Supplemental Online Content

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Supplement 3. eMethods

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eMETHODS

Inclusion and exclusion criteria

Participants were considered eligible for the study if they met the following criteria:

- Age range: healthy people aged 18+ years old;
- General good health as established by medical history and physical examination;
- Women of childbearing age are not pregnant (negative urine pregnancy test), are not breastfeeding, do not have pregnancy plan within the three months after enrollment, and have already taken effective contraceptive measures two weeks before enrollment;
- Participants are able and willing to complete the whole research procedure in about 14 months;
- Participants have the ability to understand the research procedures, to sign the informed consent voluntarily after explanation, and can comply with the requirements of the clinical research program.

Those who met the inclusion criteria were further evaluated for the following exclusion criteria:

- History of SARS-CoV, SARS-CoV-2 or MERS virus infection (identified through self-report or on-site inquiry);
- Those with fever (axillary temperature >37.0 °C), dry cough, fatigue, nasal obstruction, runny nose, sore throat, myalgia, diarrhea, shortness of breath, and dyspnea within 14 days before inoculation;
- Axillary temperature ≥37.0 °C (or ear or forehead temperature ≥37.0 °C) before inoculation;
- Those who have experienced severe allergic reactions (such as acute anaphylaxis, urticaria, eczema, dyspnea, neurovascular edema, or abdominal pain), or those who are allergic to the known gradients of COVID-19 inactivated vaccine;
- Those with history or family history of convulsion, epilepsy, encephalopathy, or mental illness;
- Those with congenital malformation, developmental disorder, genetic defect, or severe malnutrition, etc.;
- Those with confirmed or suspected serious respiratory diseases, serious cardiovascular disease, severe liver or renal diseases, malignant tumors, uncontrolled hypertension (systolic blood pressure ≥150 mmHg, diastolic blood pressure ≥90 mmHg), diabetes complications, malignant tumors, or various acute or chronic diseases (acute attack stage);
- Those diagnosed with congenital or acquired immunodeficiency, HIV infection, lymphoma, leukemia, or other autoimmune diseases;
- Those with a history of abnormal coagulation (such as lack of coagulation factors or coagulation diseases);
- Those receiving anti-TB treatment;
- Those receiving immune-enhancement or inhibitor treatment (p.o. or gtt.) over 14 days within 3 months (continuous oral or infusion for more than 14 days);
- Those receiving live-attenuated vaccines within one month before inoculation or other vaccines within 14 days before inoculation;
- Those receiving blood products within 3 months before inoculation;
- Those receiving other study drugs within 6 months before inoculation;
- Those under other conditions not suitable for the clinical trial (evaluated by researchers).

After the first injection and before the subsequent second injection, the following participants were not allowed to be injected for the second dose:

- Those with confirmed SARS-CoV-2 infection;
- Women with positive urine pregnancy tests;
- Those with high fever (axillary temperature ≥39.0 °C) lasting for three days or severe allergic reaction after

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the previous injection;
- Serious adverse reactions related to the previous injection;
- If the investigators found that the participant did not meet the inclusion criteria or the participant met the exclusion criteria after the first dose, investigators should decide whether the participants could continue to participate in the study;
- Other reasons for exclusion evaluated by investigators.

Criteria for early withdrawal from the trial if any of the following occurred:
- The participant asked for a withdrawal;
- Intolerable adverse event regardless of its relation with the injection;
- The health status of the participants does not allow them to continue to participate in this trial;
- The participants were vaccinated with other investigational vaccines during the study period.
- Reach the endpoint of clinical trials;
- Any other reason that evaluated by investigators.

Severity definition for the COVID-19 cases

Confirmed mild COVID-19 cases:

The clinical symptoms were mild, and there was no sign of pneumonia on imaging.

Confirmed moderate COVID-19 cases:

Showing fever and respiratory symptoms with radiological findings of pneumonia.

Confirmed severe COVID-19 cases:

Confirmed COVID-19 case meeting any one of the following criteria:
- Respiratory distress (RR ≥30 breaths/min);
- Oxygen saturation ≤93% at rest;
- Arterial partial pressure of oxygen (PaO2)/ fraction of inspired oxygen (FiO2) ≤300mmHg (1mmHg=0.133kPa);
- The clinical symptoms progressively worsened, and the chest imaging showed >50% obvious lesion progression within 24-48 hours.

Confirmed Critical COVID-19 cases:

Confirmed COVID-19 case meeting any one of the following criteria:
- Respiratory failure and requiring mechanical ventilation;
- Shock;
- With other organ failure that requires ICU care;
- Death.

Real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) assay

In the United Arab Emirates, Real-time fluorescent RT-PCR kits for detecting 2019-nCoV (BGI, Shenzhen, China) were used to detect COVID-19 cases. In Bahrain, COVID-19 PCR test kits (TIB MOLBIOL, Berlin, Germany) were used to detect COVID-19 cases.

Detection of specific IgG binding antibodies in serum samples with ELISA

In the United Arab Emirates, Alinity SARS-CoV-2 IgG Reagent Kit 06R90 (Abbott Laboratories, Illinois, USA) were used for IgG antibody tests. In Bahrain, ARCHITECT SARS-CoV-2 IgG Reagent Kit 6R86 (Abbott Laboratories, Illinois, USA) were used. The assays were performed according to the manufacturer's instructions.

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Method for infectious SARS-Cov-2 neutralizing assay

The neutralization antibody assays were performed at the National Institute for Food and Drug Control, Beijing, China. Serum was successively diluted 1:4 to the required concentration by a 2-fold series, and an equal volume of challenge virus solution was added. After neutralization in a 37 °C incubator for 2 h, a 1.0~2.5×105/ml cell suspension was added to the wells (0.1 ml/well) and cultured in a CO2 incubator at 37 °C for 4 days. Titers expressed as the reciprocal of the highest dilution protecting 50% cell from virus challenge. Convalescent sera is included as an internal positive control in every assay. Seroconversion was defined as an increase in post-vaccination titer of four-fold or more from baseline.

Interim analysis

To accelerate the vaccine application process, two interim analyses were planned in the protocol when the combined number of incident cases in the alum-only group and either of the vaccine groups reached 50 (1/3 of the planned cases required for final analysis) or 100 (2/3 of the planned cases), as recommended by the World Health Organization. In the interim analysis, the O'Brien-Fleming spending function was employed to control the family-wise type I error to be within two-sided 0.05. The original designed nominal significance level was 0.0001 (one-sided) for the first interim analysis and 0.0060 (one-sided) for the second interim analysis based on the planned cases of 50 and100, respectively. However, the real nominal significance level in practice would be calculated based on the observed cases.

On November 12, 2020, the first interim analysis was performed with a total of 73 incident cases adjudicated by the Endpoint Adjudication Committees. However, the Center for Drug Evaluation (CDE), National Medical Products Administration of China refused 2 cases that did not meet the case criteria and 1 case that had unclear duration of symptoms. Therefore, a total of 70 cases were involved in the interim analysis (12 in the WIV04 group, 10 in the HB02 group, and 48 in the alum-only group). Based on the real number of cases, the nominal significance level was calculated as one-sided 0.00031 to test the vaccine efficacy of HB02 group compared with alum-only control (with a combined number of cases as 58). The vaccine efficacy (VE) with 99.938% (i.e., 1-2*0.00031) CI of HB02 group was 79.34% (32.11%, 93.71%) and the positive result was concluded at the 1st interim analysis because the lower bound of 99.938% CI was larger than 30%. The nominal significance level was calculated as one-sided 0.00039 to test the vaccine efficacy of WIV04 group compared with alum-only control (with a combined number of cases as 60). The VE with 99.921% (i.e., 1-2*0.00039) CI of WIV04 group was 75.30% (27.03%, 91.64%) and the positive result was not concluded at the 1st interim analysis. Therefore, the China CDE requested the study to continue to accumulate more cases for the second interim analysis before approval of the vaccines for emergency use.

On December 20, 2020, the efficacy dataset was locked and a second interim analysis was planned. Finally, a total of 142 incident cases (26 in the WIV04 group, 21 in the HB02 group, and 95 in the alum-only group) were adjudicated by the Endpoint Adjudication Committees and confirmed by the China CDE as well. Because the HB02 vaccine already achieved success criterion, no O'Brien-Fleming spending function was needed for this group. For the WIV04 group, the nominal significance level was calculated as one-sided 0.0124 to test the vaccine efficacy of WIV04 group compared with alum-only control (with a combined number of cases as 121). The VE with 97.52% (i.e., 1-2*0.0124) CI of WIV04 vaccine was 72.80% (55.30%, 83.45%) and the positive result was concluded at the 2nd interim analysis because the lower bound of 97.52%CI was larger than 30%. Based on the results, the China CDE approved the vaccines for emergency use.

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eTable 1. Explanation of the Changes in Denominator Numbers in Various Analyses

Populations/Sample size	Explanation	Figure/table number
Safety analysis set (n = 40 382)	Included all participants who received at least one dose of vaccine.	Figure 1, Figure 3, eTable 2, eTable 5-8
Full analysis set 1 (n = 40 289)[a]	Included all participants who received at least one dose of vaccine, had a negative PCR test before randomization, and completed case monitoring at least once.	Figure 1, Figure 2, eTable 3
Modified full analysis population-1 (n = 38 206)	A subset of full analysis set. Participants received two doses of vaccines and had a negative PCR test before randomization, and had at least one case monitoring after day 14 post second dose.	Figure 1, Tables 1-2, eTable 4
Modified full analysis population-2 (n = 38 288)	Included all participants who followed intent-to-treat principle, received two doses of vaccines, and completed at least one case monitoring.	Figure 1, eTable 3
Per-protocol population-1 (n = 37 986)	A subset of modified full analysis population-1, where those who did not meet the selection criteria, received the wrong vaccination or doses, received vaccinations exceeding the window judged by researchers, sponsors, and the statistics party, or were with other factors influencing the evaluation of efficacy, were excluded.	Figure 1, eTable 3
Per-protocol population-2 (n = 38 068)	A subset of modified full analysis population-2, where those who did not meet the selection criteria, received the wrong vaccination or doses, received vaccinations exceeding the window judged by researchers, sponsors, and the statistics party, or were with other factors influencing the evaluation of efficacy, were excluded.	Figure 1, eTable 3

[a] At baseline, a total of 93 participants had positive PCR results but no symptoms, 32 in the WIV04 group, 29 in the HB02 group, and 32 in the alum-only group. They were still enrolled in the trial based on our inclusion and exclusion criteria, but not included in the full analysis set 1. The safety analysis set included those 93 participants.

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eTable 2. Baseline Characteristics of the Study Participants in the Safety Set[a]

Characteristics	WIV04	HB02	Alum-only
No. of participants	13 464	13 471	13 453
Age, mean (SD), y	36.2 (9.6)	36.2 (9.7)	36.2 (9.6)
Age groups, n (%)			
<60 y	13 170 (97.8)	13 186 (97.9)	13 170 (97.9)
≥60 y	294 (2.2)	285 (2.1)	282 (2.1)
Sex, n (%)			
Male	11 327 (84.1)	11 391 (84.6)	11 417 (84.9)
Female	2137 (15.9)	2080 (15.4)	2036 (15.1)
Study site, n (%)			
Abu Dhabi	9124 (67.8)	9128 (67.8)	9114 (67.8)
Sharjah	1755 (13.0)	1756 (13.0)	1755 (13.0)
Bahrain	2585 (19.2)	2587 (19.2)	2584 (19.2)
Nationality, n (%)			
United Arab Emirates	3210 (23.8)	3199 (23.7)	3171 (23.6)
India	1896 (14.1)	1890 (14.0)	1824 (13.6)
Bangladesh	1381 (10.3)	1266 (9.4)	1334 (9.9)
China	1267 (9.4)	1240 (9.2)	1265 (9.4)
Pakistan	1246 (9.3)	1270 (9.4)	1329 (9.9)
Bahrain	911 (6.8)	982 (7.3)	934 (6.9)
Egypt	718 (5.3)	721 (5.4)	696 (5.2)
Philippine	492 (3.7)	516 (3.8)	522 (3.9)
Nepal	297 (2.2)	295 (2.2)	334 (2.5)
Syrian	298 (2.2)	324 (2.4)	326 (2.4)
Others	1748 (13.0)	1768 (13.1)	1718 (12.8)
Height, mean (SD) [N], cm	170.4 (8.4) [13 457]	170.6 (8.4) [13 461]	170.6 (8.4) [13 447]
Weight, mean (SD) [N], kg	78.5 (16.9) [13 457]	78.8 (16.9) [13 461]	78.6 (16.8) [13 447]
BMI, mean (SD) [N], kg/m^2	26.9 (5.1) [13 457]	27.0 (5.1) [13 461]	26.9 (5.0) [13 447]
Baseline PCR status, n (%)			
Positive	32 (0.2)	29 (0.2)	32 (0.2)
Negative	13 346 (99.1)	13 337 (99.0)	13 355 (99.3)
Missing	86 (0.7)	105 (0.8)	66 (0.5)
Baseline IgG antibody, n (%)			
Positive	673 (5.0)	702 (5.2)	653 (4.9)
Negative	9821 (72.9)	9732 (72.2)	9784 (72.7)
Missing	2970 (22.1)	3037 (22.6)	3016 (22.4)

Abbreviation: alum, aluminum hydroxide; BMI, body mass index. WIV04 and HB02 groups represent the vaccine groups which were developed based on two SARS-CoV-2 strains, WIV04 and HB02 strains.

[a] Safety analysis population included all participants who received at least one dose of vaccine.

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eTable 3. Efficacy After 14 Days Following the Second Dose: Sensitivity Analysis[a]

Sensitivity analysis	WIV04	HB02	Alum-only
Full analysis population-1			
No. of participants	13 428	13 436	13 425
No. of incident cases	69	48	138
Person-years	3406.8	3413.9	3389.9
Incidence density, per 1000 person-years (95% CI)	20.3 (16.0-25.6)	14.1 (10.6-18.7)	40.7 (34.5-48.1)
Vaccine efficacy, % (95% CI)	50.3 (33.6-62.7)	65.5 (52.0-75.1)	Reference
Modified full analysis population-2			
No. of participants	12 769	12 752	12 767
No. of incident cases	26	21	95
Person-years	2144.7	2147.9	2130.8
Incidence density, per 1000 person-years (95% CI)	12.1 (8.3-17.8)	9.8 (6.4-15.0)	44.6 (36.5-54.5)
Vaccine efficacy, % (95% CI)	72.8 (58.0-82.4)	78.1 (64.8-86.3)	Reference
Per-protocol population-1			
No. of participants	12 671	12 650	12 665
No. of incident cases	26	21	94
Person-years	2134.1	2136.3	2118.7
Incidence density, per 1000 person-years (95% CI)	12.2 (8.3-17.9)	9.8 (6.4-15.1)	44.4 (36.2-54.3)
Vaccine efficacy, % (95% CI)	72.5 (57.6-82.2)	77.8 (64.4-86.2)	Reference
Per-protocol population-2			
No. of participants	12 697	12 676	12 695
No. of incident cases	26	21	94
Person-years	2138.5	2141.0	2124.0
Incidence density, per 1000 person-years (95% CI)	12.2 (8.3-17.9)	9.8 (6.4-15.0)	44.3 (36.2-54.2)
Vaccine efficacy, % (95% CI)	72.5 (57.6-82.2)	77.8 (64.4-86.2)	Reference

Abbreviation: alum, aluminum hydroxide; COVID-19, coronavirus disease 2019. WIV04 and HB02 groups represent the vaccine groups which were developed based on two SARS-CoV-2 strains, WIV04 and HB02 strains.

[a] Full analysis population-1 included all participants who followed intent-to-treat principle, undertook randomization, received at least one dose of vaccine, had a negative polymerase chain reaction test before randomization, and completed case monitoring at least once. Modified full analysis population-2 included all participants who followed intent-to-treat principle, received two doses of vaccines, and completed case monitoring at least once. Per-protocol population-1 was a subset of modified full analysis population-1 in the main analysis, and those who (1) did not meet the selection criteria, (2) received the wrong vaccination or doses, (3) received vaccinations exceeding the window judged by researchers, sponsors, and the statistics party, or (4) were with other factors influencing the evaluation of efficacy, were excluded. Per-protocol population-2 was a subset of modified full analysis population-2, and those who had the four abovementioned issues were excluded. A Poisson regression model with log link function was employed with the number of incident cases as the dependent variable, treatment group as the independent variable and the person-years as offset. Incidence density with its 95% CI was estimated using the least-square

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method. If the number of cases in any of the groups was <5, the exact method was used to estimate the incidence rate, vaccine efficacy and 95% CI by using StatXact software.

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eTable 4. Efficacy After 14 Days Following Two Doses: Subgroup Analysis[a]

Subgroup	WIV04	HB02	Alum only
Abu Dhabi			
No. of participants	8552	8538	8544
No. of incident cases	15	12	53
Person-years	1552.6	1559.2	1540.2
Incidence density, per 1000 person-years (95% CI)	9.7 (5.8-16.0)	7.7 (4.4-13.6)	34.4 (26.3-45.0)
Vaccine efficacy, % (95% CI)	71.9 (50.2-84.2)	77.6 (58.2-88.1)	Reference
Sharjah			
No. of participants	1705	1717	1713
No. of incident cases	5	4	13
Person-years	216.9	219.2	221.2
Incidence density, per 1000 person-years (95% CI)	23.1 (7.5-53.8)	18.2 (5.0-46.7)	58.8 (31.3-100.5)
Vaccine efficacy, % (95% CI)	60.8 (-17.3-89.1)	69.0 (-0.5-92.6)	Reference
Bahrain			
No. of participants	2486	2471	2480
No. of incident cases	6	5	29
Person-years	370.8	364.8	364.2
Incidence density, per 1000 person-years (95% CI)	16.2 (5.9-35.2)	13.7 (4.5-32.0)	79.6 (53.3-114.4)
Vaccine efficacy, % (95% CI)	79.7 (50.2-93.1)	82.8 (55.0-94.8)	Reference
Female			
No. of participants	2037	1976	1932
No. of incident cases	3	3	12
Person-years	345.2	329.8	322.2
Incidence density, per 1000 person-years (95% CI)	8.7 (1.8-25.4)	9.1 (1.9-26.6)	37.2 (19.2-65.1)
Vaccine efficacy, % (95% CI)	76.7 (13.5-95.8)	75.6 (9.5-95.6)	Reference
Male			
No. of participants	10 706	10 750	10 805
No. of incident cases	23	18	83
Person-years	1795.0	1813.4	1803.3
Incidence density, per 1000 person-years (95% CI)	12.8 (8.5-19.3)	9.9 (6.3-15.8)	46.0 (37.1-57.1)
Vaccine efficacy, % (95% CI)	72.2 (55.8-82.5)	78.4 (64.1-87.0)	Reference
<60 years			
No. of participants	12 530	12 525	12 539
No. of incident cases	26	21	95
Person-years	2122.7	2129.1	2109.6
Incidence density, per 1000 person-years (95% CI)	12.2 (8.3-18.0)	9.9 (6.4-15.1)	45.0 (36.8-55.1)

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Vaccine efficacy, % (95% CI)	72.8 (58.0-82.4)	78.1 (64.9-86.4)	Reference
Subgroup	**WIV04**	**HB02**	**Alum only**
≥60 years			
No. of participants	213	201	198
No. of incident cases	0	0	0
Person-years	17.6	14.2	16.0
Incidence density, per 1000 person-years (95% CI)	0	0	0
Vaccine efficacy, % (95% CI)	NA	NA	Reference
Positive baseline IgG			
No. of participants	640	666	619
No. of incident cases	0	0	1
Person-years	95.2	103.6	92.8
Incidence density, per 1000 person-years (95% CI)	0	0	10.8 (1.5-76.5)
Vaccine efficacy, % (95% CI)	100	100	Reference
Negative or borderline baseline IgG			
No. of participants	9425	9303	9382
No. of incident cases	18	16	83
Person-years	1588.5	1570.4	1568.3
Incidence density, per 1000 person-years (95% CI)	11.3 (7.1-18.0)	10.2 (6.2-16.6)	52.9 (42.7-65.6)
Vaccine efficacy, % (95% CI)	78.6 (64.4-87.1)	80.8 (67.1-88.7)	Reference
Missing baseline IgG			
No. of participants	2678	2757	2736
No. of incident cases	8	5	11
Person-years	456.6	469.2	464.4
Incidence density, per 1000 person-years (95% CI)	17.5 (8.8-35.0)	10.7 (4.4-25.6)	23.7 (13.1-42.8)
Vaccine efficacy, % (95% CI)	26.0 (-83.9-70.3)	55.0 (-29.5-84.4)	Reference

Abbreviation: alum, aluminum hydroxide; COVID-19, coronavirus disease 2019; NA, not applicable. WIV04 and HB02 groups represent the vaccine groups which were developed based on two SARS-CoV-2 strains, WIV04 and HB02 strains.

[a] Modified full analysis population-1 included all participants who followed intent-to-treat principle, received two doses of vaccines, had a negative polymerase chain reaction test before randomization, and completed case monitoring at least once. A Poisson regression model with log link function was employed with the number of incident cases as the dependent variable, treatment group as the independent variable and the person-years as offset. Incidence density with its 95% CI was estimated using the least-square method. If the number of cases in any of the groups was <5, the exact method was used to estimate the incidence rate, vaccine efficacy and 95% CI by using StatXact software.

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eTable 5. Total Adverse Reactions in the Safety Set[a]

Adverse reaction	WIV04 (n=13 464)	HB02 (n=13 471)	Alum-only (n=13 453)
0-7 d			
Total adverse reactions	5957 (44.2)	5623 (41.7)	6250 (46.5)
Solicited adverse reactions	5595 (41.6)	5270 (39.1)	5935 (44.1)
Local reactions	3450 (25.6)	2786 (20.7)	3906 (29.0)
Pain	3271 (24.3)	2614 (19.4)	3758 (27.9)
Induration	139 (1.0)	74 (0.6)	123 (0.9)
Swelling	196 (1.5)	107 (0.8)	166 (1.2)
Rash	93 (0.7)	100 (0.7)	74 (0.6)
Redness	152 (1.1)	120 (0.9)	147 (1.1)
Itching	52 (0.4)	64 (0.5)	54 (0.4)
Systemic reactions	3695 (27.4)	3810 (28.3)	3743 (27.8)
Fever	271 (2.0)	279 (2.1)	277 (2.1)
Diarrhea	497 (3.7)	478 (3.6)	539 (4.0)
Constipation	142 (1.1)	101 (0.8)	111 (0.8)
Dysphagia	51 (0.4)	58 (0.4)	62 (0.5)
Anorexia	34 (0.3)	33 (0.2)	26 (0.2)
Vomiting	77 (0.6)	81 (0.6)	82 (0.6)
Nausea	137 (1.0)	162 (1.2)	135 (1.0)
Myalgia	722 (5.4)	739 (5.5)	730 (5.4)
Arthralgia	191 (1.4)	182 (1.4)	177 (1.3)
Headache	1733 (12.9)	1761 (13.1)	1693 (12.6)
Coughing	481 (3.6)	463 (3.4)	487 (3.6)
Dyspnea	189 (1.4)	151 (1.1)	167 (1.2)
Pruritus (non-inoculated site)	175 (1.3)	195 (1.5)	184 (1.4)
Skin and mucosal abnormalities	28 (0.2)	23 (0.2)	33 (0.3)
Acute allergic reactions	34 (0.3)	38 (0.3)	39 (0.3)
Fatigue	1466 (10.9)	1510 (11.2)	1425 (10.6)
Unsolicited adverse reactions	1489 (11.1)	1437 (10.7)	1420 (10.6)
0-28 d			
Total adverse reactions	6237 (46.3)	5902 (43.8)	6504 (48.4)
Solicited adverse reactions	5595 (41.6)	5270 (39.1)	5935 (44.1)
Local reactions	3450 (25.6)	2786 (20.7)	3906 (29.0)
Systemic reactions	3695 (27.4)	3810 (28.3)	3743 (27.8)
Unsolicited adverse reactions	2161 (16.1)	2094 (15.5)	2071 (15.4)
Until 31 December, 2020			
Total adverse reactions	6237 (46.3)	5902 (43.8)	6505 (48.4)
Solicited adverse reactions	5595 (41.6)	5270 (39.1)	5935 (44.1)
Local reactions	3450 (25.6)	2786 (20.7)	3906 (29.0)
Systemic reactions	3695 (27.4)	3810 (28.3)	3743 (27.8)
Unsolicited adverse reactions	2162 (16.1)	2094 (15.5)	2075 (15.4)

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Abbreviation: alum, aluminum hydroxide. WIV04 and HB02 groups represent the vaccine groups which were developed based on two SARS-CoV-2 strains, WIV04 and HB02 strains.

[a]The safety set included all participants who received at least 1 dose. Data are shown as No. of participants with event (%). A participant was only counted once in the specific reaction category even though a participant could have more than 1 adverse reaction. For example, a participant who had the same symptom (eg, injection site pain) after each dose was counted once in the symptom category. Similarly, if a participant had more than 1 symptom in the reaction class (total, systemic, and local), they were only counted once in that adverse reaction class.

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eTable 6. Total Adverse Events in the Safety Set

Adverse event	WIV04 (n = 13 464)	HB02 (n = 13 471)	Alum only (n = 13 453)
0-28 d			
Total adverse events	6505 (48.3)	6207 (46.1)	6793 (50.5)
Grade 1	4992 (37.1)	4788 (35.6)	5268 (39.2)
Grade 2	1406 (10.5)	1323 (9.8)	1419 (10.6)
Grade 3	107 (0.8)	96 (0.7)	106 (0.8)
Solicited adverse events	5676 (42.2)	5362 (39.8)	6012 (44.7)
Grade 1	4502 (33.4)	4287 (31.8)	4815 (35.8)
Grade 2	1085 (8.1)	998 (7.4)	1112 (8.3)
Grade 3	89 (0.7)	77 (0.6)	85 (0.6)
Local events	3450 (25.6)	2786 (20.7)	3906 (29.0)
Grade 1	3123 (23.2)	2519 (18.7)	3527 (26.2)
Grade 2	320 (2.4)	264 (2.0)	372 (2.8)
Grade 3	7 (<0.1)	3 (<0.1)	7 (<0.1)
Pain	3271 (24.3)	2614 (19.4)	3758 (27.9)
Grade 1	2964 (22.0)	2370 (17.6)	3403 (25.3)
Grade 2	301 (2.2)	243 (1.8)	349 (2.6)
Grade 3	6 (<0.1)	1 (<0.1)	6 (<0.1)
Induration	139 (1.0)	74 (0.6)	123 (0.9)
Grade 1	134 (1.0)	71 (0.5)	113 (0.8)
Grade 2	4 (<0.1)	3 (<0.1)	10 (<0.1)
Grade 3	1 (<0.1)	0 (<0.1)	0 (<0.1)
Swelling	196 (1.5)	107 (0.8)	166 (1.2)
Grade 1	184 (1.4)	102 (0.8)	159 (1.2)
Grade 2	11 (<0.1)	5 (<0.1)	7 (<0.1)
Grade 3	1 (<0.1)	0 (<0.1)	0 (<0.1)
Rash	93 (0.7)	100 (0.7)	74 (0.6)
Grade 1	87 (0.7)	90 (0.7)	62 (0.5)
Grade 2	6 (<0.1)	9 (<0.1)	12 (<0.1)
Grade 3	0 (<0.1)	1 (<0.1)	0 (<0.1)
Redness	152 (1.1)	120 (0.9)	147 (1.1)
Grade 1	145 (1.1)	114 (0.9)	138 (1.0)
Grade 2	7 (<0.1)	6 (<0.1)	9 (<0.1)
Grade 3	0 (<0.1)	0 (<0.1)	0 (<0.1)
Itching	52 (0.4)	64 (0.5)	54 (0.4)
Grade 1	51 (0.4)	59 (0.4)	53 (0.4)
Grade 2	1 (<0.1)	4 (<0.1)	0 (<0.1)
Grade 3	0 (<0.1)	1 (<0.1)	1 (<0.1)
Systemic events	3815 (28.3)	3939 (29.2)	3866 (28.7)
Grade 1	2885 (21.4)	3046 (22.6)	2947 (21.9)
Grade 2	846 (6.3)	819 (6.1)	840 (6.2)

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Grade 3	84 (0.6)	74 (0.6)	79 (0.6)
Adverse event	**WIV04 (n = 13 464)**	**HB02 (n = 13 471)**	**Alum only (n = 13 453)**
Fever	293 (2.2)	295 (2.2)	292 (2.2)
Grade 1	235 (1.8)	231 (1.7)	223 (1.7)
Grade 2	30 (0.2)	41 (0.3)	34 (0.3)
Grade 3	28 (0.2)	23 (0.2)	35 (0.3)
Diarrhea	522 (3.9)	498 (3.7)	557 (4.1)
Grade 1	423 (3.1)	422 (3.1)	450 (3.3)
Grade 2	87 (0.7)	68 (0.5)	97 (0.7)
Grade 3	12 (<0.1)	8 (<0.1)	10 (<0.1)
Constipation	149 (1.1)	110 (0.8)	117 (0.9)
Grade 1	129 (1.0)	93 (0.7)	103 (0.8)
Grade 2	19 (0.1)	16 (0.1)	14 (0.1)
Grade 3	1 (<0.1)	1 (<0.1)	0 (<0.1)
Dysphagia	55 (0.4)	60 (0.5)	62 (0.5)
Grade 1	50 (0.4)	48 (0.4)	56 (0.4)
Grade 2	5 (<0.1)	11 (<0.1)	6 (<0.1)
Grade 3	0 (<0.1)	1 (<0.1)	0 (<0.1)
Anorexia	35 (0.3)	38 (0.3)	29 (0.2)
Grade 1	30 (0.2)	30 (0.2)	25 (0.2)
Grade 2	5 (<0.1)	8 (<0.1)	4 (<0.1)
Grade 3	0 (<0.1)	0 (<0.1)	0 (<0.1)
Vomiting	79 (0.6)	87 (0.7)	90 (0.7)
Grade 1	62 (0.5)	69 (0.5)	72 (0.5)
Grade 2	14 (0.1)	15 (0.1)	13 (<0.1)
Grade 3	3 (<0.1)	3 (<0.1)	5 (<0.1)
Nausea	140 (1.0)	172 (1.3)	143 (1.1)
Grade 1	132 (1.0)	156 (1.2)	130 (1.0)
Grade 2	8 (<0.1)	15 (0.1)	13 (0.1)
Grade 3	0 (<0.1)	1 (<0.1)	0 (<0.1)
Myalgia	742 (5.5)	769 (5.7)	766 (5.7)
Grade 1	613 (4.6)	644 (4.8)	650 (4.8)
Grade 2	120 (0.9)	117 (0.9)	112 (0.8)
Grade 3	9 (<0.1)	8 (<0.1)	4 (<0.1)
Arthralgia	199 (1.5)	191 (1.4)	185 (1.4)
Grade 1	155 (1.2)	151 (1.1)	155 (1.2)
Grade 2	42 (0.3)	38 (0.3)	30 (0.2)
Grade 3	2 (<0.1)	2 (<0.1)	0 (<0.1)
Headache	1799 (13.4)	1815 (13.5)	1743 (13.0)
Grade 1	1402 (10.4)	1463 (10.9)	1379 (10.3)
Grade 2	383 (2.9)	339 (2.5)	353 (2.6)
Grade 3	14 (0.1)	13 (0.1)	11 (<0.1)

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Coughing	513 (3.8)	494 (3.7)	516 (3.8)
Grade 1	415 (3.1)	413 (3.1)	418 (3.1)
Adverse event	**WIV04 (n = 13 464)**	**HB02 (n = 13 471)**	**Alum only (n = 13 453)**
Grade 2	97 (0.7)	77 (0.6)	95 (0.7)
Grade 3	1 (<0.1)	4 (<0.1)	3 (<0.1)
Dyspnea	199 (1.5)	163 (1.2)	172 (1.3)
Grade 1	161 (1.2)	127 (0.9)	139 (1.0)
Grade 2	31 (0.2)	30 (0.2)	30 (0.2)
Grade 3	7 (<0.1)	6 (<0.1)	3 (<0.1)
Pruritus (non-inoculated site)	187 (1.4)	209 (1.6)	200 (1.5)
Grade 1	153 (1.1)	171 (1.3)	168 (1.3)
Grade 2	30 (0.2)	37 (0.3)	29 (0.2)
Grade 3	4 (<0.1)	1 (<0.1)	3 (<0.1)
Skin and mucosal abnormalities	37 (0.3)	29 (0.2)	44 (0.3)
Grade 1	31 (0.2)	27 (0.2)	31 (0.2)
Grade 2	5 (<0.1)	2 (<0.1)	13 (0.1)
Grade 3	1 (<0.1)	0 (<0.1)	0 (<0.1)
Acute allergic events	36 (0.3)	42 (0.3)	43 (0.3)
Grade 1	28 (0.2)	30 (0.2)	29 (0.2)
Grade 2	8 (<0.1)	12 (<0.1)	13 (<0.1)
Grade 3	0 (<0.1)	0 (<0.1)	1 (<0.1)
Fatigue	1499 (11.1)	1540 (11.4)	1449 (10.8)
Grade 1	1241 (9.2)	1298 (9.6)	1194 (8.9)
Grade 2	247 (1.8)	223 (1.7)	245 (1.8)
Grade 3	11 (<0.1)	19 (0.1)	10 (<0.1)
Unsolicited adverse events	2673 (19.9)	2654 (19.7)	2626 (19.5)
Grade 1	2190 (16.3)	2191 (16.3)	2169 (16.1)
Grade 2	459 (3.4)	440 (3.3)	431 (3.2)
Grade 3	24 (0.2)	23 (0.2)	26 (0.2)
Until 31 December, 2020			
Total adverse events	6505 (48.3)	6207 (46.1)	6794 (50.5)
Grade 1	4991 (37.1)	4788 (35.6)	5269 (39.2)
Grade 2	1407 (10.5)	1323 (9.8)	1419 (10.6)
Grade 3	107 (0.8)	96 (0.7)	106 (0.8)
Solicited adverse events	5676 (42.2)	5362 (39.8)	6012 (44.7)
Grade 1	4502 (33.4)	4287 (31.8)	4815 (35.8)
Grade 2	1085 (8.1)	998 (7.4)	1112 (8.3)
Grade 3	89 (0.7)	77 (0.6)	85 (0.6)

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Local events	3450 (25.6)	2786 (20.7)	3906 (29.0)
Grade 1	3123 (23.2)	2519 (18.7)	3527 (26.2)
Grade 2	320 (2.4)	264 (2.0)	372 (2.8)
Grade 3	7 (<0.1)	3 (<0.1)	7 (<0.1)
Adverse event	**WIV04 (n = 13 464)**	**HB02 (n = 13 471)**	**Alum only (n = 13 453)**
Systemic events	3815 (28.3)	3939 (29.2)	3866 (28.7)
Grade 1	2885 (21.4)	3046 (22.6)	2947 (21.9)
Grade 2	846 (6.3)	819 (6.1)	840 (6.2)
Grade 3	84 (0.6)	74 (0.6)	79 (0.6)
Unsolicited adverse events	2673 (19.9)	2654 (19.7)	2629 (19.5)
Grade 1	2189 (16.3)	2191 (16.3)	2172 (16.1)
Grade 2	460 (3.4)	440 (3.3)	431 (3.2)
Grade 3	24 (0.2)	23 (0.2)	26 (0.2)

Abbreviation: alum, aluminum hydroxide. WIV04 and HB02 groups represent the vaccine groups which were developed based on two SARS-CoV-2 strains, WIV04 and HB02 strains.

[a]The safety set included all participants who received at least 1 dose. Data are shown as No. of participants with event (%). A participant was only counted once in the specific reaction category even though a participant could have more than 1 adverse reaction. For example, a participant who had the same symptom (eg, injection site pain) after each dose was counted once in the symptom category. Similarly, if a participant had more than 1 symptom in the reaction class (total, systemic, and local), they were only counted once in that adverse reaction class. If a participant had both a lower and higher Grade adverse events, he/she was only counted once into the higher Grade total adverse events. The details of grading scales for systemic and local adverse events are shown in the protocol in the Supplement 1.

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eTable 7. The Number of Serious Adverse Events (SAEs) in the Safety Set

SAEs	WIV04 (n = 13 464)	HB02 (n = 13 471)	Alum only (n = 13 453)
Total SAEs	64 (0.5)	59 (0.4)	78 (0.6)
Certain infectious and parasitic SAEs	21 (0.2)	20 (0.2)	39 (0.3)
Nutritional and metabolic SAEs	9 (0.1)	11 (0.1)	4 (<0.1)
Injury, poisoning and certain other consequences of external causes	8 (0.1)	11 (0.1)	5 (<0.1)
SAEs of the gastrointestinal system	8 (0.1)	7 (0.1)	8 (0.1)
Surgeries and medical procedures	9 (0.1)	5 (<0.1)	5 (<0.1)
SAEs of the musculoskeletal system and connective tissue	8 (0.1)	5 (<0.1)	4 (<0.1)
SAEs of kidney and urinary system	5 (<0.1)	10 (0.1)	2 (<0.1)
SAEs of the nervous system	3 (<0.1)	5 (<0.1)	8 (0.1)
Heart diseases	0	9 (0.1)	4 (<0.1)
SAEs of the respiratory system	4 (<0.1)	1 (<0.1)	5 (<0.1)
SAEs of the blood and blood-forming organs and certain disorders involving the immune mechanism	4 (<0.1)	5 (<0.1)	1 (<0.1)
Systemic or injection-site SAEs	3 (<0.1)	2 (<0.1)	2 (<0.1)
Mental and behavioral disorders	2 (<0.1)	2 (<0.1)	2 (<0.1)
SAEs of vessels and lymphatic vessels	1 (<0.1)	3 (<0.1)	1 (<0.1)
SAEs of the hepatobiliary system	0	2 (<0.1)	2 (<0.1)
Examinations	1 (<0.1)	2 (<0.1)	0
SAEs of skin and subcutaneous tissue	1 (<0.1)	1 (<0.1)	0
SAEs in pregnancy, childbirth and the puerperium	0	2 (<0.1)	0
SAEs of the reproductive system and breast	0	0	2 (<0.1)
Congenital familial genetic SAEs	0	1 (<0.1)	0
Neoplasms	1 (<0.1)	0	0
Endocrine SAEs	0	1 (<0.1)	0
SAEs of the eye and adnexa	1 (<0.1)	0	0

Abbreviation: alum, aluminum hydroxide; SAE, serious adverse event. WIV04 and HB02 groups represent the vaccine groups which were developed based on two SARS-CoV-2 strains, WIV04 and HB02 strains.

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eTable 8. The Number of Serious Adverse Events Considered as Possible Related to Vaccination in the Safety Set

SARs	WIV04 (n = 13 464)	HB02 (n = 13 471)	Alum-only (n = 13 453)
Total SAR	0	2	0
Certain infectious and parasitic SAR	0	1	0
Infection in the central nervous system	0	1	0
SAR in nervous system	0	1	0
Multiple sclerosis	0	0	0
Acute disseminated encephalomyelitis	0	1	0
Clinically isolated syndrome	0	1	0
Pathological changes in nervous system	0	1	0
Injury, poisoning and certain other consequences of external causes	0	1	0
SAR after immunization	0	1	0

Abbreviation: alum, aluminum hydroxide; SAR, serious adverse reaction. WIV04 and HB02 groups represent the vaccine groups which were developed based on two SARS-CoV-2 strains, WIV04 and HB02 strains.

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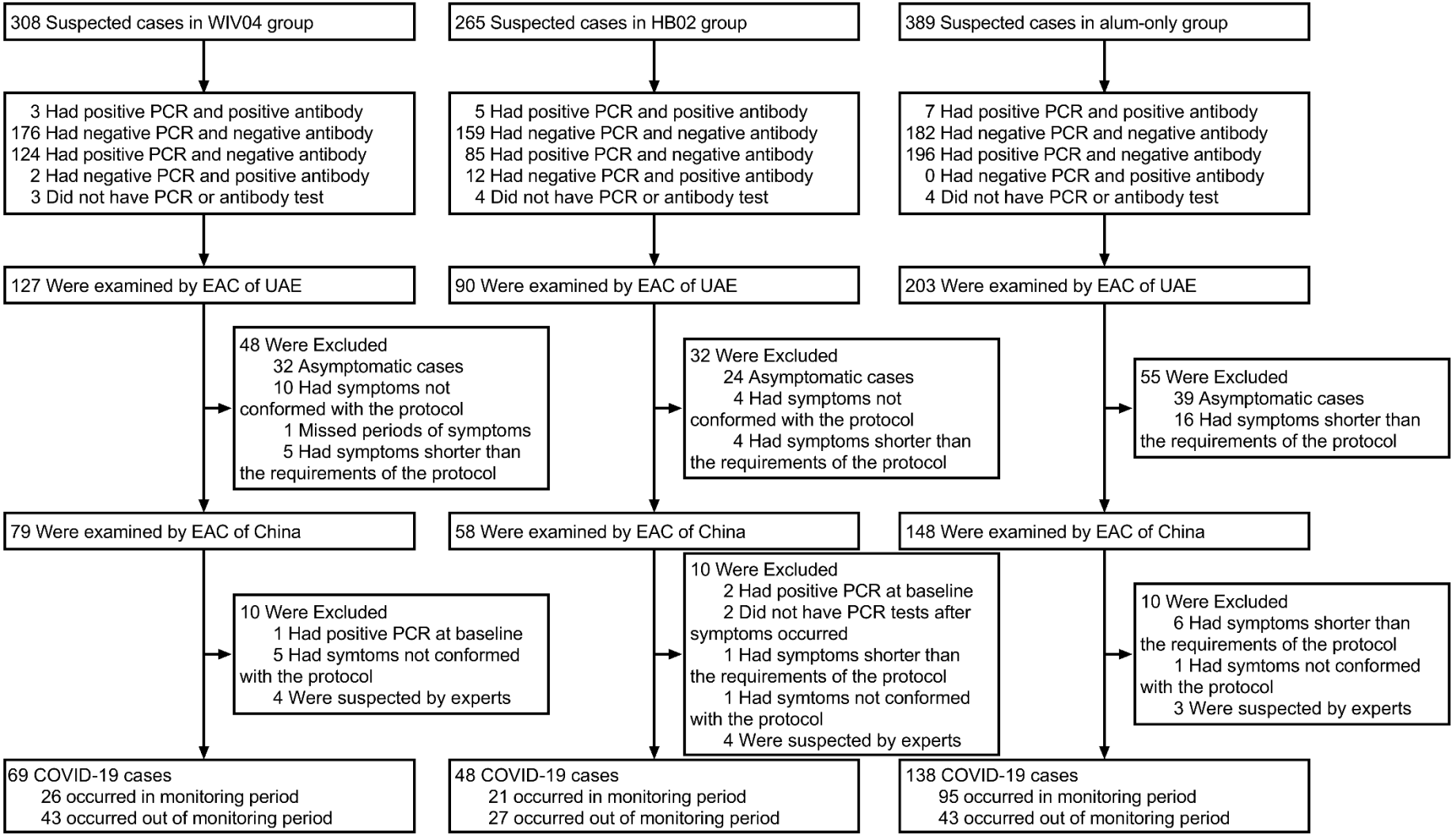
eFigure 1. Handling of the Suspected Cases



Abbreviation: alum, aluminum hydroxide; COVID-19, coronavirus disease 2019; EAC, Endpoint Adjudication Committee; PCR, polymerase chain reaction; UAE, United Arab Emirates. WIV04 and HB02 groups represent the vaccine groups which were developed based on two SARS-CoV-2 strains, WIV04 and HB02 strains.

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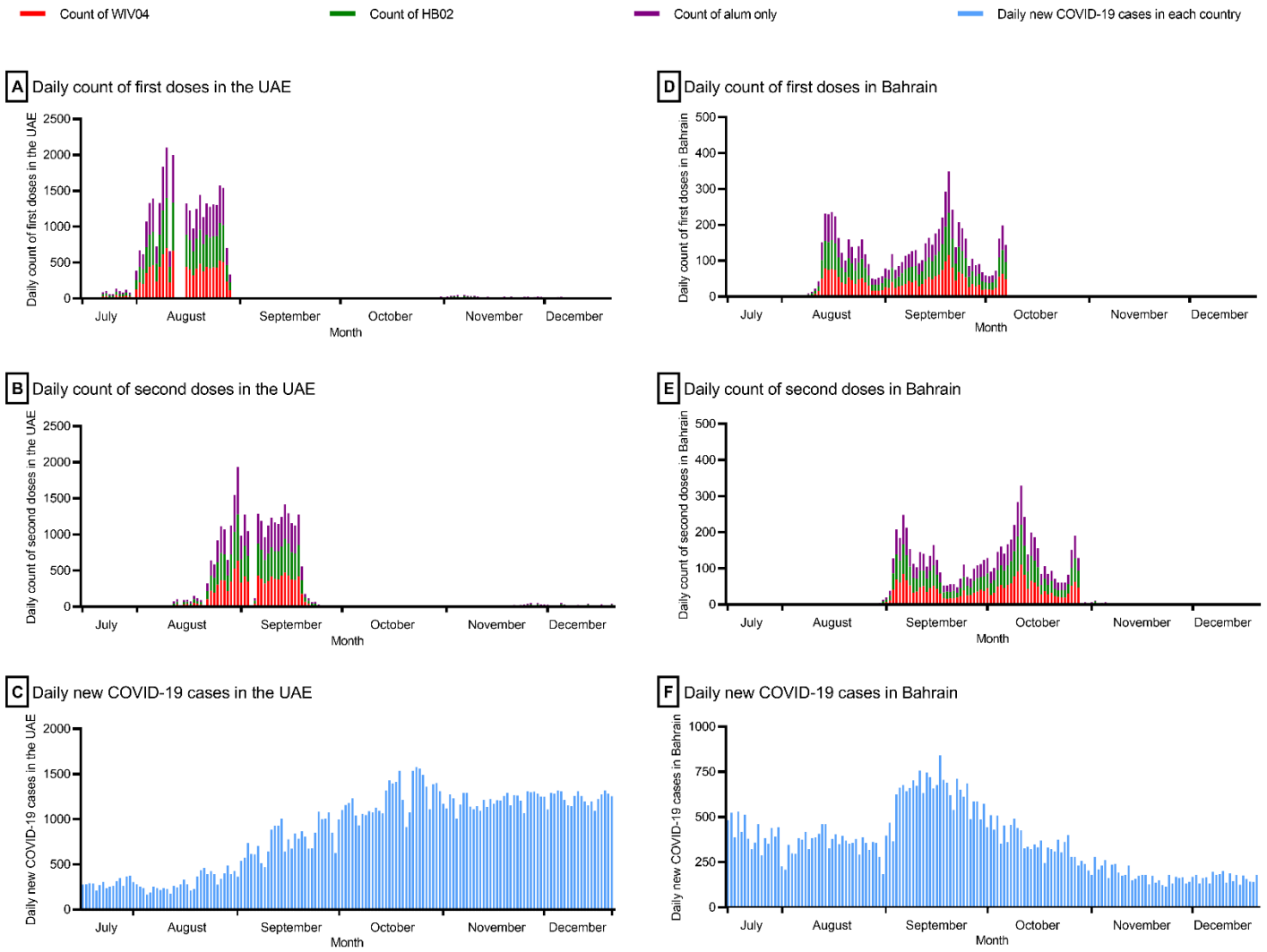
eFigure 2. Daily Count of Administered Vaccines and Number of Incident COVID-19 Cases in the United Arab Emirates and Bahrain Between July 16, 2020 and December 20, 2020.



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(A) Daily count of first dose in the United Arab Emirates; (B) Daily count of second dose in the United Arab Emirates; (C) Number of incident COVID-19 cases in the United Arab Emirates; (D) Daily count of first dose in Bahrain; (E) Daily count of second dose in Bahrain; (F) Number of incident COVID-19 cases in Bahrain. The numbers of incident COVID-19 cases between July 16, 2020 and December 20, 2020 in the United Arab Emirates and Bahrain were obtained from World Health Organization website (https://covid19.who.int/).

Abbreviation: alum, aluminum hydroxide; COVID-19, coronavirus disease 2019; UAE, United Arab Emirates. WIV04 and HB02 groups represent the vaccine groups which were developed based on two SARS-CoV-2 strains, WIV04 and HB02 strains.

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