THE LANCET
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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Abhishek A, Boyton RJ, Peckham N, et al. Effect of a 2-week interruption in methotrexate treatment versus continued treatment on COVID-19 booster vaccine immunity in adults with inflammatory conditions (VROOM study): a randomised, open label, superiority trial. *Lancet Respir Med* 2022; published online June 27. https://doi.org/10.1016/S2213-2600(22)00186-2.

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Table S1: Summary of reasons for withdrawal by study arms

Reason for withdrawal	Continue Methotrexate N=127	Suspend Methotrexate N=127	Total N=254
Participant taken off methotrexate by dermatologist and participant chose to withdraw from study	1	0	1
Personal reasons	0	1	1
Participant felt too ill to continue	0	1	1
No reason given	0	1	1

Table S2: Compliance with intervention by study arms

		Continue Methotrexate N = 127	Suspend Methotrexate N = 127
		n (%)	n (%)
Compliant[1]		122 (96)	123[3] (97)
Non-compliant		1 (1)	1 (1)
Missing data[2]		4 (3)	3 (2)
Methotrexate doses taken during the intervention period			
	0 doses	0	123[3]
	1 dose	1	1
	2 doses	122	0
	Missing data[2]	4	3

Footnotes: 1· Participants in continue with methotrexate arm should have taken 2 doses of methotrexate, and are deemed compliant if they self-report to have taken 2 doses, participants in the suspend methotrexate arm should have taken 0 doses of methotrexate, and are deemed compliant if they self-report to have taken zero doses; 2. Participants did not reply to text messages asking about compliance; 3. Two participants in the methotrexate suspend arm did not take their methotrexate dose prior to their vaccination and therefore missed three weekly doses of methotrexate. One further participant in the methotrexate suspend arm did not take their methotrexate dose for 5 weeks post COVID-19 vaccination, and then restarted it.

Table S3: Sensitivity analyses for primary outcome (Anti-S1-RBD titre [U/mL]) at 4 and 12 weeks

	Continue Methotrexate (n)	Suspend Methotrexate (n)	Sensitivity model: GMR (95% CI)[1]
Simple regression model adjusted for baseline and randomisation factors			
4 weeks	126	124	2.21 (1.58, 3.09)
12 weeks	124	117	2.14 (1.53, 3.01)
Mixed effects model using per-protocol population[1]			
4 weeks	122	119	2.21 (1.58, 3.09)
12 weeks	120	112	2.14 (1.53, 3.01)
Mixed effects model including time (days) between original vaccination and booster			
4 weeks	125	124	2·18 (1·58, 3·03)
12 weeks	126	124	2·08 (1·49, 2·89)
Interaction term (One day extra between previous vaccine dose and booster)			1·01 (1.00, 1·01)
Mixed effects model without booster vaccine type as covariate (post hoc)			
4 weeks	125	124	2·18 (1·57, 3·03)
12 weeks	126	124	2·08 (1·49, 2·89)
Mixed effects model including methotrexate dose as covariate (post hoc)			
4 weeks	125	124	2·19 (1·57, 3·04)
12 weeks	126	124	2·11 (1·51, 2·94)

Footnotes: 1· Participants were excluded from the per-protocol analysis if they did not comply with the allocated intervention; if they missed further methotrexate doses not as part of the intervention; if they did not provide compliance information; and if they did not have follow-up data available.

Table S4: Sub-group analyses for primary outcome (Anti-S1-RBD titre [U/mL]) at 4 and 12 weeks

	Continue methotrexate Geometric mean (95% CI)	Suspend methotrexate Geometric mean (95% CI)	Total Geometric mean (95% CI)	N	Linear regression: GMR (95% CI)[2]
Sub-group analyses at 4 weeks					
Methotrexate dose					
≤ 15mg/week	13809 (10340, 18442)	22872 (17699, 29556)	17555 (14407, 21392)	103	1·67 (1·20, 2·31)
>15mg/week	8978 (7076, 11393)	22670 (18240, 28176)	14402 (12076, 17177)	147	2·54 (1·94, 3·33)
Interaction effect (>15mg vs· ≤ 15mg/week)					0·66 (0·43,1·003)
Methotrexate route of administration					
Oral	11315 (8912, 14364)	24052 (19324, 29936)	16292 (13721, 19344)	151	2·15 (1·65, 2·82)
Subcutaneous injection	10007 (7385, 13561)	21007 (16313, 27053)	14663 (11922, 18034)	99	2·09 (1·50, 2·93)
Interaction effect (injection vs· oral)					0·97 (0·63, 1·49)
Disease type					
Rheumatic (+/- skin) disease	10606 (8568, 13128)	22282 (18547, 26770)	15344 (13220, 17809)	199	2·14 (1·69, 2·70)
Skin disease alone	11569 (7816, 17123)	24698 (16759, 36399)	16778 (12592, 22357)	51	2·10 (1·32, 3·33)
Interaction effect (skin disease alone vs· rheumatic (+/- skin) disease					0·98 (0·58, 1·65)
Age group					
< 40 years	17756 (10527, 29945)	17419 (9628, 31513)	17587 (12465, 24812)	16	1·83 (0·78, 4·33)
40 – 64 years	9052 (7054, 11615)	20584 (16734, 25319)	13571 (11398, 16158)	142	2·09 (1·58, 2·76)
≥ 65 years	13051 (9555, 17827)	27750 (20574, 37429)	19031 (15181, 23857)	92	2·26 (1·60, 3·19)
Interaction effect < 40 vs ≥ 65 years					0·81 (0·32, 2·06)
Interaction effect 40–64 vs ≥ 65 years					0·92 (0·59, 1·44)
Previous SARS-CoV-2 infection					

No	9453 (7727, 11564)	19738 (16724, 23296)	13635 (11865, 15669)	207	2·04 (1·62, 2·56)
Yes	20153 (13255, 30641)	45645 (29380, 70916)	30330 (22067, 41685)	42	2·64 (1·58, 4·41)
Interaction effect (infection vs· no)					0·77 (0·44, 1·36)
Primary COVID-19 vaccine type					
AstraZeneca AZD1222	9037 (7289, 11204)	21084 (17551, 25327)	13593 (11641, 15873)	165	2·42 (1·87, 3·12)
mRNA (Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273)	15833 (11265, 22251)	27202 (19653, 37651)	20890 (16471, 26495)	83	1·65 (1·150, 2·37)
Interaction effect (mRNA [BNT162b2 or mRNA-1273] vs· AZD1222)					1·46 (0·94, 2·29)
COVID-19 booster brand					
Pfizer-BioNTech BNT162b2	10512 (8543, 12935)	21716 (18128, 26014)	14923 (12897, 17267)	206	1·98 (1·58, 2·49)
AstraZeneca AZD1222	11679 (3212, 42466)	32074 (4089, 251566)	17495 (6939, 44110)	10	3·96 (1·39, 11·30)
Moderna mRNA-1273	13439 (8226, 21955)	29023 (17274, 48763)	20789 (14350, 30118)	31	2·90 (1·56, 5·38)
Interaction effect (AZD1222 vs· BNT162b2)					2·00 (0·68, 5·85)
Interaction effect (mRNA-1273 vs· BNT162b2)					1·46 (0·76, 2·89)
Sub-group analyses at 12 weeks					
Methotrexate dose					
≤ 15mg/week	11057 (8111, 15074)	15905 (12393, 20412)	13118 (10722, 16048)	100	1·44 (0·99, 2·10)
>15mg/week	6412 (4899, 8393)	16946 (13114, 21898)	10388 (8499, 12698)	141	2·66 (1·93, 3·65)
Interaction effect (>15mg/week vs· ≤ 15mg/week)					1·85 (1·12, 3·04)
Methotrexate route of administration					
Oral	8556 (6630, 11041)	17037 (13325, 21783)	11851 (9856, 14249)	148	2·03 (1·48, 2·78)
Subcutaneous injection	7367 (5140, 10558)	15779 (12015, 20721)	10826 (8564, 13686)	93	2·09 (1·40, 3·10)
Interaction effect (injection vs· oral)					1·03 (0·62, 1·70)
Disease type					

Rheumatic (+/- skin) disease	7427 (5908, 9336)	16081 (12970, 19938)	10775 (9131, 12714)	191	2·21 (1·67, 2·91)
Skin disease alone	11378 (7028, 18419)	18241 (13208, 25193)	14406 (10806, 19206)	50	1·56 (0·91, 2·67)
Interaction effect (skin disease alone vs· rheumatic (+/- skin) disease					0·71 (0·39, 1·29)
Age group					
< 40 years	18774 (9973, 35344)	11626 (6487, 20836)	14540 (9809, 21554)	15	1·18(0·42, 3·27)
40 – 64 years	7239 (5426, 9657)	13701 (10923, 17185)	9795 (8089, 11861)	135	1·74 (1·25, 2·41)
≥ 65 years	8461 (6135, 11668)	22945 (16669, 31583)	13857 (10840, 17714)	91	2·88 (1·93, 4·28)
Interaction effect < 40 vs ≥ 65 years					0·41 (0·14, 1·23)
Interaction effect 40–64 vs ≥ 65 years					0·60 (0·36, 1·01)
Previous SARS-CoV-2 infection					
No	7089 (5623, 8937)	14522 (12117, 17405)	10055 (8611, 11742)	199	1·98 (1·51, 2·59)
Yes	15204 (10321, 22397)	30868 (17822, 53464)	21477 (15322, 30106)	41	2·46 (1·34, 4·51)
Interaction effect (Infection yes vs. no)					0·80 (0·41, 1·56)
Primary COVID-19 vaccine type					
AstraZeneca AZD1222	10634 (7365, 15354)	20589 (14334, 29574)	14797 (11377, 19245)	159	2·21 (1·63, 2·99)
mRNA (Pfizer-BioNTech BNT162b2 or Moderna mRNA-1273)	7107 (5540, 9118)	15025 (12377, 18240)	10117 (8543, 11981)	80	1·78 (1·16, 2·72)
Interaction effect (mRNA [BNT162b2 or mRNA-1273] vs. AZD1222)					1·24 (0·73, 2·10)
COVID-19 booster brand					
Pfizer-BioNTech BNT162b2	7744 (6183, 9700)	16545 (13568, 20175)	11084 (9454, 12996)	199	2·01 (1·54, 2·64)
AstraZeneca AZD1222	7505 (1758, 32049)	16321 (394, 675651)	9724 (3363, 28118)	9	3·85 (1·01, 14·67)
Moderna mRNA-1273	11972 (6440, 22255)	17812 (10424, 30436)	15078 (10230, 22224)	31	1·94 (0·95, 3·98)
Interaction effect (AZD1222 vs· BNT162b2)					1·91 (0·49, 7·49)
Interaction effect (mRNA-1273 vs· BNT162b2)					0·96 (0·45, 2·09)

Footnotes 1· Mixed effects model, adjusted by baseline value, randomisation factors (age, inflammatory condition, vaccine platform), prior infection, booster platform; 2. Linear regression model at 4 weeks, adjusted by baseline value, randomisation factors (age, inflammatory condition, vaccine platform), prior infection, booster platform;

Table S5: Patient disease activity by study arms

	Continue Methotrexate n (%)	Suspend Methotrexate n (%)	Total n (%)
Patient disease activity			
4 weeks	**N = 124**	**N = 123**	**N = 247**
None (inactive)	26 (21)	14 (11)	40 (16)
Mild activity	65 (52)	63 (51)	128 (52)
Moderate activity	31 (25)	33 (27)	64 (26)
Severe activity	2 (2)	13 (11)	15 (6)
Very severe activity	0 (0)	0 (0)	0 (0)
Ordinal logistic regression OR (95% CI)[1]		1·80 (1·10, 2·92)	
12 weeks	**N = 125**	**N = 120**	**N = 245**
None (inactive)	26 (21)	15 (13)	41 (17)
Mild activity	63 (50)	64 (53)	127 (52)
Moderate activity	31 (25)	32 (27)	63 (26)
Severe activity	5 (4)	8 (7)	13 (5)
Very severe activity	0 (0)	1 (1)	1 (<1)
Ordinal logistic regression OR (95% CI)[1]		1·46 (0·90, 2·38)	

1· Ordinal logistic regression model adjusted by baseline value, randomization factors (age, inflammatory condition, vaccine platform), prior infection, booster platform

Table S6: Patient disease description by study arms

	Continue Methotrexate n (%)	Suspend Methotrexate n (%)	Total n (%)
Patient disease description since vaccination			
4 weeks	**N = 124**	**N = 123**	**N = 247**
Much better	1 (1)	0 (0)	1 (<1)
Somewhat better	4 (3)	3 (2)	7 (3)
About the same	109 (88)	89 (72)	198 (80)
Somewhat worse	9 (7)	26 (21)	35 (14)
Much worse	1 (1)	5 (4)	6 (2)
Ordinal logistic regression OR (95% CI)[1]		3·62 (1·74, 7·54)	
12 weeks	**N = 125**	**N = 120**	**N = 245**
Much better	2 (2)	2 (2)	4 (2)
Somewhat better	2 (2)	6 (5)	8 (3)
About the same	106 (85)	94 (78)	200 (82)
Somewhat worse	13 (10)	16 (13)	29 (12)
Much worse	2 (2)	2 (2)	4 (2)
Ordinal logistic regression OR (95% CI)[1]		0·99 (0·51, 1·92)	

1· Ordinal logistic regression model adjusted by baseline value, randomization factors (age, inflammatory condition, vaccine platform), prior infection, booster platform

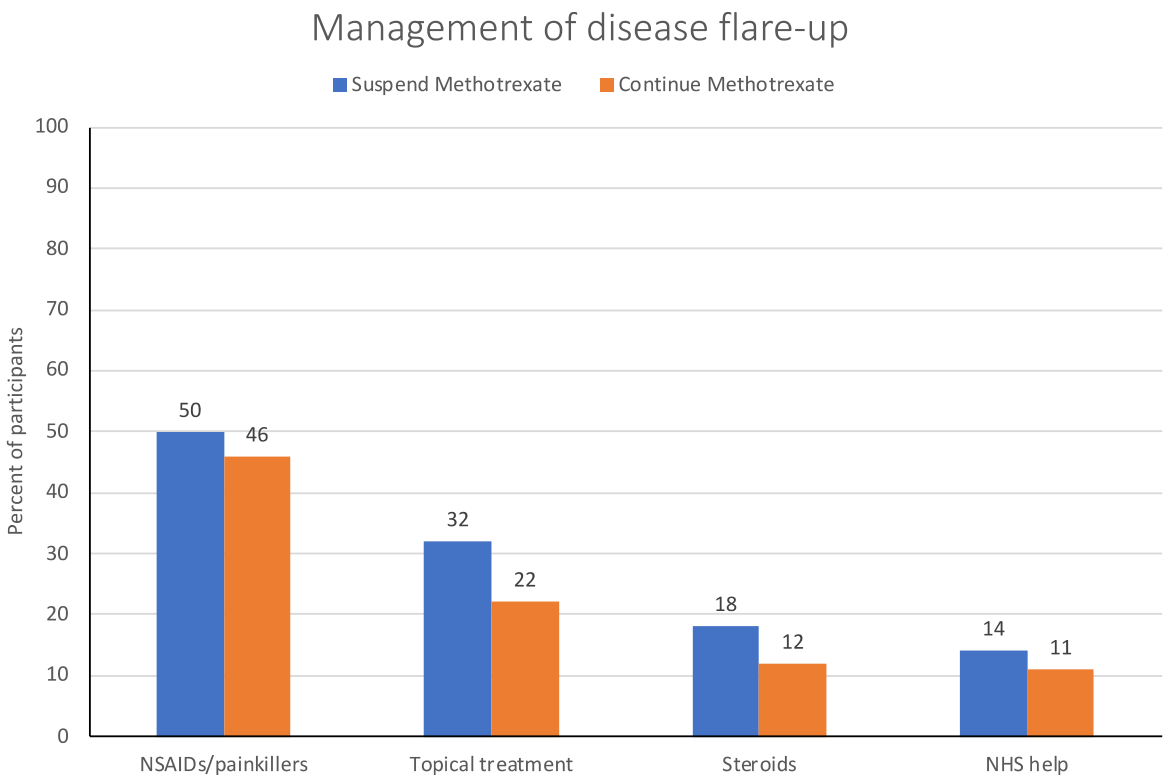
Table S7: Safety, flare outcomes and their treatment by study arms

	Continue Methotrexate	Suspend Methotrexate	Total
SAEs and disease flare-up			
Number of patients with at least one event	**n = 127**	**n = 127**	**n = 254**
SAEs related to intervention	0 (0)	0 (0)	0 (0)
SAEs unrelated to intervention	1 (1)	2 (2)	3 (1)
Self-reported flare-up by 4 weeks	**n = 124**	**n = 123**	**n = 247**
At least one	38 (31)	69 (56)	107 (43)
Self-reported flare-up by 12 weeks	**n = 125**	**n = 120**	**n = 245**
At least one	56 (45)	85 (71)	141 (58)
0-4 Weeks	**n = 124**	**n = 123**	**n = 247**
Number of separate self-reported disease flare-ups			
0	86 (69)	54 (44)	140 (57)
1	21 (17)	28 (23)	49 (20)
2	11 (9)	17 (14)	28 (11)
3	3 (2)	11 (9)	14 (6)
4	1 (1)	4 (3)	5 (2)
5	0 (0)	3 (2)	3 (1)
6+	2 (2)	6 (5)	8 (3)
Medical or nursing help sought to treat disease flare-ups[1]	**3 (2)**	**6 (5)**	**9 (4)**
Hospital helpline	0 (0)	1 (1)	1 (<1)
GP/practice nurse	1 (1)	4 (3)	5 (2)
Hospital outpatient (telephone or in person)	1 (1)	1 (1)	2 (1)
Hospital A&E	0 (0)	0 (0)	0 (0)
Other	1 (1)	0 (0)	1 (<1)
Pain killers/NSAIDs used to treat disease flare-ups			
Yes	42 (34)	53 (43)	95 (38)
No	81 (65)	70 (57)	151 (61)
Unknown[2]	1 (1)	0 (0)	1 (<1)
Glucocorticoid used to treat disease flare-ups			
Yes	8 (6)	11 (9)	19 (8)
No	115 (93)	112 (91)	227 (92)
Unknown[2]	1 (1)	0 (0)	1 (<1)
Cream used to treat flare-up of skin condition			
Yes	21 (17)	25 (20)	46 (19)
No	102 (82)	98 (80)	200 (81)
Unknown[2]	1 (1)	0 (0)	1 (<1)
0-12 Weeks	**n = 125**	**n = 120**	**n = 245**
Number of separate self-reported disease flare-ups			
0	69 (55)	35 (29)	104 (42)
1	20 (16)	22 (18)	42 (17)
2	13 (10)	14 (12)	27 (11)
3	8 (6)	8 (7)	16 (7)
4	3 (2)	11 (9)	14 (6)
5	4 (3)	9 (8)	13 (5)

	Continue Methotrexate	Suspend Methotrexate	Total
6+	8 (6)	21 (18)	29 (12)
Medical or nursing help sought to treat disease flare-ups[1]	**14 (11)**	**17 (14)**	**31 (13)**
Hospital helpline	5 (4)	5 (4)	10 (4)
GP/practice nurse	2 (2)	8 (7)	10 (4)
Hospital outpatient (telephone or in person)	6 (5)	7 (6)	13 (5)
Hospitalization	0 (0)	1 (1)	1 (<1)
Hospital A&E	0 (0)	0 (0)	0 (0)
Other	2 (2)	1 (1)	3 (1)
Pain killers/NSAIDs used to treat disease flare-ups			
Yes	58 (46)	60 (50)	118 (48)
No	67 (54)	60 (50)	127 (52)
Glucocorticoid used to treat disease flare-ups			
Yes	15 (12)	21 (18)	36 (15)
No	108 (87)	98 (82)	206 (84)
Unknown[2]	2 (2)	1 (1)	3 (1)
Cream used to treat flare-up of skin condition			
Yes	28 (22)	38 (32)	66 (27)
No	97 (78)	82 (68)	179 (73)

Footnotes: 1· Participants can seek help from more than one source; 2. Participants did not provide answer for this question

Figure S1: Flare treatment according to study arms during the 12-week study period



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