that is different from the first infection when the amount of total mcfNA comprising mcfNA from at least two different microbes exceeds the threshold amount of total mcfNA.

[005a] In another aspect, provided herein is use of a therapeutic drug in the manufacture of a medicament for treating a secondary infection in a subject with a first infection, wherein (a) (a) the secondary infection is detected in a blood sample collected from the subject with the first infection when an amount of total microbial cell-free nucleic acids (mcfNA) comprising mcfNA from at least two microbes in the blood sample exceeds a threshold amount of total mcfNA, wherein the amount of total mcfNA is calculated by next generation sequencing; and (b) the therapeutic drug is to be administered to the subject with the first infection in order to treat the secondary infection.

[006] In another aspect, a method of detecting a secondary infection in a subject with a first infection is provided, comprising: (a) preparing a plasma sample from blood obtained from the subject with the first infection, wherein the plasma sample comprises microbial cell-free nucleic acids (mcfNA) from at least two different microbes; (b) measuring an amount of total mcfNA in the plasma sample by performing next generation sequencing, wherein the total mcfNA comprises mcfNA from at least two different microbes; (c) comparing the amount of total mcfNA comprising mcfNA from at least two different microbes to a threshold amount of total mcfNA; and (d) detecting a secondary infection that is different from the first infection when the amount of total mcfNA comprising mcfNA from at least two different microbes exceeds the threshold amount of total mcfNA.

[007] In yet another aspect, a method of treating a secondary infection in a subject with a first infection is provided, the method comprising: (a) collecting a blood sample from the subject with the first infection; (b) detecting a secondary infection when an amount of total microbial cell-free nucleic acids (mcfNA) comprising mcfNA from at least two microbes in the blood sample exceeds a threshold amount of total mcfNA, wherein the amount of total mcfNA is calculated by next generation sequencing; and (c) administering a therapeutic drug to the subject with the first infection in order to treat the secondary infection. In some cases, the method further comprises (d) repeating (a), (b), and (c) until the amount of total mcfNA in the blood decreases to a value at or below the threshold amount of total mcfNA.

[008] In yet another aspect, a method of treating a secondary infection in a subject with a first infection is provided, the method comprising: (a) collecting a blood sample from the subject with the first infection; and (b) detecting a secondary infection when an amount of total microbial cell-free nucleic acids (mcfNA) comprising mcfNA from at least two microbes in the blood sample exceeds a threshold amount of total mcfNA, wherein the amount of total mcfNA is calculated by next generation sequencing.

[009] In any of the preceding methods, in some embodiments, the first infection is a COVID-19 infection. In any of the preceding methods, in some embodiments, the first infection is a viral lung infection. In any of the preceding methods, in some embodiments, the first infection is COVID-19 pneumonia. In any of the preceding methods, in some embodiments, the secondary infection is a bacterial or fungal infection. In any of the preceding methods, in some embodiments, the method further comprises determining a presence of at least one bacterium, fungus, or parasite in the subject. In any of the preceding methods, in some embodiments, the first and secondary infections are respiratory infections caused by different microbes. In

any of the preceding methods, in some embodiments, the first and second infections are pneumonia caused by different microbes. In any of the preceding methods, in some embodiments, the at least two microbes are respiratory pathogens. In any of the preceding methods, in some embodiments, the at least two microbes are at least two microbes from the group consisting of *S. aureus*, *P. aeruginosa* and *K. Pneumoniae*. In any of the preceding methods, in some embodiments, the at least two microbes are at least two microbes listed in **Table 2**. In any of the preceding methods, in some embodiments, the at least two microbes are at least two respiratory pathogens listed in Table 2. In any of the preceding methods, in some embodiments, the first