fold change in the measured concentration of MIP3B below the MIP3B reference threshold fold change (specificity) is in a range of about 0.65 to about 0.85.

14. The method of any of claims 11 to 13, wherein a fold change in the measured concentration of ITAC of greater than the ITAC reference threshold fold change corresponds to a positive predictive value (PPV) in a range of about 0.3 to about 0.5; and a fold change in the measured concentration of MIP3B of greater than the MIP3B reference threshold fold change corresponds to a positive predictive value (PPV) in a range of about 0.3 to about 0.5.

15. The method of any of claims 11 to 14, wherein a fold change in the measured concentration of ITAC of less than the ITAC reference threshold fold change corresponds to a negative predictive value

(NPV) in a range of about 0.7 to about 0.9; and a fold change in the measured concentration of MIP3B of less than the MIP3B reference threshold fold change corresponds to a negative predictive value (NPV) in a range of about 0.7 to about 0.9.

16. The method of any of claims1 or 3 to 5, wherein (b) analysing the measured concentration of ITAC and the measured concentration of MIP3B in each sample, in conjunction, comprises: comparing the measured concentration of ITAC to reference a threshold for the concentration of ITAC; and comparing the measured concentration of MIP3B to a reference threshold for the concentration of MIP3B, wherein when the measured concentration of ITAC and the measured concentration of MIP3B are above their respective reference thresholds, the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious; or the method of claim 2, wherein (d) analysing the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction, comprises: comparing the measured concentration of ITAC to reference a threshold for the concentration of ITAC; and comparing the measured concentration of MIP3B to a reference threshold for the concentration of MIP3B, wherein when the measured concentration of ITAC and the measured concentration of MIP3B are above their respective reference thresholds, the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious.

17. The method of claim 16, wherein the reference threshold concentration of ITAC and the reference threshold concentration of MIP3B are determined by:

- measuring the concentration of ITAC and the concentration of MIP3B in biological samples obtained from a group of persons after inoculation with respiratory virus;
- classifying members of the group, after inoculation, according to their risk of developing severe symptoms of disease and/or becoming contagious; and
- setting the threshold concentrations of ITAC and MIP3B, respectively, to be a concentration of ITAC and a concentration of MIP3B which together discriminate between persons at risk and persons not at risk, according to a desired measure of test performance.

18. The method of claim 16 or claim 17, wherein the reference threshold concentration of ITAC is about 14 to about 40; and the reference threshold concentration of MIP3B is about 250 to about 300, as measured using a multiplex bead-based assay, for example a multiplex bead-based assay characterised as follows: Human Multi-Analyte Profile; Luminex platform; platform and antibodies provided by Myriad Rules Based Medicine (Q2 Solutions) and expressed in arbitrary units.

19. The method of claim 18, wherein the probability that a subject who will go on to develop severe symptoms of disease and/or become contagious has a measured concentration of ITAC greater than the reference threshold concentration of ITAC (sensitivity) is in a range of about 0.4 to about 0.7;

and the probability that a subject who will go on to develop severe symptoms of disease and/or become contagious has a measured concentration of MIP3B greater than the reference threshold concentration of MIP3B (sensitivity) is in a range of about 0.4 to about 0.65.

20. The method of claim 18 or claim 19, wherein the probability that a subject who will not go on to develop severe symptoms of disease and/or become contagious has a measured concentration of ITAC below the reference threshold concentration of ITAC (specificity) is in a range of about 0.65 to about 0.85; and the probability that a subject who will not go on to develop severe symptoms of disease and/or become contagious has a measured concentration of MIP3B below the reference threshold concentration of MIP3B (specificity) is in a range of about 0.65 to about 0.85.

21. The method of any of claims 18 to 20, wherein a measured concentration of ITAC above the reference threshold concentration of ITAC corresponds to a positive predictive value (PPV) in a range of about 0.35 to about 0.5; and a measured concentration of MIP3B above the reference threshold concentration of MIP3B corresponds to a positive predictive value (PPV) in a range of about 0.3 to about 0.5.

22. The method of any of claims 18 to 21, wherein a measured concentration of ITAC below the reference threshold concentration of ITAC corresponds to a negative predictive value (NPV) in a range of about 0.75 to about 0.9; and a measured concentration of MIP3B below the reference threshold concentration of MIP3B corresponds to a negative predictive value (NPV) in a range of about 0.75 to about 0.9.

23. The method of any of claims 1 to 4 or 6 to 22, wherein the subject is tested two or more times for the concentration of ITAC and the concentration of MIP3B, and the subject is assessed to be at risk of developing severe symptoms and/or becoming contagious if the result of at least one or more than one of the tests indicates so; optionally wherein successive tests of the two or more tests are separated by a time interval of at least about 12 hours.

24. The method of claim 23, wherein the ITAC and MIP3B reference thresholds above which a positive result is obtained are different for the two or more tests; the ITAC and MIP3B reference thresholds for at least one test being calculated to minimise false positives; and the ITAC and MIP3B reference thresholds for at least another test being calculated to have fewer false negatives than the one test.

25. The method of any of claims 1 to 22, wherein the biological sample was obtained from the subject at least about 45 hours after exposure, or possible exposure, to the respiratory virus.

26. The method of any preceding claim, wherein the subject has had a positive diagnostic test for respiratory viral disease, presents with symptoms of respiratory viral disease, and/or has had prolonged exposure to at least one other person who is infected with a respiratory virus.

27. The method of any preceding claim, wherein the respiratory virus is respiratory syncytial virus (RSV), parainfluenza virus (HPIV), metapneumovirus (HMPV), rhinovirus (HRV), coronavirus such as SARS-CoV (for example, SARS-CoV-1 or SARS-CoV-2), adenovirus (HAdV), enterovirus (EV), bocavirus (HBoV), parechovirus (HPeV) or an influenza virus.

28. The method of claim 27, wherein the respiratory virus is an influenza virus.

29. The method of any preceding claim, wherein the biological sample is a blood serum sample.

30. The method of any preceding claim, wherein the concentration of ITAC and the concentration of MIP3B are measured by immunoassay of the biological sample, optionally by enzyme-linked immunosorbent assay or by single- or multi-plex bead array assay.

31. The method of any preceding claim, wherein the subject is administered one or more medicinal products before or after exposure or possible exposure to the respiratory virus.

32. The method of claim 3 or any of claims 7 to 30 when dependent on claim 3, wherein a subject who is included in the clinical trial or field study, or in the subgroup of the clinical trial or field study, is administered one or more medicinal products, and/or subjected to one or more surgical or non-surgical interventions.

33. The method of claim 1, or the method of any of claims 7 to 30 when dependent on claim 1, further comprising administering one or more medicinal products to the subject, and/or subjecting the subject to one or more surgical or non-surgical interventions, if the subject is assessed to be at risk of developing severe symptoms and/or becoming contagious.

34. The method of any of claims 31 to 33, wherein the one or more medicinal products are selected from one or more antiviral agents (e.g. oseltamivir) and/or one or more immunomodulatory agents.

35. The method of any of claims 32 to 34, wherein the one or more surgical or non-surgical interventions are selected from hospitalising the subject, allocating the subject a hospital bed in anticipation of their condition worsening; administering oxygen to the subject, e.g. by means of a ventilator or by extracorporeal membrane oxygenation.

36. A computer program comprising instructions which, when carried out by a computer, cause the computer to carry out step (b) of the method of claim 1, or any of claims 3 or 6 to 30 when dependent on claim 1; or to carry out step (d) of the method of claim 2, or any of claims 3 to 30 when dependent on claim 2.

37. A computer network comprising:

a) at least one server;

b) at least one other computing device; and

c) a data communications link between the server and the other device;

wherein the at least one other device is configured to transmit data to the at least one server, the data representing the measured concentration of ITAC and the measured concentration of MIP3B in a biological sample obtained from a subject; and the at least one server is configured to analyse the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction with one another, to assess whether the subject is at risk of developing severe symptoms of disease and/or becoming contagious by executing the method of claim 4, or by executing the method of any of claims 6 to 30 when dependent on claim 4.

38. The computer network of claim 3637, wherein the at least one server is configured to analyse the measured concentration of ITAC and the measured concentration of MIP3B, before relaying a result to the other device, the result concerning whether the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious.

39. The computer network of claim 37 or claim 38, further comprising at least one further computing device, wherein the at least one server is configured to analyse the measured concentration of ITAC and the measured concentration of MIP3B, in conjunction with one another, before relaying a result to the at least one further computing device, the result concerning whether the subject is assessed to be at risk of developing severe symptoms of disease and/or becoming contagious.

40. A kit for assessing whether a subject is at risk of developing severe symptoms of disease and/or becoming contagious after exposure, or possible exposure, to a respiratory virus, the kit comprising two or more reagents allowing quantitation of the concentrations of ITAC and MIP3B.

41. The kit of claim 40, wherein the kit comprises one or more of: two or more enzyme-linked immunosorbent assays (ELISAs), respectively comprising reporter enzymes specific to ITAC and MIP3B; two or more single-plex bead array assays respectively comprising capture and detection antibodies specific to ITAC and MIP3B; and a multi-plex bead array assay comprising capture and detection antibodies specific to ITAC and MIP3B.

42. The kit of claim 40 or claim 41, wherein the kit comprises comprise a lateral flow assay comprising immobilised labelled antibodies specific to each of ITAC and MIP3B and thus configured to detect ITAC and MIP3B in a biological sample collected from the subject; preferably a nasopharyngeal sample.

43. The method, kit or network of any preceding claim, wherein a subject having severe symptoms of disease is any subject who requires hospitalisation; and/or wherein severe symptoms of disease comprise one or more of: tachypnoea, hypoxemia, an arterial oxygen saturation of $\leq 92\%$ on room air by a transcutaneous method and radiological pulmonary infiltrates.

44. The method, kit or network of any preceding claim, wherein the subject is a mammal, optionally wherein the subject is a human, or a non-human mammal.

Quarantine Subject Symptom Diary Card
Protocol: RDO-CS-004

Subject Number: _____ Subject Initials: _____

Date: _____ Time: _____
dd mmm yyyy hh mm

Morning ☐ Afternoon ☐ Evening ☐

How much are your symptoms bothering you?

Symptoms Please report the symptoms you are experiencing at the moment	Mark the scale with a single line as demonstrated before: Not at all bothered ☺ — Severely bothered ☹	*hVIVO Staff use only* Line Length (cm): ___.___ Length of mark (cm):
Runny Nose		___.___
Stuffy Nose		___.___
Sneezing		___.___
Sore Throat		___.___
Earache		___.___
Malaise (tiredness)		___.___
Headache		___.___
Muscle and/or Joint Ache		___.___
Chillness / Feverishness		___.___
Cough		___.___
Chest Tightness		___.___
Shortness of breath		___.___
Wheeze		___.___

Subject's Initials _____

Physician's Initials _____ _____
dd mmm yyyy

FIG. 1A

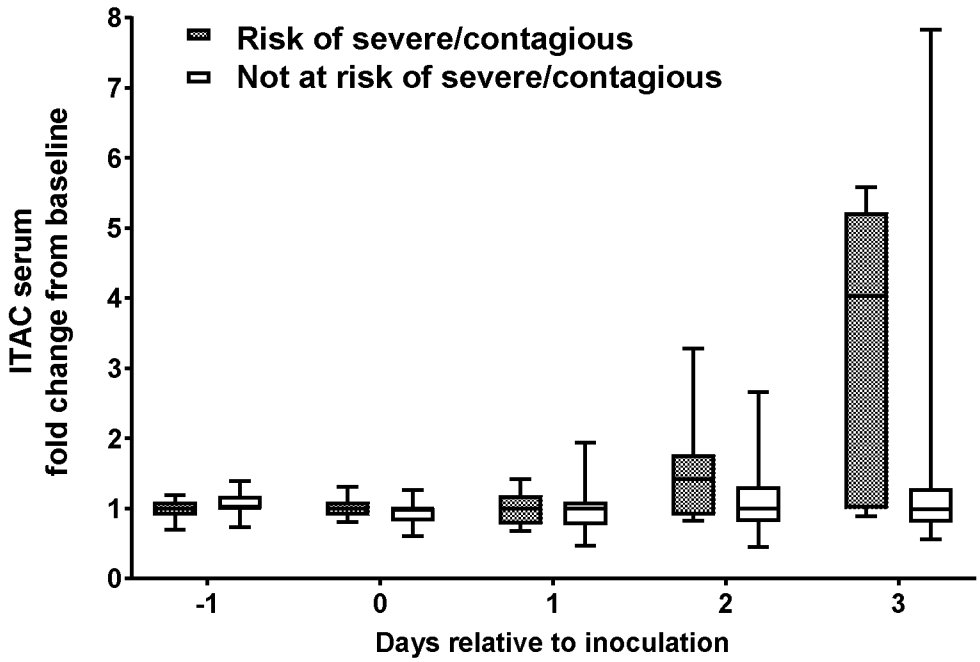
Risk of severe/contagious
Not at risk of severe/contagious
ITAC serum
fold change from baseline
0
1
2
3
4
5
6
7
8
-1
0
1
2
3
Days relative to inoculation

Fig. 1B

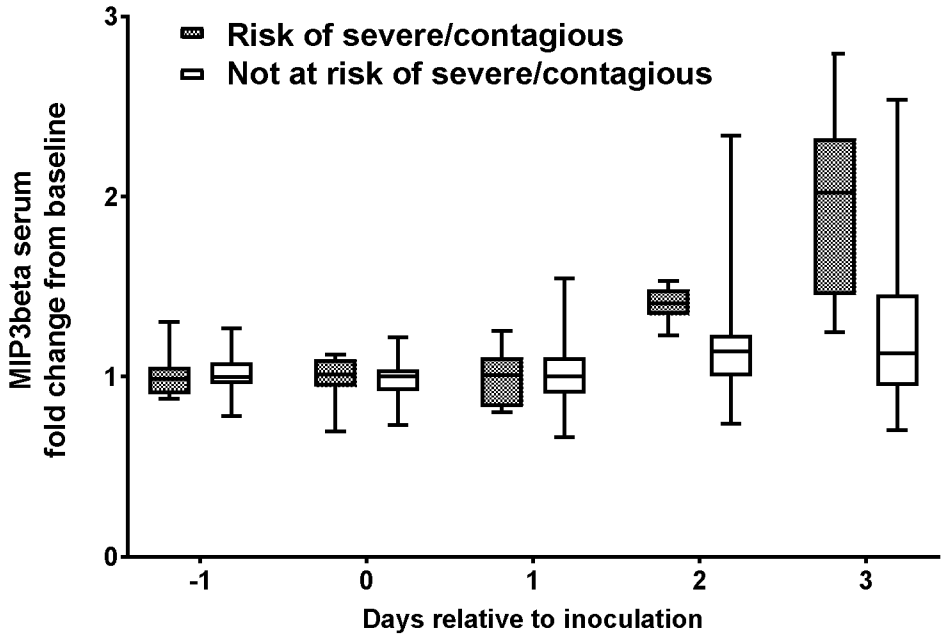
Risk of severe/contagious
Not at risk of severe/contagious
MIP3beta serum
fold change from baseline
3
2
1
0
-1
0
1
2
3
Days relative to inoculation

Fig. 1C

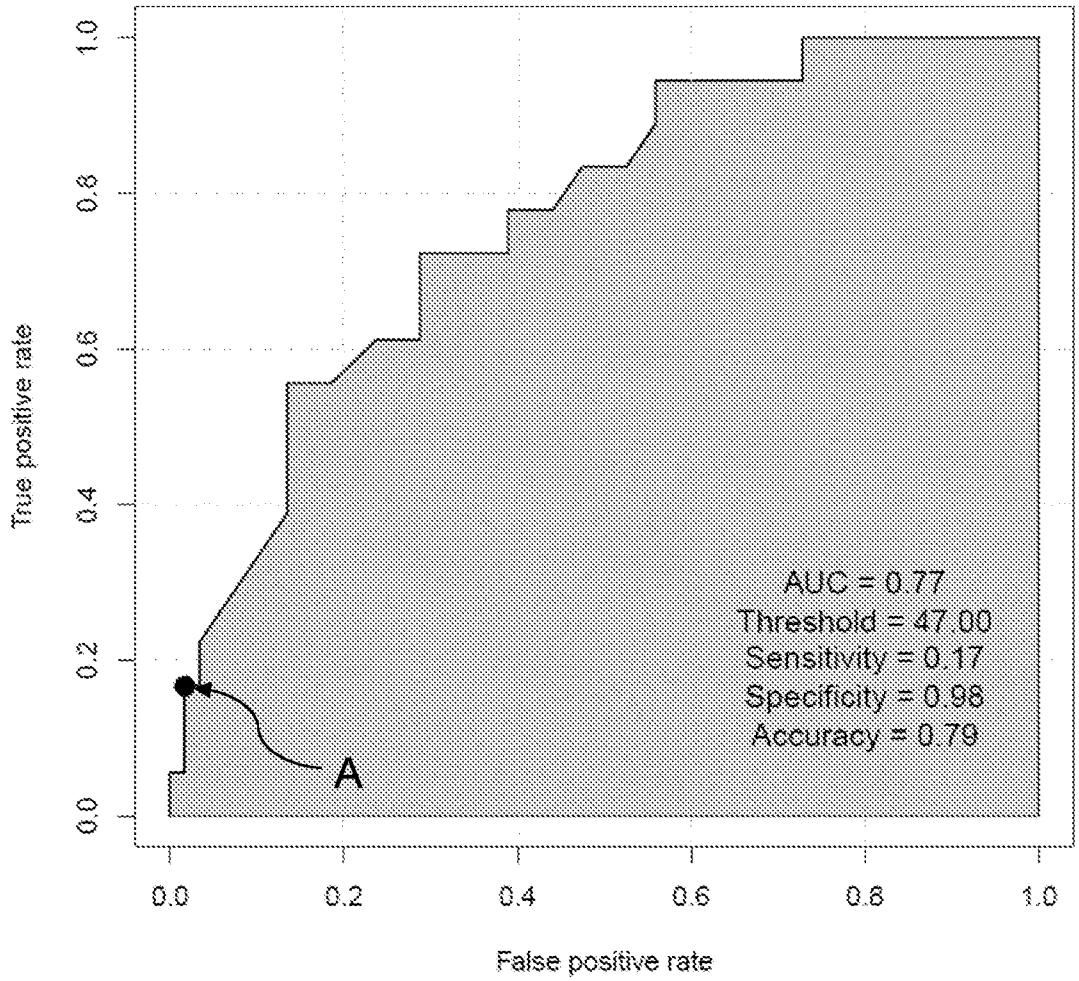
True positive rate
0.0
0.2
0.4
0.6
0.8
1.0
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUC = 0.77
Threshold = 47.00
Sensitivity = 0.17
Specificity = 0.98
Accuracy = 0.79
A

Fig. 2A

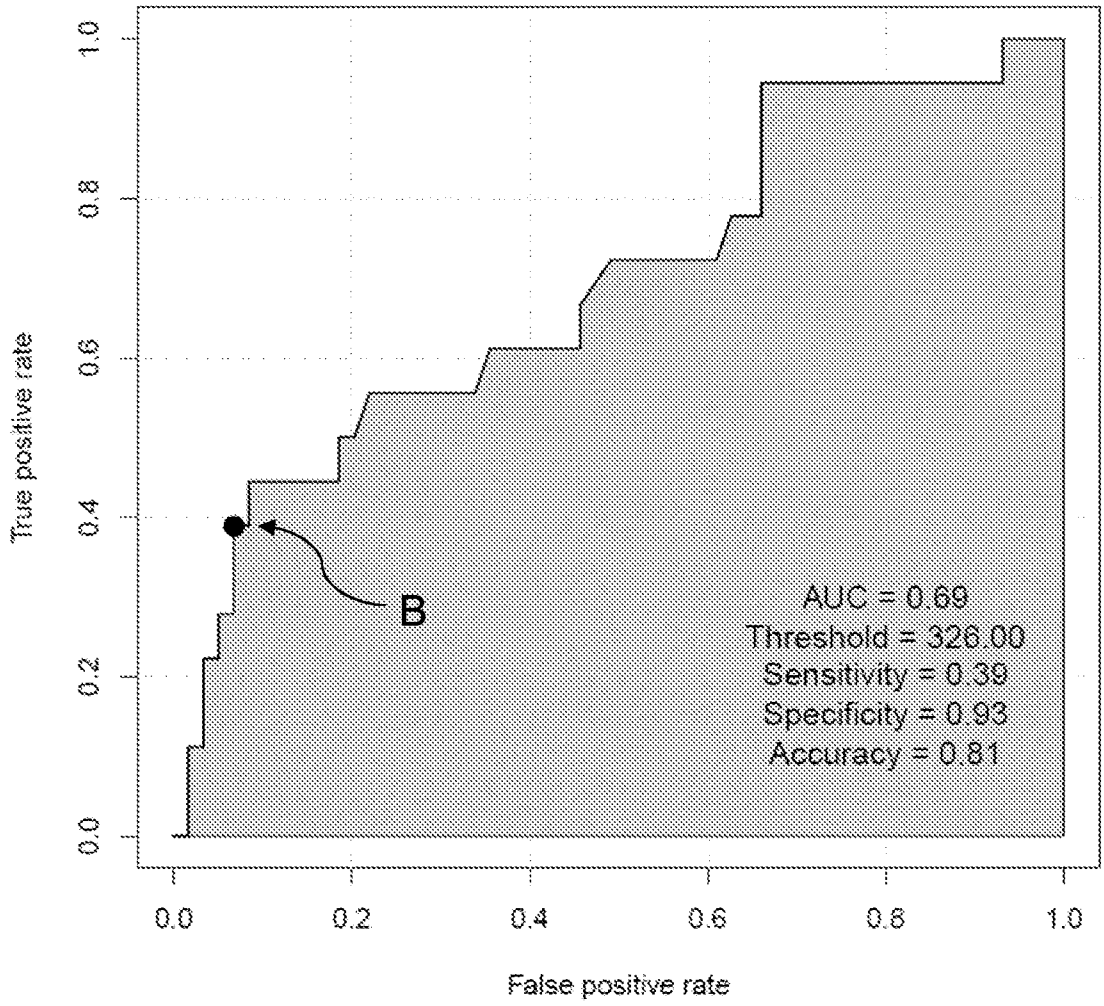
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
B
AUC = 0.69
Threshold = 326.00
Sensitivity = 0.39
Specificity = 0.93
Accuracy = 0.81

Fig. 2B

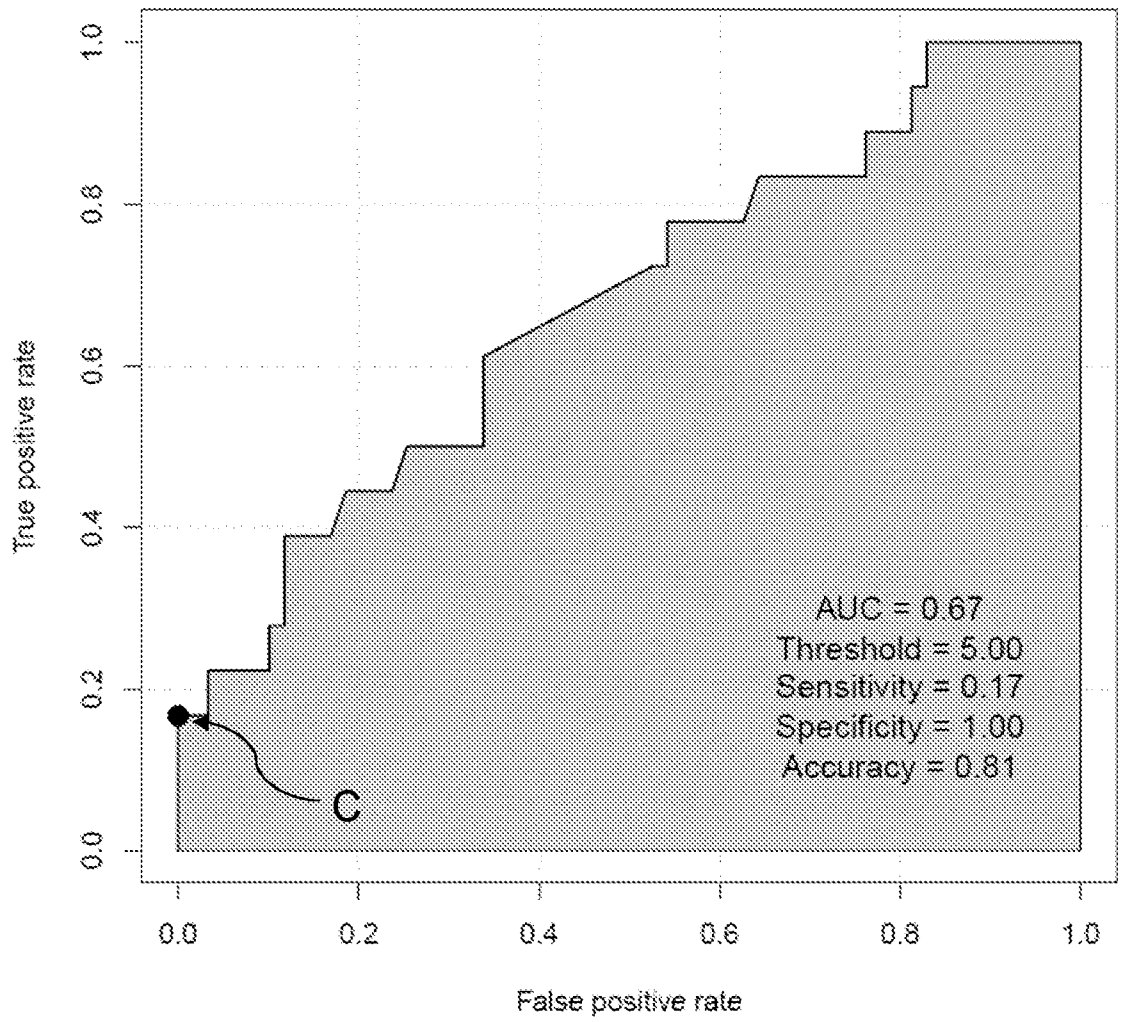
True positive rate
0.0
0.2
0.4
0.6
0.8
1.0
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUC = 0.67
Threshold = 5.00
Sensitivity = 0.17
Specificity = 1.00
Accuracy = 0.81
C

Fig. 3A

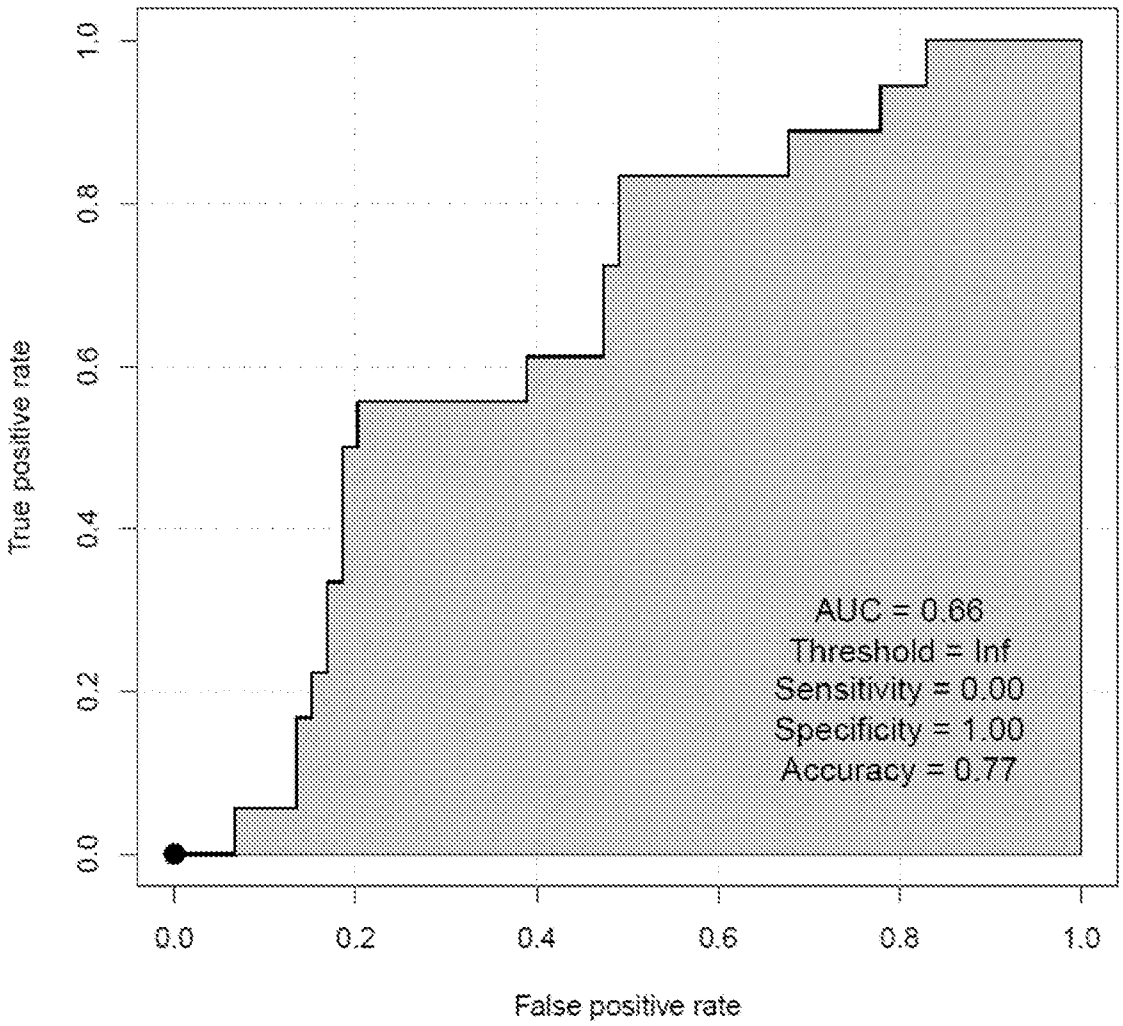
True positive rate
0.0
0.2
0.4
0.6
0.8
1.0
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
AUC = 0.66
Threshold = Inf
Sensitivity = 0.00
Specificity = 1.00
Accuracy = 0.77

Fig. 3B

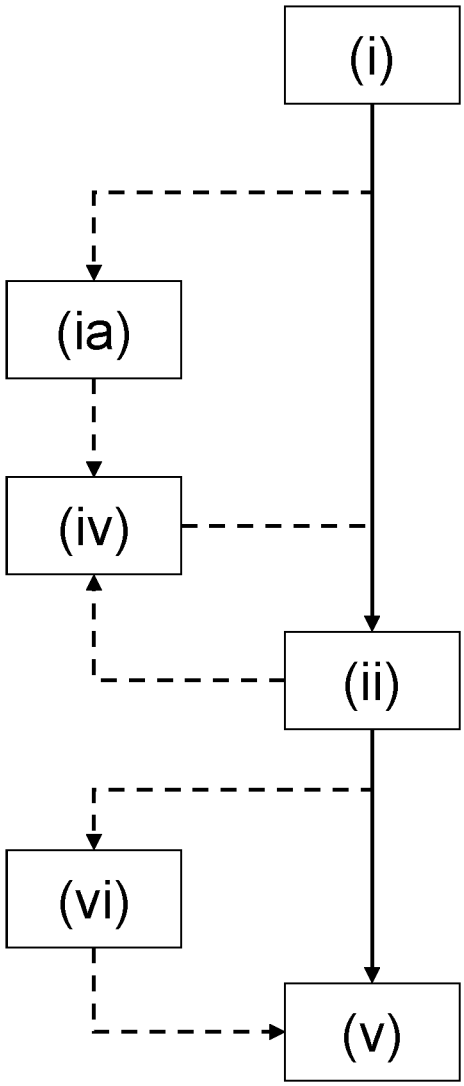

Fig. 4

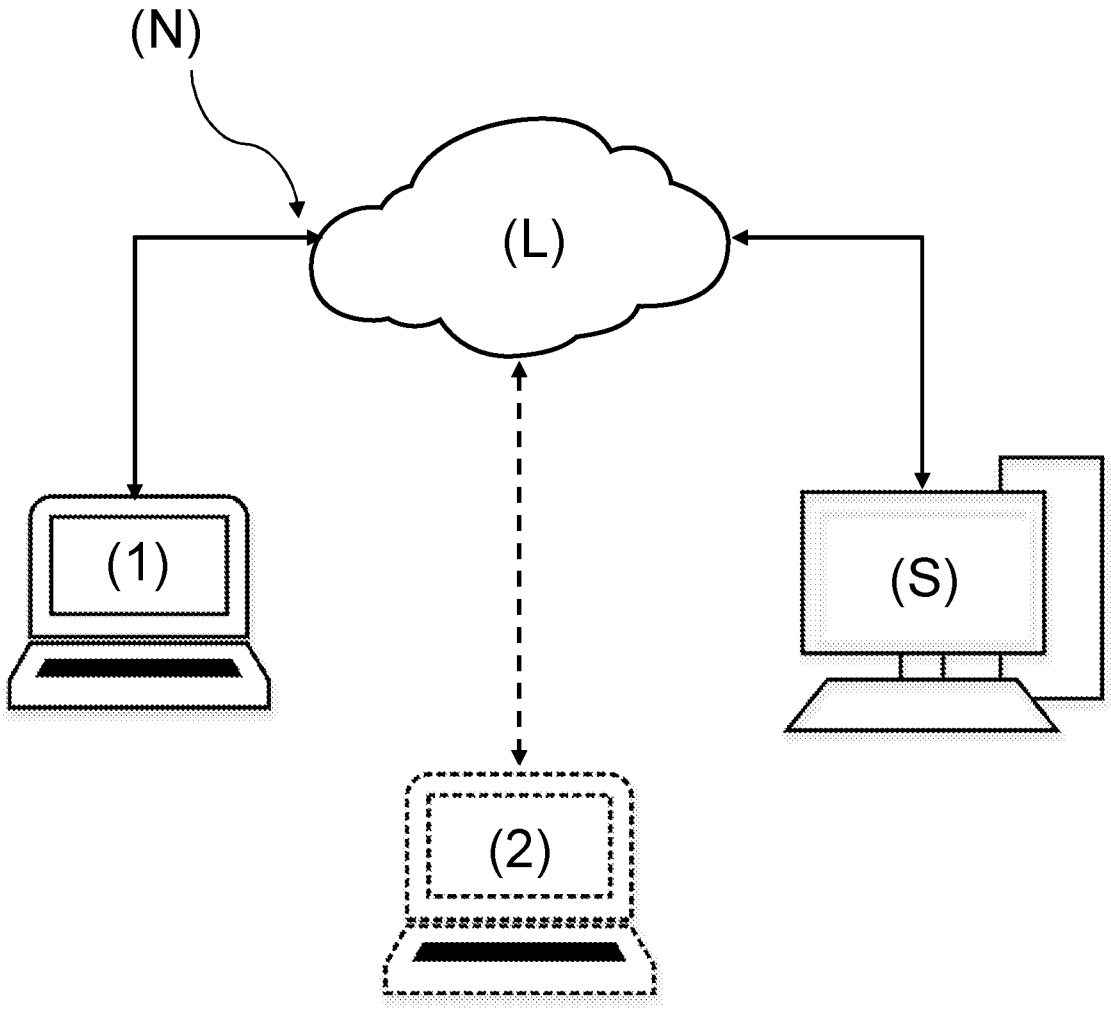

Fig. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2022/052610

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/68 G16H50/20
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N G16H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PIQUERAS BERNARD ET AL: "Upon viral exposure, myeloid and plasmacytoid dendritic cells produce 3 waves of distinct chemokines to recruit immune effectors", BLOOD, vol. 107, 1 January 2006 (2006-01-01), pages 2613-2618, XP055981581, DOI: 10.1182/blood- Retrieved from the Internet: URL:h> Materials and methods ----- -/--	36,40-44

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2023	23/01/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rosin, Oliver

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2022/052610

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KHALIL BARIAA A. ET AL: "Chemokines and chemokine receptors during COVID-19 infection", COMPUTATIONAL AND STRUCTURAL BIOTECHNOLOGY JOURNAL, vol. 19, 27 January 2021 (2021-01-27), pages 976-988, XP055956835, Sweden ISSN: 2001-0370, DOI: 10.1016/j.csbj.2021.01.034 Retrieved from the Internet: URL:http://dx.doi.org/10.1016/j.csbj.2021.01.034> chapter 3; figure 1	1-44
X	WO 2011/049886 A1 (THERANOS INC [US]; HOLMES ELIZABETH A [US]) 28 April 2011 (2011-04-28) abs; figures; par [0158] et seq.	1-44

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2022/052610

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