

Supplementary material File1

Full Search Strategy

In order to frame the main research question, we applied the PICO (Participant-Intervention-Comparator-Outcomes) framework to define our research question. (Schardt et al., 2007) The search terms were arranged using the boolean logic.

P=population

I=vaccine

C=controls (unvaccinated)

O=effectiveness in CoVID19 prevention (RR)

Search terms: COVID19 vaccine [AND] effectiveness[OR]efficacy

Last conducted on: 11/05/2021

1. PubMed

((effectiveness OR efficacy OR Real World OR Phase 3 OR Phase 4)) AND (("Vaccination"[Mesh] OR "Immunization Programs"[Mesh] OR "Vaccines"[Mesh] OR vaccin*[tiab] OR immunization*[tiab] OR immunisation*[tiab])) AND (((("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh] OR "COVID-19 Vaccines"[Mesh] OR "COVID-19 Serological Testing"[Mesh] OR "COVID-19 Nucleic Acid Testing"[Mesh] OR "SARS-CoV-2 variants" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2"))))

Search	Query	Results
#1	Search: (("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh] OR "COVID-19 Vaccines"[Mesh] OR "COVID-19 Serological Testing"[Mesh] OR "COVID-19 Nucleic Acid Testing"[Mesh] OR "SARS-CoV-2 variants" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2"))	130,245
#2	Search: ("Vaccination"[Mesh] OR "Immunization Programs"[Mesh] OR "Vaccines"[Mesh] OR vaccin*[tiab] OR immunization*[tiab] OR immunisation*[tiab])	447,082
#3	Search: (effectiveness OR efficacy OR Real World OR Phase 3 OR Phase 4)	10,214,491

#4	Search: #1 AND #2 AND #3 Filters: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review, Review	4,903
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2. MedRxiv

<https://www.medrxiv.org/search/%2528effectiveness%252Bor%252Befficacy%252Bor%252Breal%252Bworld%252Bor%252Bphase%252B3%252Bor%252Bphase%252B4%2529%252Band%252B%2528covid%252Bor%252Bsars-cov-2%2529%252Band%252Bvaccine>

Search	Query	Results
	"(covid-19 or sars-cov-2) and vaccine and (effectiveness OR efficacy OR Real World OR Phase 3 OR Phase 4)"	2,390

3. SSRN

<https://papers.ssrn.com/sol3/results.cfm?RequestTimeout=50000000>

Search	Query	Results
	covid-19 and vaccine and effectiveness	40

4. Authorea

<https://www.authorea.com/preprints>

Search	Query	Results
	VACCINE + SARS-COV-2	7

5. Clinical Trials

https://clinicaltrials.gov/ct2/results?term=vaccine+%28effectiveness+or+efficacy%29&cond=covid+19+or+sars-cov-2&Search=Clear&age_v=&gndr=&type=&rslt=

Search	Query	Results
	(covid-19 or sars-cov-2) AND vaccine AND (effectiveness or efficacy)	186

6. Cochrane Library

<https://www.cochranelibrary.com/advanced-search?cookiesEnabled>

Search	Query	Results
	(covid19 vaccine) or (sars-cov-2 vaccine) and effectiveness	201

7. COVID-NMA

<https://covid-nma.com/vaccines/mapping/>

Search	Query	Results
	vaccines	33

Supplementary material File 2

Meta-analysis: between-study heterogeneity

2.1 Partially vaccinated, first dose effectiveness, any Sars-Cov2 positive PCR

Table S1) Outliers, partially vaccinated. The outliers test identified which study's confidence interval did not overlap with the confidence interval of the random pooled effect. Concerning the meta-analysis on partially vaccinated (any positive PCR), seven studies presented an extreme effect size estimate.

Identified outliers (random-effects model)					
"Daniel", "Hall", "Shotri A", "Pritchard", "Swift", "Abu-Raddad", "Abu-Raddad"					
Results with outliers removed					
	RR [95%-CI %]		W(fixed) %	W(random)	exclude
Amit	0.2302	[0.1706; 0.3107]	1.3	7.2	
Benenson	0.2217	[0.1584; 0.3101]	1.0	7.0	
Britton	0.1483	[0.0951; 0.2314]	0.6	6.3	
Dagan	0.1846	[0.1719; 0.1982]	23.1	8.2	
Daniel	0.6987	[0.5591; 0.8731]	0.0	0.0	*
Hall	0.0075	[0.0059; 0.0096]	0.0	0.0	*
Lopez Bernal A70	0.1892	[0.1747; 0.2049]	18.3	8.2	
Lopez Bernal B70	0.2066	[0.1918; 0.2226]	21.0	8.2	
Lopez Bernal A80	0.4081	[0.3794; 0.4389]	22.0	8.2	
Pawloski	0.1487	[0.1279; 0.1728]	5.2	8.0	
Tenforde	0.5707	[0.3805; 0.8560]	0.7	6.6	
Shotri A	0.7130	[0.6042; 0.8413]	0.0	0.0	*
Shotri B	0.4422	[0.3802; 0.5143]	5.1	8.0	
Pritchard	0.0357	[0.0323; 0.0393]	0.0	0.0	*
Swift	0.7328	[0.5975; 0.8988]	0.0	0.0	*
Angel	0.5949	[0.2781; 1.2725]	0.2	4.3	
Abu Raddad	0.8283	[0.7870; 0.8717]	0.0	0.0	*
Abu Raddad	0.9080	[0.8717; 0.9458]	0.0	0.0	*
Jones A	0.2355	[0.1125; 0.4930]	0.2	4.4	
Jones B	0.1270	[0.0519; 0.3109]	0.1	3.7	
Fabiani	0.3554	[0.1863; 0.6782]	0.3	5.0	
Gras Valenti	0.5470	[0.3811; 0.7850]	0.9	6.8	
Meta-analysis with outliers removed					
Number of studies combined: k = 15					
	RR [95%-CI %]		z	p-value	
Fixed effect model	0.2397	[0.2317; 0.2481]	-81.99	0	
Random effects model	0.2679	[0.2130; 0.3369]	-11.27	< 0.0001	
Quantifying heterogeneity:					
tau^2 = 0.1657 [0.0822; 0.6127]; tau = 0.4070 [0.2867; 0.7827]					
I^2 = 97.0% [96.0%; 97.7%]; H = 5.73 [5.00; 6.56]					

Test of heterogeneity:	Q	d.f.	p-value
	459.09	14	< 0.0001
Details on meta-analytical method:			
- Inverse variance method			
- DerSimonian-Laird estimator for tau ²			
- Jackson method for confidence interval of tau ² and tau			

Figure.S1) Forest plot, partially vaccinated. Any positive PCR RR ≥14 days after first dose. Outliers excluded, RE IV method. Identified outliers: "Daniel", "Hall", "Shotri A", "Pritchard", "Swift", "Abu-Raddad A", "Abu-Raddad B". The outlying studies were still displayed. However, their weight in the meta-analysis has been set to 0%; therefore, they were excluded from pooling. Overall RR=0.27 and RRR=73%. Heterogeneity: $\tau^2 = 0.1657$ [0.0822; 0.6127]; $\tau = 0.4070$ [0.2867; 0.7827]; $I^2 = 97.0\%$ [96.0%; 97.7%]; $H = 5.73$ [5.00; 6.56]. Test of heterogeneity: $Q=459.09$ (d.f.= 14 p-value < 0.0001). The updated RE RR was 0.23[0.2130; 0.3369], with RRR=77% compared to unvaccinated.

Partially vaccinated, any positive PCR, outliers excluded

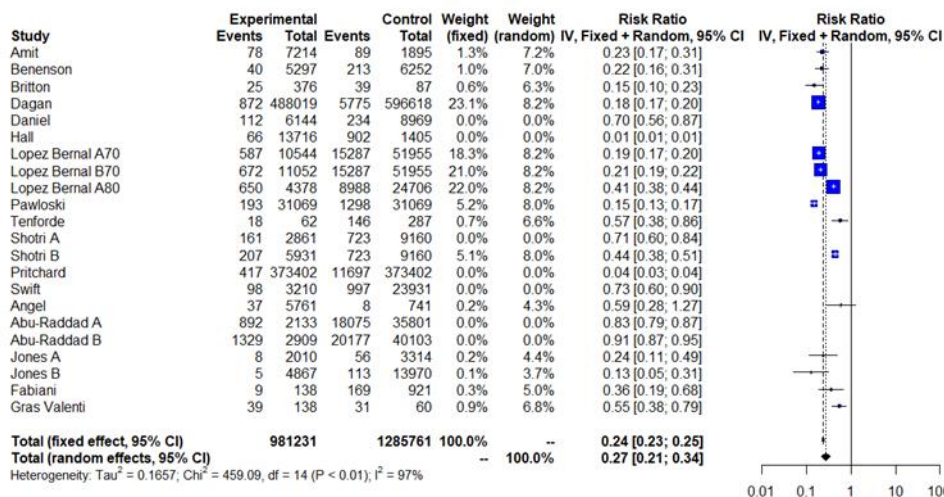


Figure.S2a) Influence analysis. Partially vaccinated, any positive PCR. Influence analysis studied the extreme values in the graphs through different influence measures. Each subplot graphs included the influence estimates for each study of our meta-analysis. Arbitrary cut-offs define an influential case, which is displayed in red.[21] "Hall" resulted as the most influential in partially vaccinated (any positive PCR) meta-analysis.

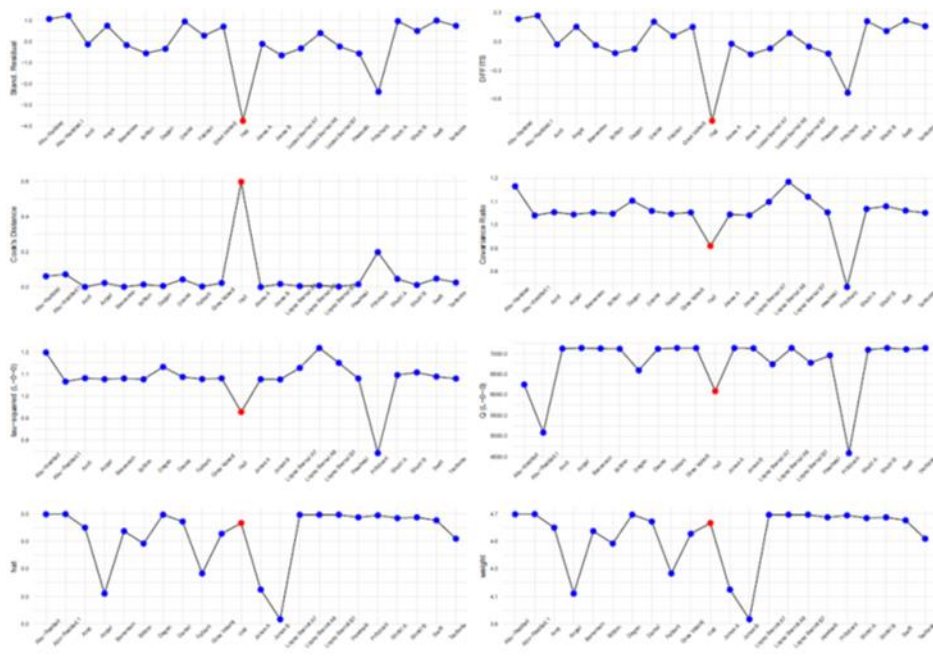


Figure.S2b) Baujat plot. Partially vaccinated, any positive PCR. Contribute to overall heterogeneity $Q(x)$ and effect size (y) . “Pritchard”, “Abu Raddad B” and “Hall” were the most influential on the overall heterogeneity. “Abu Raddad B” contributed the most to the pooled result.

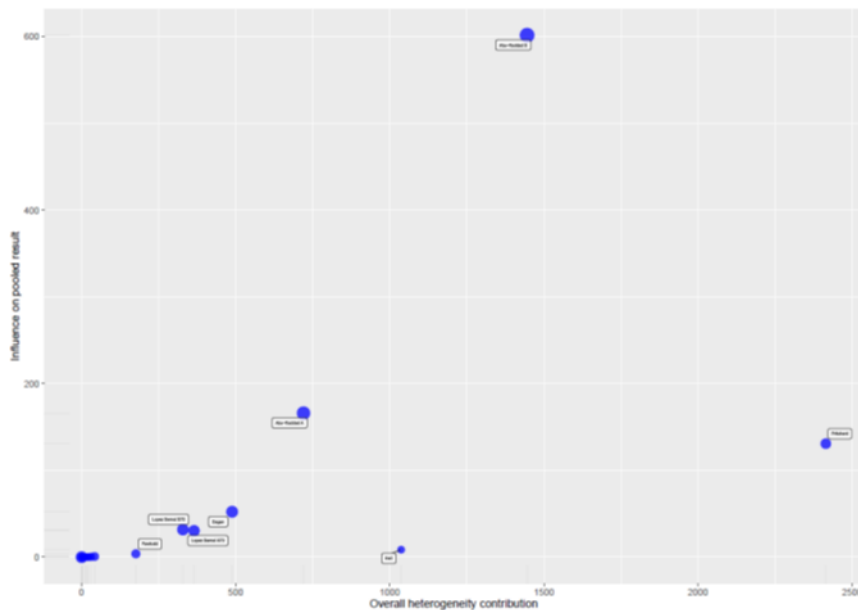


Figure.S3) Leave-One-Out Analysis. Partially vaccinated, any positive PCR. The first plot shows that by omitting “Abu-Raddad B” study, the I^2 is slightly reduced. Moreover, “Swift”, “Daniel” and “Britton” contributed to the overall heterogeneity. In the second plot the overall effect estimate changed with two studies removed. In particular, by removing “Pritchard” the RR increased to 0.29, while RR increased to 0.32 after removing “Hall”.

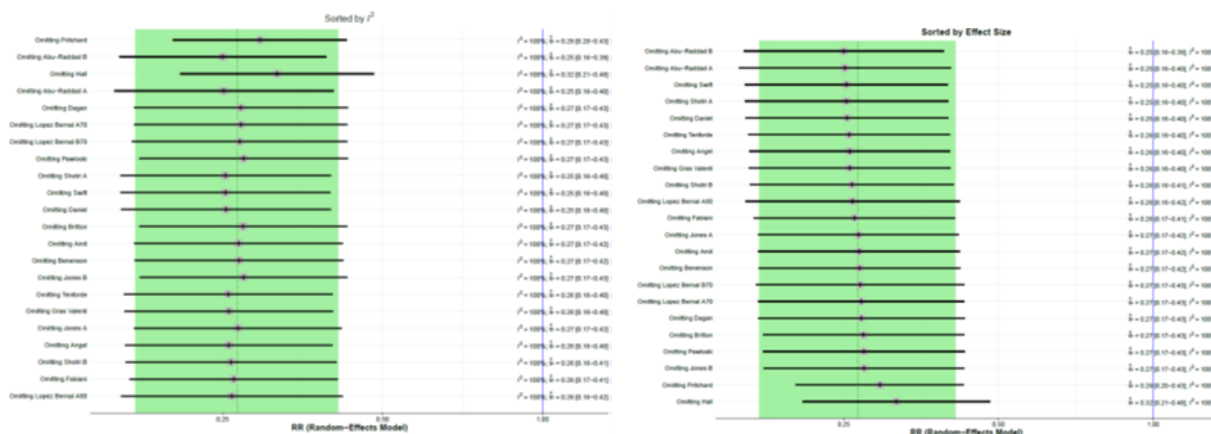
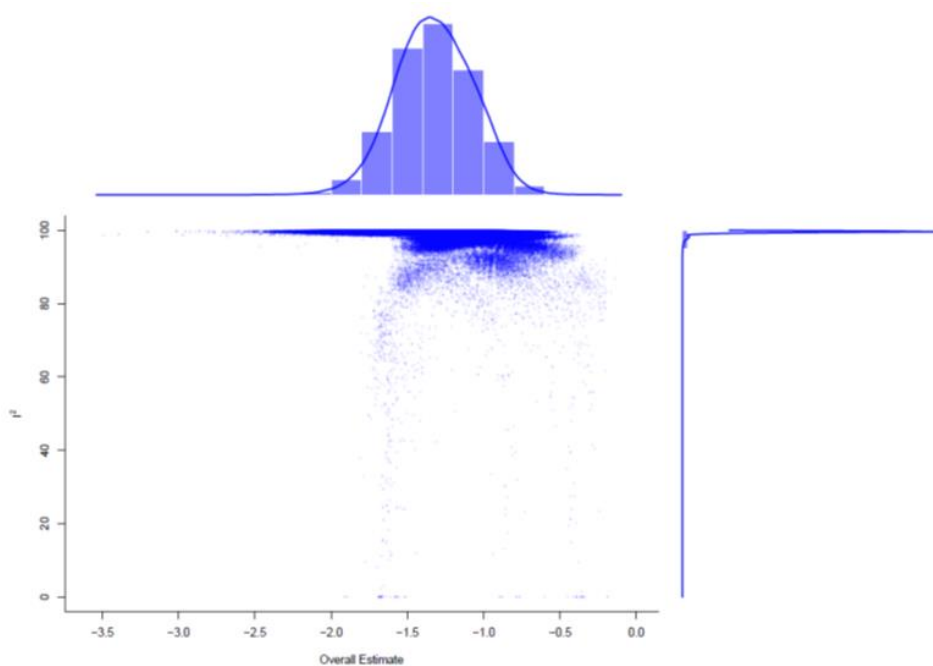


Figure.S4) GOSH Diagnostics. Partially vaccinated, any positive PCR. GOSH plots did not show clear patterns in our data. The effect size distribution was homogeneous, in contrast, the heterogeneity curve presented an asymmetric distribution with a sharp peak. The three algorithms, k -means, DBSCAN and the Gaussian Mixture Model, detected up to eleven clusters which might potentially contribute to the pooled imbalance, and all of them identified the study “Hall”(6) as contributing to the overall heterogeneity.



GOSH Diagnostics

- Number of K-means clusters detected: 3
- Number of DBSCAN clusters detected: 11
- Number of GMM clusters detected: 9

Identification of potential outliers

K-means: Study 6

DBSCAN: Study 6, Study 14, Study 11, Study 9, Study 10, Study 21, Study 1, Study 8

Gaussian Mixture Model: Study 6, Study 14, Study 11, Study 9, Study 10, Study 21, Study 1, Study 8

2.2 Fully vaccinated, any Sars-Cov2 positive PCR

Table S2) Outliers, fully vaccinated. The outliers function in full vaccination protocol meta-analysis detected seven outliers.

Identified outliers (random-effects model)						
"Dagan", "Hall", "Pawloski", "Pritchard", "Swift", "Abu Raddad A", "Abu Raddad B"						
Results with outliers removed						
	RR [95%-CI %]		W(fixed) %	W(random)	excluded	
Benenson	0.0504	[0.0259; 0.0981]	5.2	10.9		
Britton	0.0514	[0.0238; 0.1108]	3.9	10.3		
Dagan	0.0136	[0.0104; 0.0177]	0.0	0.0	*	
Daniel	0.0189	[0.0070; 0.0507]	2.4	8.9		
Hall	0.0078	[0.0039; 0.0155]	0.0	0.0	*	
Lopez Bernal B80	0.1614	[0.1283; 0.2031]	44.2	13.0		
Pawloski	0.3638	[0.3037; 0.4360]	0.0	0.0	*	
Bouton	0.0304	[0.0187; 0.0494]	9.9	11.9		
Tenforde	0.1035	[0.0153; 0.6994]	0.6	4.7		
Pritchard	0.0062	[0.0049; 0.0078]	0.0	0.0	*	
Sansone	0.1504	[0.1104; 0.2049]	24.4	12.7		
Swift	0.0164	[0.0114; 0.0235]	0.0	0.0	*	
Angel	0.1448	[0.0756; 0.2773]	5.5	11.0		
Abu Raddad A	0.1917	[0.1473; 0.2495]	0.0	0.0	*	
Abu Raddad B	0.4027	[0.3533; 0.4592]	0.0	0.0	*	
Corchado	0.2338	[0.0745; 0.7337]	1.8	8.0		
Fabiani	0.0316	[0.0110; 0.0903]	2.1	8.6		
Meta-analysis with outliers removed						
Number of studies combined: k = 10						
	RR [95%-CI %]		z	p-value		
Fixed effect model	0.1109	[0.0952; 0.1291]	-28.26	< 0.0001		
Random effects model	0.0735	[0.0440; 0.1228]	-9.97	< 0.0001		
Quantifying heterogeneity:						
tau^2 = 0.5132 [0.1894; 2.4139]; tau = 0.7164 [0.4352; 1.5537]						
I^2 = 87.3% [78.6%; 92.4%]; H = 2.80 [2.16; 3.63]						
Test of heterogeneity:						
	Q	d.f.	P-value			
	70.61	9	<0.0001			
Details on meta-analytical method:						
- Inverse variance method						
- DerSimonian-Laird estimator for tau^2						
- Jackson method for confidence interval of tau^2 and tau						

Figure.S5) Forest plot. Fully vaccinated, any positive PCR test RR ≥ 7 days after full vaccination schedule fulfilment. Outliers excluded, RE, IV method. Identified outliers: "Dagan", "Hall", "Pawloski", "Pritchard", "Swift", "Abu Raddad A", "Abu Raddad B". The RE reduced meta-analysis showed an overall RR=0.07 ($p<0.0001$), therefore, the RRR of any positive PCR approached 93% one week after the full vaccination protocol. The I^2 heterogeneity shrunk ($I^2=87.3\%$ $\tau^2= 0.5132$ [0.1894; 2.4139]), but the heterogeneity test was still significant ($Q=70.61$, $p<0.0001$).

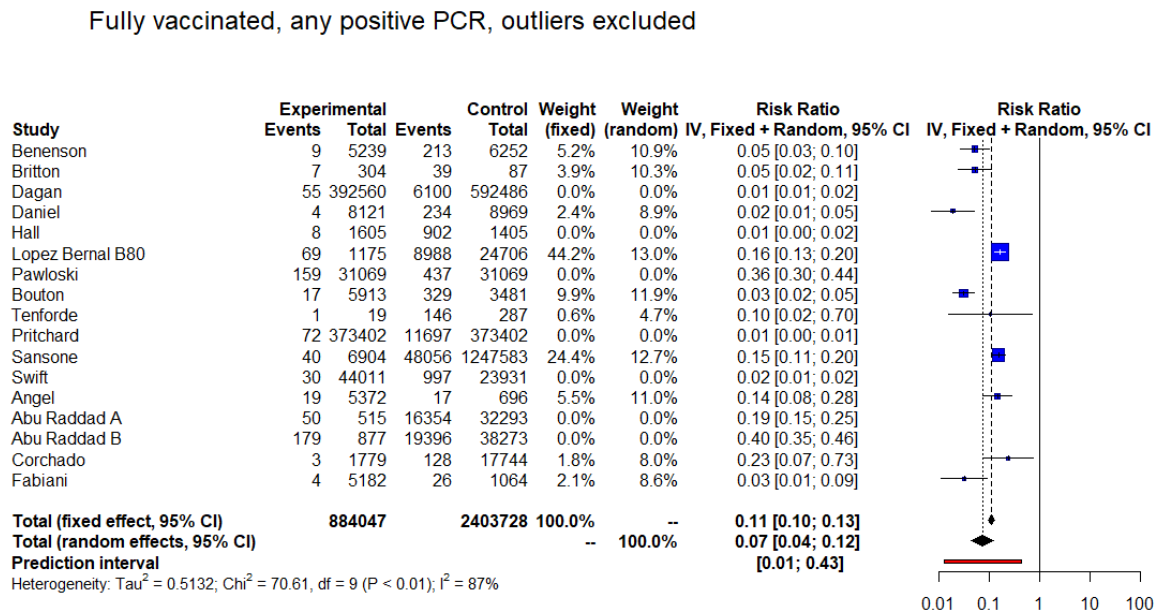
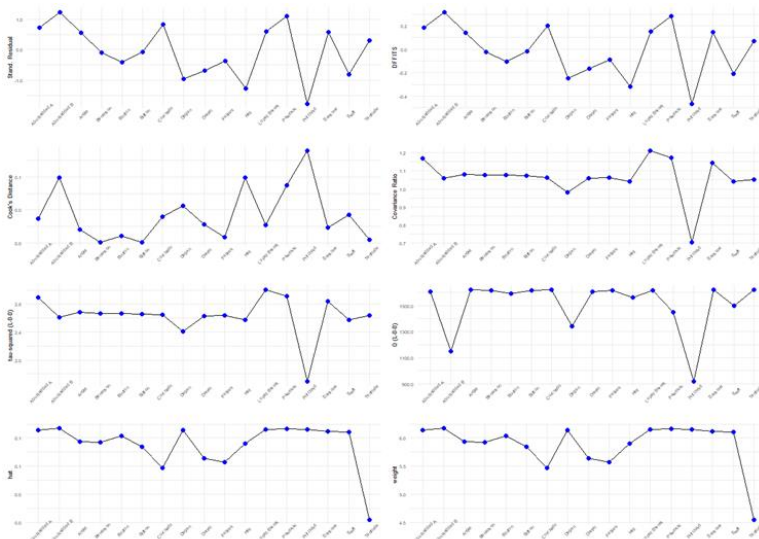
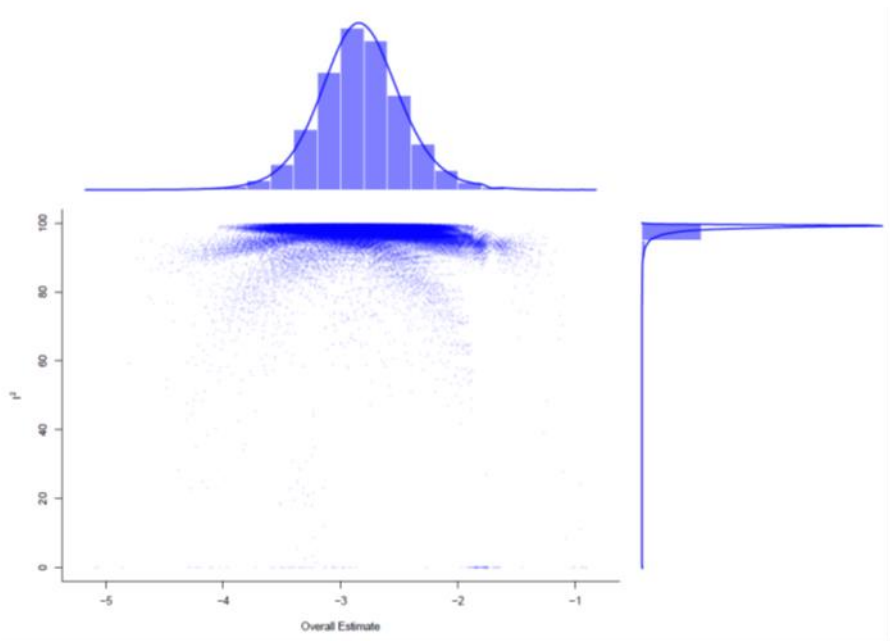


Figure. S6a) Influence analysis. Fully vaccinated, any positive PCR. Influential analysis subplot graphs included the influence estimates for each study in fully vaccinated meta-analysis. No study exceeded the cut-offs to define an influential case; however, "Pritchard" study needed further investigation.[21]



[illegible]

Figure.S8) GOSH Diagnostics. Fully vaccinated, any positive PCR. GOSH plots did not show any pattern. The effect size distribution is symmetric, in contrast, the heterogeneity curve (I^2) is right skewed and a sharp peak. The three algorithms, k -means, DBSCAN and the Gaussian Mixture Model, detected up to 15 entries which might potentially contribute to the pooled imbalance, and all of them identified “Pritchard”(10) as contributing to the overall heterogeneity.



GOSH Diagnostics
- Number of K-means clusters detected: 3
- Number of DBSCAN clusters detected: 15
- Number of GMM clusters detected: 9
Identification of potential outliers
- K-means: Study 10, Study 9
- DBSCAN: Study 15, Study 7, Study 14, Study 5, Study 13, Study 3, Study 10
- Gaussian Mixture Model: Study 15, Study 7, Study 14, Study 5, Study 13, Study 3, Study 10

2.3 At least one dose effectiveness, any Sars-Cov2 positive PCR

Table S3) Outliers, at least one dose, any positive PCR. In meta-analysis of individuals vaccinated with at least one dose, the outliers function detected nine extreme estimates.

Identified outliers (random-effects model)					
"Hall", "Lopez Bernal C80", "Moustsen Helms R", "Pawloski", "Tande", "Bouton", "Monge", "Mason", "Menni A"					
Results with outliers removed					
	RR [95%-CI %]		W(fixed) %	W(random)	excluded
Amit	0.2391	[0.1777; 0.3216]	1.6	10.5	
Benenson	0.2992	[0.2225; 0.4025]	1.6	10.5	
Britton	0.1899	[0.1266; 0.2847]	0.9	8.7	
Dagan	0.1520	[0.1419; 0.1629]	29.8	13.5	
Hall	0.0084	[0.0067; 0.0106]	0.0	0.0	*
Lopez Bernal C70	0.2251	[0.2103; 0.2410]	30.6	13.5	
Lopez Bernal C80	0.4985	[0.4671; 0.5320]	0.0	0.0	*
Lumley A	0.0879	[0.0649; 0.1192]	1.5	10.4	
Lumley B	0.0726	[0.0411; 0.1283]	0.4	6.4	
Moustsen Helms H	0.1264	[0.1120; 0.1427]	9.7	13.1	
Moustsen Helms R	0.0276	[0.0240; 0.0318]	0.0	0.0	*
Pawloski	0.3979	[0.3452; 0.4586]	0.0	0.0	*
Tande	0.4410	[0.3252; 0.5981]	0.0	0.0	*
Bouton	0.0432	[0.0296; 0.0630]	0.0	0.0	*
Monge	0.5751	[0.5623; 0.5882]	0.0	0.0	*
Mason	0.5407	[0.4953; 0.5902]	0.0	0.0	*
Menni A	0.3127	[0.3006; 0.3253]	0.0	0.0	*
Menni B	0.1481	[0.1371; 0.1600]	23.8	13.5	
Meta-analysis with outliers removed					
Number of studies combined: k = 9					
	RR [95%- CI %]		z	p-value	
Fixed effect model	0.1687	[0.1625; 0.1752]	-92.58	0	
Random effects model	0.1613	[0.1325; 0.1964]	-18.19	< 0.0001	
Quantifying heterogeneity:					
tau^2 = 0.0731 [0.0408; 0.5199]; tau = 0.2704 [0.2020; 0.7210]					
I^2 = 94.9% [92.2%; 96.6%]; H = 4.42 [3.58; 5.46]					
Test of heterogeneity:					
	Q	d.f.	p-value		
	156.58	8	<0.0001		
Details on meta-analytical method:					
- Inverse variance method					
- DerSimonian-Laird estimator for tau^2					
- Jackson method for confidence interval of tau^2 and tau					

Figure.S9) Forest plot. At least one dose, any positive PCR RR ≥ 14 days after first dose. Outliers excluded, RE, IV method. Identified outliers: "Hall", "Lopez Bernal C80", "Moustsen Helms R", "Pawloski", "Tande", "Bouton", "Monge", "Mason", "Menni A". The reduced meta-analysis output showed an overall RR=0.16 with RRR= 84%. Heterogeneity: $\tau^2 = 0.0731$ [0.0408; 0.5199]; $\tau = 0.2704$ [0.2020; 0.7210]; $I^2 = 94.9\%$ [92.2%; 96.6%]; $H = 4.42$ [3.58; 5.46]. Test of heterogeneity: $Q = 156.58$ (d.f.= 8; p-value< 0.0001).

At least one dose, any positive PCR, outliers excluded

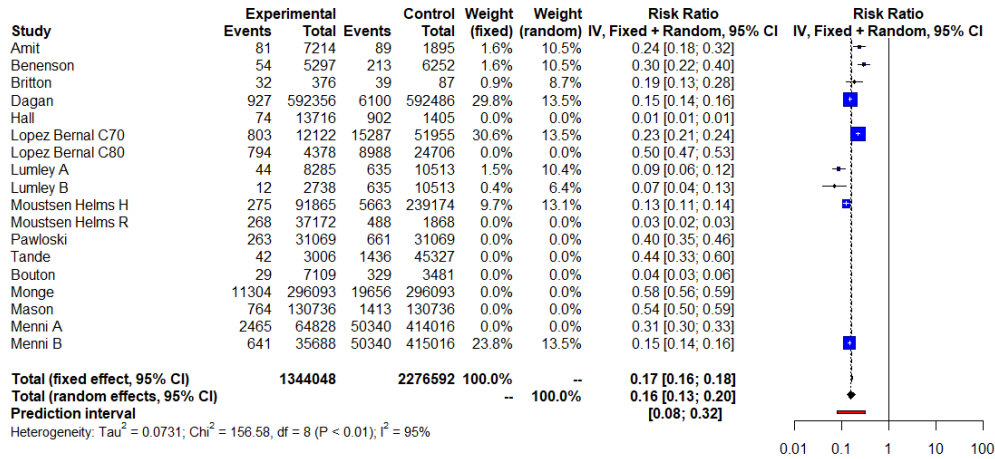


Figure. S10a) Influence analysis. At least one dose, any positive PCR. "Hall" (red dot) resulted as the most influential study as it exceeded the cut-offs to defined by Viechtbauer and Cheung in each subplot. [21]

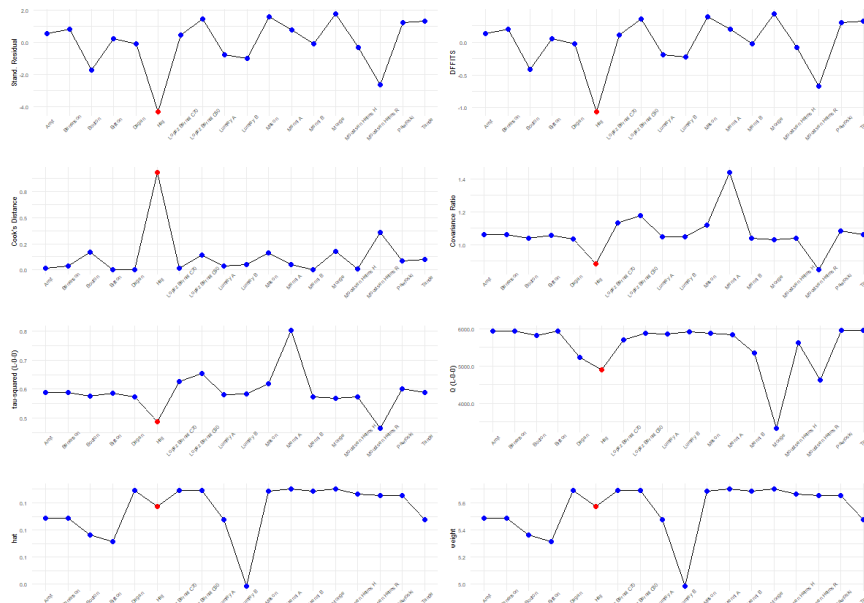


Figure.S10b) Baujat plot. At least one dose any positive PCR. Contribute to overall heterogeneity, Q (x) and effect size (y). “Hall” and “Moustsen Helms R” and “Monge” contributed to the pooled imbalance. “Monge” was the most influential on pooled effect size.

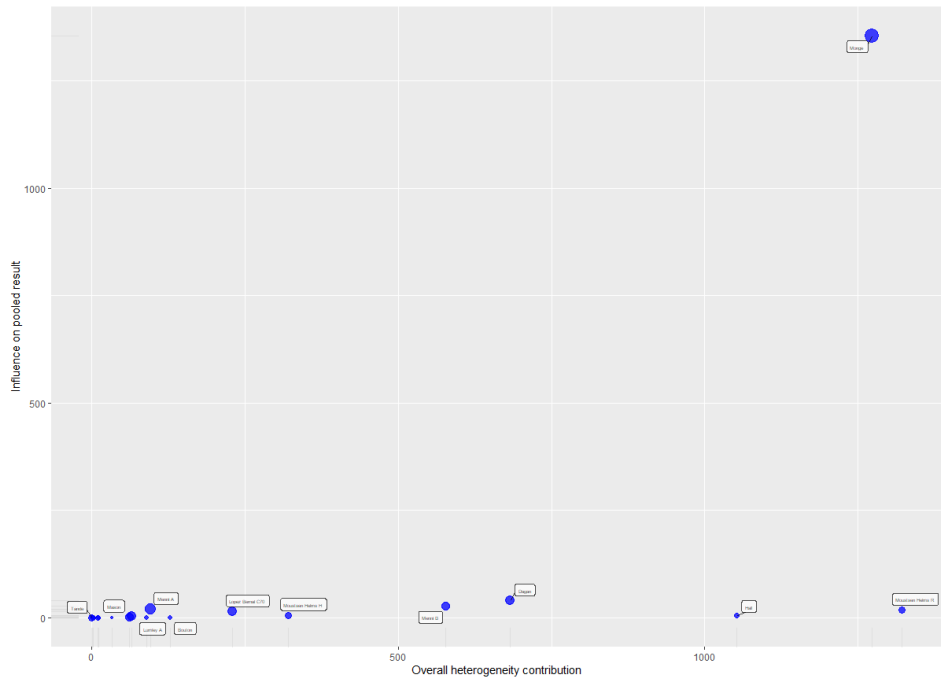


Figure.S11) Leave one out analysis. At least one dose, any positive PCR. The first plot displayed the change on the I2 heterogeneity attained by removing one study. The second plot indicated how the omission of each study influenced the overall RR estimate. The best result in both cases was achieved by omitting “Monge”.

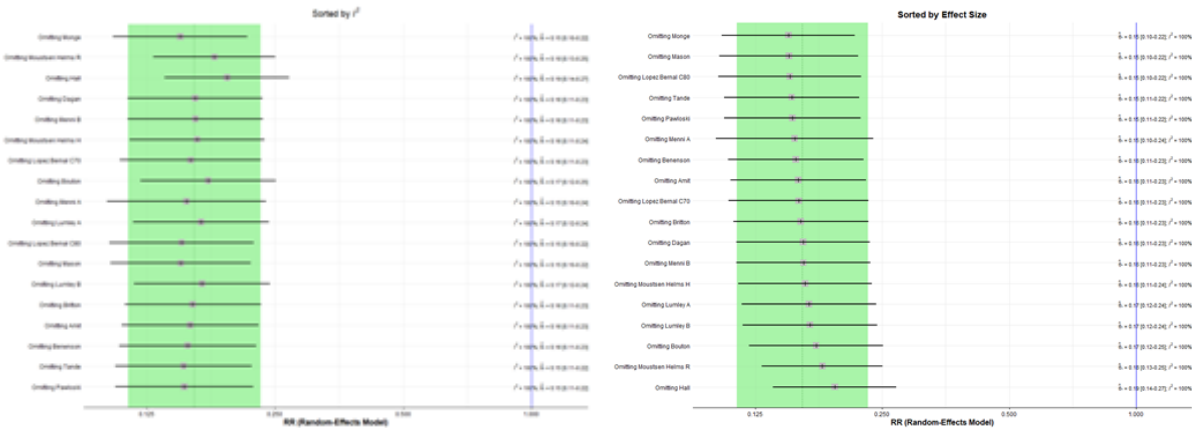
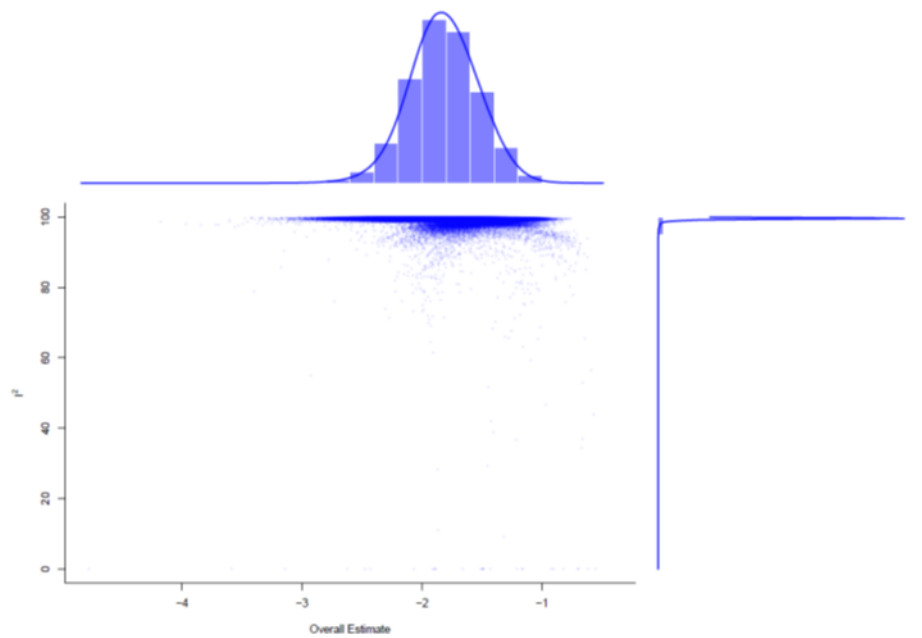


Figure.S12) GOSH Diagnostics, at least one dose, any positive PCR. GOSH plots did not show any pattern and corroborated the outliers tests and the influence analyses. The effect size distribution was symmetric, while the heterogeneity curve (I^2) was right skewed. The three algorithms, k -means, DBSCAN and the Gaussian Mixture Model, detected up to eight entries which might contribute to the pooled imbalance, as well as to the overall heterogeneity, in particular “Hall” (5), “Monge” (15) and “Lopez Bernal C80” on ≥ 80 years (7).



GOSH Diagnostics
- Number of K-means clusters detected: 3
- Number of DBSCAN clusters detected: 6
- Number of GMM clusters detected: 8
Identification of potential outliers
- K-means: Study 11, Study 15, Study 5
- DBSCAN: Study 5, Study 7
- Gaussian Mixture Model: Study 5, Study 7

2.4 Sars-Cov2 effectiveness, symptomatic positive PCR

Table S4) Outliers, partially vaccinated, symptomatic Sars-Cov-2 PCR. The outliers function identified "Pritchard".

Identified outliers (random-effects model)					
"Pritchard"					
Results with outliers removed					
	RR [95%-CI %]		W(fixed) %	W(random)	excluded
Amit	0.0482	[0.0254; 0.0914]	0.6	12.0	
Dagan	0.6899	[0.6549; 0.7267]	91.6	14.5	
Hyams A	0.4217	[0.2703; 0.6577]	1.3	13.2	
Hyams B	0.3441	[0.1763; 0.6715]	0.6	11.9	
Pritchard	0.0270	[0.0231; 0.0317]	0.0	0.0	*
Swift	0.5552	[0.4336; 0.7111]	4.1	14.1	
Angel	0.1078	[0.0673; 0.1726]	1.1	13.1	
Jones	0.2515	[0.0879; 0.7197]	0.2	9.4	
Fabiani	0.5753	[0.2985; 1.1086]	0.6	11.9	
Meta-analysis with outliers removed					
Number of studies combined: k =8					
	RR [95%-CI %]		z	p-value	
Fixed effect model	0.6503	[0.6187; 0.6836]	-16.93	< 0.0001	
Random effects model	0.2928	[0.1704; 0.5029]	-4.45	< 0.0001	
Quantifying heterogeneity:					
tau^2 = 0.5259 [0.2362; 4.0041]; tau = 0.7252 [0.4860; 2.0010]					
I^2 = 94.9% [91.9%; 96.7%]; H = 4.41 [3.52; 5.53]					
Test of heterogeneity:					
	Q	d.f.	p-value		
	136.23	7	<0.0001		
Details on meta-analytical method:					
- Inverse variance method					
- DerSimonian-Laird estimator for tau^2					
- Jackson method for confidence interval of tau^2 and tau					

Figure. S13) Forest plot. Partially vaccinated, symptomatic Covid-19 PCR RR ≥14 days after first dose. Outliers excluded, RE, IV method. The RE reduced meta-analysis was significant ($p < 0.0001$) with an overall RR=0.29 and RRR= 71%.Heterogeneity: $\tau^2=0.5259[0.2362; 4.0041]$; $\tau = 0.7252 [0.4860; 2.0010]$; $I^2 = 94.9\% [91.9\%; 96.7\%]$; $H = 4.41 [3.52; 5.53]$. Test of heterogeneity: $Q=136.23$ (d.f.=7; p -value< 0.0001).

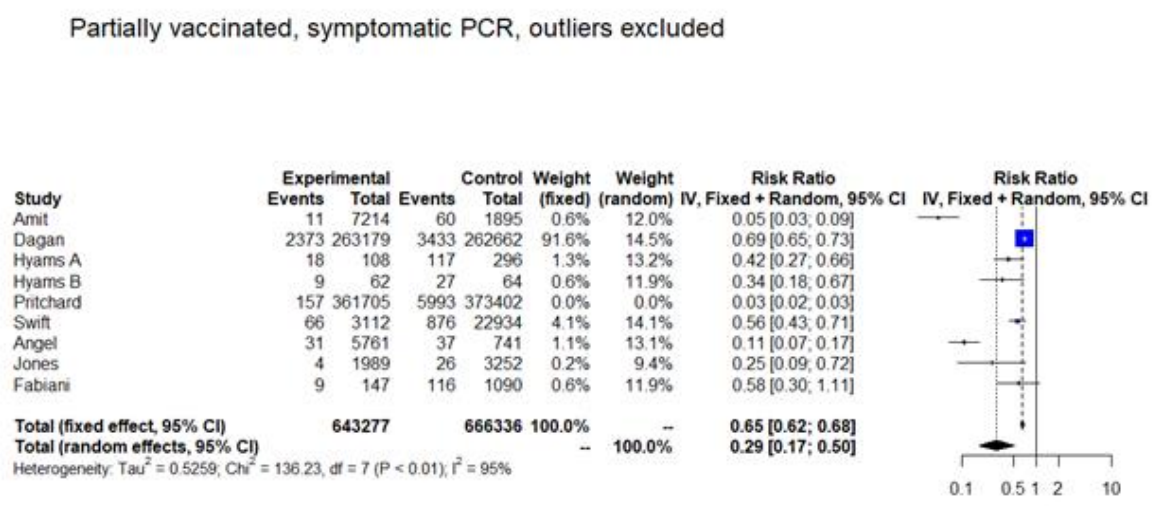


Figure.S14a) Influence analysis. Partially vaccinated, symptomatic positive Sars-Cov-2 PCR. “Pritchard” (red dot) results as the most influential study as it exceeds the cut-offs defined by Viechtbauerand Cheung in any subplot. [21]

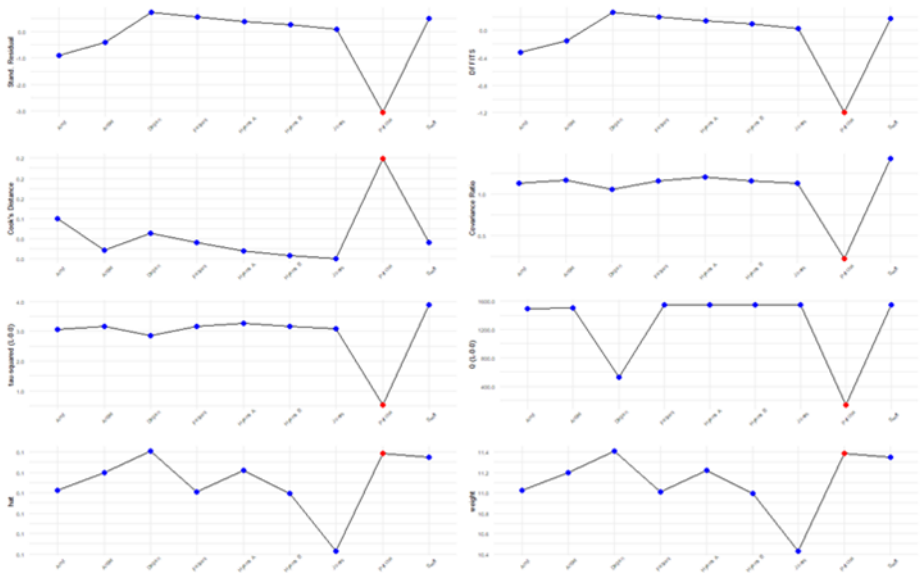


Figure.S14b) Baujat plot. Partially vaccinated, symptomatic PCR. Contribute to overall heterogeneity, Q (x) and effect size (y). “Pritchard” study contributed to the pooled imbalance. “Dagan” was the most influential on pooled effect size.

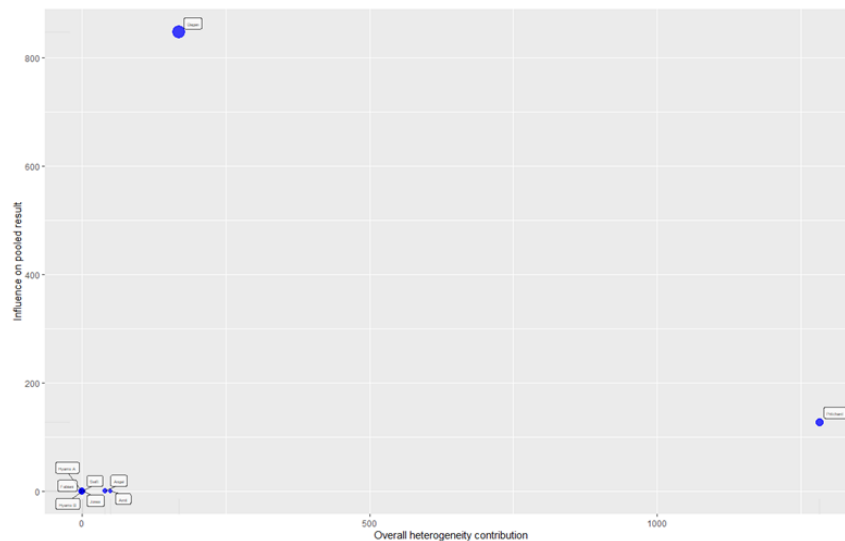


Figure.S15) Leave one out analysis. Partially vaccinated, symptomatic PCR. The first plot displays the change on the I^2 heterogeneity attained by removing one study at each step. The best result on the pooled imbalance was achieved by omitting “Pritchard”. The second plot indicates how the omission of “Dagan” influenced the overall RR estimate.

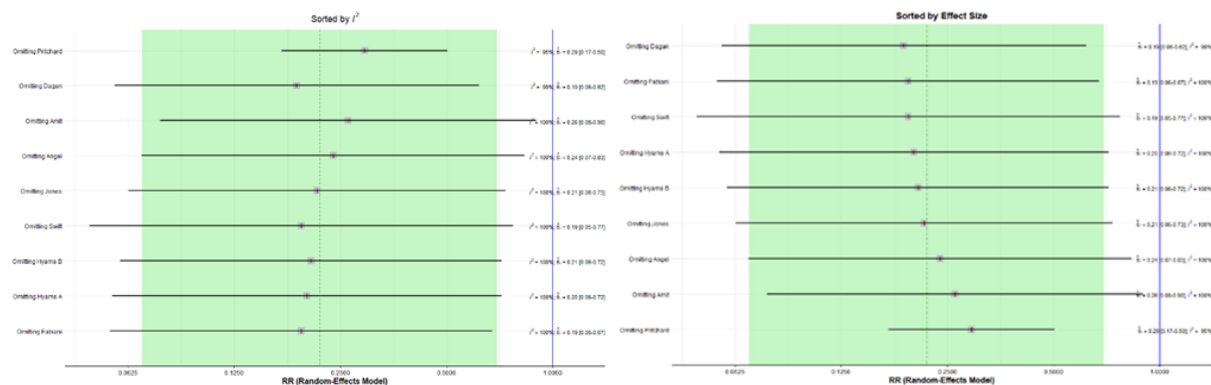
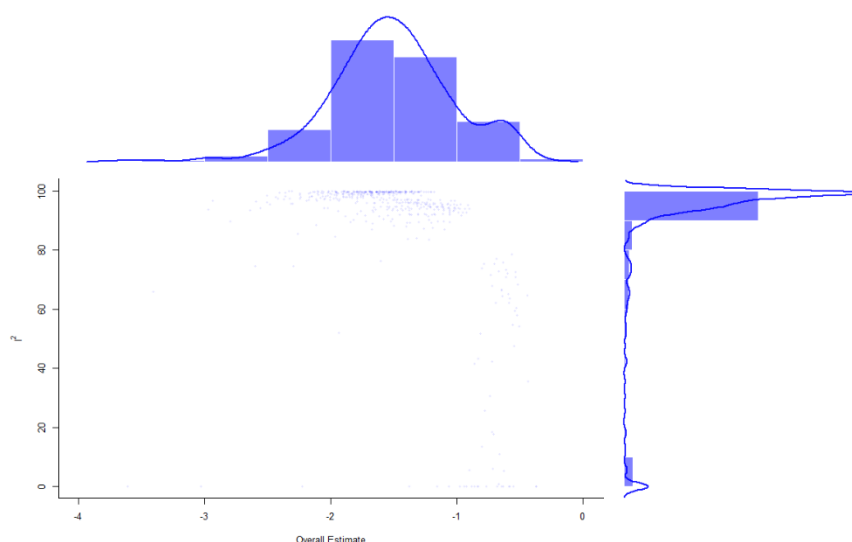


Figure.S16) GOSH Diagnostics. Partially vaccinated, symptomatic PCR. GOSH plots did not show any pattern, but a fatter right tail on the effect size distribution that was ultimately symmetric. The heterogeneity curve (I^2) was right skewed with a sharp peak. The three algorithms, k-means, DBSCAN and the Gaussian Mixture Model, detected up to six clusters which might potentially contribute to the overall heterogeneity, including “Pritchard”(5).



GOSH Diagnostics	
- Number of K-means clusters detected:	3
- Number of DBSCAN clusters detected:	5
- Number of GMM clusters detected:	6
Identification of potential outliers	
- K-means:	Study 5
- DBSCAN:	Study 3, Study 2
- Gaussian Mixture Model:	Study 3, Study 2

Table S5) Outliers fully vaccinated, symptomatic Sars-Cov-2 PCR. The outliers function identified four entries in fully vaccinated meta-analysis: "Pritchard", "Swift", "Abu-Raddad B", "Abu-Raddad C".

Identified outliers (random-effects model)					
"Pritchard", "Swift", "Abu-Raddad B", "Abu-Raddad C"					
Results with outliers removed					
	RR [95%-CI %]		W(fixed) %	W(random)	excluded
Dagan	0.0911	[0.0546; 0.1520]	20.3	27.9	
Pritchard	0.0021	[0.0012; 0.0036]	0.0	0.0	*
Swift	0.0131	[0.0086; 0.0200]	0.0	0.0	*
Angel	0.0273	[0.0128; 0.0582]	9.2	24.4	
Abu Raddad A	0.1678	[0.1266; 0.2223]	67.1	30.4	
Abu Raddad B	0.3598	[0.3111; 0.4162]	0.0	0.0	*
Abu Raddad C	0.4001	[0.3481; 0.4599]	0.0	0.0	*
Fabiani	0.1401	[0.0396; 0.4957]	3.3	17.3	
Meta-analysis with outliers removed					
Number of studies combined: k =8					
	RR [95%-CI %]		z	p-value	
Fixed effect model	0.1246	[0,0989; 0.1569]	-17.70	< 0.0001	

Random effects model	0.0881	[0.0402; 0.1927]	-6.08	< 0.0001
Quantifying heterogeneity:				
tau ² = 0.5049 [0.0877; 9.5307]; tau = 0.7105 [0.2961; 3.0872]				
I ² = 85.8% [65.3%; 94.2%]; H = 2.66 [1.70; 4.16]				
Test of heterogeneity:				
	Q	d.f.	p-value	
	21.18	3	<0.0001	
Details on meta-analytical method:				
- Inverse variance method				
- DerSimonian-Laird estimator for tau ²				
- Jackson method for confidence interval of tau ² and tau				

Figure.S17) Forest plot. Fully vaccinated, symptomatic Covid-19 PCR RR ≥ 7 days after second dose. Outliers excluded, RE, IV method. Identified outliers: "Pritchard", "Swift", "Abu-Raddad B", "Abu Raddad C". Overall RR=0.09, RRR=91%. Heterogeneity: $\tau^2 = 0.5049$ [0.0877; 9.5307]; $\tau = 0.7105$ [0.2961; 3.0872]; $I^2 = 85.8\%$ [65.3%; 94.2%]; $H = 2.66$ [1.70; 4.16]. Test of heterogeneity: $Q = 21.18$ (d.f.=3; p-value< 0.0001).

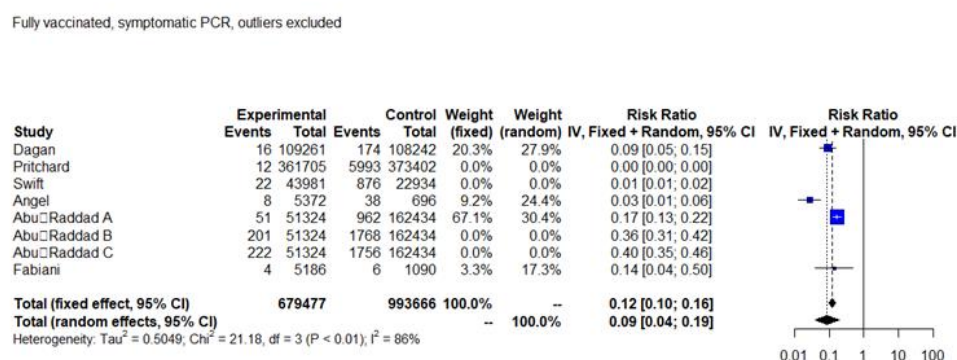


Figure.S18a) Influence analysis. Symptomatic positive Sars-Cov-2 PCR, fully vaccinated. "Pritchard" (red dot) resulted as the most influential study as it exceeded the cut-offs defined by Viechtbauer and Cheung in any subplot.[21]

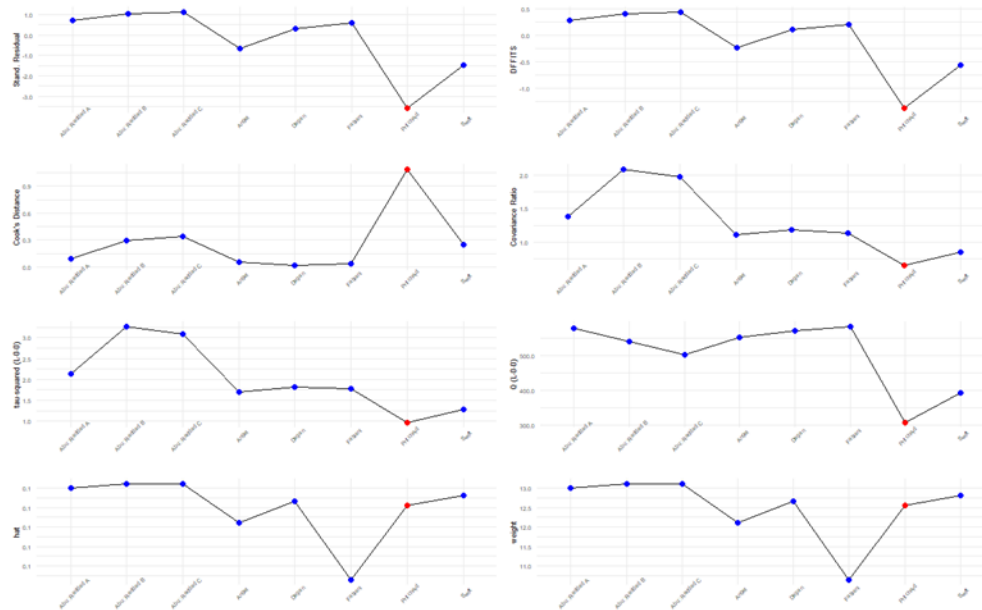


Figure.S18b) Baujat plot. Fully vaccinated, symptomatic PCR. Contribute to overall heterogeneity, $Q(x)$ and effect size (y). “Pritichard” and “Swift” studies contributed to the pooled imbalance. “Abu Raddad C” was the most influential on the pooled effect size.

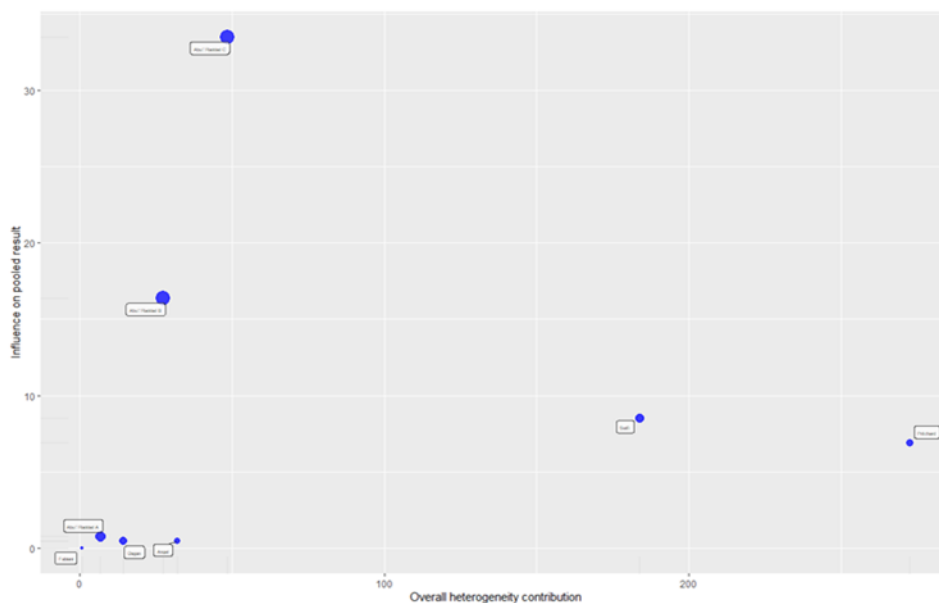


Figure.S19) Leave one out analysis. Fully vaccinated, symptomatic PCR. The first plot displayed the change on the I2 heterogeneity attained by removing one study at each step. “Pritchard” was the most influential on the pooled imbalance, while “Abu Raddad” affected the overall RR estimate.

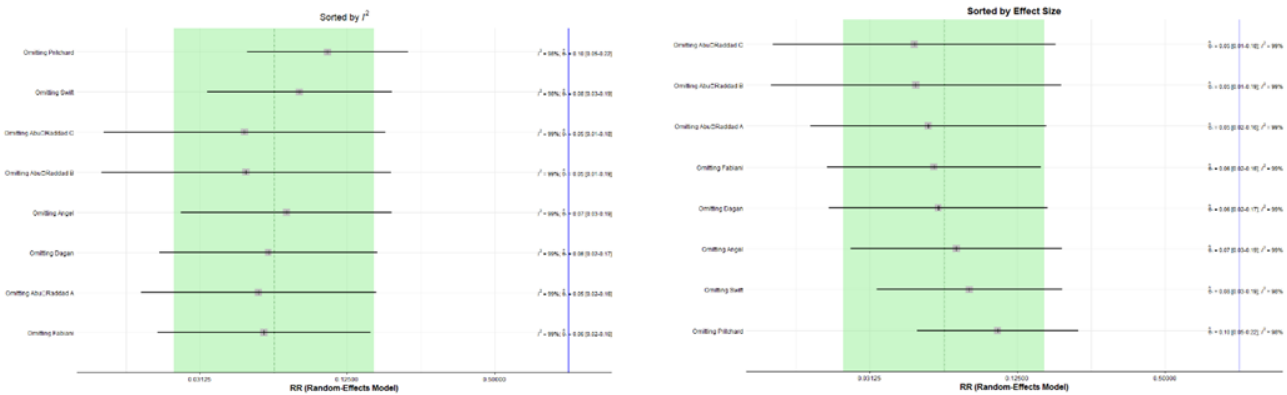
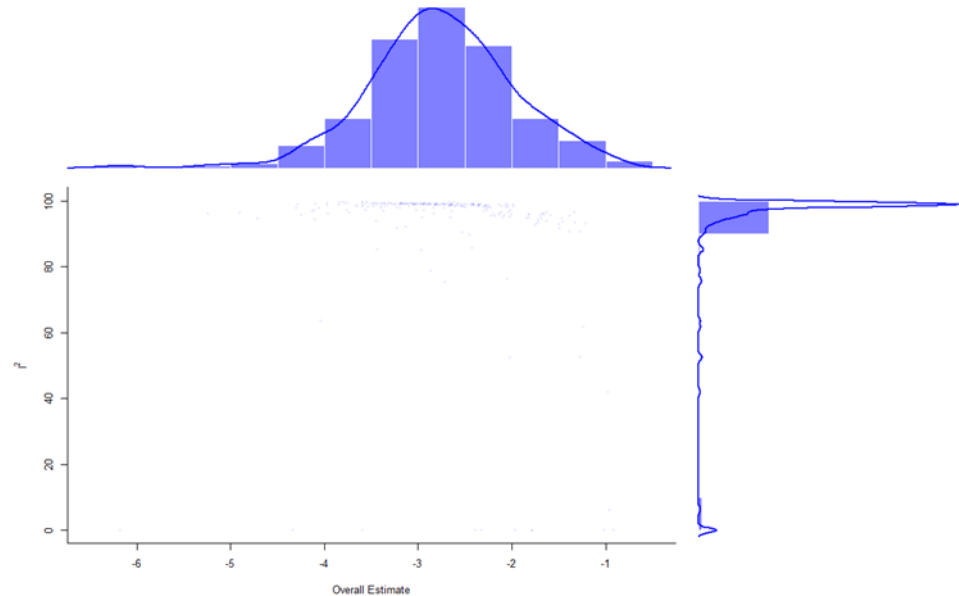


Figure.S20) GOSH Diagnostics. Fully vaccinated, symptomatic PCR. GOSH plots did not show any pattern, The effect size distribution curve was symmetric. The heterogeneity curve (I2) was right skewed with a sharp peak. The three algorithms, k -means, DBSCAN and the Gaussian Mixture Model, detected up to eight clusters which might potentially contribute to the overall heterogeneity, including “Pritchard”(5).



GOSH Diagnostics	
- Number of K-means clusters detected:	3
- Number of DBSCAN clusters detected:	4
- Number of GMM clusters detected:	8
Identification of potential outliers	
- K-means:	Study 8, Study 2
- DBSCAN:	Study 2
- Gaussian Mixture Model:	Study 2

Supplementary material File 3

3.1 Subgroup analysis

Table S6) Random and Mixed model, any positive PCR RR

Partially vaccinated, any positive PCR									
Model	Subgroups	N	Results for subgroups			Between-groups heterogeneity			
			RR [95%-CI]	I2	τ2	Q	df(Q)	p-value	
Mixed model	Vaccine	BNT162b2	16	0.2781 [0.1800; 0.4298]	99.60%	0.7443	6.07	3	0.1083
		ChAdOx1	2	0.2889 [0.0871; 0.9579]	98.90%	0.7443			
		BNT162b2/mRNA-1273	3	0.3933 [0.1463; 1.0575]	98.80%	0.7443			
		BNT162b2/ChAdOx1	1	0.0357 [0.0066; 0.1939]	--	--			
	Quality	NOS ≤6	15	0.2985 [0.1986; 0.4485]	99.60%	0.6113	0.21	1	0.6438
		NOS >6	7	0.2131 [0.0543; 0.8367]	99.70%	3.3748			
	Age	< 69 years	15	0.2394 [0.1259; 0.4554]	99.80%	1.5669	0.74	1	0.3909
		≥ 69 years	7	0.3317 [0.2278; 0.4828]	98.60%	0.2424			
	Lineage	B.1.1.7	8	0.1895 [0.0917; 0.3918]	99.70%	1.039	3.21	3	0.3606
		B.1.1.7/non B.1.1.7	5	0.2147 [0.0875; 0.5266]	99.70%	1.039			
		not specified	8	0.3615 [0.1763; 0.7415]	97.10%	1.039			
		B.1.351	1	0.9080 [0.1231; 6.6974]	--	--			
Random Effect model	Vaccine	BNT162b2	16	0.2781[0.1794;0.4310]	--	0.7549	116.47	3	< 0.0001
		ChAdOx1	2	0.2885[0.1256;0.6629]	--	0.3565			
		BNT162b2/mRNA-1273	3	0.3942[0.1210;1.2838]	--	1.0692			
		BNT162b2/ChAdOx1	1	0.0357[0.0323;0.0393]	--	--			
	Quality	NOS ≤6	15	0.2985[0.1986;0.4485]	--	0.6113	0.21	1	0.6438
		NOS >6	7	0.2131[0.0543;0.8367]	--	3.3748			
	Age	< 69 years	15	0.2394[0.1259;0.4554]	--	1.5669	0.74	1	0.3909
		≥ 69 years	7	0.3317[0.2278;0.4828]	--	0.2424			
	Lineage	B.1.1.7	8	0.1894[0.0946;0.3792]	--	0.9447	36.34	3	< 0.0001

		B.1.1.7/non B.1.1.7	5	0.2148[0.0750;0.6147]	--	1.4303		
		not specified	8	0.3618[0.2039;0.6422]	--	0.6506		
		B.1.351	1	0.9080[0.8717;0.9458]	--	--		
Fully vaccinated, any positive PCR								
Mixed model	Vaccine	BNT162b2	11	0.0628 [0.0261; 0.1511]	98.40%	2.1113	3.21	3 0.3609
		BNT162b2/mRNA-1273	4	0.0639 [0.0144; 0.2844]	98.90%	2.1113		
		BNT162b2/ChAdOx1	1	0.0062 [0.0004; 0.1072]	--	--		
		Ad26.COV2.S	1	0.2338 [0.0109; 5.0306]	--	--		
	Quality	NOS ≤6	11	0.0785 [0.0383; 0.1609]	98.50%	1.3935	1.66	1 0.1973
		NOS >6	6	0.0332 [0.0111; 0.0991]	95.90%	1.2835		
	Age	< 69 years	13	0.0479 [0.0182; 0.1256]	99.30%	3.0726	2.29	1 0.1304
		≥ 69 years	4	0.1200 [0.0597; 0.2412]	65.00%	0.2931		
	Lineage	B.1.1.7	4	0.0786 [0.0190; 0.3240]	95.90%	2.0252	3.27	3 0.3515
		B.1.1.7/non B.1.1.7	5	0.0285 [0.0081; 0.1005]	98.60%	2.0252		
		not specified	7	0.0632 [0.0206; 0.1934]	97.70%	2.0252		
		B.1.351	1	0.4027 [0.0247; 6.5721]	--	--		
Random Effect model	Vaccine	BNT162b2	11	0.0631 [0.0281; 0.1416]	--	1.7775	67.41	3 < 0.0001
		BNT162b2/mRNA-1273	4	0.0646 [0.0092; 0.4548]	--	3.7392		
		BNT162b2/ChAdOx1	1	0.0062 [0.0049; 0.0078]	--	--		
		Ad26.COV2.S	1	0.2338 [0.0745; 0.7337]	--	--		
	Quality	NOS ≤6	11	0.0785 [0.0383; 0.1609]	--	1.3935	1.66	1 0.1973
		NOS >6	6	0.0332 [0.0111; 0.0991]	--	1.6474		
	Age	< 69 years	13	0.0479 [0.0182; 0.1256]	--	3.0726	2.29	1 0.1304
		≥ 69 years	4	0.1200 [0.0597; 0.2412]	--	0.2931		
	Lineage	B.1.1.7	4	0.0810 [0.0323; 0.2031]	--	0.817	33.99	3 < 0.0001
		B.1.1.7/non B.1.1.7	5	0.0284 [0.0081; 0.0996]	--	1.9969		

		not specified	7	0.0634 [0.0151; 0.2658]	--	3.4732		
		B.1.351	1	0.4027 [0.3533; 0.4592]	--	--		
At least one dose, any positive PCR								
Mixed model	Vaccine	BNT162b2	12	0.1473 [0.0946; 0.2292]	99.60%	0.5994	2.24	2 0.3256
		BNT162b2/mRNA-1273	4	0.2622 [0.1215; 0.5656]	98.50%	0.5994		
		ChAdOx1	2	0.1061 [0.0350; 0.3214]	83.10%	0.5994		
	Quality	NOS ≤6	16	0.1793 [0.1206; 0.2666]	99.40%	0.6388	2.35	1 0.1252
		NOS >6	2	0.0711 [0.0233; 0.2165]	99.90%	0.6388		
	Age	< 69 years	12	0.1325 [0.0879; 0.1998]	99.30%	0.5076	2.53	1 0.1116
		≥ 69 years	6	0.2395 [0.1311; 0.4375]	99.80%	0.5585		
	Lineage	B.1.1.7	4	0.1523 [0.0690; 0.3362]	99.80%	0.6484	2.2	2 0.3325
		B.1.1.7/non B.1.1.7	5	0.1059 [0.0514; 0.2184]	95.00%	0.6484		
		not specified	9	0.2081 [0.1224; 0.3538]	99.80%	0.6484		
Random Effect model	Vaccine	BNT162b2	12	0.1473 [0.0939; 0.2310]	--	0.6218	3.68	0.1588
		BNT162b2/mRNA-1273	4	0.2646 [0.1402; 0.4994]	--	0.4039		
		ChAdOx1	2	0.1099 [0.0551; 0.2190]	--	0.2114		
	Quality	NOS ≤6	16	0.1800 [0.1296; 0.2499]	--	0.432	0.2	0.6541
		NOS >6	2	0.0696 [0.0011; 4.3786]	--	8.9219		
	Age	< 69 years	12	0.1325 [0.0879; 0.1998]	--	0.5076	2.53	0.1116
		≥ 69 years	6	0.2395 [0.1311; 0.4375]	--	0.5585		
	Lineage	B.1.1.7	4	0.1518 [0.0602; 0.3827]	--	0.8863	3.13	0.2096
		B.1.1.7/non B.1.1.7	5	0.1070 [0.0629; 0.1822]	--	0.3366		
		not specified	9	0.2081 [0.1250; 0.3464]	--	0.5975		

Table S7) Random and Mixed model, symptomatic PCR RR

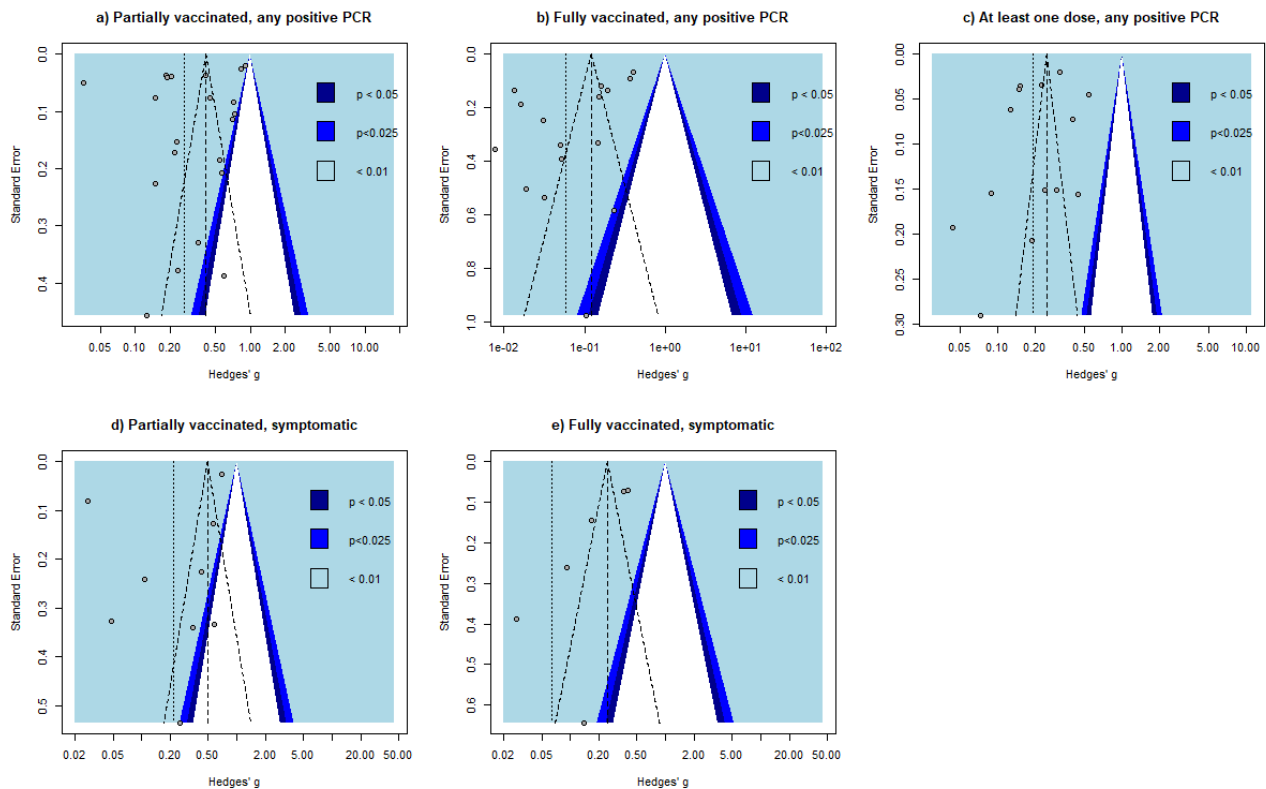
Partially vaccinated, symptomatic PCR								
----------------------------------------------	--	--	--	--	--	--	--	--

Model	Subgroups		N	Results for subgroups			Between-groups heterogeneity		
				RR [95%-CI]	I2	τ2	Q	df(Q)	p-value
Mixed model	Vaccine	BNT162b2	6	0.2488 [0.1035; 0.5980]	96.20 %	1.104 4	4.96	3	0.1748
		ChAdOx1	1	0.3441 [0.0395; 3.0002]	--	--			
		BNT162b2/ChAdOx1	1	0.0270 [0.0034; 0.2134]	--	--			
		BNT162b2/mRNA-1273	1	0.5552 [0.0697; 4.4200]	--	--			
	Quality	NOS ≤6	6	0.3007 [0.0875; 1.0332]	93.60 %	2.270 7	0.76	1	0.3823
		NOS >6	3	0.1172 [0.0211; 0.6514]	99.50 %	2.270 7			
	Age	< 69 years	7	0.1860 [0.0468; 0.7385]	99.60 %	3.384	1.08	1	0.2993
		≥ 69 years	2	0.3962 [0.2736; 0.5737]	0.00%	0			
	Lineage	B.1.1.7	3	0.2498 [0.0226; 2.7633]	89.10 %	4.436 9	0.13	2	0.9384
		B.1.1.7/non B.1.1.7	2	0.1367 [0.0074; 2.5364]	99.90 %	4.436 9			
		not specified	4	0.2504 [0.0308; 2.0320]	94.10 %	4.436 9			
Random Effect model	Vaccine	BNT162b2	6	0.2488 [0.1035; 0.5980]	96.20 %	1.104 4	437.4 7	3	< 0.0001
		ChAdOx1	1	0.3441 [0.1763; 0.6715]	--	--			
		BNT162b2/mRNA-1273	1	0.0270 [0.0231; 0.0317]	--	--			
		BNT162b2/ChAdOx1	1	0.5552 [0.4336; 0.7111]	--	--			
	Quality	NOS ≤6	6	0.3062 [0.1465; 0.6400]	93.60 %	0.744 7	0.69	1	0.4071
		NOS >6	3	0.1173 [0.0137; 1.0027]	99.50 %	3.569 4			
	Age	< 69 years	7	0.1860 [0.0468; 0.7385]	99.60 %	3.384	1.08	1	0.2993
		≥ 69 years	2	0.3962 [0.2736; 0.5737]	0.00%	0			
	Lineage	B.1.1.7	3	0.2482 [0.1001; 0.6152]	89.10 %	0.569 5	0.13	2	0.936
		B.1.1.7/non B.1.1.7	2	0.1367 [0.0057; 3.2685]	99.90 %	5.242			
		not specified	4	0.2526 [0.0776; 0.8228]	94.10 %	1.327 8			
Fully vaccinated, symptomatic PCR									
Mixed model	Vaccine	BNT162b2	6	0.1603 [0.0966; 0.2661]	94.90 %	0.324 5	48.24	2	< 0.0001
		BNT162b2/mRNA-1273	1	0.0131 [0.0040; 0.0432]	--	--			
		BNT162b2/ChAdOx1	1	0.0021 [0.0006; 0.0072]	--	--			
	Quality	NOS ≤6	5	0.2156 [0.1279; 0.3633]	93.00 %	0.292 2	52.21	1	< 0.0001

Random Effect model	Lineage	NOS >6	3	0.0087 [0.0043; 0.0174]	94.60 %	0.292 2			
		B.1.1.7	2	0.0684 [0.0025; 1.8450]	94.80 %	5.569 9	0.69	3	0.8757
		B.1.1.7/non B.1.1.7	3	0.0427 [0.0029; 0.6248]	99.40 %	5.569 9			
		not specified	2	0.0413 [0.0015; 1.1598]	91.80 %	5.569 9			
		B.1.351	1	0.3598 [0.0035; 36.8088]	--	--			
	Vaccine	BNT162b2	6	0.1603 [0.0966; 0.2661]	94.90 %	0.324 5	129.8 6	3	< 0.0001
		BNT162b2/mRNA-1273	1	0.0131 [0.0086; 0.0200]	--	--			
		BNT162b2/ChAdOx1	1	0.0021 [0.0012; 0.0036]	--	--			
	Quality	NOS ≤6	5	0.2214 [0.1435; 0.3416]	93.00 %	0.191 1	18.17	1	< 0.0001
		NOS >6	3	0.0089 [0.0022; 0.0366]	94.60 %	1.462 4			
	Lineage	B.1.1.7	2	0.0701 [0.0118; 0.4152]	94.80 %	1.565	8.61	3	0.035
		B.1.1.7/non B.1.1.7	3	0.0426 [0.0022; 0.8254]	99.40 %	6.806 2			
		not specified	2	0.0396 [0.0039; 0.4023]	91.80 %	2.577 9			
		B.1.351	1	0.3598 [0.3111; 0.4162]	--	--			

3.2 Publication bias

Figure. S21) Funnel plot and Eggers' test. Any positive PCR (a, b, c). Symptomatic PCR (d, e). The contour-enhanced funnels included three colours signifying the significance level into which the effects size of each study fell. The dots' distribution was overall quite sparse and concentrated at the upper half of the funnel except "Tenforde" at the bottom.



Eggers' test of the intercept			
intercept	95% CI	t	p
a) Any positive PCR partially vaccinated			
-8.868	-20.25 - 2.51	-1.527	0.1423509
b) Any positive PCR fully vaccinated			
-6.792	-14.78 - 1.2	-1.667	0.1163403
c) Any positive PCR at least one dose			
-3.843	-11.65 - 3.96	-0.965	0.3537481
d) Symptomatic positive PCR partially vaccinated			
-6.858	-18.21 - 4.5	-1.184	0.2751005
e) Symptomatic positive PCR fully vaccinated			
-11.271	-18.76 - -3.78	-2.948	0.02567738

Figure.S22) PRISMA Flow Diagram

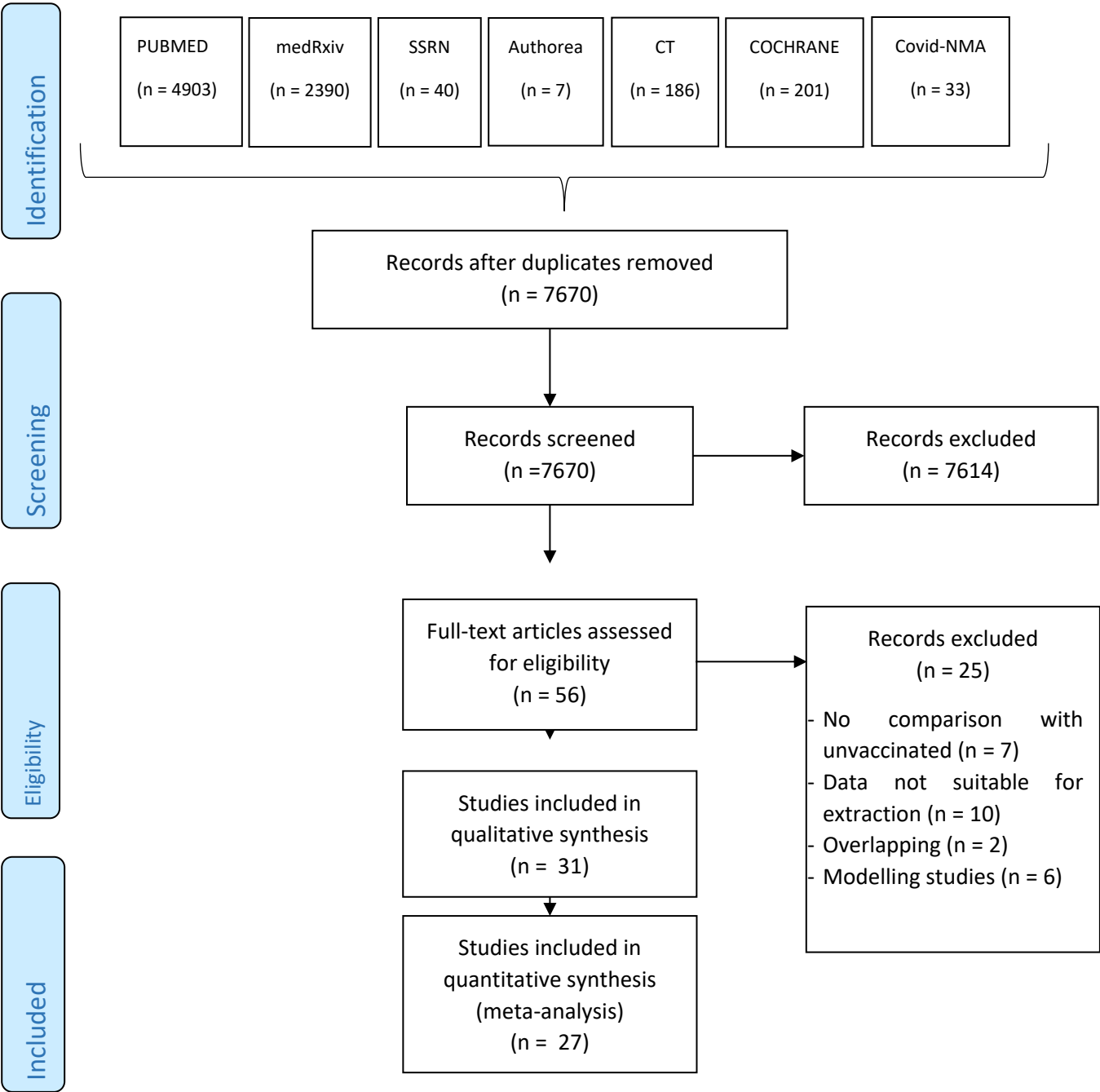


Table S8) Characteristics of 31 included studies.

N	First Author	Country	Study Design	Vaccine	Population (N)	Population type
1	Abu-Raddad	Qatar	Test Negative-Case-Control	Comirnaty (BNT162b2)	3,734	General population
2	Amit	Israel	Retrospective Cohort	Comirnaty (BNT162b2)	9,109	Healthcare workers
3	Angel	Israel	Retrospective Cohort	Comirnaty (BNT162b2)	6,710	Healthcare workers
4	Benenson	Israel	Retrospective Cohort	Comirnaty (BNT162b2)	6,252	Healthcare workers
5	Britton	USA	Retrospective Cohort	Comirnaty (BNT162b2)	463	Residents of long-term care facilities
6	Corchado	USA	Matched Cohort	Janssen (Ad26.COV2.S)	24,145	General population
7	Dagan	Israel	Matched Observational	Comirnaty (BNT162b2)	1,193,236	General population
8	Daniel	USA	Retrospective Cohort	Comirnaty (BNT162b2) Moderna (mRNA-1273)	23,234	General population (symptomatic)
9	Druri	UK	Cohort	Comirnaty (BNT162b2), Vaxzevria (ChAdOx1/AZD1222)	627,383	General population
10	Fabiani	Italy	Retrospective Cohort	Comirnaty (BNT162b2)	6,423	Healthcare workers
11	Gras Valenti	Spain	Case-Control Study	Comirnaty (BNT162b2)	268	Healthcare workers
12	Haas	Israel	Cohort	Comirnaty (BNT162b2)	281,903	General population
13	Hall	UK	Cohort	Comirnaty (BNT162b2)	23,324	Healthcare workers
14	Hyams	UK	Test Negative Case Control	Comirnaty (BNT162b2), Vaxzevria (ChAdOx1/AZD1222)	434	Elderly patients
15	Jones	UK	Cross-Sectional	Comirnaty (BNT162b2)	8,819	Healthcare workers
16	Lopez-Bernal	UK	Test Negative Case Control	Comirnaty (BNT162b2), Vaxzevria (ChAdOx1/AZD1222)	156,930	Elderly population
17	Lumley	UK	Cohort	Comirnaty (BNT162b2)	23,411	Healthcare workers
18	Mason	UK	Cohort	Comirnaty (BNT162b2)	301,461	Elderly population
19	Menni	UK	Prospective Observational	Comirnaty (BNT162b2), Vaxzevria (ChAdOx1/AZD1222)	627,383	General population
20	Monge	Spain	Cohort	Comirnaty (BNT162b2)	299,209	Residents in long-term care facilities (LTCF)
21	Mouststen-Helms	Denmark	Retrospective Cohort	Comirnaty (BNT162b2)	370,079	Residents in long-term care facilities (LTCF) and Healthcare workers

22	Pawlosky	USA	Retrospective Cohort	Comirnaty (BNT162b2), Moderna (mRNA-1273)	62,138	Residents in long-term care facilities (LTCF) and Healthcare workers
23	Pritchard	UK	Cohort	Comirnaty (BNT162b2), Vaxzevria (ChAdOx1/AZD1222)	373,402	General population
24	Sansone	Italy	Cohort	Comirnaty (BNT162b2)	6,904	Healthcare workers
25	Shotri	UK	Cohort	Comirnaty (BNT162b2), Vaxzevria (ChAdOx1/AZD1222)	10,412	Residents of Long-Term Care Facilities (LTCF)
26	Swift	USA	Cohort	Comirnaty (BNT162b2), Moderna (mRNA-1273)	71,152	Healthcare workers
27	Tande	USA	Retrospective Cohort	Comirnaty (BNT162b2)	39,156	General population
28	Tara	USA	Cohort	Comirnaty (BNT162b2) Moderna	7,109	Healthcare workers
29	Tenforde	USA	Case-Control	Comirnaty (BNT162b2), Moderna (mRNA-1273)	417	Elderly patients
30	Thompson	USA	Cohort	Comirnaty (BNT162b2) Moderna (mRNA-1273)	3,950	Healthcare workers
31	Vasileious	Scotland	Cohort	Comirnaty (BNT162b2), Vaxzevria (ChAdOx1/AZD1222)	4,409,611	General population

Table S9) Quality assessment Newcastle Ottawa Scale (NOS).

n	Author	Selection	Comparability	Outcome	Exposure	Total score
1	Abu-Raddad	3	1	2		6
2	Amit	2	1	2		5
3	Angel	4	2	2		8
4	Benenson	2	1	2		5
5	Britton	2	1	2		5
6	Corchado	4	2	1		7
7	Dagan	3	1	2		6
8	Daniel	2	1	2		5
9	Druri	3	1	2		6
10	Fabiani	3	1	2		6
11	Gras Valenti	2	2		2	6
12	Haas	3	1	2		6
13	Hall	4	1	2		7
14	Hyams	3	1		2	6
15	Jones	2	1	2		5
16	Lopez-Bernal	1	1		2	6
17	Lumley	3	1	2		6
18	Mason	3	1	2		6
19	Menni	3	1	2		6
20	Monge	3	1	3		7
21	Mouststen-Helms	3	1	2		6

22	Pawlosky	3	1	2		6
23	Pritchard	4	2	2		8
24	Sansone	2	0	1		3
25	Shotri	4	1	2		7
26	Swift	3	1	3		7
27	Tande	3	1	2		6
28	Tara	3	1	1		5
29	Tenforde	2	2		2	6
30	Thompson	2	1	2		5
31	Vasileious	3	1	2		6