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# Accelerated waning of the humoral response to COVID-19 vaccines in obesity

In the format provided by the authors and unedited

**Supplementary Data Table 1:** Association between BMI and COVID-19 hospitalization or death among individuals from the EAVE II cohort

| BMI category ($kg/m^2$) | Adjusted rate ratios (95% CI) | |
|---|---|---|
| | **BMI (imputed)** | **BMI (recorded)** |
| **18.5-24.9** | 1.0 | 1.0 |
| **<18.5** | 1.28 (1.12-1.47) | 1.47 (1.27-1.69) |
| **25-29.9** | 0.91 (0.86-0.96) | 0.92 (0.83-1.01) |
| **30-39.9** | 1.11 (1.05-1.18) | 0.94 (0.84-1.04) |
| **40+** | 1.76 (1.60-1.94) | 1.36 (1.13-1.64) |

Adjusted rate ratios (aRRs) were estimated adjusting for all confounders including age, sex, Scottish Index of Multiple Deprivation, time since receiving the second dose of vaccine, number of pre-existing comorbidities, the gap between vaccine doses, previous history of SARS-CoV-2 infection and calendar time. Where the BMI was missing, it was imputed using ordinary least squares regression with all other independent variables included as predictors (BMI (imputed)). CI, confidence intervals. BMI=body mass index.

**Supplementary Data Table 2:** Population characteristics of the EAVE II population above the age of 80 years old

| Characteristic | | All individuals over 80 years of age | |
|---|---|---|---|
| | | **Total vaccination (n, %)** | **Severe COVID-19 outcome (n, rate per 1000 person-years)** |
| **Total** | | 225,947 (100.0) | 2988 (26.8) |
| **BMI (kg/m$^2$)** | <18.5 | 5115 (2.3) | 120 (44.9) |
| | 18.5-24.9 | 52658 (23.3) | 776 (30.5) |
| | 25-29.9 | 124650 (55.2) | 1479 (24.0) |
| | 30-39.9 | 41132 (18.2) | 579 (28.1) |
| | 40+ | 2365 (1.0) | 34 (32.3) |

**Supplementary Data Table 3:** Sensitivity analysis (association between BMI and COVID-19 hospitalization or death among individuals from the EAVE II cohort) restricted to BMI imputed through multiple imputations method and clinically diagnosed severe COVID-19 outcomes

| **BMI category ($kg/m^2$)** | **Adjusted rate ratios (95% CI)** | |
|---|---|---|
| | **Multiple imputed BMI** | **Clinically confirmed severe COVID-19 events** |
| **18.5-24.9** | 1.0 | 1.0 |
| **<18.5** | 1.23 (1.09-1.39) | 1.37 (1.16-1.62) |
| **25-29.9** | 0.95 (0.89-1.03) | 0.91 (0.85-0.98) |
| **30-39.9** | 1.08 (1.00-1.16) | 1.21 (1.12-1.30) |
| **40+** | 1.62 (1.48-1.79) | 2.09 (1.87-2.35) |

Adjusted rate ratios (aRRs) were estimated adjusting for all confounders including age, sex, Scottish Index of Multiple Deprivation, time since receiving the second dose of vaccine, number of pre-existing comorbidities, the gap between vaccine doses, previous history of SARS-CoV-2 infection and calendar time. Where the BMI was missing, it was imputed using ordinary least squares regression with all other independent variables included as predictors (BMI (imputed)). CI, confidence intervals. BMI=body mass index.

**Supplementary Data Table 4:** Population characteristics of individuals from EAVE-II who received at least second (of the primary vaccination schedule) or third dose of a SARS-CoV-2 vaccine, and individuals who were unvaccinated during the study period.

| | | EAVE II study cohort i.e. individuals who had received at least received second dose (of the primary vaccination schedule) or booster dose | | Unvaccinated individuals in the Scottish population during the study period | |
|---|---|---|---|---|---|
| **Characteristic** | | **Total vaccination (n, %)** | **Severe COVID-19 outcome (n, rate per 1000 person-years)** | **Total vaccination (n, %)** | **Severe COVID-19 outcome (n, rate per 1000 person-years)** |
| **Total** | | 3,588,340 (100.0) | 10,938 (6.0) | 569,218 (100.0) | 17,884 (31.4) |
| **BMI (kg/m$^2$)** | <18.5 | 36,197 (1.0) | 252 (13.7) | 10,319 (1.8) | 413 (40.0) |
| | 18.5-24.9 | 456,128 (12.7) | 1,813 (7.7) | 76,289 (13.4) | 2,765 (36.2) |
| | 25-29.9 | 2,428,889 (67.7) | 5,599 (4.5) | 422,229 (74.2) | 10,698 (25.3) |
| | 30-39.9 | 568,420 (15.8) | 2,710 (9.3) | 52,135 (9.2) | 3,374 (64.7) |
| | 40+ | 98,706 (2.8) | 609 (12.2) | 8,246 (1.4) | 634 (76.9) |

**Supplementary Data Table 5:** Population characteristics of the EAVE II population, stratified by BMI groups

| | <18.5 (number of individuals, number of events) | 18.5-24.9 (number of individuals, number of events) | 25.0-29.9 (number of individuals, number of events) | 30.0-39.9 (number of individuals, number of events) | 40+ (number of individuals, number of events) |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| Female | 26,187 (179) | 303,678 (997) | 1,163,267 (2,683) | 318,072 (1,293) | 68,374 (376) |
| Male | 10,010 (73) | 152,450 (816) | 1,265,622 (2,916) | 250,348 (1,417) | 30,332 (233) |
| **Age groups (years)** | | | | | |
| 18-49 | 18,753 (38) | 217,886 (296) | 1,188,635 (1,319) | 170,045 (402) | 39,105 (162) |
| 50-64 | 5,811 (30) | 93,801 (233) | 692,170 (1,264) | 192,959 (718) | 36,611 (202) |
| 65-79 | 6518 (64) | 91,756 (508) | 423,434 (1,537) | 164,284 (1,011) | 20,625 (211) |
| 80+ | 5,115 (120) | 52,685 (776) | 124,650 (1,479) | 41,132 (579) | 2,365 (34) |
| **Deprivation status (SIMD)** | | | | | |
| 1 - High | 8,719 (81) | 77,198 (450) | 417,411 (1,503) | 121,531 (791) | 26,797 (244) |
| 2 | 7,388 (54) | 82,661 (420) | 457,123 (1,282) | 125,192 (694) | 24,308 (147) |
| 3 | 6,576 (40) | 90,111 (335) | 486,432 (1,068) | 118,072 (524) | 19,708 (79) |
| 4 | 6,423 (41) | 97,147 (298) | 520,800 (934) | 111,684 (420) | 16,552 (77) |
| 5 - Low | 6,770 (33) | 105,774 (297) | 531,767 (787) | 89,150 (270) | 10,902 (60) |
| NA | 330 (<10) | 3,237 (13) | 15,356 (25) | 2,791 (<10) | 439 (<10) |
| **Number of risk groups** | | | | | |
| 0 | 15,816 (33) | 229,528 (239) | 1,549,890 (1,869) | 208,753 (356) | 33,671 (100) |
| 1 | 10,128 (63) | 129,770 (416) | 610,365 (1,452) | 187,235 (341) | 33,825 (173) |
| 2 | 5,362 (53) | 54,626 (432) | 178,034 (1,005) | 97,780 (656) | 18,404 (127) |
| 3 | 2,766 (52) | 24,203 (320) | 56,525 (628) | 43,786 (499) | 7,866 (101) |
| 4 | 1,280 (28) | 10,773 (219) | 21,447 (361) | 18,899 (273) | 3,056 (51) |
| 5+ | 845 (23) | 7,174 (187) | 12,628 (284) | 11,967 (285) | 1,884 (57) |

**Supplementary Data Table 6:** STROBE and RECORD checklists

| | Item No. | STROBE items | RECORD items | Location in the pdf manuscript where items are reported |
|---|---|---|---|---|
| **Title and abstract** | | | | |
| | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found | RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract. | p. 1 |
| **Introduction** | | | | |
| Background rationale | 2 | Explain the scientific background and rationale for the investigation being reported | | p. 2 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | | p. 2 |
| **Methods** | | | | |
| Study Design | 4 | Present key elements of study design early in the paper | | P 2 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | | p. 2 |
| Participants | 6 | *(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility | RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. | p. 2-3 |

| | | | | |
|---|---|---|---|---|
| | | criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants<br><br>*(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study* - For matched studies, give matching criteria and the number of controls per case | RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.<br><br>RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage. | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. | RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided. | p.10 |
| Data sources/ measurement | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | | p. 10 |
| Bias | 9 | Describe any efforts to address potential sources of bias | | p. 10 |
| Study size | 10 | Explain how the study size was arrived at | | N/A |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which | | p. 10 |

| | | | | |
|---|---|---|---|---|
| | | groupings were chosen, and why | | |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) *Cohort study* - If applicable, explain how loss to follow-up was addressed<br>*Case-control study* - If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | | p. 10 |
| Data access and cleaning methods | | .. | RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.<br><br>RECORD 12.2: Authors should provide information on the data cleaning methods used in the study. | p. 10 |
| Linkage | | .. | RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided. | p. 10 |
| **Results** | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed | RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of | p. 2-3 |

| | | | | |
|---|---|---|---|---|
| | | eligible, included in the study, completing follow-up, and analysed)<br>(b) Give reasons for non-participation at each stage.<br>(c) Consider use of a flow diagram | included persons can be described in the text and/or by means of the study flow diagram. | |
| Descriptive data | 14 | (a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount) | | p. 2-3 |
| Outcome data | 15 | *Cohort study* - Report numbers of outcome events or summary measures over time<br>*Case-control study* - Report numbers in each exposure category, or summary measures of exposure<br>*Cross-sectional study* - Report numbers of outcome events or summary measures | | p. 2-3 |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when | | p. 2-3 |

| | | | | |
|---|---|---|---|---|
| | | continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | | |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | | p. 2-3 |
| **Discussion** | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | | p. 4-5 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported. | p. 5&7 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | | p. 4,5 & 7 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | | p. 7 |
| **Other Information** | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if | | p. 12-13 |

| | | | | |
|---|---|---|---|---|
| | | applicable, for the original study on which the present article is based | | |
| Accessibility of protocol, raw data, and programming code | | .. | RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code. | p. 12 |

**Supplementary Data Table 7:** Co-morbidities included as the covariates in the modelling

| QCOVID risk group | Code |
|---|---|
| Atrial fibrillation | Q_DIAG_AF |
| Asthma | Q_DIAG_ASTHMA |
| Blood cancer | Q_DIAG_BLOOD_CANCER |
| Heart failure | Q_DIAG_CCF |
| Cerebral palsy | Q_DIAG_CEREBALPALSY |
| Coronary heart disease | Q_DIAG_CHD |
| Cirrhosis | Q_DIAG_CIRRHOSIS |
| Congenital heart disease | Q_DIAG_CONGEN_HD |
| COPD | Q_DIAG_COPD |
| Dementia | Q_DIAG_DEMENTIA |
| Diabetes type 1 | Q_DIAG_DIABETES_1 |
| Diabetes type 2 | Q_DIAG_DIABETES_2 |
| Epilepsy | Q_DIAG_EPILEPSY |
| Fracture | Q_DIAG_FRACTURE |
| Neurological disorder | Q_DIAG_NEURO |
| Parkinson's | Q_DIAG_PARKINSONS |
| Pulmonary hypertension | Q_DIAG_PULM_HYPER |
| Pulmonary rare | Q_DIAG_PULM_RARE |
| Peripheral vascular disease | Q_DIAG_PVD |
| Rheumatoid arthritis or SLE | Q_DIAG_RA_SLE |
| Respiratory cancer | Q_DIAG_RESP_CANCER |
| Severe mental illness | Q_DIAG_MENT_ILL |
| Sickle cell disease | Q_DIAG_SICKLE_CELL |
| Stroke/TIA | Q_DIAG_STROKE |
| Thrombosis or pulmonary embolus | Q_DIAG_VTE |
| Care housing category | Q_HOME_CAT |
| Learning disability or Down's | Q_LEARN_CAT |
| Kidney disease | Q_DIAG_CKD_LEVEL |
| More information on codes: https://github.com/EAVE-II/EAVE-II-data-dictionary<br>Ref: Clift, A.K., et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ 371, m3731 (2020). | |

**Supplementary Data Table 8:** Characteristics of people with severe obesity and normal BMI controls (SCORPIO study)

| | **Normal BMI controls (n=16)** | **PITCH normal BMI controls (V3D0 comparison) (n=25)** | **Severe obesity (n=28)** | **P value for normal BMI controls vs Severe obesity** | **P value for PITCH normal BMI controls and Severe obesity** |
|---|---|---|---|---|---|
| **Age (mean, range in years)** | 46 (38-60) | 33 (21-59) | 54 (37-69) | 0.0870 | <0.0001 |
| **Sex (F/M)** | 10/6 | 19/6 | 20/8 | 0.7376 | 0.7632 |
| **BMI (mean, range in kg/m2)** | 22.9 (18-25) | 21.0 (18-25) | 47.4 (38-67) | <0.0001 | <0.0001 |
| **Primary vaccination course (ChadOx1 vs BNT162b2)** | 10/6 | 19/6 | 18/10 | 0.3791 | 0.3869 |
| **Time after second dose of SARS-CoV-2 vaccination (mean, range in days)** | 183 (140-239) | 186 (155-223) | 196 (182-215) | 0.1531 | 0.2576 |
| **Hypertension (number of individuals)** | 0 | 1 | 15 | | |
| **Diabetes mellitus 2 (number of individuals)** | 0 | 0 | 11 | | |
| | | Diet controlled | 3 | | |
| | | Oral glucose lowering drugs | 6 | | |
| | | Insulin treatment | 2 | | |
| **Cardiovascular disease (number of individuals)** | 0 | 0 | 6 | | |
| **Non-alcoholic fatty liver disease (number of individuals)** | 0 | 0 | 2 | | |
| **Obstructive sleep apnoea (number of individuals)** | 0 | 0 | 8 | | |

Groups were compared using ANOVA or non-parametric Kruskall-Wallis tests where appropriate.

**Supplementary Data Table 9:** Antibody dilutions in high-dimensional spectral flow cytometry

| Surface mix | | | | | Total volume: | Overnight mix | | | Total volume: |
|---|---|---|---|---|---|---|---|---|---|
| **Peak Channel** | **Fluor** | **Marker** | **Dilution** | **ul to add** | **4400** | **Marker** | **Dilution** | **ul to add** | **4400** |
| **UV2** | BUV395 | | | | | CD27 | 2000 | 2.2 | |
| **UV6** | AF350 | | | | | CD57 | 500 | 8.8 | |
| **UV7** | BUV496 | | | | | CD4 | 2000 | 2.2 | |
| **UV8** | BUV563 | FcRL5 | 500 | 8.800 | | | | | |
| **UV9** | BUV615 | CD19 | 2000 | 2.200 | **FACS buffer:** | | | | **perm buffer:** |
| **UV11** | BUV661 | | | | 4400 | CD11c | 2000 | 2.2 | 4400 |
| **UV14** | BUV737 | CD10 | 1000 | 4.400 | | | | | |
| **UV16** | BUV805 | | | | | CD38 | 2000 | 2.2 | |
| **V1/2** | eFluor450 | | | | | Tbet | 2000 | 2.2 | |
| **V1/2** | BV421 | | | | **Samples** | ICOS | 1000 | 4.4 | **Samples** |
| **V4** | BV480 | CD21 | 2000 | 2.200 | 40 | | | | 40 |
| **V6** | BV510 | | | | | TCRgd | 1000 | 4.4 | |
| **V8** | SB570 | | | | | CD45RA | 500 | 8.8 | |
| **V10** | BV605 | Spike | 500 | 8.800 | | | | | |
| **V11** | BV650 | CXCR3 | 500 | 8.800 | | | | | |
| **V13** | BV711 | | | | | GATA3 | 500 | 8.8 | |
| **V14** | BV750 | | | | | PD-1 | 1000 | 4.4 | |
| **V15** | BV785 | HLA-DR | 2000 | 2.200 | **Total stains:** | | | | **Total stains:** |
| **B2** | KIRAVIA Blue 520 | | | | 40 | CD25 | 1000 | 4.4 | 40 |
| **B3** | Alexa 532 | | | | | IgM | 1000 | 4.4 | |
| **B3** | SparkBlue 550 | | | | | CD3 | 2000 | 2.2 | |
| **B8** | PerCP | CD14 | 2000 | 2.200 | | | | | |
| **B9** | PerCPeFluor 710 | CCR6 | 500 | 8.800 | | | | | |
| **B9** | BB700 | CD71 | 1000 | 4.400 | | | | | |
| **B10** | BB790 | | | | | IRF4 | 500 | 8.8 | |
| **YG1** | PE | RBD | 500 | 8.800 | | | | | |
| **YG2** | SparkYG593 | | | | | CD11b | 2000 | 2.2 | |
| **YG3** | AlexaFluor 594 | | | | | CD44 | 1000 | 4.4 | |
| **YG3** | PE-dazzle594 | CXCR5 | 2000 | 2.200 | | | | | |
| **YG4** | PE-AlexaFluor610 | CD24 | 2000 | 2.200 | | | | | |
| **YG5** | PE-Cy5 | CXCR4 | 2000 | 2.200 | | | | | |
| **YG7** | PE-Cy5.5 | | | | | Foxp3 | 500 | 8.8 | |
| **YG9** | PE-Cy7 | | | | | RORGT | 1000 | 4.4 | |
| **YG10** | PE-Fire810 | CCR7 | 500 | 8.800 | | | | | |
| **R1** | APC | Spike | 500 | 8.800 | | | | | |
| **R2** | Alexa 647 | RBD | 500 | 8.800 | | | | | |
| **R2** | Spark NIR685 | CD20 | 2000 | 2.200 | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **R4** | Alexa Fluor 700 | | | | | Ki67 | 1000 | 4.4 | |
| **R5** | ViaKrome808 | Viability | 2000 | 2.200 | | | | | |
| **R7** | APC-Fire750 | IgD | 2000 | 2.200 | | | | | |
| **R8** | APCFire810 | | | | | CD8 | 2000 | 2.2 | |
| | Blocking | Fc block | 100 | 44.000 | | Fc block | 100 | 44 | |

## **Supplementary Data Table 10:** PITCH consortium

| First Name | Middle Name(s)/Initial(s) | Last Name | Department (if appropriate) | Institution |
|---|---|---|---|---|
| **Eleanor** | | Barnes | Nuffield Department of Medicine | University of Oxford |
| **Sagida** | | Bibi | Oxford Vaccine Group, Department of Paediatrics | University of Oxford |
| **Miles** | | Carroll | Nuffield Department of Medicine | University of Oxford |
| **Christopher** | P. | Conlon | Nuffield Department of Medicine | University of Oxford |
| **Thushan** | I. | de Silva | Department of Infection, Immunity and Cardiovascular Disease | University of Sheffield |
| **Alexandra** | S | Deeks | Nuffield Department of Medicine | University of Oxford |
| **Susan** | L | Dobson | Institute of Infection, Veterinary and Ecological Sciences | University of Liverpool |
| **Christina** | | Dold | Oxford Vaccine Group, Department of Paediatrics | University of Oxford |
| **Susanna** | | Dunachie | Nuffield Department of Medicine | University of Oxford |
| **Christopher** | JA | Duncan | Translational and Clinical Research Institute | Newcastle University |
| **Sian** | | Faustini | Institute for Immunology and Immunotherapy, College of Medical and Dental Science | University of Birmingham |
| **Sarah** | | Foulkes | | UK Health Security Agency |
| **John** | | Frater | Nuffield Department of Medicine | University of Oxford |
| **Victoria** | | Hall | | UK Health Security Agency |
| **Susan** | | Hopkins | | UK Health Security Agency |
| **Jasmin** | | Islam | | UK Health Security Agency |
| **Katie** | | Jeffery | Radcliffe Department of Medicine | University of Oxford |
| **Paul** | | Klenerman | Nuffield Department of Medicine | University of Oxford |
| **Barbara** | | Kronsteiner | Nuffield Department of Medicine | University of Oxford |
| **Teresa** | | Lambe | Oxford Vaccine Group, Department of Paediatrics | University of Oxford |
| **Stephanie** | | Longet | Nuffield Department of Medicine | University of Oxford |
| **Alexander** | J. | Mentzer | Nuffield Department of Medicine | University of Oxford |
| **Shona** | C | Moore | Institute of Infection, Veterinary and Ecological Sciences | University of Liverpool |
| **Ashley** | | Otter | | UK Health Security Agency |
| **Rebecca** | P. | Payne | Translational and Clinical Research Institute | Newcastle University |
| **Alex Richter** | | Richter | Institute for Immunology and Immunotherapy, College of Medical and Dental Science | University of Birmingham |
| **Sarah** | L. | Rowland-Jones | Department of Infection, Immunity and Cardiovascular Disease | University of Sheffield |
| **Donal** | | Skelly | Nuffield Department of Clinical Neurosciences | University of Oxford |
| **Lizzie** | | Stafford | Nuffield Department of Medicine | University of Oxford |
| **James** | E.D. | Thaventhiran | MRC Toxicology Unit | University of Cambridge |
| **Lance** | | Turtle | Institute of Infection, Veterinary and Ecological Sciences | University of Liverpool |
| **Daniel** | G. | Wootton | Institute of Infection, Veterinary and Ecological Sciences | University of Liverpool |