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Supplementary appendix

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1. ComFluCOV Protocol

Version 4.0 dated 10th May 2021

A single-blind, phase IV UK multi-centre randomised controlled trial to determine reactogenicity and immunogenicity of COVID-19 vaccines administered concomitantly with seasonal influenza vaccines

Combining Influenza and COVID-19 vaccination (ComFluCOV) study

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Glossary / abbreviations

ACE2	Angiotensin-converting enzyme 2
ADEM	Acute disseminated encephalomyelitis
AE	Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.
AESI	Adverse Event of Special Interest
AR	Adverse reaction - is any undesirable experience that has happened to a subject while taking a drug that is suspected to be caused by the drug or drugs.
BTC CTEU	Bristol Trials Centre Clinical Trials and Evaluation Unit
C-19P	COVID-19 Pathway
ChAdOx1	Chimpanzee adenovirus 1
CI	Chief investigator
e-CRF	Electronic case report form
CTA	Clinical Trials Authorisation
DMSC	Data monitoring and safety committee
DSUR	Development Safety Update Report
NHS	National Health Service
NIHR	National Institute for Health Research
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HA	Haemagglutinin
ICF	Informed Consent Form
IM	Intramuscular
IMP	Investigational Medicinal Product
ISF	Investigator site file
IV	Intravenous
MERS-COV	Middle East respiratory syndrome due to coronavirus
MHRA	Medicines and healthcare products regulatory agency
µg	Microgram
MRC	Medical Research Council
NISEC	National Immunisation Schedule Evaluation Consortium
PI	Principal Investigator
PIL	Patient information leaflet
PPI	Patient and public involvement
RCT	Randomised controlled trial
REC	Research ethics committee
RSI	Reference safety information
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SAR	Serious adverse reaction
SSAR	Suspected serious adverse reaction (SSAR) is any serious adverse event that is suspected to be related to the drug or drugs being taken.
SARS-CoV-2	Severe acute respiratory syndrome due to coronavirus
SOP	Standard operating procedure
SMPC	Summary of Medicinal Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction - an untoward medical occurrence suspected to be related to a medicinal product that is not consistent with the applicable product information and is serious.
TMF	Trial master file
TMG	Trial management group
TSC	Trial steering committee
UHBW	University Hospitals Bristol and Weston NHS Foundation Trust
UKCRC	UK Clinical Research Collaboration
Vp	Viral particle
VTF	Vaccine Task Force
WHO	World Health Organisation

1. Trial summary

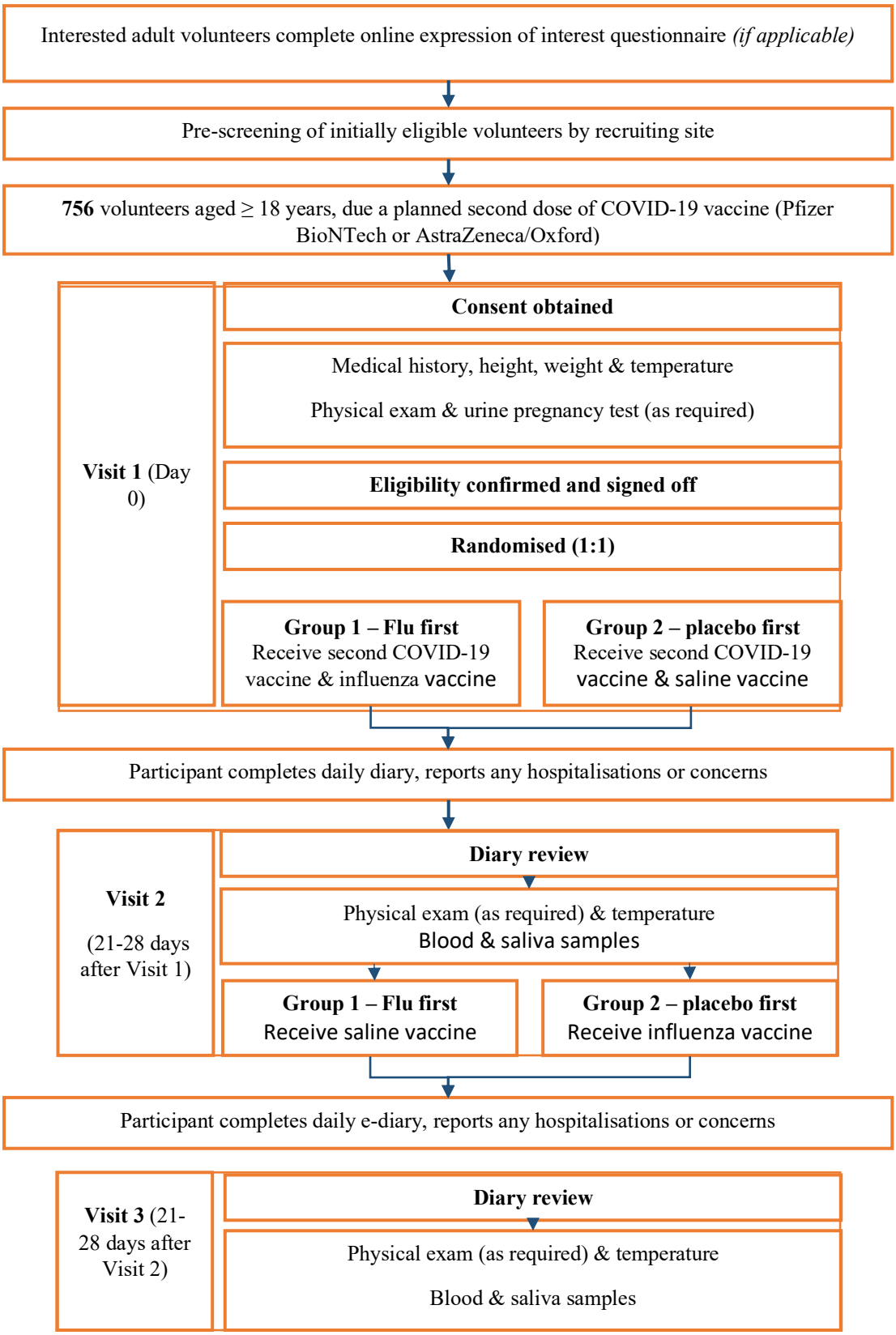
Mass vaccination against COVID-19 started in the UK in early December 2020 and is likely to continue until mid-2021. Whilst rates of COVID-19 infection have decreased, the emergence of variants of interest and planned easing of lockdown measures has led to predictions of potential resurgence of infection from autumn 2021. The duration of protection of the current COVID-19 vaccines is unknown but it may be that further booster doses will be required in 9 to 12 months' time with current or potentially strain-modified vaccines to afford continued protection into the autumn. The timing of the booster doses is likely to coincide with seasonal influenza vaccination, which is usually September to February. Delivering COVID-19 and influenza vaccines at separate appointments will cause significant logistical challenges therefore it would be desirable to immunise with both vaccines at the same appointment, in different arms.

The ComFluCOV trial will determine the safety, as well as the immune responses, to administration of the currently approved COVID-19 vaccines at the same time as the recommended influenza vaccines from the 2020/21 season.

Participants who are having their second COVID-19 vaccine will be randomised into two groups; one group will receive the influenza vaccine and the other group will receive saline (placebo) at the same time as the COVID-19 vaccine. Participants will not know whether they receive the influenza vaccine or the placebo. After 3 weeks participants who received the influenza vaccine will receive the saline injection and participants who received the saline injection will receive the influenza vaccine. Participants will be followed up for a further 3 weeks after the second injection. We hope to recruit 756 participants into the trial. The trial will be conducted in at least 5 UK NHS centres. The trial is expected to take about 6 months to complete.

1.1 Trial schema

Figure 1 Trial schema



2. Background & Rationale

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China and were later confirmed to be infected with a novel coronavirus, known as 2019-nCoV . The virus was subsequently renamed to SARS-CoV2 because it is similar to the coronavirus responsible for severe acute respiratory syndrome (SARS-CoV), a lineage B betacoronavirus. SARS-CoV-2 shares more than 79% of its sequence with SARS-CoV, and 50% with the coronavirus responsible for Middle East respiratory syndrome (MERS-CoV), a member of the lineage C betacoronavirus . COVID-19 is the infectious disease caused by SARS-CoV-2. By January 2020 there was increasing evidence of human-to-human transmission as the number of cases rapidly began to increase in China. Despite unprecedented containment measures adopted by the Chinese government, SARS-CoV-2 rapidly spread across the world. The World Health Organisation (WHO) declared the COVID-19 outbreak a public health emergency of international concern on 30th January 2020. Globally, as of 22nd October 2020, there have been 40,890,712 confirmed cases of COVID-19, including 1,126,351 deaths, reported to the WHO.

Coronaviruses (CoVs) are spherical, enveloped, large positive-sense single-stranded RNA genomes. One-fourth of their genome is responsible for coding structural proteins, such as the spike (S) glycoprotein, envelope (E), membrane (M) and nucleocapsid (N) proteins. E, M, and N are mainly responsible for virion assembly whilst the S protein is involved in receptor binding, mediating virus entry into host cells during CoVs infection via different receptors . SARS-CoV-2 belongs to the phylogenetic lineage B of the genus Betacoronavirus and it recognises the angiotensin-converting enzyme 2 (ACE2) as the entry receptor . It is the seventh CoV known to cause human infections and the third known to cause severe disease after SARS-CoV and MERS-CoV.

Several vaccines effective against SARS-CoV-2 have now been developed. The first to be approved for use in the United Kingdom (UK) was the Pfizer/BioNTech BNT162b2 vaccine which the European Medicines Agency then granted conditional authorisation on 21st December 2020. This was followed by emergency authorisation of the Oxford/AstraZeneca ChAdOx1 nCOV-19 vaccine on the 29 December 2020 by the UK Medicines and Healthcare products Regulatory Agency (MHRA). On the 29 January 2021 it was approved by the European Medicines Agency (EMA). Both of these vaccines are approved for use as homologous two-dose regimens. Further vaccines, using different platforms are expected to be approved for use against COVID-19 during 2021.

Rates of COVID-19 have been decreasing in the UK since early January 2021 secondary to social control measures and the roll-out of the mass vaccination programmes. There is concern however, that with the relaxation of social control measures, the emergence of viral variants of concern and the seasonality of respiratory viruses that there could be increased transmission over the winter period. Given this concern it is likely that the COVID-19 vaccine schedule will be extended to include a booster dose for some age and at-risk groups and could potentially become an annual vaccination. This time period for vaccination would coincide with the usual time period for influenza vaccination therefore to manage both vaccination programmes it would be preferable to permit administration of both vaccines at the same appointment. Safety and immunogenicity data to support concomitant administration of both vaccines is urgently needed to support resource management and planning. Accordingly, this trial will determine the safety and immunogenicity of concomitant immunisation with currently available COVID-19 and influenza vaccines given timelines of this study. Expansion of the study to include future COVID-19 vaccines could be considered in the future.

A quadrivalent influenza vaccine is recommended for adults under the age of 65 whilst for adults aged over 65 an adjuvanted trivalent vaccine is recommended therefore data collection on concomitant administration to represent all permutations that are likely is planned. Further COVID vaccines may be added as they become available.

Given that the mass vaccination programme has only been running since December 2020 it will not be possible to replicate the likely autumn scenario where individuals will be receiving influenza vaccine with their third dose of a COVID-19 vaccine, 9 to 12 months from their first COVID-19 dose. Therefore, in order to provide preliminary safety data participants will be offered influenza vaccine alongside their second scheduled dose of COVID-19 vaccine.

3. Aims and objectives

The ComFluCOV trial aims to evaluate whether the reactogenicity of concomitant administration of COVID-19 and influenza vaccine is 'no worse' than COVID-19 vaccine alone.

Specific objectives of the trial are to evaluate:

1. The difference in reactogenicity of concomitant administration of COVID-19 and influenza vaccine and COVID-19 vaccine alone (primary outcome)
2. The difference in i) severity of solicited local and systemic reactions, ii) unsolicited reactions and iii) safety between concomitant administration of COVID-19 and influenza vaccine and COVID-19 vaccine alone
3. The immunogenicity of second dose of COVID-19 vaccine given alone or concomitantly with influenza vaccine
4. The immunogenicity of influenza vaccine concomitantly with COVID-19 vaccine or 3 weeks after COVID-19 vaccine

The trial will also provide further characterisation of immune response.

4. Primary and secondary outcomes

4.1 Primary outcome

The primary outcome is one or more solicited systemic reaction in the 7 days following 2nd COVID-19 vaccination (plus/minus flu vaccine). Solicited systemic and local adverse reactions (ARs) are listed in Table 1. Solicited ARs are collected using post-vaccination diary cards.

Table 1 Solicited adverse events collected on post vaccination diary cards

Local solicited AEs	Systemic solicited AEs
• Pain	• Fever
• Tenderness	• Feverishness
• Redness	• Chills
• Warmth	• Joint pains
• Itch	• Muscle pains
• Swelling	• Fatigue
• Induration	• Headache
	• Malaise
	• Nausea
	• Vomiting
	• Diarrhoea

Note: The above AEs are assumed to be related and will be classed as adverse reactions.

4.2 Secondary outcomes

Data will be collected to characterise the following secondary outcomes:

1. Type and severity of solicited adverse reactions (systemic or local reaction) in the 7 days following 2nd COVID-19 vaccination (visit 1)
2. Unsolicited adverse reactions during trial participation
3. Medically attended events or serious adverse events (SAEs) during trial participation
4. Anti-spike protein immunoglobulins measured from a blood sample taken at visit 1 and visit 2 to assess response to second dose of COVID-19 vaccine

5. Neutralising antibodies against SARS-CoV-2 measured from a blood sample taken at visit 1 and visit 2 to assess response to second dose of COVID-19 vaccine
6. Haemagglutination inhibition assay from a blood sample taken at visits 1, 2 and 3 to assess response to influenza vaccine
7. Investigation of mucosal immune responses to COVID-19 vaccines in saliva
8. Success of participant blinding using the Bang Blinding Index [1]
9. Participant willingness to receive concomitant influenza and COVID-19 vaccinations in the future
10. Days off work for participants in employment

Note: visit 2 will be 21 days (+7 days) after visit 1, visit 3 will be 21 days (+7 days) after visit 2. Vaccinations due at visit 1 and visit 2 will be administered AFTER blood samples have been taken.

[1] The participant is asked to indicate which treatment they think they received first (influenza, placebo or don't know). If they answer don't know they are asked to guess which they received first.

5. Plan of Investigation

5.1 Trial design

The ComFluCOV trial is a multicentre, parallel-group placebo-controlled RCT in which participants, laboratory staff and clinicians assessing causality will be blinded to the treatment.

5.2 Key design features to minimise bias

Selection/allocation bias will be prevented by concealed randomisation. The allocation will not be revealed until sufficient information to uniquely identify the participant has been entered into the allocation database.

Performance and detection bias will be minimised by blinding participants, laboratory staff and clinicians assessing causality to the vaccine received. We will also define procedures for follow-up and monitor adherence to the protocol. The participant information leaflet (PIL) and the process of obtaining informed consent will describe the uncertainty about the effects giving the two vaccines together compared to separately. Therefore, in the event of inadvertent unblinding of a participant, he or she should not have a strong expectation that one should be better than the other.

Attrition bias will be minimised by using established methods developed in the Coordinating Centre to maximise the quality and completeness of the data (e.g., regular monitoring of data, querying of data in the trial database). Instances of non-adherence will be fully documented and reviewed at trial meetings and an action plan for maximising compliance drawn up as appropriate. Data will be analysed by intention to treat (i.e., according to the treatment allocation, irrespective of future management and events), and every effort will be made to include all randomised patients.

Reporting bias will be minimised by pre-specifying trial outcomes and following a detailed analysis plan which will be prepared in advance of any comparative analyses of the trial data.

5.3 Setting

Participating NHS hospitals offering a second dose of COVID-19 vaccine as part of this trial.

5.4 Trial population

Adult volunteers undergoing planned second dose of an approved COVID-19 vaccine. Recruitment of those from the global majority (black, asian and non-caucasian) is particularly encouraged. Both men and women will be encouraged to participate.

5.4.1 Inclusion criteria

1. Adult aged 18 or over
2. Received one dose of either

ChAdOx1 – 56[1] to 90 days prior to trial enrolment
or BNT162b2 vaccine between 28 and 90 days prior to trial enrolment

3. Agreement to refrain from blood donation in the 7 days following vaccination (i.e., in the 7 days following visits 1 and 2)
4. Willing to allow their General Practitioner (GP) and consultant, if appropriate, to be notified of participation in the trial
5. Willing to allow investigators to discuss their medical history and confirm vaccination status with their GP, and access all medical records when relevant to trial procedures
6. Willing and able to give written informed consent for participation in the trial
7. Able to use and has access to an electronic device (e.g., laptop, tablet, smart phone) to complete trial procedures (e.g., e-diary)
8. In the Investigator's opinion, is able and willing to comply with all trial requirements

[1] this is based on WHO guidance that a second dose should not be given within 8 weeks

5.4.2 Exclusion criteria

1. Receipt of any vaccine (licensed or investigational) other than ChAdOx1 or BNT162b2 within 30 days before visit 1 (first trial vaccination)
2. Administration of immunoglobulins and/or any blood products within three months before visit 1 (first trial vaccination)
3. History of allergic disease or reactions likely to be exacerbated by any component of trial vaccines (e.g., hypersensitivity to the active substance or any of the SmPC-listed ingredients)
4. Bleeding disorder (e.g., factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following intramuscular injections or venepuncture and any history of cerebral venous sinus thrombosis, acquired or hereditary thrombophilia, heparin-induced thrombocytopenia or antiphospholipid syndrome. Those who have experienced major venous and arterial thrombosis occurring with thrombocytopenia following vaccination with any COVID-19 vaccine should not receive a second dose of COVID-19 Vaccine AstraZeneca.
5. Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e., warfarin) or novel oral anticoagulants (i.e., apixaban, rivaroxaban, dabigatran and edoxaban)
6. Suspected or known current alcohol or drug dependency
7. Any other significant disease, disorder or finding which may significantly increase the risk to the participant, affect their ability to participate in the trial or impair interpretation of the trial data
8. Current, active and progressive neurological disorders (e.g., multiple sclerosis, Guillain-Barre syndrome, transverse myelitis). Bell's palsy will not be an exclusion criterion
9. Scheduled elective surgery during trial participation if this interferes with study protocol
10. Participated in another research trial involving an investigational product in the 12 weeks prior to visit 1 or if receipt of any IMP is planned during the trial period
11. Acute, ongoing respiratory illness (moderate or severe illness with or without fever) at visit 1
12. Fever (oral temperature greater than 37.8°C) at visit 1

Note: Vaccines with lower egg concentrations (ovalbumin <0.12mcg/ml) are not contraindicated for those with egg allergy unless they have been admitted to intensive care through anaphylaxis in the previous 12 months.

5.5 Randomisation

Participants will be randomised after consent has been given, and eligibility has been confirmed by the Principal Investigator (PI) or a delegated medically qualified doctor.

Participants will be allocated in a 1:1 ratio to COVID-19 vaccine plus influenza vaccine or COVID-19 vaccine plus placebo vaccine. The allocation will be computer-generated and will be stratified by age (under 65 years, 65 years or over), type of vaccine (ChAdOx1 or BNT162b2) and centre by an independent BTC CTEU statistician, not involved in the trial, before recruitment begins.

Randomisation will be performed using a secure internet-based randomisation system ensuring allocation concealment by a member of the local research team.

5.6 Blinding

Participants, laboratory staff and clinicians assessing causality of adverse events will not be informed of the treatment allocation. Staff involved in delivery of the trial treatment will be aware of whether the participant is receiving the influenza vaccine or placebo.

Vaccines will be prepared out of sight of the participant and the blind will be maintained by i) asking participants to look away, ii) applying a blinding label over the vaccine syringe and iii) using syringes that as similar as possible. The success of blinding will be assessed using the Bang Blinding Index.

5.7 Unblinding

Requests to unblind on clinical grounds are not anticipated. However, if unblinding is requested on safety grounds (e.g., a participant may be unblinded if they experience anaphylaxis), this will be facilitated by contacting the coordinating centre (during normal office hours) or UHBW pharmacy (outside normal office hours). Any such request will be fully documented including who requested the unblinding and the reason for unblinding. Unblinding will only be permitted if it is required for clinical management. Details of the trial treatment received will be sent to the attending physician.

If a suspected unexpected serious adverse reaction (SUSAR) is reported, the Sponsor will receive an unblinded report from the BTC for further reporting purposes as required by the MHRA. The CI, local PI and blinded clinicians will not be unblinded unless it is indicated on safety grounds.

Unblinding rates will be monitored throughout the trial by the trial team and by the independent Data Monitoring and Safety Committee (DMSC) established to oversee participant safety in the trial (see Section 13 for further details).

Participants will be made aware before entering the trial that they will not be told which treatment they will receive until after the trial has completed.

5.8 Research procedures: participants

Participants will be required to do, or undergo, the following tasks or investigations specifically for the trial which are also outlined in Table 2.

5.8.1 Interest in participation

Volunteers interested in participating will be required to complete an 'expression of interest/initial screening' questionnaire available via a public website. See section 11.3 for details of how the public will be made aware of the trial.

The 'expression of interest/initial screening' questionnaire will assess whether the volunteer meets the key inclusion criteria for the participation (e.g., due to have their second COVID-19 vaccine in the recruitment period). If these criteria are met, they will be asked to indicate their electronic consent to proceed to more detailed screening, and for the research team to contact their GP for further clarification of medical history (if required) and confirmation of vaccination record.

If the direct care team are responsible for recruitment, registration of interest via the 'expression of interest/initial screening' questionnaire will not be needed and the direct care team can contact potentially eligible volunteers directly. In this case the direct care team will go straight to the detailed pre-screening as described in 0.

5.8.2 Detailed pre-screening

This second stage includes the following elements:

- Reporting their medical history
- Telephone appointment with a member of the research team to review the medical history (if required, depending on responses)

Volunteers without a past medical history or drug history requiring review may be invited directly to enrolment/vaccination visits once their vaccination status has been confirmed.

Volunteers will be asked to contact the trial team if there are significant changes to their health status between pre-screening and their first trial visit.

5.8.3 Visit 1: Recruitment and administration of trial vaccine

At this visit volunteers' medical history and eligibility will be confirmed by the PI or delegated medically qualified doctor. If eligible, volunteers will be invited to

- Confirm they understand the contents of the ComFluCOV trial PIL (this will be available via the pre-screening website)
- Discuss the trial with a member of the research team
- Provide informed consent to participate, if willing to do so

If consent is given the participant will undergo the following:

- Physical examination (if required)
- Measurement of height, weight, and temperature
- Provide blood sample for assessment of COVID-19 and influenza vaccine immunogenicity
- Provide saliva sample for assessment of vaccine induced mucosal immunity
- Provide urine sample for a pregnancy test (females of childbearing potential only)[2]

[2] A woman of childbearing potential is defined as a pre-menopausal female who is capable of becoming pregnant. Menopause can be diagnosed in a woman aged over 50 after one year of amenorrhoea (this applies only if the woman is not using hormonal contraception).

Following consent and collection of baseline data and samples, the participant will be randomised and the trial vaccines (COVID-19 plus either influenza or placebo) will be administered.

The participant will remain at the trial site for observation for at least 15 minutes following the vaccination, in case of immediate adverse events.

5.8.4 Between visit 1 and visit 2

In the period following the first visit and the second visit approximately 3 weeks later participants will be required to:

- Complete an electronic diary card. This diary card will be used to capture:
    - adverse events, including their timing and severity
    - unplanned or non-routine visits to, or consultation with a doctor or dentist
    - medications taken to relieve symptoms
- Report any hospitalisation as soon as is practically possible using the emergency 24-hour telephone number provided
- Report any other urgent medical concerns using the emergency 24-hour telephone number provided

Diary cards will be reviewed by the local research team daily for 7 days after visit 1 and as required thereafter, and participants may be telephoned by the PI or delegated clinician if there are any concerns. Participants will be provided with a ruler and thermometer to aid their reporting of adverse events.

5.8.5 Visit 2: administration of second trial vaccine

At this visit, approximately 3 weeks after visit 1, participants will undergo the following:

- Review and reconciliation of diary card data submitted
- Assessment for local and systemic adverse reactions and events and medical history since visit 1
- Physical examination (if clinically indicated)
- Measurement of temperature
- Provide blood sample for assessment of COVID-19 and influenza vaccine immunogenicity
- Provide saliva sample for assessment of vaccine induced mucosal immunity
- Administration of second trial vaccine (influenza or placebo)

The participant will remain at the trial site for observation for at least 15 minutes following the vaccination, in case of immediate adverse events.

5.8.6 Between visit 2 and visit 3

In the period between the second visit and the third visit approximately 3 weeks later participants will be required to follow the same protocol as for between visit 1 and visit 2.

Diary cards will be reviewed by the local research team daily for 7 days after visit 2 and as required thereafter, and participants may be telephoned by the PI or delegated clinician if there are any concerns.

5.8.7 Visit 3

At this final trial visit, approximately 3 weeks after visit 2, participants will undergo the same assessments as visit 2, except that no vaccine will be administered at this visit.

5.8.8 Participants with confirmed SARS-CoV-2 infection

It will be explained at enrolment that should a participant receive a positive SARS-CoV-2 test (e.g., an antigen detection or nucleic acid amplification test, for example, via test and trace or occupational health services) they should contact the local trial team on receipt of the positive result.

Participants who develop COVID-19 symptoms and have a positive SARS-CoV-2 antigen test after the first trial vaccination will be unable to receive the second immunisation at Visit 2.

For participants who are asymptomatic and have a positive SARS-CoV-2 test, a minimum of 2 weeks from first test positivity will be required before second immunisation at Visit 2, provided they remain asymptomatic. COVID-19 infection will be considered to be an adverse event and reported as such.

5.8.9 Safety concerns

If participants experience adverse events (laboratory or clinical), which the PI or delegated clinician, determine necessary for further close observation, the participant may be admitted to an NHS hospital for observation and further medical management under the care of the Consultant on call.

5.8.10 Missed visits

If a participant cannot attend a visit for any reason (including if they are quarantining or self-isolating), where possible, this should be re-arranged to an in-person visit within the time window. If this is not possible, in exceptional circumstances a visit may be conducted outside of the window, but this must be discussed with BTC first who will assess the impact of the allowing a visit outside of the specified window. A telephone visit may be conducted instead to ascertain as much relevant information as possible if the participant is unable to attend a visit in person and a visit out of window is not possible or not agreed by BTC (see Section 7, Table 2 for visit windows).

6. Trial intervention

6.1 Trial interventions

Study participants will be randomly allocated to receive either;

- **IMP:** Influenza vaccine
    - Flucelvax QIV or Flublok Quadrivalent (QIVr) if participant is aged under 65 years Note: individual sites will administer just one influenza vaccine in this age group, unless recruitment using their allocated influenza vaccine is complete at the site and all participants have completed visit 2, and the site has capacity to recruit to further participants using the other influenza vaccine.
    - Adjuvanted Trivalent Influenza Vaccine (FluAd (MF59)) if participant is aged 65 years or over
- **Placebo:** Sodium chloride 0.9% injection

At visit 1 at the same time as their second COVID-19 vaccine, which will be either the ChadOx1-nCOV-19 (AstraZeneca/Oxford) vaccine or the BNT162b2 (Pfizer BioNTech) vaccine. COVID-19 and influenza/placebo vaccines must be given in different arms.

At visit 2, approximately 3 weeks later participants will receive the other intervention (i.e., participants receiving the influenza vaccine at visit 1 will receive the placebo at visit 2 and participants receiving the placebo at visit 1 will receive the influenza vaccine at visit 2). No COVID-19 vaccine will be administered at visit 2 or 3.

6.1.1 ChadOx1-nCOV-19 (AstraZeneca/Oxford) vaccine

ChAdOx1 nCoV-19 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 spike (S) surface glycoprotein with a leading tissue plasminogen activator (TPA) signal sequence. S is a type I, trimeric, transmembrane protein located at the surface of the viral envelope, giving rise to spike shaped protrusions from the virion. The S proteins subunits are responsible for cellular receptor ACE-2 binding via the receptor-binding domain and fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range.

ChAdOx1 nCoV-19 expresses a codon-optimised coding sequence for Spike protein from the SARS-CoV-2 genome sequence accession MN908947. ChAd is a non-enveloped virus, and the glycoprotein antigen is not present in the vector but is only expressed once the genetic code within the vector enters the target cells. The vector genes are also modified to render the virus replication incompetent, and to enhance immunogenicity (Garafalo et al, 2020). Once the vector is in the nucleus, mRNA encoding the spike protein is produced that then enters the cytoplasm. This then leads to translation of the target protein which act as an intracellular antigen.

6.1.2 BNT162b2 (Pfizer BioNTech) vaccine

BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein. BNT162b2 encodes the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation and more closely mimic the intact virus with which the elicited virus-neutralizing antibodies must interact. mRNA vaccines use the pathogen's genetic code as the vaccine; this then exploits the host cells to translate the code and then make the target spike protein. The protein then acts as an intracellular antigen to stimulate the immune response. The mRNA is then degraded within days. The vaccine RNA is formulated in lipid nanoparticles (LNPs) for more efficient delivery into cells after intramuscular injection.

6.1.3 Flucelvax QIV

Flucelvax is subunit virion influenza vaccine prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells, a continuous cell line. The vaccine antigens consist of inactivated surface antigens from the influenza virus, haemagglutinin (HA) and neuraminidase of the following strains in 2020:

- A/Hawaii/70/2019 (H1N1) pdm09-like strain (A/Nebraska/14/2019, wild type) 15 micrograms HA
- A/Hong Kong/45/2019 (H3N2)-like strain (A/Delaware/39/2019, wild type) 15 micrograms HA
- B/Washington/02/2019-like strain (B/Darwin/7/2019, wild type) 15 micrograms HA
- B/Phuket/3073/2013-like strain (B/Singapore/INFTT-16-0610/2016, wild type) 15 micrograms HA

The vaccine antigens are recognised directly by the immune system stimulating the response.

6.1.4 Flublok Quadrivalent (QIVr)

Flublok Quadrivalent [Quadrivalent Influenza Vaccine] is a solution of recombinant HA proteins from four influenza viruses.

For the 2020-2021 influenza season it is formulated to contain 180 micrograms HA per 0.5 mL dose, with 45 micrograms HA of each of the following 4 influenza virus strains:

- A/Hawaii/70/2019 (H1N1)
- A/Minnesota/41/2019 (an A/Hong Kong/45/2019-like virus) (H3N2)
- B/Washington/02/2019
- B/Phuket/3073/2013.

6.1.5 Adjuvanted Trivalent Influenza Vaccine (FluAd (MF59))

Adjuvanted Trivalent Influenza Vaccine (FluAd) is an inactivated subunit vaccine. The vaccine antigens consist of inactivated surface antigens from the influenza virus, HA and neuraminidase of the following strains in 2020:

- A/Guandong-Maonan/SWL1536/2019 (H1N1) pdm09-like strain (A/Victoria/2454/2019 IVR-207) 15 micrograms HA
- A/Hong Kong/2671/2019 (H3N2)-like strain (A/Hong Kong/2671/2019 IVR-208) 15 micrograms HA
- B/Washington/02/2019-like strain (B/Victoria/705/2018 BVR-11) 15 micrograms HA

The vaccine contains an adjuvant MF59C which is a squalene-based adjuvant.

6.1.6 Placebo (saline)

Any commercially available Sodium Chloride Injection BP 0.9% w/v can be used.

6.2 Dosing schedule

6.2.1 ChadOx1-nCOV-19 (AstraZeneca/Oxford) vaccine

The dose of ChadOx1-nCOV-19 vaccine is 0.5ml ($5x10^{10}$vp). The vaccine should be administered intramuscularly.

The ChadOx1-nCOV-19 vaccine is supplied in packs of 10 vials. Each vial contains 8 or 10 doses of vaccine, and is a colourless to slightly yellow, clear to slightly opaque liquid. Each dose is prepared by withdrawing 0.5 mL from a vial in a sterile 1 mL or equivalent syringe.

6.2.2 BNT162b2 (Pfizer BioNTech) vaccine

The dose of BNT162b2 vaccine is 30µg contained in 0.3ml of the diluted vaccine. The vaccine should be administered intramuscularly.

Each pack of the Pfizer BioNTech vaccine contains 195 vials with 5 doses per vial (975 doses per pack). It is supplied with 0.9% sodium chloride diluent for injection plastic ampoules. The vaccine should be stored out of the light prior to use.

6.2.3 Flucelvax QIV

The dose contains 15µg of each strain in a 0.5ml dose. The vaccine is administered by intramuscular injection with the preferred site being the deltoid muscle of the upper arm. The vaccines come in pre-filled syringes with or without needles.

6.2.4 Flublok Quadrivalent (QIVr)

The dose contains 45µg of each strain in a 0.5ml dose. The vaccine is administered by intramuscular injection with the preferred site being the deltoid muscle of the upper arm.

6.2.5 Adjuvanted Trivalent Influenza Vaccine (FluAd (MF59))

The dose contains 15µg of each strain in a 0.5ml dose. The vaccine is administered by intramuscular injection with the preferred site being the deltoid muscle of the upper arm. The vaccines come in pre-filled syringes with or without needles. The vaccine should be allowed to reach room temperature before use.

6.2.6 Dose modifications

Dose modifications are not expected to occur.

6.3 Regulatory status

6.3.1 COVID-19 vaccines

The marketing authorisation status of the COVID-19 vaccines considered for inclusion in this trial are:

- ChadOx1-nCOV-19 (AstraZeneca/Oxford) vaccine - approved for use under a temporary authorisation of the supply of an unlicensed vaccine; regulation 174 of the Human Medicines Regulations 2012.
- BNT162b2 (Pfizer BioNTech) vaccine - granted a conditional marketing authorisation from the European Medicines Agency on the 21 December 2020.

6.3.2 Influenza vaccines

The marketing authorisation status of the influenza vaccines considered for inclusion in this trial are:

- Flucevlax Tetra received marketing authorisation from the European Medicines Agency on the 12 December 2018 (EU/1/18/1326/004)
- Flublok Quadrivalent (QIVr) is approved for use under a temporary authorisation of the supply of an unlicensed vaccine; regulation 174 of the Human Medicines Regulations 2012.
- Adjuvanted Trivalent Influenza Vaccine (FluAd) received marketing authorisation from the European Medicines Agency on the 9 August 2017 (PL 46752/0001). The product supplied to the trial is Adjuvanted Trivalent Influenza Vaccine (PL 47991/0001) which is the same product but does not use the brand name.

6.3.3 Placebo (saline)

Not applicable, any commercially available Sodium Chloride Injection BP 0.9% w/v can be used.

6.4 Preparation and labelling

There will not be investigational medicinal product (IMP) labelling for this trial. Products will be used as supplied by the manufacturer (as for national supply) and blinding will be performed as per section 5.6.

6.5 Drug storage and supply

Vaccines and placebo will be stored in accordance with manufacturers' recommendations, in accordance with GCP, Good Manufacturing Practice and pharmacy department standard operating procedures (SOPs).

6.5.1 ChadOx1-nCOV-19 (AstraZeneca/Oxford) vaccine

The ChadOx1-nCOV-19 vaccine should be stored at +2ºC to +8ºC. The vaccine does not contain any preservative. After first opening the vial, it should be used within 6 hours when stored at room temperature (up to 30º C). After this time, the vial must be discarded.

6.5.2 BNT162b2 (Pfizer BioNTech) vaccine

The BNT162b2 vaccine should be stored at -70°C +/- 10°C. Once thawed, the vaccine may be stored for 5 days at 2-8°C.

6.5.3 Flucelvax QIV

This vaccine should be stored in a refrigerator at 2-8°C.

6.5.4 Flublok Quadrivalent (QIVr)

This vaccine should be stored in a refrigerator at 2-8°C.

6.5.5 Adjuvanted Trivalent Influenza Vaccine (FluAd (MF59))

This vaccine should be stored in a refrigerator at 2-8°C.

6.5.6 Placebo (saline)

Manufacturer's storage conditions and expiry dates should be observed.

6.6 Accountability of the trial treatments

All movements of the trial vaccines will be documented in accordance with existing pharmacy department SOPs. Vaccine accountability, storage, shipment and handling will be in accordance with local relevant SOPs.

6.7 Reference Safety Information

See safety section 10.

6.8 Contraindications to receipt of second vaccine (influenza or placebo) at visit 2

The following adverse events, identified on or before the day of vaccination, constitute absolute contraindications to further administration of a trial vaccine to the participant in question. If any of these events occur on or before the day of the second trial vaccination (visit 2), the participant will not be eligible to receive the influenza/placebo at visit 2 and will be followed up by the clinical team or their GP as required:

- Anaphylactic reaction following administration of vaccine
- Any adverse event that in the opinion of the local PI or delegated clinician may affect the safety of the participant or the interpretation of the trial results
- Symptomatic COVID-19 symptoms and a positive SARS-CoV-2 antigen test.

6.9 Concomitant medications

Concomitant medications taken at enrolment will be recorded, as will new medications taken during trial participation.

6.10 Post-trial Treatment

No specific post-trial treatment considerations.

6.11 Other Treatments

Participants will be advised that they may take paracetamol prophylactically after vaccine administration. This will be from the participants' own supplies rather than supplied by the trial team.

6.12 Other Interventions

There are no additional investigations other than those specified in this protocol.

6.13 Treatment adherence

All vaccinations will be administered by the research team. The trial medication will be at no time in the possession of the participant. Problems with adherence (e.g., failure to follow randomisation allocation) are not expected to be an issue. The research team will document whether the allocated treatment was given, if there were any deviations from the allocated intervention and the reason.

Withdrawals during treatment are expected to be low. All participants will receive their first treatment (COVID vaccine plus influenza vaccine/placebo). If a participant withdraws after the first visit, they will not receive their second treatment (influenza vaccine/placebo alone). All withdrawals and reasons for withdrawal will be documented.

6.14 Duration of treatment period

The duration of the treatment commences when the participant receives their first vaccines (COVID vaccine plus influenza vaccine/placebo) and concludes when the participant receives the second vaccine approximately 3 weeks later (influenza vaccine/placebo alone).

7. Data collection

Each participant will be assigned a unique trial number. Administrative data recorded on paper relating to the participant will be stored securely. Staff with authorisation to make changes to the trial records on the trial database, will be listed on the site delegation log.

Baseline data will be collected after written informed consent. Volunteers will be contacted by an authorised member of the local research team (as specified in the delegation log) who will provide the opportunity to understand the nature, significance, implications and risks of the trial so that they may make an informed decision if they should take part. If the patient decides to take part the member of the local research team will obtain informed consent.

Data collection will include the following elements:

a) A log of all volunteers who express interest in joining the trial and pass the pre-screening eligibility checks.
b) Volunteers assessed against the full eligibility criteria and, if ineligible, reasons for ineligibility.
c) Consent information collected prior to randomisation for all participants.
d) Baseline information (e.g., medical history and assessments) collected for all participating patients.
e) Data collected from participant diaries completed throughout their participation in the trial.
f) Data collected at trial visits.
g) Data derived from analyses of blood and saliva samples.

Further details are given in Table 2.

Table 2 Schedule of assessments

	Pre screening	Screening	Visit 1 (day 0)	Visit 2	Visit 3
Study window			As per inclusion criteria (see section 5.4.1)	Between days 21–28 after visit 1**	Between days 21–28 after visit 2**
Eligibility screen	X				
Medical history		X	X		
Informed consent	X		X		
Height/weight and observations			X	X	
Urine test for pregnancy (if applicable)			(X)		
Physical examination (as required)			(X)	(X)	(X)
Blood samples			X	X	X
Saliva sample			X	X	X
Randomisation			X		
COVID-19 vaccination			X		
Influenza vaccine or placebo			X	X	
Diary card completion* (participant)			←	→	→
Diary card review			←	→	→
Medical history since last visit				X	X
Safety review				X	X
Bang blinding index					X

**Solicited events for 7 days post-vaccination, unsolicited events thereafter*

*** visits outside of window may be conducted in exceptional circumstances, see 0*

8. Sample collection

8.1 Blood samples

One 10 ml plain tube (usually red topped) or Serum Separator Tube (SST, usually Gold topped) vacutainer of blood will be taken at each visit. Smaller multiple vacutainers may be used to a total volume of 10ml. This will be prior to randomisation and vaccination at visit 1 and 2.

8.2 Salivary samples

Saliva samples will be taken from all subjects at each visit. Participants will be required to spit into a 15ml conical tube.

8.3 Urine sample

Urinary pregnancy testing for female participants of child-bearing potential only, urine will be tested for beta-human chorionic gonadotrophin (β-HCG) at visit 1. This will be a point of care test and no sample will be stored.

8.4 Samples remaining after all testing for this trial is completed

Participants will be informed that there may be leftover samples of their blood (after all testing for this trial is completed). Participants will be able to decide if they permit future use of any leftover samples.

With the participants' informed consent, any leftover serum or saliva will be frozen indefinitely for future analysis of COVID-19 and other coronavirus-related diseases or vaccine-related responses and other future research (exploratory immunology), including genotypic testing of genetic polymorphisms potentially relevant to vaccine immunogenicity.

If a participant elects not to permit this, all that participants' leftover samples will be discarded at the end of the trial.

Samples that are to be stored for future research will be transferred to the University of Bristol, (Infection and Immunity) Biobank.

9. Definition of end of trial

The definition of the end of the trial is the date when all participants have completed visit 3, or are lost to follow-up, all samples have been analysed, the database has been locked and all data queries have been resolved.

The end of the trial for an individual patient is defined as completion of visit 3 or loss to follow-up.

10. Safety reporting

10.1 Overview

Serious adverse events (SAEs) will be recorded and reported in accordance with GCP guidelines and the Coordinating Centre Serious Adverse Events and Safety Reporting Standard Operating Procedure (see Figure 2).

10.2 Definitions

Adverse event (AE) is any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.

Adverse reaction (AR) is any undesirable experience that has happened to a subject while taking a drug that is suspected to be caused by the drug or drugs.

Serious adverse event (SAE) is any event which results in death, is life threatening, requires hospitalisation or prolongs hospitalisation, results in persistent or significant disability or incapacity.

Suspected serious adverse reaction (SSAR) is any serious adverse event that is suspected to be related to the drug or drugs being taken.

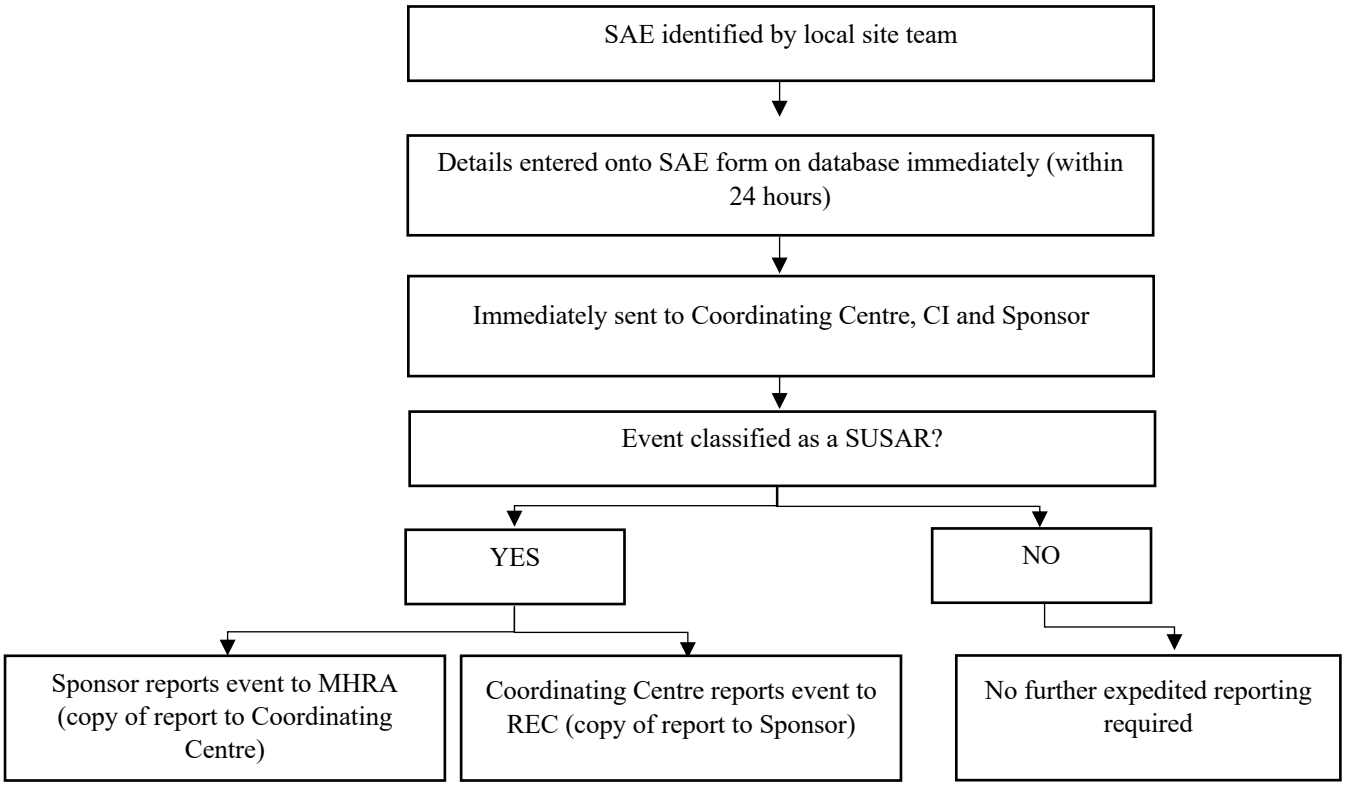
Suspected unexpected serious adverse reaction (SUSAR) is an untoward medical occurrence suspected to be related to the drug or drugs being taken that is not consistent with the applicable product information and is serious.

All AEs must be reviewed, and causality must be assessed by the PI or delegated individual not involved in the administration of the trial vaccines (to maintain blinding).

If an event meets any of the 'serious' criteria listed below it is classified as an SAE:

a) Results in death
b) Life threatening
c) Requires hospitalisation (unless hospitalisation is pre-planned)
d) Prolongation of existing hospitalisation
e) Results in persistent or significant disability or incapacity
f) Congenital anomaly / birth defect
g) Any other event which may jeopardise the participant or require intervention to prevent one of the other outcomes listed above

Figure 2 SAE reporting process



10.3 Period for recording adverse events

Data on adverse events, including serious adverse events, will be collected for the period the participant is taking part in the trial, i.e., from visit 1 to visit 3.

10.4 Process for reporting serious adverse events

Centres should expedite reporting of SAEs to the coordinating centre and the Sponsor within 24 hours of becoming aware, using an SAE report form. The Sponsor will report SUSARs to the MHRA and copy all reports to the coordinating centre; coordinating centre will report SUSARs to the REC. These reports will be sent within 8 days for fatal or life-threatening events and 15 days for all other SUSARs.

10.5 Expected adverse events associated with trial interventions

Expected events are those listed in the Reference Safety Information (RSI), which for this trial is the summary of product characteristics (SmPC) for the vaccines or placebo (see Appendix). All other events that are not consistent in nature or severity with the SmPC should be considered unexpected. Fatal events will always be considered unexpected. The RSI will not be changed within the lifecycle of this trial even if the SmPCs are updated. This is because of the short duration of this trial. Events are unlikely to be removed from the SmPC, and it is more likely that events will be added to the SmPC as use of the COVID-19 vaccines becomes more widespread. By not adopting these new events as expected events, the trial may over report expected events as unexpected events and the safety of participants will not be compromised.

10.6 Expected adverse events associated with trial procedures

Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. These will not be documented as adverse events if they occur.

10.7 Events that will not be reported as serious adverse events (SAEs)

The following events will not be reported as SAEs:

- hospitalisation for a pre-existing condition, including planned elective procedures
- attendances at an emergency department unless they meet the SAE definition as described in Section 10.2.

10.8 Adverse events of special interest

The following adverse events are considered adverse events of special interest.

Table 3 Adverse events of special interest

Immunologic	Anaphylaxis	
Neurological	Isolated anosmia/ageusia* Guillain-Barre Syndrome Acute disseminated encephalomyelitis (ADEM) Aseptic meningitis	Meningoencephalitis Peripheral facial nerve palsy Generalised convulsion Myelitis
Haematological	Thrombosis** Stroke Thrombocytopaenia (G3 or above) Eosinophilia	Coagulation disorder (includes coagulopathy, thrombosis, thromboembolism, internal/external bleed and stroke)
Cardiac	Acute cardiovascular injury (includes myocarditis, pericarditis, arrhythmias, heart failure, infarction)	
Dermatological	Chilblain-like lesions Single organ cutaneous vasculitis	Erythema multiforme Alopecia
Gastrointestinal	Acute liver injury	Appendicitis
Respiratory	ARDS	
Renal	Acute kidney injury	
Other	COVID-19 disease	SARS-CoV2 positivity on a validated test

*In the absence of COVID-19

** Excluding superficial thrombophlebitis (including line-associated)

11. Trial methods

11.1 Source data

Outcome data will be collected using a purpose-designed database. Where the trial database is the site of original recording this will be considered source data. Data will be captured at each trial visit (see Table 2 for schedule of data collection). Volunteers and participants will enter data directly into the screening and trial databases. These will be the source data for these responses.

Where the database isn't the original recording the source data will include, but is not limited to medical history, medication records, vital signs, physical examination records, urine assessments, blood results, and details of vaccinations.

11.2 Planned recruitment rate

The ComFluCOV trial will recruit eligible volunteers. Similar trials (e.g., Com-COV, https://comcovstudy.org.uk/) recruited the target sample size of 820 participants across 7 sites in 12 days. This trial will recruit across at least 5 sites and we anticipate that there will be similar interest in this trial.

11.3 Participant recruitment

The public will be made aware of the trial via

- Press announcements
- On a website
- Social media
- Notification via the National Vaccines Studies Register
- Notification via vaccination centres
- Contact from their direct care team (e.g. the GP practice responsible for their vaccinations)

Volunteers interested in joining the trial will be directed to a 2-stage online screening process using a purpose-designed website hosted by the University of Oxford and approved by the Research Ethics Committee (REC). The REC-approved participant information leaflet (PIL) will be available via this website to download. A REC-approved video presentation of the PIL may be made available for volunteers to access remotely.

Study sites will access the details of volunteers in their local area and will follow the process outlined in Section 5.8. Direct care teams can contact potential volunteers directly without prior registration on the website, as described in 0.

Prior to consent volunteers will have an opportunity to discuss the trial with a member of the research team, who will answer any questions and take written informed consent if the volunteer decides to participate. The consent form will include permission to inform their GP of their participation and optional consent to allow indefinite storage of any leftover samples for use in other ethically approved research. A copy of the signed informed consent form will be given to the participant.

Prior to consent the volunteer will be given an explanation of the exact nature of the trial, what it involves for the participant, implications and constraints of the protocol, known side effects and any risks involved in taking part, and that anonymised samples taken during the trial may be shared for future research. The voluntary nature of participation and that the participant can withdraw at any time will be emphasised. It will also be explained that participants will not be exempt from following the contemporaneous government COVID-19 guidance to minimise viral transmission.

11.4 Discontinuation/withdrawal of participants

Each participant has the right to withdraw at any time for any reason and is not obliged to give their reasons for doing so. Data and samples collected prior to withdrawal will be retained and reported.

A clinician may withdraw a participant at any time if they feel it is in the participant's best interests (e.g., due to ineligibility, either arising during the trial or retrospectively having been overlooked at screening, significant protocol deviation, participant non-compliance with trial requirements, adverse event which requires discontinuation of the trial involvement or results in inability to continue to comply with trial procedures, administrative reason).

Reasons for all discontinuations and withdrawals will be captured in the trial database and reported.
The DSMC may recommend cessation of treatment for participants.

11.5 Frequency and duration of follow up

Participants are followed up for 6-8 weeks from enrolment and randomisation. Pregnant women will be followed-up to delivery.

11.6 Likely rate of loss to follow-up

With a short period of participation of 6-8 weeks loss to follow-up is expected to be minimal (less than 5%).

11.7 Expenses

Volunteers will be compensated for their time, the inconvenience of having blood tests and procedures, and their travel expenses. The total amount compensated will depend on the exact number of visits, and whether any repeat or additional visits are necessary. For all trial visits compensation will be calculated according to the following:

- Travel expenses including parking: £15 per visit
- Inconvenience of blood and saliva tests: £10 per visit
- Time required for visit: £20 per visit

12. Statistics

12.1 Sample size calculation

The primary analysis of this trial will be a non-inferiority comparison of the reactogenicity (defined as one or more solicited systemic reaction in the 7 days following vaccination) of concomitant administration of COVID-19 and influenza vaccine and COVID-19 vaccine alone. The trial is evaluating two COVID-19 vaccines and three influenza vaccines (determined by age, two given to people aged under 65 years, one given to people aged 65 and over) giving six cohorts. The trial has been powered to test for non-inferiority within each cohort.

The sample size required to test a non-inferiority hypothesis is dependent on the non-inferiority margin and the expected event frequency in the group receiving the COVID-19 vaccine alone. Table 4 below shows the total sample within cohort for different event frequencies and non-inferiority margins assuming the true difference in frequency is zero and using 2.5% one-sided statistical significance.

Table 4 Sample size estimates

Event frequency with COVID-19 vaccine alone	Non-inferiority margin	Total per cohort (power)	
		80%	90%
10%	25%	46	62
20%	25%	82	108
30%	25%	106	142
40%	25%	122	162
50%	25%	**126**	170
60%	25%	122	162

The sample size has been set at 126 per cohort, which will provide 80% power to assess the non-inferiority of concomitant administration of COVID-19 and influenza vaccine, assuming an event frequency of 50% and an increase of less than 25% will be considered non-inferior. This sample size will also have at least 80% power to assess the non-inferiority concomitant administration of COVID-19 and influenza vaccine at lower event frequencies.

12.2 Stopping rules

There will be no formal pausing rules given the vaccines used in this trial will be approved for use. The anticipated recruitment period is short, so an interim analysis is not planned.

The trial can be put on hold upon advice of the DMSC, Chief Investigator, Study Sponsor, regulatory authority, REC, for any single event or combination of multiple events which, in their professional opinion, jeopardise the safety of the participants or the reliability of the data.

12.3 Plan of analysis – primary and secondary outcomes

Analyses will be performed on the intention-to-treat basis and will be directed by a pre-specified statistical analysis plan. Analyses will use data from all patients randomised. The primary outcome at 7 days will be compared using a generalised linear model, and the risk ratio and risk difference will be reported for each cohort with 95% confidence intervals. The combined administration of COVID-19 and influenza vaccines will be considered non-inferior to the COVID-19 vaccine alone if the upper limit of the confidence interval for the risk difference is less than 25%.

Other binary outcomes will be analysed similarly. Count variables will be analysed using poisson regression and continuous variables measured at multiple time points will be analysed using a mixed regression model. All analyses will use placebo as the reference group. Mixed models allow all participants with data to be included in the analysis, i.e., partial missing data (assumed missing at random) is permitted. Interactions between treatment and time will be examined and if significant at the 10% level, results will be reported separately for each post-operative time point; otherwise overall treatment effects will be reported. Model validity will be checked using standard methods; if a model is a poor fit, alternative models or transformations will be explored. Outcomes analysed on a logarithmic scale will be transformed back to the original scale after analysis and results presented as geometric mean ratios.

Analyses will be adjusted for baseline values, and models will include the stratification variables (i.e., trial site, type of COVID vaccine and type of influenza vaccine) and the interactions between type of COVID vaccine, type of influenza vaccine and treatment allocated (influenza or placebo) to allow the treatment effect to be estimated separately for each cohort. The results will be reported in line with the CONSORT reporting guidelines.

12.4 Frequency of analyses

The analysis of the primary outcome will take place when all recruited participants have submitted 7-day diary information, that this has been reviewed at visit 2, the data relating to the 7-day outcomes are checked and complete and that element of the database can be locked.

Analyses of other outcomes will take place when the trial is complete, and the database is locked.

12.5 Criteria for the termination of the trial

The trial may be terminated early by the DSMC.

13. Trial management

University Hospitals Bristol and Weston NHS Foundation Trust will act as Sponsor. The BTC CTEU will act as the coordinating centre for the trial. Responsibility for running the ComFluCOV trial will be established via a collaboration agreement with the University of Bristol. Agreements between the Sponsor and participating centres will be required, as well as standard site initiation documents, before recruitment commences. Appropriate contractual arrangements will also be put in place with other third parties.

The trial will be conducted in accordance with GCP guidelines, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, the Data Protection Act and the UK Policy Framework for Health and Social Care Research. The trial will be registered on an open access clinical trial database (ISRCTN).

Clinical trial documents will be archived and held by the Sponsor for 15 years after trial closure in accordance with the standard operating procedures of the Sponsor and in compliance with the principles of GCP.

The trial will be managed by the Chief Investigator (CI), with mentoring and support from senior members of the research team who will provide experience of implementing large scale clinical trials, and the Trial Managers, with full support from the wider BTC CTEU, which is a UK Clinical Research Collaboration registered clinical trial unit (UKCRC Reg. No 11). The BTC CTEU has an established track record of designing, conducting, managing and reporting multi-centre clinical trials.

The CI and coordinating centre team will work with the co-applicants to prepare the final protocol and submit the REC, MHRA and associated Health Research Authority (HRA) applications. The coordinating centre will prepare the trial documents, provide the randomisation service and design and implement the data management system.

The CI, coordinating team and Sponsor will endeavour to ensure that the trial runs according to the agreed timetable, recruitment targets are met, the CRFs are completed accurately, the trial complies with relevant ethical and other regulatory standards, and that all aspects of the trial are performed to the highest quality. The CI and coordinating centre team will also train investigators at participating centres, check that each centre is ready to start ("green light") and monitor their progress during the trial. The Trial Managers will be the contact point to provide support and guidance to the participating centres throughout the trial.

13.1 Day-to-day management

The ComFluCOV trial will be managed by a Trial Management Group (TMG), which will meet face-to-face or virtually regularly. The TMG will be chaired by the Chief Investigator and others will be invited as appropriate (see Chief Investigator & Research Team Contact Details).

13.2 Monitoring of sites

13.2.1 Initiation visit

Before the trial commences, training session(s) will be organised by the coordinating centre. These sessions will ensure that personnel at each site involved fully understand the protocol, e-CRFs, interventions, the operational requirements of the trial and the assessments to be conducted within the trial.

13.2.2 Site monitoring

The trial coordinating centre will carry out regular monitoring and audit of compliance of centres with GCP and data collection procedures, as described in section 13.2. Monitoring of data collection will be via the trial database (checks for data completeness and routine data query review), which will be carried out on a regular basis. All consent forms will be self-monitored by sites. The TMG will review accumulating data on, including but not limited to, screening, eligibility, recruitment, data completeness, adherence to trial visits and procedures, adverse events and protocol deviations in the form of central monitoring reports.

13.3 Trial Steering Committee and Data Monitoring and Safety Committee

The independent Trial Steering Committee (TSC) established to oversee the conduct of the Com-COV studies will oversee this trial. Their remit will include, but not limited to, recommending trial pauses due to safety concerns on the advice of the DMSC.

The independent DSMC established to review safety and efficacy data from the of the Com-COV studies will review data from this trial in line with the DMSC charter and will make recommendations concerning the conduct, continuation, or modification of the trial for safety reasons.

The DMSC will receive reports of SAEs deemed possibly, probably or definitively related to trial interventions within 24 hours of the site being aware of their occurrence. The DMSC can recommend placing the trial on hold if deemed necessary following a trial intervention-related SAE.

14. Ethical considerations

14.1 Review by an NHS Research Ethics Committee

The research will be performed subject to a favourable opinion from an NHS REC and HRA approval. Ethics review of the protocol for the trial and other trial related essential documents (e.g., PIL and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

14.2 Risks and anticipated benefits

14.2.1 Potential benefits

There are no immediate benefits for participants taking part in this trial. The influenza vaccine may provide protection against influenza infection at a later point in the year, for those who do not routinely receive an influenza vaccine in the Autumn.

14.2.2 Potential risks

Phlebotomy
Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. These will not be documented as adverse events if they occur. The total volume of blood drawn over a 6-week period will be approximately 90mL (blood volumes may vary slightly for participants at different investigator sites due to use of different volume vacutainers, following local Trust procedures). This should not compromise these otherwise healthy volunteers, as these volumes are within the limits of 470mL every 3 – 4 months for blood donations to the National Blood Transfusion Service.

Allergic reactions
Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product's preparation. Anaphylaxis is extremely rare (about 1 in 1,000,000 vaccine doses) but can occur in response to any vaccine or medication (Public Health England 2020b).

Behaviour change
Participants might feel they can modify their COVID-19 risk behaviours on the assumption that they are protected once vaccinated. Participants will be extensively counselled that they should continue to follow all up to date government advice in relation to COVID-19 precautions during the trial.

Specific risk from vaccines
Please refer to Section 10 for full details.

Unwanted media attention

Trial participants can be subjected to unwanted attention from the media. They will therefore be provided with access to a document outlining some suggested media guidance.

14.3 Informing potential trial participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL.

14.4 Obtaining informed consent from participants

All participants will be required to give written informed consent. This process, including the information about the trial given to patients in advance of recruitment, is described above in section 11.3.

The PI or members of the team delegated by the PI will be responsible for obtaining informed consent. The consent process will be described in detail in the trial documents. Research personnel authorised to obtain consent will be recorded on the Delegation of Responsibilities Log. All individuals obtaining informed consent will have received GCP training.

14.5 Co-enrolment

Subject to agreement with the Chief Investigator, a participant may be co-enrolled to a non-interventional study as well as to the ComFluCOV trial. A participant must not be co-enrolled to another interventional study while they are actively participating (up to visit 3) in the ComFluCOV trial.

15. Research governance

This trial will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004 and subsequent amendments
- Good Clinical Practice (GCP) guidelines
- UK Policy Framework for Health and Social Care Research

15.1 Sponsor approval

Any amendments to the trial documents must be approved by the sponsor prior to submission to the HRA, REC and MHRA as applicable.

15.2 NHS confirmation of capacity and capability

Confirmation of capacity and capability is required from each participating site prior to their participation in the trial.

Any amendments to the trial documents approved by the REC, HRA and MHRA (if applicable) will be submitted to participating sites for information and implementation, as required.

15.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and trial documents and with completion of the e-CRFs. Investigators will be required to allow access to trial documentation or source data on request for monitoring and audits performed by the Sponsor or the coordinating centre or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC that they receive and ensure that the changes are complied with.

15.4 Monitoring by sponsor

The trial will be monitored and audited in accordance with University Hospitals Bristol and Weston's Monitoring and Oversight of Research Activity SOP, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. All trial related documents will be made available on request for monitoring and audit by the sponsor (or the coordinating centre if they have been delegated to monitor), the relevant REC and for inspection by the MHRA or other licensing bodies. A monitoring plan will be prepared by the Sponsor.

15.5 Indemnity

This is an NHS-sponsored research trial. For NHS sponsored research if there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

15.6 Clinical Trial Authorisation

COVID and influenza vaccines are classed as investigational medicinal products and a Clinical Trial Authorisation (CTA) from the MHRA must be in place before starting the trial.

15.7 Serious breaches

The Medicines for Human Use (Clinical Trials) Regulations require "serious breaches" to be notified to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as *"A breach of GCP or the trial protocol which is likely to affect to a significant degree: (a) the safety or physical or mental integrity of the subjects of the trial; or*

(b) the scientific value of the trial".

In the event that a serious breach is suspected, the Sponsor must be contacted within 1 working day. The serious breach will be reviewed by the Sponsor in collaboration with the CI and, if appropriate, the Sponsor will report it to the REC, MHRA and the relevant NHS host organisation within seven calendar days.

16. Data protection and participant confidentiality

16.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and UK General Data Protection Regulation (GDPR) 2016.

16.2 Data handling, storage and sharing

16.2.1 Data handling

The ComFluCOV trial team will provide the Sponsor with a Data Management Plan prior to the trial opening to recruitment.

Data will be entered into a purpose-designed database hosted on the University of Bristol network. Information capable of identifying participants will not be held in the database. Database access will be password-controlled and restricted to ComFluCOV trial staff at the participating site and the co-ordinating centre. The processing of personal data of participants will be minimised by making use of a unique participant trial number on trial documents and the database, with the exception of signed consent forms and the screening log.

The database and randomisation system will be designed to protect participant information in line with data protection legislation. Trial staff will ensure that the participant's confidentiality is maintained through secure handling and storage of participant information at participating sites and in accordance with ethics approval. All documents will be stored securely and only accessible by trial staff and authorised personnel. Data will be collected and retained in accordance with data protection legislation.

Access to the database will be via a secure password-protected web-interface. Study data extracted from the database for statistical analyses will contain the participant's unique trial number only. Data validation and cleaning will be carried out throughout the trial.

Each recruiting centre will have access to trial materials, which will cover database use, data validation and data cleaning. The coordinating centre will maintain and update the trial materials as required.

16.2.2 Data storage

All trial documentation will be retained in a secure location during the conduct of the trial and for 15 years after the end of the trial, when all participant identifiable paper records will be destroyed by confidential means. Where trial related information is documented in the medical records, these records will be identified by a label

bearing the name and duration of the trial and clearly stating the 'do not destroy before' date. Where electronic records are in use, local site policy will be followed. In compliance with the Medical Research Council (MRC) Policy on Data Sharing, relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique participant number, will be held indefinitely.

16.2.3 Data sharing

Anonymised trial data will only be made available for sharing outside the ComCOV studies group after publication of the main results of the trial. Thereafter, individual participant data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. 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.

17. Dissemination of findings

The Investigators will be involved in drafting and reviewing manuscripts, abstracts, press releases and any other publications arising from the trial. Social networking media will be used to disseminate and publicise the trial results via the trial website and Twitter streams. Patient and Public Involvement groups will be consulted to identify how to best publicise the trial findings.

Expected outputs include publication of the trial results, informing the UK government, the NIHR, clinicians and the public on the safety of giving the COVID-19 and influenza vaccines together. It is anticipated that the results of the trial will inform national and international guidelines.

18. References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33. Epub 2020/01/25.
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74. Epub 2020/02/03.
3. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016;3(1):237-61. Epub 2016/09/01.
4. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3. Epub 2020/02/06.
5. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Control Clin Trials. 2004;25(2):143-56. Epub 2004/03/17.

19. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
1	1	12 March 2021	2	1 April 2021	• Added a second influenza vaccine, Flublok Quadrivalent (QIVr) for administration to participants aged under 65 years. • Increased the sample size from 504 to 726 participants	7 April 2021

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					to reflect the inclusion of the additional vaccine • Clarified the storage of the ChadOx1-nCOV-19 (AstraZeneca/Oxford) vaccine	
2	2	1 April 2021	3	14 April 2021	• Expanded exclusion criterion 4 in response to urgent safety measure received from MHRA • Clarified that clinicians will be blinded when assessing causality for all events, including solicited events and the blinding arrangements for SUSARs • Clarified vacutainers that can be used for blood samples and when samples should be taken • Added that the public may be made aware of the trial via mass vaccination centres.	
5	3	14 April 2021	4	10 May 2021	• Clarification that visits can be made outside of window if there is no other option • Clarification that direct care teams can contact potential volunteers directly rather than wait for completion of prescreening website	

20. Appendix 1

Please see the following pages for the SmPCs relating to the below vaccines:

- FluAd (MF59)
- Flucelvax QIV
- Flublok QIVr
- ChadOx1-nCOV-19
- BNT162b2

2. Statistical methods – additional information

Intention to treat population –all randomised participants, grouped according to their randomised allocation (influenza vaccine or placebo first), regardless of whether they are ineligible, prematurely discontinued treatment or are otherwise protocol deviators.

Per-protocol population - all randomised participants, grouped according to their randomised allocation, excluding those who were deemed a major protocol deviation

Data summaries - Continuous variables are summarised using the mean and standard deviation (SD) (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data are summarised as a number (n/N) and percentage.

Model adjustment – Models include the following covariates fitted as fixed effects: cohort, time period (i.e., following vaccination at D0 and before vaccination at D21, or following vaccination at D21), treatment allocated (influenza first or placebo first), the two-way interactions between each of cohort, time period and treatment allocated and a three-way cohort by time period by treatment allocated interaction, to allow the treatment effect to be estimated separately for each cohort at each time period. Participant and study site are included as random effects. Covariates are excluded if the regression coefficient is not estimable due to insufficient data or collinearity (see table for further details).

Primary outcome analyses - Intention-to-treat and per-protocol analyses were conducted for the primary outcome (complete case analysis). Sensitivity analyses for the primary outcome was also performed by a) imputing missing outcome data as an occurrence, and b) imputing missing outcome data as an absence of a solicited systemic reaction in the 7 days following vaccination.

Missing data – Multiple imputation was used to account for missing data (10 imputed datasets) for the number of different solicited systemic reactions. Conditional multiple imputation and predictive mean matching were used in the imputation model where appropriate.

Outcome(s)	Model	Adjustment	Effect(s) reported
• Proportion of participants who experienced one or more solicited systemic reaction of any severity in the 7 days following D0 and D21 • Proportion of participants who experienced one or more solicited local adverse reaction of any severity following D0 and D21 • Proportion of participants who experienced one or more unsolicited adverse reaction following D0 and D21 • Proportion of participants who experienced one or more medically attended event following D0 and D21	Generalised linear model (GLM) and mixed-effects modified Poisson regression	Clustered sandwich estimator used in GLM to account for clustering within participant. Robust standard errors used in modified Poisson regression.	Risk difference and risk ratio
• Anti-spike protein immunoglobulins at D21	Linear regression after transformation using log base 10	Baseline D0 titre fitted as fixed effect	Geometric mean ratio
• Haemagglutination inhibition at D21 and D42	Longitudinal linear mixed-effects model after transformation using log base 10	Baseline D0 titre fitted as fixed effect; site fitted as random effect	Geometric mean ratio
• Number of different solicited systemic reactions following D0 and D21 • Number of different solicited local reactions following D0 and D21	Longitudinal mixed-effects Poisson regression	Site fitted as random effect	Incidence rate ratio

3. Supplementary tables and figures

Supplementary Table 1 Site recruitment by cohort

Sites	Cohort (COVID-19 vaccine/ Influenza vaccine)						
	ChAdOx1 / QIVc	**BNT162b2 / QIVc**	**ChAdOx1 / aTIV**	**BNT162b2 / aTIV**	**ChAdOx1 / QIVr**	**BNT162b2 / QIVr**	**Total recruited by site**
Royal United Hospitals Bath NHS Foundation Trust	20	13	20	27	-	-	**80**
Cardiff and Vale University Health Board	-	-	-	-	128	-	**128**
Royal Cornwall Hospitals NHS Trust	27	17	48	9	-	-	**101**
Gloucestershire Hospitals NHS Foundation Trust	20	24	13	6	-	-	**63**
North Bristol NHS Trust	20	41	32	18	-	-	**111**
Newquay Health Centre, Newquay	-	-	-	-	-	16	**16**
The Alverton Practice, Penzance	-	-	-	-	-	3	**3**
Knowle House Surgery, Plymouth	-	-	-	-	-	20	**20**
Rotherham, Doncaster and South Humber NHS Foundation Trust	-	-	-	-	-	5	**5**
Great Western Hospitals NHS Foundation Trust	3	8	5	10	-	-	**26**
University College London Hospitals NHS Foundation Trust	-	-	-	1	-	14	**15**
University Hospitals Bristol and Weston NHS Foundation Trust	39	36	28	8	-	-	**111**
TOTAL recruited by cohort	**129**	**139**	**146**	**79**	**128**	**58**	**679**

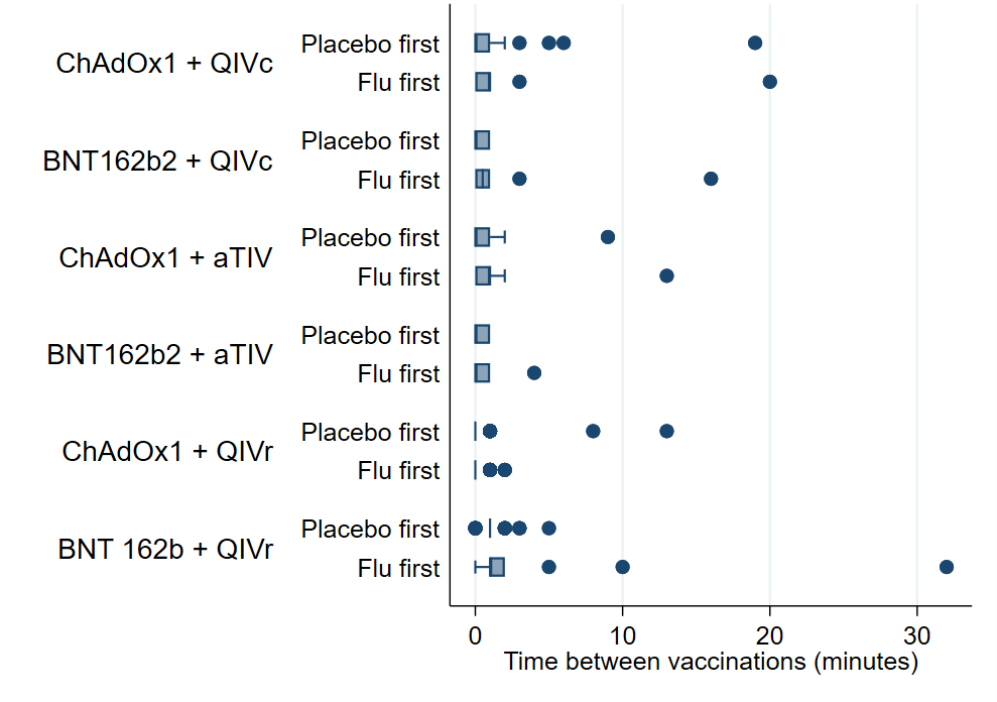
Supplementary Table 2 Protocol deviations

	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)
Any protocol deviation	6/64 (9%)	7/65 (11%)	5/71 (7%)	8/68 (12%)	5/73 (7%)	4/73 (5%)	3/38 (8%)	1/41 (2%)	1/64 (2%)	5/64 (8%)	1/29 (3%)	2/29 (7%)
Any protocol deviation relating to the primary outcome	0/64 (0%)	0/65 (0%)	0/71 (0%)	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%)
D0 deviations												
Participant randomised in error	0/64 (0%)	0/65 (0%)	0/71 (0%)	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%)
Participant randomised to incorrect age category strata	0/64 (0%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	1/73 (1%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Participant randomised to incorrect COVID-19 vaccine strata	1/64 (2%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
Samples not taken prior to vaccination at D0	0/64 (0%)	0/65 (0%)	0/71 (0%)	1/68 (1%)	0/72 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
D21 deviations												
Participant did not attend visit 2 at D21	0/64 (0%)	4/65 (6%)	2/71 (3%)	0/68 (0%)	0/72 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
D21 occurred out of window	1/64 (2%)	0/61 (0%)	2/69 (3%)	2/68 (3%)	2/72 (3%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	1/64 (2%)	1/64 (2%)	1/29 (3%)	2/29 (7%)
Participant did not receive a vaccination at visit 2	0/64 (0%)	1/61 (2%)	0/69 (0%)	0/68 (0%)	0/72 (0%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/63 (0%)	0/29 (0%)	0/29 (0%)
Participant received the incorrect influenza vaccine for their age at D21	1/64 (2%)	-	1/69 (1%)	-	0/72 (0%)	-	0/38 (0%)	-	0/64 (0%)	-	0/29 (0%)	-
D42 deviations												
Participant did not attend visit 3 at D42	0/64 (0%)	5/65 (8%)	1/71 (1%)	0/68 (0%)	1/72 (1%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
D42 occurred out of window	3/64 (5%)	1/60 (2%)	2/70 (3%)	5/68 (7%)	1/71 (1%)	4/73 (5%)	3/38 (8%)	1/41 (2%)	0/64 (0%)	1/63 (2%)	0/29 (0%)	0/29 (0%)

Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0. Note there were no instances of the following deviations: D0 occurred out of window for second COVID-19 vaccination, participant did not receive a vaccination at D0, participant received incorrect COVID-19 vaccine, participant received the alternative vaccine to that they were allocated at D0, participant received the incorrect influenza vaccine for their age at D0, COVID-19 and influenza vaccine given in same location, COVID-19 vaccine expired, influenza/saline vaccine expired at D0, samples not taken prior to vaccination at D21, participant received the alternative vaccine to that they were allocated at D21, influenza/saline vaccine expired at D21.

Note: Of the two participants who attended but were not vaccinated at visit 2 (D21) one participant declined vaccination due to an adverse event following D0. This event was deemed related to the study intervention. The other one was because the participant had a respiratory tract infection. There were no clinical decisions not to vaccinate at D21 for safety reasons.

Supplementary Figure 1 Time elapsed between first and second vaccination injection on D0



One extreme outlier excluded from graph. Participant in BNT162b + QIVr cohort and flu first group received vaccinations 176 minutes apart. Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 3 Comorbidities

	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)
Any cardiovascular disorder	6/64 (9%)	9/65 (14%)	13/71 (18%)	14/68 (21%)	35/73 (48%)	28/73 (38%)	10/38 (26%)	11/41 (27%)	7/64 (11%)	24/64 (38%)	5/29 (17%)	2/29 (7%)
Chronic heart failure	0/64 (0%)	0/65 (0%)	0/71 (0%)	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%)
Ischaemic heart disease	1/64 (2%)	1/65 (2%)	0/71 (0%)	1/68 (1%)	2/73 (3%)	1/73 (1%)	0/38 (0%)	1/41 (2%)	1/64 (2%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
Atrial fibrillation	0/64 (0%)	0/65 (0%)	1/71 (1%)	0/68 (0%)	0/73 (0%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	1/29 (3%)	0/29 (0%)
Peripheral vascular disease	0/64 (0%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	1/29 (3%)	0/29 (0%)
Valvular heart disease	0/64 (0%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	2/73 (3%)	3/73 (4%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
Hypertension	3/64 (5%)	4/65 (6%)	8/71 (11%)	7/68 (10%)	16/73 (22%)	18/73 (25%)	6/38 (16%)	5/41 (12%)	3/64 (5%)	19/64 (30%)	2/29 (7%)	1/29 (3%)
Myocardial infarction	0/64 (0%)	0/65 (0%)	0/71 (0%)	2/68 (3%)	3/73 (4%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	2/64 (3%)	3/64 (5%)	1/29 (3%)	0/29 (0%)
Other cardiovascular disorder	3/64 (5%)	4/65 (6%)	4/71 (6%)	5/68 (7%)	16/73 (22%)	7/73 (10%)	5/38 (13%)	5/41 (12%)	1/64 (2%)	3/64 (5%)	0/29 (0%)	1/29 (3%)
Any respiratory disorder	14/64 (22%)	16/65 (25%)	15/71 (21%)	15/68 (22%)	13/73 (18%)	12/73 (16%)	6/38 (16%)	3/41 (7%)	11/64 (17%)	9/64 (14%)	5/29 (17%)	4/29 (14%)
COPD	1/64 (2%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	5/73 (7%)	0/73 (0%)	1/38 (3%)	0/41 (0%)	0/64 (0%)	1/64 (2%)	0/29 (0%)	2/29 (7%)
Bronchiectasis	1/64 (2%)	0/65 (0%)	0/71 (0%)	1/68 (1%)	1/73 (1%)	2/73 (3%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Asthma	10/64 (16%)	16/65 (25%)	12/71 (17%)	12/68 (18%)	4/73 (5%)	8/73 (11%)	4/38 (11%)	3/41 (7%)	9/64 (14%)	7/64 (11%)	5/29 (17%)	3/29 (10%)
Other respiratory disorder	3/64 (5%)	0/65 (0%)	3/71 (4%)	3/68 (4%)	3/73 (4%)	2/73 (3%)	1/38 (3%)	0/41 (0%)	2/64 (3%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
Any diabetes	7/64 (11%)	6/65 (9%)	4/71 (6%)	3/68 (4%)	3/73 (4%)	5/73 (7%)	2/38 (5%)	1/41 (2%)	10/64 (16%)	13/64 (20%)	6/29 (21%)	2/29 (7%)
Type 1 diabetes	2/64 (3%)	1/65 (2%)	1/71 (1%)	0/68 (0%)	0/73 (0%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	2/64 (3%)	1/64 (2%)	3/29 (10%)	0/29 (0%)
Type 2 diabetes not using insulin	2/64 (3%)	5/65 (8%)	3/71 (4%)	2/68 (3%)	2/73 (3%)	1/73 (1%)	1/38 (3%)	1/41 (2%)	7/64 (11%)	11/64 (17%)	3/29 (10%)	2/29 (7%)
Type 2 diabetes using insulin	1/64 (2%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	0/73 (0%)	0/73 (0%)	1/38 (3%)	0/41 (0%)	1/64 (2%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
Other diabetes	2/64 (3%)	0/65 (0%)	0/71 (0%)	1/68 (1%)	1/73 (1%)	3/73 (4%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Any renal disorder	3/64 (5%)	1/65 (2%)	3/71 (4%)	0/68 (0%)	1/73 (1%)	2/73 (3%)	0/38 (0%)	0/41 (0%)	2/64 (3%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
Chronic kidney disease	0/64 (0%)	1/65 (2%)	1/71 (1%)	0/68 (0%)	0/73 (0%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Other renal disorder	3/64 (5%)	0/65 (0%)	2/71 (3%)	0/68 (0%)	1/73 (1%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	2/64 (3%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
Any history of stroke or TIA	1/64 (2%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	1/73 (1%)	2/73 (3%)	0/38 (0%)	0/41 (0%)	1/64 (2%)	1/64 (2%)	0/29 (0%)	1/29 (3%)
Stroke	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%)	1/29 (3%)
TIA	0/64 (0%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	1/73 (1%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
Other stroke/TIA	1/64 (2%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	0/73 (0%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
Any gastrointestinal disorder	8/64 (13%)	9/65 (14%)	9/71 (13%)	9/68 (13%)	11/73 (15%)	16/73 (22%)	0/38 (0%)	7/41 (17%)	6/64 (9%)	11/64 (17%)	5/29 (17%)	3/29 (10%)
Any liver disorder	1/64 (2%)	1/65 (2%)	0/71 (0%)	1/68 (1%)	1/73 (1%)	0/73 (0%)	1/38 (3%)	0/41 (0%)	3/64 (5%)	2/64 (3%)	0/29 (0%)	2/29 (7%)
Any endocrine disorder	4/64 (6%)	5/65 (8%)	4/71 (6%)	5/68 (7%)	6/73 (8%)	9/73 (12%)	3/38 (8%)	8/41 (20%)	4/64 (6%)	6/64 (9%)	0/29 (0%)	2/29 (7%)
Any neurological disorder	3/64 (5%)	1/65 (2%)	1/71 (1%)	2/68 (3%)	1/73 (1%)	5/73 (7%)	0/38 (0%)	1/41 (2%)	1/64 (2%)	2/64 (3%)	2/29 (7%)	2/29 (7%)
Any past or current cancer diagnosis	7/64 (11%)	6/65 (9%)	7/71 (10%)	2/68 (3%)	10/73 (14%)	9/73 (12%)	8/38 (21%)	8/41 (20%)	7/64 (11%)	4/64 (6%)	1/29 (3%)	1/29 (3%)
Any other medical comorbidities	14/64 (22%)	18/65 (28%)	15/71 (21%)	20/68 (29%)	33/73 (45%)	22/73 (30%)	12/38 (32%)	14/41 (34%)	18/64 (28%)	14/64 (22%)	8/29 (28%)	6/29 (21%)
Any surgical history	36/64 (56%)	39/65 (60%)	45/71 (63%)	32/68 (47%)	50/73 (68%)	56/73 (77%)	28/38 (74%)	33/41 (80%)	33/64 (52%)	34/64 (53%)	16/29 (55%)	19/29 (66%)

Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 4 Total number of e-diary days capturing systemic solicited adverse reactions completed following each visit by cohort

Number of days	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)
D0												
8	58/64 (91%)	57/65 (88%)	65/71 (92%)	63/68 (93%)	66/73 (90%)	66/73 (90%)	35/38 (92%)	39/41 (95%)	57/64 (89%)	59/64 (92%)	23/29 (79%)	24/29 (83%)
7	6/64 (9%)	5/65 (8%)	5/71 (7%)	5/68 (7%)	6/73 (8%)	7/73 (10%)	3/38 (8%)	2/41 (5%)	5/64 (8%)	4/64 (6%)	3/29 (10%)	3/29 (10%)
6	0/64 (0%)	2/65 (3%)	0/71 (0%)	0/68 (0%)	0/73 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	1/64 (2%)	0/64 (0%)	3/29 (10%)	0/29 (0%)
5	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%)	1/29 (3%)
4	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%)	1/29 (3%)
3	0/64 (0%)	0/65 (0%)	0/71 (0%)	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%)
2	0/64 (0%)	0/65 (0%)	0/71 (0%)	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%)
1	0/64 (0%)	0/65 (0%)	0/71 (0%)	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%)
0	0/64 (0%)	0/65 (0%)	0/71 (0%)	0/68 (0%)	1/73 (1%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
D21												
8	59/64 (92%)	52/61 (85%)	53/69 (77%)	56/68 (82%)	67/72 (93%)	67/73 (92%)	35/38 (92%)	40/41 (98%)	60/64 (94%)	61/64 (95%)	21/29 (72%)	22/29 (76%)
7	3/64 (5%)	5/61 (8%)	10/69 (14%)	9/68 (13%)	5/72 (7%)	3/73 (4%)	3/38 (8%)	1/41 (2%)	1/64 (2%)	1/64 (2%)	5/29 (17%)	5/29 (17%)
6	1/64 (2%)	2/61 (3%)	5/69 (7%)	3/68 (4%)	0/72 (0%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	2/64 (3%)	0/64 (0%)	2/29 (7%)	1/29 (3%)
5	0/64 (0%)	0/61 (0%)	1/69 (1%)	0/68 (0%)	0/72 (0%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	1/64 (2%)	0/29 (0%)	1/29 (3%)
4	0/64 (0%)	0/61 (0%)	0/69 (0%)	0/68 (0%)	0/72 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
3	1/64 (2%)	1/61 (2%)	0/69 (0%)	0/68 (0%)	0/72 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	1/64 (2%)	0/64 (0%)	0/29 (0%)	0/29 (0%)
2	0/64 (0%)	0/61 (0%)	0/69 (0%)	0/68 (0%)	0/72 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	1/29 (3%)	0/29 (0%)
1	0/64 (0%)	0/61 (0%)	0/69 (0%)	0/68 (0%)	0/72 (0%)	0/73 (0%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	1/64 (2%)	0/29 (0%)	0/29 (0%)
0	0/64 (0%)	1/61 (2%)	0/69 (0%)	0/68 (0%)	0/72 (0%)	1/73 (1%)	0/38 (0%)	0/41 (0%)	0/64 (0%)	0/64 (0%)	0/29 (0%)	0/29 (0%)

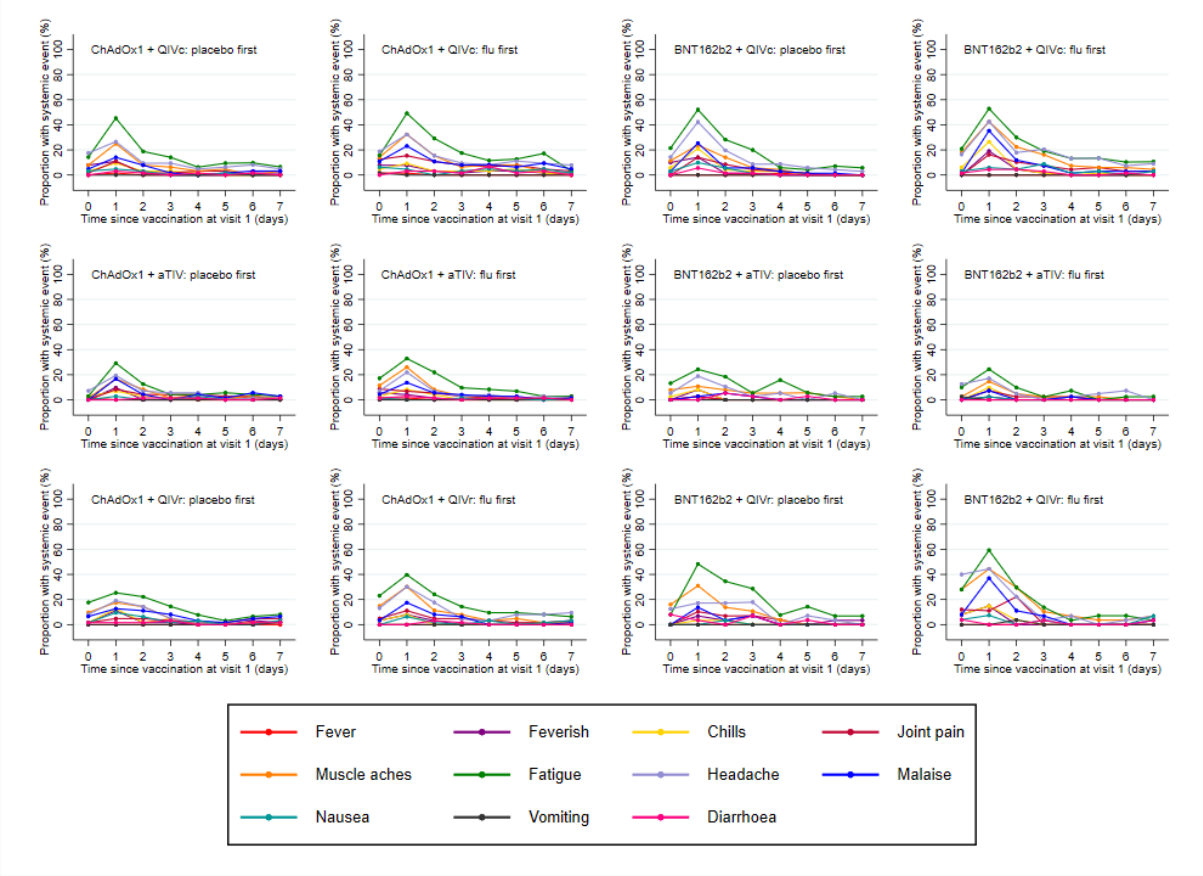
Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 5 Completion of e-diary capturing systemic solicited adverse reactions by visit, day and cohort

Day completed	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)
D0												
0	63/64 (98%)	64/65 (98%)	70/71 (99%)	67/68 (99%)	69/73 (95%)	70/73 (96%)	38/38 (100%)	40/41 (98%)	62/64 (97%)	61/64 (95%)	25/29 (86%)	25/29 (86%)
1	64/64 (100%)	65/65 (100%)	71/71 (100%)	68/68 (100%)	72/73 (99%)	73/73 (100%)	37/38 (97%)	41/41 (100%)	63/64 (98%)	63/64 (98%)	29/29 (100%)	27/29 (93%)
2	64/64 (100%)	65/65 (100%)	71/71 (100%)	67/68 (99%)	72/73 (99%)	73/73 (100%)	38/38 (100%)	41/41 (100%)	63/64 (98%)	62/64 (97%)	29/29 (100%)	27/29 (93%)
3	64/64 (100%)	63/65 (97%)	70/71 (99%)	68/68 (100%)	72/73 (99%)	73/73 (100%)	38/38 (100%)	41/41 (100%)	62/64 (97%)	63/64 (98%)	28/29 (97%)	29/29 (100%)
4	63/64 (98%)	61/65 (94%)	68/71 (96%)	68/68 (100%)	72/73 (99%)	72/73 (99%)	38/38 (100%)	41/41 (100%)	64/64 (100%)	63/64 (98%)	26/29 (90%)	29/29 (100%)
5	64/64 (100%)	63/65 (97%)	69/71 (97%)	67/68 (99%)	71/73 (97%)	72/73 (99%)	36/38 (95%)	41/41 (100%)	64/64 (100%)	63/64 (98%)	28/29 (97%)	28/29 (97%)
6	62/64 (97%)	64/65 (98%)	70/71 (99%)	68/68 (100%)	71/73 (97%)	71/73 (97%)	38/38 (100%)	41/41 (100%)	62/64 (97%)	62/64 (97%)	29/29 (100%)	28/29 (97%)
7	62/64 (97%)	63/65 (97%)	70/71 (99%)	66/68 (97%)	71/73 (97%)	73/73 (100%)	38/38 (100%)	40/41 (98%)	62/64 (97%)	63/64 (98%)	29/29 (100%)	29/29 (100%)
D21												
0	61/64 (95%)	58/61 (95%)	61/69 (88%)	65/68 (96%)	70/72 (97%)	70/73 (96%)	37/38 (97%)	41/41 (100%)	62/64 (97%)	64/64 (100%)	25/29 (86%)	27/29 (93%)
1	64/64 (100%)	59/61 (97%)	63/69 (91%)	65/68 (96%)	71/72 (99%)	71/73 (97%)	37/38 (97%)	41/41 (100%)	63/64 (98%)	63/64 (98%)	28/29 (97%)	28/29 (97%)
2	63/64 (98%)	57/61 (93%)	68/69 (99%)	67/68 (99%)	72/72 (100%)	71/73 (97%)	38/38 (100%)	41/41 (100%)	61/64 (95%)	63/64 (98%)	28/29 (97%)	28/29 (97%)
3	63/64 (98%)	60/61 (98%)	67/69 (97%)	66/68 (97%)	72/72 (100%)	70/73 (96%)	38/38 (100%)	41/41 (100%)	62/64 (97%)	63/64 (98%)	28/29 (97%)	28/29 (97%)
4	63/64 (98%)	59/61 (97%)	68/69 (99%)	67/68 (99%)	71/72 (99%)	72/73 (99%)	38/38 (100%)	41/41 (100%)	64/64 (100%)	62/64 (97%)	26/29 (90%)	28/29 (97%)
5	62/64 (97%)	57/61 (93%)	69/69 (100%)	68/68 (100%)	72/72 (100%)	72/73 (99%)	38/38 (100%)	41/41 (100%)	64/64 (100%)	63/64 (98%)	29/29 (100%)	27/29 (93%)
6	63/64 (98%)	59/61 (97%)	66/69 (96%)	66/68 (97%)	72/72 (100%)	72/73 (99%)	38/38 (100%)	40/41 (98%)	62/64 (97%)	62/64 (97%)	27/29 (93%)	28/29 (97%)
7	63/64 (98%)	57/61 (93%)	67/69 (97%)	65/68 (96%)	71/72 (99%)	70/73 (96%)	37/38 (97%)	41/41 (100%)	64/64 (100%)	61/64 (95%)	26/29 (90%)	28/29 (97%)

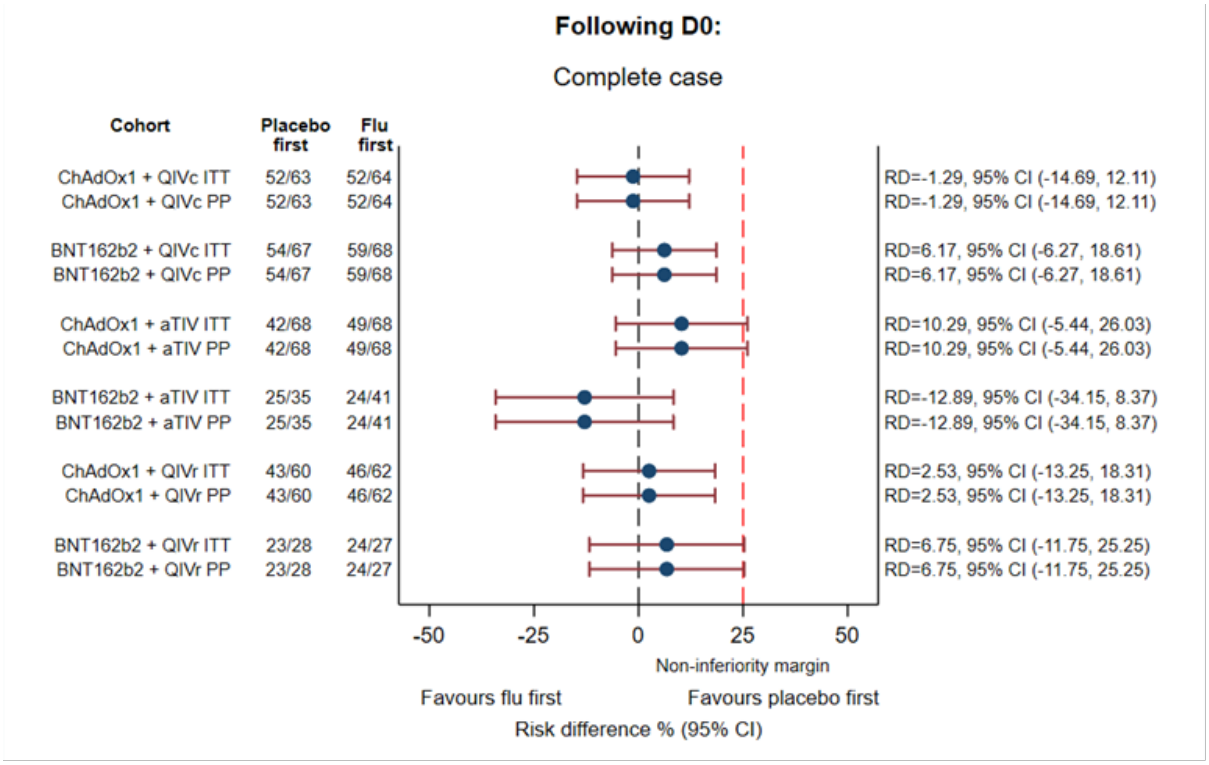
Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

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



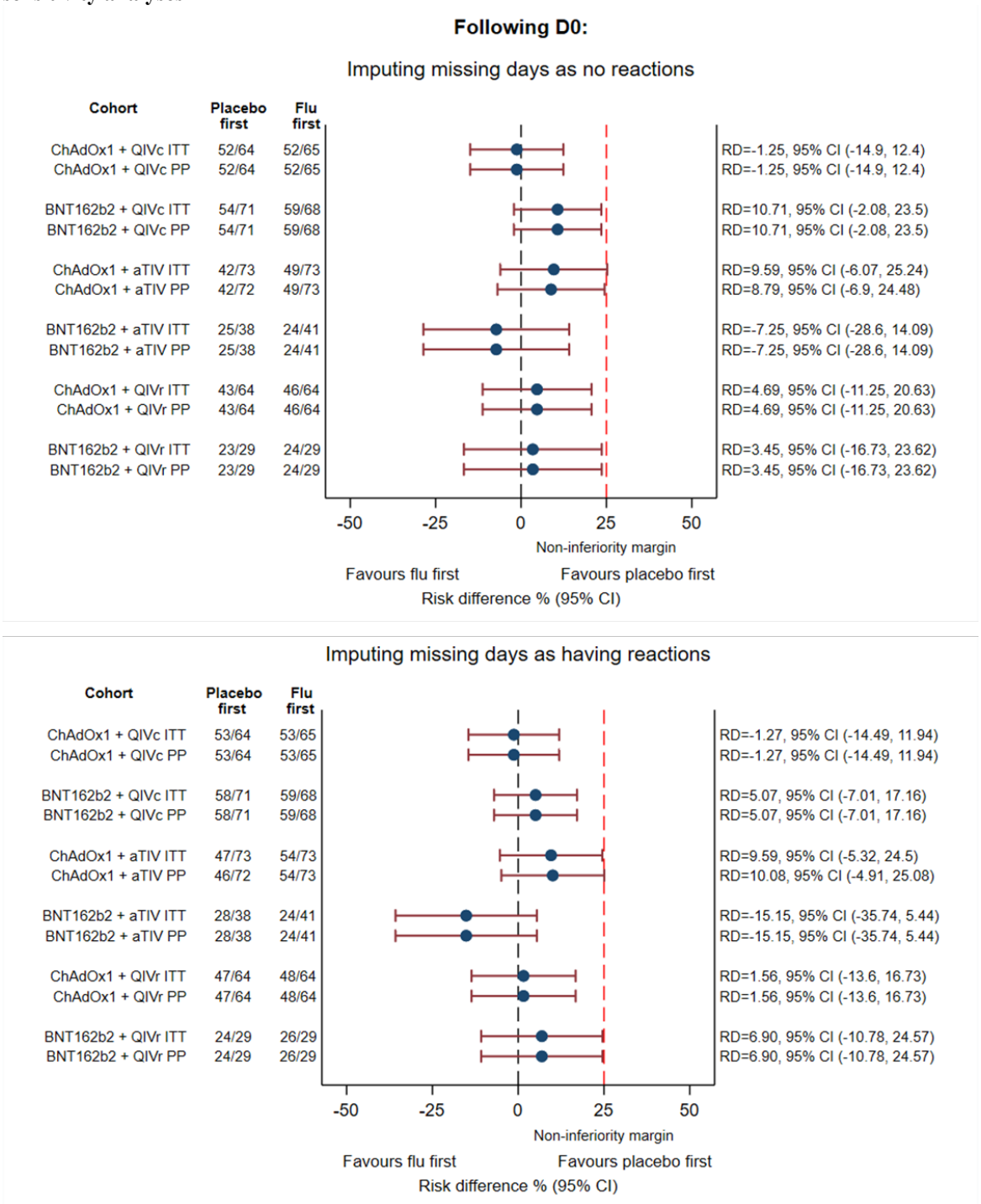
Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary 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: intention to treat and per protocol analyses



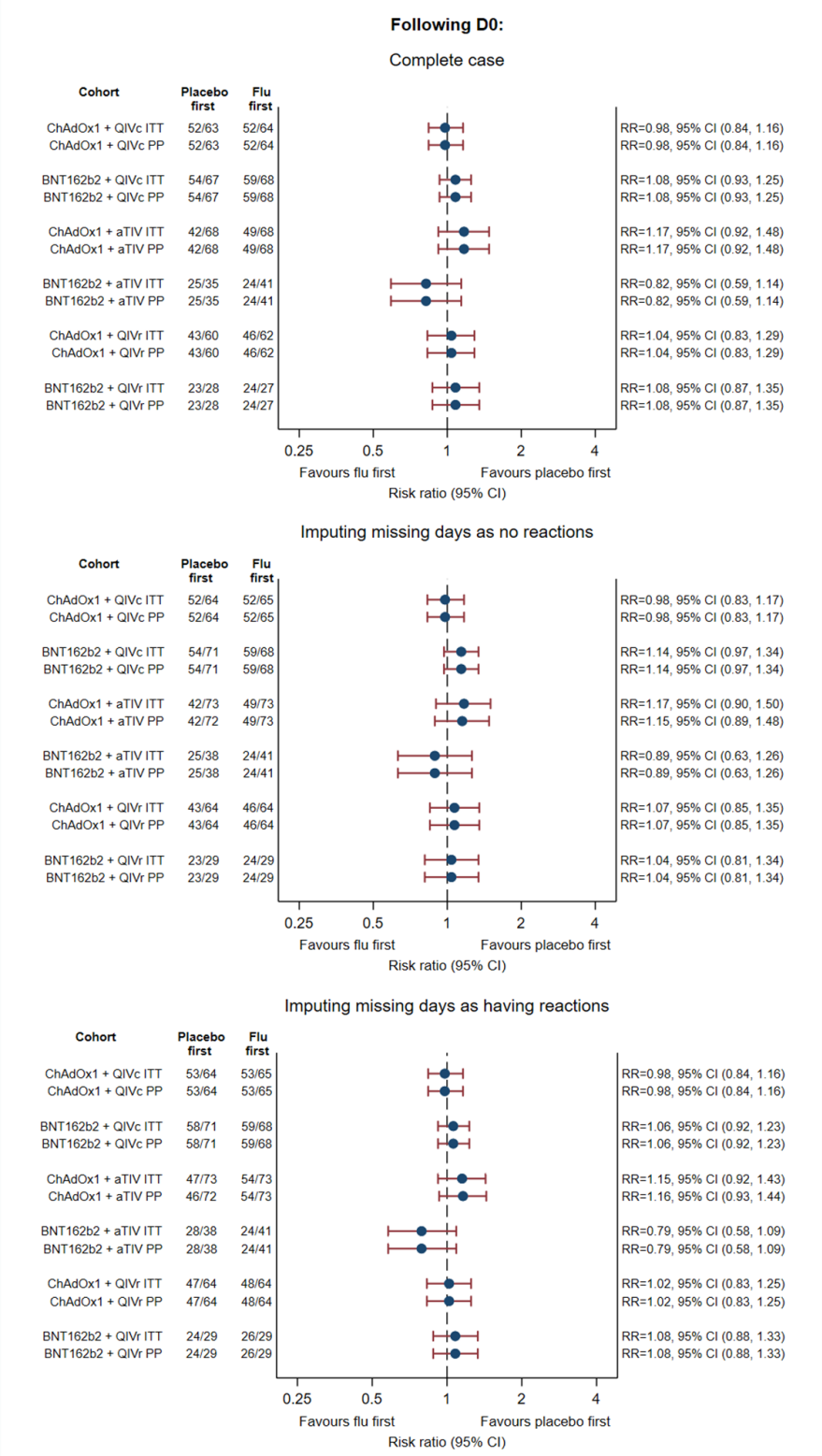
Data are number of participants experiencing one or more solicited systemic event in the 7 days following second COVID-19 vaccination / number of participants with the primary outcome in each group for each cohort. Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza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

Supplementary Figure 4 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: sensitivity analyses



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. 'Imputing missing days as no' = assuming these participants did not experience the primary outcome, and 'Imputing missing days as yes' = assuming these participants did experience the primary outcome. 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.

Supplementary Figure 5 Risk ratios for the number of participants reporting one or more solicited systemic adverse reaction in the 7 days following vaccination on D0



Data are number of participants experiencing one or more solicited systemic event in the 7 days following placebo or influenza vaccine / number of participants included in analysis in each group for each cohort. 'Imputing missing days as no' = assuming these participants did not experience the primary outcome, and 'Imputing missing days as yes' = assuming these participants did experience the primary outcome. 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. RR = risk ratio. CI = confidence interval.

Supplementary Table 6 Solicited adverse reactions in the seven days following D0, cohorts 1 to 3

	ChAdOx1 + QIVc				BNT162b2 + QIVc				ChAdOx1 + aTIV			
	Placebo first (n=64)		Flu first (n=65)		Placebo first (n=71)		Flu first (n=68)		Placebo first (n=72)		Flu first (n=73)	
	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+
Systemic reactions												
Fever	1/54 (2%)	-	2/53 (4%)	-	1/59 (2%)	-	0/57 (0%)	-	1/60 (2%)	-	1/61 (2%)	-
Feverish	12/60 (20%)	0/60 (0%)	9/58 (16%)	1/58 (2%)	14/66 (21%)	0/66 (0%)	14/65 (22%)	1/65 (2%)	10/67 (15%)	0/67 (0%)	8/67 (12%)	1/67 (1%)
Chills	10/60 (17%)	1/60 (2%)	11/58 (19%)	0/58 (0%)	19/67 (28%)	0/67 (0%)	20/65 (31%)	0/65 (0%)	11/66 (17%)	0/66 (0%)	9/66 (14%)	1/66 (2%)
Joint pain	10/58 (17%)	0/58 (0%)	18/60 (30%)	0/60 (0%)	16/66 (24%)	0/66 (0%)	19/65 (29%)	0/65 (0%)	10/67 (15%)	0/67 (0%)	14/68 (21%)	0/68 (0%)
Muscle aches	20/61 (33%)	0/61 (0%)	28/61 (46%)	1/61 (2%)	25/66 (38%)	1/66 (2%)	37/67 (55%)	1/67 (1%)	14/67 (21%)	0/67 (0%)	24/68 (35%)	0/68 (0%)
Fatigue	36/62 (58%)	1/62 (2%)	41/63 (65%)	4/63 (6%)	44/67 (66%)	2/67 (3%)	45/65 (69%)	1/65 (2%)	29/68 (43%)	0/68 (0%)	36/70 (51%)	0/70 (0%)
Headache	31/61 (51%)	0/61 (0%)	36/61 (59%)	2/61 (3%)	36/67 (54%)	0/67 (0%)	42/67 (63%)	1/67 (1%)	21/68 (31%)	0/68 (0%)	22/68 (32%)	1/68 (1%)
Malaise	17/61 (28%)	0/61 (0%)	25/62 (40%)	3/62 (5%)	25/66 (38%)	2/66 (3%)	28/66 (42%)	1/66 (2%)	22/68 (32%)	0/68 (0%)	14/66 (21%)	1/66 (2%)
Nausea	7/59 (12%)	0/59 (0%)	13/58 (22%)	0/58 (0%)	8/66 (12%)	0/66 (0%)	14/64 (22%)	0/64 (0%)	4/67 (6%)	0/67 (0%)	2/66 (3%)	0/66 (0%)
Vomiting	0/58 (0%)	0/58 (0%)	1/57 (2%)	0/57 (0%)	0/65 (0%)	0/65 (0%)	0/63 (0%)	0/63 (0%)	0/66 (0%)	0/66 (0%)	1/66 (2%)	0/66 (0%)
Diarrhoea	5/59 (8%)	0/59 (0%)	10/59 (17%)	0/59 (0%)	5/65 (8%)	0/65 (0%)	9/64 (14%)	0/64 (0%)	3/67 (4%)	0/67 (0%)	4/66 (6%)	0/66 (0%)
Local flu/placebo injection site reactions												
Pain	7/61 (11%)	0/61 (0%)	39/63 (62%)	0/63 (0%)	13/66 (20%)	0/66 (0%)	43/67 (64%)	0/67 (0%)	8/66 (12%)	0/66 (0%)	46/71 (65%)	0/71 (0%)
Itching	1/58 (2%)	0/58 (0%)	6/59 (10%)	0/59 (0%)	2/66 (3%)	0/66 (0%)	1/63 (2%)	0/63 (0%)	0/66 (0%)	0/66 (0%)	1/66 (2%)	0/66 (0%)
Warmth	1/58 (2%)	0/58 (0%)	9/58 (16%)	0/58 (0%)	6/66 (9%)	0/66 (0%)	12/63 (19%)	0/63 (0%)	2/66 (3%)	0/66 (0%)	8/65 (12%)	0/65 (0%)
Redness	11/60 (18%)	-	6/57 (11%)	-	6/65 (9%)	-	4/62 (6%)	-	6/66 (9%)	-	9/67 (13%)	-
Swelling	5/59 (8%)	-	3/57 (5%)	-	3/64 (5%)	-	4/62 (6%)	-	3/67 (4%)	-	9/67 (13%)	-
Hardness	4/59 (7%)	-	5/58 (9%)	-	6/65 (9%)	-	5/62 (8%)	-	5/67 (7%)	-	9/67 (13%)	-
Local COVID injection site reactions												
Pain	42/61 (69%)	1/61 (2%)	45/63 (71%)	1/63 (2%)	63/71 (89%)	3/71 (4%)	63/68 (93%)	1/68 (1%)	37/72 (51%)	0/72 (0%)	32/71 (45%)	0/71 (0%)
Itching	1/58 (2%)	0/58 (0%)	11/58 (19%)	0/58 (0%)	5/66 (8%)	0/66 (0%)	7/63 (11%)	0/63 (0%)	1/66 (2%)	0/66 (0%)	1/67 (1%)	0/67 (0%)
Warmth	15/58 (26%)	0/58 (0%)	19/59 (32%)	1/59 (2%)	26/67 (39%)	0/67 (0%)	27/65 (42%)	0/65 (0%)	5/67 (7%)	0/67 (0%)	1/66 (2%)	0/66 (0%)
Redness	13/60 (22%)	-	18/59 (31%)	-	14/64 (22%)	-	14/63 (22%)	-	6/67 (9%)	-	8/68 (12%)	-
Swelling	17/62 (27%)	-	8/58 (14%)	-	14/65 (22%)	-	13/63 (21%)	-	5/66 (8%)	-	8/67 (12%)	-
Hardness	16/61 (26%)	-	17/58 (29%)	-	19/64 (30%)	-	14/62 (23%)	-	10/68 (15%)	-	7/67 (10%)	-

Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 7 Solicited adverse reactions in the seven days following D0, cohorts 4 to 6

	BNT162b2 + aTIV				ChAdOx1 + QIVr				BNT162b2 + QIVr			
	Placebo first (n=38)		Flu first (n=41)		Placebo first (n=64)		Flu first (n=64)		Placebo first (n=29)		Flu first (n=29)	
	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+
Systemic reactions												
Fever	1/33 (3%)	-	0/37 (0%)	-	0/52 (0%)	-	0/58 (0%)	-	0/20 (0%)	-	0/19 (0%)	-
Feverish	3/35 (9%)	0/35 (0%)	2/39 (5%)	0/39 (0%)	9/60 (15%)	0/60 (0%)	5/59 (8%)	1/59 (2%)	3/24 (13%)	0/24 (0%)	6/25 (24%)	0/25 (0%)
Chills	4/35 (11%)	0/35 (0%)	4/39 (10%)	0/39 (0%)	11/59 (19%)	0/59 (0%)	6/59 (10%)	2/59 (3%)	2/23 (9%)	0/23 (0%)	6/25 (24%)	0/25 (0%)
Joint pain	1/35 (3%)	0/35 (0%)	3/39 (8%)	0/39 (0%)	9/59 (15%)	0/59 (0%)	9/59 (15%)	1/59 (2%)	4/22 (18%)	0/22 (0%)	8/26 (31%)	0/26 (0%)
Muscle aches	6/36 (17%)	0/36 (0%)	6/39 (15%)	0/39 (0%)	20/59 (34%)	0/59 (0%)	24/60 (40%)	1/60 (2%)	11/23 (48%)	0/23 (0%)	16/25 (64%)	0/25 (0%)
Fatigue	19/36 (53%)	0/36 (0%)	17/41 (41%)	0/41 (0%)	30/60 (50%)	0/60 (0%)	37/60 (62%)	1/60 (2%)	17/27 (63%)	1/27 (4%)	22/27 (81%)	0/27 (0%)
Headache	13/36 (36%)	0/36 (0%)	14/40 (35%)	0/40 (0%)	21/59 (36%)	0/59 (0%)	27/61 (44%)	1/61 (2%)	12/23 (52%)	0/23 (0%)	18/26 (69%)	0/26 (0%)
Malaise	2/35 (6%)	0/35 (0%)	4/39 (10%)	0/39 (0%)	18/61 (30%)	1/61 (2%)	17/59 (29%)	1/59 (2%)	5/24 (21%)	1/24 (4%)	11/25 (44%)	1/25 (4%)
Nausea	0/35 (0%)	0/35 (0%)	1/39 (3%)	0/39 (0%)	14/58 (24%)	0/58 (0%)	8/59 (14%)	0/59 (0%)	1/23 (4%)	0/23 (0%)	6/24 (25%)	0/24 (0%)
Vomiting	0/35 (0%)	0/35 (0%)	1/39 (3%)	0/39 (0%)	1/57 (2%)	0/57 (0%)	0/59 (0%)	0/59 (0%)	0/23 (0%)	0/23 (0%)	1/24 (4%)	0/24 (0%)
Diarrhoea	3/35 (9%)	0/35 (0%)	0/39 (0%)	0/39 (0%)	4/57 (7%)	0/57 (0%)	2/60 (3%)	0/60 (0%)	4/25 (16%)	0/25 (0%)	3/24 (13%)	0/24 (0%)
Local flu/placebo injection site reactions												
Pain	4/35 (11%)	0/35 (0%)	18/39 (46%)	0/39 (0%)	12/59 (20%)	0/59 (0%)	32/60 (53%)	0/60 (0%)	1/24 (4%)	0/24 (0%)	17/25 (68%)	0/25 (0%)
Itching	0/35 (0%)	0/35 (0%)	0/39 (0%)	0/39 (0%)	1/57 (2%)	0/57 (0%)	4/59 (7%)	0/59 (0%)	0/23 (0%)	0/23 (0%)	2/24 (8%)	0/24 (0%)
Warmth	1/35 (3%)	0/35 (0%)	1/39 (3%)	0/39 (0%)	6/58 (10%)	0/58 (0%)	7/59 (12%)	0/59 (0%)	0/23 (0%)	0/23 (0%)	4/24 (17%)	0/24 (0%)
Redness	5/35 (14%)	-	3/39 (8%)	-	5/57 (9%)	-	9/60 (15%)	-	2/23 (9%)	-	4/25 (16%)	-
Swelling	2/35 (6%)	-	0/39 (0%)	-	1/57 (2%)	-	3/60 (5%)	-	2/22 (9%)	-	1/24 (4%)	-
Hardness	3/35 (9%)	-	1/39 (3%)	-	5/58 (9%)	-	2/59 (3%)	-	1/23 (4%)	-	2/24 (8%)	-
Local COVID injection site reactions												
Pain	25/38 (66%)	0/38 (0%)	24/40 (60%)	0/40 (0%)	45/62 (73%)	0/62 (0%)	39/60 (65%)	0/60 (0%)	23/27 (85%)	0/27 (0%)	23/25 (92%)	1/25 (4%)
Itching	3/35 (9%)	0/35 (0%)	2/39 (5%)	0/39 (0%)	5/57 (9%)	0/57 (0%)	2/59 (3%)	0/59 (0%)	0/23 (0%)	0/23 (0%)	1/24 (4%)	0/24 (0%)
Warmth	9/37 (24%)	0/37 (0%)	3/39 (8%)	0/39 (0%)	13/58 (22%)	0/58 (0%)	10/59 (17%)	0/59 (0%)	1/23 (4%)	0/23 (0%)	6/24 (25%)	0/24 (0%)
Redness	6/35 (17%)	-	6/40 (15%)	-	13/57 (23%)	-	11/60 (18%)	-	4/24 (17%)	-	3/25 (12%)	-
Swelling	4/35 (11%)	-	4/39 (10%)	-	10/57 (18%)	-	8/60 (13%)	-	6/24 (25%)	-	3/24 (13%)	-
Hardness	12/36 (33%)	-	5/39 (13%)	-	11/57 (19%)	-	8/59 (14%)	-	6/24 (25%)	-	2/24 (8%)	-

Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

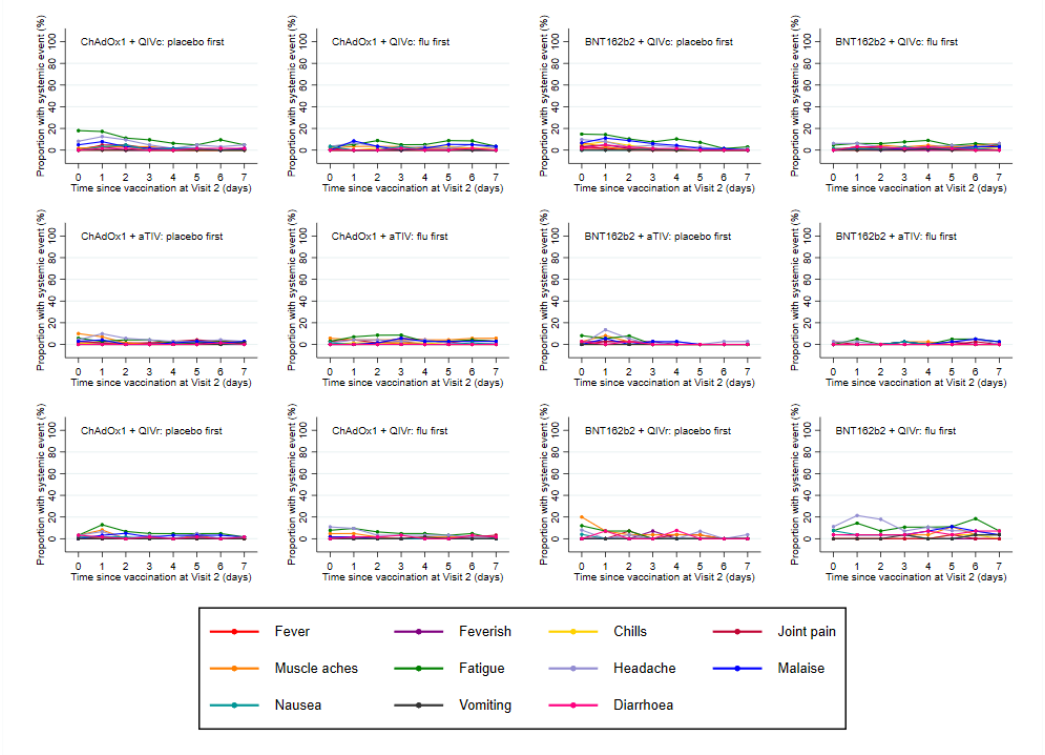
Supplementary Table 8 Reactogenicity primary and secondary outcome summaries by cohort

Outcome		ChAdOx1 + QIVc		BNT 162b2 + QIVc		ChAdOx1 + aTIV		BNT 162b2 + aTIV		ChAdOx1 + QIVr		BNT 162b2 + 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)
D0													
One or more solicited systemic reaction following D0		52/63 (83%)	52/64 (81%)	54/67 (81%)	59/68 (87%)	42/68 (62%)	49/68 (72%)	25/35 (71%)	24/41 (59%)	43/60 (72%)	46/62 (74%)	23/28 (82%)	24/27 (89%)
Number of different systemic reactions following D0	0	11/54 (20%)	12/53 (23%)	13/59 (22%)	9/57 (16%)	26/60 (43%)	19/61 (31%)	10/33 (30%)	17/37 (46%)	17/52 (33%)	16/58 (28%)	5/20 (25%)	3/19 (16%)
	1	19/54 (35%)	6/53 (11%)	7/59 (12%)	9/57 (16%)	11/60 (18%)	12/61 (20%)	10/33 (30%)	9/37 (24%)	7/52 (13%)	8/58 (14%)	4/20 (20%)	0/19 (0%)
	2	7/54 (13%)	9/53 (17%)	10/59 (17%)	3/57 (5%)	3/60 (5%)	9/61 (15%)	5/33 (15%)	5/37 (14%)	11/52 (21%)	13/58 (22%)	3/20 (15%)	4/19 (21%)
	3	7/54 (13%)	3/53 (6%)	6/59 (10%)	10/57 (18%)	8/60 (13%)	10/61 (16%)	6/33 (18%)	2/37 (5%)	8/52 (15%)	7/58 (12%)	4/20 (20%)	4/19 (21%)
	4	1/54 (2%)	9/53 (17%)	8/59 (14%)	11/57 (19%)	5/60 (8%)	3/61 (5%)	1/33 (3%)	3/37 (8%)	4/52 (8%)	5/58 (9%)	1/20 (5%)	2/19 (11%)
	5	4/54 (7%)	7/53 (13%)	6/59 (10%)	5/57 (9%)	6/60 (10%)	4/61 (7%)	0/33 (0%)	1/37 (3%)	1/52 (2%)	5/58 (9%)	1/20 (5%)	3/19 (16%)
	6	1/54 (2%)	5/53 (9%)	4/59 (7%)	5/57 (9%)	1/60 (2%)	2/61 (3%)	0/33 (0%)	0/37 (0%)	0/52 (0%)	1/58 (2%)	1/20 (5%)	1/19 (5%)
	7	2/54 (4%)	2/53 (4%)	4/59 (7%)	2/57 (4%)	0/60 (0%)	1/61 (2%)	1/33 (3%)	0/37 (0%)	1/52 (2%)	2/58 (3%)	1/20 (5%)	1/19 (5%)
	8	1/54 (2%)	0/53 (0%)	1/59 (2%)	3/57 (5%)	0/60 (0%)	0/61 (0%)	0/33 (0%)	0/37 (0%)	2/52 (4%)	1/58 (2%)	0/20 (0%)	1/19 (5%)
	9	1/54 (2%)	0/53 (0%)	0/59 (0%)	0/57 (0%)	0/60 (0%)	1/61 (2%)	0/33 (0%)	0/37 (0%)	1/52 (2%)	0/58 (0%)	0/20 (0%)	0/19 (0%)
Number of different systemic reactions following D0		1 (1.0, 3.0)	2 (1.0, 5.0)	2 (1.0, 5.0)	3 (1.0, 5.0)	1 (0.0, 3.0)	1 (0.0, 3.0)	1 (0.0, 2.0)	1 (0.0, 2.0)	2 (0.0, 3.0)	2 (0.0, 3.0)	2 (0.5, 3.0)	3 (2.0, 5.0)
One or more local adverse reactions following D0		51/63 (81%)	54/64 (84%)	67/71 (94%)	65/68 (96%)	47/72 (65%)	55/71 (77%)	30/38 (79%)	31/41 (76%)	54/63 (86%)	52/61 (85%)	24/27 (89%)	25/26 (96%)
Number of different local reactions following D0	0	12/58 (21%)	10/57 (18%)	4/64 (6%)	3/62 (5%)	25/66 (38%)	16/65 (25%)	8/35 (23%)	10/39 (26%)	9/57 (16%)	9/59 (15%)	3/22 (14%)	1/24 (4%)
	1	21/58 (36%)	24/57 (42%)	24/64 (38%)	27/62 (44%)	24/66 (36%)	30/65 (46%)	14/35 (40%)	19/39 (49%)	21/57 (37%)	25/59 (42%)	14/22 (64%)	14/24 (58%)
	2	9/58 (16%)	6/57 (11%)	18/64 (28%)	15/62 (24%)	11/66 (17%)	8/65 (12%)	8/35 (23%)	5/39 (13%)	14/57 (25%)	13/59 (22%)	1/22 (5%)	4/24 (17%)
	3	8/58 (14%)	6/57 (11%)	6/64 (9%)	3/62 (5%)	5/66 (8%)	4/65 (6%)	0/35 (0%)	2/39 (5%)	5/57 (9%)	5/59 (8%)	1/22 (5%)	1/24 (4%)
	4	3/58 (5%)	4/57 (7%)	1/64 (2%)	8/62 (13%)	1/66 (2%)	6/65 (9%)	1/35 (3%)	2/39 (5%)	4/57 (7%)	7/59 (12%)	2/22 (9%)	1/24 (4%)
	5	5/58 (9%)	3/57 (5%)	10/64 (16%)	3/62 (5%)	0/66 (0%)	1/65 (2%)	2/35 (6%)	1/39 (3%)	4/57 (7%)	0/59 (0%)	1/22 (5%)	3/24 (13%)
	6	0/58 (0%)	4/57 (7%)	1/64 (2%)	3/62 (5%)	0/66 (0%)	0/65 (0%)	2/35 (6%)	0/39 (0%)	0/57 (0%)	0/59 (0%)	0/22 (0%)	0/24 (0%)
Number of different local reactions following D0		1 (1.0, 3.0)	1 (1.0, 3.0)	2 (1.0, 3.0)	2 (1.0, 3.0)	1 (0.0, 2.0)	1 (1.0, 2.0)	1 (1.0, 2.0)	1 (0.0, 2.0)	1 (1.0, 2.0)	1 (1.0, 2.0)	1 (1.0, 1.0)	1 (1.0, 2.0)
One or more reaction grade 3+ following D0		3/54 (6%)	5/55 (9%)	4/58 (7%)	4/58 (7%)	0/60 (0%)	2/60 (3%)	0/33 (0%)	0/37 (0%)	1/53 (2%)	2/58 (3%)	1/19 (5%)	2/20 (10%)
One or more unsolicited reaction following D0		23/60 (38%)	26/59 (44%)	27/65 (42%)	31/65 (48%)	22/69 (32%)	21/68 (31%)	7/34 (21%)	7/39 (18%)	14/55 (25%)	21/60 (35%)	6/22 (27%)	6/24 (25%)
One or more medically attended event following D0		6/58 (10%)	4/56 (7%)	6/63 (10%)	5/62 (8%)	5/65 (8%)	7/64 (11%)	1/33 (3%)	1/38 (3%)	2/55 (4%)	4/54 (7%)	0/20 (0%)	1/23 (4%)
Any SAE following D0		0/58 (0%)	1/56 (2%)	1/63 (2%)	0/62 (0%)	0/65 (0%)	0/64 (0%)	0/33 (0%)	0/38 (0%)	1/55 (2%)	1/54 (2%)	0/20 (0%)	1/23 (4%)
D21													

Outcome		ChAdOx1 + QIVc		BNT 162b2 + QIVc		ChAdOx1 + aTIV		BNT 162b2 + aTIV		ChAdOx1 + QIVr		BNT 162b2 + 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)**
One or more solicited systemic reaction following D21		31/56 (55%)	20/49 (41%)	33/51 (65%)	30/59 (51%)	27/68 (40%)	19/63 (30%)	14/35 (40%)	10/39 (26%)	27/58 (47%)	23/55 (42%)	17/23 (74%)	17/25 (68%)
Number of different systemic reactions following D21	0	25/51 (49%)	29/45 (64%)	18/41 (44%)	29/48 (60%)	41/63 (65%)	44/58 (76%)	21/30 (70%)	29/38 (76%)	31/51 (61%)	32/50 (64%)	6/18 (33%)	8/19 (42%)
	1	10/51 (20%)	7/45 (16%)	12/41 (29%)	9/48 (19%)	14/63 (22%)	5/58 (9%)	6/30 (20%)	6/38 (16%)	12/51 (24%)	10/50 (20%)	8/18 (44%)	4/19 (21%)
	2	5/51 (10%)	1/45 (2%)	4/41 (10%)	4/48 (8%)	2/63 (3%)	4/58 (7%)	1/30 (3%)	0/38 (0%)	4/51 (8%)	3/50 (6%)	3/18 (17%)	0/19 (0%)
	3	6/51 (12%)	5/45 (11%)	1/41 (2%)	3/48 (6%)	2/63 (3%)	2/58 (3%)	1/30 (3%)	1/38 (3%)	1/51 (2%)	2/50 (4%)	1/18 (6%)	1/19 (5%)
	4	2/51 (4%)	2/45 (4%)	3/41 (7%)	1/48 (2%)	2/63 (3%)	2/58 (3%)	0/30 (0%)	1/38 (3%)	2/51 (4%)	2/50 (4%)	0/18 (0%)	3/19 (16%)
	5	0/51 (0%)	1/45 (2%)	1/41 (2%)	0/48 (0%)	1/63 (2%)	0/58 (0%)	0/30 (0%)	1/38 (3%)	1/51 (2%)	0/50 (0%)	0/18 (0%)	2/19 (11%)
	6	0/51 (0%)	0/45 (0%)	1/41 (2%)	0/48 (0%)	1/63 (2%)	1/58 (2%)	1/30 (3%)	0/38 (0%)	0/51 (0%)	0/50 (0%)	0/18 (0%)	0/19 (0%)
	7	2/51 (4%)	0/45 (0%)	1/41 (2%)	1/48 (2%)	0/63 (0%)	0/58 (0%)	0/30 (0%)	0/38 (0%)	0/51 (0%)	1/50 (2%)	0/18 (0%)	0/19 (0%)
	8	1/51 (2%)	0/45 (0%)	0/41 (0%)	1/48 (2%)	0/63 (0%)	0/58 (0%)	0/30 (0%)	0/38 (0%)	0/51 (0%)	0/50 (0%)	0/18 (0%)	1/19 (5%)
Number of different systemic reactions following D21		1 (0.0, 2.0)	0 (0.0, 1.0)	1 (0.0, 2.0)	0 (0.0, 1.0)	0 (0.0, 1.0)	0 (0.0, 0.0)	0 (0.0, 1.0)	0 (0.0, 0.0)	0 (0.0, 1.0)	0 (0.0, 1.0)	1 (0.0, 1.0)	1 (0.0, 4.0)
One or more local adverse reactions following D21		33/62 (53%)	7/52 (13%)	44/63 (70%)	16/59 (27%)	35/70 (50%)	7/68 (10%)	19/37 (51%)	6/40 (15%)	36/60 (60%)	13/62 (21%)	18/24 (75%)	5/22 (23%)
Number of different local reactions following D21	0	29/59 (49%)	45/52 (87%)	19/53 (36%)	43/56 (77%)	35/67 (52%)	61/67 (91%)	18/35 (51%)	34/40 (85%)	24/58 (41%)	49/61 (80%)	6/21 (29%)	17/22 (77%)
	1	16/59 (27%)	5/52 (10%)	23/53 (43%)	7/56 (13%)	23/67 (34%)	3/67 (4%)	12/35 (34%)	6/40 (15%)	20/58 (34%)	8/61 (13%)	11/21 (52%)	5/22 (23%)
	2	6/59 (10%)	0/52 (0%)	5/53 (9%)	2/56 (4%)	8/67 (12%)	1/67 (1%)	2/35 (6%)	0/40 (0%)	7/58 (12%)	4/61 (7%)	1/21 (5%)	0/22 (0%)
	3	4/59 (7%)	2/52 (4%)	3/53 (6%)	3/56 (5%)	0/67 (0%)	2/67 (3%)	1/35 (3%)	0/40 (0%)	2/58 (3%)	0/61 (0%)	1/21 (5%)	0/22 (0%)
	4	4/59 (7%)	0/52 (0%)	2/53 (4%)	1/56 (2%)	1/67 (1%)	0/67 (0%)	0/35 (0%)	0/40 (0%)	3/58 (5%)	0/61 (0%)	1/21 (5%)	0/22 (0%)
	5	0/59 (0%)	0/52 (0%)	1/53 (2%)	0/56 (0%)	0/67 (0%)	0/67 (0%)	2/35 (6%)	0/40 (0%)	2/58 (3%)	0/61 (0%)	1/21 (5%)	0/22 (0%)
Number of different local reactions following D21		1 (0.0, 1.0)	0 (0.0, 0.0)	1 (0.0, 1.0)	0 (0.0, 0.0)	0 (0.0, 1.0)	0 (0.0, 0.0)	0 (0.0, 1.0)	0 (0.0, 0.0)	1 (0.0, 1.0)	0 (0.0, 0.0)	1 (0.0, 1.0)	0 (0.0, 0.0)
One or more reaction grade 3+ following D21		0/51 (0%)	1/45 (2%)	1/42 (2%)	1/48 (2%)	0/63 (0%)	1/58 (2%)	0/30 (0%)	0/38 (0%)	0/51 (0%)	0/50 (0%)	0/18 (0%)	0/19 (0%)
One or more unsolicited reaction following D21		11/54 (20%)	11/52 (21%)	11/54 (20%)	13/59 (22%)	11/67 (16%)	11/67 (16%)	7/36 (19%)	4/41 (10%)	9/57 (16%)	7/58 (12%)	8/22 (36%)	3/22 (14%)
One or more medically attended event following D21		5/53 (9%)	3/48 (6%)	2/52 (4%)	6/55 (11%)	1/62 (2%)	5/64 (8%)	2/33 (6%)	0/40 (0%)	1/56 (2%)	1/56 (2%)	3/22 (14%)	0/21 (0%)
Any SAE following D21		0/53 (0%)	0/48 (0%)	0/52 (0%)	0/55 (0%)	0/62 (0%)	0/64 (0%)	0/33 (0%)	0/40 (0%)	1/56 (2%)	0/56 (0%)	1/22 (5%)	0/21 (0%)

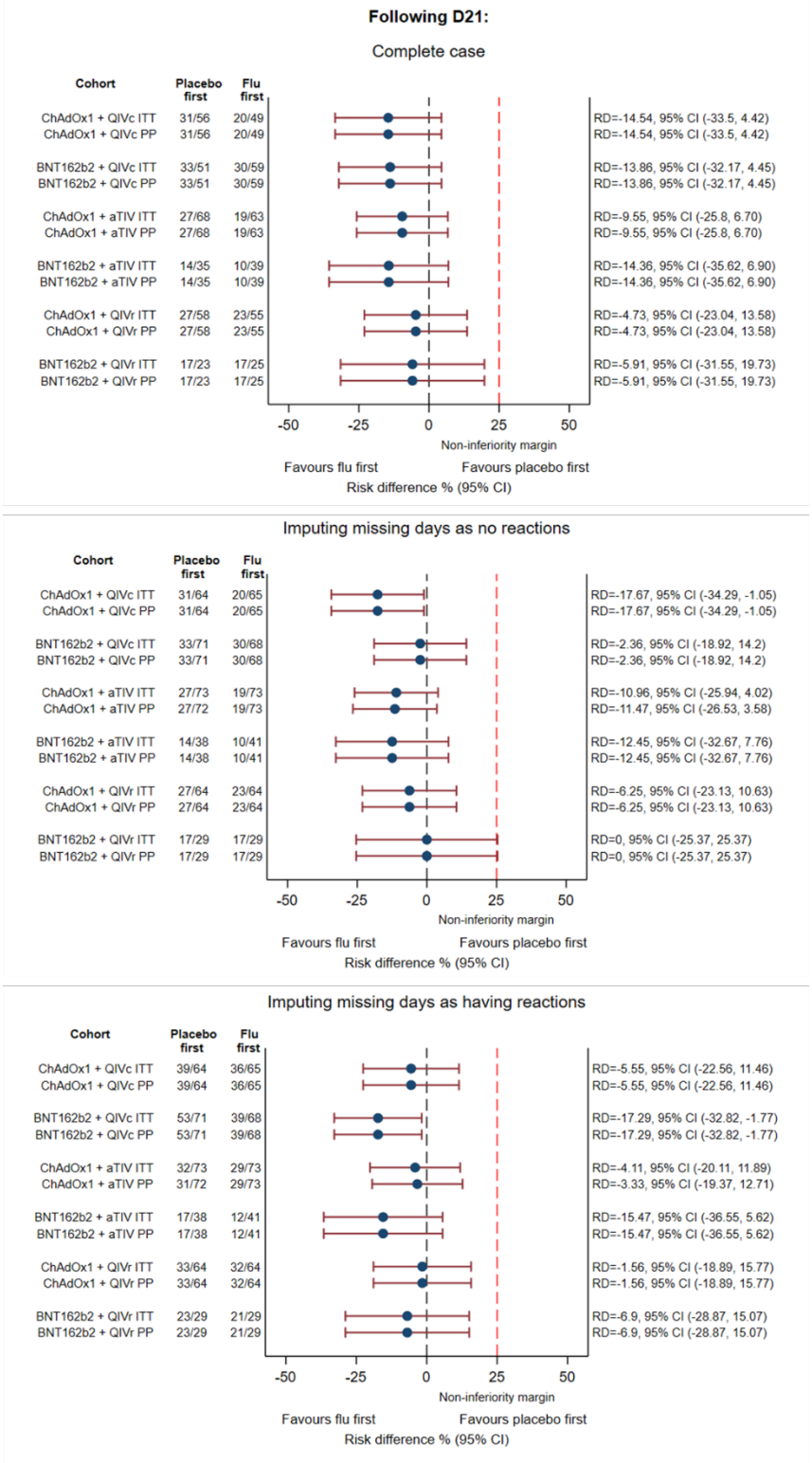
Data are presented as n/N (%) or median (interquartile range). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Figure 6 Seven-day profiles of systemic adverse reactions following D21



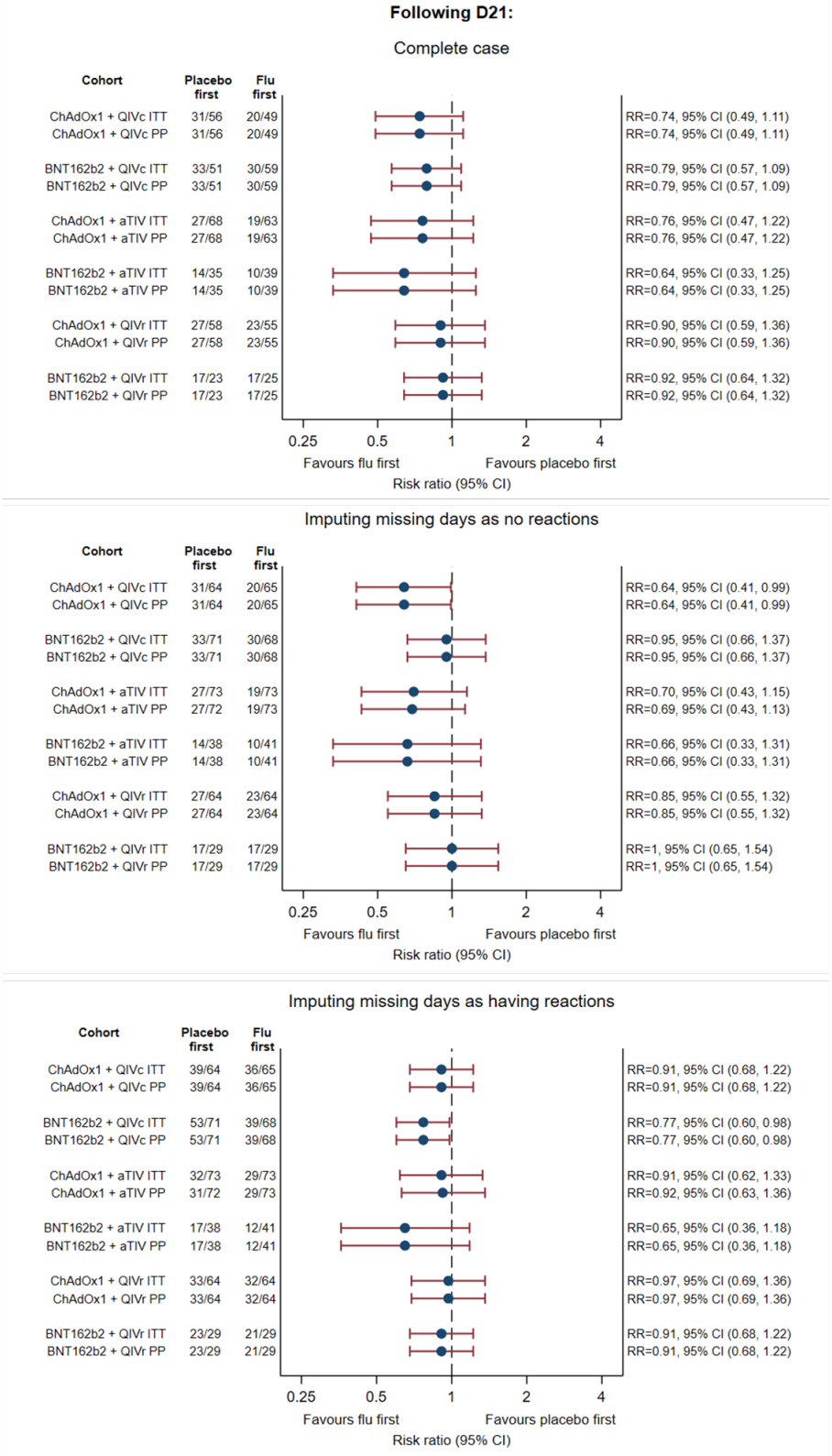
Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Figure 7 Risk differences for the number of participants reporting one or more solicited systemic adverse reaction in the 7 days following vaccination on D21



Data are number of participants experiencing one or more solicited systemic event in the 7 days following placebo or influenza vaccine / number of participants included in analysis in each group for each cohort. 'Imputing missing days as no' = assuming these participants did not experience the primary outcome, and 'Imputing missing days as yes' = assuming these participants did experience the primary outcome. 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.

Supplementary Figure 8 Risk ratios for the number of participants reporting one or more solicited systemic adverse reaction in the 7 days following vaccination on D21



Data are number of participants experiencing one or more solicited systemic event in the 7 days following placebo or influenza vaccine / number of participants included in analysis in each group for each cohort. 'Imputing missing days as no' = assuming these participants did not experience the primary outcome, and 'Imputing missing days as yes' = assuming these participants did experience the primary outcome. 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. RR = risk ratio. CI = confidence interval.

Supplementary Table 9 Solicited adverse reactions in the seven days following D21, cohorts 1 to 3

	ChAdOx1 + QIVc				BNT162b2 + QIVc				ChAdOx1 + aTIV			
	Placebo first (n=64)		Flu first (n=65)		Placebo first (n=71)		Flu first (n=68)		Placebo first (n=72)		Flu first (n=73)	
	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+
Systemic reactions												
Fever	0/51 (0%)	-	0/45 (0%)	-	2/41 (5%)	-	0/48 (0%)	-	0/63 (0%)	-	1/58 (2%)	-
Feverish	4/59 (7%)	0/59 (0%)	1/52 (2%)	0/52 (0%)	6/55 (11%)	0/55 (0%)	2/56 (4%)	0/56 (0%)	4/67 (6%)	0/67 (0%)	3/67 (4%)	0/67 (0%)
Chills	5/59 (8%)	0/59 (0%)	2/52 (4%)	0/52 (0%)	7/54 (13%)	0/54 (0%)	4/56 (7%)	0/56 (0%)	3/69 (4%)	0/69 (0%)	3/67 (4%)	0/67 (0%)
Joint pain	5/59 (8%)	0/59 (0%)	1/53 (2%)	0/53 (0%)	4/53 (8%)	0/53 (0%)	4/56 (7%)	1/56 (2%)	5/67 (7%)	0/67 (0%)	4/67 (6%)	0/67 (0%)
Muscle aches	7/60 (12%)	0/60 (0%)	7/54 (13%)	0/54 (0%)	6/53 (11%)	0/53 (0%)	7/56 (13%)	0/56 (0%)	11/68 (16%)	0/68 (0%)	6/67 (9%)	0/67 (0%)
Fatigue	21/60 (35%)	0/60 (0%)	13/53 (25%)	0/53 (0%)	22/57 (39%)	0/57 (0%)	14/57 (25%)	0/57 (0%)	10/69 (14%)	0/69 (0%)	11/67 (16%)	0/67 (0%)
Headache	16/60 (27%)	0/60 (0%)	10/54 (19%)	0/54 (0%)	15/56 (27%)	0/56 (0%)	16/58 (28%)	0/58 (0%)	13/68 (19%)	0/68 (0%)	6/68 (9%)	1/68 (1%)
Malaise	9/60 (15%)	0/60 (0%)	7/54 (13%)	1/54 (2%)	10/55 (18%)	0/55 (0%)	5/56 (9%)	0/56 (0%)	7/69 (10%)	0/69 (0%)	7/67 (10%)	0/67 (0%)
Nausea	5/59 (8%)	0/59 (0%)	3/53 (6%)	0/53 (0%)	1/53 (2%)	0/53 (0%)	6/57 (11%)	0/57 (0%)	0/67 (0%)	0/67 (0%)	2/67 (3%)	0/67 (0%)
Vomiting	0/59 (0%)	0/59 (0%)	0/52 (0%)	0/52 (0%)	0/53 (0%)	0/53 (0%)	1/56 (2%)	0/56 (0%)	1/67 (1%)	0/67 (0%)	0/67 (0%)	0/67 (0%)
Diarrhoea	5/59 (8%)	0/59 (0%)	2/52 (4%)	0/52 (0%)	4/53 (8%)	1/53 (2%)	6/58 (10%)	0/58 (0%)	1/67 (1%)	0/67 (0%)	0/67 (0%)	0/67 (0%)
Local flu/placebo injection site reactions												
Pain	30/62 (48%)	0/62 (0%)	4/52 (8%)	0/52 (0%)	39/62 (63%)	0/62 (0%)	9/56 (16%)	0/56 (0%)	28/69 (41%)	0/69 (0%)	6/68 (9%)	0/68 (0%)
Itching	0/59 (0%)	0/59 (0%)	1/52 (2%)	0/52 (0%)	2/53 (4%)	0/53 (0%)	2/57 (4%)	0/57 (0%)	3/68 (4%)	0/68 (0%)	2/67 (3%)	0/67 (0%)
Warmth	6/59 (10%)	0/59 (0%)	0/52 (0%)	0/52 (0%)	9/54 (17%)	0/54 (0%)	8/57 (14%)	0/57 (0%)	7/68 (10%)	0/68 (0%)	0/67 (0%)	0/67 (0%)
Redness	10/59 (17%)	-	3/52 (6%)	-	6/54 (11%)	-	4/57 (7%)	-	6/69 (9%)	-	2/67 (3%)	-
Swelling	6/59 (10%)	-	1/52 (2%)	-	5/53 (9%)	-	2/57 (4%)	-	3/68 (4%)	-	2/68 (3%)	-
Hardness	7/59 (12%)	-	2/52 (4%)	-	7/55 (13%)	-	4/57 (7%)	-	4/68 (6%)	-	2/68 (3%)	-

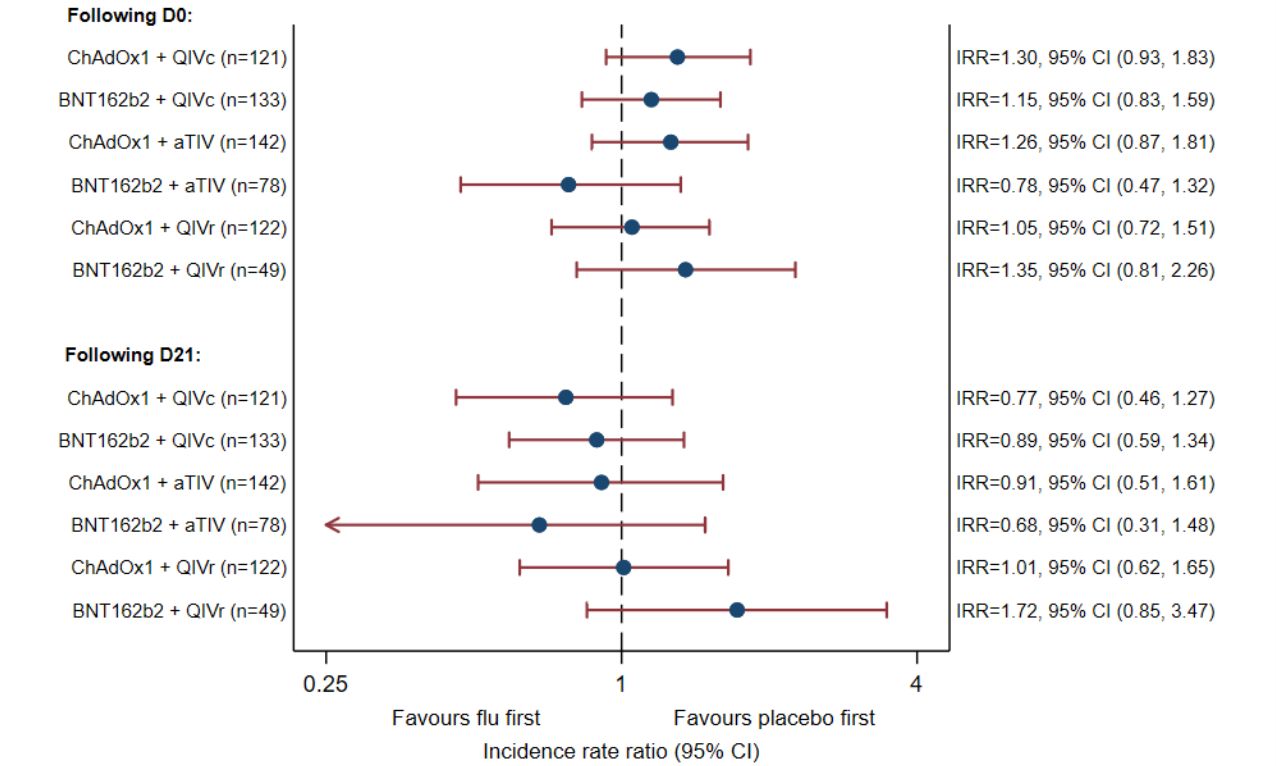
Data are n/N (%). Grading was not defined for fever, redness, swelling or hardness. Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 10 Solicited adverse reactions in the seven days following D21, cohorts 4 to 6

	BNT162b2 + aTIV				ChAdOx1 + QIVr				BNT162b2 + QIVr			
	Placebo first (n=38)		Flu first (n=41)		Placebo first (n=64)		Flu first (n=64)		Placebo first (n=29)		Flu first (n=29)	
	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+	All events	Grade 3+
Systemic reactions												
Fever	0/30 (0%)	-	0/38 (0%)	-	0/52 (0%)	-	0/51 (0%)	-	0/18 (0%)	-	0/19 (0%)	-
Feverish	3/36 (8%)	0/36 (0%)	1/40 (3%)	0/40 (0%)	1/59 (2%)	0/59 (0%)	0/61 (0%)	0/61 (0%)	2/21 (10%)	0/21 (0%)	0/22 (0%)	0/22 (0%)
Chills	0/35 (0%)	0/35 (0%)	1/40 (3%)	0/40 (0%)	1/59 (2%)	0/59 (0%)	1/61 (2%)	0/61 (0%)	0/21 (0%)	0/21 (0%)	1/22 (5%)	0/22 (0%)
Joint pain	1/35 (3%)	0/35 (0%)	3/40 (8%)	0/40 (0%)	1/58 (2%)	0/58 (0%)	4/61 (7%)	0/61 (0%)	4/22 (18%)	0/22 (0%)	1/22 (5%)	0/22 (0%)
Muscle aches	3/35 (9%)	0/35 (0%)	1/40 (3%)	0/40 (0%)	7/58 (12%)	0/58 (0%)	4/61 (7%)	0/61 (0%)	7/23 (30%)	0/23 (0%)	6/22 (27%)	0/22 (0%)
Fatigue	7/36 (19%)	0/36 (0%)	5/40 (13%)	0/40 (0%)	13/59 (22%)	0/59 (0%)	13/61 (21%)	0/61 (0%)	4/23 (17%)	0/23 (0%)	11/25 (44%)	0/25 (0%)
Headache	6/36 (17%)	0/36 (0%)	4/40 (10%)	0/40 (0%)	10/58 (17%)	0/58 (0%)	12/62 (19%)	0/62 (0%)	5/22 (23%)	0/22 (0%)	12/24 (50%)	0/24 (0%)
Malaise	4/37 (11%)	0/37 (0%)	3/40 (8%)	0/40 (0%)	9/58 (16%)	0/58 (0%)	2/61 (3%)	0/61 (0%)	0/21 (0%)	0/21 (0%)	6/22 (27%)	0/22 (0%)
Nausea	0/35 (0%)	0/35 (0%)	1/40 (3%)	0/40 (0%)	2/58 (3%)	0/58 (0%)	0/61 (0%)	0/61 (0%)	1/21 (5%)	0/21 (0%)	4/23 (17%)	0/23 (0%)
Vomiting	0/35 (0%)	0/35 (0%)	0/40 (0%)	0/40 (0%)	0/58 (0%)	0/58 (0%)	1/61 (2%)	0/61 (0%)	0/21 (0%)	0/21 (0%)	1/22 (5%)	0/22 (0%)
Diarrhoea	2/36 (6%)	0/36 (0%)	0/40 (0%)	0/40 (0%)	4/58 (7%)	0/58 (0%)	5/60 (8%)	0/60 (0%)	4/22 (18%)	0/22 (0%)	6/23 (26%)	0/23 (0%)
Local flu/placebo injection site reactions												
Pain	16/37 (43%)	0/37 (0%)	5/40 (13%)	0/40 (0%)	32/60 (53%)	0/60 (0%)	6/62 (10%)	0/62 (0%)	17/24 (71%)	0/24 (0%)	4/22 (18%)	0/22 (0%)
Itching	4/35 (11%)	0/35 (0%)	0/40 (0%)	0/40 (0%)	3/58 (5%)	0/58 (0%)	2/61 (3%)	0/61 (0%)	2/21 (10%)	0/21 (0%)	0/22 (0%)	0/22 (0%)
Warmth	2/35 (6%)	0/35 (0%)	0/40 (0%)	0/40 (0%)	11/58 (19%)	0/58 (0%)	4/61 (7%)	0/61 (0%)	4/23 (17%)	0/23 (0%)	1/22 (5%)	0/22 (0%)
Redness	2/35 (6%)	-	0/40 (0%)	-	10/58 (17%)	-	4/61 (7%)	-	4/22 (18%)	-	0/22 (0%)	-
Swelling	5/36 (14%)	-	0/40 (0%)	-	3/58 (5%)	-	0/61 (0%)	-	5/23 (22%)	-	0/22 (0%)	-
Hardness	4/36 (11%)	-	1/40 (3%)	-	5/58 (9%)	-	1/61 (2%)	-	1/21 (5%)	-	0/22 (0%)	-

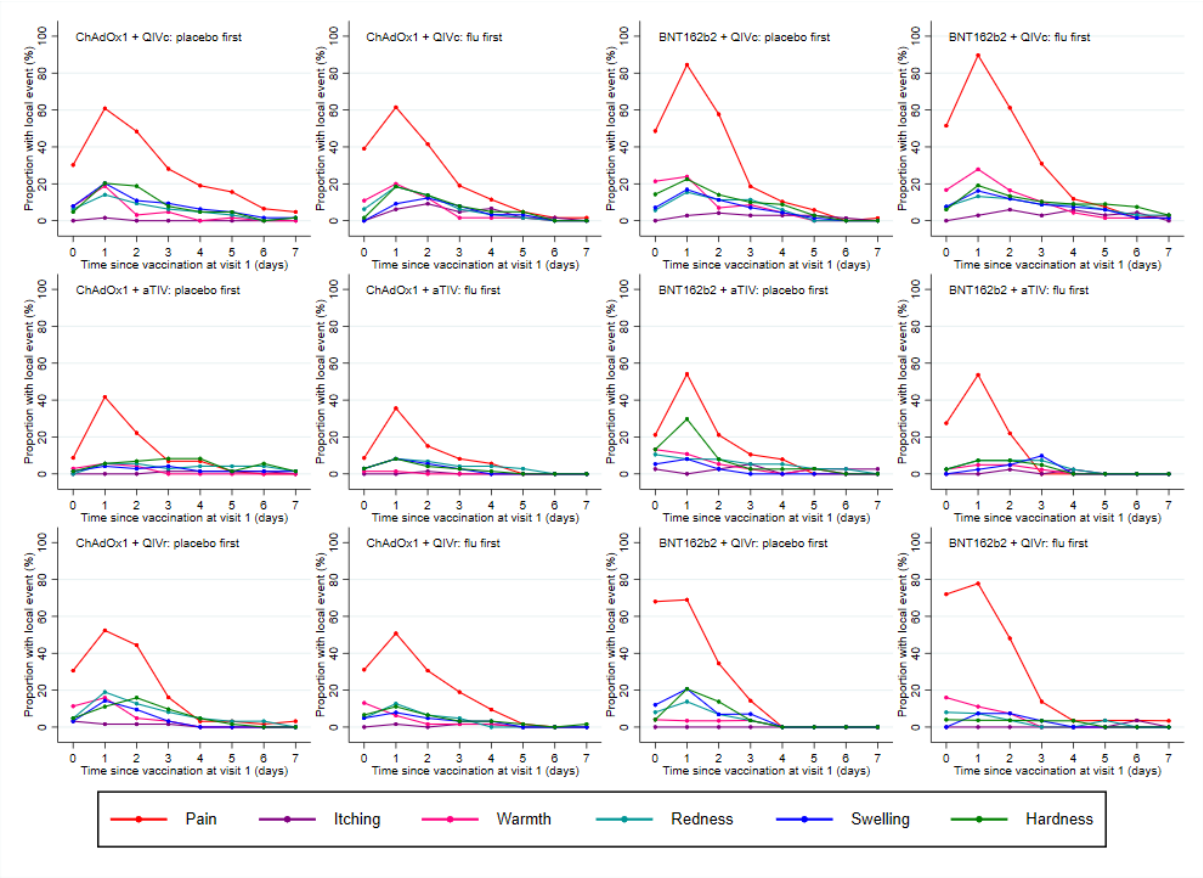
Data are n/N (%). Grading was not defined for fever, redness, swelling or hardness. Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Figure 9 Incidence rate ratios for number of different solicited systemic adverse reactions



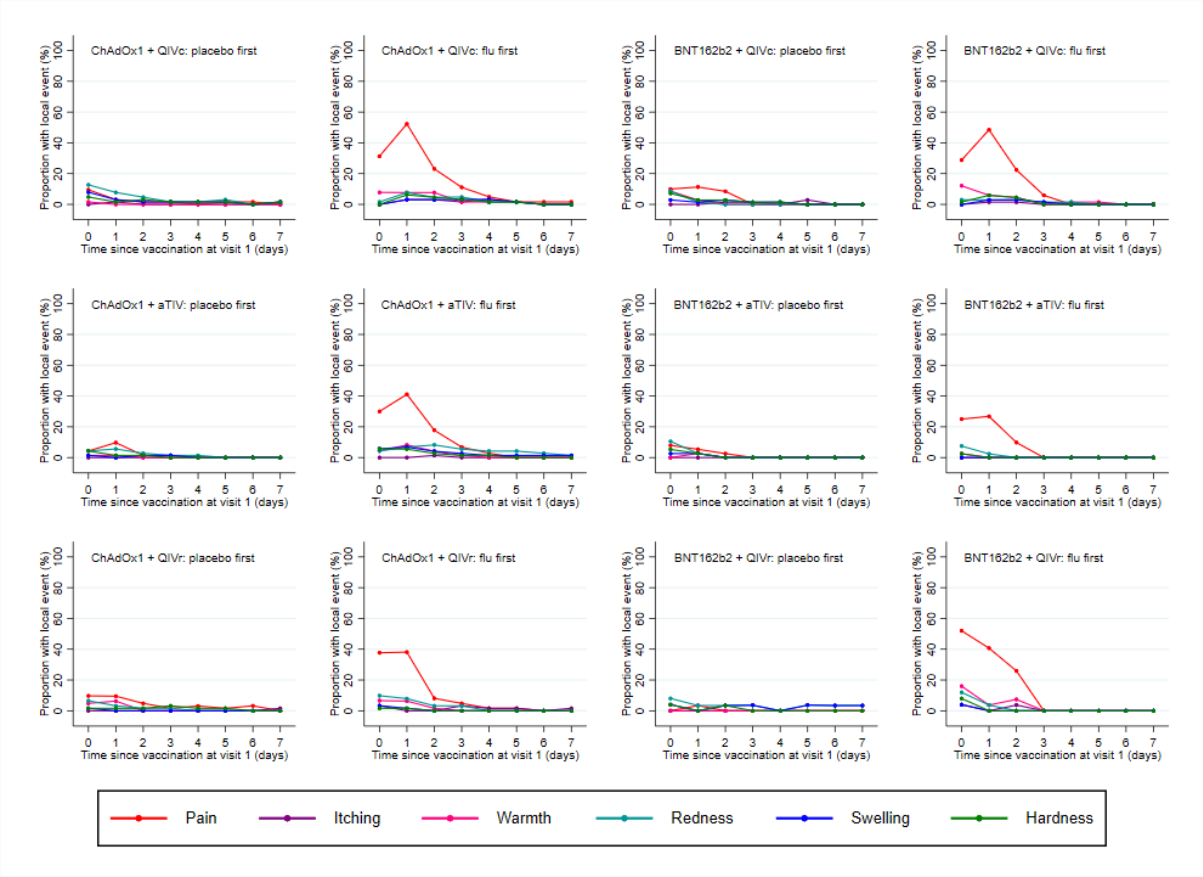
IRR = incidence rate ratio. CI = confidence interval. Multiple imputation (10 imputed datasets) used to account for missing data. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

Supplementary Figure 10 Seven-day profiles of local solicited reactions reported in the limb receiving the COVID-19 vaccination on D0



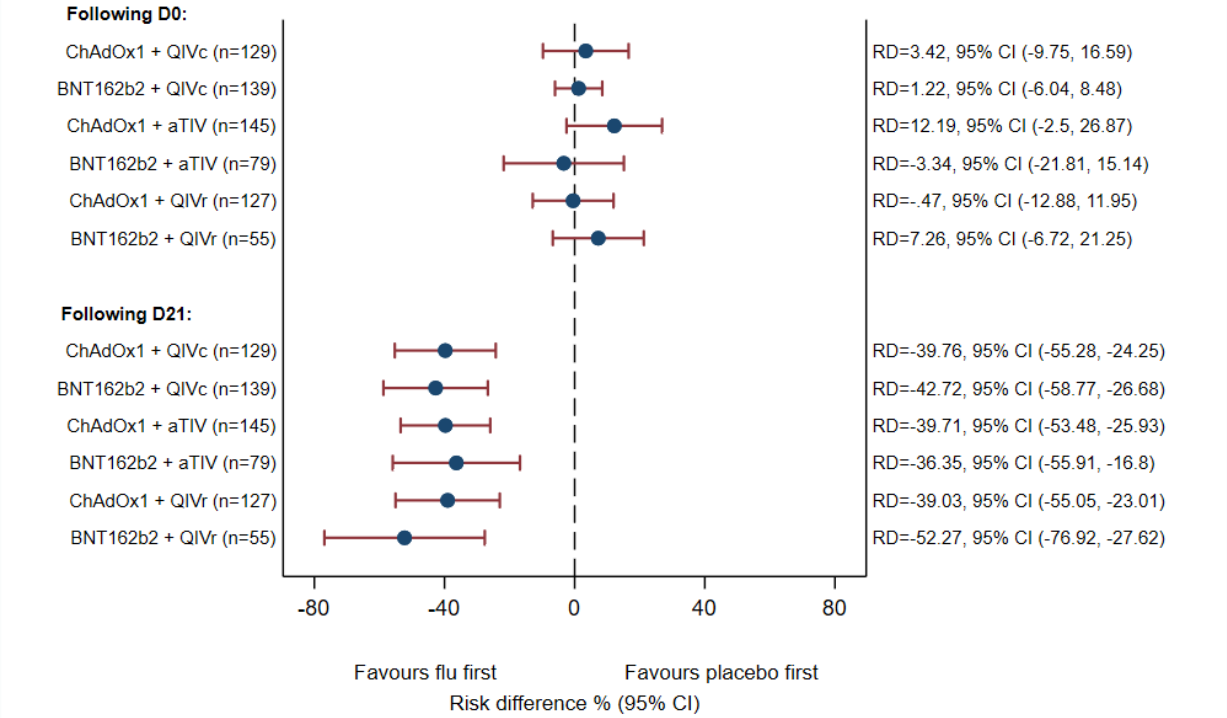
Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Figure 11 Seven-day profiles of local solicited reactions reported in the limb receiving the influenza/placebo vaccination on D0



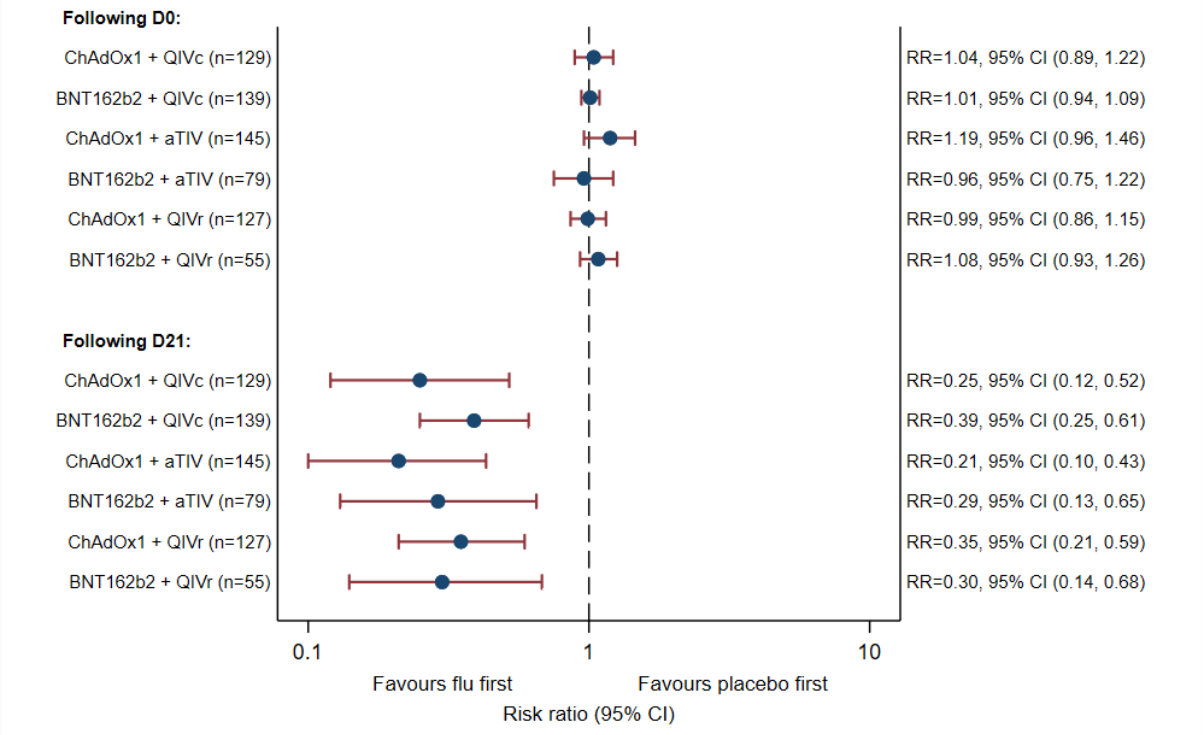
Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Figure 12 Risk differences for the number of participants reporting one or more local solicited reaction



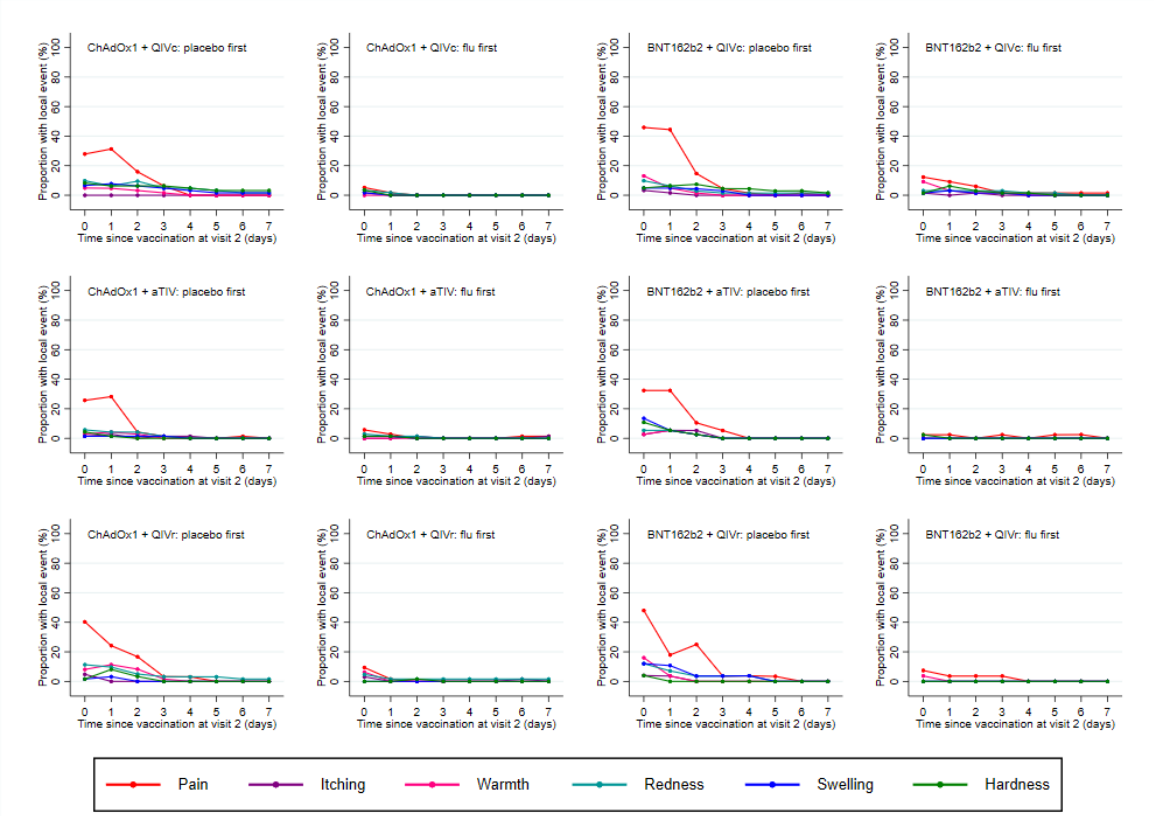
RD = risk difference. CI = confidence interval. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

Supplementary Figure 13 Risk ratios for the number of participants reporting one or more local solicited reaction



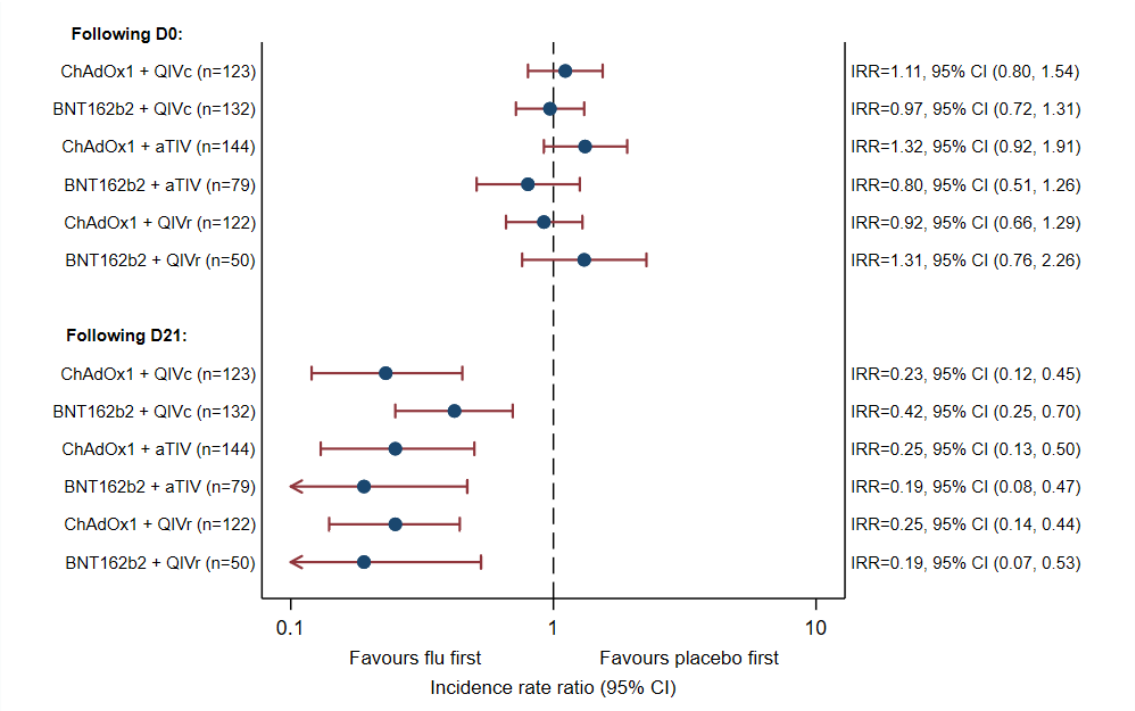
RR = risk ratio. CI = confidence interval. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

Supplementary Figure 14 Seven-day profiles of local solicited reactions reported in the limb receiving the IMP/placebo vaccination on D21



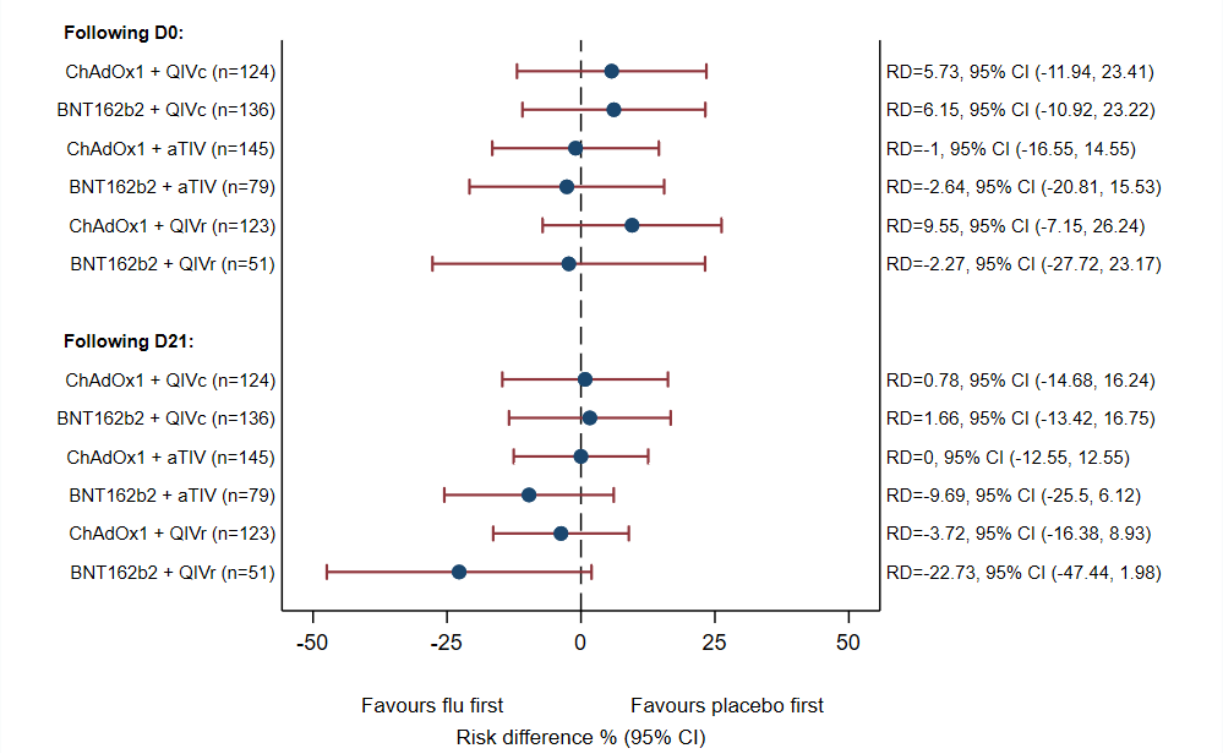
Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Figure 15 Incidence rate ratios for number of different local adverse reactions



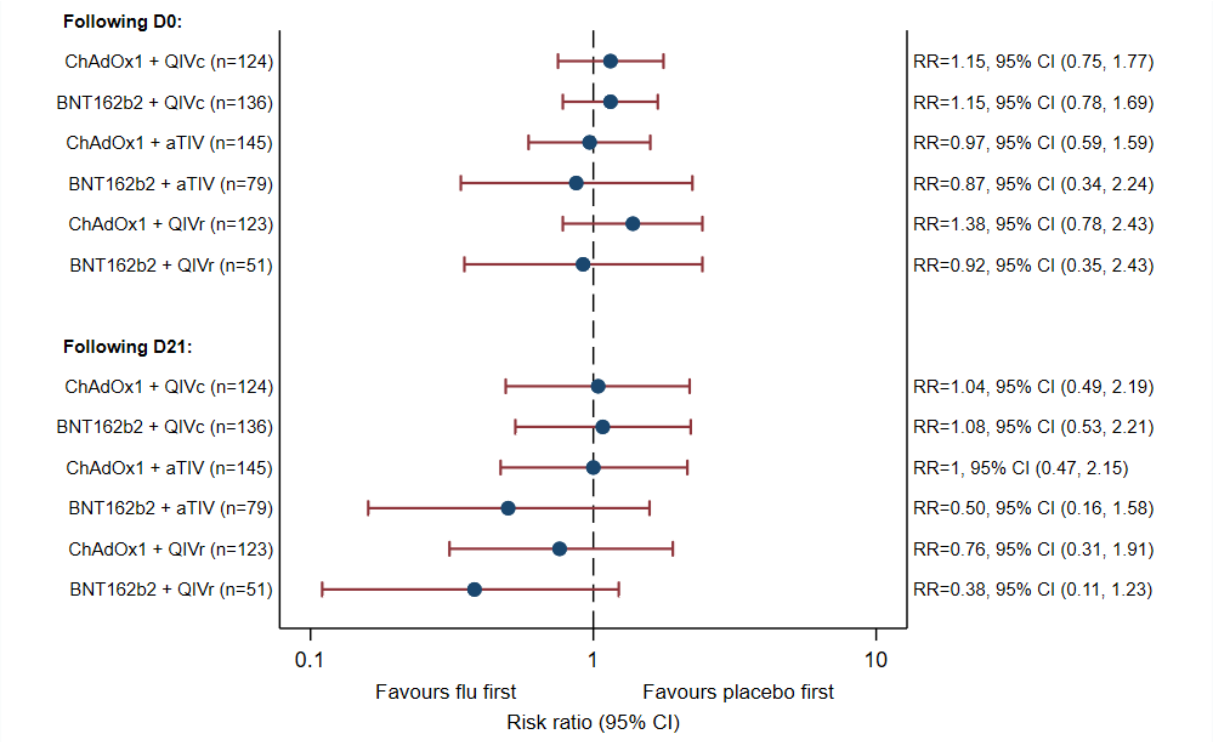
IRR = incidence rate ratio. CI = confidence interval. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

Supplementary Figure 16 Risk differences for the number of participants reporting one or more unsolicited adverse reaction



RD = risk difference. CI = confidence interval. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

Supplementary Figure 17 Risk ratios for the number of participants reporting one or more unsolicited adverse reaction



RR = risk ratio. CI = confidence interval. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

Supplementary Table 11 Unsolicited adverse reactions reported between D0 and D21

	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=72)	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)
Total unsolicited events	51/23 (43%)	38/26 (50%)	38/27 (50%)	53/31 (53%)	31/22 (33%)	38/21 (31%)	11/7 (21%)	7/7 (18%)	15/14 (25%)	29/21 (36%)	9/6 (27%)	8/6 (27%)
Blood and lymphatic system disorders	0/0 (0%)	2/2 (4%)	5/5 (9%)	4/4 (7%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	2/2 (4%)	1/1 (2%)	2/2 (9%)	1/1 (5%)
Lymphadenopathy	0/0 (0%)	2/2 (4%)	4/4 (7%)	4/4 (7%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	2/2 (4%)	1/1 (2%)	2/2 (9%)	1/1 (5%)
Lymphoedema	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Cardiac disorders	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Supraventricular tachycardia	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ear and labyrinth disorders	1/1 (2%)	3/3 (6%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ear pain	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Labyrinthitis	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Vertigo	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Vertigo positional	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Endocrine disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (4%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Diabetic ketoacidosis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Diabetic neuropathy	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Hyperglycaemia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Eye disorders	1/1 (2%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Eye irritation	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ocular hyperaemia	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Swelling of eyelid	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Visual impairment	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Gastrointestinal disorders	7/7 (13%)	4/4 (8%)	5/5 (9%)	5/5 (8%)	1/1 (1%)	5/4 (6%)	3/3 (9%)	0/0 (0%)	3/3 (5%)	2/1 (2%)	0/0 (0%)	2/2 (9%)
Abdominal cramp	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Abdominal discomfort	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Abdominal pain	0/0 (0%)	0/0 (0%)	2/2 (4%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Abdominal pain lower	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Abdominal pain upper	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Angular cheilitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Bruxism	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Change in bowel habit	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Constipation	2/2 (4%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Diarrhoea	1/1 (2%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dry mouth	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dysgeusia	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dyspepsia	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Gastrointestinal disorder	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)
Gingival pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Lip pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Mouth ulcer	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Nausea	3/3 (6%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Oral pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)
Tooth impacted	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Toothache	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Vomiting	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

	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=72)**	**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)**
General disorders and administration site conditions	12/8 (15%)	6/6 (12%)	8/7 (13%)	12/10 (17%)	7/7 (10%)	6/4 (6%)	2/2 (6%)	1/1 (3%)	2/2 (4%)	3/3 (5%)	0/0 (0%)	0/0 (0%)
Axillary pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Chest pain	1/1 (2%)	1/1 (2%)	1/1 (2%)	2/2 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Chills	3/2 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Fatigue	2/2 (4%)	2/2 (4%)	2/2 (4%)	2/2 (3%)	2/2 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Feeling abnormal	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Influenza like illness	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injection site bruising	1/1 (2%)	0/0 (0%)	1/1 (2%)	3/3 (5%)	2/2 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Injection site pain	2/2 (4%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (1%)	3/3 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injection site pruritus	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injection site reaction	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injection site swelling	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injection site warmth	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Lethargy	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	0/0 (0%)
Malaise	1/1 (2%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Night sweats	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Oedema peripheral	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Pain	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Peripheral swelling	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Pyrexia	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Thirst	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Immune system disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Seasonal allergy	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Infections and infestations	4/4 (7%)	2/2 (4%)	3/3 (6%)	4/4 (7%)	2/2 (3%)	4/3 (4%)	1/1 (3%)	1/1 (3%)	2/2 (4%)	4/4 (7%)	2/2 (9%)	0/0 (0%)
Cellulitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Cystitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Gastroenteritis	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Gastroenteritis viral	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Herpes virus infection	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Herpes zoster	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Infected cyst	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Infection	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Lower respiratory tract infection	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Mastitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Oral candidiasis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Oral herpes	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Tooth infection	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Upper respiratory tract infection	1/1 (2%)	2/2 (4%)	2/2 (4%)	2/2 (3%)	1/1 (1%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Urinary tract infection	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Viral infection	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injury, poisoning and procedural complications	4/3 (6%)	1/1 (2%)	1/1 (2%)	2/2 (3%)	1/1 (1%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

	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=72)	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)
Accidental overdose	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Animal scratch	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Chemical burn	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Chilblains	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Fall	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Joint injury	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Soft tissue injury	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Sports injury	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Investigations	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Blood glucose fluctuation	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Body temperature fluctuation	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Metabolism and nutrition disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Hypercholesterolaemia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Musculoskeletal and connective tissue disorders	5/3 (6%)	3/3 (6%)	4/4 (7%)	7/7 (12%)	3/3 (4%)	11/9 (13%)	1/1 (3%)	1/1 (3%)	3/3 (5%)	6/5 (9%)	2/2 (9%)	3/3 (14%)
Arthralgia	0/0 (0%)	1/1 (2%)	0/0 (0%)	2/2 (3%)	1/1 (1%)	3/3 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/1 (2%)	0/0 (0%)	1/1 (5%)
Back pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	1/1 (3%)	2/2 (4%)	0/0 (0%)	0/0 (0%)	2/2 (9%)
Gout	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Joint stiffness	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Joint swelling	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ligament sprain	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Muscle spasms	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Muscle strain	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Musculoskeletal pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Myalgia	4/2 (4%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (1%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Neck pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (5%)	0/0 (0%)
Pain in extremity	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Psoriatic arthropathy	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Radius fracture	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Sacroiliitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Sciatica	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Nervous system disorders	7/7 (13%)	6/6 (12%)	5/5 (9%)	8/8 (14%)	3/3 (4%)	5/4 (6%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	6/5 (9%)	0/0 (0%)	0/0 (0%)
Dizziness	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	0/0 (0%)
Headache	5/5 (9%)	4/4 (8%)	3/3 (6%)	3/3 (5%)	3/3 (4%)	1/1 (1%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	0/0 (0%)
Migraine	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Nerve injury	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Neuralgia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Paraesthesia	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Presyncope	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Restless legs syndrome	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Tension headache	0/0 (0%)	0/0 (0%)	1/1 (2%)	2/2 (3%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Psychiatric disorders	2/2 (4%)	2/2 (4%)	0/0 (0%)	2/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	0/0 (0%)
Anxiety	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Emotional distress	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

	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=72)	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)
Insomnia	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Mixed anxiety and depressive disorder	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Panic attack	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Restlessness	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Renal and urinary disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (1%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Pollakiuria	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Polyuria	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Urinary tract discomfort	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Reproductive system and breast disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (5%)
Balanoposthitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Breast pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Dysmenorrhoea	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ovarian cyst ruptured	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)
Respiratory, thoracic and mediastinal disorders	5/3 (6%)	5/5 (10%)	2/1 (2%)	5/5 (8%)	8/7 (10%)	2/2 (3%)	0/0 (0%)	2/2 (5%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (5%)
Asthma	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Cough	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dry throat	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dyspnoea	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dyspnoea exertional	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Epistaxis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Nasal congestion	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)
Oropharyngeal pain	2/2 (4%)	2/2 (4%)	0/0 (0%)	1/1 (2%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Rhinitis	0/0 (0%)	2/2 (4%)	0/0 (0%)	1/1 (2%)	3/2 (3%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Rhinorrhoea	0/0 (0%)	0/0 (0%)	1/1 (2%)	3/3 (5%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Sinusitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Sneezing	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Skin and subcutaneous tissue disorders	3/3 (6%)	3/3 (6%)	3/3 (6%)	2/2 (3%)	1/1 (1%)	1/1 (1%)	1/1 (3%)	1/1 (3%)	1/1 (2%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Blister	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Contusion	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Eczema	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Pain of skin	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Pruritus	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Psoriasis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Rash	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Rash erythematous	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Skin lesion	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Urticaria	0/0 (0%)	0/0 (0%)	2/2 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Vascular disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Conjunctival haemorrhage	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Hypertension	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Telangiectasia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 12 Unsolicited adverse reactions reported between D21 and D42

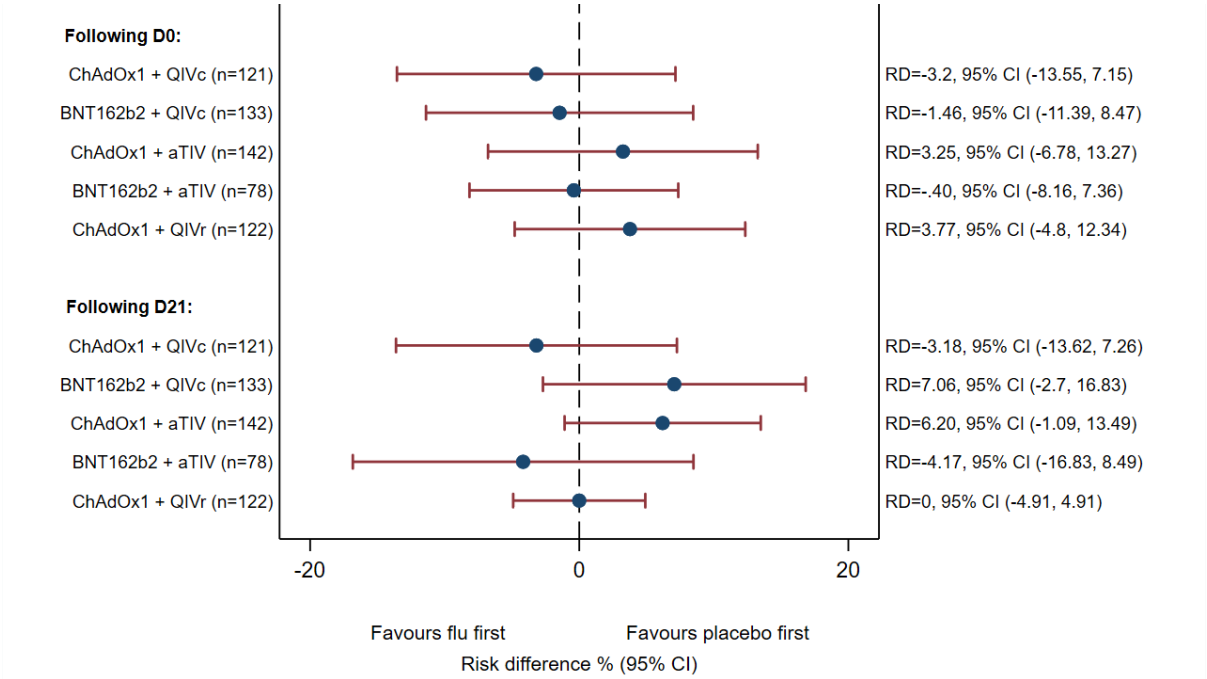
	ChAdOx1 + QIVc		BNT162b2 + QIVc		ChAdOx1 + aTIV		BNT162b2 + aTIV		ChAdOx1 + QIVr		BNT162b2 + QIVr	
	Placebo first (n=64)	Flu first (n=65)	Placebo first (n=71)	Flu first (n=68)	Placebo first (n=72)	Flu first (n=73)	Placebo first (n=38)	Flu first (n=41)	Placebo first (n=64)	Flu first (n=64)	Placebo first (n=29)	Flu first (n=29)
Total unsolicited events	18/11 (20%)	12/11 (21%)	17/11 (20%)	18/13 (22%)	14/11 (16%)	16/11 (16%)	11/7 (21%)	4/4 (10%)	10/9 (16%)	13/7 (12%)	14/8 (36%)	3/3 (14%)
Blood and lymphatic system disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	2/2 (4%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Anaemia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Lymphadenopathy	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	1/1 (2%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Cardiac disorders	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Palpitations	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dental and gingival conditions	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Gingivitis	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ear and labyrinth disorders	2/2 (4%)	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Labyrinthitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Vertigo	2/2 (4%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Vertigo positional	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Endocrine disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Type 2 diabetes mellitus	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Gastrointestinal disorders	2/2 (4%)	2/2 (4%)	2/2 (4%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	1/1 (3%)	0/0 (0%)	2/2 (4%)	1/1 (2%)	3/2 (9%)	0/0 (0%)
Abdominal discomfort	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Abdominal pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Diarrhoea	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Diverticulitis	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dysgeusia	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Nausea	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Odynophagia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Tongue ulceration	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Toothache	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Vomiting	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
General disorders and administration site conditions	3/2 (4%)	0/0 (0%)	3/2 (4%)	4/4 (7%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Facial pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Fatigue	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Influenza like illness	0/0 (0%)	0/0 (0%)	2/2 (4%)	1/1 (2%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injection site bruising	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Lethargy	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Malaise	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Night sweats	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Pyrexia	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Immune system disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Angioedema	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Seasonal allergy	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Infections and infestations	3/2 (4%)	2/2 (4%)	3/3 (6%)	1/1 (2%)	1/1 (1%)	0/0 (0%)	3/3 (9%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	3/3 (14%)	1/1 (5%)
Coronavirus infection	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)

	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=72)**	**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)**
Gastroenteritis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Oral herpes	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Pilonidal cyst	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Respiratory tract infection	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Upper respiratory tract infection	0/0 (0%)	1/1 (2%)	1/1 (2%)	1/1 (2%)	1/1 (1%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Urinary tract infection	3/2 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (6%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Viral infection	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injury, poisoning and procedural complications	1/1 (2%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	2/2 (3%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Arthropod bite	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Arthropod sting	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Fall	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Joint injury	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Road traffic accident	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Soft tissue injury	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Metabolism and nutrition disorders	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dehydration	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Hypercholesterolaemia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Musculoskeletal and connective tissue disorders	2/2 (4%)	1/1 (2%)	2/2 (4%)	3/3 (5%)	4/4 (6%)	4/3 (4%)	3/2 (6%)	2/2 (5%)	0/0 (0%)	1/1 (2%)	1/1 (5%)	0/0 (0%)
Arthralgia	0/0 (0%)	0/0 (0%)	1/1 (2%)	2/2 (3%)	0/0 (0%)	2/1 (1%)	0/0 (0%)	2/2 (5%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Bone pain	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Muscle spasms	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Muscle strain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Musculoskeletal injury	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Musculoskeletal pain	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Myalgia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	1/1 (1%)	3/2 (6%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Rotator cuff syndrome	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Sciatica	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Synovial rupture	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Tenosynovitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Nervous system disorders	1/1 (2%)	3/3 (6%)	4/3 (6%)	2/2 (3%)	2/2 (3%)	0/0 (0%)	2/2 (6%)	0/0 (0%)	2/2 (4%)	3/2 (3%)	2/2 (9%)	0/0 (0%)
Allodynia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Dizziness	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Headache	1/1 (2%)	1/1 (2%)	2/1 (2%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	1/1 (5%)	0/0 (0%)
Migraine	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Paraesthesia	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Syncope	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Tension headache	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Psychiatric disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Acute stress disorder	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Reproductive system and breast disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

	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=72)**	**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)**
Ovarian cyst	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Respiratory, thoracic and mediastinal disorders	2/2 (4%)	2/2 (4%)	2/1 (2%)	1/1 (2%)	3/3 (4%)	4/4 (6%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	6/3 (5%)	2/2 (9%)	1/1 (5%)
Cough	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dry throat	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Dysphonia	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dyspnoea	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Oropharyngeal pain	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (5%)	0/0 (0%)
Productive cough	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Rhinitis	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	3/3 (5%)	0/0 (0%)	0/0 (0%)
Rhinorrhoea	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)
Sinusitis	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Wheezing	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Skin and subcutaneous tissue disorders	1/1 (2%)	0/0 (0%)	0/0 (0%)	3/3 (5%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	2/2 (9%)	1/1 (5%)
Contusion	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Eczema	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Hyperhidrosis	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Increased tendency to bruise	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)
Pruritus	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Rash	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Rash erythematous	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Skin discolouration	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (1%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Surgical and medical procedures	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Cataract operation	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

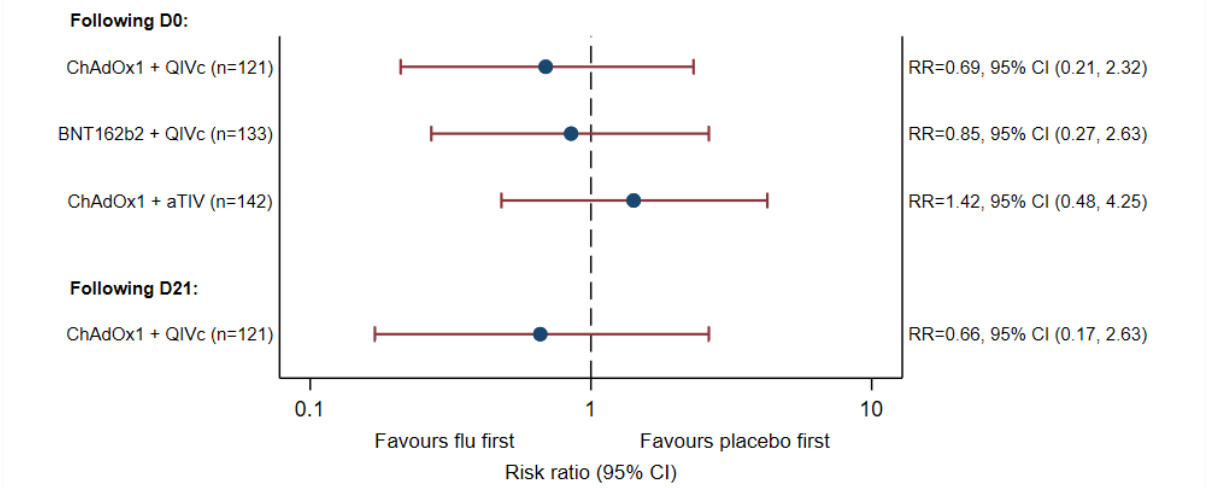
Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Figure 18 Risk differences for number of participants reporting one or more medically attended event



RD = risk difference. CI = confidence interval. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

Supplementary Figure 19 Risk ratios for number of participants reporting one or more medically attended event



RR = risk ratio. CI = confidence interval. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

Supplementary Table 13 Medically attended events reported between D0 and D21

	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=72)**	**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)**
Total medically attended events	12/6 (11%)	5/4 (8%)	6/6 (12%)	5/5 (9%)	6/5 (8%)	9/7 (11%)	1/1 (3%)	1/1 (3%)	2/2 (4%)	4/4 (7%)	0/0 (0%)	1/1 (4%)
Cardiac disorders	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Supraventricular tachycardia	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ear and labyrinth disorders	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Labyrinthitis	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Endocrine disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Diabetic ketoacidosis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Eye disorders	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Visual impairment	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Gastrointestinal disorders	1/1 (2%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	2/2 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Angular cheilitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Bruxism	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Constipation	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Tooth impacted	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Toothache	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
General disorders and administration site conditions	1/1 (2%)	0/0 (0%)	2/2 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Chest pain	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Fatigue	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Peripheral swelling	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Infections and infestations	3/3 (6%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (3%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Cellulitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Infected cyst	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Infection	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Lower respiratory tract infection	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Tooth infection	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Urinary tract infection	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injury, poisoning and procedural complications	3/2 (4%)	1/1 (2%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Accidental overdose	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Animal scratch	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Chemical burn	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Fall	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Joint injury	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Soft tissue injury	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Metabolism and nutrition disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Hypercholesterolaemia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Musculoskeletal and connective tissue disorders	1/1 (2%)	1/1 (2%)	1/1 (2%)	1/1 (2%)	1/1 (2%)	2/2 (3%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	2/2 (4%)	0/0 (0%)	0/0 (0%)
Arthralgia	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Back pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ligament sprain	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Myalgia	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

	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=72)**	**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)**
Neck pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Pain in extremity	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Radius fracture	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Nervous system disorders	2/2 (4%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Headache	2/2 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Migraine	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Psychiatric disorders	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Anxiety	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Insomnia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Renal and urinary disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Urinary tract discomfort	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Reproductive system and breast disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (4%)
Balanoposthitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ovarian cyst ruptured	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (4%)
Respiratory, thoracic and mediastinal disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (3%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dyspnoea exertional	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Epistaxis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Sinusitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Skin and subcutaneous tissue disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	2/2 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Contusion	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Rash	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Vascular disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Hypertension	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Telangiectasia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 14 Medically attended events reported between D21 and D42

	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=72)**	**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)**
Total medically attended events	6/5 (9%)	3/3 (6%)	2/2 (4%)	7/6 (11%)	1/1 (2%)	7/5 (8%)	2/2 (6%)	0/0 (0%)	1/1 (2%)	1/1 (2%)	3/3 (14%)	0/0 (0%)
Blood and lymphatic system disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Anaemia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Dental and gingival conditions	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Gingivitis	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ear and labyrinth disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Labyrinthitis	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Endocrine disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Type 2 diabetes mellitus	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Gastrointestinal disorders	2/2 (4%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Diverticulitis	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Tongue ulceration	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Toothache	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
General disorders and administration site conditions	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Facial pain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)
Influenza like illness	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Infections and infestations	2/2 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Pilonidal cyst	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Urinary tract infection	2/2 (4%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Injury, poisoning and procedural complications	1/1 (2%)	0/0 (0%)	0/0 (0%)	2/2 (4%)	1/1 (2%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Arthropod bite	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Fall	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Joint injury	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Road traffic accident	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Soft tissue injury	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Metabolism and nutrition disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Hypercholesterolaemia	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Musculoskeletal and connective tissue disorders	1/1 (2%)	1/1 (2%)	0/0 (0%)	2/2 (4%)	0/0 (0%)	3/2 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Arthralgia	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	2/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Muscle strain	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Musculoskeletal injury	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Rotator cuff syndrome	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Synovial rupture	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Reproductive system and breast disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Ovarian cyst	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Respiratory, thoracic and mediastinal disorders	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Dyspnoea	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (5%)	0/0 (0%)
Productive cough	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

	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=72)	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)
Sinusitis	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Skin and subcutaneous tissue disorders	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Rash	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (2%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Surgical and medical procedures	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
Cataract operation	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	1/1 (3%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)

Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 15 Serious adverse events

Cohort	Allocation	Age	Gender	Event name(s)	Timing	Days since randomisation	Visit 2 attended	Duration of event (days)	Outcome	Type of SAE	Expected event	Severity	Causality	AESI
ChAdOx1 + QIVc	Flu first	20	Male	Anxiety, Migraine	After D0, before D21	2	Attended in person, no vaccine received (withdrew from vaccinations)	4	Recovered	Requires hospitalisation	No	Grade 3	Possible	No
BNT162b2 + QIVc	Placebo first	62	Female	Chest pain	After D0, before D21	13	Attended in person, vaccine received	2	Recovered	Requires hospitalisation	No	Grade 4	Unlikely	No
ChAdOx1 + QIVr	Placebo first	45	Female	Anaemia	After D21	28	Attended in person, vaccine received	1	Recovered	Requires hospitalisation	No	Grade 4	Unlikely	No
ChAdOx1 + QIVr	Flu first	28	Female	Lower respiratory tract infection	After D0, before D21	1	Telephone consultation, no vaccine received	1	Recovered	Requires hospitalisation	No	Grade 2	Unlikely	No
ChAdOx1 + QIVr	Placebo first	47	Female	Diabetic ketoacidosis	After D0, before D21	6	Attended in person, vaccine received	8	Recovered with sequelae	Requires hospitalisation	No	Grade 4	Unlikely	No
BNT162b2 + QIVr	Placebo first	37	Male	Pilonidal cyst	After D21	40	Attended in person, vaccine received	1	Recovered	Requires hospitalisation	No	Grade 3	No relationship	No
BNT162b2 + QIVr	Flu first	25	Female	Ovarian cyst ruptured	After D0, before D21	1	Attended in person, vaccine received	2	Recovered	Requires hospitalisation	No	Grade 4	Unlikely	No

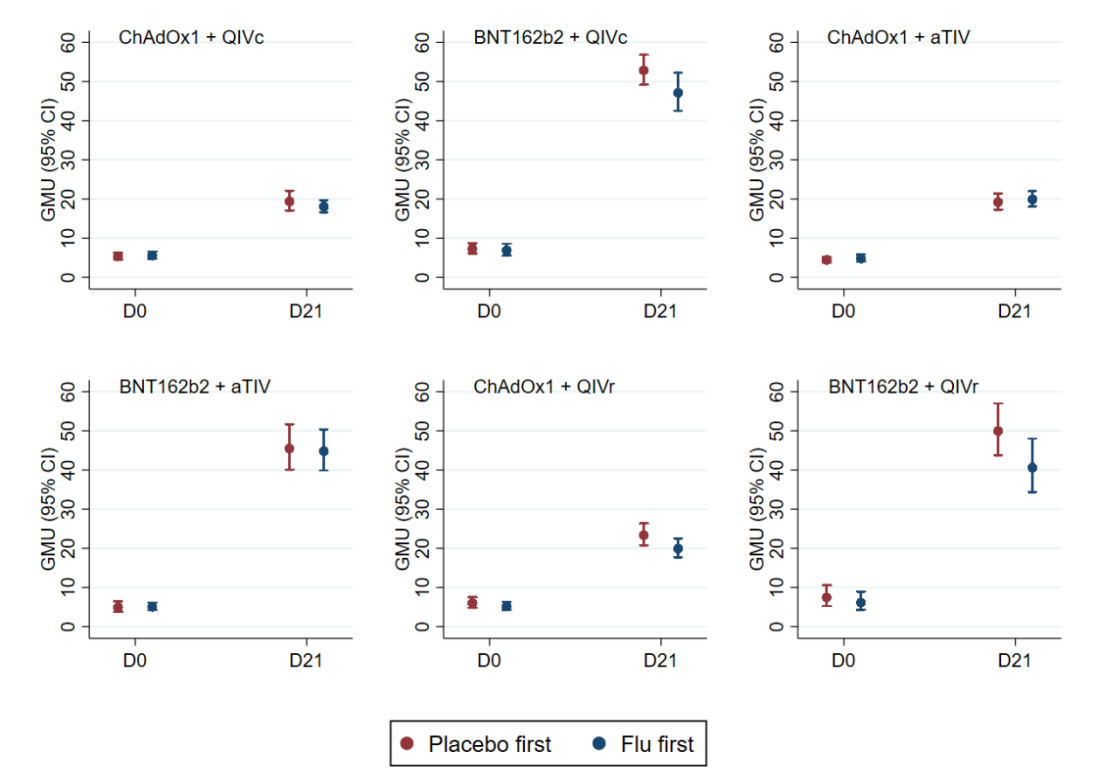
Severity: Grade 0 No symptoms; Grade 1 Mild - easily tolerated with no limitation on normal activity; Grade 2 Moderate - some limitation of daily activity; Grade 3 Severe - unable to perform normal daily activity; Grade 4 Emergency department or hospital admission required**.** Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 16 Adverse events of special interest

Cohort	Allocation	Age	Gender	Event name	Timing	Days since randomisation	Visit 2 attended	Duration of event (days)	Severity	Causality
ChAdOx1 + aTIV	Placebo first	71	Female	Chilblains	After D0, before D21	4	Attended in person, vaccine received	6	Grade 2	Possible

Severity: Grade 0 No symptoms; Grade 1 Mild - easily tolerated with no limitation on normal activity; Grade 2 Moderate - some limitation of daily activity; Grade 3 Severe - unable to perform normal daily activity; Grade 4 Emergency department or hospital admission required. Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Figure 20 Anti-S Ig GMT ratio between COVID-19 vaccine given with or without influenza vaccine



GMU=geometric mean units. CI=confidence interval. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

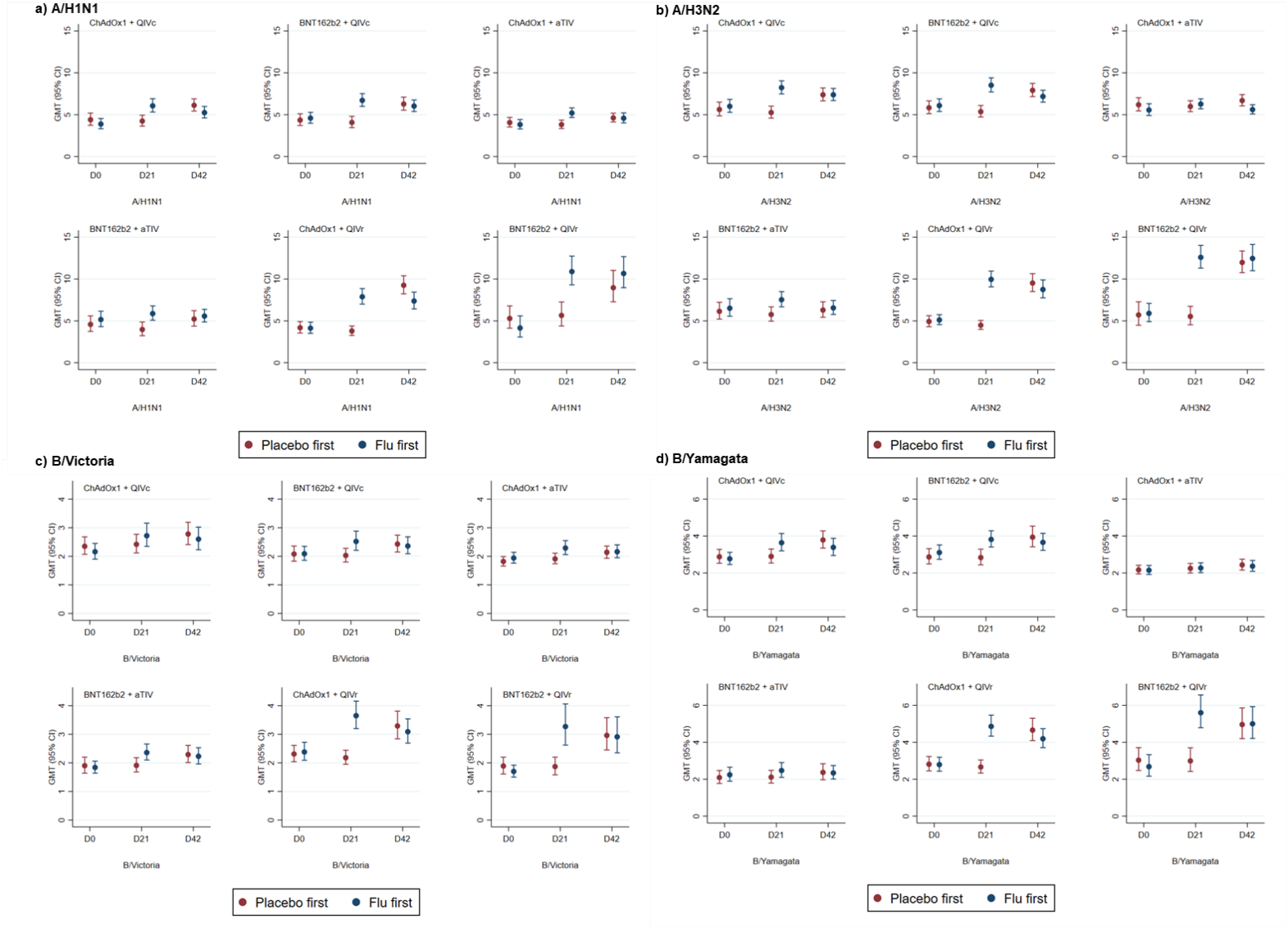
Supplementary Table 17 ECLIA geometric mean and seroconversion rates for anti-spike protein immunoglobulins and haemagglutination inhibition assay geometric mean titre and seroconversion rates for influenza strains

	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)
Anti-spike protein Ig												
GMU												
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	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%)
HAI												
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 GMU (95% CI) or 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. HAI = Haemagglutination inhibition assay. GMU= Geometric mean unit. GMT=Geometric mean titre.

SCR=Seroconversion rate. CI=confidence interval. *1 participant with missing data, ^ 2 participants with missing data, ◊ 3 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.

Supplementary Figure 21 HAI Influenza geometric mean titres by cohort



GMT=geometric mean titre. CI=confidence interval. Note, the group that had flu first i.e., concomitant COVID-19 and influenza vaccines at D0 received placebo at D21 and vice versa.

Supplementary Table 18 Willingness to receive concomitant influenza and COVID-19 vaccinations in the future

	ChAdOx1 + QIVc		BNT162b2 + QIVc		ChAdOx1 + aTIV		BNT162b2 + aTIV		ChAdOx1 + QIVr		BNT162b2 + QIVr	
	Placebo first (n=64)	Flu first (n=65)	Placebo first (n=72)	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)
Willing to receive concomitant vaccinations in the future	61/64 (95%)	60/60 (100%)	69/70 (99%)	68/68 (100%)	70/71 (99%)	72/73 (99%)	37/38 (97%)	40/41 (98%)	64/64 (100%)	62/63 (98%)	29/29 (100%)	29/29 (100%)

Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 19 Days off work for participants in employment

		ChAdOx1 + QIVc		BNT162b2 + QIVc		ChAdOx1 + aTIV		BNT162b2 + aTIV		ChAdOx1 + QIVr		BNT162b2 + QIVr	
		Placebo first (n=45)	Flu first (n=48)	Placebo first (n=53)	Flu first (n=54)	Placebo first (n=4)	Flu first (n=6)	Placebo first (n=8)	Flu first (n=4)	Placebo first (n=42)	Flu first (n=46)	Placebo first (n=23)	Flu first (n=23)
Any time off work		1/45 (2%)	2/48 (4%)	1/53 (2%)	1/54 (2%)	0/4 (0%)	0/6 (0%)	0/8 (0%)	0/4 (0%)	1/42 (2%)	3/46 (7%)	1/23 (4%)	1/23 (4%)
Number of days off work	0	44/45 (98%)	46/48 (96%)	52/53 (98%)	53/54 (98%)	4/4 (100%)	6/6 (100%)	8/8 (100%)	4/4 (100%)	41/42 (98%)	43/46 (93%)	22/23 (96%)	22/23 (96%)
	0.5	0/45 (0%)	0/48 (0%)	1/53 (2%)	0/54 (0%)	0/4 (0%)	0/6 (0%)	0/8 (0%)	0/4 (0%)	0/42 (0%)	1/46 (2%)	0/23 (0%)	0/23 (0%)
	1	0/45 (0%)	1/48 (2%)	0/53 (0%)	0/54 (0%)	0/4 (0%)	0/6 (0%)	0/8 (0%)	0/4 (0%)	0/42 (0%)	1/46 (2%)	1/23 (4%)	0/23 (0%)
	2	0/45 (0%)	0/48 (0%)	0/53 (0%)	1/54 (2%)	0/4 (0%)	0/6 (0%)	0/8 (0%)	0/4 (0%)	0/42 (0%)	1/46 (2%)	0/23 (0%)	1/23 (4%)
	4	1/45 (2%)	0/48 (0%)	0/53 (0%)	0/54 (0%)	0/4 (0%)	0/6 (0%)	0/8 (0%)	0/4 (0%)	0/42 (0%)	0/46 (0%)	0/23 (0%)	0/23 (0%)
	10	0/45 (0%)	1/48 (2%)	0/53 (0%)	0/54 (0%)	0/4 (0%)	0/6 (0%)	0/8 (0%)	0/4 (0%)	1/42 (2%)	0/46 (0%)	0/23 (0%)	0/23 (0%)

Data are n/N (%). Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.

Supplementary Table 20 Blinding indices

Assignment	Response			
	Flu first	Placebo	Don't know	Total
Flu first	162	52	120	334
Placebo first	70	157	109	336
Total	232	209	229	670

Bang blinding indices: 0.33 (95% CI: 0.26, 0.40) for flu first arm; 0.26 (95% CI: 0.19, 0.33) for placebo first arm. Placebo first=COVID-19 vaccine alone at D0; Flu first=concomitant COVID-19 and influenza vaccines at D0.