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Supplemental information

A systems immunology study comparing innate and adaptive immune responses in adults to COVID-19 mRNA and adenovirus vectored vaccines

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Supplementary information

Supplementary Figures:

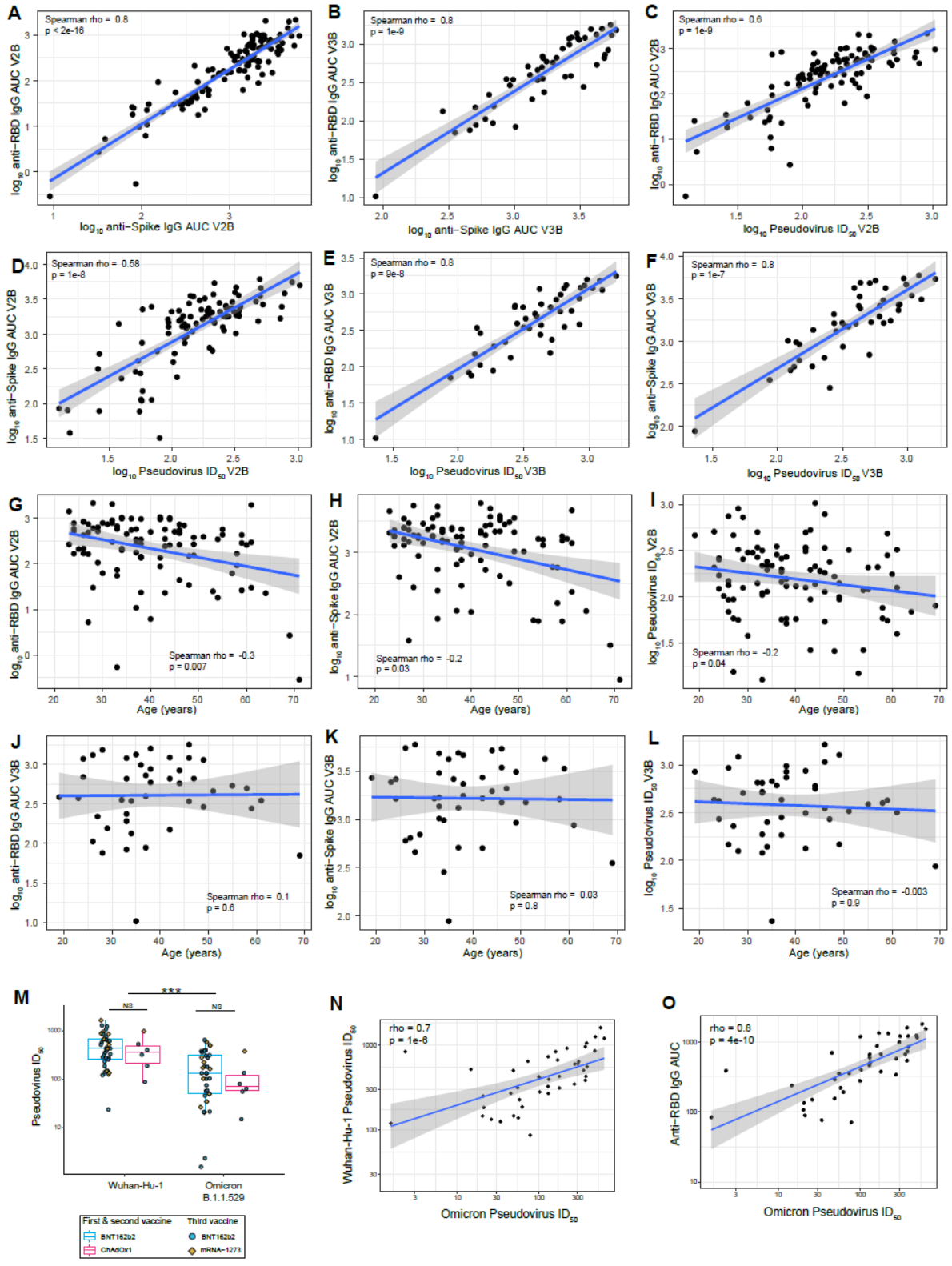


Figure S1: Correlation analyses of Spike-specific humoral immune responses, Related to Figure 1. (A-F) Correlations between anti-RBD, anti-Spike and pseudovirus neutralizing antibody titers at V2B and V3B. Correlations between anti-RBD, anti-Spike and Wuhan-Hu-1 pseudovirus neutralizing antibody titers at (G-I) V2B, and V3B (J-L), with participant age. (M) Comparison between Wuhan-Hu-1 & Omicron pseudovirus neutralizing antibody titers (ID_{50}) at V3B. Correlations between Omicron pseudovirus neutralizing antibody titers at V3B and Wuhan-Hu-1 pseudovirus neutralizing antibody titres (N) and anti-RBD IgG (O) also at V3B. Spearman correlations shown in A-L. Statistical significance assessed in M with a Wilcox rank sum test. *P < 0.05, ***P < 0.001.

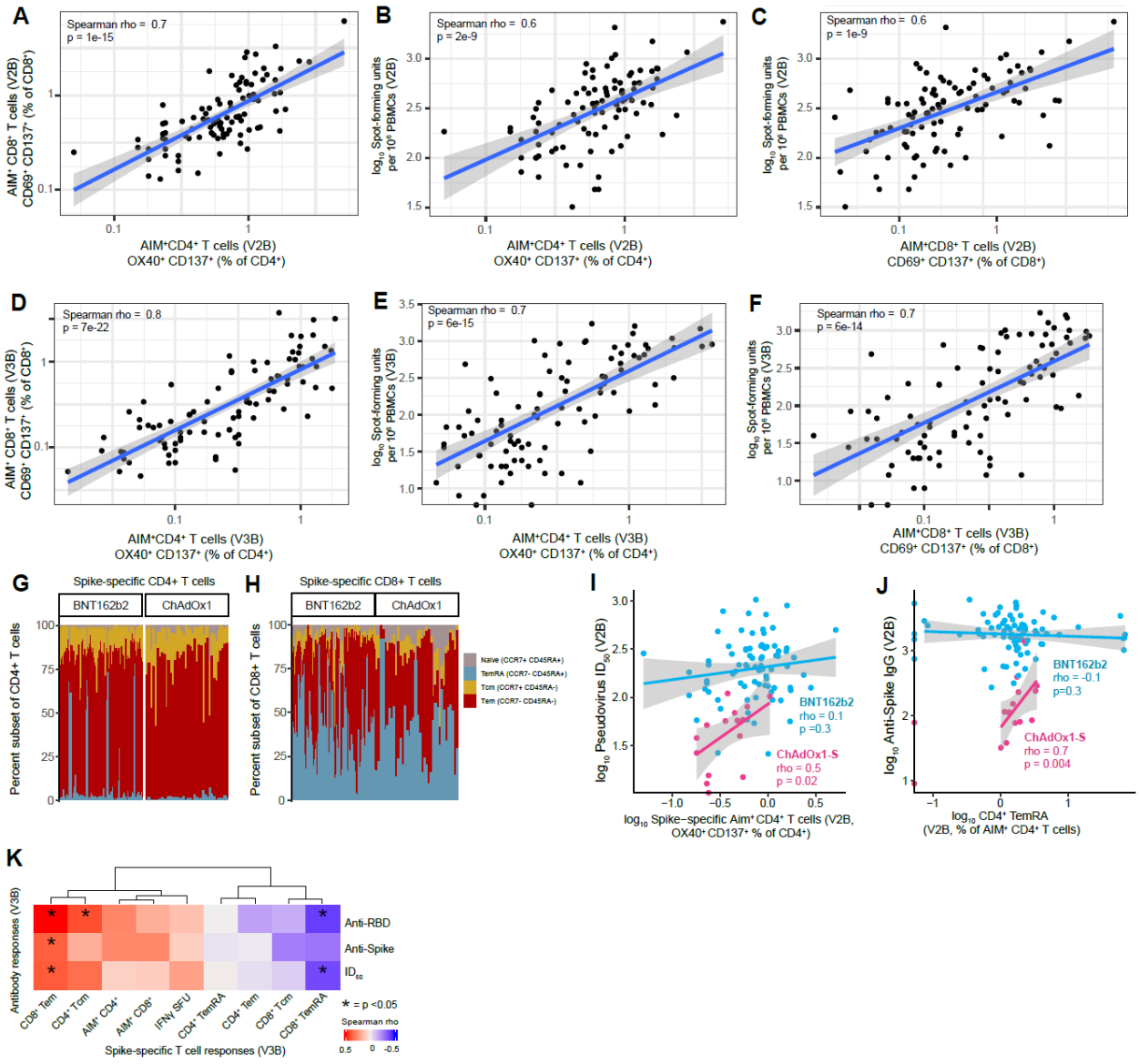


Figure S2: Assessment of Spike-specific T cell responses, Related to Figure 1. (A-F) Correlations between Spike-specific T-cell responses (the number of Spike-specific IFNγ SFU, the proportion of Spike-specific AIM$^+$CD4$^+$ T cells, the proportion of Spike-specific AIM$^+$CD8$^+$ T cells) at V2B and V3B. Bar plots showing the composition of the AIM$^+$ (G) CD4$^+$ and (H) CD8$^+$ T cell compartments. (I) Correlation (Spearman) between Wuhan-Hu-1 ID_{50} and the proportion of Spike-specific AIM$^+$CD4$^+$ T cells at V2B, in participants vaccinated with BNT162b2 or ChAdOx1-S. (J) Correlation (Spearman) between anti-Spike IgG titers and the proportion of Spike-specific CD4$^+$ TemRA cells (CD45RA$^+$CCR7$^-$) at V2B. (K) Heatmap of Spearman correlations between Spike-specific T cell responses and antibody responses at V3B (combined data for all vaccines) Spearman correlations shown in A-F.

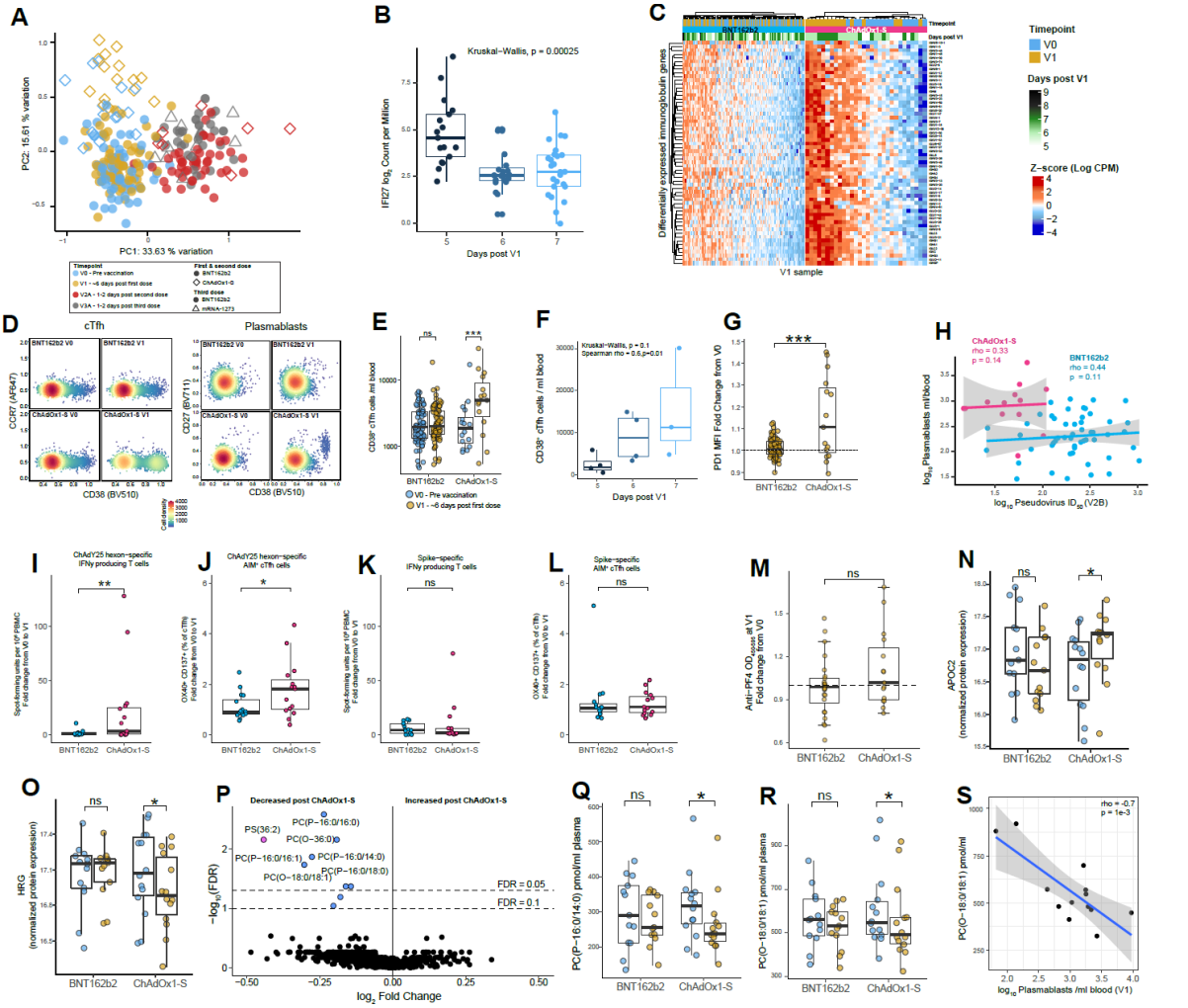


Figure S3: Characterisation of memory-like immune response to primary ChAdOx1-S vaccination, Related to Figure 2. (A) MDS analysis of whole-blood gene expression profiles (RNAseq) in participants pre-vaccination (V0), ~6 days after a 1st dose of BNT162b2 (n=66) or ChAdOx1-S (n=15), ~1-2 days after a 2nd dose (V2A) of BNT162b2 (n=46) or ChAdOx1-S (n=8), and ~1-2 days after a 3rd dose (V3A) of BNT162b2 (n=32) Or mRNA-1273 (n=10). (B) Normalized gene expression of *IFI27* in blood of BNT162b2 vaccinated participants plotted by day of sample collection post the 1st dose. (C) Heatmap showing the expression of immunoglobulin genes identified as differentially expressed (DE) between V0 and V1. Data were adjusted for gender and batch effects prior to MDS analysis and visualization of the heatmap. (D) Representative dot plot of CCR7 and CD38 expression on cTfh ($CD3^+CD4^+CXCR5^+PD1^+$) and plasmablasts ($CD19^{+/dim}CD20^{-/dim}CD38^{++}CD27^{++}$) at V0 and V1 after 1st dose of BNT162b2 or ChAdOx1-S. (E) The number of $CD38^+$ cTfh cells at V1 in participants vaccinated with ChAdOx1-S (n=16) or BNT162b2 (n=77). (F) $CD38^+$ cTfh cells plotted by day of sample collection for ChAdOx1-S participants. (G) Fold-change in the mean fluorescence intensity (MFI) of PD-1 expression on cTfh cells at V1 compared to V0. (H) Correlation (Spearman) between the number of plasmablasts at V1 and Wuhan-Hu-1 ID_{50} at V2B. (I) Fold-change in ChAdY25 hexon-specific IFNɣ spot-forming units from V0 to V1. (J) Fold-change in ChAdY25 hexon-specific AIM+ cTfh cells from V0 to V1. (K) Fold-change in Spike-specific IFNɣ spot-forming units from V0 to V1. (L) Fold-change in Spike-specific AIM+ cTfh cells from V0 to V1. Normalized protein abundance in plasma of (M) APOC2 and (N) HRG. vsn = Variance stabilizing normalization. See Table S4 for complete list of differentially abundant proteins. (O) Fold-change in anti-PF4 optical density (OD) at V1 compared to V0. (P) Volcano plot of differentially abundant lipid species at V1 compared to V0 in participants vaccinated with ChAdOx1-S (Q-R) Selected lipid species identified as differentially abundant at V1 in participants vaccinated with ChAdOx1-S. See Table S4 for complete list. (S) Correlation between plasmablasts at V1 and the level of phosphocholine (O-18:0/18:1) in plasma. See Table S4 for all significant correlations. Statistical significant assessed in G and I-M with a Wilcox rank sum test, in N-R with a generalized linear model. *P < 0.05, ***P < 0.001. Related to Figure 2.

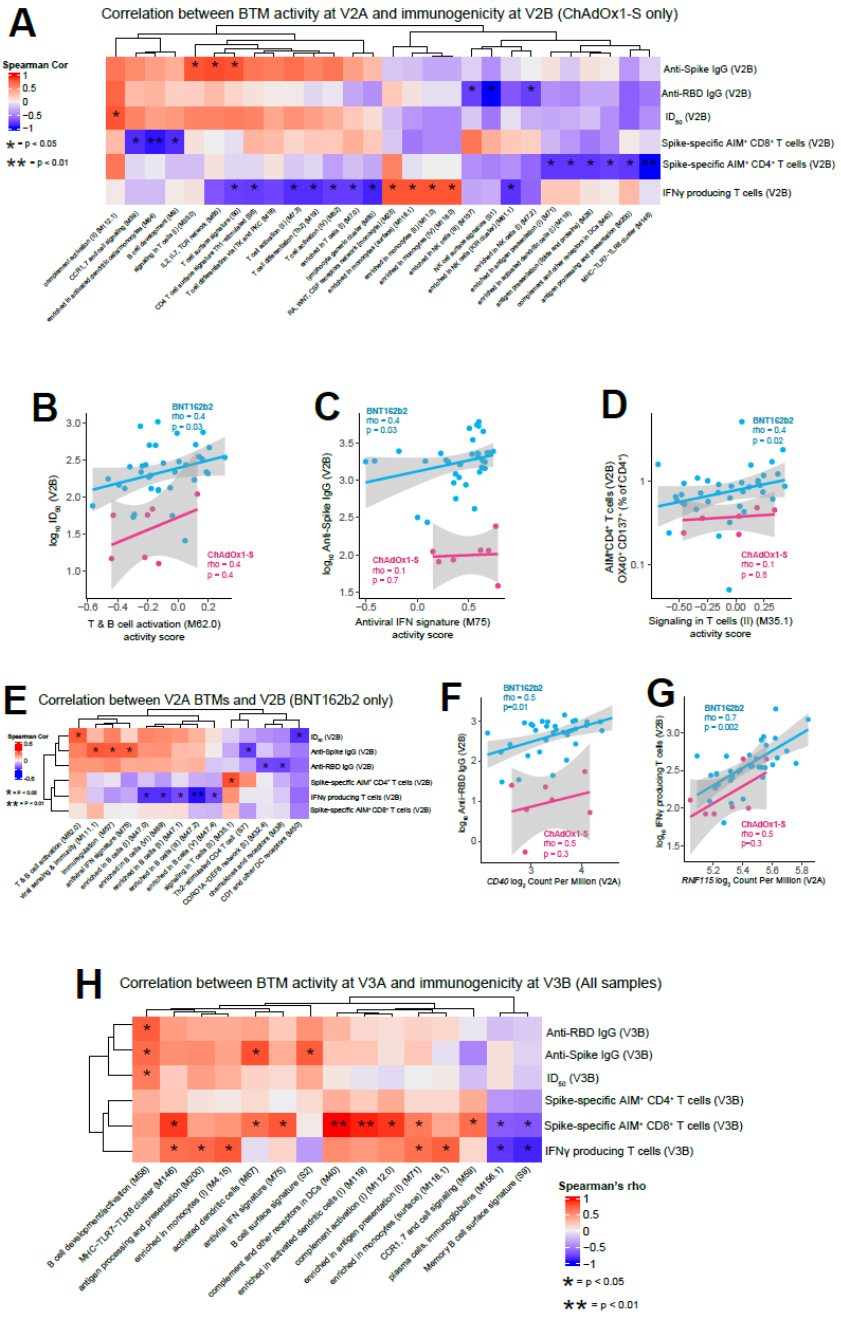


Figure S4: Correlations between blood transcriptomics at V2A and V3A and subsequent spike-specific T and B cell responses at V2B and V3B, Related to Figure 3. (A) Heatmap of Spearman correlations between BTM activity at V2A and antigen-specific antibody and T cell responses at V2B for participants who received ChAdOx1-S. Only BTMs with at least one statistically significant correlation ($p < 0.05$) are shown. Correlation between the activity of (B) T and B cell activation BTM (M62.0) with Wuhan-Hu-1 ID50 at V2B, (C) antiviral IFN signature BTM (M75) and anti-Spike IgG at V2B and (D) signaling in T cells BTM (M35.1) with Spike-specific AIM+ CD4+ T cells at V2B. (E) Heatmap of Spearman correlations between BTM activity at V2A and antigen-specific antibody and T cell responses at V2B for participants who received BNT162b2. Correlation (Spearman) between gene expression of (F) CD40 at V2A and anti-RBD IgG titers at V2B and (G) RNF115 at V2A and Spike-specific IFNγ SFU at V2B. (H) Heatmap of correlations between BTM activity at V3A and antigen-specific antibody and T cell responses at V3B (All participants). Only BTMs with at least one statistically significant correlation ($p < 0.05$) are shown. *P < 0.05, **P < 0.01.

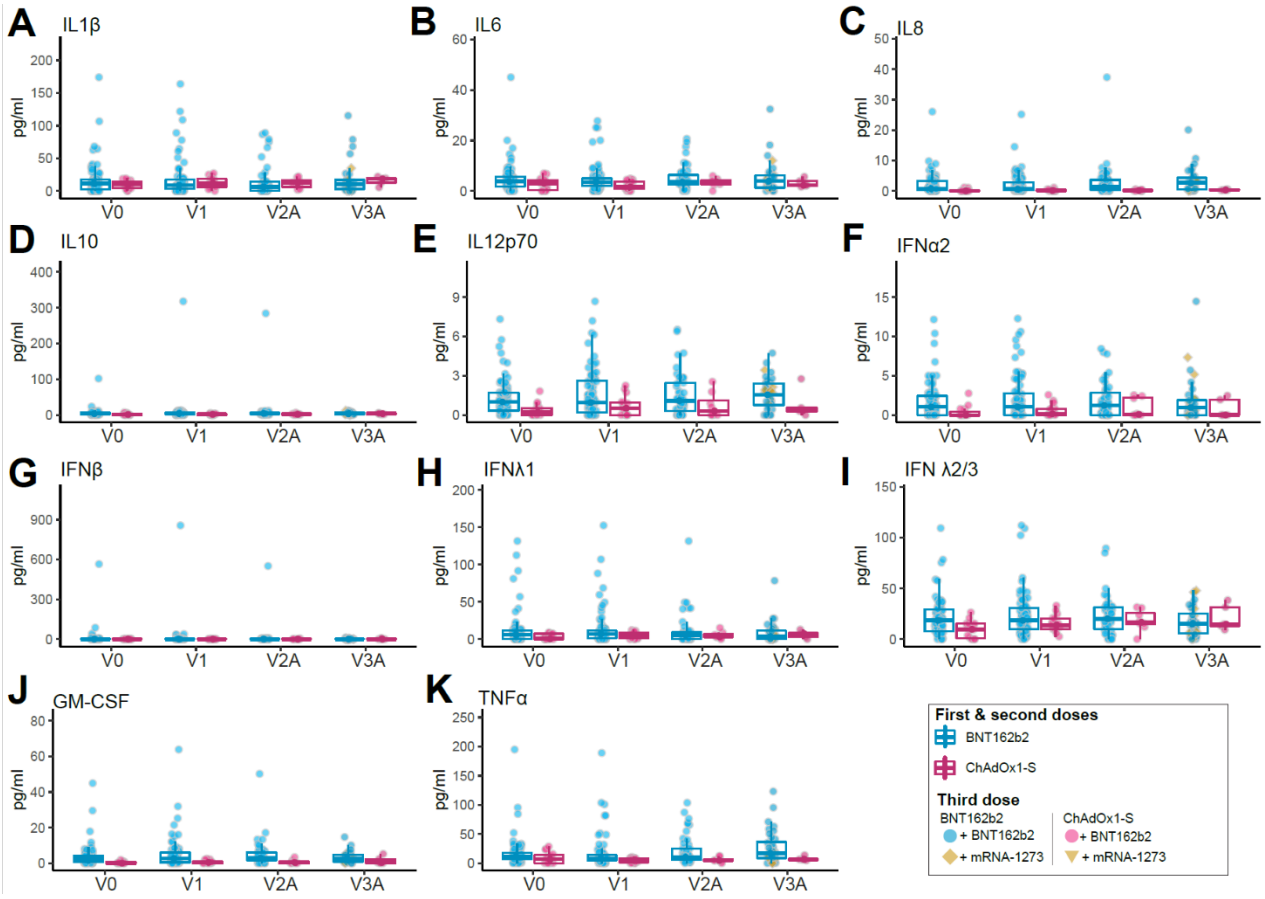


Figure S5: Assessment of serum cytokine levels at baseline and in the first week following 1st, 2nd, or 3rd vaccination, Related to Figure 3. Cytokine concentrations in plasma pre-vaccination (V0) and at V1, V2A and V3A post-vaccination with BNT162b2 or ChAdOx1-S. Data are represented as Tukey style boxplots. Statistical significance in A-K was assessed using a generalized linear model. No statistically significant ($p < 0.05$) differences were detected for these cytokines.

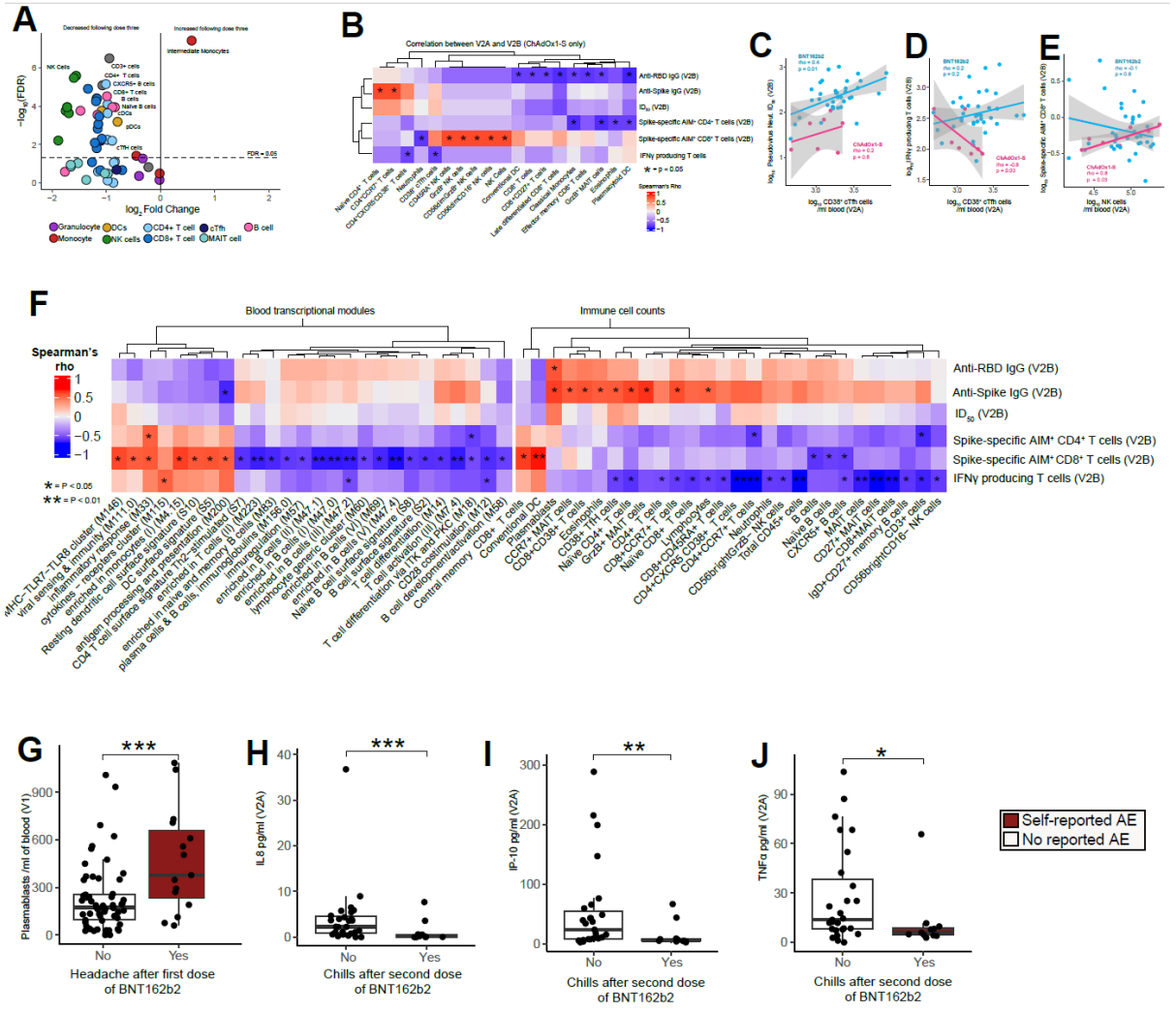


Figure S6: Longitudinal multi-omics assessment of vaccine immunogenicity and reactogenicity, Related to Figure 5 and 6. (A) Volcano plot of immune cell counts at V3A relative to V0. (B) Heatmap of correlations between immune cell populations at V2A and antigen-specific antibody and T cell responses at V2B following ChAdOx1-S. Correlation between the number of CD38+ cTfh cells at V2A with (C) Wuhan-Hu-1 ID50 and (D) Spike-specific IFNγ SFU, at V2B. (E) Correlation between NK cells at V2A with Spike-specific AIM+CD8+ T cells at V2B. (F) Heatmap showing Spearman correlations between BTM activity score, counts of immune cells or cytokine concentration, at V0 and antigen-specific antibody or T cell responses at V2B following 2 doses of ChAdOx1-S. (G) Plasmablasts per mL of blood in participants who reported headache after the 1st dose of BNT162b2. Concentration of (H) IL8, (I) IP-10, and (J) TNFα at V2A in participants who reported chills after the 2nd dose of BNT162b2. *P < 0.05, **P < 0.01.

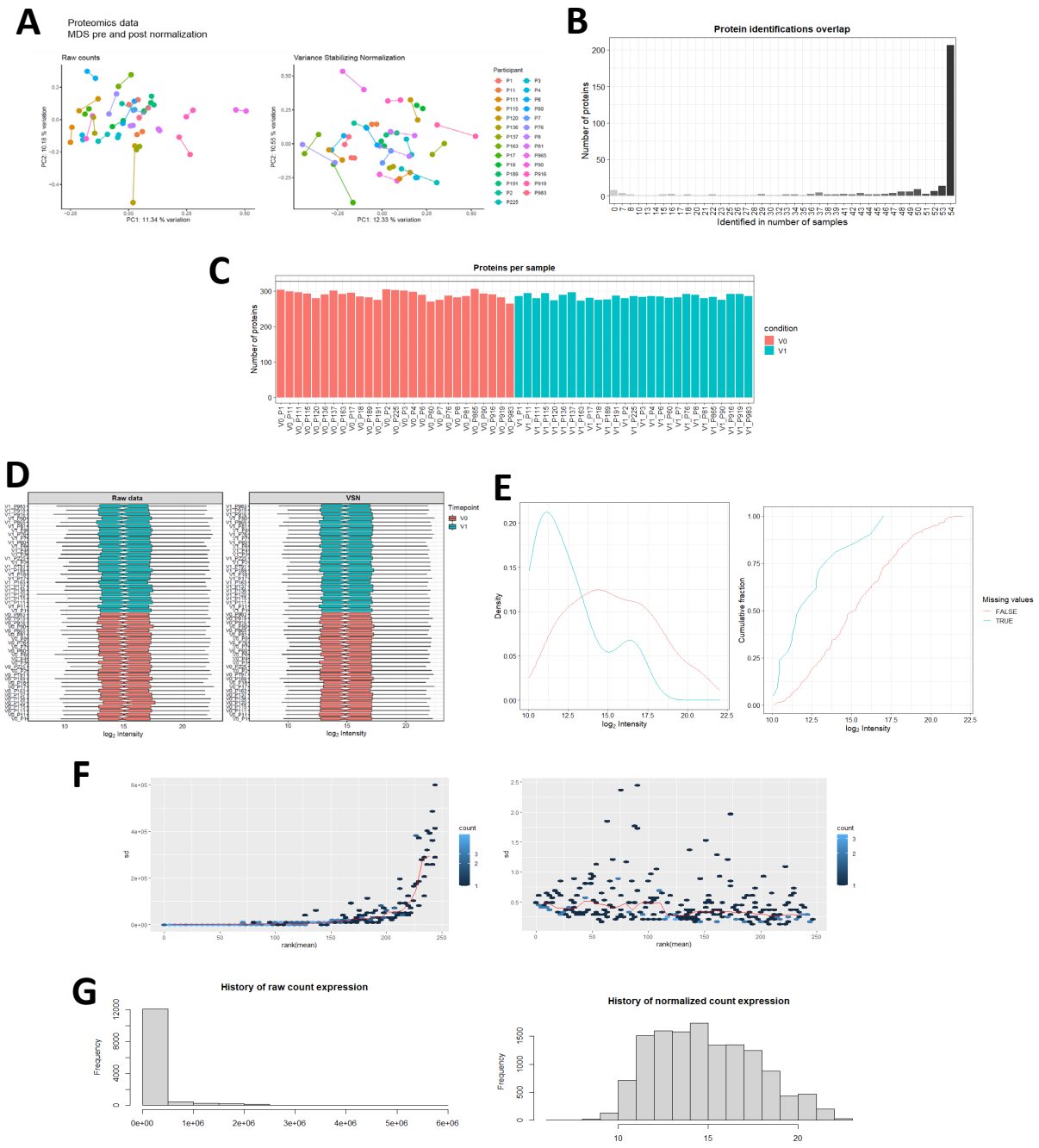


Figure S7: Impact of normalization on plasma proteomics data, Related to STAR Methods: QUANTIFICATION AND STATISTICAL ANALYSIS, proteomics. (A) MDS analysis of plasma proteomics profiles in participants pre-vaccination (V0) and post-vaccination (V1) demonstrating the impact of the variance stabilising normalization (VSN) employed. Lines connect samples from the same participant. (B) Histogram showing number of proteins detected across samples. (C) Barplot showing the number of proteins detected in each sample. (D) Boxplots showing the range of protein intensities per sample pre- and post- VSN normalization. (E) Line plot comparing the expression distribution of proteins with/without missing values. (F) Scatter plot of the mean and standard deviation (SD) of each protein pre- and post- VSN normalization. (G) Histogram showing distribution of protein expression pre- and post- VSN normalization.

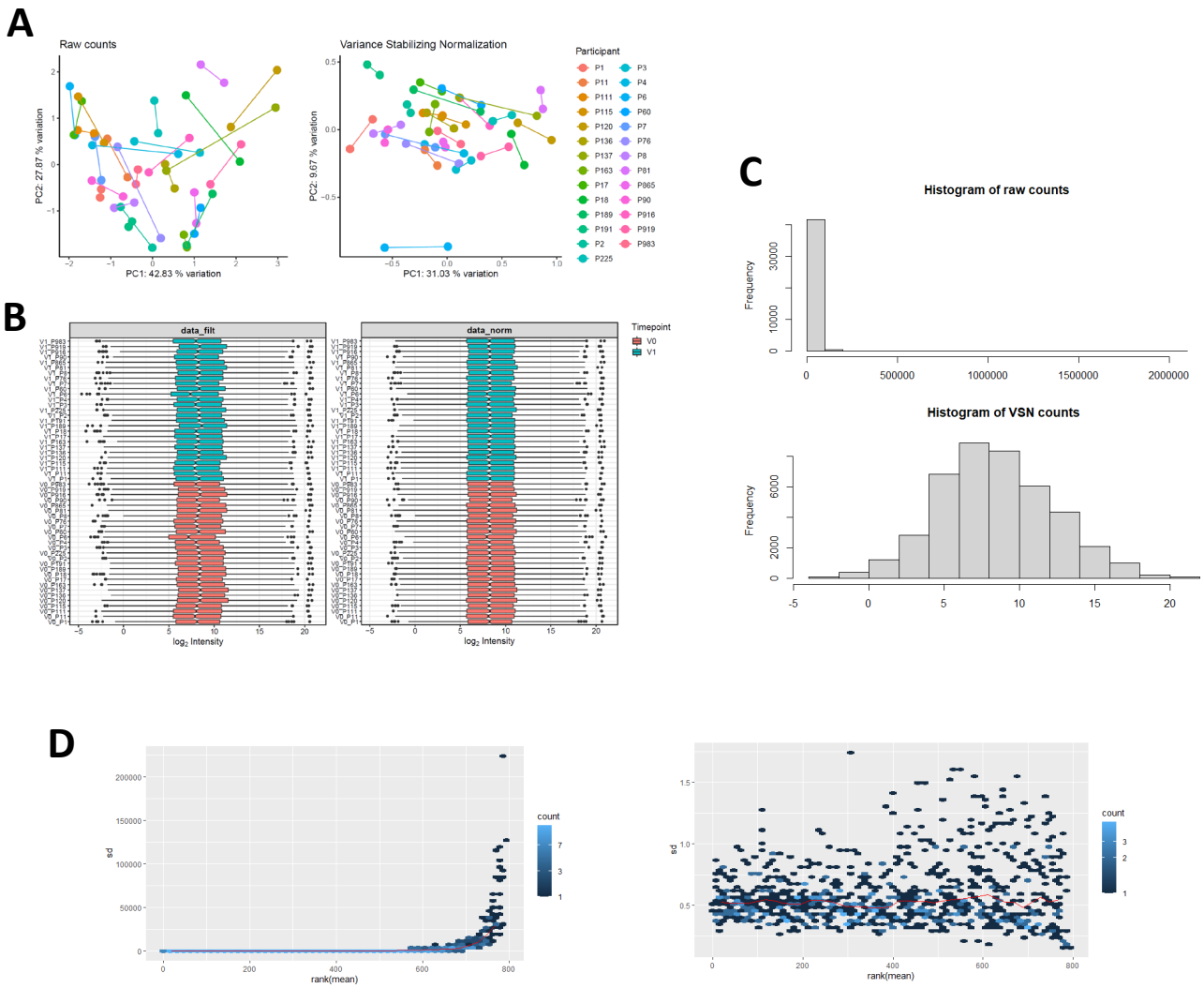
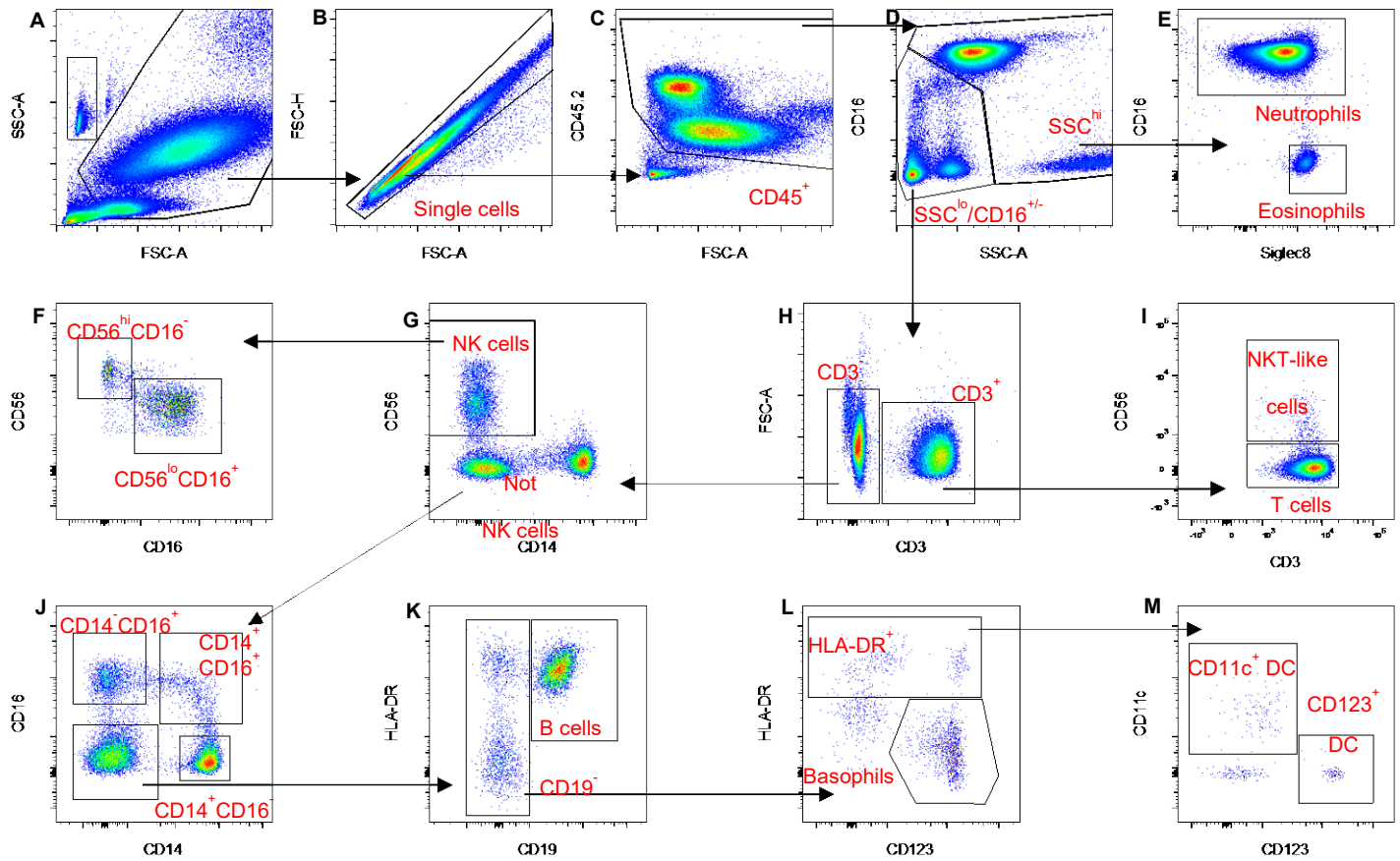


Figure S8: Impact of normalization of plasma lipidomics, Related to STAR Methods: QUANTIFICATION AND STATISTICAL ANALYSIS, lipidomics. (A) MDS analysis of plasma lipidomics profiles in participants pre-vaccination (V0) and post-vaccination (V1) demonstrating the impact of the variance stabilising normalization (VSN) employed. Lines connect samples from the same participant. (B) Boxplots showing the range of lipid intensities per sample pre- and post- VSN normalization. (C) Histogram showing distribution of lipid expression pre- and post- VSN normalization. (D) Scatter plot of the mean and standard deviation (SD) of each lipid pre- and post- VSN normalization.

Supplementary Methods:



Supplemental Methods S1: Gating strategy for the identification of leukocyte populations in participant PBMC samples by flow cytometry, Related to Figure 2, STAR Methods: METHOD DETAILS, Flow cytometry data acquisition & analysis.

A) Leukocytes identified based on FSC and SSC. Count beads also identified by high SSC and low SSC, and counted based on uniform fluorescence into Blue 530/30 and Yellow Green 780/60 channels.

B) Doublets eliminated based on FSC and FSH.

C) Identification of $CD45^+$ leukocytes within single cell population.

D) Separation of $CD45^+$ cells into $CD16^{+/-}$, high SSC (granulocyte) and $CD16^{+/-}$ low SSC (lymphocyte and monocyte) populations.

E) Identification of neutrophils ($CD16^+$) and eosinophils ($Siglec8^+CD16^-$) within the $CD16^{+/-}$, high SSC population.

F) Identification of $CD56^{high}CD16^-$ and $CD56^{low}CD16^+$ natural killer (NK; $CD3^-CD56^+$) cell populations.

G) Identification of NK cells ($CD56^+$) within the $CD3^-$, $CD16^{+/-}$ low SSC population.

H) Identification of T-cells ($CD3^+$) within $CD16^{+/-}$ low SSC population.

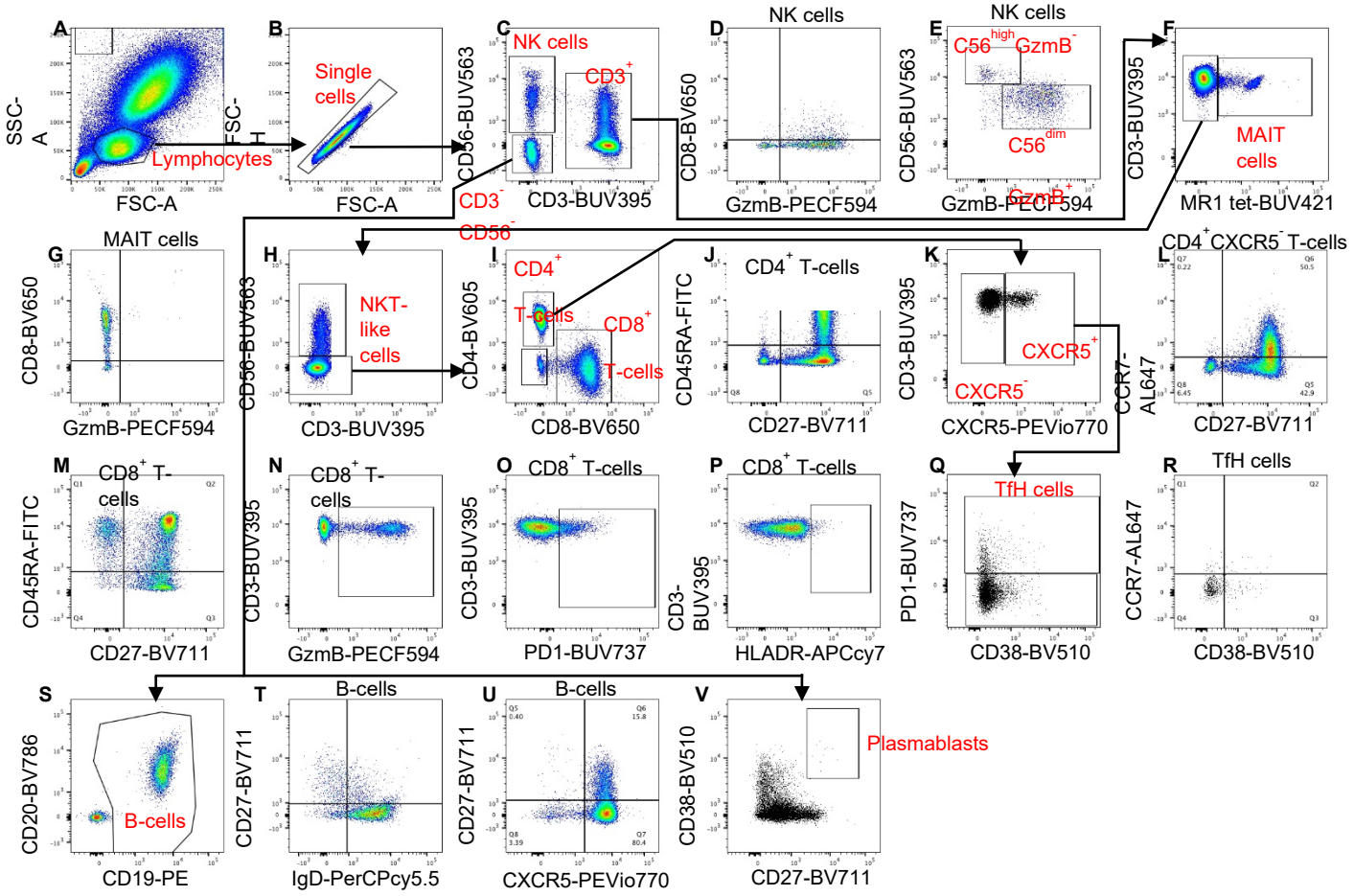
I) Identification of natural killer T (NKT) like cells ($CD3^+CD56^+$) and conventional T cells ($CD3^+CD56^-$) within the $CD3^+$, $CD16^{+/-}$ low SSC population.

J) Identification of classical monocytes ($CD14^+CD16^-$), intermediate monocytes ($CD14^+CD16^+$), and non-classical monocytes ($CD14^-CD16^+$) cells within the $CD3^-$, $CD56^-$, low SSC population.

K) Identification of B-cells ($CD19^+HLA\text{-}DR^+$) cells within $CD14^-$,$CD16^-$, $CD3^-$, $CD56^-$, low SSC population.

L) Identification of dendritic cells (DC; $HLA\text{-}DR^+$, $CD123^{+/-}$) and basophils ($CD123^+HLA\text{-}DR^-$) within the $CD19^-$, $CD14^-$,$CD16^-$, $CD3^-$, $CD56^-$, low SSC population.

M) Identification of conventional DCs ($CD11c^+$) and plasmacytoid DCs ($CD123^+$) within the dendritic cell population.



Supplemental Methods S2: Gating strategy for the identification of lymphocyte populations in participant PBMC samples by flow cytometry, Related to Figure 2, STAR Methods: METHOD DETAILS, Flow cytometry data acquisition & analysis.

A) Lymphocytes identified based on FSC and SSC. Count beads also identified by high SSC and low SSC, and counted based on uniform fluorescence into Blue 530/30 and Yellow Green 780/60 channels.

B) Doublets eliminated based on FSC and FSH.

C) Identification of natural killer (NK) cells ($CD56^{+}CD3^{-}$), T cells ($CD3^{+}CD56^{+/-}$) and $CD3^{-}CD56^{-}$ lymphocytes.

D) Expression of granzyme β and CD8 on NK cells.

E) Identification of $CD56^{high}GRNZ\beta^{-}$ and $CD56^{low}GRNZ\beta^{+}$ NK cell populations.

F) Identification of mucosal-associated invariant T-cells (MAIT) cells ($CD3^{+}$MR1-tetramer^{+}) from $CD3^{+}CD56^{+/-}$ population.

G) Expression of granzyme β and CD8 on MAIT cells.

H) Identification of natural killer (NKT)-like cells from $CD3^{+}CD56^{+/-}$MR1-tet^{-} population.

I) Identification of conventional $CD4^{+}$ and $CD8^{+}$ T-cells from $CD3^{+}$MR1-tet$^{-}CD56^{-}$ population.

J) Identification of naïve ($CD45RA^{+}CD27^{+}$), central memory ($CD45RA^{-}CD27^{+}$), effector memory ($CD45RA^{+}CD27^{-}$) and late differentiated ($CD45RA^{-}CD27^{-}$) cells within the $CD4^{+}$ Conventional T-cell population.

K) Identification of $CXCR5^{+}$ and $CXCR5^{-}$ cells within the $CD4^{+}$ Conventional T-cell population.

L) Expression of CCR7 and CD27 within the $CXCR5^{-}CD4^{+}$ Conventional T-cell population.

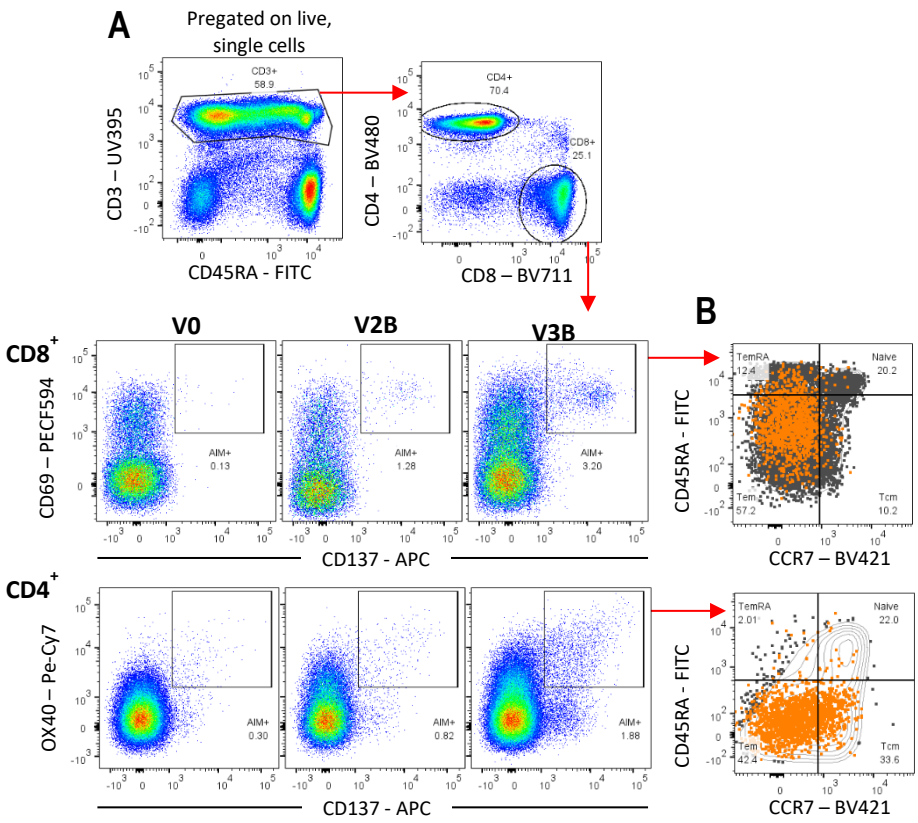
M) Identification of naïve ($CD45RA^{+}CD27^{+}$), central memory ($CD45RA^{-}CD27^{+}$), effector memory ($CD45RA^{+}CD27^{-}$) and late differentiated ($CD45RA^{-}CD27^{-}$) cells within the $CD8^{+}$ Conventional T-cell population.

N) Expression of granzyme β within the $CD8^{+}$ Conventional T-cell population.

O) Expression of PD1 within the $CD8^{+}$ Conventional T-cell population.

P) Expression of HLA-DR within the $CD8^{+}$ Conventional T-cell population.

Q) Identification of circulating T follicular helper (cTfH) cells by PD1 expression on $CXCR5^{+}CD4^{+}$ Conventional T-cells.
R) Identification of $CCR7^{-}CD38^{+}$ and $CCR7^{-}CD38^{-}$ populations within cTfH cells.
S) Identification of B-cells ($CD19^{+}CD20^{+/-}$) within $CD3^{-}CD56^{-}$ lymphocyte population.
T) Identification of naïve ($CD27^{-}IgD^{+}$), IgD^{+} memory ($CD27^{+}IgD^{+}$) and IgD^{-} memory ($CD27^{+}IgD^{-}$) B-cells.
U) Expression of CD27 and CXCR5 within the B-cell gate.
V) Identification of plasmablasts ($CD19^{+/-}$, $CD20^{-}$, $CD27^{++}CD38^{++}$) within the $CD3^{-}CD56^{-}$ population.



Supplemental Methods S3: Gating strategy for the identification of activation-induced marker-positive CD4+ and CD8+ T cells after *in vitro* stimulation with spike peptide pools, Related to Figure 1, STAR Methods: METHOD DETAILS, AIM-assay. A) Representative strategy to define CD3+CD4+ and CD3+CD8+ cells and expression of the activation-induced markers CD69 and CD137 on CD8+ T cells and OX40 and CD137 on CD4 T cells at V0, V2B and V3B. B) AIM+ memory subsets (orange) were defined based on the expression of CCR7 and CD45RA: central memory (TCM, CCR7+CD45RA−), effector memory (TEM, CCR7-CD45RA−), and terminally differentiated effector cells (TEMRA, CCR7-CD45RA+) overlaid on total CD4 and CD8 T cell subsets.

Supplementary Data

Supplementary Data S1: COVIRS participant survey, Related to Figure 1 and 6.

COVIRS Survey 1 (1 week post 1st vaccination date)

Thank you for providing a blood sample in the COVIRS study. The main purpose of this survey is to confirm the date you received DOSE 1 of the COVID-19-specific vaccine and to confirm which COVID-19-specific vaccine you had. In addition, we will ask about any reactions you may have had to the vaccine. The second purpose is to collect information about episodes of COVID-19 you may have had since you had your COVID-19-specific vaccine.

Date survey 1 completed: _____

Details about DOSE 1 of the COVID-19-specific vaccination

You have previously confirmed having DOSE 1 of the following COVID-19 specific vaccination:

Vaccine: [bc_covac_which_01] on [bc_covac_date_01].

Are these details correct?

- Yes
- No, I have not received a COVID-19 specific vaccination as yet
- No, the date or type of vaccination is incorrect

Do you have an expected date for your second COVID-19 specific vaccine?
_____ (Leave blank if you do not know)

Are you booked in to receive a COVID-19 specific vaccination?

- Yes
- No

Please tell us your booking date: _____

Which COVID-19-specific vaccine are you booked to receive?

- AstraZeneca/Oxford (ChAdOx1, Covishield)
- Pfizer/BioNTech (BNT162b2, Comirnaty)
- Moderna (mRNA-1273)
- Sinovac (CoronaVac)
- Novavax (NVX-CoV2373)
- Johnson and Johnson (Ad26.COV2.S)
- Gam-Covid-Vac (Sputnik V)
- Other

Adverse events after DOSE 1 of the COVID-19-specific vaccine

Did you experience any adverse event up to seven days after receiving DOSE 1 of the COVID-19-specific vaccine?

- None
- Pain at the vaccination site
- Redness at the vaccination site
- Swelling at the vaccination site

- Tenderness at the vaccination site
- Itchiness at the vaccination site
- Lymph node enlargement in region draining the vaccination site
- Fever
- Chills
- Fatigue
- Headache
- Nausea and/or vomiting
- Diarrhoea
- Muscle pain
- Joint pain

On what day after vaccination did the pain start? At day number:
_____ (NB: Day number 1 is the day you received your vaccination)

For how many days did the pain last? _____ (Days)

On what day after vaccination did the redness start? At day number:
_____ (NB: Day number 1 is the day you received your vaccination)

For how many days did the redness last? _____ (Days)

What was the largest diameter of the redness, at its worst (in cm)?
_____ (Please provide answer in cm)

On what day after vaccination did the swelling start? At day number:
_____ (NB: Day number 1 is the day you received your vaccination)

For how many days did the swelling last? _____ (Days)

What was the largest diameter of the swelling at its worst (in cm)?
_____ (Please provide answer in cm)

On what day after vaccination did the tenderness start? At day number:
_____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the tenderness last? _____ (Days)

Regarding the level of tenderness only: How would you describe the level of discomfort at its worst?

- Mild discomfort to touch
- Discomfort with movement
- Significant discomfort at rest

Did the pain/tenderness and/or swelling at the vaccination site significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities

- It somewhat interfered with my daily activities
- It prevented me from doing my daily activities

Please describe how the pain/tenderness and/or swelling interfered, and for how long:
_____

On what day after vaccination did the itchiness start? At day number:
_____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the itchiness last? _____ (Days)

Where was it itchy?

- Only my vaccination site felt itchy
- The itching extended beyond my vaccination site, but not all over my body
- I was itchy all over my body

Did you have to use medication for the itch?

- I did not need to take any medication
- I had to use antihistamine (e.g. Zyrtec, Claratyne, Telfast) for less than 48 hours
- I had to use antihistamine (e.g. Zyrtec, Claratyne, Telfast) for 48 hours or longer
- Other

If other, please tell us where: _____

On what day after vaccination did the lymph node enlargement start? At day number:
_____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the lymph node enlargement last? _____ (Days)

Where have you noticed or felt a swollen gland?

- Under the armpit
- In the neck
- Other

If other, please tell us where: _____

How big was the swollen gland (in cm) under the armpit? _____ (Please provide answer in cm)

How big was the swollen gland (in cm) in the neck? _____ (Please provide answer in cm)

How big was the swollen gland (in cm) in another location?
_____ (Please provide answer in cm)

On what day after vaccination did the fever start? At day number:
_____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the fever last? _____ (Days)

What was your maximum temperature? _____

On what day after vaccination did the chills start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the chills last? _____ (Days)

On what day after vaccination did the fatigue start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the fatigue last? _____ (Days)

Did the fatigue significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities
- It somewhat interfered with my daily activities
- It prevented me from doing my daily activities

Please describe how the fatigue interfered, and for how long:

_____

On what day after vaccination did the headache start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the headache last? _____ (Days)

Did the headache significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities
- It somewhat interfered with my daily activities
- It prevented me from doing my daily activities

Please describe how the headache interfered, and for how long:

_____

On what day after vaccination did the nausea and/or vomiting start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the nausea and/or vomiting last? _____ (Days)

How many episodes per day did you have of vomiting at its worst?

_____

Did the nausea and/or vomiting significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities
- It somewhat interfered with my daily activities

- It prevented me from doing my daily activities

Please describe how the nausea and/or vomiting interfered, and for how long:
_____

On what day after vaccination did the diarrhoea start? At day number:
_____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the diarrhoea last? _____ (Days)

How many episodes per day did you have of diarrhoea at its worst?
_____

On what day after vaccination did the muscle pain start? At day number:
_____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the muscle pain last? _____ (Days)

On what day after vaccination did the joint pain start? At day number:
_____ (Note: Day number 1 is the day you received your vaccination) For how many days did the joint pain last? _____ (Days)

Did the muscle and/or joint pain significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities
- It somewhat interfered with my daily activities
- It prevented me from doing my daily activities

Please describe how the muscle and/or joint pain interfered, and for how long:
_____

Did you have to use medication or consult a medical doctor?

I did not need to take any medication, nor see a medical doctor

I had to consult a medical doctor or be hospitalised

I had to use pain medication

Please describe when you saw the doctor, and what was discussed:
_____

Which medication did you take? _____

For how many days did you use this medication? _____ (Days)

<u>Allergic reactions after DOSE 1 of the COVID-19-specific vaccine</u>

Did you have an allergic reaction after DOSE 1 of the vaccination? Please select all that apply:

- None

- Urticaria (hives) or cutaneous rash
- Runny or stuffy nose and sneezing
- Vomiting, diarrhea, or abdominal cramps
- Swollen or itchy lips or tongue
- Swollen or itchy throat, hoarse voice, trouble swallowing, tightness in your throat
- Coughing, wheezing, shortness of breath
- Fainting, dizziness, confusion, or weakness
- Other

Other allergic reaction, please describe: _____

How long after vaccination (in minutes) did the allergic reaction start?

_____

What treatment did you receive? Please select all that apply:

- No treatment
- Anti-histamine
- Adrenaline Inhaler
- Prednisolone or other steroids
- Transferred to the Emergency department
- Hospitalisation in normal unit (non-ICU)
- Hospitalisation in Intensive Care Unit (ICU)
- Other

If other, please specify: _____

Please describe what happened: _____

<u>Other vaccinations</u>

Did you receive any other vaccines since the start of COVIRS?

- Yes
- No

If yes, which vaccine(s) did you receive?

- Diphtheria-tetanus vaccine (ADT Booster)
- Diphtheria-tetanus-pertussis vaccine (Boostrix, Adacel, Tripacel)
- Diphtheria-tetanus-pertussis-polio vaccine (Boostrix-IPV, Adacel Polio, Quadracel)
- Polio vaccine (IPOL)
- Hepatitis B vaccine (Engerix-B, H-B-Vax II)
- Hepatitis A vaccine (Havrix, Avaxim, Vaqta)
- Hepatitis A-hepatitis B vaccine (Twinrix)
- Hepatitis A-typhoid vaccine (Vivaxim)
- Typhoid injected vaccine (Typhim Vi)
- Typhoid oral vaccine (Vivotif Oral)
- Influenza vaccine (Afluria, Fluad Quad, Fluarix, FluQuadri, Influvac, Vaxigrip, Vaxigroup)
- Papillomavirus vaccine (Cervarix, Gardasil)
- Meningococcal vaccine (Menveo, Menactra, MenQuadfi, NeisVac, Bexsero, Trumenba)
- Pneumococcal vaccine (Prevenar, Synflorix, Pneumosil, Pneumovax)

- Japanese encephalitis vaccine (Imojev, JEspect)
- Rabies vaccine (Rabipur)
- Yellow fever vaccine (Stamaril)
- Measles-mumps-rubella (Priorix, M-M-R II, ProQuad)
- Measles-mumps-rubella-varicella (Priorix-tetra, ProQuad)
- Varicella vaccine (Varilrix, Varivax)
- Zoster live vaccine (Zostavaq)
- Zoster non-live vaccine (Shingrix)
- Tuberculosis vaccine (BCG)
- Other

If other, please specify: _____

COVIRS Survey 2 (1 week post 2nd vaccination date)

Thank you for providing a blood sample in the COVIRS study. The main purpose of this survey is to confirm the date you received DOSE 2 of the COVID-19-specific vaccine and to confirm which COVID-19-specific vaccine you had. In addition, we will ask about any reactions you may have had to the vaccine. The second purpose is to collect information about episodes of COVID-19 you may have had since you had your COVID-19-specific vaccine.

Date survey 2 completed: _____

Details about DOSE 2 of the COVID-19-specific vaccination

You have previously confirmed having DOSE 2 of the following COVID-19 specific vaccination:

Vaccine: [bc_covac_which_01] on [bc_covac_date_01].

Are these details correct?

- Yes
- No, I have not received a COVID-19 specific vaccination as yet
- No, the date or type of vaccination is incorrect

Adverse events after DOSE 2 of the COVID-19-specific vaccine

Did you experience any adverse event up to seven days after receiving DOSE 1 of the COVID-19-specific vaccine?

- None
- Pain at the vaccination site
- Redness at the vaccination site
- Swelling at the vaccination site
- Tenderness at the vaccination site
- Itchiness at the vaccination site
- Lymph node enlargement in region draining the vaccination site
- Fever
- Chills
- Fatigue
- Headache

- Nausea and/or vomiting
- Diarrhoea
- Muscle pain
- Joint pain

On what day after vaccination did the pain start? At day number:
_____ (NB: Day number 1 is the day you received your vaccination)

For how many days did the pain last? _____ (Days)

On what day after vaccination did the redness start? At day number:
_____ (NB: Day number 1 is the day you received your vaccination)

For how many days did the redness last? _____ (Days)

What was the largest diameter of the redness, at its worst (in cm)?
_____ (Please provide answer in cm)

On what day after vaccination did the swelling start? At day number:
_____ (NB: Day number 1 is the day you received your vaccination)

For how many days did the swelling last? _____ (Days)

What was the largest diameter of the swelling at its worst (in cm)?
_____ (Please provide answer in cm)

On what day after vaccination did the tenderness start? At day number:
_____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the tenderness last? _____ (Days)

Regarding the level of tenderness only: How would you describe the level of discomfort at its worst?

- Mild discomfort to touch
- Discomfort with movement
- Significant discomfort at rest

Did the pain/tenderness and/or swelling at the vaccination site significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities
- It somewhat interfered with my daily activities
- It prevented me from doing my daily activities

Please describe how the pain/tenderness and/or swelling interfered, and for how long:
_____

On what day after vaccination did the itchiness start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the itchiness last? _____ (Days)

Where was it itchy?

- Only my vaccination site felt itchy
- The itching extended beyond my vaccination site, but not all over my body
- I was itchy all over my body

Did you have to use medication for the itch?

- I did not need to take any medication
- I had to use antihistamine (e.g. Zyrtec, Claratyne, Telfast) for less than 48 hours
- I had to use antihistamine (e.g. Zyrtec, Claratyne, Telfast) for 48 hours or longer
- Other

If other, please tell us where: _____

On what day after vaccination did the lymph node enlargement start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the lymph node enlargement last? _____ (Days)

Where have you noticed or felt a swollen gland?

- Under the armpit
- In the neck
- Other

If other, please tell us where: _____

How big was the swollen gland (in cm) under the armpit? _____ (Please provide answer in cm)

How big was the swollen gland (in cm) in the neck? _____ (Please provide answer in cm)

How big was the swollen gland (in cm) in another location? _____ (Please provide answer in cm)

On what day after vaccination did the fever start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the fever last? _____ (Days)

What was your maximum temperature? _____

On what day after vaccination did the chills start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the chills last? _____ (Days)

On what day after vaccination did the fatigue start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the fatigue last? _____ (Days)

Did the fatigue significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities
- It somewhat interfered with my daily activities
- It prevented me from doing my daily activities

Please describe how the fatigue interfered, and for how long:

_____

On what day after vaccination did the headache start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the headache last? _____ (Days)

Did the headache significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities
- It somewhat interfered with my daily activities
- It prevented me from doing my daily activities

Please describe how the headache interfered, and for how long:

_____

On what day after vaccination did the nausea and/or vomiting start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the nausea and/or vomiting last? _____ (Days)

How many episodes per day did you have of vomiting at its worst?

_____

Did the nausea and/or vomiting significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities
- It somewhat interfered with my daily activities
- It prevented me from doing my daily activities

Please describe how the nausea and/or vomiting interfered, and for how long:

_____

On what day after vaccination did the diarrhoea start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the diarrhoea last? _____ (Days)

How many episodes per day did you have of diarrhoea at its worst?

_____

On what day after vaccination did the muscle pain start? At day number: _____ (Note: Day number 1 is the day you received your vaccination)

For how many days did the muscle pain last? _____ (Days)

On what day after vaccination did the joint pain start? At day number: _____ (Note: Day number 1 is the day you received your vaccination) For how many days did the joint pain last? _____ (Days)

Did the muscle and/or joint pain significantly interfere with your daily activities?

- It did not significantly interfere with my daily activities
- It somewhat interfered with my daily activities
- It prevented me from doing my daily activities

Please describe how the muscle and/or joint pain interfered, and for how long:

_____

Did you have to use medication or consult a medical doctor?

I did not need to take any medication, nor see a medical doctor

I had to consult a medical doctor or be hospitalised

I had to use pain medication

Please describe when you saw the doctor, and what was discussed:

_____

Which medication did you take? _____

For how many days did you use this medication? _____ (Days)

<u>Allergic reactions after DOSE 2 of the COVID-19-specific vaccine</u>

Did you have an allergic reaction after DOSE 1 of the vaccination? Please select all that apply:

- None
- Urticaria (hives) or cutaneous rash
- Runny or stuffy nose and sneezing
- Vomiting, diarrhea, or abdominal cramps
- Swollen or itchy lips or tongue
- Swollen or itchy throat, hoarse voice, trouble swallowing, tightness in your throat

- Coughing, wheezing, shortness of breath
- Fainting, dizziness, confusion, or weakness
- Other

Other allergic reaction, please describe: _____

How long after vaccination (in minutes) did the allergic reaction start?

_____

What treatment did you receive? Please select all that apply:

- No treatment
- Anti-histamine
- Adrenaline Inhaler
- Prednisolone or other steroids
- Transferred to the Emergency department
- Hospitalisation in normal unit (non-ICU)
- Hospitalisation in Intensive Care Unit (ICU)
- Other

If other, please specify: _____

Please describe what happened: _____

Other vaccinations

Did you receive any other vaccines since the start of COVIRS?

- Yes
- No

If yes, which vaccine(s) did you receive?

- Diphtheria-tetanus vaccine (ADT Booster)
- Diphtheria-tetanus-pertussis vaccine (Boostrix, Adacel, Tripacel)
- Diphtheria-tetanus-pertussis-polio vaccine (Boostrix-IPV, Adacel Polio, Quadracel)
- Polio vaccine (IPOL)
- Hepatitis B vaccine (Engerix-B, H-B-Vax II)
- Hepatitis A vaccine (Havrix, Avaxim, Vaqta)
- Hepatitis A-hepatitis B vaccine (Twinrix)
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- Varicella vaccine (Varilrix, Varivax)
- Zoster live vaccine (Zostavaq)
- Zoster non-live vaccine (Shingrix)

- Tuberculosis vaccine (BCG)
- Other

If other, please specify: _____