Safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults in the UK (ComFluCOV): a multicentre, randomised, controlled, phase 4 trial

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

Summary

Background Concomitant administration of COVID-19 and influenza vaccines could reduce burden on health-care systems. We aimed to assess the safety of concomitant administration of ChAdOx1 or BNT162b2 plus an age-appropriate influenza vaccine.

Methods In this multicentre, randomised, controlled, phase 4 trial, adults in receipt of a single dose of ChAdOx1 or BNT162b2 were enrolled at 12 UK sites and randomly assigned (1:1) to receive concomitant administration of either an age-appropriate influenza vaccine or placebo alongside their second dose of COVID-19 vaccine. 3 weeks later the group who received placebo received the influenza vaccine, and vice versa. Participants were followed up for 6 weeks. The influenza vaccines were three seasonal, inactivated vaccines (trivalent, MF59C adjuvanted or a cellular or recombinant quadrivalent vaccine). Participants and investigators were masked to the allocation. The primary endpoint was one or more participant-reported solicited systemic reactions in the 7 days after first trial vaccination(s), with a difference of less than 25% considered non-inferior. Analyses were done on an intention-to-treat basis. Local and unsolicited systemic reactions and humoral responses were also assessed. The trial is registered with ISRCTN, ISRCTN14391248.

Findings Between April 1 and June 26, 2021, 679 participants were recruited to one of six cohorts, as follows: 129 ChAdOx1 plus cellular quadrivalent influenza vaccine, 139 BNT162b2 plus cellular quadrivalent influenza vaccine, 146 ChAdOx1 plus MF59C adjuvanted, trivalent influenza vaccine, 79 BNT162b2 plus MF59C adjuvanted, trivalent influenza vaccine, 128 ChAdOx1 plus recombinant quadrivalent influenza vaccine, and 58 BNT162b2 plus recombinant quadrivalent influenza vaccine. 340 participants were assigned to concomitant administration of influenza and a second dose of COVID-19 vaccine at day 0 followed by placebo at day 21, and 339 participants were randomly assigned to concomitant administration of placebo and a second dose of COVID-19 vaccine at day 0 followed by influenza vaccine at day 21. Non-inferiority was indicated in four cohorts, as follows: ChAdOx1 plus cellular quadrivalent influenza vaccine (risk difference for influenza vaccine minus placebo –1·29%, 95% CI –14·7 to 12·1), BNT162b2 plus cellular quadrivalent influenza vaccine (6·17%, –6·27 to 18·6), BNT162b2 plus MF59C adjuvanted, trivalent influenza vaccine (–12·9%, –34·2 to 8·37), and ChAdOx1 plus recombinant quadrivalent influenza vaccine (2·53%, –13·3 to 18·3). In the other two cohorts, the upper limit of the 95% CI exceeded the 0·25 non-inferiority margin (ChAdOx1 plus MF59C adjuvanted, trivalent influenza vaccine 10·3%, –5·44 to 26·0; BNT162b2 plus recombinant quadrivalent influenza vaccine 6·75%, –11·8 to 25·3). Most systemic reactions to vaccination were mild or moderate. Rates of local and unsolicited systemic reactions were similar between the randomly assigned 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 with ChAdOx1 or BNT162b2 plus an age-appropriate influenza vaccine raises no safety concerns and preserves antibody responses to both vaccines. Concomitant vaccination with both COVID-19 and influenza vaccines over the next immunisation season should reduce the burden on health-care services for vaccine delivery, allowing for timely vaccine administration and protection from COVID-19 and influenza for those in need.

Funding National Institute for Health Research Policy Research Programme

Published **Online** November 11, 2021 https://doi.org/10.1016/S0140-6736(21)02329-1

University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK (R Lazarus DPhil, A Middleditch FRCA, L McCullagh BPharmS); **Bristol Trials Centre, University of Bristol, Bristol, UK** (S Baos PhD, H Cappel-Porter MMath, M Clout BSc, L Culliford PhD, R A Harris MSc, D Hutton BSc, K Joyce MSc, R Thirard MSc, R Todd MSc, Prof 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, North Coast Medical, Newquay, UK** (N Jacobsen MRCGP); **Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK** (R Kaminski MBBS); **University College Hospitals NHS Foundation Trust, London, UK** (Prof 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, Atlantic Medical, Penzance, UK** (J Ryan BM); **Oxford Vaccine Group,**

Department of Paediatrics, University of Oxford, Oxford, UK (M D Snape MD)**; Oxford NIHR—Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK** (M D Snape)**; Royal Cornwall Hospitals NHS Trust, Truro, UK** (D Tucker DPhil)**; Division of Epidemiology and Public Health, University of Nottingham School of Medicine, Nottingham, UK** (Prof J S Nguyen-Van-Tam DM)**; Bristol Vaccine Centre, Bristol Medical School, Bristol Population Health Sciences and School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK** (Prof A Finn PhD)

Correspondence to:
Dr Rajeka Lazarus, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol BS2 8HW, UK
rajeka.lazarus@uhbw.nhs.uk

Research in context

Evidence before this study

We did a search of PubMed from inception to Sept 10, 2021, restricted to papers published in English. Search terms included "influenza vaccine", "COVID-19 vaccine", "concomitant", and "co-administration". No published studies relating to influenza and COVID-19 vaccine co-administration were found. We were aware of one study published as a preprint. In this preprint, concomitant administration of an age-appropriate influenza vaccine and the first dose of a novel subunit COVID-19 vaccine was 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 with COVID-19 vaccination alone, but with no effect 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 second doses of the ChAdOx1 and BNT162b2 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 second and potentially later doses of both ChAdOx1 and BNT162b2 COVID-19 vaccines in adults. Concomitant vaccination might reduce the burden on health-care services and could support public vaccine uptake.

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 health-care 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, could lessen the burden on health-care 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 vaccines 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 insufficient data to inform concomitant vaccination. It is necessary to establish whether concomitant vaccination is safe and whether this would increase reactogenicity rates, as increased rates might negatively influence vaccine uptake—this is particularly important as the most widely used COVID-19 vaccines produce relatively high rates of expected systemic adverse reactions, such as fever, compared with other vaccines.[5,6] Additionally, in some cases concomitant vaccination alters the immunogenicity of administered vaccines.[7]

In this study, we investigated the safety and immunogenicity of concomitant administration of a COVID-19 vaccine (either an adenovirus viral vector COVID-19 vaccine, ChAdOx1, or an RNA COVID-19 vaccine, BNT162b2) with an inactivated influenza vaccine (either an MF59C adjuvanted, trivalent vaccine or a cellular or recombinant quadrivalent vaccine).

See Online for appendix

Methods

Study design and participants

ComFluCOV was a multicentre, randomised, controlled, phase 4 trial with masking, across 12 UK National Health Service (NHS) sites (appendix p 35) across the UK. The trial was designed to investigate concomitant administration of second doses of two COVID-19 vaccines (ChAdOx1; Oxford–AstraZeneca and BNT162b2; Pfizer–BioNTech) with three influenza vaccines (MF59C adjuvanted, trivalent vaccine, cellular quadrivalent vaccine, and recombinant quadrivalent vaccine). Participants were recruited into one of six cohorts defined by the six COVID-19 and influenza vaccine combinations.

The trial was done 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 (Bristol, UK). The protocol is included in the appendix (pp 3–33).

Two substantial amendments were made to the study protocol. An influenza vaccine (recombinant quadrivalent vaccine) was added after the start of recruitment at the request of the UK 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 April 8, 2021, in relation to incidents of

thromboembolic events after vaccination with ChAdOx1, recruitment of those aged under 30 years in receipt of ChAdOx1 was temporarily suspended on April 9, 2021, and then resumed on April 14, 2021. Exclusion criteria were updated to exclude participants at risk of thrombotic events.

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 years and older and had received a single dose of either ChAdOx1 in the preceding 56–90 days or BNT162b2 in the preceding 28–90 days, in line with UK recommendations. Volunteers had to agree to their general practitioner being contacted and to refrain from blood donation in the 7 days after vaccination, and needed access to an electronic device. Volunteers were ineligible if they had received any other vaccine in the 30 days before recruitment or had received immunoglobulins or blood products in the previous 3 months, had a history of allergy or reactions to any component of the trial vaccines, had a bleeding disorder or continuous use of anticoagulants, suspected or known drug or alcohol dependence, or a progressive neurological disorder. Partway through the trial, the exclusion criteria were updated to exclude volunteers at risk of thrombotic events, in line with UK recommendations. Participants with other comorbidities that made them eligible for routine influenza vaccine were included (appendix p 38). Full inclusion and exclusion criteria are provided in the appendix (pp 10–11). Written informed consent was received from all participants at the first trial visit (day 0).

Randomisation and masking

At day 0, participants were randomly assigned (1:1) 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, with blocks of varying size. The sequence was generated by a statistician who was 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 not masked.

Procedures

At day 0, eligible volunteers who consented to take part were randomly assigned and received the trial vaccinations (ie, 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 days and 28 days later (day 21), those who received an influenza vaccine at day 0 received a placebo injection and vice versa. Participants attended a final trial visit at between 42 days and 56 days (day 42) for safety assessments. Participants provided up to 10 mL of sera and up to 2 mL of saliva at all three trial visits.

ChAdOx1 (0·5 mL 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 (0·3 mL 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 years and older received FluAd (Seqirus UK; Maidenhead, UK) a trivalent, surface antigen inactivated influenza vaccine adjuvanted with MF59C. Adults younger than 65 years received one of two quadrivalent influenza vaccines: Flucelvax (Seqirus UK), a surface antigen, inactivated vaccine prepared in cell culture, or Flublok (Sanofi; Paris, France) a recombinant influenza vaccine. 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 WHO recommendations for the northern hemisphere. The influenza vaccines were provided in commercially available pre-filled syringes as a 0·5 mL dose. Commercially available 0·5 mL of sodium chloride injection BP 0·9% was used as a saline placebo. Influenza vaccine(s) available at each participating site are shown in the appendix (p 35). Study sites only had one quadrivalent vaccine available; therefore the allocation was dependent on enrolment site.

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 the influenza vaccine or 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 min after vaccination.

Outcomes

The primary outcome was one or more solicited systemic reactions in the 7 days after vaccination at day 0. The solicited systemic reactions were fever (body temperature >38°C, with or without symptoms), feverishness (feeling hot, sweating, and shivery, with or without an elevated body temperature), 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, and 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 7 days after vaccination at day 0 and day 21; tenderness was not captured explicitly but was covered under pain), solicited systemic reactions (as listed for the primary outcome) in the 7 days after vaccination at day 21, and unsolicited adverse events for the whole trial period. Adverse events included serious adverse events, medically attended adverse events, and adverse events of special interest. The local research team reviewed diary entries daily to assess adverse events for severity, determined in accordance with US 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 spike-protein immunoglobulin concentration in serum samples collected at day 0 and day 21 analysed using the Elecsys anti-SARS-CoV-2 S electrochemiluminescence immunoassay (Roche; Basel, Switzerland)[9] and haemagglutinin antibody inhibition in sera collected at day 0, day 21, and day 42 against the four strains of influenza vaccine virus (H1N1, H3N2, Yamagata, and Victoria) contained in the 2020–21 season vaccines using a validated assay.[10] To maintain masking, all serum samples, including from those who received the trivalent vaccine, were tested for all four influenza strains. All assays were done at Porton Down, UK by Public Health England (PHE).

Other immunological outcomes, which will be reported in a subsequent publication, included measurement of neutralising antibodies against SARS-CoV-2 from serum samples at day 0 and day 21 to assess the response to a 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 writing.

Qualitative outcomes included days of work lost (if employed), acceptability to participants of future concomitant vaccine administration, and an assessment of the success of participant masking using the Bang Blinding Index[11] completed at day 42. Participants were asked to indicate which group they thought they were allocated to (influenza first, placebo first, or did not know). The index ranges from –1 to 1, with 0 indicating successful blinding. A positive value indicates more correct guesses than expected by chance and gives an indication of the proportion of participants unblinded.

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 with COVID-19 vaccine alone, assuming a primary outcome frequency of 50% and a non-inferiority margin of 25%. The non-inferiority margin was agreed by the clinical members of the study team, and was both acceptable and requiring a sample size that was achievable in the timescale for the study.

Analyses were done on an intention-to-treat basis. A per-protocol analysis, and sensitivity analyses imputing missing outcome data were also done for the primary outcome (appendix p 26). Binary outcomes were compared using a generalised linear model, and risk differences and risk ratios 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 participant and trial site fitted as random effects (where estimable; see appendix p 26). Immunogenicity outcomes were transformed to the logarithmic scale (base 10) for analysis and results are presented as geometric mean ratios. Placebo injection at day 0 was used as the reference group.

Unsolicited adverse events were coded using version 23.1 of the Medical Dictionary for Regulatory Activities and summarised by severity and relationship to the trial vaccine. Seroconversion for anti-spike protein immunoglobulin concentration was defined as a 4-times increase in the Elecsys anti-SARS-CoV-2 S electrochemiluminescence immunoassay units from day 0 to day 21 and for haemagglutinin antibody inhibition titres seroconversion was defined as a post-vaccination titre of at least 32 if the baseline titre was less than eight and a 4-times 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% CI for the risk difference for the primary outcome of any solicited systemic reaction in the 7 days after concomitant vaccination at day 0 was less than 0·25 in both the intention-to-treat and per-protocol analyses.

Statistical analysis was done using STATA release 17. An independent data monitoring and safety committee reviewed trial safety data. The trial is registered with ISRCTN, ISRCTN14391248.

Role of the funding source

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

Results

Between April 1 and June 26, 2021, 679 participants were enrolled and randomly assigned—340 participants were assigned to concomitant administration of influenza and a second dose of COVID-19 vaccine at day 0 followed by placebo at day 21, and 339 participants were randomly assigned to concomitant administration of placebo and a second dose of COVID-19 vaccine at day 0 followed by influenza vaccine at day 21 (figure 1). For two of the cohorts—BNT162b2 plus MF59C adjuvanted, trivalent

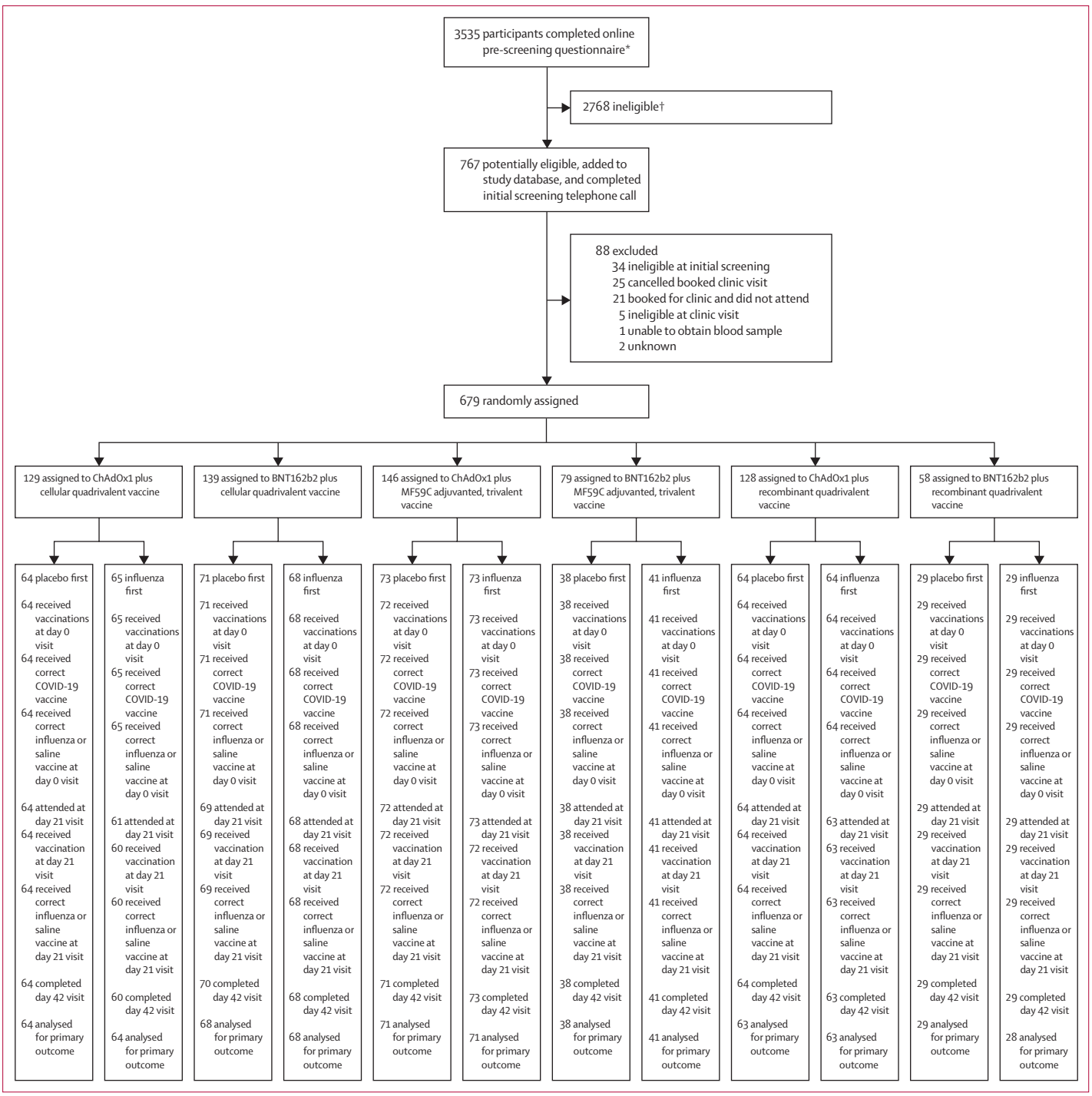

Figure 1: **Trial profile**

Placebo first indicates that COVID-19 vaccine alone was received at day 0. Influenza first indicates that concomitant COVID-19 and influenza vaccines were received at day 0. *Pre-screening questionnaire data were not available for one site that recruited three participants. †Ineligible on initial screening, unavailable on planned clinic dates, unable to contact, or cohort complete.

vaccine and BNT162b2 plus recombinant quadrivalent vaccine—fewer participants than planned were enrolled (79 [63%] of 126 and 58 [46%] of 126, respectively).

One participant was considered ineligible after randomisation because of 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 (appendix p 36). These participants were analysed according to the COVID-19 and influenza vaccines received. A further two

	ChAdOx1 plus cellular quadrivalent vaccine		BNT162b2 plus cellular quadrivalent vaccine		ChAdOx1 plus MF59C adjuvanted, trivalent vaccine		BNT162b2 plus MF59C adjuvanted, trivalent vaccine		ChAdOx1 plus recombinant quadrivalent vaccine		BNT162b2 plus recombinant quadrivalent vaccine	
	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)
Sex												
Female	38 (59%)	43 (66%)	48 (68%)	51 (75%)	31 (42%)	44 (60%)	14 (37%)	24 (59%)	37 (58%)	34 (53%)	15 (52%)	18 (62%)
Male	26 (41%)	22 (34%)	23 (32%)	17 (25%)	42 (58%)	29 (40%)	24 (63%)	17 (41%)	27 (42%)	30 (47%)	14 (48%)	11 (38%)
Body-mass index, kg/m²	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, or British	57 (89%)	54 (83%)	65 (92%)	60 (88%)	70 (96%)	71 (97%)	38 (100%)	39 (95%)	59 (92%)	64 (100%)	25 (86%)	25 (86%)
White Irish	2 (3%)	2 (3%)	2 (3%)	0	1 (1%)	0	0	0	0	0	0	0
Any other White background	3 (5%)	2 (3%)	2 (3%)	3 (4%)	1 (1%)	1 (1%)	0	2 (5%)	1 (2%)	0	2 (7%)	3 (10%)
White and Asian	0	1 (2%)	0	0	0	0	0	0	1 (2%)	0	0	0
Any other mixed or multiple ethnic background	0	3 (5%)	1 (1%)	2 (3%)	1 (1%)	1 (1%)	0	0	0	0	0	0
Indian	1 (2%)	3 (5%)	0	2 (3%)	0	0	0	0	0	0	1 (3%)	1 (3%)
Pakistani	1 (2%)	0	0	0	0	0	0	0	1 (2%)	0	0	0
Chinese	0	0	0	0	0	0	0	0	1 (2%)	0	0	0
Any other ethnic group	0	0	0	1 (1%)	0	0	0	0	1 (2%)	0	1 (3%)	0
Prefer not to give	0	0	1 (1%)	0	0	0	0	0	0	0	0	0
Occupation												
Employed—health-care worker	15 (23%)	18 (28%)	19 (27%)	21 (31%)	0	0	1 (3%)	0	3 (5%)	3 (5%)	5 (17%)	1 (3%)
Employed— other	30 (47%)	34 (52%)	35 (49%)	33 (49%)	4 (5%)	6 (8%)	7 (18%)	4 (10%)	39 (61%)	43 (67%)	18 (62%)	22 (76%)
Unemployed	4 (6%)	3 (5%)	3 (4%)	2 (3%)	0	0	1 (3%)	0	3 (5%)	3 (5%)	3 (10%)	2 (7%)
Student	2 (3%)	0	4 (6%)	3 (4%)	0	0	0	0	5 (8%)	0	2 (7%)	2 (7%)
Retired	13 (20%)	10 (15%)	10 (14%)	9 (13%)	69 (95%)	67 (92%)	29 (76%)	37 (90%)	14 (22%)	15 (23%)	1 (3%)	2 (7%)
Participant received influenza vaccination in winter 2020–21 programme	48 (75%)	48 (74%)	52 (73%)	55 (81%)	72 (99%)	70 (96%)	35 (92%)	40 (98%)	41 (64%)	52 (81%)	22 (76%)	13 (45%)

Data are median (IQR) or n (%). Placebo first indicates that COVID-19 vaccine alone was received at day 0. Flu first indicates that concomitant COVID-19 and influenza vaccines were received at day 0.

Table: **Participant demographics**

participants were randomly assigned using the correct cohort assignment, but received the wrong influenza vaccine at day 21; these participants were analysed according to the cohort they were randomly assigned to. The median time between the two vaccinations at day 0 was 0 min (IQR 0–1; range 0–176; appendix p 37). Ten (1%) participants did not receive a second trial injection at day 21 and nine (1%) did not attend at the day 42 visit.

Baseline characteristics were similar across the two randomly assigned groups in each cohort (table). The median age of participants by influenza vaccine type was 51 years (IQR 37–60) for those receiving the cellular quadrivalent vaccine, 52 years (41–59) for those receiving the recombinant quadrivalent vaccine, and 69 years (67–72) for those receiving the MF59C adjuvanted, trivalent vaccine. 397 (58%) of 679 participants were female and 627 (92%) were White British. No participants were known to be pregnant at the time of enrolment, but one participant reported that they were pregnant at the day 21 visit. In total, 548 (81%) of 679 participants had received an influenza vaccine in the 2020–21 season, with a higher percentage vaccinated in MF59C adjuvanted, trivalent vaccine cohorts (217 [96%] of 225 participants). Of those younger than 65 years, 85 (19%) of 454 participants were health-care workers. 276 (41%) of 679 participants were retired. A range of comorbidities associated with an indication for influenza vaccine were represented (appendix p 38).

Electronic participant diaries were well completed (appendix pp 39–40) and the primary outcome could be determined for 651 (96%) of 679 participants. 254 (77%) of 330 participants in the group that was randomly assigned

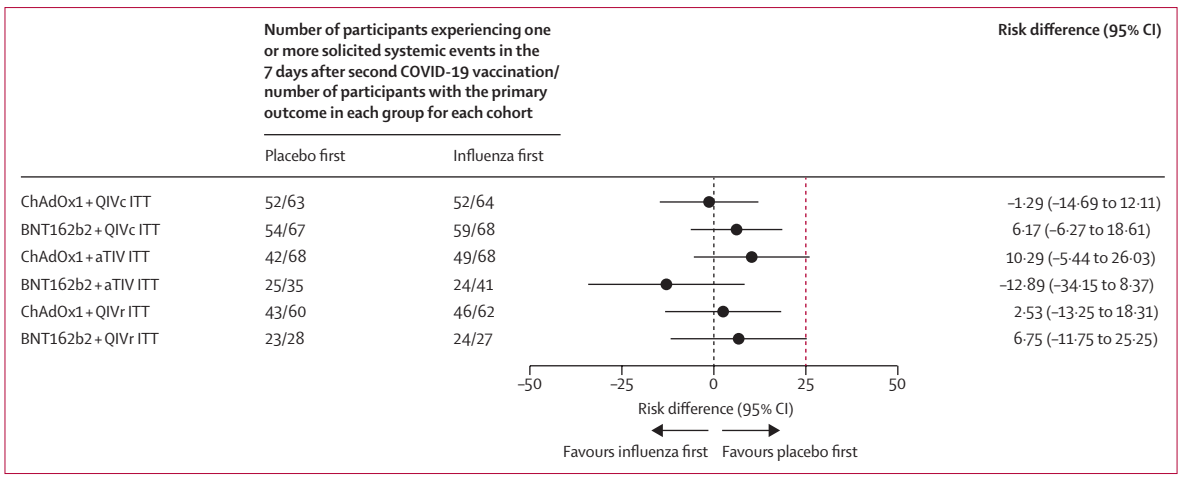

Figure 2: **Participants reporting one or more solicited systemic adverse reactions in the 7 days after second COVID vaccination plus influenza vaccination or placebo—complete case analysis**

Placebo first indicates that COVID-19 vaccine alone was received at day 0. Influenza first indicates that concomitant COVID-19 and influenza vaccines were received at day 0. QIVc=cellular quadrivalent vaccine. ITT=intention to treat. aTIV=MF59C adjuvanted, trivalent vaccine. QIVr=recombinant quadrivalent vaccine.

to concomitant COVID-19 and influenza vaccines at day 0 had one or more systemic solicited reactions over 7 days after vaccination compared with 239 (75%) of 321 participants in the group that was randomly assigned to COVID-19 vaccine alone at day 0, with fatigue the most commonly reported systemic reaction (appendix p 41). Concomitant administration of the two vaccines was found to be non-inferior to administration of the COVID-19 vaccine alone with respect to the primary outcome of any systemic adverse reaction in the 7 days after day 0 in four cohorts: ChAdOx1 plus cellular quadrivalent influenza vaccine (risk difference for influenza vaccine minus placebo –1·29%, 95% CI –14·7 to 12·1), BNT162b2 plus cellular quadrivalent influenza vaccine (6·17%, –6·27 to 18·6), BNT162b2 plus MF59C adjuvanted, trivalent influenza vaccine (–12·9%, –34·2 to 8·37), and ChAdOx1 plus recombinant quadrivalent influenza vaccine (2·53%, –13·3 to 18·3). In the other two cohorts, the upper limit of the 95% CI exceeded the 0·25 non-inferiority margin (ChAdOx1 plus MF59C adjuvanted, trivalent influenza vaccine 10·3%, –5·44 to 26·0; BNT162b2 plus recombinant quadrivalent influenza vaccine 6·75%, –11·8 to 25·3; figure 2; appendix p 42). The only major protocol deviation recorded was an ineligible participant who was randomly assigned in error with high blood pressure. This patient did not complete any diary entries. The per-protocol analyses are therefore identical to the intention-to-treat analyses. Risk ratios and results of the sensitivity analyses are shown in the appendix (pp 43–44). In all cohorts most systemic reactions were mild or moderate. 14 (5%) of 254 participants who reported one or more systemic reactions in the concomitant COVID-19 and influenza vaccine group reported at least one severe adverse reaction compared with six (3%) of 239 participants in the COVID-19 vaccine alone group. There were four severe systemic reactions (feverishness, chills, headache, and malaise) in the ChAdOx1 plus MF59C adjuvanted, trivalent influenza vaccine cohort, reported by two participant(s), both of whom received the MF59C adjuvanted, trivalent influenza vaccine at day 0, and three severe systemic reactions in the BNT162b2 plus recombinant quadrivalent vaccine cohort (two participants with fatigue and malaise in the group that received the placebo, and one participant with malaise in the group that received the recombinant quadrivalent vaccine at day 0; appendix pp 45–46). The proportion of participants who reported one or more systemic events after receiving either influenza vaccine or saline injection at day 21 was similar (appendix pp 47–53). The number of different systemic solicited reactions reported by each participant was similar in the two randomly assigned groups at both timepoints (appendix pp 47–48, 54).

555 (83%) of 665 participants reported at least one solicited local adverse reaction after vaccination at day 0 (282 [85%] of 331 participants in the concomitant COVID-19 and influenza vaccine group and 273 [82%] of 334 participants in the COVID-19 vaccine alone group), with injection site pain the most commonly reported reaction in all cohorts (appendix pp 55–56). The number of participants reporting one or more local reactions over the 7 days after day 0 was similar in the two groups for all cohorts (appendix pp 47–48, 57). 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 report of warmth. There was a significantly higher proportion of individuals who reported local adverse reactions when receiving the influenza vaccine at day 21 compared with those who received placebo (appendix pp 57–58), but no severe local reactions were reported (appendix pp 52–53). The number of different local solicited reactions reported by each participant was similar in the two randomly assigned groups after day 0

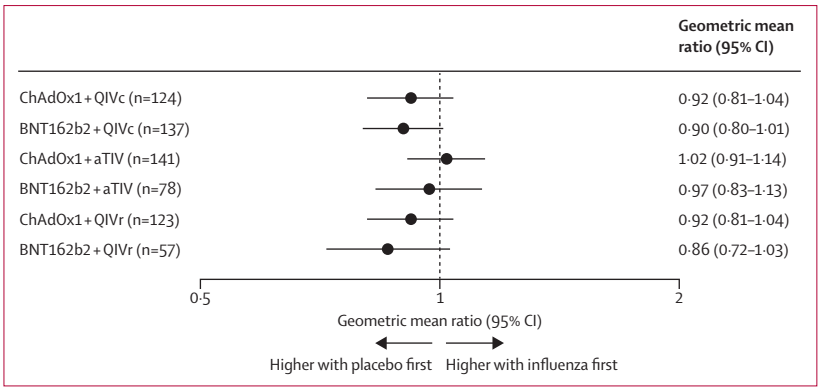

Figure 3: **Anti-spike immunoglobulin geometric mean titre ratio between COVID-19 vaccine given with or without influenza vaccine**

Placebo first indicates that COVID-19 vaccine alone was received at day 0. Influenza first indicates that concomitant COVID-19 and influenza vaccines were received at day 0. QIVc=cellular quadrivalent vaccine. aTIV=MF59C adjuvanted, trivalent vaccine. QIVr=recombinant quadrivalent vaccine.

but was significantly higher after day 21 in the COVID-19 vaccine alone group who received the influenza vaccine at day 21 (appendix pp 47–48, 58).

There were 173 unsolicited adverse events after vaccination reported by 112 participants in the concomitant COVID-19 and influenza vaccine group after day 0 and 155 unsolicited adverse events reported by 99 participants in the COVID-19 vaccine alone group. After day 21, 66 unsolicited adverse events were reported by 49 participants in the concomitant COVID-19 and influenza vaccine group compared with 84 unsolicited adverse events reported by 57 participants in the COVID-19 alone group (appendix pp 47–48, 59–66). Rates of medically attended adverse events were similar between groups after day 0 (25 medically attended adverse events reported by 22 participants in the concomitant COVID-19 and influenza vaccine group and 27 medically attended adverse events reported by 20 participants in the COVID-19 alone group) and after day 21 (18 medically attended adverse events reported by 15 participants in the concomitant COVID-19 and influenza vaccine group who received placebo at day 21 compared with 15 medically attended adverse events reported by 14 participants in the COVID-19 alone group who received the influenza vaccine at day 21; appendix pp 47–48, 67–71).

Seven serious adverse events were reported by seven participants, including one considered related to vaccination. A participant was admitted to hospital with severe headache and visual disturbance 48 h after vaccination with ChAdOx1 and influenza and given a diagnosis of migraine (appendix pp 47–48, 71). One adverse event of special interest—mild chilblain-like lesions—was reported as starting 4 days after vaccination with ChAdOx1 and saline placebo. The lesions resolved within 7 days with no ongoing sequelae and were reported as having a possible association with vaccination (appendix p 72).

Anti-spike immunoglobulin geometric mean units, 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 3). Seroconversion rates 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 vaccine alone (appendix pp 73–75).

No significant differences were seen in the haemagglutinin antibody inhibition geometric mean ratio for any influenza strain 21 days after receiving influenza vaccine with a COVID-19 vaccine compared with receiving the influenza vaccine alone in the cellular quadrivalent vaccine and MF59C adjuvanted, trivalent vaccine cohorts or in the cohort that received ChAdOx1 plus recombinant quadrivalent influenza vaccine (figure 4). In the BNT162b2 plus recombinant quadrivalent influenza vaccine cohort, the geometric mean titres of A/H1N1 and both B strains were higher when given with BNT162b2 compared with when recombinant quadrivalent influenza vaccine was given alone but were similar for A/H3N2 (figure 4; appendix p 76). Seroconversion rates ranged from 1% to 72%, tending to be lower in the MF59C adjuvanted, trivalent influenza vaccine cohorts than in either of the quadrivalent influenza vaccine cohorts, and lower for B strains compared with A strains (appendix p 59).

Nine (1%) of 670 participants 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. 11 (3%) of 356 participants in employment reported between 0·5 and 2 lost workdays after vaccination (appendix p 77). The Bang blinding indices for assessing the success of masking were 0·33 (95% CI 0·26–0·40) for the group given concomitant COVID-19 and influenza vaccines and 0·26 (0·19–0·33) in the group given the two vaccines separately (appendix p 77).

Discussion

Our findings show that concomitant administration of six different combinations of COVID-19 and influenza vaccines raised no safety concerns, produced acceptable reactogenicity profiles, and preserved binding antibody responses. The systemic reactogenicity profiles were considered acceptable despite an increase in the rate of systemic events above 25% in two cohorts. In the ChAdOx1 plus MF59C adjuvanted, trivalent influenza vaccine cohort, the upper limit of the 95% CI only narrowly exceeded 25%, with most additional reactions—predominantly fatigue, headache, and myalgia—recorded as mild or moderate. The BNT162b2 plus recombinant quadrivalent influenza vaccine cohort was smaller than planned; therefore definitive conclusions are unable to be drawn. It is reassuring that most participants were supportive of concomitant vaccination.

The anti-spike immunoglobulin responses to both BNT162b2 and ChAdOx1 were preserved with all three types of influenza vaccine. The geometric mean ratios ranged between 0·80 and 1·13 for the six vaccine

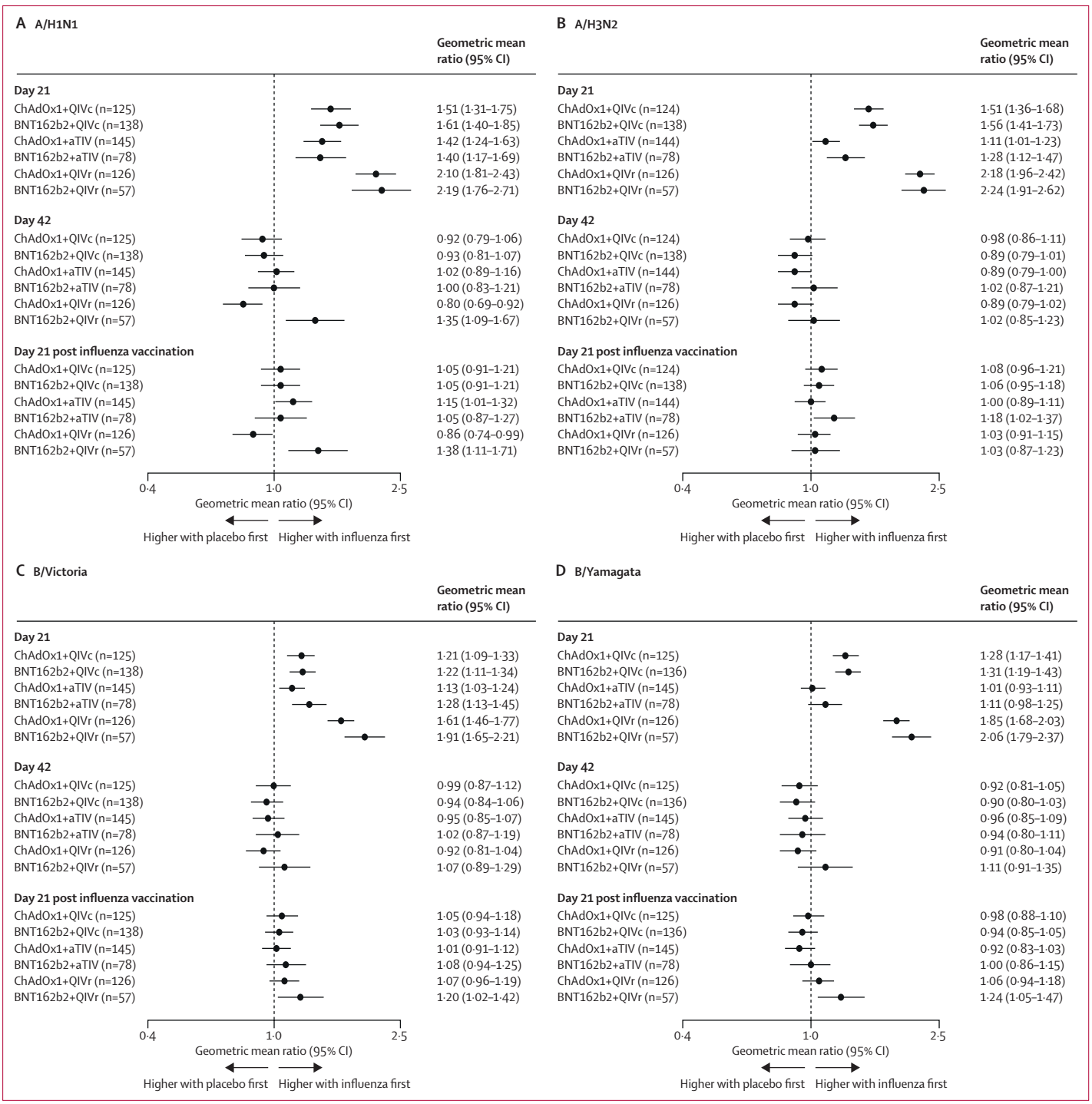

Figure 4: **Haemagglutination inhibition influenza geometric mean ratios**
Placebo first indicates that COVID-19 vaccine alone was received at day 0. Influenza first indicates that concomitant COVID-19 and influenza vaccines were received at day 0. QIVc=cellular quadrivalent vaccine. aTIV=MF59C adjuvanted, trivalent vaccine. QIVr=recombinant quadrivalent vaccine.

combinations evaluated. The geometric mean ratios in all six cohorts were above 0·67, which is the cutoff applied by WHO when approving new vaccines as non-inferior to existing products, using geometric mean ratio as an endpoint.[12] 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 plus recombinant quadrivalent influenza vaccine cohort, where geometric mean titres were significantly higher for three strains when given with the COVID-19 vaccine. It is possible that the RNA contained within BNT162b2, acting as adjuvant, augments responses. However, it is unclear why this would only influence the recombinant influenza vaccine and not the others.

To our knowledge, these are the first data to describe concomitant administration of any vaccine with either an adenovirus 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] In a substudy of a phase 3 trial that assessed the safety and efficacy of a protein subunit COVID-19 vaccine with Matrix-M adjuvant ($NVX\text{-}CoV_{2373}$), cellular quadrivalent influenza vaccine was co-administered to participants aged 18–64 years with the first dose of the two dose COVID-19 vaccine schedule.[13,14] Similar to our findings, Toback and colleagues[14] found no significant differences in reactogenicity between those receiving concomitant vaccination compared with the COVID-19 vaccine alone. By 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 geometric mean ratio of 0·57 (95% CI 0·47–0·70), below the WHO 0·67 geometric mean ratio cutoff, suggesting immune interference.[14] Importantly, there was no difference in the efficacy of concomitant vaccination. The key difference between Toback and colleagues' trial[14] and ours is that the influenza vaccine was administered with the first dose, not the second dose, of COVID-19 vaccine.[14] Pertinently, Toback and collegaues[14] showed that higher geometric mean units were reached when the $NVX\text{-}CoV_{2373}$ COVID-19 vaccine and influenza vaccine were co-administered to participants with serological evidence of previous COVID-19 infection. Natural infection with COVID-19 primes the immune system, resulting in significantly higher anti-spike IgG responses to the first dose of COVID-19 vaccine compared with those who are COVID-19 naive.[15] This finding suggests that concomitant immunisation might effect priming but not subsequent responses, meaning that it might be optimal to co-administer an influenza vaccine with second or later doses of COVID-19 vaccine. However, given that the efficacy of the subunit COVID-19 vaccine was preserved despite a reduction in the humoral response, there would 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. The effect of the immune interference with priming doses might have implications for less immunogenic COVID-19 vaccines, such as whole virion, inactivated vaccines.[16]

Concomitant administration of influenza vaccines with other vaccines has been studied for other vaccine types, including pneumococcal polysaccharide and conjugate vaccines.[17,18] Relative reductions have been reported for some pneumococcal serotypes in some studies, but these have not proven to be clinically significant.[7] These studies show that concomitant administration has no effect on humoral responses to influenza vaccine, consistent with the findings reported here.

The strengths of this trial are that we did not exclude individuals who were pregnant, had severe, uncontrolled medical problems, were immunocompromised, or aged 65 years and over, so the trial population is reflective 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.

The study has several limitations. The participant-reported primary outcome is subject to potential bias. The influenza vaccine is likely to cause more local reactions than placebo, which could unmask the allocation. The Bang Blinding Index suggests that more participants guessed their allocation correctly than would be expected by chance. Given the novelty of the adenovirus 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 a matter for discussion and further studies are required with these specific vaccine types. Two of the cohorts had lower recruitment than planned, which was related to the expiry dates of some influenza vaccines and the timing of the roll-out of specific COVID-19 vaccines in the UK. The cellular quadrivalent influenza cohorts were added partway 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 could affect the generalisability of results pertaining to the cellular quadrivalent influenza vaccine cohorts. The concomitant administration was done with a second dose of COVID-19 vaccine, and not third, booster doses, which are most likely to be administered with influenza vaccine. The absence of SARS-CoV2 neutralising antibody data in this report limits the evaluation of the humoral response. Finally, T-cell responses were not evaluated; it is clear that cellular immunity has a role in protection against natural SARS-CoV-2 infection and that vaccine-induced cellular responses might behave independently to neutralising antibodies; therefore further studies investigating T-cell responses to concomitant vaccination are warranted.[19,20]

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 health-care 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, RTo, KJ, and MC led the implementation of the trial. RK, EP, EM, DT, SRE, AM, AC-S, AP, VL, NJ, JR, JG, and LG acted as principal investigators. RAH, RTh, and CAR did 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. RLW was the regional coordinator for sites in the southwest 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 the National Institute for Health Research (NIHR) during the conduct of the trial, and grants from Elizabeth Blackwell Institute, AstraZeneca, Janssen, and Valneva outside the submitted work. CAR reports grants from NIHR, during the conduct of the trial. JSN-V-T reports that 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, Sanofi Pasteur, VBI Vaccines, Pfizer, Janssen, GSK, MedImmune, Novavax, and Valneva outside the submitted work. AM reports grants from NIHR 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, GSK, Pfizer, Novavax, Pfizer, Janssen, Medimmune, and MCM. All other authors declare no competing interests.

Data sharing

After 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 National Institute for Health Research policy on data sharing. A minimum requirement with respect to scientific quality will be a publicly available prespecified protocol describing the purpose, methods, and analysis of the secondary research (eg, 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.

Acknowledgments

We would like to thank all the trial participants, without whom this trial would not have been possible. We thank all site staff involved in recruitment, coordination, and data collection for this trial. We also thank the clinical, nursing, vaccination, and administrative teams at participating centres for their support in the conduct of the trial. We would like to acknowledge the contribution of the Oxford Vaccine Group to the trial and documentation design. We 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. We would like to thank the sponsor organisation, University Hospitals Bristol and Weston NHS Foundation Trust, and the National Immunisation Schedule Evaluation Consortium. This trial was funded by the National Institute for Health Research Policy Research Programme (PR-R17-0916-22001, NIHR203243). The views in this Article are those of the authors and not necessarily those of the UK Department of Health and Social Care.

References

1 Public Health England. COVID-19 vaccine surveillance report. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1016465/Vaccine_surveillance_report_-_week_36.pdf (accessed Sept 10, 2021).

2 Olsen SH, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic—United States. Australia, Chile, and South Africa, 2020. Centres for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep* 2020; **69:** 1305–09.

3 Australian Government Department of Health. Early advice on 2021 influenza vaccination. https://www.health.gov.au/news/early-advice-on-2021-influenza-vaccination (accessed Sept 10, 2021).

4 US Centers for Disease Control and Prevention. Interim clinical consideration for use of COVID-19 vaccines currently approved or authorized in the United States. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html (accessed Sept 10, 2021).

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:** 2603–15.

6 Ramasamy MN, 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* 2021; **396:** 1979–93.

7 Frenck RW Jr, 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:** 1296–303.

8 US Department of Health and Human Services, US Food and Drug Administration, US Center for Biologics Evaluation and Research. Guidance for industry. Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. September, 2007. https://www.fda.gov/media/73679/download (accessed Sept 10, 2021).

9 Manisty C, Otter AD, Treibel TA, et al. Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals. *Lancet* 2021; **397:** 1057–58.

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 Technol Assess* 2011; **14:** 115–92.

11 Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004; **25:** 143–56.

12 WHO. 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 Sept 21, 2021).

13 Heath PT, Galiza EP, Baxter DN, et al. Safety and efficacy of NVX-CoV2373 COVID-19 vaccine. *N Engl J Med* 2021; **385:** 1172–83.

14 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. *medRxiv* 2021; published online June 13. https://doi.org/10.1101/2021.06.09.21258556 (preprint).

15 Krammer F, Srivastava K, Alshammary H, et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. *N Engl J Med* 2021; **384:** 1372–74.

16 Earle KA, Ambrosino DM, Fiore-Gartland A, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. *Vaccine* 2021; **39:** 4423–28.

17 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.

18 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 from a phase III, randomized, non-inferiority trial. *Vaccine* 2017; **35:** 6321–28.

19 Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. *Nat Rev Immunol* 2021; **21:** 475–84.

20 Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-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:** 1351–62.