Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Search Strategy

A systematic literature search of studies published up to July 14, 2021 was conducted across the Medline database (PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL). As a first step, these databases were searched for Medical Sub Heading (Mesh) terms ("COVID-19 Vaccines" [Mesh] AND "Randomized Controlled Trial" [Publication Type]). In addition, a free text search was conducted using the following keywords:

(vaccination[Title/Abstract] OR inoculation[Title/Abstract] OR immunis*[Title/Abstract] OR vaccine[Title/Abstract] OR immuniz*[Title/Abstract]) AND (COVID-19[Title/Abstract] OR COVID[Title/Abstract] OR sars[Title/Abstract] OR sars-cov-2*[Title/Abstract]) AND (placebo*[Title/Abstract] OR saline[Title/Abstract]) AND (adverse events[Title/Abstract] OR AE[Title/Abstract] OR AEs[Title/Abstract] OR AEFI[Title/Abstract] OR safety[Title/Abstract] OR tolera*[Title/Abstract] OR side-effects[Title/Abstract] OR adverse reactions[Title/Abstract])

Supplemental Data

eTable 1

Numbers and percentages of solicited adverse events in the twelve analyzed randomized controlled trials of COVID-19 vaccines

	N with AE reports	Any AEs, n (%)	Local adverse events, n (%)					Systemic adverse events, n (%)									
			Any	Pain	Redness	Swelling	Tender-ness	Any	Fever	Chills	Fatigue	Malaise	Joint pain	Muscle pain	Headache	Nausea / vomiting	Diarrhea
mRNA vaccines																	
Baden et al., 2021																	
1st dose P	15155	7284 (48)	2997 (20)	2658 (18)	67 (0.4)	52 (0.3)	722 (5)	6399 (42)	44 (0.3)	878 (6)	4133 (27)	NA	1783 (12)	2071 (14)	4027 (27)	1074 (7)	NA
1st dose V	15168	13319 (88)	12765 (84)	12690 (84)	430 (3)	932 (6)	1553 (10)	8320 (55)	115 (1)	1253 (8)	5635 (37)	NA	2511 (17)	3441 (23)	4951 (33)	1262 (8)	NA
2nd dose P	14566	6232 (43)	2735 (19)	2477 (17)	56 (0.4)	49 (0.3)	567 (4)	5323 (37)	43 (0.3)	809 (6)	3403 (23)	NA	1569 (11)	1809 (12)	3410 (23)	934 (6)	NA
2nd dose V	14677	13534 (92)	13006 (89)	12943 (88)	1257 (9)	1789 (12)	2090 (14)	11652 (79)	2278 (16)	6482 (44)	9582 (65)	NA	6284 (43)	8508 (58)	8602 (59)	2785 (19)	NA
Chu et al., 2021																	
1st dose P	199	77 (39)	27 (14)	21 (11)	1 (0.5)	1 (0.5)	5 (3)	64 (32)	0 (0)	6 (3)	35 (18)	NA	10 (5)	14 (7)	36 (18)	10 (5)	NA
1st dose V	200	176 (88)	168 (84)	166 (83)	0 (0)	8 (4)	18 (9)	89 (45)	1 (0.5)	10 (5)	50 (25)	NA	18 (9)	28 (14)	43 (22)	6 (3)	NA
2nd dose P	193	66 (34)	16 (8)	15 (8)	5 (3)	1 (0.5)	1 (0.5)	58 (30)	1 (0.5)	5 (3)	41 (21)	NA	13 (7)	15 (8)	33 (17)	2 (1)	NA
2nd dose V	199	178 (89)	170 (85)	169 (85)	15 (8)	21 (11)	20 (10)	153 (77)	26 (13)	78 (39)	128 (64)	NA	77 (39)	104 (52)	104 (52)	41 (21)	NA
Polack et al., 2020																	
1st dose P	4040-4090	NA	525 (13)	488 (12)	45 (1)	32 (1)	NA	1922 (47)	27 (1)	203 (5)	1172 (29)	NA	247 (6)	398 (10)	1100 (27)	37 (1)	388 (10)
1st dose V	4040-4093	NA	3216 (79)	3186 (79)	189 (5)	250 (6)	NA	2421 (59)	111 (3)	434 (11)	1700 (42)	NA	406 (10)	738 (18)	1413 (35)	37 (1)	402 (10)
2nd dose P	3699-3749	NA	396 (11)	372 (10)	26 (1)	16 (0.4)	NA	1267 (34)	14 (0.4)	125 (3)	756 (20)	NA	170 (5)	260 (7)	735 (20)	30 (1)	276 (7)
2nd dose V	3705-3758	NA	2748 (73)	2730 (74)	243 (7)	256 (7)	NA	2627 (70)	512 (14)	1114 (30)	2086 (56)	NA	772 (21)	1260 (34)	1732 (47)	51 (1)	356 (10)
Li et al., 2021																	
Overall P	48	6 (13)	2 (4)	2 (4)	0 (0)	0 (0)	NA	5 (10)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	3 (6)	0 (0)	1 (2)
Overall V	48	46 (95)	45 (94)	44 (92)	12 (25)	12 (25)	NA	39 (81)	34 (71)	11 (23)	24 (50)	13 (27)	11 (23)	11 (23)	21 (44)	3 (6)	1 (2)
1st dose P	48	NA	NA	1 (2)	0 (0)	0 (0)	NA	NA	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
1st dose V	48	NA	NA	41 (85)	10 (21)	5 (10)	NA	NA	19 (40)	6 (13)	11 (23)	7 (15)	5 (10)	7 (15)	10 (21)	3 (6)	0 (0)
2nd dose P	48	NA	NA	1 (2)	0 (0)	0 (0)	NA	NA	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	2 (4)	0 (0)	1 (2)
2nd dose V	47	NA	NA	35 (74)	5 (11)	9 (19)	NA	NA	39 (83)	8 (17)	22 (47)	10 (21)	11 (23)	8 (17)	17 (36)	1 (2)	0 (0)
Walsh et al., 2020																	
Overall P	39	10 (26)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Overall V	48	17 (35)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1st dose P	36-39	NA	NA	1 (3)	0 (0)	0 (0)	NA	NA	0 (0)	2 (6)	11 (31)	NA	2 (6)	3 (8)	5 (14)	0 (0)	1 (3)
1st dose V	48	NA	NA	43 (90)	3 (6)	4 (8)	NA	NA	6 (13)	13 (27)	20 (42)	NA	3 (6)	11 (23)	18 (38)	1 (2)	2 (4)
2nd dose P	36	NA	NA	5 (14)	0 (0)	0 (0)	NA	NA	0 (0)	1 (3)	10 (28)	NA	1 (3)	1 (3)	3 (8)	1 (3)	0 (0)
2nd dose V	48	NA	NA	39 (81)	3 (6)	6 (13)	NA	NA	16 (33)	21 (44)	32 (67)	NA	8 (17)	21 (44)	32 (67)	1 (2)	3 (6)
Viral vector vaccines																	
Madhi et al., 2021																	
1st dose P	935-968	NA	NA	NA	0 (0)	0 (0)	122 (13)	NA	5 (1)	25 (3)	181 (19)	NA	115 (12)	137 (14)	250 (26)	NA	NA
1st dose V	918-952	NA	NA	NA	1 (0.1)	2 (0.2)	345 (36)	NA	5 (1)	87 (9)	304 (32)	NA	215 (23)	290 (30)	361 (38)	NA	NA
2nd dose P	886-941	NA	NA	NA	0 (0)	0 (0)	75 (8)	NA	3 (0.3)	14 (2)	114 (12)	NA	70 (7)	79 (8)	161 (17)	NA	NA
2nd dose V	877-926	NA	NA	NA	1 (0.1)	1 (0.1)	245 (27)	NA	1 (0.1)	26 (3)	158 (17)	NA	95 (10)	153 (17)	190 (21)	NA	NA
Sadoff et al., 2021																	
Placebo	163	48 (29)	19 (12)	NA	NA	NA	NA	40 (25)	0 (0)	NA	NA	NA	NA	NA	NA	NA	NA
Vaccine	323	220 (68)	170 (53)	NA	NA	NA	NA	179 (55)	32 (10)	NA	NA	NA	NA	NA	NA	NA	NA
Protein-based vaccines																	
Goepfert et al., 2021																	
1st dose P	29	NA	NA	4 (14)	0 (0)	0 (0)	NA	NA	0 (0)	NA	NA	5 (17)	NA	2 (7)	7 (24)	NA	NA
1st dose V	80	NA	NA	53 (67)	1 (1)	1 (1)	NA	NA	1 (1)	NA	NA	16 (20)	NA	22 (28)	20 (25)	NA	NA
2nd dose P	29	NA	NA	3 (10)	1 (3)	0 (0)	NA	NA	0 (0)	NA	NA	3 (10)	NA	3 (10)	3 (10)	NA	NA
2nd dose V	80	NA	NA	70 (89)	19 (24)	15 (19)	NA	NA	28 (36)	NA	NA	59 (75)	NA	60 (75)	57 (71)	NA	NA
Heath et al., 2021																	
1st dose P	1350	NA	2828 (21)	138 (10)	5 (0.4)	7 (1)	236 (17)	512 (38)	20 (1)	NA	259 (19)	130 (10)	66 (5)	192 (14)	290 (21)	73 (5)	NA
1st dose V	1364	NA	809 (59)	419 (31)	26 (2)	12 (1)	749 (55)	649 (48)	31 (2)	NA	280 (21)	158 (12)	90 (7)	304 (22)	334 (24)	71 (5)	NA
2nd dose P	1335	NA	227 (17)	122 (9)	3 (0.2)	4 (0.3)	187 (14)	411 (31)	11 (1)	NA	223 (17)	123 (9)	68 (5)	130 (10)	239 (18)	51 (4)	NA

2nd dose V	1348	NA	1081 (80)	700 (52)	112 (8)	100 (7)	1033 (77)	871 (65)	69 (5)	NA	553 (41)	425 (32)	231 (17)	554 (41)	549 (41)	144 (11)	NA
Keech et al., 2020																	
1st dose P	23	NA	7 (30)	3 (13)	0 (0)	NA	7 (30)	9 (39)	0 (0)	NA	4 (17)	2 (9)	1 (4)	2 (9)	7 (30)	1 (4)	NA
1st dose V	26	NA	18 (70)	10 (38)	0 (0)	NA	17 (65)	12 (46)	0 (0)	NA	8 (31)	3 (12)	1 (4)	6 (23)	6 (23)	1 (4)	NA
2nd dose P	21	NA	4 (19)	2 (10)	1 (5)	NA	2 (10)	7 (33)	0 (0)	NA	3 (14)	3 (14)	2 (10)	3 (14)	6 (29)	0 (0)	NA
2nd dose V	26	NA	24 (92)	15 (58)	2 (8)	NA	21 (81)	17 (65)	0 (0)	NA	12 (46)	9 (35)	7 (27)	12 (46)	12 (46)	2 (8)	NA
Richmond et al., 2021																	
1st dose P	30	NA	1 (3)	1 (3)	0 (0)	0 (0)	NA	3 (10)	0 (0)	NA	0 (0)	NA	NA	1 (3)	1 (3)	0 (0)	0 (0)
1st dose V	16	NA	7 (44)	5 (31)	1 (6)	1 (6)	NA	3 (19)	0 (0)	NA	0 (0)	NA	NA	0 (0)	3 (19)	0 (0)	0 (0)
2nd dose P	30	NA	0 (0)	0 (0)	0 (0)	0 (0)	NA	6 (20)	0 (0)	NA	2 (7)	NA	NA	1 (3)	3 (10)	0 (0)	1 (3)
2nd dose V	16	NA	7 (44)	7 (44)	2 (13)	1 (6)	NA	5 (31)	0 (0)	NA	2 (13)	NA	NA	1 (6)	2 (13)	0 (0)	0 (0)
Shinde et al., 2021																	
1st dose P	484	NA	96 (20)	73 (15)	2 (0.4)	2 (0.4)	60 (12)	167 (35)	7 (1)	NA	59 (12)	44 (9)	41 (8)	49 (19)	114 (24)	31 (6)	NA
1st dose V	484	NA	197 (41)	181 (37)	7 (1)	10 (2)	119 (25)	188 (39)	9 (2)	NA	75 (15)	52 (11)	67 (14)	89 (18)	118 (24)	41 (8)	NA
2nd dose P	470	NA	64 (14)	53 (11)	0 (0)	2 (0.4)	41 (9)	131 (28)	7 (1)	NA	53 (11)	38 (8)	34 (7)	38 (8)	89 (19)	36 (8)	NA
2nd dose V	471	NA	185 (39)	172 (37)	6 (1)	10 (2)	112 (24)	162 (34)	17 (4)	NA	68 (14)	46 (10)	65 (14)	82 (17)	97 (21)	32 (7)	NA

Note: AE = adverse event; P = placebo; V = vaccine. Decimals are provided for percentages ≤ 0.5.

Supplemental Results

eTable 2

Coefficients of the mixed random-effects meta-analysis of adverse event proportions in the placebo groups, controlling for risk of bias

				95% CI		
	k	Proportion	SE	Lower	Upper	I^2, %
Any Adverse Event	5	0.218	0.11	0.003	0.432	89.48
Any Local AE	9	0.110	0.05	0.012	0.208	98.02
Dose 1	8	0.182	0.02	0.140	0.225	97.00
Dose 2	8	0.150	0.02	0.108	0.192	97.29
Pain	10	0.042	0.04	−0.044	0.127	94.05
Dose 1	10	0.137	0.02	0.105	0.170	93.94
Dose 2	10	0.118	0.02	0.079	0.157	96.33
Redness	11	< 0.001	< 0.01	−0.007	0.007	91.61
Dose 1	11	0.004	< 0.01	< 0.001	0.007	94.51
Dose 2	11	0.001	< 0.01	< 0.001	0.002	63.56
Swelling	10	< 0.001	< 0.01	−0.007	0.007	91.26
Dose 1	10	0.004	< 0.01	< 0.001	0.006	92.84
Dose 2	10	0.003	< 0.01	< 0.001	0.005	91.13
Tenderness	6	0.102	0.02	0.055	0.149	97.24
Dose 1	6	0.117	0.03	0.065	0.170	97.57
Dose 2	6	0.086	0.02	0.044	0.127	96.98
Any Systemic AE	9	0.204	0.07	0.068	0.340	97.89
Dose 1	8	0.405	0.04	0.329	0.482	98.29
Dose 2	8	0.326	0.02	0.290	0.362	92.27
Fever	12	0.002	< 0.01	−0.003	0.007	63.81
Dose 1	12	0.006	< 0.01	0.003	0.010	77.57
Dose 2	12	0.004	< 0.01	0.002	0.006	52.61
Chills	6	< 0.001	0.02	−0.033	0.033	95.16
Dose 1	6	0.045	0.01	0.027	0.063	93.66
Dose 2	6	0.035	0.01	0.014	0.056	96.41
Fatigue	10	< 0.001	0.07	−0.146	0.146	98.36
Dose 1	10	0.213	0.04	0.131	0.295	98.93
Dose 2	10	0.169	0.03	0.117	0.221	97.60
Malaise	5	0.021	0.02	−0.020	0.061	0.00[1]
Dose 1	5	0.096	0.01	0.082	0.109	0.17[2]
Dose 2	5	0.089	0.01	0.076	0.102	0.00[3]
Joint pain	9	0.021	0.03	−0.044	0.085	95.68
Dose 1	9	0.086	0.01	0.059	0.113	96.51
Dose 2	9	0.070	0.01	0.048	0.093	95.48
Muscle pain	11	< 0.001	0.02	−0.035	0.035	83.95
Dose 1	11	0.122	0.01	0.104	0.141	85.14
Dose 2	11	0.092	0.01	0.073	0.112	88.88
Headache	11	0.063	0.04	−0.019	0.144	81.00

	k	Proportion	SE	95% CI		I^2, %
				Lower	Upper	
Dose 1	11	0.250	0.02	0.219	0.281	90.41
Dose 2	11	0.192	0.01	0.168	0.217	86.82
Nausea/vomiting	9	< 0.001	0.02	−0.048	0.048	97.79
Dose 1	9	0.049	0.01	0.022	0.076	98.53
Dose 2	9	0.045	0.01	0.020	0.071	98.05
Diarrhea	4	0.021	0.02	−0.020	0.061	0.00[4]
Dose 1	4	0.096	0.01	0.087	0.105	0.00[5]
Dose 2	4	0.075	0.01	0.066	0.084	0.50[5]

Note. AE = adverse event; k = number of studies included in analyses; SE = standard error; CI = confidence interval. Analyses control for risk of bias due to selective reporting (no AE reports over both doses or time interval of AE assessment > 7 days), incomplete outcome data (high drop-out rate in placebo group) and other source of bias (inclusion of sentinel participants in AE reports). [1]95 % CI 0.00–99.23; [2]95 % CI 0.00–99.71; [3]95 % CI 0.00–94.33; [4]95 % CI 0.00–98.97; [5]95 % CI 0.00–99.90.

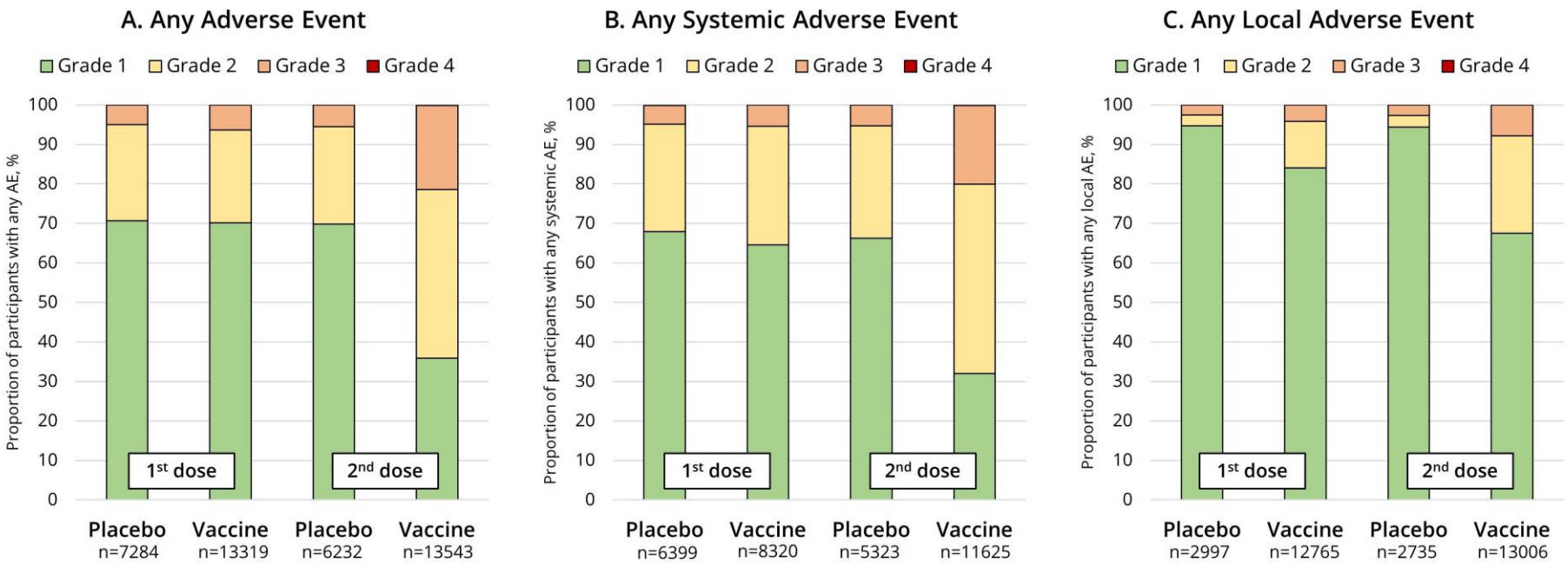
eTable 3

Coefficients of the mixed random-effects meta-analysis of logarithmic odds ratios to compare the frequency of adverse events in the placebo and vaccine groups, controlling for risk of bias

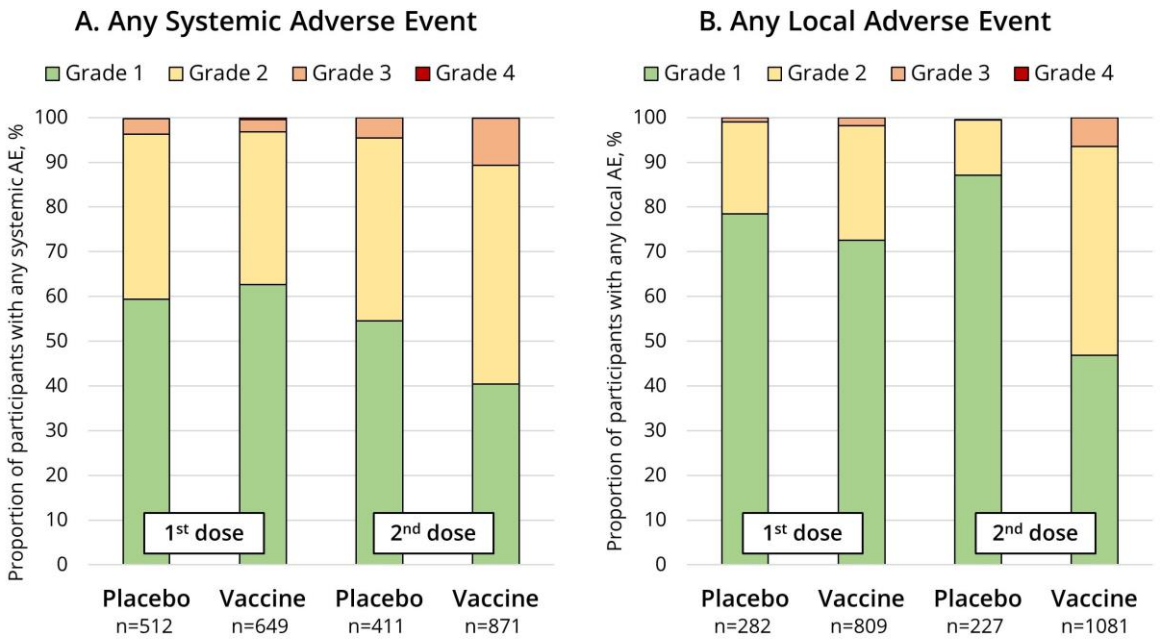
	Log OR	SE	z	p	95 % CI		I^2, %	d
					Lower	Upper		
Any Adverse Event	−4.16	1.33	−3.12	.002	−6.78	−1.55	91.83	−2.30
Any Local AE	−3.73	1.29	−2.89	.004	−6.25	−1.20	99.62	−2.05
Dose 1	−2.26	0.49	−4.63	< .001	−3.22	−1.30	99.41	−1.25
Dose 2	−2.77	0.43	−6.42	< .001	−3.62	−1.93	99.08	−1.53
Pain	−5.53	1.22	−4.55	< .001	−7.92	−3.15	98.54	−3.05
Dose 1	−2.32	0.46	−5.02	< .001	−3.22	−1.41	99.05	−1.28
Dose 2	−2.89	0.41	−7.13	< .001	−3.68	−2.09	98.56	−1.59
Redness	−3.50	1.52	−2.31	.02	−6.48	−0.53	54.33	−1.93
Dose 1	−1.66	0.16	−10.35	< .001	−1.97	−1.34	22.75[1]	−0.91
Dose 2	−2.81	0.31	−9.09	< .001	−3.42	−2.20	58.46	−1.55
Swelling	−3.50	1.56	−2.25	.02	−6.56	−0.45	63.99	−1.93
Dose 1	−1.79	0.44	−4.09	< .001	−2.65	−0.94	82.31	−0.99
Dose 2	−2.99	0.33	−9.03	< .001	−3.64	−2.34	60.32	−1.65
Tenderness	−1.46	0.30	−4.82	< .001	−2.06	−0.87	97.39	−0.81
Dose 1	−1.20	0.23	−5.29	< .001	−1.64	−0.76	95.74	−0.66
Dose 2	−1.76	0.42	−4.18	< .001	−2.59	−0.94	98.44	−0.97
Any Systemic AE	−2.43	0.63	−3.87	< .001	−3.66	−1.20	98.80	−1.34
Dose 1	−0.46	0.04	−10.83	< .001	−0.54	−0.37	50.96	−0.25
Dose 2	−1.29	0.35	−3.67	< .001	−1.98	−0.60	99.14	−0.71
Fever	−4.35	1.48	−2.95	.003	−7.24	−1.46	91.00	−2.40

	Log OR	SE	z	p	95 % CI		I^2, %	d
					Lower	Upper		
Dose 1	−0.76	0.24	−3.14	.002	−1.24	−0.29	56.79	−0.42
Dose 2	−2.29	0.72	−3.21	.001	−3.69	−0.89	94.06	−1.26
Chills	−3.39	1.46	−2.32	.02	−6.26	−0.53	0.00[2]	−1.87
Dose 1	−0.81	0.28	−2.96	.003	−1.35	−0.28	94.22	−0.45
Dose 2	−1.97	0.54	−3.68	< .001	−3.02	−0.92	98.18	−1.09
Fatigue	−4.58	1.48	−3.09	.002	−7.48	−1.68	93.58	−2.52
Dose 1	−0.43	0.11	−4.15	< .001	−0.64	−0.23	88.86	−0.24
Dose 2	−1.09	0.28	−3.86	< .001	−1.65	−0.54	98.32	−0.60
Malaise	−2.86	1.22	−2.35	.02	−5.25	−0.47	86.85	−1.58
Dose 1	−0.20	0.11	−1.89	.06	−0.41	0.01	0.00[3]	−0.11
Dose 2	−1.56	0.84	−1.86	.06	−3.21	0.08	97.13	−0.86
Joint pain	−2.64	1.09	−2.41	.02	−4.78	−0.49	83.84	−1.45
Dose 1	−0.51	0.08	−6.73	< .001	−0.65	−0.36	57.77	−0.28
Dose 2	−1.21	0.27	−4.44	< .001	−1.74	−0.68	96.62	−0.67
Muscle pain	−3.39	1.49	−2.29	.02	−6.30	−0.48	86.90	−1.87
Dose 1	−0.70	0.07	−10.37	< .001	−0.84	−0.57	58.31	−0.39
Dose 2	−1.73	0.31	−5.54	< .001	−2.34	−1.12	97.74	−0.95
Headache	−2.46	0.74	−3.32	< .001	< .001	−3.91	94.09	−1.35
Dose 1	−0.30	0.08	−4.00	< .001	−0.44	−0.15	76.93	−0.16
Dose 2	−1.12	0.38	−2.96	.003	−1.86	−0.38	99.08	−0.62
Nausea/vomiting	−2.01	1.54	−1.31	.19	−5.02	1.00	48.75[4]	−1.11
Dose 1	0.29	0.36	0.82	.41	−0.41	1.00	90.65	0.16
Dose 2	−0.77	0.32	−2.42	.02	−1.40	−0.15	91.00	−0.43
Diarrhea	< −0.01	1.43	< −0.01	1.00	−2.80	2.80	0.00[5]	0.00
Dose 1	−0.04	0.08	−0.53	.60	−0.19	0.11	0.00[6]	−0.02
Dose 2	−0.28	0.08	−3.30	< .001	−0.44	−0.11	0.00[7]	−0.15

Note. AE = adverse event; log OR = logarithmic odds ratio; SE = standard error; CI = confidence interval; d = standard mean difference. Analyses control for risk of bias due to selective reporting (no AE reports over both doses or time interval of AE assessment > 7 days), incomplete outcome data (high drop-out rate in placebo group) and other source of bias (inclusion of sentinel participants in AE reports). [1]95 % CI 0.00–49.22; [2]95 % CI 0.00–98.98; [3]95 % CI 0.00–0.00; [4]95 % CI 0.00–94.99; [5]95 % CI 0.00–97.30; [6]95 % CI 0.00–85.35; [7]95 % CI 0.00–97.52.



eFigure 1. Adverse event severity grading in the phase-3 trial of the Moderna vaccine (Baden et al., 2021). Plots show fractions of severity grades within participants who reported any adverse events (A), any systemic adverse event (B) or any local adverse event (C). Grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening.



eFigure 2. Adverse event severity grading in the phase-3 trial of the Novavax vaccine (Heath et al., 2021). Plots show fractions of severity grades within participants who reported any adverse events (A), any systemic adverse event (B) or any local adverse event (C). Grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life-threatening.

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