

## Heterologous prime-boost COVID-19 vaccination: initial reactogenicity data

There is significant international interest in heterologous prime-boost COVID-19 vaccination to mitigate against supply shocks or shortages that might otherwise reduce the speed of vaccine roll-out. Additionally, in light of changing recommendations regarding use of the ChAdOx1 nCoV-19 (ChAd) COVID-19 vaccine (Vaxzevria, AstraZeneca), several countries are now advising that individuals previously primed with this vaccine should now receive an alternative vaccine as their second dose, most commonly mRNA vaccines such as the BNT162b2 (BNT) COVID-19 vaccine (Comirnaty, Pfizer-BioNTech), administered in a heterologous prime-boost schedule.<sup>1-3</sup> To date there are no data on the immunogenicity, reactogenicity, or safety of such schedules. Com-COV (ISRCTN 69254139) is a UK multi-centre, participant-masked, randomised heterologous prime-boost COVID-19 vaccination study comparing all four prime-boost permutations of the ChAd and BNT vaccines both at 28-day and 84-day prime-boost intervals. Participants are 50 years and older with no or mild-to-moderate, well controlled comorbidity and were recruited across eight sites. The protocol is available online.

Following consultation with the study trial steering committee, here we present the initial reactogenicity and safety data, ahead of the primary immunological outcome, which is projected to be available in June, 2021. Reactogenicity data presented here consist of self-reported solicited local and systemic symptoms collected in the 7 days after both prime and boost vaccination in participants randomised to receive vaccines at 28-day intervals. Haematology and biochemistry safety monitoring blood results are also reported from the immunology cohort

(100 participants with additional visits), at baseline (before the prime dose), at day 28 (before the boost dose) and 7 days post-boost, graded according to a modified US Food and Drug Administration toxicity scale (appendix). All analyses are descriptive, as the study was not powered for reactogenicity, with endpoints reported as frequencies and percentages, together with absolute differences between heterologous and homologous vaccine schedules and corresponding 95% CIs.

Recruitment commenced on Feb 11, 2021, and was completed on Feb 26, 2021, with 830 participants enrolled and randomised from 978 screened (the CONSORT flow diagram is available in the appendix). 463 participants were randomly assigned to the four groups with a 28-day prime-boost interval, and 367 participants randomised to groups with an 84-day prime-boost interval. All 463 participants in the 28-day prime-boost interval group received their prime vaccine, and 461 participants received their boost vaccine. Among the 463 participants, the median age was 57 years (range 50–69), 212 (46%) participants were female, and 117 (25%) from ethnic minorities, with baseline characteristics well balanced across study groups. In groups with homologous vaccine schedules, systemic reactogenicity was greater after the prime dose in the ChAd group, and after the boost dose in the BNT group (figure).

Both heterologous vaccine schedules induced greater systemic reactogenicity following the boost dose than their homologous counterparts, with feverishness reported by 37 (34%) of 110 recipients of ChAd for prime and BNT for boost compared with 11 (10%) of 112 recipients of ChAd for both prime and boost (difference 24%, 95% CI 13–35%). Feverishness was reported by 47 (41%) of 114 recipients of BNT for prime and ChAd for boost, compared with

24 (21%) of 112 recipients of BNT for both prime and boost (difference 21%, 95% CI 8–33%). Similar increases were observed for chills, fatigue, headache, joint pain, malaise, and muscle ache (figure; appendix). There were no hospitalisations due to solicited symptoms, and most of this increase in reactogenicity was observed in the 48 h after immunisation (appendix).

Participants were advised that paracetamol might reduce vaccine side-effects but were not actively counselled to medicate prophylactically. Paracetamol use in the 48 h post-boost vaccine was reported by 40 (36%) of 112 recipients of ChAd for both prime and boost, 63 (57%) of 110 recipients of ChAd for prime and BNT for boost, 48 (41%) of 117 recipients of BNT for both prime and boost, and 68 (60%) of 114 recipients of BNT for prime and ChAd for boost, thereby mirroring the reactogenicity pattern.

Haematology and biochemistry profiles were similar between heterologous and homologous vaccine schedules, with all laboratory adverse events of grade 2 severity or less in the heterologous vaccine schedule, and no thrombocytopenia in any group at day 7 post-boost (appendix).

In this interim safety analysis, we found an increase in systemic reactogenicity after the boost dose reported by participants in heterologous vaccine schedules in comparison to homologous vaccine schedules, and this was accompanied by increased paracetamol usage. Of note, these data were obtained in participants aged 50 years and older, and reactogenicity might be higher in younger age groups<sup>4,5</sup> for whom a mixed vaccination schedule is being advocated in Germany, France, Sweden, Norway, and Denmark among those who have received a ChAd prime dose, in light of concerns regarding thrombotic thrombocytopenia after the first dose of ChAd.<sup>6</sup>

Pending availability of a more complete safety dataset and immunogenicity results for heterologous



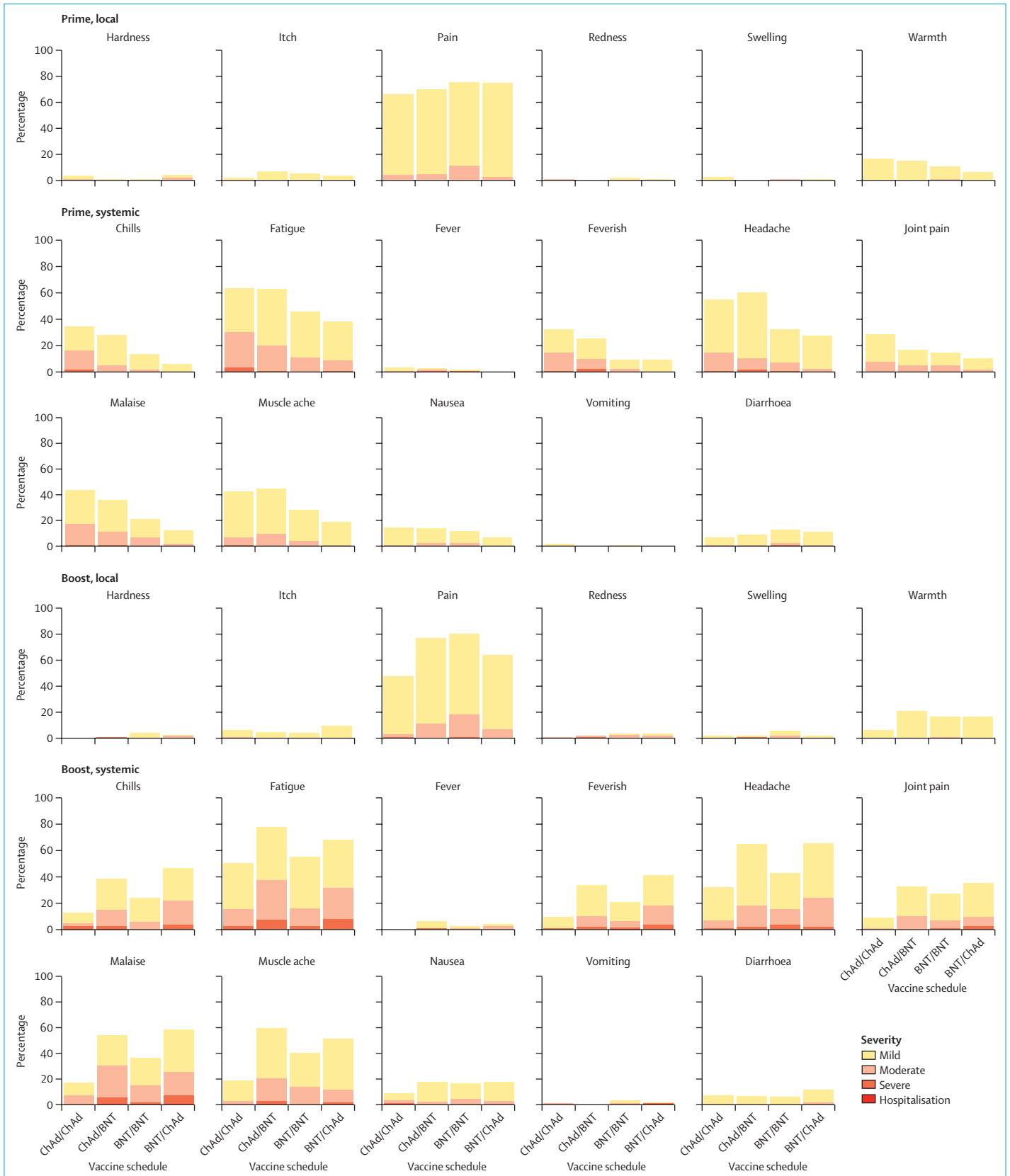
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See Online for appendix

For the Com-COV protocol see <https://comcovstudy.org.uk/study-protocol>

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prime-boost schedules (to be reported shortly), these data suggest that the two heterologous vaccine schedules in this trial might have some short-term disadvantages. Routine prophylactic use of paracetamol after immunisation could help mitigate these<sup>7</sup> and is being studied in Com-COV participants receiving prime and boost vaccines at 12-week intervals. Regardless, it is reassuring that all reactogenicity symptoms were short lived, and there were no concerns from the limited haematology and biochemistry data available. Further studies evaluating heterologous prime-boost schedules, incorporating vaccines manufactured by Moderna and Novavax, are ongoing, and are crucial to informing the appropriateness of mixed COVID-19 vaccine schedules.

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**Figure: Severity of solicited local and systemic reactions in days 0–7 after vaccination with ChAdOx1 nCoV-19 (ChAd) or BNT162b2 (BNT), by prime and boost vaccination and by vaccination group, as self-reported in participant electronic diaries**

ChAd/ChAd denotes a ChAd vaccine for prime and boost doses. ChAd/BNT denotes a ChAd vaccine for prime dose and a BNT vaccine for boost dose. BNT/BNT denotes a BNT vaccine for prime and boost doses. BNT/ChAd denotes a BNT for prime dose and a ChAd vaccine for boost dose. The severity presented is the participant's highest severity across 7 days after vaccination for each solicited adverse event. Fever was categorised as mild (38.0°C to <38.5°C), moderate (38.5°C to <39.0°C), or severe (≥39.0°C). Feverish was a self-reported feeling of feverishness. For systemic symptoms, grading was classified as mild (easily tolerated with no limitation on normal activity), moderate (some limitation of daily activity), and severe (unable to perform normal daily activity).

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