The safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults: a phase IV, multicentre randomised controlled trial with blinding (ComFluCOV).

Rajeka Lazarus, DPhil; Sarah Baos, PhD; Heike Cappel-Porter, MMath; Andrew Carson-Stevens, PhD; Madeleine Clout, BSc; Lucy Culliford, PhD; Stevan R Emmett, DPhil; Jonathan Garstang, MBBS; Lukuman Gbadamoshi, MBBS; Bassam Hallis, PhD; Rosie A Harris, MSc; David Hutton, BSc; Nick Jacobsen, MRCGP; Katherine Joyce, MSc; Rachel Kaminski, MBBS; Vincenzo Libri, MD; Alex Middleditch FRCA FFICM; Liz McCullagh, BPharmS; Ed Moran, PhD; Adrian Phillipson, MSc; Elizabeth Price, MD; John Ryan, BM; Russell Thirard, MSc; Rachel Todd, MSc; Matthew D Snape, MD; David Tucker, DPhil; Rachel Lauren Williams, MSc; Prof Jonathan S Nguyen-Van-Tam, DM; Prof Adam Finn, PhD; Prof Chris A Rogers, PhD and the ComfluCOV Trial Group*

University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK (R Lazarus DPhil, A Middleditch FRCA FFICM, L McCullagh BPharmS), Bristol Trials Centre, University of Bristol, Bristol, UK (S Baos PhD, H Cappel-Porter MMath, M Clout BSc, L Culliford PhD, K Joyce MSc, R A Harris MSc, D Hutton BSc, R Thirard MSc, R Todd MSc, C A Rogers PhD), Division of Population Medicine, School of Medicine, Cardiff University, Cardiff, UK (A Carson-Stevens PhD), Royal United Hospitals NHS Foundation Trust, Bath, UK (S R Emmett DPhil, L Gbadamoshi MBBS), Knowle House Surgery, Plymouth, UK (J Garstang MBBS), Porton Down, Public Health England, Salisbury, UK (B Hallis PhD) Newquay Health Centre, Newquay, UK (N Jacobsen MRCGP), Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK (R Kaminski MBBS), NIHR UCLH Clinical Research Facility and NIHR UCLH Biomedical Research Centre, University College Hospitals NHS Foundation Trust, London, UK (V Libri MD), North Bristol NHS Trust, Bristol, UK (E Moran PhD, R L Williams MSc), Rotherham Doncaster and South Humber NHS Foundation Trust, Doncaster, UK (A Phillipson MSc), Great

Western Hospitals NHS Foundation Trust, Swindon, UK (E Price MD), The Alverton Practice, Penzance, UK (J Ryan BM), Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK; Oxford NIHR – Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK (M D Snape MD), Royal Cornwall Hospitals NHS Trust, Truro, UK (D Tucker DPhil), Division of Epidemiology and Public Health, University of Nottingham School of Medicine, Nottingham, UK (J S Nguyen-Van-Tam DM), Bristol Medical School, Bristol Population Health Sciences and School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK (A Finn PhD)

Corresponding Author: Rajeka Lazarus rajeka.lazarus@uhbw.nhs.uk

Department of Microbiology, University Hospitals Bristol and Weston, NHS Foundation Trust, BS2 8HW

Abstract

Background Concomitant administration of COVID-19 and influenza vaccines would reduce burden on healthcare systems. We assess the safety of concomitant administration.

Methods Adults in receipt of a single dose of ChAdOx1 or BNT162b2 were enrolled at 12 UK sites and randomised 1:1 to receive concomitant administration of either age-appropriate influenza or placebo alongside second COVID-19 vaccine. Three weeks later the group who received placebo received the influenza vaccine, and vice versa. Participants were followed to six weeks. The influenza vaccines were three seasonal, inactivated vaccines (trivalent, MF59C adjuvanted (aTIV) or a cellular or recombinant quadrivalent vaccine (QIVc/QIVr)). Participants and investigators were masked to the allocation. The primary endpoint was one or more participant-reported solicited systemic reaction in the seven days after first trial vaccination(s), with a difference of <25% considered non-inferior. Local and unsolicited systemic reactions and humoral responses were also assessed (ISRCTN14391248).

Findings Between 1st April and 26th June 2021, 679 participants were recruited to one of six cohorts: (129 ChAdOx1/QIVc; 139 BNT162b2/QIVc; 146 ChAdOx1/aTIV; 79 BNT162b2/aTIV; 128 ChAdOx1/QIVr; 58 BNT162b2/QIVr). Overall, 340 participants were randomised to concomitant administration of influenza and COVID-19 vaccine and 339 were randomised to placebo and COVID-19 vaccine. Non-inferiority was indicated in four cohorts; ChAdOx1/QIVc: risk difference (influenza vaccine minus placebo) -1·29% (95% confidence interval (CI) -14·7%, 12·1%); BNT162b2/QIVc: 6·17% (-6·27%, 18·6%); BNT162b2/aTIV: -12·9% (-34·2%, 8·37%); ChAdOx1/QIVr: 2·53% (-13·3%, 18·3%). In two cohorts the upper limit of the 95%CI exceeded 25%; ChAdOx1/aTIV: 10·3% (-5·44%, 26·0%) and BNT162b2/QIVr: 6·75% (-11·8%, 25·3%). Most reactions were mild or moderate. Rates of local and

unsolicited systemic reactions were similar between randomised groups. One serious adverse event, hospitalisation with severe headache, was considered related to the trial intervention. Immune responses were not adversely affected.

Interpretation Concomitant vaccination raises no safety concerns and preserves the immune response to both vaccines.

Funding

The trial is commissioned and funded by the Department of Health and Social Care (DHSC) through the National Institute for Health Research (NIHR). This research was supported by the Vaccine Task Force (VTF) and NIHR Policy Research Programme (PR-R17-0916-22001, NIHR203243). This trial was designed and delivered in collaboration with the Bristol Trials Centre, a UKCRC registered clinical trials unit (CTU) which is in receipt of NIHR CTU support funding, and the NIHR-funded National Immunisation Schedule Evaluation Consortium. The views expressed are those of the author(s) and not necessarily those of the NIHR, VTF or DHSC.

Introduction

COVID-19 vaccination programmes have prevented millions of cases of SARS-CoV-2 infection and many deaths around the world.[1] However, mass vaccination efforts have added to the burden placed by the COVID-19 pandemic on healthcare systems. In some parts of the world, COVID-19 and seasonal influenza vaccination programmes will overlap, and so administration of both vaccines at the same appointment, concomitantly, would lessen the burden on healthcare systems, support vaccine uptake and afford timely protection against both infections. High rates of influenza, alongside further waves of COVID-19, are predicted for the coming Northern hemisphere winter, as there was little circulating influenza virus detected during the first wave of the COVID-19 pandemic[2]. Therefore, it is important that further doses of COVID-19 and influenza vaccines are delivered in a timely, efficient and safe manner.

International recommendations in the 2020/21 influenza season were to separate influenza and COVID-19 vaccine by 14 days.[3,4] The main reasons for this were to avoid inaccurate attribution of side effects to the newly approved COVID-19 vaccines and a lack of data to inform concomitant vaccination. It is necessary to establish whether concomitant vaccination is safe and whether it would increase reactogenicity rates, as increased rates may negatively influence vaccine uptake. This is particularly important as the most widely used COVID-19 vaccines produce relatively high rates of expected adverse reactions, such as fever, compared to other vaccines.[5,6] In addition, in some cases concomitant vaccination alters the immunogenicity of administered vaccines.[7]

Here, we present the safety and immunogenicity results of concomitant administration of a COVID-19 vaccine (either an adenovirus viral vector COVID-19 vaccine (ChAdOx1) or a ribonucleic acid (RNA)

COVID-19 vaccine (BNT162b2)) with an inactivated influenza vaccine (either a MF59C adjuvanted, trivalent vaccine (aTIV) or a cellular or recombinant quadrivalent vaccine (QIVc/QIVr)).

Methods

Trial design

ComFluCOV was a randomised, controlled, phase IV trial with blinding, conducted across 12 National Health Service sites (Supplementary Material, Table 1) across the United Kingdom (UK). The trial was designed to investigate concomitant administration of second doses of two COVID-19 vaccines (ChAdOx1 and BNT162b2) with three influenza vaccines (aTIV, QIVc and QIVr). Participants were recruited into one of six cohorts defined by the six COVID-19/influenza vaccine combinations.

The trial was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. Approvals were received from the Medicines and Healthcare products Regulatory Agency (MHRA) (EudraCT number 2021-001124-18) and the South-Central Berkshire Research Ethics Committee (21/SC/0100). The trial was sponsored by University Hospitals Bristol and Weston NHS Foundation Trust and coordinated by the Bristol Trials Centre, University of Bristol. The trial is registered (ISRCTN14391248) and the protocol is included in the Supplementary Material.

Two substantial amendments were made to the study protocol. An influenza vaccine (QIVr) was added after the start of recruitment at the request of the Department of Health and Social Care (DHSC). The sample size was increased from 504 to 756 and the number of cohorts increased from four to six. In response to the Urgent Safety Measure initiated by the MHRA on 8th April in relation to incidents of thromboembolic events after vaccination with ChAdOx1, recruitment of under 30-year-

olds in receipt of ChAdOx1 was temporarily suspended on 9th April and then resumed on 14th April. The exclusion criteria were updated to exclude participants at risk of thrombotic events.

Trial participants

We used social media and local advertising to raise awareness of the trial. Volunteers registered their interest by completing an online questionnaire. Volunteers were eligible if they were aged 18 and over and had received a single dose of either ChAdOx1 in the preceding 56 to 90 days or BNT162b2 in the preceding 28 to 90 days. Volunteers had to agree to their GP being contacted and to refrain from blood donation in the seven days following vaccination, and they needed access to an electronic device. Volunteers were ineligible if they had received any other vaccine in the 30 days prior to recruitment, or immunoglobulins or blood products in the previous three months, had a history of allergy or reactions to any component of the trial vaccines, a bleeding disorder or continuous use of anticoagulants, suspected or known drug or alcohol dependence, or progressive neurological disorders. Participants with other co-morbidities that made them eligible for routine influenza vaccine were included (see Supplementary Material for full details). Written informed consent was received from all participants at the first trial visit (day 0, D0).

Randomisation and masking

At D0, participants were randomly assigned in a 1:1 ratio to receive either an age-appropriate influenza vaccine or a placebo injection, alongside their second dose of a COVID-19 vaccine homologous to their first dose, using a secure internet-based system to ensure allocation concealment. The randomisation schedule was stratified by cohort and blocked using blocks of varying size. The sequence was generated by a statistician not otherwise involved in the trial.

Participants, clinicians assessing causality of adverse events, and laboratory staff were masked to the treatment allocation. Vaccines were prepared out of sight of the participant, and masking was maintained by asking participants to look away during the injection and applying a masking label over the vaccine syringe. Trial staff who administered the vaccines and entered these data were unmasked.

Procedures and interventions

At D0, eligible volunteers who consented to take part were randomised and received the trial vaccinations (i.e., either an age-appropriate influenza vaccine or a placebo injection in addition to their second dose of a COVID-19 vaccine). At the second visit between 21 and 28 days later (D21), those who received an influenza vaccine at D0 received a placebo injection and vice versa. Participants attended a final trial visit at between 42 and 56 days (D42) for safety assessments. Participants provided up to 10mls of sera and up to 2ml of saliva at all three trial visits.

ChAdOx1 (0·5ml dose) is a recombinant, replication-deficient chimpanzee adenovirus vectored vaccine, expressing the SARS-CoV-2 spike surface glycoprotein with a leading tissue plasminogen activator signal sequence. BNT162b2 (0·3ml dose) is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding trimeric SARS-CoV-2 spike glycoprotein.

The influenza vaccines used were in keeping with age-based influenza vaccine recommendations in the UK. Adults aged 65 and over received FluAd, Seqirus UK Ltd; a trivalent, surface antigen inactivated influenza vaccine adjuvanted with MF59C (aTIV). Adults aged under 65 received one of

two quadrivalent influenza vaccines: Flucelvax, Seqirus UK Ltd; a surface antigen, inactivated vaccine prepared in cell culture (QIVc), or Flublok, Sanofi; a recombinant influenza vaccine (QIVr). The influenza vaccines were from the 2020/21 season and contained A strains (H1N1 and H3N2) and B strains (Yamagata and Victoria) that complied with World Health Organization (WHO) recommendations for the Northern Hemisphere. The influenza vaccines were provided in commercially available pre-filled syringes as a 0·5ml dose. Commercially available 0·5ml of sodium chloride injection BP 0·9% was used as a saline placebo. Influenza vaccine(s) available at each participating site are shown in Supplementary Material, Table 1.

All vaccines were administered intramuscularly in the upper arm by appropriately trained staff at trial sites. The COVID-19 vaccine was given in one arm and influenza/placebo was given in the other arm. The upper thigh was used if the arm could not be used. Participants were observed for at least 15 minutes after vaccination.

Outcomes

The primary outcome was one or more solicited systemic reaction in the seven days after vaccination at D0. The solicited systemic reactions were fever, feverishness, chills, joint pains, muscle pains, fatigue, headache, malaise, nausea, vomiting and diarrhoea. Reactions were collected daily via a purpose-designed participant-completed electronic diary. Participants were asked to record their temperature each day which was used to assess fever (they were provided with an oral thermometer for this purpose).

Secondary outcomes included safety and reactogenicity as measured by solicited local reactions, (namely pain, tenderness, redness, warmth, itch, swelling, and induration in the seven days after vaccination at D0 and D21 (tenderness was not captured explicitly but was covered under pain)), solicited systemic reactions in the seven days after vaccination at D21, and unsolicited adverse events (AEs) for the whole trial period. AEs included serious adverse events (SAEs), medically attended adverse events (MAAE) and adverse events of special interest (AESI). The local research team reviewed diary entries daily to assess adverse events for severity, determined in accordance with Food and Drug Administration toxicity grading criteria.[8] Diaries were also reviewed at trial visits, when any adverse events not captured in the diary were collected.

Secondary immunological outcomes included SARS-CoV-2 S-protein Immunoglobulin G (anti-S IgG) concentration in sera collected at D0 and D21 analysed using the Roche Elecsys®Anti-SARS-CoV-2 S electrochemiluminescence immunoassay (ECLIA)[9] and haemagglutinin antibody inhibition (HAI) in sera collected at D0, D21 and D42 against the four strains of influenza vaccine virus (H1N1, H3N2, Yamagata and Victoria) contained in the 2020/2021 season vaccines using a validated assay.[10] To maintain masking, all sera including from those who received the trivalent vaccine was tested for all four strains and reported here. All assays were performed at Porton Down, UK by Public Health England (PHE).

Other immunological outcomes, which will be reported at a later date, include measurement of neutralising antibodies against SARS-CoV-2 from sera at D0 and D21 to assess response to second dose of COVID-19 vaccine and mucosal immune responses to COVID-19 vaccines in saliva. These data were not available at the time of reporting.

Qualitative outcomes included an assessment of the success of participant blinding using the Bang Blinding Index[11] completed at D42 (a positive value for the Bang blinding index suggests more participants guessed correctly than would be expected by chance), days of work lost (if employed) and acceptability to participants of future concomitant vaccine administration.

Statistical analysis

The sample size was set at 126 participants per cohort (756 in total), which provided 80% power to assess the non-inferiority of concomitant administration of COVID-19 and influenza vaccine compared to COVID-19 vaccine alone, assuming a primary outcome frequency of 50% and a non-inferiority margin of 25%.

Analyses were performed on the intention-to-treat (ITT) basis. A per-protocol (PP) analysis, and sensitivity analyses imputing missing outcome data were also conducted for the primary outcome. (see Supplementary Material for details). Binary outcomes were compared using a generalised linear model, and risk differences (RD) and risk ratios (RR) are reported. Count variables were analysed using Poisson regression and continuous variables were analysed using a mixed regression model. Models included cohort by treatment by time interactions to allow changes in treatment effect with time within each cohort to be described. Analyses were adjusted for baseline measures (where recorded) and for trial site fitted as a random effect (where estimable). Immunogenicity outcomes were transformed to the logarithmic scale (base 10) for analysis and results are presented as geometric mean ratios (GMR). Placebo injection at D0 was the reference group.

Unsolicited AEs were coded using version 23·1 of the Medical Dictionary for Regulatory Activities and summarised by severity and relationship to the trial vaccine.[12] Seroconversion for anti-S protein IgG concentration was defined as a four-fold increase in ECLIA units from D0 to D21 and for HAI titres seroconversion was defined as a post vaccination titre of at least 32 if the baseline titre was less than eight and a four-fold increase if the baseline titre was eight or more.

Concomitant administration of the two vaccines was considered non-inferior to the COVID-19 vaccine alone if the upper limit of the 95% confidence interval (CI) for the RD for the primary outcome was less than 0·25 in both the ITT and PP analyses.

Statistical analysis was performed using STATA (StataCorp. 2021. Release 17. College Station, TX.).

An independent Data Monitoring and Safety Committee reviewed trial safety data.

Role of the funding source

The funders determined which vaccines were used in the trial, but had no role in data collection, analysis, interpretation, or writing of the report. COVID-19 vaccines were supplied by PHE and influenza vaccines were supplied by the DHSC.

Results

Between 1st April and 26th June 2021, 679 participants were enrolled and randomised; 340 participants were randomised to concomitant administration of influenza and second COVID-19

vaccine at D0 followed by placebo at D21, and 339 participants were randomised to concomitant administration of placebo and second COVID-19 vaccine at D0 followed by influenza vaccine at D21. The number enrolled and randomised in each cohort is shown in Figure 1. For two of the cohorts, BNT162b2/aTIV and BNT162b2/QIVr, fewer participants than planned were enrolled (79/126 (63%) and 58/126 (46%), respectively).

One participant was considered ineligible after randomisation due to raised blood pressure so did not receive any trial vaccinations. For four participants, the incorrect cohort randomisation scheme was selected but the correct vaccines were administered (Supplementary Material, Table 2). These participants were analysed according the COVID-19/influenza vaccines received. A further two participants were randomised using the correct cohort assignment, but they received the wrong influenza vaccine at D21; these participants are analysed according to the cohort they were randomised to. The median time between the two vaccinations at D0 was 0 minutes (interquartile range 0-1, range 0-176, Supplementary Material, Figure 1). Eight participants (1·2%) did not receive a second trial injection at D21 and nine (1·2%) did not attend at D42.

Baseline characteristics were well balanced across the two randomised groups in each cohort (Table 1). Median age of participants by influenza vaccine type was QIVc 51 years; QIVr 52 years and aTIV 69 years. Overall, 397/679 (58·5%) participants were female and 627/679 (92·3%) were White British. In total, 548/679 (80·7%) participants had received an influenza vaccine in the 2020/21 season, with a higher percentage vaccinated in the aTIV cohorts (217/225, 96·4%). Of those aged under 65, 85/454 (18·7%) were healthcare workers. Overall, 276/679 (40·6%) participants were retired. A range of co-morbidities associated with an indication for influenza vaccine were represented (Supplementary Material, Table 3).

Electronic participant diaries were completed (Supplementary Material, Tables 4 and 5) and the primary outcome could be determined for 651/679 (96%) participants. Overall, 254/330 (77·0%) participants in the group randomised to concomitant COVID-19 and influenza vaccines at D0 had one or more systemic solicited reaction over seven days following vaccination compared to 239/321 (74·5%) participants in the group randomised to COVID-19 vaccine alone at D0, with fatigue the most commonly reported reaction (Figure 2). Concomitant administration of the two vaccines was found to be non-inferior to administration of the COVID-19 vaccine alone in four cohorts: ChAdOx1/QIVc, BNT162b2/QIVc, BNT162b2/aTIV, and ChAdOx1/QIVr; in the other two cohorts, ChAdOx1/aTIV and BNT162b2/QIVr, the upper limit of the 95% CI exceeded the 0·25 non-inferiority margin (Figure 3). Risk ratios and results of the sensitivity analyses are shown in Supplementary Material, Figures 2 and 3. In all cohorts most reactions were mild or moderate; of the 254 participants reporting one or more systemic reaction in the concomitant COVID-19 and influenza vaccine group, 14 reported at least one severe adverse reaction (5·4%) compared to 6/239 (2·5%) participants in the COVID-19 vaccine alone group. There were four severe reactions (feverishness, chills, headache and malaise) in the ChAdOx1/aTIV cohort, reported by two participant(s), both of whom received the aTIV vaccine at D0, and three severe reactions in the BNT162b2/QIVr cohort (two, fatigue and malaise, in the group that received the placebo and one, malaise in the group that received the QIVr vaccine at D0) (Supplementary Material, Tables 6 and 7). The proportion of participants reporting one or more systemic events after receiving either influenza vaccine or saline injection at D21 was similar (Supplementary Material, Tables 8 - 10, Figures 4 - 6). The number of different systemic solicited reactions reported by each participant was similar in the two randomised groups at both time points (Supplementary Material, Figure 7 and Table 8).

Overall, 555/665 (83·5%) participants reported at least one solicited local adverse reaction after vaccination at D0 (282/331 (85·2%) in the concomitant COVID-19 and influenza vaccine group and 273/334 (81·7%) in the COVID-19 vaccine alone group), with injection site pain the most commonly reported reaction in all cohorts (Figures 4 and 5). The number of participants reporting one or more local reaction over the seven days following D0 was similar in the two groups for all cohorts (Supplementary Material, Figures 8 and 9 and Table 8). Most reactions were mild or moderate with eight reports of severe reactions in the limb receiving the COVID-19 vaccine; seven reports of pain and one of warmth. There was a significantly higher proportion of individuals who reported local adverse reactions when receiving influenza vaccine at D21 compared to those who received placebo (Supplementary Material, Figures 8 to 10), but no severe local reactions were reported (Supplementary Material, Tables 9 and 10). The number of different local solicited reactions reported by each participant was similar in the two randomised groups following D0 but was significantly higher following D21 in the COVID-19 vaccine alone group who received the influenza vaccine at D21 (Supplementary Material, Figure 11 and Table 8). There were 173 unsolicited adverse events following vaccination reported by 112 participants in the concomitant COVID-19 and influenza vaccine group after D0 and 155 reported by 99 participants in the COVID-19 vaccine alone group. After D21, 66 unsolicited adverse events were reported by 49 participants in the concomitant COVID-19 and influenza vaccine group compared to 84 events reported by 57 participants in the COVID-19 alone group (see Supplementary Material, Tables 8, 11 and 12 and Figures 12 and 13 for further details). Rates of MAAE were similar between groups following D0 (25 MAAEs reported by 22 participants in the concomitant COVID-19 and influenza vaccine group and 27 MAAEs reported by 20 participants in the COVID-19 alone group) and following D21 (18 MAAEs reported by 15 participants in the concomitant COVID-19 and influenza vaccine group who received placebo at D21 compared to 15 MAAEs reported by 14 participants in the COVID-19 alone group who received the influenza vaccine at D21) (Supplementary Material, Figures 14 and 15, and Tables 8, 13 and 14).

Seven SAEs were reported by seven participants, including one considered related to vaccination. A participant was admitted to hospital with severe headache and visual disturbance 48 hours after vaccination with ChAdOx1 and saline placebo, and given a diagnosis of migraine (Supplementary Material, Tables 8 and 15). One AESI, mild chilblain-like lesions, was reported as starting four days after vaccination with ChAdOx1 and saline placebo. The lesions resolved within seven days with no ongoing sequelae, and were reported as having a possible relationship to vaccination (Supplementary Material, Table 16).

Anti-S IgG geometric mean units (GMU), measured 21 days after receiving either ChAdOx1 or BNT162b2, were similar between those who received concomitant vaccination or COVID-19 alone in all cohorts (Figure 6). Seroconversion rates (SCR) ranged from 89% to 100% and 79% to 93% 21 days after either BNT162b2 or ChAdOx1, respectively, when given concomitantly with the influenza vaccine or COVID-19 alone (Table 2 and Supplementary Material, Figure 16).

No significant differences were seen in the HAI GMR for any influenza strain 21 days after receiving influenza vaccine with a COVID-19 vaccine compared to receiving the influenza vaccine alone in the QIVc and aTIV cohorts or in the cohort that received ChAdOx1/QIVr (Figure 7). In the BNT162b2/QIVr cohort, the geometric mean titres (GMT) of A/H1N1 and both B strains were higher when given with BNT162b2 compared to when QIVr was given alone but were similar for A/H3N2 (Figure 7). SCR ranged from 1% to 72%, with SCR tending to be lower in the aTIV cohorts than either of the QIV cohorts, and lower to B strains compared to A strains (Table 3 and Supplementary Material, Figure 17).

Nine out of 670 participants (1·3%) reported that they would not be willing to receive concomitant vaccination in the future; six in the COVID-19 vaccine alone group and three in the concomitant COVID-19 and influenza vaccine group. Eleven of the 356 participants in employment (3·1%) reported between a half to two lost work days following vaccination (Supplementary Material, Tables 17 and 18). The bang blinding indices for assessing the success of blinding were 0·33 (95% CI: 0·26, 0·40) for the group given concomitant COVID-19 and influenza vaccines and 0·26 (95% CI: 0·19, 0·33) in the group given the two vaccines separately (Supplementary Material, Table 19).

Discussion

Our findings demonstrate that concomitant administration of six different combinations of COVID-19 and influenza vaccines raises no safety concerns, produces acceptable reactogenicity profiles and preserves immunogenicity. The systemic reactogenicity profiles were considered acceptable despite the upper limit of 95% CI being just above 25% in two cohorts. In the ChAdOx1/aTIV cohort, the upper limit of the 95% CI only narrowly exceeded 25%, with most additional reactions recorded as mild or moderate. The BNT162b2/QIVr cohort was smaller than planned, therefore definitive conclusions cannot be drawn.

The anti-S IgG responses to both BNT162b2 and ChAdOx1 were preserved with all three types of influenza vaccine. The GMRs ranged between 0·80 and 1·13 for the six vaccine combinations evaluated. The GMRs in all six cohorts were above 0·67, which is the cut off applied by the WHO when approving new vaccines using GMR as an endpoint.[13] This criterion acts as a useful reference point for contextualising our results in the absence of an agreed correlate of protection for COVID-19 vaccines. The humoral responses to all influenza vaccines were similar between groups within each cohort, except for the BNT162b2/QIVr cohort where GMTs were significantly higher for three strains

when given with the COVID-19 vaccine. It may be that some component within BNT162b2, acting as adjuvant, augments responses. However, it is not clear why this influence is only demonstrated with recombinant influenza vaccine and not others in this trial.

These are the first data to describe concomitant administration of any vaccine with either an adenoviral vector or mRNA COVID-19 vaccine, as previous trials have excluded those receiving other vaccines at or near the time of the COVID-19 vaccination.[5,6] A sub-study of a phase III study assessing the safety and efficacy of a protein subunit COVID-19 vaccine with Matrix-M adjuvant (NVX-CoV_{2373}) co-administered QIVc to participants aged 18 to 64 with the first dose of the two dose COVID-19 vaccine schedule.[14,15] In keeping with our findings, there were no significant differences in reactogenicity between those receiving concomitant vaccination compared to the COVID-19 vaccine alone. In contrast, a significant difference was seen in the geometric mean ELISA units between the group receiving concomitant vaccination versus COVID-19 vaccine alone, with a GMR of 0·57 (95% CI: 0·47, 0·70), below the WHO 0·67 GMR cut off, suggesting immune interference. Importantly, there was no difference in the efficacy of concomitant vaccination against virologically confirmed COVID-19 disease. A key difference between that study and ours, is that the influenza vaccine was administered with the first dose, not second dose of COVID-19 vaccine.[15] They demonstrated that higher GMUs were reached when the NVX-CoV_{2373} COVID-19 vaccine and influenza vaccine were co-administered to those participants with serological evidence of previous COVID-19 infection. It has been shown that natural infection with COVID-19 primes the immune system, resulting in significantly higher anti-S IgG responses to the first dose of COVID-19 vaccine compared to those who are COVID-19 naïve.[16] This raises the possibility that concomitant immunisation may impact priming but not subsequent responses, meaning that it may be optimal to co-administer an influenza vaccine with second or later doses of COVID-19 vaccine. However, given that efficacy of the subunit COVID-19 vaccine was preserved despite a reduction in the humoral response, there may still be

advantages of concomitant administration with the first dose of COVID-19 vaccine if this were necessary to prevent delays in the uptake of either vaccine. However, the impact of the immune interference with priming doses, may have implications for less immunogenic COVID-19 vaccines, such as whole virion, inactivated vaccines.[17]

Concomitant administration of influenza vaccines with other vaccines has been studied for other vaccine types, including pneumococcal polysaccharide and conjugate vaccines.[18,19] Relative reductions have been reported for some pneumococcal serotypes in some studies, but these have not been proven to be clinically significant.[7] These studies demonstrate that concomitant administration has no impact on humoral responses to influenza vaccine, consistent with findings reported here.

The strengths of this trial are that it did not exclude individuals who were pregnant, had severe, uncontrolled medical problems, were immunocompromised, or aged 65 and over, and so the trial population is representative of the population who are most likely to receive both influenza and COVID-19 vaccines. The trial also included the two most widely used COVID-19 vaccines and the most frequently used influenza vaccine types, and so should be applicable in many settings. By performing the trial in relation to the second rather than the first dose of COVID-19 vaccine, we have evaluated safety and immunogenicity in primed individuals; therefore, the findings are also likely to be more relevant to the question of concomitant administration of booster doses and seasonal influenza vaccines, which over time may become the policy 'norm' in many parts of the world.

Given the novelty of the adenoviral vector and mRNA vaccines, it is not known whether these findings would apply to other COVID-19 vaccines in the same class. Similarly, whether these findings

could apply to live, attenuated or high dose influenza vaccines is uncertain and further studies are required with these specific vaccine types. Two of the cohorts had lower recruitment than planned, which was related to expiry dates of some influenza vaccines and the timing of the roll out of specific COVID-19 vaccines in the UK. The QIVc cohorts were added part way through the trial which meant that the sites recruiting these cohorts enrolled participants into these two cohorts whereas earlier sites recruited into four cohorts which may impact on the generalisability of results pertaining to the QIVc cohorts. Finally, T-cell responses were not evaluated; it is likely that cell mediated immunity plays a role in protection against natural SARS-CoV-2 infection and that vaccine-induced cellular responses may vary independently of neutralising antibody responses, therefore further studies investigating T-cell responses in concomitant vaccination are warranted.[20,21]

In conclusion, there are no safety concerns raised in this trial over administering BNT162b2 and ChAdOx1 in adults alongside standard dose inactivated influenza vaccines including those with MF59C adjuvant. Concomitant vaccination with both COVID-19 and influenza vaccines over the next immunisation season should reduce the burden on the healthcare services for vaccine delivery, allowing for timely vaccine administration and protection from COVID-19 and influenza for those in need.

Contributors

RL, MDS, JSN-V-T and AF conceived and designed the trial.

RL was the Chief Investigator.

LC, SB, RT, KJ and MC led the implementation of the trial.

RK, EP, EM, DT, SE, AM, AC-S, AP, VL, NJ, JR, JG and LG acted as Principal Investigators.

RH, RT and CR conducted the statistical analysis and have accessed and verified the underlying data.

DH and HC-P designed, created and maintained the trial database and trial management system.

LM was the lead pharmacist and provided expert advice on the management of the trial drugs.

RW was the regional coordinator for sites in the South West of the UK.

BH managed analyses of the trial samples at Public Health England.

All authors contributed to the implementation of the trial protocol and data collection.

RL drafted this report. All authors reviewed and approved the final manuscript.

Declaration of interests

RL reports grants from National Institute for Health Research during the conduct of the trial, and grants from Elizabeth Blackwell Institute, AstraZeneca, Janssen and Valneva outside the submitted work. CR reports grants from National Institute for Health Research, during the conduct of the trial. JSN-V-T reports he is seconded to the Department of Health and Social Care, England. AF reports grants from Pfizer during the conduct of the trial, and grants from Elizabeth Blackwell Institute, Gates Foundation, Sanofi Pasteur, VBI Vaccines, Pfizer, Janssen, GSK, MedImmune, Novavax and Valneva outside the submitted work. Between May 2015 and May 2019 AF was President of the European Society for Paediatric Infectious Diseases which, during this period, received sponsorship from GSK for its annual congress. He currently serves as chief investigator on the Valneva (Covid-19) vaccine phase 1/2 and 2/3 studies .He also serves as co-investigator on the Janssen (Covid-19) vaccine 2 dose phase 3 study. He does advisory work related to vaccines for the UK government, the World Health Organisation and several companies developing vaccines. He also leads clinical trials of vaccines funded by the UK government, charities and vaccine manufacturers. He receives no personal remuneration or benefits in kind for any of this work apart from his salary via the University

of Bristol from the Higher Education Funding Council and the NHS. He is a member of the UK Department of Health's Joint Committee on Vaccination, Chair of the WHO European Technical Advisory Group of Experts in which capacity he attends SAGE. AM reports grants from National Institute for Health Research during the conduct of the trial, and grants from AstraZeneca, Janssen and Valneva outside the submitted work. MDS acts on behalf of the University of Oxford as an investigator on studies funded or sponsored by vaccine manufacturers, including AstraZeneca, GlaxoSmithKline, Pfizer, Novavax, Pfizer, Janssen, Medimmune and MCM. The views in this paper are those of its authors and not necessarily those of the DHSC.

Data sharing statement

Following publication, anonymised individual patient data will be made available upon request to the corresponding author for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the Medical Research Council Policy on Data Sharing regarding scientific quality, ethical requirements and value for money, and is compliant with the NIHR policy on data sharing. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g., a protocol for a Cochrane systematic review, approved by a UK Research Ethics Committee or other similar, approved ethics review body. Participant identifiers will not be passed on to any third party.

Acknowledgements

The trial team would like to thank all the trial participants without whom this trial would not be possible. The authors would like to thank all site staff involved in recruitment, coordination and data collection for this trial. Special thanks are also given to the clinical, nursing, vaccination and

administrative teams at participating centres for their support in the conduct of the trial. The authors would like to acknowledge the contribution of the Oxford Vaccine Group to trial and documentation design. The authors would like to acknowledge the Data Monitoring and Safety Committee (DMSC) and Trial Steering Committee (TSC) for their support and oversight of the trial. The independent DMSC members are David Lewis (Chair), Krishnan Bhaskaran, Judith Breuer, Stephen JW Evans, Ian M Feavers, Hanna Nohynek, Mark Toshner and Paul Moss. The independent TSC members are Robert Read (Chair), Mary Ramsay, Claire Cameron and Paul J Turner. Nick Andrews is a non-independent member of the TSC. The authors would like to thank the Sponsor organisation, University Hospitals Bristol and Weston NHS Foundation Trust, and the National Immunisation Schedule Evaluation Consortium (NISEC). This trial was funded by the NIHR Policy Research Programme (PR-R17-0916-22001, NIHR203243).

References

1. COVID-19 vaccine surveillance report Week 36. Public Health England COVID-19 vaccine surveillance report - week 36 (publishing.service.gov.uk)
2. Decreased Influenza Activity During the COVID-19 Pandemic -United States, Austrailia, Chile, and South Africa, 2020. Centres for Disease Control and Prevention. Morbidity and Mortality Weekly Report 2020 69 (37): 1305-1309
3. Early advice on 2021 influenza vaccination. Australian Government, Department of Health Early advice on 2021 influenza vaccination | Australian Government Department of Health accessed 10th September 2021
4. Interim Clinical Consideration for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States. Centres for Disease Control and Prevention Interim Clinical Considerations for Use of COVID-19 Vaccines | CDC

5. Polack FP, Thomas SJ, Kitchin N et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020;**383(21):** 2603-2615
6. Ramasamy NM, Minassian AM, Ewer KJ et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled phase 2/3 trial. *Lancet* 2020; **396**:1979-93
7. French RW, Gurtman A, Rubino J et al., Randomized, controlled trial of a 13-valent pneumococcal conjugate vaccine administered concomitantly with an influenza vaccine in healthy adults. *Clin Vaccine Immunol* 2012; **19(8):**1296-303
8. Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. September 2007 Available at: Guidance for Industry: Toxicity Grading Scale for Health Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (fda.gov)
9. Mainstay C, Otter DA, Treibel TA et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. *Lancet*. 2021;**397**: 1057-1058 A
10. Hardelid P, Andrews N, Hoschler K et al., Assessment of baseline age-specific antibody prevalence and incidence of infection to novel influenza A/H1N1 2009. *Health Technology Assessment* 2011;**14**(55 Article 3)
11. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004;**25(2):** 143-56
12. Medical Dictionary for Regulatory activities meddra.org Accessed 21st September 2021
13. World Health Organization Guidelines on clinical evaluation of vaccines: regulatory expectations. 2016 https://www.who.int/biologicals/BS2287 Clinical guidelines final LINE NOs 20 July 2016.pdf Accessed 21st September 2021
14. Heath PT, Galiza EP, Baxter DN et al., Safety and Efficacy of NVX-CoV2371 Covid-19 Vaccine. *NEJM* 2021; doi: 10.1056/NEJMoa2107659. Online ahead of print.

15. Toback S, Galiza E, Cosgrove C et al., Safety, Immunogencity, and Efficacy of a COVID-19 Vaccine (NVX-CoV2373) Co-administered with Seasonal Influenza Vaccine https://www.medrxiv.org/content/10.1101/2021.06.09.21258556v1
16. Krammer F, Srivastava K, Alshammary H et al., Antibody Responses in Seropositive Persons after a Single Dose of SARS-CoV mRNA Vaccine. *NEJM* 2021; **384**: 1372-1374
17. Earle KA, Ambrosino DM, Fiore-Gartland A et al. Evidence for antibody as a protective correlate for COVID-19. *Vaccine* 2021; **32**:4423-4428
18. Song JY, Cheong HJ, Hyun HJ, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine and an MF59-adjuvanted influenza vaccine after concomitant vaccination in ≥60-year-old adults. *Vaccine* 2017; **35**: 313–20
19. Ofori-Anyinam O, Leroux-Roels G, Drame M et al., Immunogenicity and safety of an inactivated quadrivalent influenza vaccine co-administered with a 23-valent pneumococcal polysaccharide vaccine versus separate administration, in adults > 50 years of age: Results for a phase III, randomized, non-inferiority trial Vaccine. 2017; **35(46)**: 6321-6328
20. Sadrangani M, Marchant A and Kollman TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. *Nature reviews Immunology* 2021; **21**: 475 – 484
21. Emary KRW, Golubchik T, Aley PK et al., Efficacy of ChAdOx1-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *Lancet* 2021; **397**:1351-1362

Research in context

Evidence before this study

Concomitant administration of age-appropriate influenza vaccine and first dose of a novel subunit COVID-19 vaccine has been shown to have similar reactogenicity profiles to administration of the COVID-19 vaccine alone. However, concomitant administration resulted in a reduction in the anti-Spike IgG concentration response to COVID-19 vaccine compared to COVID-19 vaccination alone, but with no impact on efficacy. Data on concomitant administration of other types of COVID-19 vaccine and influenza vaccine are needed to inform public health policy in the UK.

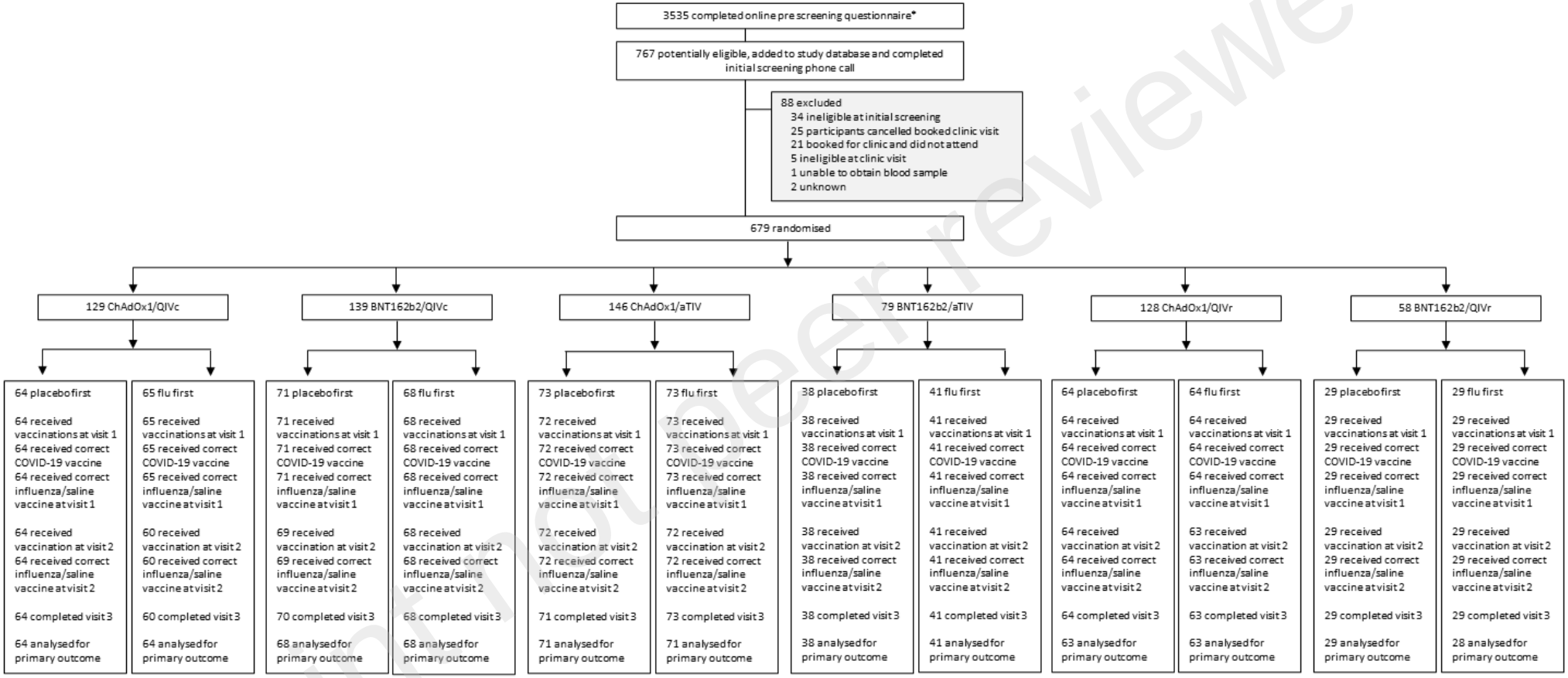
Added value of this study

This trial presents data to support the concomitant administration of viral vector and mRNA COVID-19 vaccines with age-appropriate inactivated, influenza vaccines. We show that concomitant vaccination is possible as it raises no safety concerns, most systemic reactions are mild or moderate and the immune response is not adversely affected.

Implications of all the available evidence

These data will inform public health policy in the UK relating to seasonal influenza vaccine delivery, alongside COVID-19 vaccination in adults. Concomitant vaccination will reduce the burden on healthcare services and may support public vaccine uptake.

Figure 1 Participant flow



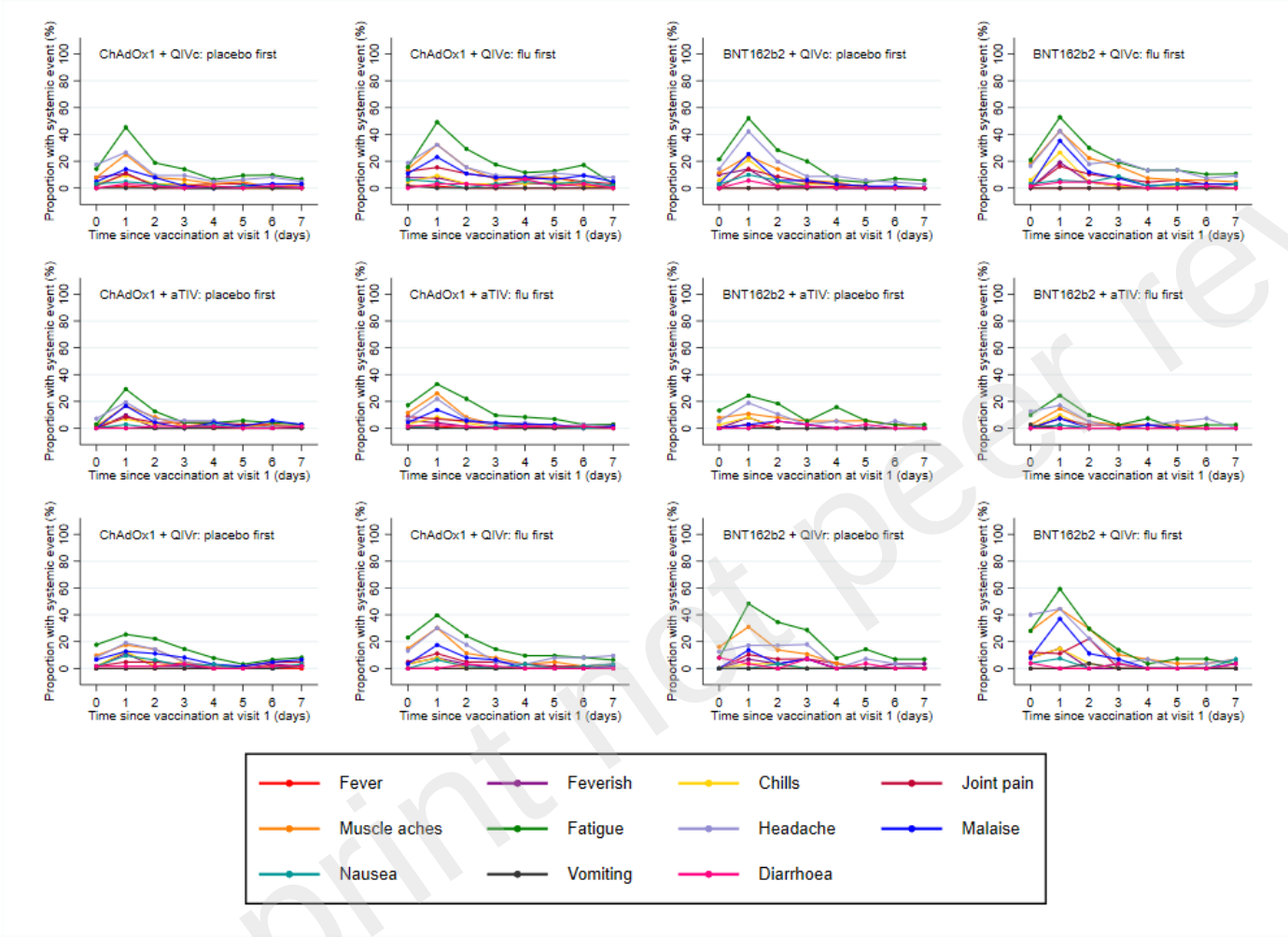
* Pre-screening questionnaire data not available for one site who recruited 3 participants. Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Table 1 Participant demographics

	ChAdOx1 + QIVc		BNT162b2 + QIVc		ChAdOx1 + aTIV		BNT162b2 + aTIV		ChAdOx1 + QIVr		BNT162b2 + QIVr	
	Placebo first (n=64)	Flu first (n=65)	Placebo first (n=71)	Flu first (n=68)	Placebo first (n=73)	Flu first (n=73)	Placebo first (n=38)	Flu first (n=41)	Placebo first (n=64)	Flu first (n=64)	Placebo first (n=29)	Flu first (n=29)
Age at screening (years)^	54 (43, 61)	52 (40, 57)	47 (34, 58)	48 (35, 60)	71 (69, 72)	69 (67, 72)	68 (67, 70)	68 (67, 70)	52 (44, 60)	56 (51, 60)	39 (33, 47)	42 (31, 53)
Female	38/64 (59%)	43/65 (66%)	48/71 (68%)	51/68 (75%)	31/73 (42%)	44/73 (60%)	14/38 (37%)	24/41 (59%)	37/64 (58%)	34/64 (53%)	15/29 (52%)	18/29 (62%)
BMI	27 (24, 29)	28 (25, 35)	27 (23, 34)	27 (24, 31)	27 (24, 30)	28 (26, 32)	28 (25, 31)	28 (26, 31)	29 (24, 33)	31 (26, 37)	26 (23, 29)	27 (25, 29)
Ethnicity												
English/Welsh/Scottish/Northern Irish/British	57/64 (89%)	54/65 (83%)	65/71 (92%)	60/68 (88%)	70/73 (96%)	71/73 (97%)	38/38 (100%)	39/41 (95%)	59/64 (92%)	64/64 (100%)	25/29 (86%)	25/29 (86%)
White Irish	2/64 (3%)	2/65 (3%)	2/71 (3%)	0/68 (0%)	1/73 (1%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Any other White background	3/64 (5%)	2/65 (3%)	2/71 (3%)	3/68 (4%)	1/73 (1%)	1/73 (1%)	0/38 (0%)	2/41 (5%)	1/64 (2%)	0/64 (0%)	2/29 (7%)	3/29 (10%)
White and Asian	0/64 (0%)	1/65 (2%)	0/71 (0%)	0/68 (0%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	1/64 (2%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Any other Mixed/Multiple ethnic background	0/64 (0%)	3/65 (5%)	1/71 (1%)	2/68 (3%)	1/73 (1%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Indian	1/64 (2%)	3/65 (5%)	0/71 (0%)	2/68 (3%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	1/29 (3%)	1/29 (3%)
Pakistani	1/64 (2%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	1/64 (2%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Chinese	0/64 (0%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	1/64 (2%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Any other ethnic group	0/64 (0%)	0/65 (0%)	0/71 (0%)	1/68 (1%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	1/64 (2%)	0/64 (0%)	1/29 (3%)	0/29 (0%)
Prefers not to give	0/64 (0%)	0/65 (0%)	1/71 (1%)	0/68 (0%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Occupation												
Employed - healthcare worker	15/64 (23%)	18/65 (28%)	19/71 (27%)	21/68 (31%)	0/73 (0%)	0/73 (0%)	1/38 (3%)	0/41 (0%)	3/64 (5%)	3/64 (5%)	5/29 (17%)	1/29 (3%)
Employed - other	30/64 (47%)	34/65 (52%)	35/71 (49%)	33/68 (49%)	4/73 (5%)	6/73 (8%)	7/38 (18%)	4/41 (10%)	39/64 (61%)	43/64 (67%)	18/29 (62%)	22/29 (76%)
Unemployed	4/64 (6%)	3/65 (5%)	3/71 (4%)	2/68 (3%)	0/73 (0%)	0/73 (0%)	1/38 (3%)	0/41 (0%)	3/64 (5%)	3/64 (5%)	3/29 (10%)	2/29 (7%)
Student	2/64 (3%)	0/65 (0%)	4/71 (6%)	3/68 (4%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	5/64 (8%)	0/64 (0%)	2/29 (7%)	2/29 (7%)
Retired	13/64 (20%)	10/65 (15%)	10/71 (14%)	9/68 (13%)	69/73 (95%)	67/73 (92%)	29/38 (76%)	37/41 (90%)	14/64 (22%)	15/64 (23%)	1/29 (3%)	2/29 (7%)
Participant received influenza vaccination in winter 2020/21 programme	48/64 (75%)	48/65 (74%)	52/71 (73%)	55/68 (81%)	72/73 (99%)	70/73 (96%)	35/38 (92%)	40/41 (98%)	41/64 (64%)	52/64 (81%)	22/29 (76%)	13/29 (45%)

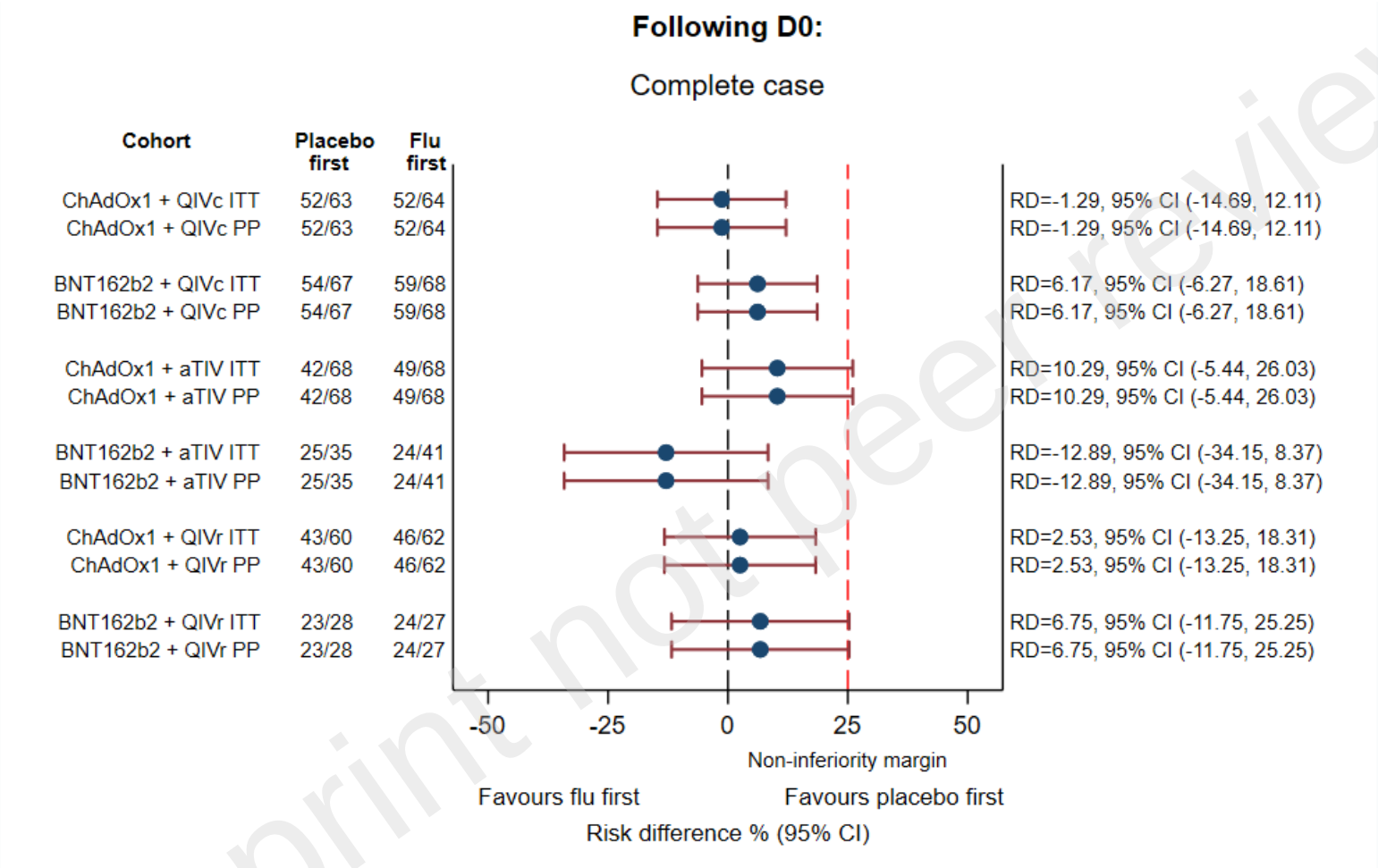
Data are presented as n/N (%) or median (IQR). ^ Age is collected as years, months. Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Figure 2 Seven-day profiles of systemic adverse reactions following D0



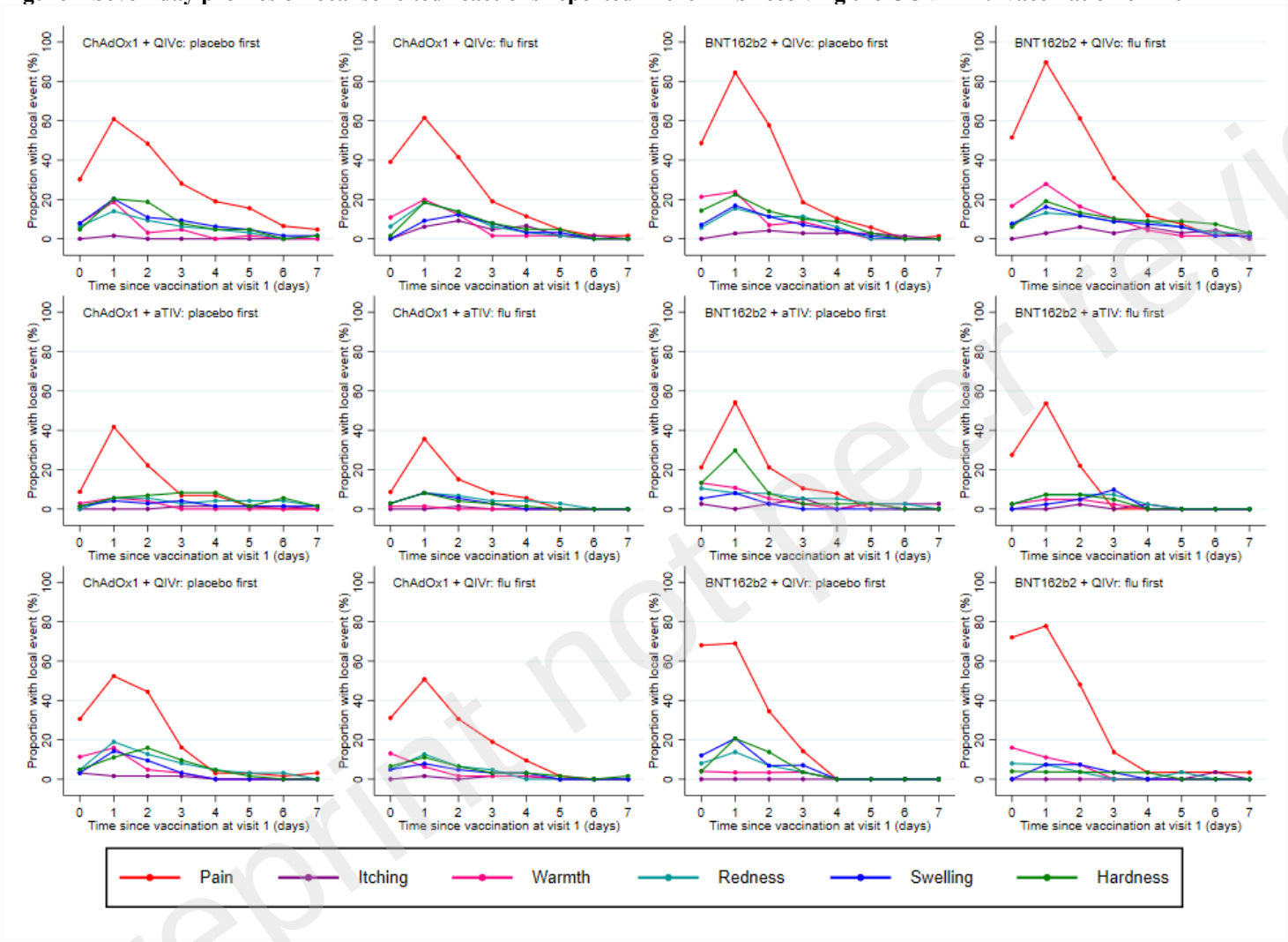
Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Figure 3 Comparison of the number of participants reporting one or more solicited systemic adverse reaction in the 7 days following second COVID vaccination plus influenza or placebo: complete case analysis



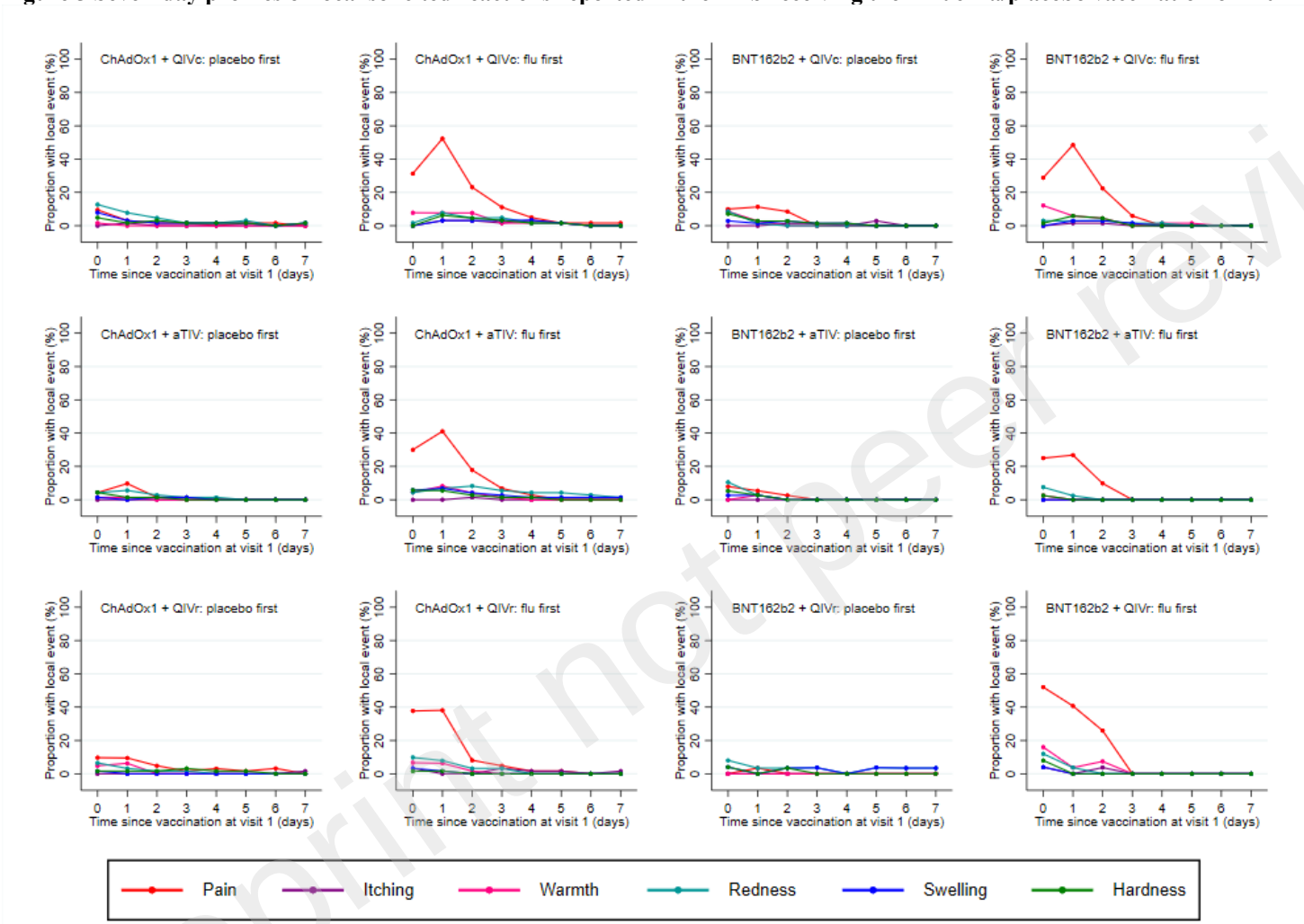
Data are number of participants experiencing one or more solicited systemic event in the 7 days following second COVID-19 vaccination / number of participants with the primary outcome in each group for each cohort. Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0. ITT = intention to treat. PP = per-protocol. RD = risk difference. CI = confidence interval.

Figure 4 Seven-day profiles of local solicited reactions reported in the limb receiving the COVID-19 vaccination on D0



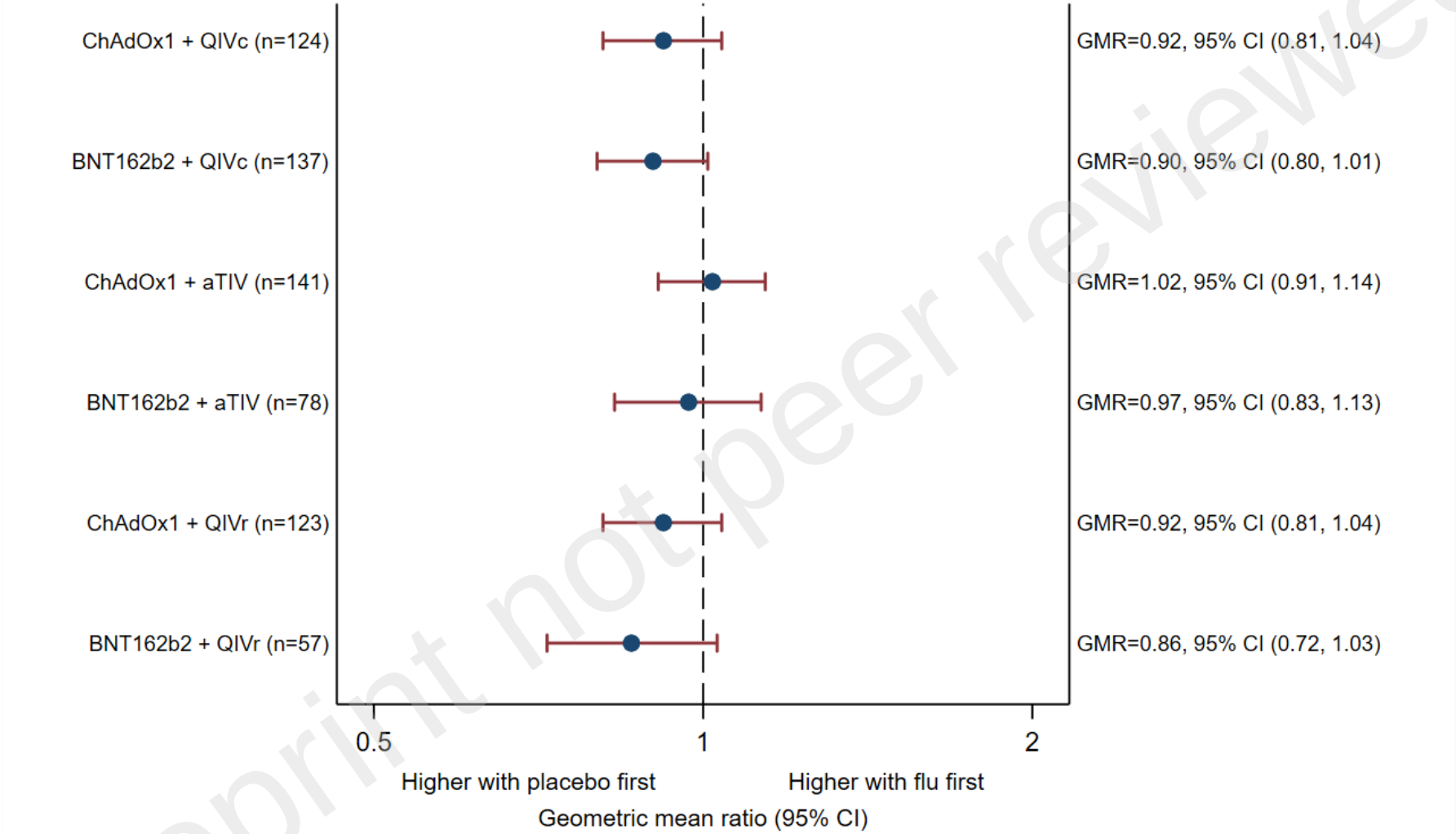
Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Figure 5 Seven-day profiles of local solicited reactions reported in the limb receiving the influenza/placebo vaccination on D0



Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Figure 6 Anti-S IgG GMT ratio between COVID-19 vaccine given with or without influenza vaccine



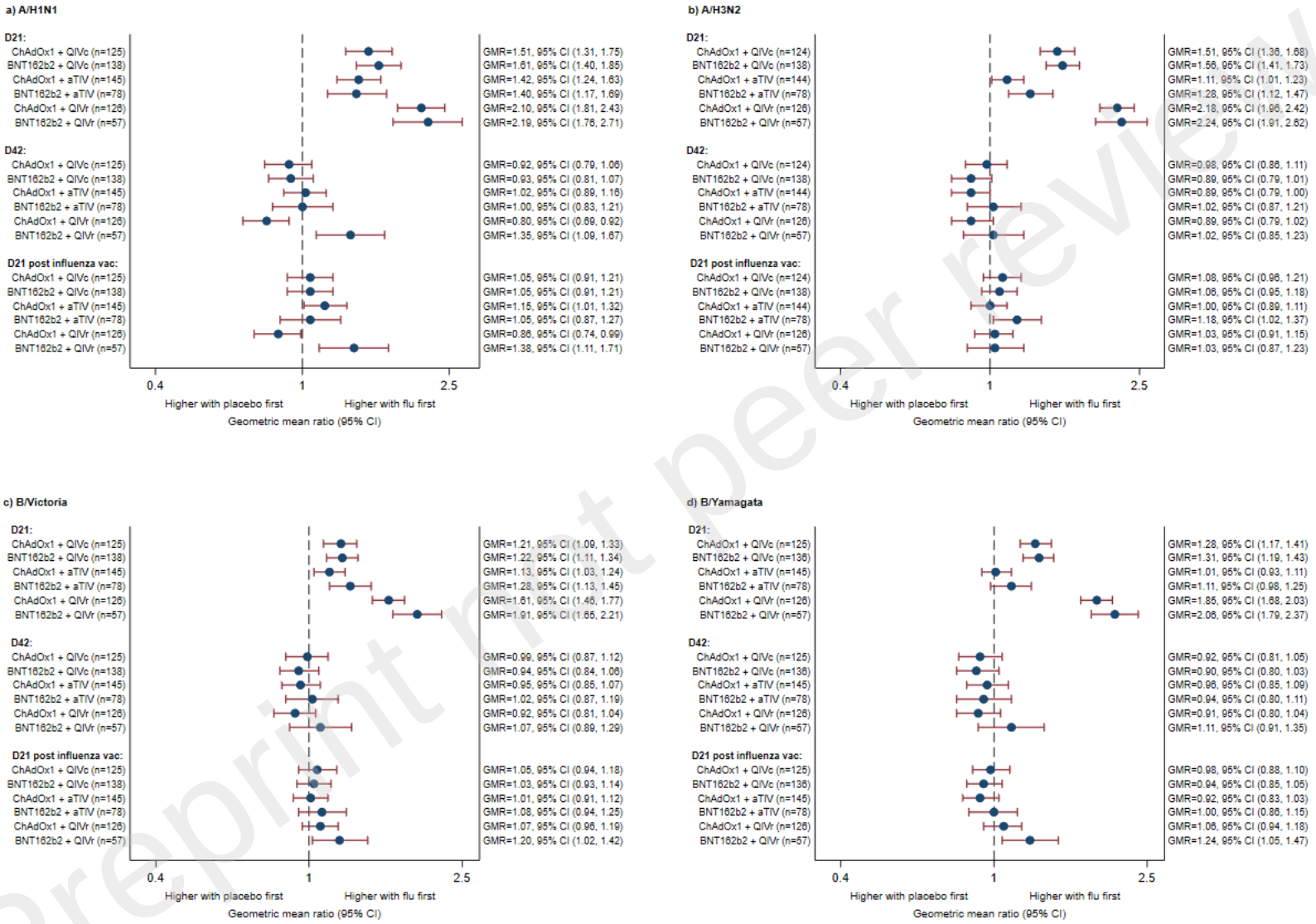
Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0. GMR=geometric mean ratio. CI=confidence interval.

Table 2 ECLIA geometric mean and seroconversion rates for anti-spike protein immunoglobulins

	ChAdOx1 + QIVc		BNT162b2 + QIVc		ChAdOx1 + aTIV		BNT162b2 + aTIV		ChAdOx1 + QIVr		BNT162b2 + QIVr	
	Placebo first (n=64)	**Flu first (n=65)**	**Placebo first (n=71)**	**Flu first (n=68)**	**Placebo first (n=73)**	**Flu first (n=73)**	**Placebo first (n=38)**	**Flu first (n=41)**	**Placebo first (n=64)**	**Flu first (n=64)**	**Placebo first (n=29)**	**Flu first (n=29)**
GMU, Anti-S IgG												
Visit 1, D0	5.3 (4.5, 6.2)	5.5 (4.7, 6.5)	7.3 (6.1, 8.7)	6.9 (5.5, 8.6)	4.4 (3.8, 5.2) *	4.8 (4.0, 5.8)	4.9 (3.8, 6.5)	5.1 (4.2, 6.1) *	6.0 (4.8, 7.5) *	5.2 (4.2, 6.3) ^	7.5 (5.3, 10.6) *	6.1 (4.3, 8.9)
Visit 2, D21	19.4 (17.1, 22.0)	18.1 (16.6, 19.7) ×	52.9 (49.2, 56.8) ^	47.1 (42.5, 52.2)	19.2 (17.3, 21.3) ^	19.9 (18.0, 22.0) *	45.5 (40.1, 51.6)	44.8 (39.9, 50.3)	23.3 (20.7, 26.3) *	19.9 (17.6, 22.5) *	50.0 (43.8, 57.0) *	40.6 (34.4, 48.0)
SCR												
Anti-S IgG	53/64 (83%)	49/60 (82%)	64/69 (93%)	63/68 (93%)	64/69 (93%)	64/72 (89%)	37/38 (97%)	40/40 (100%)	49/62 (79%)	56/61 (92%)	25/28 (89%)	26/29 (90%)

Data are presented as GMU (95% CI) or n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0. GMU=Geometric mean unit. SCR=Seroconversion rate. CI=confidence interval. * 1 participant with missing data, ^ 2 participants with missing data, × 5 participants with missing data.

Figure 7 HAI influenza geometric mean ratios



Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0. GMR = geometric mean ratio. CI = confidence interval.

Table 3 Haemagglutination inhibition assay geometric mean titre and seroconversion rates for influenza strains

	ChAdOx1 + QIVc		BNT162b2 + QIVc		ChAdOx1 + aTIV		BNT162b2 + aTIV		ChAdOx1 + QIVr		BNT162b2 + QIVr	
	Placebo first (n=64)	Flu first (n=65)	Placebo first (n=71)	Flu first (n=68)	Placebo first (n=73)	Flu first (n=73)	Placebo first (n=38)	Flu first (n=41)	Placebo first (n=64)	Flu first (n=64)	Placebo first (n=29)	Flu first (n=29)
GMT, A/H1N1												
Visit 1, D0	4.4 (3.7, 5.2)	3.9 (3.3, 4.5)	4.4 (3.7, 5.1)	4.6 (4.0, 5.3)	4.1 (3.5, 4.7)	3.8 (3.3, 4.4)	4.6 (3.7, 5.6)	5.2 (4.3, 6.2) *	4.2 (3.6, 4.9)	4.1 (3.5, 4.9) ^	5.3 (4.1, 6.8) *	4.2 (3.1, 5.6)
Visit 2, D21	4.2 (3.6, 4.9)	6.1 (5.3, 6.9) °	4.1 (3.5, 4.8) ^	6.7 (6.0, 7.5)	3.8 (3.4, 4.4) ^	5.2 (4.7, 5.8)	4.0 (3.2, 4.9)	5.9 (5.1, 6.8)	3.8 (3.3, 4.4)	7.9 (7.0, 8.9) *	5.7 (4.4, 7.3) *	10.9 (9.3, 12.7)
Visit 3, D42	6.1 (5.4, 6.9)	5.3 (4.6, 6.0) ▪	6.3 (5.5, 7.1) *	6.0 (5.4, 6.8) °	4.6 (4.1, 5.2) ^	4.6 (4.0, 5.2)	5.2 (4.4, 6.2) *	5.6 (4.9, 6.4)	9.3 (8.2, 10.4)	7.4 (6.4, 8.4) *	9.0 (7.3, 11.0) *	10.7 (9.0, 12.7)
GMT, A/H3N2												
Visit 1, D0	5.6 (4.9, 6.5)	6.0 (5.3, 6.8) *	5.8 (5.1, 6.7)	6.1 (5.4, 6.9)	6.2 (5.5, 7.0) *	5.6 (4.9, 6.3)	6.1 (5.2, 7.2)	6.5 (5.5, 7.7) *	4.9 (4.3, 5.6)	5.1 (4.5, 5.7) ^	5.7 (4.5, 7.3) *	5.9 (4.9, 7.1)
Visit 2, D21	5.3 (4.6, 6.0)	8.2 (7.5, 9.1) ~	5.4 (4.7, 6.1) ^	8.5 (7.7, 9.4)	6.0 (5.4, 6.7) ^	6.3 (5.7, 6.9)	5.8 (5.0, 6.7)	7.5 (6.7, 8.5)	4.5 (4.0, 5.0)	10.0 (9.1, 11.0) *	5.5 (4.5, 6.7) *	12.6 (11.3, 14.0)
Visit 3, D42	7.4 (6.7, 8.2)	7.4 (6.7, 8.1) ×	7.9 (7.2, 8.7) *	7.2 (6.5, 7.9) °	6.7 (6.0, 7.4) ^	5.6 (5.1, 6.2)	6.3 (5.4, 7.3) *	6.6 (5.8, 7.4)	9.5 (8.5, 10.6)	8.8 (7.8, 9.9) *	12.0 (10.8, 13.4) *	12.5 (11.0, 14.1)
GMT, B/Victoria												
Visit 1, D0	2.4 (2.1, 2.7)	2.2 (1.9, 2.5)	2.1 (1.8, 2.4)	2.1 (1.9, 2.4)	1.8 (1.7, 2.0)	1.9 (1.8, 2.1)	1.9 (1.6, 2.2)	1.8 (1.6, 2.1) *	2.3 (2.0, 2.6)	2.4 (2.1, 2.7) ^	1.9 (1.6, 2.2) *	1.7 (1.5, 1.9)
Visit 2, D21	2.4 (2.1, 2.8)	2.7 (2.4, 3.2) °	2.0 (1.8, 2.3) ^	2.5 (2.2, 2.9)	1.9 (1.7, 2.1) ^	2.3 (2.1, 2.6)	1.9 (1.7, 2.2)	2.4 (2.1, 2.7)	2.2 (2.0, 2.4)	3.7 (3.2, 4.2) *	1.9 (1.6, 2.2) *	3.3 (2.6, 4.1)
Visit 3, D42	2.8 (2.4, 3.2)	2.6 (2.2, 3.0) ▪	2.4 (2.1, 2.7) *	2.4 (2.1, 2.7) °	2.1 (1.9, 2.4) ^	2.2 (2.0, 2.4)	2.3 (2.0, 2.6) *	2.2 (2.0, 2.5)	3.3 (2.8, 3.8)	3.1 (2.7, 3.5) *	3.0 (2.5, 3.6) *	2.9 (2.4, 3.6)
GMT, B/Yamagata												
Visit 1, D0	2.9 (2.5, 3.3)	2.8 (2.5, 3.1)	2.9 (2.5, 3.3)	3.1 (2.7, 3.5)	2.2 (2.0, 2.4)	2.1 (1.9, 2.4)	2.1 (1.8, 2.5)	2.2 (1.9, 2.6) *	2.8 (2.5, 3.2)	2.8 (2.4, 3.2) ^	3.0 (2.5, 3.7) *	2.7 (2.2, 3.3)
Visit 2, D21	2.9 (2.5, 3.3)	3.6 (3.2, 4.1) °	2.8 (2.4, 3.3) ^	3.8 (3.4, 4.3)	2.3 (2.0, 2.5) ^	2.3 (2.0, 2.6)	2.1 (1.8, 2.5)	2.5 (2.1, 2.9)	2.7 (2.3, 3.0)	4.9 (4.3, 5.5) *	3.0 (2.4, 3.7) *	5.6 (4.8, 6.6)
Visit 3, D42	3.8 (3.4, 4.3)	3.4 (3.0, 3.9) ▪	3.9 (3.4, 4.5) *	3.7 (3.2, 4.2) °	2.4 (2.2, 2.8) ^	2.4 (2.1, 2.7)	2.4 (2.0, 2.8) *	2.3 (2.0, 2.7)	4.7 (4.1, 5.3)	4.2 (3.7, 4.7) *	5.0 (4.2, 5.9) *	5.0 (4.2, 5.9)
SCR												
Influenza A/H1N1	17/64 (27%)	20/61 (33%)	19/70 (27%)	22/68 (32%)	7/71 (10%)	16/73 (22%)	2/37 (5%)	6/40 (15%)	40/64 (63%)	28/61 (46%)	11/28 (39%)	19/29 (66%)
Influenza A/H3N2	14/64 (22%)	21/60 (35%)	23/70 (33%)	20/68 (29%)	6/70 (9%)	8/73 (11%)	3/37 (8%)	5/40 (13%)	37/64 (58%)	41/61 (67%)	17/28 (61%)	21/29 (72%)
Influenza B/Victoria	4/64 (6%)	7/61 (11%)	2/70 (3%)	6/68 (9%)	2/71 (3%)	1/73 (1%)	1/37 (3%)	1/40 (3%)	16/64 (25%)	13/61 (21%)	6/28 (21%)	11/29 (38%)
Influenza B/Yamagata	13/64 (20%)	9/61 (15%)	9/68 (13%)	9/68 (13%)	2/71 (3%)	1/73 (1%)	1/37 (3%)	0/40 (0%)	22/64 (34%)	23/61 (38%)	7/28 (25%)	17/29 (59%)

Titre data are presented as GMT (95% CI) and seroconversion data are presented as n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0. GMT=Geometric mean titre. SCR=Seroconversion rate. CI=confidence interval. *1 participant with missing data, ^ 2 participants with missing data, ° 4 participants with missing data, ~ 5 participants with missing data, ▪ 6 participants with missing data and × 7 participants with missing data.