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**Supplementary Table 1.** Data sources

| <b>Data</b>                   | <b>Source</b>  | <b>Extracted</b> | <b>Censored</b> | <b>Content</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------|----------------|------------------|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Suspected mild COVID-19       | e-SUS notifica | 29/04/2022       | 22/04/2022      | COVID-19 suspected individuals of any age in Brazil, from public and private sectors, with mild clinical presentation, including those asymptomatic, not tested, those tested negative and tested positive. COVID-19 suspected cases notification is compulsory.                                                                                                                                                                                                |
| Suspected Severe COVID-19     | SIVEP-Gripe    | 29/04/2022       | 22/04/2022      | Severe Acute Respiratory Infections (SARI) at any age in Brazil, from public and private sectors. Includes those not tested, those tested negative and those tested positive. It also includes SARI caused by other respiratory viruses, other aetiologies and those without an etiology. During COVID-19 pandemic, the official system to which COVID-19 hospital admissions and deaths must be notified. COVID-19 suspected cases notification is compulsory. |
| COVID-19 vaccination status   | SI-PNI         | 29/04/2022       | 22/04/2022      | National database from the Brazilian National Programme of Vaccination. COVID-19 vaccines notification is compulsory.                                                                                                                                                                                                                                                                                                                                           |
| Variants of Concern in Brazil | GISAID         | 09/05/2022       | 22/04/2022      | Public genomic repository data                                                                                                                                                                                                                                                                                                                                                                                                                                  |

**Supplementary Table 2.** General characteristics of who received homologous or heterologous booster

|                                                                                | <b>Homologous booster<br/>(CoronaVac)<br/>(n=69,111)</b> | <b>Heterologous booster<br/>(BNT152b2)<br/>(n=984,444)</b> | <b>SMD</b> |
|--------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------|------------|
| <b>Demographics</b>                                                            |                                                          |                                                            |            |
| <b>Age, mean (SD), years</b>                                                   | 65.1 (21.5)                                              | 53.2 (19.1)                                                | 0.602      |
| <b>Age categories, n (%)</b>                                                   |                                                          |                                                            | 0.645      |
| <b>18-39 years</b>                                                             | 12890 (18.7)                                             | 321694 (32.7)                                              |            |
| <b>40-59 years</b>                                                             | 8313 (12.0)                                              | 227987 (23.2)                                              |            |
| <b>60-79 years</b>                                                             | 31925 (46.2)                                             | 380315 (38.6)                                              |            |
| <b>≥80 years</b>                                                               | 15983 (23.1)                                             | 54448 (5.5)                                                |            |
| <b>Male sex, n (%)</b>                                                         | 27431 (39.7)                                             | 336163 (34.1)                                              | 0.115      |
| <b>Self-reported race†, n (%),</b>                                             |                                                          |                                                            | 0.399      |
| <b>White/Branca</b>                                                            | 42677 (61.8)                                             | 461276 (46.9)                                              |            |
| <b>Mixed/Pardo</b>                                                             | 9464 (13.7)                                              | 278390 (28.3)                                              |            |
| <b>Black/Preta</b>                                                             | 1750 (2.5)                                               | 34897 (3.5)                                                |            |
| <b>Asian/ Amarela</b>                                                          | 652 (0.9)                                                | 15873 (1.6)                                                |            |
| <b>Indigenous/Indigena</b>                                                     | 25 (0.0)                                                 | 2377 (0.2)                                                 |            |
| <b>Missing</b>                                                                 | 14543 (21.0)                                             | 191631 (19.5)                                              |            |
| <b>Region of residence</b>                                                     |                                                          |                                                            | 1.234      |
| <b>North</b>                                                                   | 278 (0.4)                                                | 49932 (5.1)                                                |            |
| <b>Northeast</b>                                                               | 302 (0.4)                                                | 173982 (17.7)                                              |            |
| <b>Central-West</b>                                                            | 350 (0.5)                                                | 75923 (7.7)                                                |            |
| <b>Southeast</b>                                                               | 66494 (96.2)                                             | 489057 (49.7)                                              |            |
| <b>South</b>                                                                   | 1687 (2.4)                                               | 195550 (19.9)                                              |            |
| <b>Reported number of chronic comorbidities‡, n (%)</b>                        |                                                          |                                                            | 0.221      |
| <b>None</b>                                                                    | 56094 (81.2)                                             | 875843 (89.0)                                              |            |
| <b>One or two</b>                                                              | 12457 (18.0)                                             | 104856 (10.7)                                              |            |
| <b>Three or more</b>                                                           | 560 (0.8)                                                | 3745 (0.4)                                                 |            |
| <b>Prior SARS-CoV-2 exposure</b>                                               |                                                          |                                                            |            |
| <b>Previous symptomatic events notified to the surveillance system¶, n (%)</b> | 14381 (20.8)                                             | 253801 (25.8)                                              | 0.118      |

|                                                                                           |              |               |       |
|-------------------------------------------------------------------------------------------|--------------|---------------|-------|
| <b>Positive SARS-CoV-2 test result††, n (%)</b>                                           | 3268 (4.7)   | 52378 (5.3)   | 0.027 |
| <b>Interval between symptoms onset and RT-PCR/Antigen testing, median (p25-p75), days</b> | 3 [2, 4]     | 3.00 [2, 4]   | 0.038 |
| <b>Interval between third dose and testing, median (p25-p75), days</b>                    | 93 [50, 116] | 87 [56, 105]  | 0.123 |
| <b>Omicron period</b>                                                                     | 67747 (98.0) | 966813 (98.2) | 0.013 |

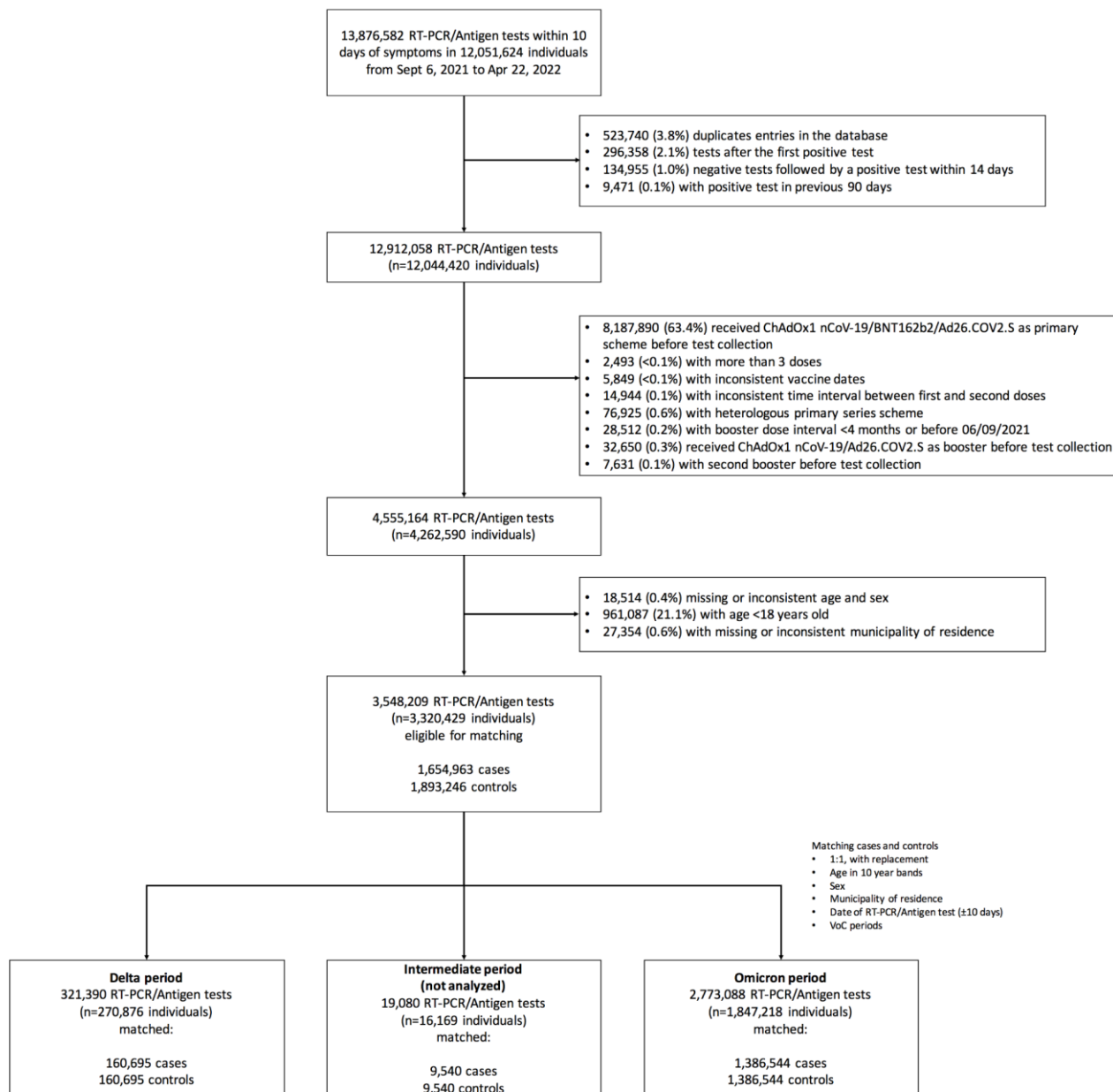
RT-PCR=reverse transcription polymerase chain reaction; SMD=standardized mean difference; SD=standard deviation; SMD=standardized mean difference. † Race/skin colour as defined by the Brazilian national census bureau (Instituto Nacional de Geografia e Estatísticas). ‡ Comorbidities included cardiovascular, or renal conditions, diabetes, chronic respiratory disorder, obesity, or immunosuppression. ¶ Reported illness with covid-19 associated symptoms in eSUS and SIVEP-Gripe databases before the start of study on 06 September 2021.. †† Defined as a positive SARS-CoV-2 RT-PCR or antigen detection test result before the start of study on 06 September 2021.

**Supplementary Figure 1.** Number of SARS-CoV-2 RT-PCR and rapid antigen tests in symptomatic individuals performed in Brazil since January 2021.



Red refers to rapid antigen test for SARS-CoV-2; green to RT-PCR test for SARS-CoV-2

**Supplementary Figure 2.** Study flow chart showing inclusion of cases and controls for the primary analysis



**Supplementary Table 3.** Unadjusted vaccine effectiveness of CoronaVac and homologous or heterologous booster against symptomatic Covid-19 and hospital admissions or deaths in adults in Brazil

|                                           | Symptomatic COVID-19 |                      | Hospitalization or death |                   |
|-------------------------------------------|----------------------|----------------------|--------------------------|-------------------|
|                                           | Delta                | Omicron              | Delta                    | Omicron           |
| <b>Not vaccinated</b>                     | Reference            | Reference            | Reference                | Reference         |
| <b>Single dose, within 0-13 days</b>      | 5% (-1-10.7)         | 25.8% (20.4-30.9)    | -1% (-28.7-27.3)         | 0.8% (-50.9-51.7) |
| <b>Single dose, ≥14 days</b>              | 29% (26.9-31.1)      | 18.4% (17.3-19.4)    | 44% (36.8-50.4)          | 42.4% (36-48.1)   |
| <b>Two doses, within 0-13 days</b>        | 40.1% (37.1-43)      | 23% (19-26.8)        | 79% (71.4-84.6)          | 22.5% (-38.4-63)  |
| <b>Two doses, 14-59 days</b>              | 52.4% (51-53.7)      | 29.7% (28.2-31.2)    | 86.6% (83.8-88.9)        | 56.2% (42.7-66.5) |
| <b>Two doses, 60-179 days</b>             | 38.7% (37.2-40.1)    | 5.4% (4.6-6.2)       | 70.4% (68.1-72.5)        | 63.6% (60.2-66.7) |
| <b>Two doses, ≥180 days</b>               | 34.2% (32.5-35.9)    | 4.5% (3.5-5.5)       | 55.6% (52.1-59)          | 53.1% (50-55.9)   |
| <b>Third dose of CoronaVac, 0-7 days</b>  | 40.1% (20.3-54.9)    | 10.2% (2.4-17.4)     | 73.4% (56.9-83.6)        | 77.6% (42.7-91.2) |
| <b>Third dose of CoronaVac, 8-59 days</b> | 54.2% (47.2-60.3)    | 7.4% (4.3-10.3)      | 69% (60.1-75.9)          | 77.4% (70.7-82.5) |
| <b>Third dose of CoronaVac, ≥60 days</b>  | 50.7% (27.2-66.7)    | -13.2% (-15.2--11.1) | 71.2% (47.2-84.3)        | 55.8% (51.9-59.4) |
| <b>Third dose of BNT162b2, 0-7 days</b>   | 43% (38.9-46.8)      | 16.7% (14.8-18.5)    | 76.5% (71.6-80.5)        | 63.5% (53.6-71.3) |
| <b>Third dose of BNT162b2, 8-59 days</b>  | 86.8% (86.1-87.5)    | 56.4% (55.9-56.9)    | 90.8% (89.4-91.9)        | 86.2% (85-87.4)   |
| <b>Third dose of BNT162b2, ≥60 days</b>   | 82.8% (79.4-85.7)    | 31.1% (30.5-31.8)    | 88.2% (81.6-92.4)        | 85.5% (84.6-86.4) |

**Supplementary Table 4.** Adjusted vaccine effectiveness of CoronaVac and homologous or heterologous booster against symptomatic Covid-19 and hospital admissions or deaths in adults in Brazil

|                                           | Symptomatic COVID-19 |                   | Hospitalization or death |                    |
|-------------------------------------------|----------------------|-------------------|--------------------------|--------------------|
|                                           | Delta                | Omicron           | Delta                    | Omicron            |
| <b>Not vaccinated</b>                     | Reference            | Reference         | Reference                | Reference          |
| <b>Single dose, within 0-13 days</b>      | 2.2% (-4-8.1)        | 24.6% (19.1-29.8) | 1.7% (-28.4-30.8)        | -3.1% (-57.5-54.7) |
| <b>Single dose, ≥14 days</b>              | 27.2% (25.1-29.3)    | 17% (15.9-18)     | 46.6% (38.9-53.3)        | 47.5% (40.7-53.5)  |
| <b>Two doses, within 0-13 days</b>        | 38.5% (35.3-41.5)    | 21.3% (17.3-25.2) | 76.7% (67.3-83.4)        | 14.8% (-46-60.8)   |
| <b>Two doses, 14-59 days</b>              | 51.3% (49.9-52.7)    | 28.1% (26.5-29.6) | 86.5% (83.4-88.9)        | 56.1% (40.6-67.5)  |
| <b>Two doses, 60-179 days</b>             | 37.6% (36.1-39.1)    | 3.9% (3.1-4.8)    | 71% (68.5-73.2)          | 61.4% (57.4-65)    |
| <b>Two doses, ≥180 days</b>               | 34% (32.3-35.7)      | 6.3% (5.3-7.3)    | 60.9% (57.3-64.2)        | 57.6% (54.4-60.6)  |
| <b>Third dose of CoronaVac, 0-7 days</b>  | 44.7% (26.2-58.5)    | 9.6% (1.7-16.9)   | 80.8% (67.7-88.6)        | 75.6% (26.7-91.8)  |
| <b>Third dose of CoronaVac, 8-59 days</b> | 57.1% (50.4-62.9)    | 8.6% (5.6-11.5)   | 75.9% (67.8-81.9)        | 73.6% (63.9-80.7)  |
| <b>Third dose of CoronaVac, ≥60 days</b>  | 53.5% (30.9-68.6)    | -2.9% (-5.2--0.6) | 75.6% (52.8-87.4)        | 67.8% (64.3-71)    |
| <b>Third dose of BNT162b2, 0-7 days</b>   | 42.6% (38.5-46.5)    | 16.6% (14.7-18.4) | 80.4% (75.8-84)          | 62.6% (50.7-71.6)  |
| <b>Third dose of BNT162b2, 8-59 days</b>  | 86.7% (86-87.4)      | 56.8% (56.3-57.3) | 92.3% (91-93.4)          | 86% (84.5-87.4)    |
| <b>Third dose of BNT162b2, ≥60 days</b>   | 83.2% (79.8-86.1)    | 33.8% (33.2-34.4) | 90.8% (84.8-94.4)        | 86.4% (85.4-87.3)  |

**Supplementary Table 5.** Unadjusted vaccine effectiveness of homologous or heterologous booster against symptomatic Covid-19 and Covid-19 hospital admissions or deaths in adults stratified by age during Omicron period in Brazil

|                                    | <60 years      |                   | 60-74 years    |                   | ≥75 years      |                   |
|------------------------------------|----------------|-------------------|----------------|-------------------|----------------|-------------------|
| Symptomatic                        | Controls/Cases | VE (95% CI)       | Controls/Cases | VE (95% CI)       | Controls/Cases | VE (95% CI)       |
| Not vaccinated                     | 149451/172793  | Reference         | 12394/17467    | Reference         | 4005/6954      | Reference         |
| Two doses, ≥180 days               | 84833/102591   | -0.9% (-2-0.3)    | 34007/39122    | 18% (15.7-20.3)   | 15539/19463    | 29.6% (26.3-32.7) |
| Homologous booster                 |                |                   |                |                   |                |                   |
| Third dose of CoronaVac, 8-59 days | 6058/6725      | 6.1% (2.6-9.5)    | 1238/1493      | 8.8% (1.1-15.9)   | 370/371        | 39.7% (29.8-48.2) |
| Third dose of CoronaVac, ≥60 days  | 2578/3567      | -13.6% (-18--8.9) | 7352/9141      | -2.2% (-6.2-2)    | 11434/15139    | 11.8% (7.3-16.1)  |
| Heterologous booster               |                |                   |                |                   |                |                   |
| Third dose of BNT162b2, 8-59 days  | 108819/57507   | 56.4% (55.9-57)   | 23479/15053    | 56.4% (55-57.8)   | 4932/3273      | 64.2% (62-66.3)   |
| Third dose of BNT162b2, ≥60 days   | 183245/156962  | 29.6% (28.9-30.3) | 130148/116955  | 37.4% (35.8-38.9) | 64910/64495    | 46.5% (44.2-48.7) |
| Hospitalization or Death           |                |                   |                |                   |                |                   |
| Not vaccinated                     | 1169/2894      | Reference         | 693/2108       | Reference         | 877/2683       | Reference         |
| Two doses, ≥180 days               | 732/688        | 67.3% (62.3-71.6) | 2035/3180      | 49% (42.8-54.5)   | 2750/5207      | 41.2% (35.2-46.6) |
| Homologous booster                 |                |                   |                |                   |                |                   |
| Third dose of CoronaVac, 8-59 days | 34/16          | 87% (75.2-93.2)   | 73/50          | 77.2% (65.8-84.8) | 49/51          | 65.6% (47.5-77.5) |
| Third dose of CoronaVac, ≥60 days  | 23/21          | 68% (37.7-83.6)   | 511/462        | 64.1% (57.2-69.9) | 2146/2964      | 43% (36.4-49)     |
| Heterologous booster               |                |                   |                |                   |                |                   |
| Third dose of BNT162b2, 8-59 days  | 775/183        | 91.8% (90-93.3)   | 1203/537       | 85.7% (83.4-87.7) | 755/540        | 78.7% (75.4-81.6) |
| Third dose of BNT162b2, ≥60 days   | 1397/370       | 90.7% (89.1-92)   | 7441/3099      | 86.9% (85.4-88.3) | 9755/7063      | 79.8% (77.8-81.5) |

**Supplementary Table 6.** Characteristics of adults in Brazil, who were selected into case test negative pairs for the for the analysis of relative vaccine effectiveness analysis during the Omicron period (December 25, 2021 to Apr 22, 2022),

|                                                                    | Matched pairs for Omicron period |                   |        |
|--------------------------------------------------------------------|----------------------------------|-------------------|--------|
|                                                                    | Controls (n=620,133)             | Cases (n=620,133) | SMD    |
| <b>Demographics</b>                                                |                                  |                   |        |
| <b>Age, mean (SD), years</b>                                       | 54.23 (18.9)                     | 54.5 (19.1)       | 0.016  |
| <b>Age categories, n (%)</b>                                       |                                  |                   | 0.058  |
| 18-39 years                                                        | 185374 (29.9)                    | 181268 (29.2)     |        |
| 40-59 years                                                        | 150442 (24.3)                    | 154755 (25.0)     |        |
| 60-79 years                                                        | 247298 (39.9)                    | 238998 (38.5)     |        |
| ≥80 years                                                          | 37019 ( 6.0)                     | 45112 ( 7.3)      |        |
| <b>Male sex, n (%)</b>                                             | 214071 (34.5)                    | 214071 (34.5)     | <0.001 |
| <b>Self-reported race<sup>†</sup>, n (%)</b>                       |                                  |                   | 0.052  |
| White/Branca                                                       | 289223 (46.6)                    | 293911 (47.4)     |        |
| Mixed/Pardo                                                        | 178933 (28.9)                    | 168763 (27.2)     |        |
| Black/Preta                                                        | 23067 ( 3.7)                     | 21092 ( 3.4)      |        |
| Asian/ Amarela                                                     | 9970 ( 1.6)                      | 9487 ( 1.5)       |        |
| Indigenous/Indigena                                                | 2818 ( 0.5)                      | 2098 ( 0.3)       |        |
| Missing                                                            | 116122 (18.7)                    | 124782 (20.1)     |        |
| <b>Region of residence</b>                                         |                                  |                   | <0.001 |
| North                                                              | 33438 ( 5.4)                     | 33438 ( 5.4)      |        |
| Northeast                                                          | 100347 (16.2)                    | 100347 (16.2)     |        |
| Central-West                                                       | 45755 ( 7.4)                     | 45755 ( 7.4)      |        |
| Southeast                                                          | 328824 (53.0)                    | 328824 (53.0)     |        |
| South                                                              | 111769 (18.0)                    | 111769 (18.0)     |        |
| <b>Reported number of chronic comorbidities<sup>‡</sup>, n (%)</b> |                                  |                   | 0.014  |
| None                                                               | 546266 (88.1)                    | 548356 (88.4)     |        |

|                                                                                      |                |                |       |
|--------------------------------------------------------------------------------------|----------------|----------------|-------|
| One or two                                                                           | 71314 (11.5)   | 68945 (11.1)   |       |
| Three or more                                                                        | 2553 ( 0.4)    | 2832 ( 0.5)    |       |
| <b>Prior SARS-CoV-2 exposure</b>                                                     |                |                |       |
| Previous symptomatic events notified to the surveillance system <sup>¶</sup> , n (%) | 164774 (26.6)  | 151882 (24.5)  | 0.124 |
| Positive SARS-CoV-2 test result <sup>††</sup> , n (%)                                | 40970 ( 6.6)   | 23827 ( 3.8)   | 0.127 |
| <b>Interval between symptoms onset and RT-PCR testing, median (p25-p75), days</b>    | 3 [2, 4]       | 3 [2, 4]       | 0.127 |
| <b>Hospitalization or Death</b>                                                      | 15771 ( 2.5)   | 24395 ( 3.9)   | 0.079 |
| <b>Vaccination status</b>                                                            |                |                | 0.223 |
| Two doses, ≥180 days, n (%)                                                          | 120128 (19.4)  | 157410 (25.4)  |       |
| Third dose of CoronaVac, 0-7 days, n (%)                                             | 878 ( 0.1)     | 1140 ( 0.2)    |       |
| Third dose of CoronaVac, 8-59 days, n (%)                                            | 6757 ( 1.1)    | 8384 ( 1.4)    |       |
| Third dose of CoronaVac, 60-89 days, n (%)                                           | 5380 ( 0.9)    | 6518 ( 1.1)    |       |
| Third dose of CoronaVac, 90-119 days, n (%)                                          | 9410 (1.5)     | 12579 ( 2.0)   |       |
| Third dose of CoronaVac, ≥90 days, n (%)                                             | 5931 (1.0)     | 8582 ( 1.4)    |       |
| Third dose of BNT162b2, 0-7 days, n (%)                                              | 14117 ( 2.3)   | 17905 ( 2.9)   |       |
| Third dose of BNT162b2, 8-59 days, n (%)                                             | 113848 (18.4)  | 74009 (11.9)   |       |
| Third dose of BNT162b2, 60-89 days, n (%)                                            | 124797 (20.1)  | 110356 ( 17.8) |       |
| Third dose of BNT162b2, 90-119 days, n (%)                                           | 170478 (27.5)  | 170754 ( 27.5) |       |
| Third dose of BNT162b2, ≥120 days, n (%)                                             | 48409 (7.8)    | 52496 ( 8.5)   |       |
| <b>Interval between second dose and RT-PCR/Antigen test, mean (SD), days</b>         | 269 [228, 305] | 269 [223, 306] | 0.012 |
| <b>Interval between third dose and RT-PCR/Antigen test, mean (SD), days</b>          | 87 [56, 105]   | 91 [65, 109]   | 0.133 |

RT-PCR=reverse transcription polymerase chain reaction; SMD=standardized mean difference; SD=standard deviation; † Race/skin colour as defined by the Brazilian national census bureau (Instituto Nacional de Geografia e Estatísticas). ‡ Comorbidities included cardiovascular, or renal conditions, diabetes, chronic respiratory disorder, obesity, or immunosuppression. ¶ Reported illness with covid-19 associated symptoms in eSUS and SIVEP-Gripe databases before the start of study on 06 September 2021. †† Defined as a positive SARS-CoV-2 RT-PCR or antigen detection test result before the start of study on 06 September 2021..

**Supplementary Table 7.** Unadjusted vaccine effectiveness of a homologous and heterologous booster dose, relative to primary vaccination with CoronaVac during the period greater or equal to 180 days after the 2nd dose during Omicron period

|                                          | Symptomatic Covid-19 |                      | Hospitalization or Death |                      |
|------------------------------------------|----------------------|----------------------|--------------------------|----------------------|
|                                          | Controls/Cases       | Relative VE (95% CI) | Controls/Cases           | Relative VE (95% CI) |
| Two doses, $\geq 180$ days               | 120128/157410        | Reference            | 4360/8977                | Reference            |
| Homologous booster                       |                      |                      |                          |                      |
| Third dose of CoronaVac, 8-59 days       | 6757/8384            | 5.3% (1.9-8.5)       | 148/117                  | 59.1% (47-68.5)      |
| Third dose of CoronaVac, 60-89 days      | 5380/6518            | -3.1% (-6.9-0.8)     | 352/326                  | 49.6% (40.2-57.5)    |
| Third dose of CoronaVac, 90-119 days     | 9410/12579           | -18.7% (-21.3--16.1) | 964/1200                 | 20.8% (11.7-29)      |
| Third dose of CoronaVac, $\geq 120$ days | 5931/8582            | -34.6% (-37.3--31.8) | 1164/1906                | -17% (-25--8)        |
| Heterologous booster                     |                      |                      |                          |                      |
| Third dose of BNT162b2, 8-59 days        | 113848/74009         | 53.6% (53-54.2)      | 2005/1243                | 71.5% (68.9-73.8)    |
| Third dose of BNT162b2, 60-89 days       | 124797/110356        | 35.3% (34.6-36.1)    | 4804/2668                | 76% (74.4-77.6)      |
| Third dose of BNT162b2, 90-119 days      | 170478/170754        | 24.3% (23.5-25.1)    | 7033/4653                | 70.3% (68.6-72)      |
| Third dose of BNT162b2, $\geq 120$ days  | 48409/52496          | 11.3% (9.8-12.8)     | 3449/3134                | 55.2% (51.8-58.3)    |

**Supplementary Table 8.** Characteristics of adults in Brazil, who were selected into case test negative pairs for the analysis of vaccine effectiveness during the Delta period (September 6, 2021 to December 14, 2021) and the Omicron period (December 25, 2021 to Apr 22, 2022) - **Sensitivity analysis for matching**

|                                              | Matched pairs for Delta period |                   |       | Matched pairs for Omicron period |                     |       |
|----------------------------------------------|--------------------------------|-------------------|-------|----------------------------------|---------------------|-------|
|                                              | Controls (n=360,045)           | Cases (n=132,355) | SMD   | Controls (n=982,144)             | Cases (n=1,213,302) | SMD   |
| <b>Demographics</b>                          |                                |                   |       |                                  |                     |       |
| <b>Age, mean (SD), years</b>                 | 40.4 (17.9)                    | 44.6 (19.4)       | 0.225 | 41.7 (18.5)                      | 42.2 (18.4)         | 0.025 |
| <b>Age categories, n (%)</b>                 |                                |                   | 0.227 |                                  |                     | 0.034 |
| 18-39 years                                  | 222864 (61.9)                  | 68163 (51.5)      |       | 573177 (58.4)                    | 696053 (57.4)       |       |
| 40-59 years                                  | 68145 (18.9)                   | 27948 (21.1)      |       | 196976 (20.1)                    | 256255 (21.1)       |       |
| 60-79 years                                  | 61653 (17.1)                   | 31947 (24.1)      |       | 187718 (19.1)                    | 227151 (18.7))      |       |
| ≥80 years                                    | 7383 ( 2.1)                    | 4297 ( 3.2)       |       | 24273 ( 2.5)                     | 33843 ( 2.8)        |       |
| <b>Male sex, n (%)</b>                       | 148640 (41.3)                  | 59822 (45.2)      | 0.079 | 388595 (39.6)                    | 495040 (40.8)       | 0.025 |
| <b>Self-reported race<sup>†</sup>, n (%)</b> |                                |                   | 0.071 |                                  |                     | 0.087 |
| White/Branca                                 | 165235 (45.9)                  | 58768 (44.4)      |       | 431055 (43.9)                    | 540505 (44.5)       |       |
| Mixed/Pardo                                  | 99280 (27.6)                   | 37519 (28.3)      |       | 306878 (31.2)                    | 346765 (28.6)       |       |
| Black/Preta                                  | 15917 ( 4.4)                   | 5106 ( 3.9)       |       | 43312 ( 4.4)                     | 46625 ( 3.8)        |       |
| Asian/ Amarela                               | 4090 ( 1.1)                    | 1861 ( 1.4)       |       | 17671 ( 1.8)                     | 20763 ( 1.7)        |       |
| Indigenous/Indigena                          | 1101 ( 0.3)                    | 898 ( 0.7)        |       | 2800 ( 0.3)                      | 2233 ( 0.2)         |       |
| Missing                                      | 74422 (20.7)                   | 28203 (21.3)      |       | 180428 (18.4)                    | 256411 (21.1)       |       |

|                                                                                      |               |               |       |               |                |       |
|--------------------------------------------------------------------------------------|---------------|---------------|-------|---------------|----------------|-------|
| <b>Region of residence</b>                                                           |               |               | 0.216 |               |                | 0.031 |
| North                                                                                | 14887 ( 4.1)  | 8488 ( 6.4)   |       | 40809 ( 4.2)  | 55841 ( 4.6)   |       |
| Northeast                                                                            | 34766 ( 9.7)  | 15319 (11.6)  |       | 135724 (13.8) | 168228 (13.9)  |       |
| Central-West                                                                         | 20801 ( 5.8)  | 11562 ( 8.7)  |       | 78255 ( 8.0)  | 89169 ( 7.3)   |       |
| Southeast                                                                            | 211159 (58.6) | 64695 (48.9)  |       | 541177 (55.1) | 668797 (55.1)  |       |
| South                                                                                | 78432 (21.8)  | 32291 (24.4)  |       | 186179 (19.0) | 231267 (19.1)  |       |
| <b>Reported number of chronic comorbidities<sup>‡</sup>, n (%)</b>                   |               |               | 0.122 |               |                | 0.014 |
| None                                                                                 | 325084 (90.3) | 114438 (86.5) |       | 908535 (92.5) | 1126250 (92.8) |       |
| One or two                                                                           | 33518 ( 9.3)  | 16900 (12.8)  |       | 71502 ( 7.3)  | 84147 (6.9)    |       |
| Three or more                                                                        | 1443 ( 0.4)   | 1017 ( 0.8)   |       | 2107(0.2)     | 2905 (0.2)     |       |
| <b>Prior SARS-CoV-2 exposure</b>                                                     |               |               |       |               |                |       |
| Previous symptomatic events notified to the surveillance system <sup>¶</sup> , n (%) | 117610 (32.7) | 25033 (18.9)  | 0.318 | 307779 (31.3) | 310788 (25.6)  | 0.127 |
| Positive SARS-CoV-2 test result <sup>††</sup> , n (%)                                | 24952 ( 6.9)  | 2212 ( 1.7)   | 0.261 | 79126 ( 8.1)  | 58724 ( 4.8)   | 0.131 |
| <b>Interval between symptoms onset and RT-PCR testing, median (p25-p75), days</b>    | 3 [2, 4]      | 3 [2, 5]      | 0.143 | 3 [2, 4]      | 3 [2, 4]       | 0.105 |
| <b>Hospitalization or death</b>                                                      | 9980 ( 2.8)   | 14547 (11.0)  | 0.329 | 13538 ( 1.4)  | 28387 ( 2.3)   | 0.071 |
| <b>Vaccination status</b>                                                            |               |               | 0.422 |               |                | 0.217 |
| Not vaccinated, n (%)                                                                | 73296 (20.4)  | 40165 (30.3)  |       | 115379 (11.7) | 168224 (13.9)  |       |
| <i>Primary vaccination with CoronaVac</i>                                            |               |               |       |               |                |       |

|                                                                         |              |               |       |                |                |       |
|-------------------------------------------------------------------------|--------------|---------------|-------|----------------|----------------|-------|
| Single dose, 0-13 days, n (%)                                           | 4477 ( 1.2)  | 2135 ( 1.6)   |       | 1025 ( 0.1)    | 1298 ( 0.1)    |       |
| Single dose, ≥14 days, n (%)                                            | 32487 ( 9.0) | 11580 ( 8.7)  |       | 53933 ( 5.5)   | 64038 ( 5.3)   |       |
| Two doses, 0-13 days, n (%)                                             | 11889 ( 3.3) | 3205 ( 2.4)   |       | 2803 (0.2)     | 2657(0.2)      |       |
| Two doses, 14-89 days, n (%)                                            | 92035 (25.6) | 21210 (16.0)  |       | 41152 ( 4.2)   | 44794 ( 3.7)   |       |
| Two doses, 90-179 days, n (%)                                           | 65840 (18.3) | 29431 (22.2)  |       | 268947 (27.4)  | 391160 (32.2)  |       |
| Two doses, ≥180 days, n (%)                                             | 47556 (13.2) | 20348 (15.4)  |       | 98996 (10.1)   | 137720 (11.4)  |       |
| <i>Booster vaccination</i>                                              |              |               |       |                |                |       |
| Third dose of CoronaVac, 0-7 days, n (%)                                | 225 ( 0.1)   | 81 ( 0.1)     |       | 647 ( 0.1)     | 1072 ( 0.1)    |       |
| Third dose of CoronaVac, 8-59 days, n (%)                               | 1384 ( 0.4)  | 349 ( 0.3)    |       | 5202 ( 0.5)    | 7414 ( 0.6)    |       |
| Third dose of CoronaVac, ≥60 days, n (%)                                | 241 ( 0.1)   | 61 ( 0.0)     |       | 12747 ( 1.3)   | 21818 ( 1.8)   |       |
| Third dose of BNT162b2, 0-7 days, n (%)                                 | 4041 ( 1.1)  | 1573 ( 1.2)   |       | 11747 ( 1.2)   | 16677 ( 1.4)   |       |
| Third dose of BNT162b2, 8-59 days, n (%)                                | 24942 ( 6.9) | 2046 ( 1.5)   |       | 96675 ( 9.8)   | 66339 ( 5.5)   |       |
| Third dose of BNT162b2, ≥60 days, n (%)                                 | 1632 ( 0.5)  | 171 ( 0.1)    |       | 273307 (27.8)  | 290091 (23.9)  |       |
| <b>Interval between first dose and testing, median (p25-p75), days</b>  | 34 [21, 62]  | 33 [19, 62]   | 0.032 | 138 [95, 169]  | 140 [99, 170]  | 0.033 |
| <b>Interval between second dose and testing, median (p25-p75), days</b> | 96 [45, 172] | 145 [66, 184] | 0.283 | 138 [115, 177] | 141 [119, 176] | 0.048 |
| <b>Interval between third dose and testing, median (p25-p75), days</b>  | 24 [13, 41]  | 10 [6, 29]    | 0.451 | 86 [53, 107]   | 91 [64, 107]   | 0.073 |

RT-PCR=reverse transcription polymerase chain reaction; SMD=standardized mean difference; SD=standard deviation; † Race/skin colour as defined by the Brazilian national census bureau (Instituto Nacional de Geografia e

Estatísticas). ‡ Comorbidities included cardiovascular, or renal conditions, diabetes, chronic respiratory disorder, obesity, or immunosuppression. . ¶ Reported illness with covid-19 associated symptoms in eSUS and SIVEP-Gripe

databases before the start of study on 06 September 2021. \*\* Defined as a positive SARS-CoV-2 RT-PCR or antigen detection test result before the start of study on 06 September 2021

**eTable 9.** Sensitivity analysis of matching strategy to evaluate the adjusted vaccine effectiveness of CoronaVac and homologous or heterologous booster against symptomatic Covid-19 using RT-PCR or Antigen tests

|                                    | Delta Period      |                    | Omicron Period    |                    |
|------------------------------------|-------------------|--------------------|-------------------|--------------------|
|                                    | Matching 1:1      | Stratified by sets | Matching 1:1      | Stratified by sets |
| Not vaccinated                     | Reference         | Reference          | Reference         | Reference          |
| Single dose, within 0-13 days      | 2.2% (-4-8.1)     | 4.6% (-1.3-10.2)   | 24.6% (19.1-29.8) | 17.8% (10.1-24.9)  |
| Single dose, ≥14 days              | 27.2% (25.1-29.3) | 23.9% (21.8-26)    | 17% (15.9-18)     | 14.6% (13.3-15.9)  |
| Two doses, within 0-13 days        | 38.5% (35.3-41.5) | 35.9% (32.8-38.8)  | 21.3% (17.3-25.2) | 27.2% (22.6-31.4)  |
| Two doses, 14-59 days              | 51.3% (49.9-52.7) | 48.3% (46.9-49.7)  | 28.1% (26.5-29.6) | 26.5% (24.6-28.4)  |
| Two doses, 60-179 days             | 37.6% (36.1-39.1) | 33.2% (31.7-34.7)  | 3.9% (3.1-4.8)    | 0.6% (-0.4-1.6)    |
| Two doses, ≥180 days               | 34% (32.3-35.7)   | 29.7% (27.9-31.5)  | 6.3% (5.3-7.3)    | 3.6% (2.4-4.9)     |
| Third dose of CoronaVac, 0-7 days  | 44.7% (26.2-58.5) | 50.4% (34.2-62.7)  | 9.6% (1.7-16.9)   | -0.5% (-10.5-9.6)  |
| Third dose of CoronaVac, 8-59 days | 57.1% (50.4-62.9) | 63.6% (58-68.5)    | 8.6% (5.6-11.5)   | 9.8% (6-13.3)      |
| Third dose of CoronaVac, ≥60 days  | 53.5% (30.9-68.6) | 60.1% (42.7-72.2)  | -2.9% (-5.2--0.6) | -5.8% (-8.6--2.9)  |
| Third dose of BNT162b2, 0-7 days   | 42.6% (38.5-46.5) | 36.1% (31.6-40.3)  | 16.6% (14.7-18.4) | 13.9% (11.5-16.1)  |
| Third dose of BNT162b2, 8-59 days  | 86.7% (86-87.4)   | 86.4% (85.6-87.1)  | 56.8% (56.3-57.3) | 55.2% (54.6-55.9)  |
| Third dose of BNT162b2, ≥60 days   | 83.2% (79.8-86.1) | 81.1% (77.2-84.3)  | 33.8% (33.2-34.4) | 29.9% (29.1-30.7)  |

**Supplementary Table 10.** Sensitivity analysis of matching strategy to evaluate the adjusted vaccine effectiveness of CoronaVac and homologous or heterologous booster against Severe Covid-19 using RT-PCR or Antigen tests

|                                    | Delta Period      |                          | Omicron Period     |                          |
|------------------------------------|-------------------|--------------------------|--------------------|--------------------------|
|                                    | Matching 1:1      | Matching stratified sets | Matching 1:1       | Matching stratified sets |
| Not vaccinated                     | Reference         | Reference                | Reference          | Reference                |
| Single dose, within 0-13 days      | 1.7% (-28.4-30.8) | 22.4% (-7.8-44.5)        | -3.1% (-57.5-54.7) | -64.1% (-87.3-1.7)       |
| Single dose, ≥14 days              | 46.6% (38.9-53.3) | 51.8% (44.9-57.8)        | 47.5% (40.7-53.5)  | 46.4% (38.9-53)          |
| Two doses, within 0-13 days        | 76.7% (67.3-83.4) | 79.2% (70.5-85.3)        | 14.8% (-46-60.8)   | 61.2% (22.4-80.6)        |
| Two doses, 14-59 days              | 86.5% (83.4-88.9) | 87.3% (84.6-89.5)        | 56.1% (40.6-67.5)  | 55.2% (38.9-67.2)        |
| Two doses, 60-179 days             | 71% (68.5-73.2)   | 73.4% (71.1-75.5)        | 61.4% (57.4-65)    | 63.5% (59.4-67.2)        |
| Two doses, ≥180 days               | 60.9% (57.3-64.2) | 64.2% (60.9-67.2)        | 57.6% (54.4-60.6)  | 58.4% (54.9-61.6)        |
| Third dose of CoronaVac, 0-7 days  | 80.8% (67.7-88.6) | 81% (66.8-89.2)          | 75.6% (26.7-91.8)  | 79.6% (36.1-93.5)        |
| Third dose of CoronaVac, 8-59 days | 75.9% (67.8-81.9) | 82.7% (77.2-86.8)        | 73.6% (63.9-80.7)  | 79.9% (72.3-85.4)        |
| Third dose of CoronaVac, ≥60 days  | 75.6% (52.8-87.4) | 81.7% (66.6-89.9)        | 67.8% (64.3-71)    | 72.8% (69.6-75.7)        |
| Third dose of BNT162b2, 0-7 days   | 80.4% (75.8-84)   | 81.9% (77.6-85.4)        | 62.6% (50.7-71.6)  | 67.5% (56.5-75.7)        |
| Third dose of BNT162b2, 8-59 days  | 92.3% (91-93.4)   | 93% (91.8-93.9)          | 86% (84.5-87.4)    | 87.1% (85.5-88.5)        |
| Third dose of BNT162b2, ≥60 days   | 90.8% (84.8-94.4) | 89% (82.7-93)            | 86.4% (85.4-87.3)  | 87.2% (86.1-88.1)        |

**Supplementary Table 11.** Adjusted vaccine effectiveness of CoronaVac and homologous or heterologous booster against severe Covid-19 in adults in Brazil: main analysis vs sensitivity analysis of the severe COVID-19 definition

|                                           | Delta                                       |                                                                              | Omicron                                     |                                                                              |
|-------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------|
|                                           | Hospitalization or death<br>(Main analysis) | Use of Respiratory Support, ICU admission or death<br>(Sensitivity analysis) | Hospitalization or death<br>(Main analysis) | Use of Respiratory Support, ICU admission or death<br>(Sensitivity analysis) |
| <b>Not vaccinated</b>                     | Reference                                   | Reference                                                                    | Reference                                   | Reference                                                                    |
| <b>Single dose, within 0-13 days</b>      | 1.7% (-28.4-30.8)                           | 3.9% (-33.2-38.3)                                                            | -3.1% (-57.5-54.7)                          | -8.5% (-69.7-63.8)                                                           |
| <b>Single dose, ≥14 days</b>              | 46.6% (38.9-53.3)                           | 46.8% (37.8-54.5)                                                            | 47.5% (40.7-53.5)                           | 50.3% (42.1-57.4)                                                            |
| <b>Two doses, within 0-13 days</b>        | 76.7% (67.3-83.4)                           | 82% (72-88.4)                                                                | 14.8% (-46-60.8)                            | 6.7% (-59.7-64.9)                                                            |
| <b>Two doses, 14-59 days</b>              | 86.5% (83.4-88.9)                           | 87.5% (83.8-90.3)                                                            | 56.1% (40.6-67.5)                           | 58.7% (36.7-73.1)                                                            |
| <b>Two doses, 60-179 days</b>             | 71% (68.5-73.2)                             | 72.6% (69.9-75.1)                                                            | 61.4% (57.4-65)                             | 63.1% (57.8-67.7)                                                            |
| <b>Two doses, ≥180 days</b>               | 60.9% (57.3-64.2)                           | 63.7% (59.8-67.2)                                                            | 57.6% (54.4-60.6)                           | 59.1% (55.3-62.6)                                                            |
| <b>Third dose of CoronaVac, 0-7 days</b>  | 80.8% (67.7-88.6)                           | 86.7% (75.7-92.7)                                                            | 75.6% (26.7-91.8)                           | 81.6% (21.3-95.7)                                                            |
| <b>Third dose of CoronaVac, 8-59 days</b> | 75.9% (67.8-81.9)                           | 78% (69.8-83.9)                                                              | 73.6% (63.9-80.7)                           | 74.3% (62.6-82.3)                                                            |
| <b>Third dose of CoronaVac, ≥60 days</b>  | 75.6% (52.8-87.4)                           | 69.2% (34.4-85.6)                                                            | 67.8% (64.3-71)                             | 70.7% (66.8-74)                                                              |
| <b>Third dose of BNT162b2, 0-7 days</b>   | 80.4% (75.8-84)                             | 81% (75.8-85.1)                                                              | 62.6% (50.7-71.6)                           | 68.5% (55.4-77.8)                                                            |
| <b>Third dose of BNT162b2, 8-59 days</b>  | 92.3% (91-93.4)                             | 92.5% (91.1-93.7)                                                            | 86% (84.5-87.4)                             | 87.3% (85.6-88.8)                                                            |
| <b>Third dose of BNT162b2, ≥60 days</b>   | 90.8% (84.8-94.4)                           | 91.1% (84-95.1)                                                              | 86.4% (85.4-87.3)                           | 87.5% (86.4-88.6)                                                            |

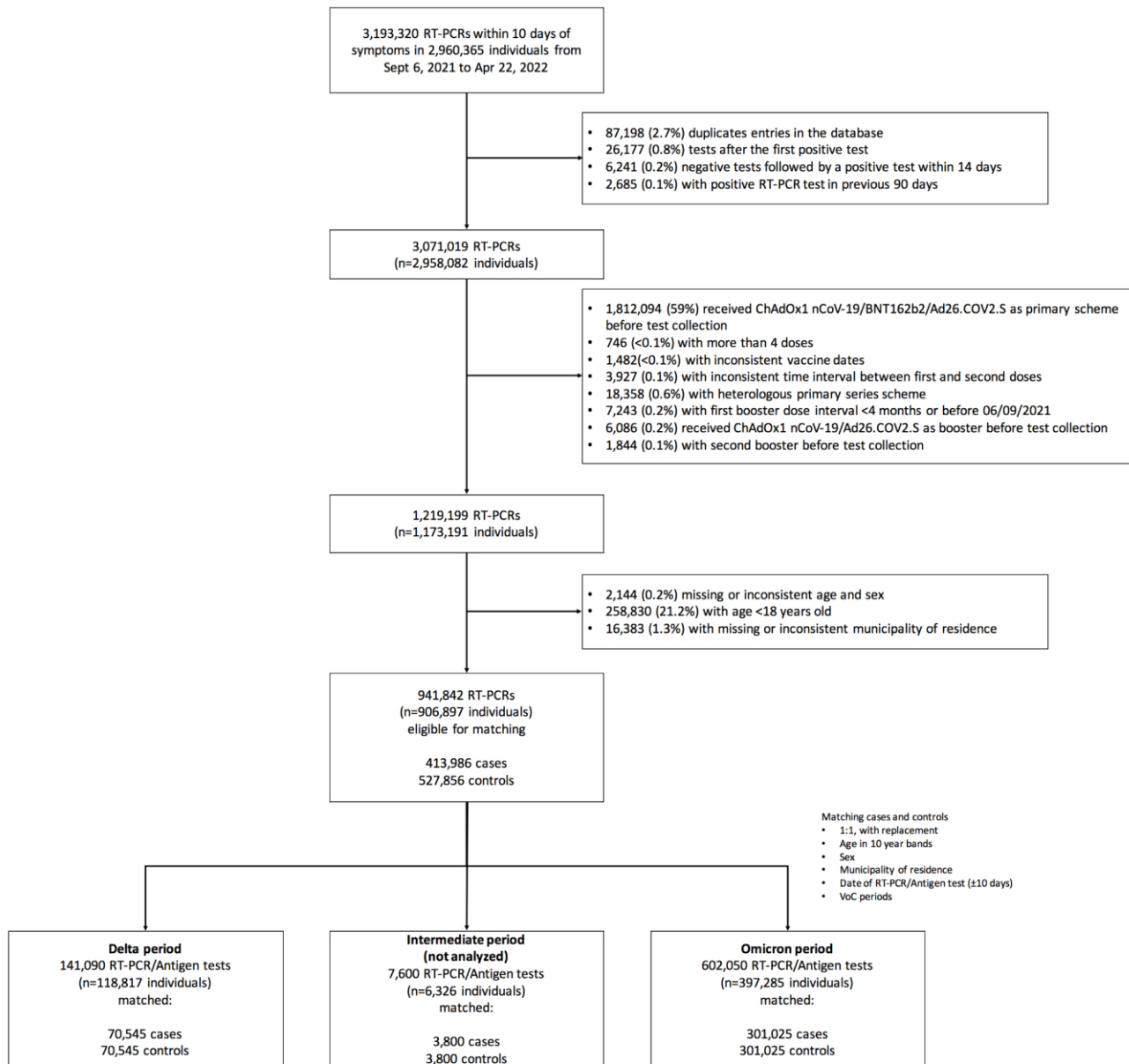
**Supplementary Table 12.** Adjusted vaccine effectiveness of homologous or heterologous booster against severe Covid-19 in adults stratified by age during Omicron period in Brazil: main analysis vs sensitivity analysis of the severe COVID-19 definition

|                                    | Hospitalization or Death<br>(Main analysis) |                   |                   | Use of Respiratory Support, ICU admission or death<br>(Sensitivity analysis) |                   |                   |
|------------------------------------|---------------------------------------------|-------------------|-------------------|------------------------------------------------------------------------------|-------------------|-------------------|
|                                    | <60 years                                   | 60-74 years       | ≥75 years         | <60 years                                                                    | 60-74 years       | ≥75 years         |
| Not vaccinated                     | Reference                                   | Reference         | Reference         | Reference                                                                    | Reference         | Reference         |
|                                    |                                             |                   |                   |                                                                              |                   |                   |
| Two doses, ≥180 days               | 71% (65.9-75.3)                             | 63.4% (58.3-67.9) | 40.7% (33.7-46.9) | 74% (67.6-79.2)                                                              | 65% (59.2-70)     | 44.7% (37.1-51.4) |
| Homologous booster                 |                                             |                   |                   |                                                                              |                   |                   |
| Third dose of CoronaVac, 8-59 days | 86% (71.7-93.1)                             | 80.7% (68.6-88.1) | 47.7% (12.4-68.8) | 91.6% (74.2-97.3)                                                            | 79.7% (64.9-88.2) | 53.2% (15.2-74.1) |
| Third dose of CoronaVac, ≥60 days  | 82% (60.9-91.7)                             | 76.1% (70.8-80.4) | 51.4% (44.6-57.3) | 86.1% (53.5-95.9)                                                            | 78.4% (72.6-83)   | 57.6% (50.7-63.6) |
| Heterologous booster               |                                             |                   |                   |                                                                              |                   |                   |
| Third dose of BNT162b2, 8-59 days  | 92.1% (90.2-93.7)                           | 88.4% (86.2-90.2) | 77.3% (73.1-80.8) | 94% (91.7-95.7)                                                              | 89.6% (87.3-91.6) | 79.8% (75.4-83.4) |
| Third dose of BNT162b2, ≥60 days   | 90.2% (88.3-91.7)                           | 90.4% (89.1-91.5) | 78.5% (76.1-80.6) | 93.2% (91.2-94.7)                                                            | 91.2% (89.8-92.4) | 81% (78.5-83.2)   |

**Supplementary Table 13.** Adjusted vaccine effectiveness of a homologous and heterologous booster dose, relative to primary vaccination with CoronaVac during the period greater or equal to 180 days after the 2nd dose during Omicron period, further adjusted by month of second dose (sensitivity analysis)

|                                             | Symptomatic Covid-19 |                                                    | Hospitalization or Death |                                                    |
|---------------------------------------------|----------------------|----------------------------------------------------|--------------------------|----------------------------------------------------|
|                                             | Main analysis        | Sensitivity analysis adjusted by month of 2nd dose | Main analysis            | Sensitivity analysis adjusted by month of 2nd dose |
|                                             | Relative VE (95% CI) | Relative VE (95% CI)                               | Relative VE (95% CI)     | Relative VE (95% CI)                               |
| <b>Two doses, ≥180 days</b>                 | Reference            | Reference                                          | Reference                | Reference                                          |
| <b>Homologous booster</b>                   |                      |                                                    |                          |                                                    |
| <b>Third dose of CoronaVac, 8-59 days</b>   | 4.9% (1.5-8.1)       | 1.4% (-2.1-4.8)                                    | 47.1% (27.8-61.2)        | 45.8% (26-60.3)                                    |
| <b>Third dose of CoronaVac, 60-89 days</b>  | -3.8% (-7.5-0.2)     | -4.5% (-8.3--0.6)                                  | 36% (21.5-47.8)          | 35.8% (21.3-47.7)                                  |
| <b>Third dose of CoronaVac, 90-119 days</b> | -13.8% (-16.5--11)   | -14% (-16.7--11.1)                                 | 23.5% (12.4-33.1)        | 25.1% (14.3-34.6)                                  |
| <b>Third dose of CoronaVac, ≥120 days</b>   | -24.8% (-28--21.6)   | -23.4% (-26.6--20.1)                               | 20.7% (10.1-30)          | 24.3% (14-33.4)                                    |
| <b>Heterologous booster</b>                 |                      |                                                    |                          |                                                    |
| <b>Third dose of BNT162b2, 8-59 days</b>    | 53.4% (52.8-54)      | 51.7% (51.1-52.4)                                  | 67.3% (63.9-70.4)        | 66.7% (63.2-69.9)                                  |
| <b>Third dose of BNT162b2, 60-89 days</b>   | 34.7% (34-35.5)      | 34.5% (33.7-35.3)                                  | 71% (68.7-73.2)          | 70.9% (68.5-73)                                    |
| <b>Third dose of BNT162b2, 90-119 days</b>  | 25.2% (24.4-26)      | 25% (24.1-25.9)                                    | 68.6% (66.4-70.7)        | 69.1% (66.8-71.1)                                  |
| <b>Third dose of BNT162b2, ≥120 days</b>    | 15.7% (14.2-17.1)    | 16.9% (15.4-18.5)                                  | 62.8% (59.3-65.9)        | 64.3% (60.9-67.5)                                  |

**Supplementary Figure 3.** Flow chart showing inclusion of cases and controls for the sensitivity analysis including only RT-PCR SARS-CoV-2 tests



**Supplementary Table 14.** Characteristics of adults in Brazil, who were selected into case-test negative pairs for the sensitivity analysis including only RT-PCR tests during the Delta period (September 6, 2021 to December 14, 2021) and Omicron period (December 25, 2021 to Apr 22, 2022)

|                                              | Matched pairs for<br>Delta period |                      |        | Matched pairs for<br>Omicron period |                      |        |
|----------------------------------------------|-----------------------------------|----------------------|--------|-------------------------------------|----------------------|--------|
|                                              | Controls<br>(n=70,545 )           | Cases<br>(n=70,545 ) | SMD    | Controls<br>(n=301,025)             | Cases<br>(n=301,025) | SMD    |
| <b>Demographics</b>                          |                                   |                      |        |                                     |                      |        |
| <b>Age, mean (SD), years</b>                 | 47.4 (20.2)                       | 47.5 (20.3)          | 0.007  | 42.7 (19)                           | 43.0 (19.2)          | 0.015  |
| <b>Age categories, n (%)</b>                 |                                   |                      | 0.024  |                                     |                      | 0.043  |
| 18-39 years                                  | 32535 (46.1)                      | 31990 (45.3)         |        | 173722 (57.7)                       | 170224 (56.5)        |        |
| 40-59 years                                  | 14878 (21.1)                      | 15426 (21.9)         |        | 59687 (19.8)                        | 63234 (21.0)         |        |
| 60-79 years                                  | 19447 (27.6)                      | 19256 (27.3)         |        | 54828 (18.2)                        | 53014 (17.6)         |        |
| ≥80 years                                    | 3685 ( 5.2)                       | 3873 ( 5.5)          |        | 12788 ( 4.2)                        | 14553 ( 4.8)         |        |
| <b>Male sex, n (%)</b>                       | 32130 (45.5)                      | 32130 (45.5)         | <0.001 | 125368 (41.6)                       | 125368 (41.6)        | <0.001 |
| <b>Self-reported race<sup>†</sup>, n (%)</b> |                                   |                      | 0.092  |                                     |                      | 0.094  |
| White/Branca                                 | 28649 (40.6)                      | 29984 (42.5)         |        | 128775 (42.8)                       | 133966 (44.5)        |        |
| Mixed/Pardo                                  | 23789 (33.7)                      | 21471 (30.4)         |        | 93042 (30.9)                        | 82110 (27.3)         |        |
| Black/Preta                                  | 3498 ( 5.0)                       | 2957 ( 4.2)          |        | 12804 ( 4.3)                        | 11176 ( 3.7)         |        |
| Asian/ Amarela                               | 922 ( 1.3)                        | 1218 ( 1.7)          |        | 4694 ( 1.6)                         | 5618 ( 1.9)          |        |
| Indigenous/Indigena                          | 197 ( 0.3)                        | 281 ( 0.4)           |        | 399 ( 0.1)                          | 291 ( 0.1)           |        |
| Missing                                      | 13490 (19.1)                      | 14634 (20.7)         |        | 61311 (20.4)                        | 67864 (22.5)         |        |

|                                                                                      |              |              |        |               |               |        |
|--------------------------------------------------------------------------------------|--------------|--------------|--------|---------------|---------------|--------|
| <b>Region of residence</b>                                                           |              |              | <0.001 |               |               | <0.001 |
| North                                                                                | 3424 ( 4.9)  | 3424 ( 4.9)  |        | 8355 ( 2.8)   | 8355 ( 2.8)   |        |
| Northeast                                                                            | 10216 (14.5) | 10216 (14.5) |        | 50186 (16.7)  | 50186 (16.7)  |        |
| Central-West                                                                         | 5758 ( 8.2)  | 5758 ( 8.2)  |        | 15313 ( 5.1)  | 15313 ( 5.1)  |        |
| Southeast                                                                            | 38529 (54.6) | 38529 (54.6) |        | 199212 (66.2) | 199212 (66.2) |        |
| South                                                                                | 12618 (17.9) | 12618 (17.9) |        | 27959 ( 9.3)  | 27959 ( 9.3)  |        |
| <b>Reported number of chronic comorbidities<sup>‡</sup>, n (%)</b>                   |              |              | 0.037  |               |               | 0.064  |
| None                                                                                 | 58550 (83.0) | 57585 (81.6) |        | 265890 (88.3) | 271794 (90.3) |        |
| One or two                                                                           | 11258 (16.0) | 12088 (17.1) |        | 32894 (10.9)  | 27565 ( 9.2)  |        |
| Three or more                                                                        | 737 ( 1.0)   | 872 ( 1.2)   |        | 2241 ( 0.7)   | 1666 ( 0.6)   |        |
| <b>Prior SARS-CoV-2 exposure</b>                                                     |              |              |        |               |               |        |
| Previous symptomatic events notified to the surveillance system <sup>¶</sup> , n (%) | 17825 (25.3) | 12137 (17.2) | 0.198  | 88840 (29.5)  | 78548 (26.1)  | 0.076  |
| Positive SARS-CoV-2 test result <sup>††</sup> , n (%)                                | 3881 ( 5.5)  | 1402 ( 2.0)  | 0.186  | 24261 ( 8.1)  | 16613 ( 5.5)  | 0.101  |
| <b>Interval between symptoms onset and RT-PCR testing, median (p25-p75), days</b>    | 3 [2, 5]     | 3 [2, 5]     | 0.115  | 3 [2, 4]      | 3 [2, 4]      | 0.151  |
| <b>Hospitalization or Death</b>                                                      | 8097 (11.5)  | 12842 (18.2) | 0.191  | 26664 ( 8.9)  | 19851 ( 6.6)  | 0.085  |
| <b>Vaccination status</b>                                                            |              |              | 0.294  |               |               | 0.223  |
| Not vaccinated, n (%)                                                                | 14100 (20.0) | 19354 (27.4) |        | 31413 (10.4)  | 36865 (12.2)  |        |
| Single dose, within 0-13 days, n (%)                                                 | 676 ( 1.0)   | 956 ( 1.4)   |        | 301 ( 0.1)    | 305 ( 0.1)    |        |

|                                                                         |               |               |       |                |                |       |
|-------------------------------------------------------------------------|---------------|---------------|-------|----------------|----------------|-------|
| Single dose, ≥14 days, n (%)                                            | 5695 ( 8.1)   | 5810 ( 8.2)   |       | 14809 ( 4.9)   | 14667 ( 4.9)   |       |
| Two doses, within 0-13 days, n (%)                                      | 1904 ( 2.7)   | 1697 ( 2.4)   |       | 796 ( 0.3)     | 601 ( 0.2)     |       |
| Two doses, 14-89 days, n (%)                                            | 13248 (18.8)  | 10877 (15.4)  |       | 10758 ( 3.6)   | 9808 ( 3.3)    |       |
| Two doses, 90-179 days, n (%)                                           | 17605 (25.0)  | 17009 (24.1)  |       | 84500 (28.1)   | 100216 (33.3)  |       |
| Two doses, ≥180 days, n (%)                                             | 11431 (16.2)  | 12351 (17.5)  |       | 30159 (10.0)   | 35974 (12.0)   |       |
| Third dose of CoronaVac, 0-7 days, n (%)                                | 68 (0.1)      | 54(0.1)       |       | 411 ( 0.1)     | 368 ( 0.1)     |       |
| Third dose of CoronaVac, 8-59 days, n (%)                               | 328 (0.5)     | 271(0.4)      |       | 2416 ( 0.8)    | 2545 ( 0.8)    |       |
| Third dose of CoronaVac, ≥60 days, n (%)                                | 54(0.1)       | 47(0.1)       |       | 6412 ( 2.1)    | 8309 ( 2.8)    |       |
| Third dose of BNT162b2, 0-7 days, n (%)                                 | 929 (1.3)     | 837(1.2)      |       | 3913 ( 1.3)    | 4132 ( 1.4)    |       |
| Third dose of BNT162b2, 8-59 days, n (%)                                | 42421(6.0)    | 1187 (17)     |       | 29257 ( 9.7)   | 17102 ( 5.7)   |       |
| Third dose of BNT162b2, ≥60 days, n (%)                                 | 265 (0.4)     | 95(0.1)       |       | 85880 (28.5)   | 70133 (23.3)   |       |
| <b>Interval between first dose and testing, median (p25-p75), days</b>  | 36 [23, 67]   | 35 [21, 67]   | 0.006 | 138 [93, 170]  | 143 [101, 173] | 0.072 |
| <b>Interval between second dose and testing, median (p25-p75), days</b> | 144 [60, 181] | 150 [73, 187] | 0.105 | 140 [119, 176] | 142 [122, 178] | 0.039 |
| <b>Interval between third dose and testing, median (p25-p75), days</b>  | 21 [11, 38]   | 10 [6, 30]    | 0.307 | 86 [53, 103]   | 90 [62, 106]   | 0.123 |

RT-PCR=reverse transcription polymerase chain reaction; SMD=standardized mean difference; SD=standard deviation; † Race/skin colour as defined by the Brazilian national census bureau (Instituto Nacional de Geografia e Estatísticas). ‡ Comorbidities included cardiovascular, or renal conditions, diabetes, chronic respiratory disorder, obesity, or immunosuppression. ¶ Reported illness with covid-19 associated symptoms in eSUS and SIVEP-Gripe databases before the start of study on 06 September 2021. \*\* Defined as a positive SARS-CoV-2 RT-PCR or antigen detection test result before the start of study on 06 September 2021.

**Supplementary Table 15.** Adjusted vaccine effectiveness of CoronaVac and homologous or heterologous booster against symptomatic Covid-19 and Covid-19 hospital admission or deaths in adults in Brazil, from the sensitivity analysis including RT-PCR SARS-CoV-2 tests only

|                                           | Symptomatic COVID-19 |                   | Hospitalization or death |                    |
|-------------------------------------------|----------------------|-------------------|--------------------------|--------------------|
|                                           | Delta                | Omicron           | Delta                    | Omicron            |
| <b>Not vaccinated</b>                     | Reference            | Reference         | Reference                | Reference          |
| <b>Single dose, within 0-13 days</b>      | -11.9% (-20.8--2)    | 7.8% (-7.8-21.6)  | -16.5% (-49.1-27.1)      | -                  |
| <b>Single dose, ≥14 days</b>              | 25.5% (22-28.8)      | 10.5% (7.9-12.9)  | 45.2% (36-53.1)          | 47.1% (38.7-54.3)  |
| <b>Two doses, within 0-13 days</b>        | 34.5% (29.3-39.2)    | 30.7% (22.7-37.8) | 78.2% (67-85.6)          | 67.8% (15.3-87.8)  |
| <b>Two doses, 14-59 days</b>              | 49% (46.8-51.2)      | 22.2% (18.2-26)   | 85.4% (81.4-88.5)        | 23% (-15.7-50)     |
| <b>Two doses, 60-179 days</b>             | 35.5% (33.1-37.8)    | -7.1% (-8.9--5.3) | 68.1% (65-71)            | 53.4% (47.2-58.9)  |
| <b>Two doses, ≥180 days</b>               | 30.1% (27.3-32.8)    | 7% (4.8-9.1)      | 57.3% (52.7-61.5)        | 55.8% (51.8-59.5)  |
| <b>Third dose of CoronaVac, 0-7 days</b>  | 52.3% (31-67.1)      | 18.2% (5.4-29.2)  | 76% (57.6-86.4)          | 18.4% (-72.3-81.6) |
| <b>Third dose of CoronaVac, 8-59 days</b> | 56.9% (47.8-64.4)    | 10.5% (5-15.7)    | 74.1% (64.5-81.1)        | 72.1% (59.7-80.7)  |
| <b>Third dose of CoronaVac, ≥60 days</b>  | 64.1% (41.4-78)      | -1.6% (-5.8-2.8)  | 84.2% (67.5-92.3)        | 63.6% (58.9-67.7)  |
| <b>Third dose of BNT162b2, 0-7 days</b>   | 46.4% (40.4-51.7)    | 6.9% (2.3-11.2)   | 78.5% (72.5-83.2)        | 63.8% (48.8-74.4)  |
| <b>Third dose of BNT162b2, 8-59 days</b>  | 85% (83.8-86.2)      | 53.5% (52.3-54.7) | 90.5% (88.7-92)          | 84.4% (82.3-86.2)  |
| <b>Third dose of BNT162b2, ≥60 days</b>   | 84.8% (79.9-88.5)    | 39.6% (38.4-40.8) | 87.3% (78.1-92.6)        | 82.9% (81.4-84.3)  |

**Supplementary Table 16.** Characteristics of adults in Brazil, who were selected into case-test negative pairs for the sensitivity analysis using RT-PCR SARS-CoV-2 tests only, during the Omicron period (December 25, 2021 to Apr 10, 2022), for the analysis of relative vaccine effectiveness

|                                                                    | Matched pairs for Omicron period |                      |        |
|--------------------------------------------------------------------|----------------------------------|----------------------|--------|
|                                                                    | Controls<br>(n=135,053)          | Cases<br>(n=135,053) | SMD    |
| <b>Demographics</b>                                                |                                  |                      |        |
| <b>Age, mean (SD), years</b>                                       | 54.1 (19.4)                      | 54.2 (19.7)          | 0.006  |
| <b>Age categories, n (%)</b>                                       |                                  |                      | 0.042  |
| 18-39 years                                                        | 41810 (31.0)                     | 41514 (30.7)         |        |
| 40-59 years                                                        | 34262 (25.4)                     | 34931 (25.9)         |        |
| 60-79 years                                                        | 48057 (35.6)                     | 46309 (34.3)         |        |
| ≥80 years                                                          | 10924 ( 8.1)                     | 12299 ( 9.1)         |        |
| <b>Male sex, n (%)</b>                                             | 46477 (34.4)                     | 46477 (34.4)         | <0.001 |
| <b>Self-reported race<sup>†</sup>, n (%)</b>                       |                                  |                      | 0.126  |
| White/Branca                                                       | 61832 (45.8)                     | 63243 (46.8)         |        |
| Mixed/Pardo                                                        | 38848 (28.8)                     | 32776 (24.3)         |        |
| Black/Preta                                                        | 5334 ( 3.9)                      | 4561 ( 3.4)          |        |
| Asian/ Amarela                                                     | 2067 ( 1.5)                      | 2350 ( 1.7)          |        |
| Indigenous/Indigena                                                | 194 ( 0.1)                       | 176 ( 0.1)           |        |
| Missing                                                            | 26778 (19.8)                     | 31947 (23.7)         |        |
| <b>Region of residence</b>                                         |                                  |                      | <0.001 |
| North                                                              | 3859 ( 2.9)                      | 3859 ( 2.9)          |        |
| Northeast                                                          | 24618 (18.2)                     | 24618 (18.2)         |        |
| Central-West                                                       | 7255 ( 5.4)                      | 7255 ( 5.4)          |        |
| Southeast                                                          | 86825 (64.3)                     | 86825 (64.3)         |        |
| South                                                              | 12496 ( 9.3)                     | 12496 ( 9.3)         |        |
| <b>Reported number of chronic comorbidities<sup>‡</sup>, n (%)</b> |                                  |                      | 0.087  |

|                                                                                      |                |                |       |
|--------------------------------------------------------------------------------------|----------------|----------------|-------|
| None                                                                                 | 110250 (81.6)  | 114600 (84.9)  |       |
| One or two                                                                           | 22967 (17.0)   | 19083 (14.1)   |       |
| Three or more                                                                        | 1836 ( 1.4)    | 1370 ( 1.0)    |       |
| <b>Prior SARS-CoV-2 exposure **</b>                                                  |                |                |       |
| Previous symptomatic events notified to the surveillance system <sup>¶</sup> , n (%) | 41841 (31.0)   | 34182 (25.3)   | 0.126 |
| Positive SARS-CoV-2 test result <sup>††</sup> , n (%)                                | 10419 ( 7.7)   | 6303 ( 4.7)    | 0.127 |
| <b>Interval between symptoms onset and RT-PCR testing, median (p25-p75), days</b>    | 3 [2, 4]       | 3 [1, 4]       | 0.164 |
| <b>Hospitalization or Death</b>                                                      | 18040 (13.4)   | 13484 (10.0)   | 0.106 |
| <b>Vaccination status</b>                                                            |                |                | 0.218 |
| Two doses, ≥180 days, n (%)                                                          | 26610 (19.7)   | 34817 (25.8)   |       |
| Third dose of CoronaVac, 0-7 days, n (%)                                             | 262 ( 0.2)     | 357 ( 0.3)     |       |
| Third dose of CoronaVac, 8-59 days, n (%)                                            | 1929 ( 1.4)    | 2458 ( 1.8)    |       |
| Third dose of CoronaVac, 60-89 days, n (%)                                           | 1613 ( 1.2)    | 1858 ( 1.4)    |       |
| Third dose of CoronaVac, 90-119 days, n (%)                                          | 2694 ( 2.0)    | 3811 ( 2.8)    |       |
| Third dose of CoronaVac, ≥120 days, n (%)                                            | 1888 ( 1.4)    | 2561 ( 1.9)    |       |
| Third dose of BNT162b2, 0-7 days, n (%)                                              | 2649 ( 2.0)    | 3954 ( 2.9)    |       |
| Third dose of BNT162b2, 8-59 days, n (%)                                             | 23637 ( 17.5)  | 16503 ( 12.2)  |       |
| Third dose of BNT162b2, 60-89 days, n (%)                                            | 26921 ( 19.9)  | 23643 ( 17.5)  |       |
| Third dose of BNT162b2, 90-119 days, n (%)                                           | 38587 ( 28.6)  | 36377 ( 26.9)  |       |
| Third dose of BNT162b2, ≥120 days, n (%)                                             | 8263 ( 6.1)    | 8714 ( 6.5)    |       |
| <b>Interval between second dose and RT-PCR/Antigen test, mean (SD), days</b>         | 272 [239, 309] | 273 [237, 313] | 0.003 |
| <b>Interval between third dose and RT-PCR/Antigen test, mean (SD), days</b>          | 88 [57, 104]   | 90 [63, 106]   | 0.078 |

RT-PCR=reverse transcription polymerase chain reaction; SMD=standardized mean difference; SD=standard deviation; † Race/skin colour as defined by the Brazilian national census bureau (Instituto Nacional de Geografia e Estatísticas). ‡ Comorbidities included cardiovascular, or renal conditions, diabetes, chronic respiratory disorder, obesity, or immunosuppression. \*\* Before the start of study on 06 September 2021. ¶ Reported illness with covid-19 associated symptoms in eSUS and SIVEP-Gripe databases. †† Defined as a positive SARS-CoV-2 RT-PCR or antigen detection test result

**Supplementary Table 17.** Adjusted vaccine effectiveness of homologous or heterologous booster against symptomatic Covid-19 and Covid-19 hospital admission or deaths in adults stratified by age during Omicron period in Brazil from the sensitivity analysis including RT-PCR SARS-CoV-2 tests only

|                                    | Symptomatic COVID-19 |                   |                   | Hospitalization or Death |                   |                   |
|------------------------------------|----------------------|-------------------|-------------------|--------------------------|-------------------|-------------------|
|                                    | <60 years            | 60-74 years       | ≥75 years         | <60 years                | 60-74 years       | ≥75 years         |
| Not vaccinated                     | Reference            | Reference         | Reference         | Reference                | Reference         | Reference         |
|                                    |                      |                   |                   |                          |                   |                   |
| Two doses, ≥180 days               | -3.6% (-6.2--1)      | 34.1% (30-38)     | 23.6% (17.3-29.4) | 72% (65.4-77.4)          | 63.8% (57.8-69)   | 31.5% (22.2-39.7) |
| Homologous booster                 |                      |                   |                   |                          |                   |                   |
| Third dose of CoronaVac, 8-59 days | 9.2% (2.9-15)        | 24.4% (11.1-35.6) | 21.8% (-2.2-40.2) | 91.4% (78-96.6)          | 74.3% (55.3-85.2) | 51.1% (8.8-73.8)  |
| Third dose of CoronaVac, ≥60 days  | -15.7% (-23.9--6.7)  | 23% (16.3-29.2)   | 3.6% (-4.8-11.6)  | 78.4% (44.1-91.6)        | 73.1% (65.7-78.9) | 40.9% (31.5-49)   |
| Heterologous booster               |                      |                   |                   |                          |                   |                   |
| Third dose of BNT162b2, 8-59 days  | 51.5% (50.1-52.8)    | 63.3% (60.6-65.8) | 66.6% (62.5-70.2) | 91.9% (89.2-93.9)        | 86.8% (83.7-89.3) | 74.2% (68.6-78.8) |
| Third dose of BNT162b2, ≥60 days   | 40% (38.6-41.3)      | 48.6% (45.7-51.4) | 42.8% (38.4-46.8) | 93.9% (92.3-95.2)        | 87.6% (85.6-89.4) | 70.2% (66.4-73.6) |

**Supplementary Table 18.** Adjusted Vaccine effectiveness of homologous and heterologous booster relative to those at least 180 days after the second dose of a primary series of CoronaVac during the Omicron period, from the sensitivity analysis including RT-PCR SARS-CoV-2 tests only

|                                          | Symptomatic COVID-19    | Hospitalization or Death |
|------------------------------------------|-------------------------|--------------------------|
|                                          | Relative<br>VE (95% CI) | Relative<br>VE (95% CI)  |
| Two doses, $\geq 180$ days               | Reference               | Reference                |
| <b>Homologous booster</b>                |                         |                          |
| Third dose of CoronaVac, 8-59 days       | 1.5% (-5.0-7.7)         | 37% (7.5-57.1)           |
| Third dose of CoronaVac, 60-79 days      | 2.7% (-4.7-9.7)         | 34.6% (17.2-48.4)        |
| Third dose of CoronaVac, 90-119 days     | -19.3% (-24--14.4)      | 7.8% (-7.6-21.5)         |
| Third dose of CoronaVac, $\geq 120$ days | -20.6% (-26.4--14.3)    | 15.9% (3.2-27)           |
| <b>Heterologous booster</b>              |                         |                          |
| Third dose of BNT162b2, 8-59 days        | 49.8% (48.5-51.2)       | 62.8% (57.9-67.1)        |
| Third dose of BNT162b2, 60-89 days       | 35.9% (34.3-37.5)       | 68.3% (65.1-71.1)        |
| Third dose of BNT162b2, 90-119 days      | 30.9% (29.2-32.4)       | 62.0% (58.8-64.9)        |
| Third dose of BNT162b2, $\geq 120$ days  | 16.6% (13.2-19.9)       | 50.3% (44.8-55.3)        |