Optimal timing and immunogenicity of COVID19 booster vaccination: the EU-COVAT-2 BOOSTAVAC trial

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BACKGROUND

Few randomised trials have examined the extent or persistence of immune responses after multiple booster COVID-19 vaccines. It remains unclear if there is an upper limit of antibody responses with repeated vaccination beyond which the immune response is saturated.

OBJECTIVE

To determine the **need for, optimal timing of, and immunogenicity of administering a booster vaccination** dose against SARS-CoV-2 in the general population (18+ years) already vaccinated against SARS-CoV-2.

METHODS

Design: An international, randomised, controlled, multicentre, phase II trial (EudraCT: 2021-004889-35).
Adults with >3 prior mRNA COVID19 vaccines, and last vaccine administered 3 to 7 months prior enrollment.

Intervention: booster dose of either Pfizer BNT162b2 or one of the Pfizer Bivalent COVID-19 Vaccines (COMIRNATY® Original/Omicron BA.1 or Original/Omicron BA.4-5) or COMIRNATY® Omicron XBB.1.5, administered at a number of time points from baseline visit:

- Arm 1: control (no booster vaccination)
- Arm 2: booster at month 0 (Baseline – Bl)
- Arm 3: booster at month 2 (2m)
- Arm 4: booster at month 4 (4m)
- Arm 5: booster at month 6 (6m)

Randomisation was stratified by age: 18-49; 50-59; ≥60

Study assessments: 6 study visits after enrolment over 7 months of follow-up. Plasma receptor binding domain (RBD) antibodies (IU/mL) were measured at each visit and 2 weeks post booster (Immune response visit). Safety assessments included solicited AEs for 7 days after booster dose and unsolicited AEs until the end of the trial.

Composite primary endpoint: two-fold increase in RBD titre at 2 weeks post boost and/or RBD titre ≥500IU/mL (1,2) in those with pre-boost RBD<500IU/ml immediately before booster dose vaccination.

Efficacy was met if >50% subjects in a booster arm met the primary endpoint using a 1 sample proportion test (adjusted 1-sided alpha 0.0125). We explored optimal booster vaccine timing by logistic regression with best fitting fractional polynomial. Data are mean (SD) unless specified.

In previously vaccinated adults for COVID-19, further booster vaccination at 0, 2, 4 or 6 months provided short lived increases in RBD titres suggesting a saturable humoral response to repeated COVID-19 vaccination

Only month 2 booster arm achieved efficacy

We did not find an optimal time for booster vaccination

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

A total of 255 participants were recruited between March 2022 and September 2023, across 14 European clinical sites.

Variables Mean (SD)	Total (N=255)	Control (N=50)	Booster Bl (N=51)	Booster 2m (N=53)	Booster 4m (N=50)	Booster 6m (N=51)
Age (years)	52 (14)	54 (14)	52 (14)	54 (14)	51 (15)	51 (15)
Female (%)	154 (60)	28 (56)	33 (65)	34 (64)	29 (58)	30 (59)
White (%)	249 (98)	49 (98)	49 (96)	53 (100)	48 (96)	50 (98)
Immunocompromised (%)	10 (4)	2 (4)	1 (2)	6 (11)	1 (2)	0 (0)
Prior COVID-19 (%)	130 (51)	22 (44)	28 (55)	26 (49)	25 (50)	29 (57)
No previuos vaccines (%)						
3	58 (23)	12 (24)	12 (24)	11 (21)	9 (18)	14 (27)
≥3	145 (57)	30 (60)	29 (57)	25 (47)	31 (62)	30 (59)
Last vaccination to randomisation (days)	154 (44)	150 (39)	163 (63)	152 (40)	154 (42)	150 (33)
Anti-RBD (IU/ml)	15143 (16088)	14034 (15286)	12465 (12211)	14017 (15336)	19422 (18292)	16040 (18479)

In the trial, 20% participants received Original Comirnaty, 62% Original/Omicron BA4-5, and 16% Omicron BXX.1.5-specific vaccines. 32 (13%) participants reported incident COVID-19 with **no difference in infection rates between vaccine arms and controls.**

ANALYSIS OF THE PRIMARY ENDPOINT

- Only one of the four vaccine arms (2m) reached the primary endpoint (Fig 1).
- Two weeks post boost, anti-RBD titres increased in all four vaccine arms (Fig 2) but then declined rapidly to levels similar to those pre-entering the study (Fig 3).
- Every participant boosted to RBD ≥500 IU/mL.
- No dose-response for time to booster-vaccination was found (Fig 4).

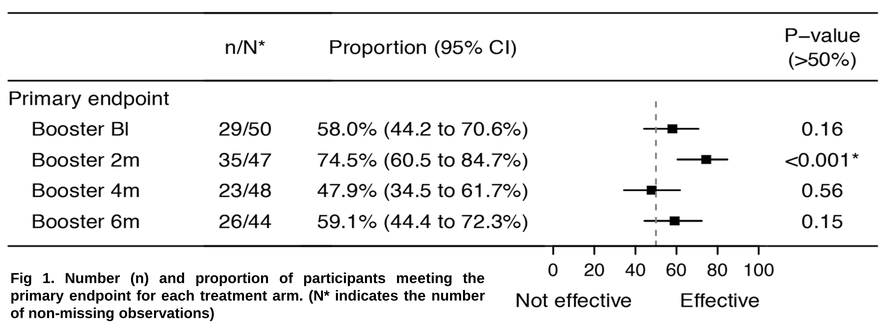


Fig 1. Number (n) and proportion of participants meeting the primary endpoint for each treatment arm. (N* indicates the number of non-missing observations)

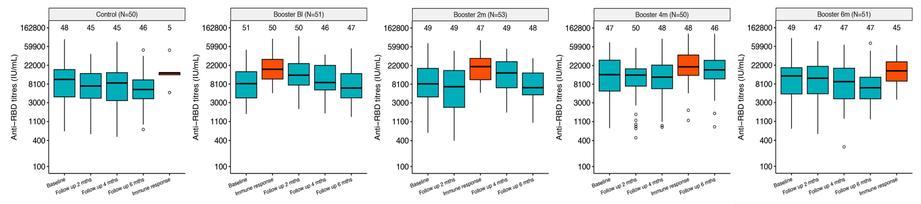


Fig 2. Boxplot for Anti-RBD titres (IU/mL) by visit time point and randomisation group. The time point of the immunogenicity visit (2-weeks post booster) is shown in red according to the randomisation group.

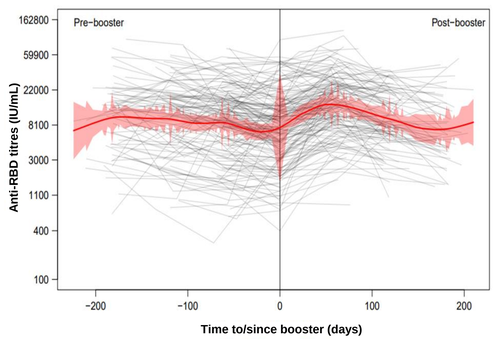


Fig 3. Anti-RBD titre trajectories relative to booster time point. Only participants who received a booster dose are included. The red line represents a cubic smoothing

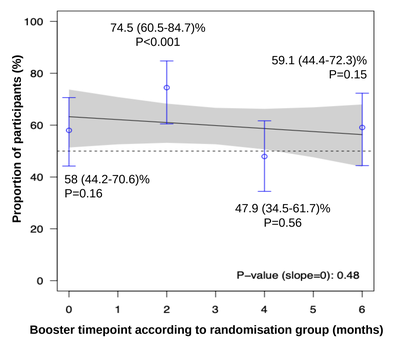


Fig 4. Primary outcome in dependence of the booster timepoint (according to the randomisation group) with 95% confidence area calculated from a logistic regression with the best fitting fractional polynomial

- Neither age nor prior COVID-19 were associated with the primary endpoint.
- However, those with a longer time since last pre-study vaccine and lower pre-boost RBD were more likely to reach the primary endpoint (P=0.005 and P<0.001), regardless of study arm (P=0.79 and P=0.16 for interaction).

SAFETY

- Of 169 participants with evaluable data, 144 (85%) reported AE post-booster.
- Systemic side effects such as tiredness, headache and muscle pain were each reported in >20%.
- Of 7 serious AE reported, none were causally linked to booster vaccine.

CONCLUSIONS

Booster COVID19 vaccination provided only short-lived increases in RBD titre but with systemic side effects commonly reported. Lower pre-booster RBD and time since last vaccine were associated with greater likelihood of booster immune responses. These data suggest a saturable humoral response to repeated COVID-19 vaccinations.

ADDITIONAL INFORMATION

References: 1. Kenny, G., et al., Nat Commun. 2023 Nov 2;14(1):7015. doi: 10.1038/s41467-023-42717-1. PMID: 37919289; PMCID: PMC10622572.; 2. Robert W Aldridge, et al. medRxiv 2021.11.05.21265968; doi:https://doi.org/10.1101/2021.11.05.21265968. **Funding:** This project has received funding from the European's Union Horizon 2020 Research and Innovation Programme under Grant Agreement No 101037867

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