

## SYNOPSIS

10/06/2021

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

**Article citation:** Lazarus R, Baos S, Cappel-Porter H, Carson-Stevens A, Clout M, Culliford L, et al. The safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults: a phase IV, multicentre randomised controlled trial with blinding (ComFluCOV). SSRN [Preprint]. 2021 Sept 30 [cited 2021 Oct 6]. Available from: [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3931758](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3931758)

## One-minute summary

- The authors performed a multicentre randomised phase IV control trial with blinding to examine the safety and immunogenicity of concomitant administration of a Coronavirus Disease 2019 (COVID-19) vaccine (BNT162b2 = Pfizer-BioNTech; ChAdOx1 = AstraZeneca) and an influenza vaccine (FluAd, inactivated adjuvanted trivalent; Flucelvax, inactivated quadrivalent; Flublok, recombinant quadrivalent) in 679 adults aged 18 years and older in the United Kingdom.
- Patients were enrolled between April 1 and June 26, 2021. 340 participants were assigned to concomitant administration of an influenza vaccine and the second dose of a COVID-19 vaccine at Day 0 and placebo at Day 21. 339 participants were assigned to administration of a placebo (saline) and the second dose of the COVID-19 vaccine at Day 0, followed by an influenza vaccine at Day 21.
- Concomitant administration of the two vaccines was found to be non-inferior to administration of the COVID-19 vaccine alone (i.e., non-inferiority) in four of the six cohorts; therefore, the risk difference (RD; influenza vaccine minus placebo) was less than 25% and **concomitant vaccination did not lead to increased reporting of systemic adverse reactions during the 7 days after vaccination.**
  - Pfizer-BioNTech + Flucelvax: RD = 6.17% (95% confidence interval [CI]: -6.27 to 18.6)
  - Pfizer-BioNTech + FluAd: RD = -12.9% (95% CI: -34.2 to 8.37)

- AstraZeneca + Flublok: RD = 2.53% (95% CI: -13.3 to 18.3)
- AstraZeneca + Flucelvax: RD = -1.29% (95% confidence interval (CI): -14.7 to 12.1)
- In the remaining two cohorts, the upper limit of the 95% CI exceeded 25% and did not meet non-inferiority. However, the systemic reactogenicity profiles were considered acceptable despite the upper limit of 95% CI just being exceeded.
  - Pfizer-BioNTech + Flublok: RD = 6.75% (95% CI: -11.8 to 25.3)
  - AstraZeneca + FluAd: RD = 10.3% (95% CI: -5.44 to 26.0)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anti-Spike protein IgG geometric mean units at 21 days after receiving Pfizer-BioNTech or AstraZeneca vaccines were similar between those who received concomitant vaccination or the COVID-19 vaccine alone in all cohorts. **Seroconversion ranged from 89–100% for the Pfizer-BioNTech vaccine and 79–93% for the AstraZeneca vaccine when given concomitantly with influenza vaccine or when given alone.**
- There were no significant differences in the haemagglutinin antibody inhibition (HAI) geometric mean ratios (GMR) for any of the influenza strains at 21 days after concomitant vaccination with a COVID-19 vaccine compared to receiving the influenza vaccine alone in the Flucelvax and FluAd cohorts or in the cohort that received AstraZeneca + Flublok. In the Pfizer-BioNTech + Flublok cohort, the geometric mean titres (GMT) of A/H1N1 and both B strains were higher in concomitant vaccination compared to when Flucelvax was given alone. **Seroconversion rates ranged from 1–72%, with lower seroconversion rates in the FluAd cohorts compared to the Flucelvax or Flublok cohorts, and lower in influenza B strains compared to influenza A strains regardless of influenza vaccine used.**
- **Most reactions were mild or moderate during the study and rates of local and unsolicited systemic reactions were similar between randomised groups in each cohort.** Fever was the most commonly reported systemic reaction. There was a significantly higher proportion of individuals who reported local adverse reactions when the influenza vaccine was administered at Day 21 compared to those who received placebo. There was only one single serious adverse event following vaccination, in which the participant had severe headaches and visual disturbances requiring hospitalization (participant received AstraZeneca + placebo).
- **The authors conclude that concomitant vaccination raises no safety concerns and preserved the immune response to COVID-19 and seasonal influenza vaccines.** The delivery of both vaccines at the same time will reduce the burden on the healthcare services.

## Additional information

- Volunteers were eligible if they were  $\geq 18$  years and had received a single dose of the AstraZeneca vaccine in the preceding 56–90 days or the Pfizer-BioNTech vaccine in the preceding 28–90 days. Volunteers were ineligible if they received another vaccine in 30 days prior to recruitment, or immunoglobulins/blood products in the previous 3 months, had a history of allergy or reactions to any component of the vaccines, a bleeding disorder/continuous

use of anticoagulants, suspected or known drug or alcohol dependence, or progressive neurological disorders.

- The influenza vaccines used in the trial were from the 2020/21 season and contained influenza A strains (H1N1, H3N2) and influenza B strains (Yamagata, Victoria). The COVID-19 vaccine was given in one arm and influenza vaccine or placebo given in the other arm.
  - FluAd (administered to those  $\geq 65$  years) is a trivalent, surface antigen inactivated influenza vaccine adjuvanted with MF59C (aTIV).
  - Flucelvax (administered to those  $< 65$  years) is a surface antigen, inactivated quadrivalent vaccine prepared in cell culture (QIVc).
  - Flublok (administered to those  $< 65$  years) is a recombinant quadrivalent influenza vaccine (QIVr).
- The median age of participants by influenza vaccine type was Flucelvax = 51 years; Flublok = 52 years; and FluAd = 69 years. 58.5% (397/679) of participants were female, 92.3% (627/679) were white and British and 40.6 % (276/679) were retired. Baseline characteristics (i.e., age, sex, body mass index, ethnicity, occupation, 2020/21 influenza vaccination status) of participants were similar across the two randomised groups within each cohort. The proportion of participants that received a seasonal influenza vaccine the previous winter ranged from 45–99%. Participants reported reactions daily using an electronic diary and recorded their temperature with an oral thermometer.
- **Primary outcomes were one or more solicited systemic reaction(s) in 7 days after vaccination (Day 0).** The solicited systemic reactions were fever, feverishness, chills, joint pains, muscle pains, fatigue, headache, malaise, nausea, vomiting and diarrhea.
- **Secondary outcomes were safety and reactogenicity as measured by: 1) solicited local reactions at Day 0 and Day 21 after vaccination, 2) solicited systemic reactions in the 7 days after vaccination at Day 21, and 3) unsolicited adverse events for the whole trial period.** The solicited local reactions were pain, tenderness, redness, warmth, itch, swelling and induration.
- Secondary immunological outcomes included: 1) HAI in sera collected at Day 0, Day 21 and Day 42 against the strains of influenza vaccine virus (H1N1, H3N2, Yamagata, Victoria) for the 2020/21 season; and 2) SARS-CoV-2 S-protein IgG in sera collected at Day 0 and Day 21 (anti-S IgG) using electrochemiluminescence immunoassay (ECLIA).
- Concomitant administration of the two vaccines was considered non-inferior to the COVID-19 vaccine alone if the upper limit of the RD 95% CI for the primary outcomes was less than 0.25 in both the intention to treat and the per protocol analyses.
- Qualitative outcomes included days of work lost (if employed) and acceptability to participants of future concomitant vaccine administration. 3.1% (11/365 employed) of participants reported 0.5–2 lost workdays following vaccination. 1.3% (9/670) of participants reported they would not be willing to receive concomitant vaccination in the future (COVID-19 vaccine alone, n=6; concomitant vaccines, n=3).

- Blinding was considered successful in the trial, as the bang blinding index (0 = perfect blinding; 1 = complete lack of blinding) for the group with concomitant vaccination was 0.33 (95% CI: 0.26–0.40) and for the groups given the vaccines separately was 0.26 (95% CI: 0.19–0.33).
- **Amendments made to the study protocol:**
  - Flublok was added after the start of recruitment, as the Department of Health and Social Care requested it.
  - The sample size was increased from 504 to 756 and the cohorts increased from four to six.
  - Participants were excluded if at risk of thrombotic events in April 2021, due to reports of thromboembolic events after receiving the AstraZeneca vaccine.
- **Limitations:**
  - The authors acknowledge that more research is needed to confirm the results in other vaccines, such as the Moderna vaccine, and in other seasonal influenza vaccines (i.e., live, attenuated or high dose).
  - The two Flucelvax cohorts had less participants than planned and during the trial, potentially affecting the generalizability of the findings for this influenza vaccine.
  - T-cell responses were not examined in participants; therefore, research is needed to assess the role of cell-mediated immunity following concomitant vaccination.
  - For two of the cohorts, fewer participants were enrolled than planned in the Pfizer-BioNTech + FluAd (79/126, 63%) and Pfizer-BioNTech + Flublok (58/126, 46%) groups. The authors did not comment on whether these cohorts were sufficiently powered to detect a difference in their study.

## PHO reviewer's comments

- The study consisted primarily of older white participants, making the generalizability of the findings uncertain for younger adults and those from different racial backgrounds.
- For this trial, it will be interesting to see vaccine effectiveness results from longer-term follow-up for laboratory-confirmed infection outcomes (i.e., symptomatic infections, hospitalizations, deaths).
- We should note that as of May 11, 2021, Ontario stopped the administration of the AstraZeneca vaccine as a first dose but continued its administration as a second dose.
- The publicly funded influenza vaccines available for the 2021/22 in Ontario are the following which don't include the Flublok vaccine that was included in this study:
  - Quadrivalent Inactivated Vaccine (QIV) for ≥6 months of age (i.e., Flucelvax Quad)
  - Adjuvanted Trivalent Inactivated Vaccine (TIV-adj) for ≥65 years only (i.e., Fluad)

- High-Dose Quadrivalent Inactivated Vaccine (QIV-HD) for  $\geq 65$  years only (i.e., Fluzone High-Dose Quadrivalent)
- A reminder from The Lancet should be highlighted “The findings should not be used for clinical or public health decision making and should not be presented to a lay audience without highlighting that they are preliminary and have not been peer-reviewed.”

## Citation

Ontario Agency for Health Protection and Promotion (Public Health Ontario). Review of “The safety and immunogenicity of concomitant administration of COVID-19 vaccines (ChAdOx1 or BNT162b2) with seasonal influenza vaccines in adults: a phase IV, multicentre randomised controlled trial with blinding (ComFluCOV)”. Toronto, ON: Queen’s Printer for Ontario; 2021.

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