Rapid review on the effects of vaccination in the immunocompromised and those on dialysis

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Population

- Immunocompromised
  - HIV infection
  - Primary immune or complement deficiency
  - On immunosuppressive therapy
  - Malignancy
  - Transplant
- Dialysis
  - Hemodialysis
  - Peritoneal dialysis

Intervention

- COVID-19 vaccine approved in Canada
  - BNT162b2 (Pfizer-BioNTech)
  - mRNA-1273 (Moderna)
  - AZD1222 (ChAdOx1) (AstraZeneca-Oxford)
  - Ad26.COV2.S (Johnson & Johnson)

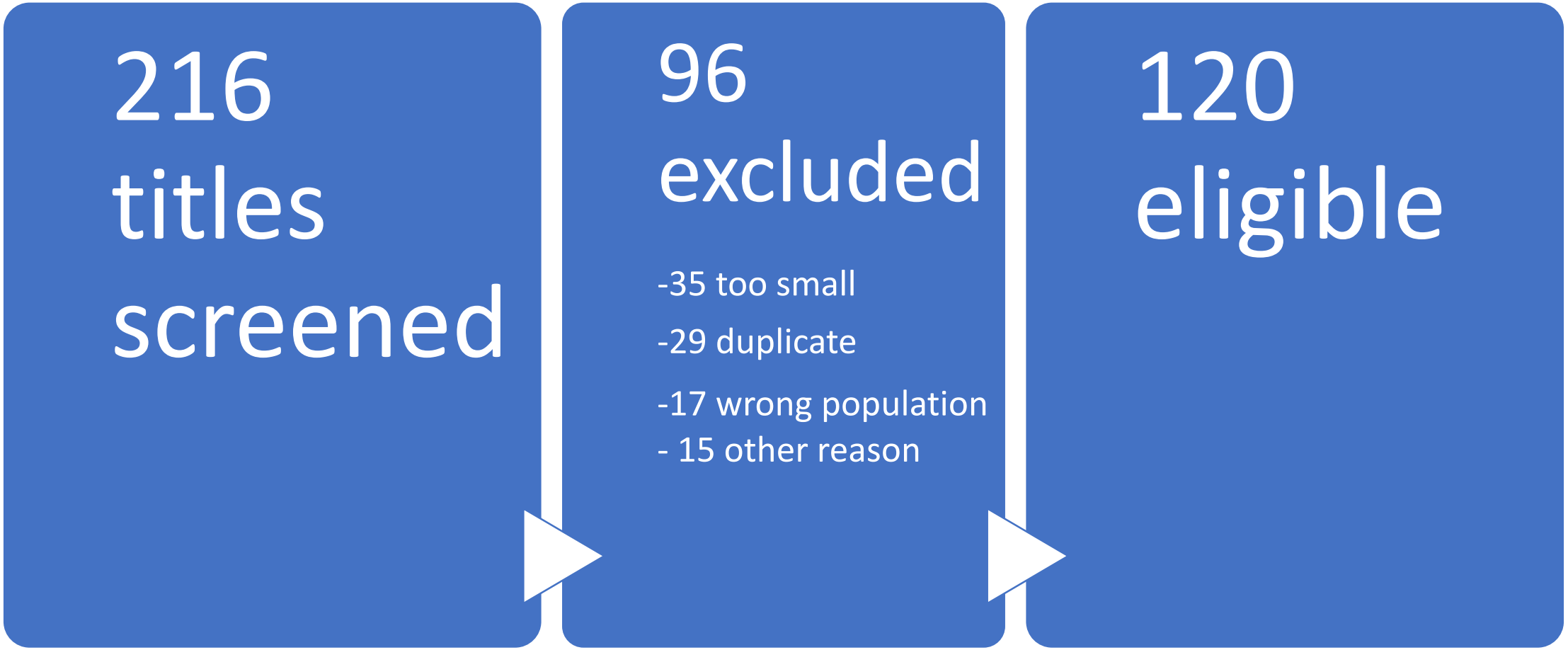
Comparator

- Healthy control
- Disease control (for immunosuppression e.g. inflammatory bowel disease – outcome of vaccines in those with and without immunosuppressive therapy)

Outcome

- Protection against developing symptomatic COVID-19
- Immunogenicity in disease subgroups
- Harms of COVID vaccines in immunocompromised or dialysis patients

Overview


216 titles screened
96 excluded
-35 too small
-29 duplicate
-17 wrong population
- 15 other reason
120 eligible

Efficacy in preventing COVID-19 infections

Author	Country	Overall population	Immunocompromised	Infections over follow up	Vaccine effectiveness well popn (95% CI)	Vaccine effectiveness immunocomp (95% CI)
Dagan 2021	Israel	3,159,136	32,003	10,561	91% (83-96%)	90% (49-100%)
Young-Xu 2021	US (VA system)	6,710,750	99,107	15,404	94% (92-95%)	88% (82-92%)

Both studies compared vaccinated with unvaccinated and defined protection period as ≥ 7 days after 2nd vaccine
Pooled population vaccine effectiveness = 94% (95% CI = 92-95%)
Pooled immunocompromised vaccine effectiveness = 88% (95% CI = 83-93%)

Dagan N et al. NEJM 2021; 384:1412-23 and Young-Xu Y et al. doi2021.06.14.21258906 (not peer reviewed)

Efficacy in preventing COVID-19 infections: IBD

- Another study provided contributing evidence but could not be pooled with the previous two studies.
- Evaluated 5,562 inflammatory bowel disease (53% on biologics) versus 864,575 controls after vaccination (both first and second).
- During follow up 19 (0.36%) IBD patients were diagnosed with COVID-19 compared with 2227 (0.28%) controls (RR = 1.3; 95% CI = 0.83-2.05)
- After adjustment RR = 0.95; 95% CI = 0.51- 1.78)
- Did not give data for biologic therapies separately but noted that there was less than 50% of the COVID-19 IBD infections in this group.

Hadi YB et al. Gastroenterology 2021 in press

Efficacy summary

- Only a modest reduction in vaccine efficacy for COVID-19 vaccination in the immunocompromised in population studies
- These studies have only a small number of certain groups such as primary immune deficiencies and transplant patients
- These data are largely reassuring but need more granular immunogenicity data for immunocompromised subgroups

Immunogenicity of vaccines in HIV

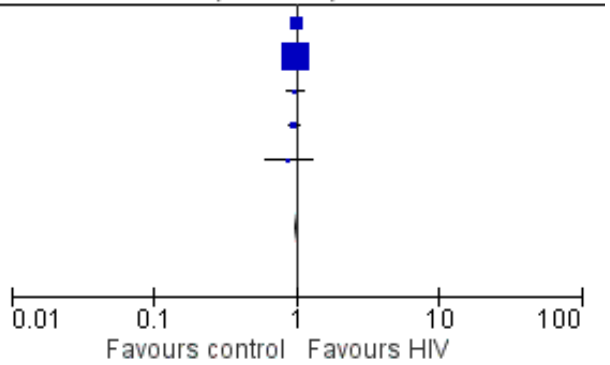
Evaluation of seroconversion after 2nd vaccine

- 5 studies
- 258 HIV – 97% converted (titres similar to controls)
- 948 controls – 99% converted
- RR = 1.00 (95% CI = 0.98-1.01)
- I^2 = 0%

	HIV +ve		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Frater 2021	51	51	49	49	24.7%	1.00 [0.96, 1.04]
Levy 2021	139	141	269	272	67.1%	1.00 [0.97, 1.02]
Madhi 2021	30	32	22	23	2.4%	0.98 [0.87, 1.11]
Haidar 2021	35	37	105	107	5.6%	0.96 [0.89, 1.05]
Shrotri 2021	3	3	494	497	0.3%	0.88 [0.61, 1.28]
Total (95% CI)		**264**		**948**	**100.0%**	**1.00 [0.98, 1.01]**
Total events	258		939			

Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 4 (P = 0.79); I² = 0%

Test for overall effect: Z = 0.51 (P = 0.61)



Seroconversion in malignancy

- 30 studies
- 17 cohort studies and 13 case series
- 3459 cancer patients
- 1969 healthy controls
- All studies that reported stated IgG titres lower in malignancy cases than controls

Overall seroconversion in patients with malignancy

Group	Number of studies	Number of patients	Proportion converted (95% CI)
Solid malignancy 1st vaccine	8	635	54% (38-69%)
Solid malignancy 2nd vaccine	9	850	91% (86-95%)
Hematological 1st vaccine	8	606	48% (32-63%)
Hematological 2nd vaccine	14	2197	64% (56-73%)

Comparison of malignancy with healthy controls after second vaccine

Malignancy	No. studies	Total participants	RR seroconversion (95% CI)
Solid	6	792	0.91 (0.86 to 0.97)
Hematological	9	2600	0.65 (0.55 to 0.77)

Solid malignancy slightly worse seroconversion than healthy controls
Risk factors for poor outcome are age and having active treatment at time of vaccine
Hematological malignancy significantly worse than healthy controls and worse than solid malignancy (p=0.00001)

Immunogenicity after 2nd vaccine in immunosuppressive therapy patients

- 16 studies
- 1320 patients
- 1250 healthy or disease (not in immunosuppressive therapy) controls
- No difference between control groups so these controls combined

Immunogenicity after 2nd vaccine in immunosuppressive therapy patients

Group	Number of studies	Number of patients	Proportion converted (95% CI)
Inflammatory Bowel Diseases	3	59	95% (82-100%)
Rheumatological diseases	3	538	88% (79-95%)
Multiple Sclerosis	3	145	42% (33-52%)
Various autoimmune disease	7	578	64% (56-73%)

Comparison of response to 2nd vaccine in those on immunosuppressive therapy compared to controls

Group	No. studies	Total participants	RR seroconversion (95% CI)
Inflammatory bowel disease	3	110	1.00 (0.89 to 1.12)
Various autoimmune diseases	8	1571	0.92 (0.87 to 0.97)
Unclear indication	1	175	0.34 (0.11 to 1.06)
Multiple Sclerosis	2	202	0.42 (0.30 to 0.59)

Modest impact of immunosuppressive therapy on seroconversion rates although titres lower than healthy controls
No impact for biologics used in IBD although number studies are small. We have more data after the first vaccine and one study (1) suggested a slightly lower seroconversion rate for anti-TNF in 1293 participants (RR = 0.88; 95% 0.80 to 0.97)
Immunosuppressive drugs used in MS seem to have a greater impact on seroconversion rates – particularly for Fingolimod and Ocerlizumab (Cladribine seems to have little impact on seroconversion).

Kennedy NA et al. Gut 2021 in press

Seroconversion in transplant patients after their second vaccine

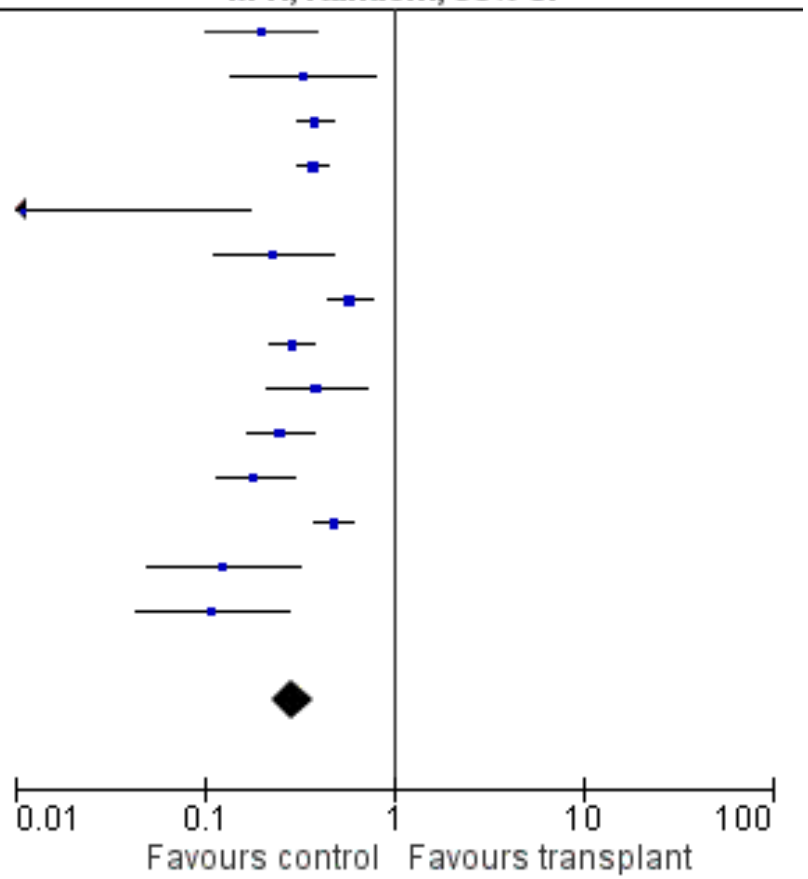
- 22 studies
  - 14 cohort studies
  - 8 case series
- 2729 participants
  - 2038 transplant patients
  - 691 healthy controls
- Various solid organ transplants – predominantly kidney, liver, heart, lung
- Overall seroconversion rate = 27% (95%CI = 22 to 33%)

Comparison of seroconversion in transplant patients compared to healthy controls after second vaccine

Study or Subgroup	Transplant Events	Transplant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bertrand 2021	8	45	8	9	6.2%	0.20 [0.10, 0.39]
Firket 2021	3	10	10	10	4.8%	0.33 [0.14, 0.80]
Grupper 2021	51	136	25	25	10.2%	0.38 [0.31, 0.48]
Haidar 2021	68	183	105	107	10.4%	0.38 [0.31, 0.46]
Havlin 2021	0	46	10	10	0.8%	0.01 [0.00, 0.18]
Korth 2021	5	23	23	23	5.7%	0.23 [0.11, 0.49]
Marinaki 2021	20	34	116	116	9.8%	0.59 [0.45, 0.78]
Mazzola 2021	38	133	25	25	9.8%	0.29 [0.22, 0.38]
Miele 2021	6	16	23	23	6.8%	0.39 [0.21, 0.72]
Narasimhan 2021	18	73	49	49	8.7%	0.25 [0.17, 0.38]
Peled 2021	14	77	134	136	8.0%	0.18 [0.11, 0.30]
Rabinowich 2021	38	80	25	25	10.1%	0.48 [0.38, 0.61]
Rincon-Arevalo 2021	4	40	55	69	4.4%	0.13 [0.05, 0.32]
Sattler 2021	4	39	60	64	4.4%	0.11 [0.04, 0.28]
Total (95% CI)		**935**		**691**	**100.0%**	**0.29 [0.23, 0.38]**
Total events	277		668			

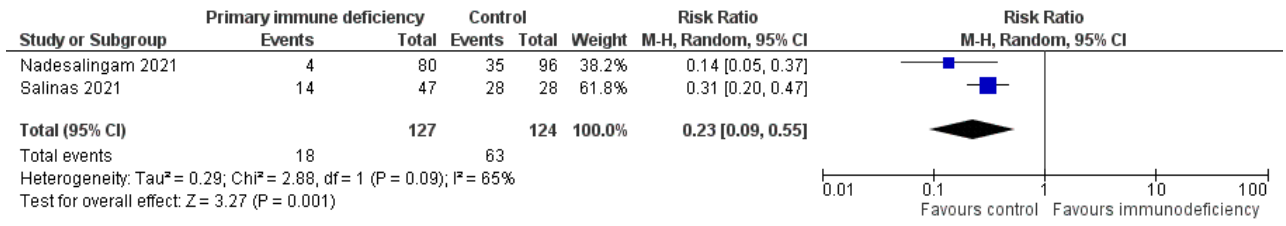
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 68.74$, $df = 13$ ($P < 0.00001$); $I^2 = 81\%$

Test for overall effect: $Z = 9.48$ ($P < 0.00001$)



Seroconversion after 2nd vaccination in patients with primary immune deficiencies

- These are all rare disorders
- Three studies
  - Two cohort studies, one case series
- 277 participants
  - 153 cases
  - 124 healthy controls
- 31% (95% CI 4 to 70%) converted
- RR = 0.23 (95% CI 0.09 to 0.55) compared to healthy



Primary immunodeficiencies

- A number of different disorders with varying ability to mount a response to vaccination
- For example, none of the 10 X-linked Aglobulinemia (XLA) seroconverted. This is entirely expected as these individuals cannot produce immunoglobulin (which is what is measured when evaluating response to vaccines).
- However, XLA had a more pronounced T-cell response to vaccination than other immunodeficiencies or healthy controls. This suggest the immune system of XLA is trying to compensate to provide some protection against COVID-19.

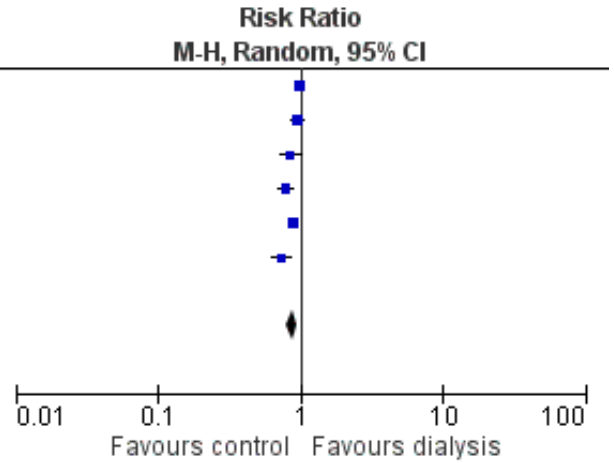
Seroconversion from 2nd vaccination in dialysis patients

- Twenty one studies
  - 6 cohort
  - 15 case series
- 2588 participants
  - 2186 cases
  - 402 controls
- 89% (95% CI = 85 to 93%) converted
- RR = 0.87 (95%CI = 0.79 to 0.96)

Study or Subgroup	Dialysis Events	Dialysis Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Grupper 2021	54	55	95	95	20.2%	0.98 [0.93, 1.02]
Jahn 2021	67	72	16	16	16.9%	0.95 [0.86, 1.06]
Schrezenmeier 2021	29	36	42	44	12.6%	0.84 [0.71, 1.00]
Simon 2021	64	81	80	80	16.3%	0.79 [0.71, 0.89]
Yanay 2021	144	160	132	132	19.9%	0.90 [0.85, 0.95]
Yau 2021	52	72	35	35	14.1%	0.73 [0.63, 0.85]
Total (95% CI)		**476**		**402**	**100.0%**	**0.87 [0.79, 0.96]**
Total events	410		400			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 37.53$, df = 5 ($P < 0.00001$); $I^2 = 87\%$

Test for overall effect: $Z = 2.78$ ($P = 0.005$)



Summary

Impact on seroconversion	Diseases
None	HIV infection
Minor	Most immunosuppressive medication Solid malignancy patients Dialysis patients
Moderate	Hematologic malignancy
Severe	MS patients on Fingolimod or Ocerlizumab Some patients with primary immunodeficiencies Transplant patients

Additional data

- Three studies have reported on response to a third vaccination in high risk groups. All report an increase in seroconversion and also a rise in antibody titres towards that seen in healthy controls.
- For example Ducloux reported and increase in seroconversion from 40/45 to 42/45 with titres rising from a median of 672 to 6435 with the third vaccination.

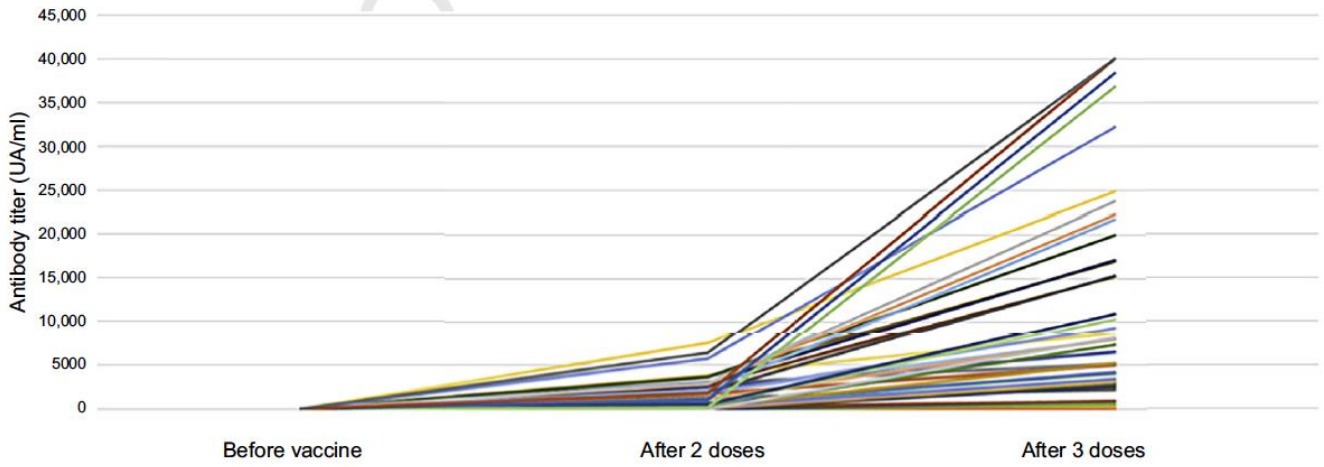


Figure 3 | Individual variations in antibody titers (severe acute respiratory syndrome coronavirus 2 [SARS-Cov-2] immunoassay, which Abbott designed to detect IgG antibodies to the receptor-binding domain of the S1 subunit of the spike protein of SARS-CoV-2) during the vaccine scheme. UA, xxx.

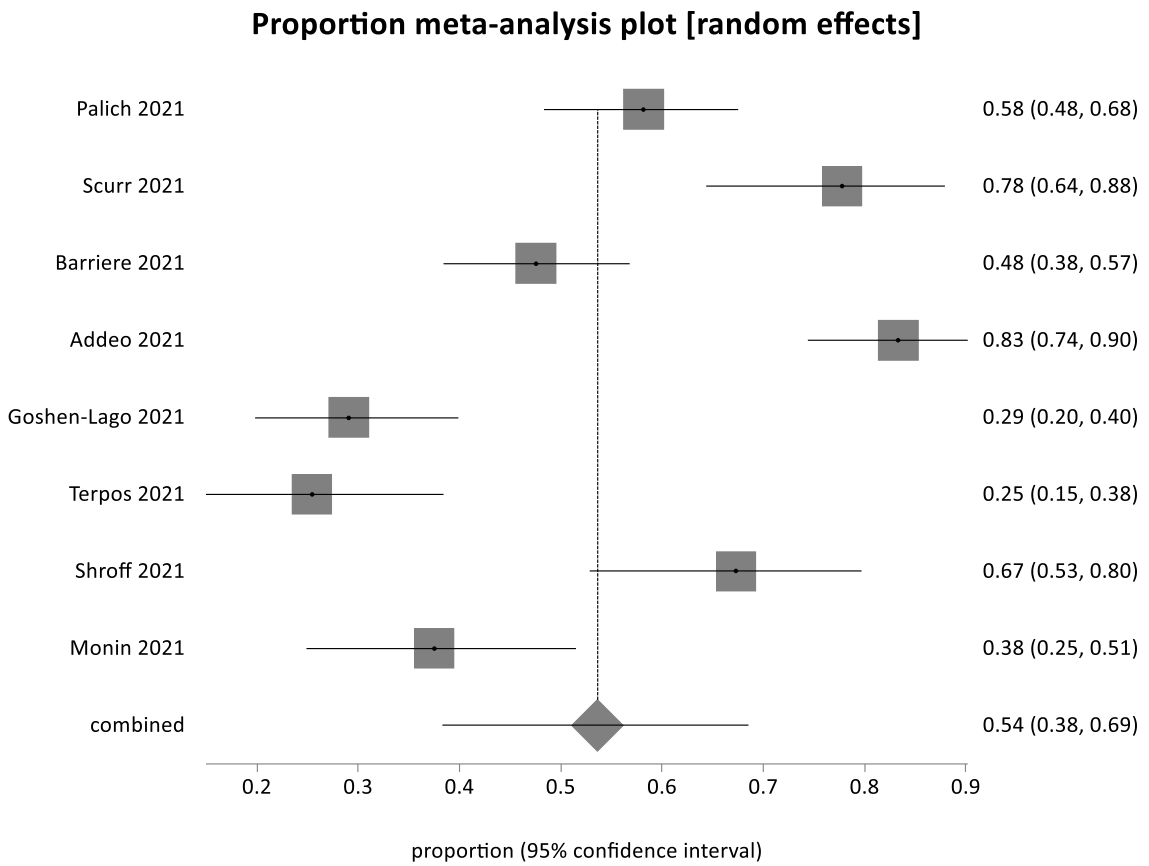
Ducloux D et al. Kidney International 2021 in press

Safety of vaccination in the immunocompromised

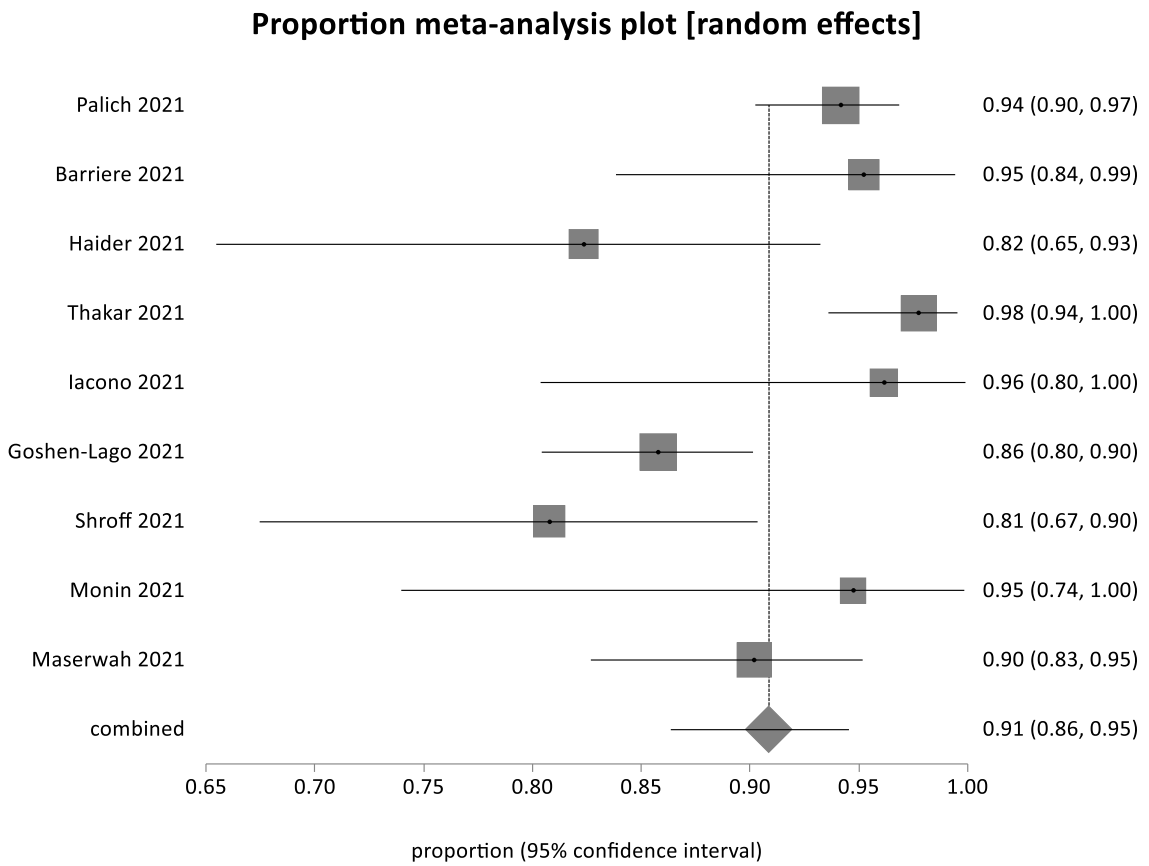
- Less data
- Combined all diseases
- Evaluated overall adverse events
- 9 studies, 1023 participants
- Less adverse events in immunocompromised
- No reports of worsening disease after immunization
- No serious adverse event signal

Appendix figures

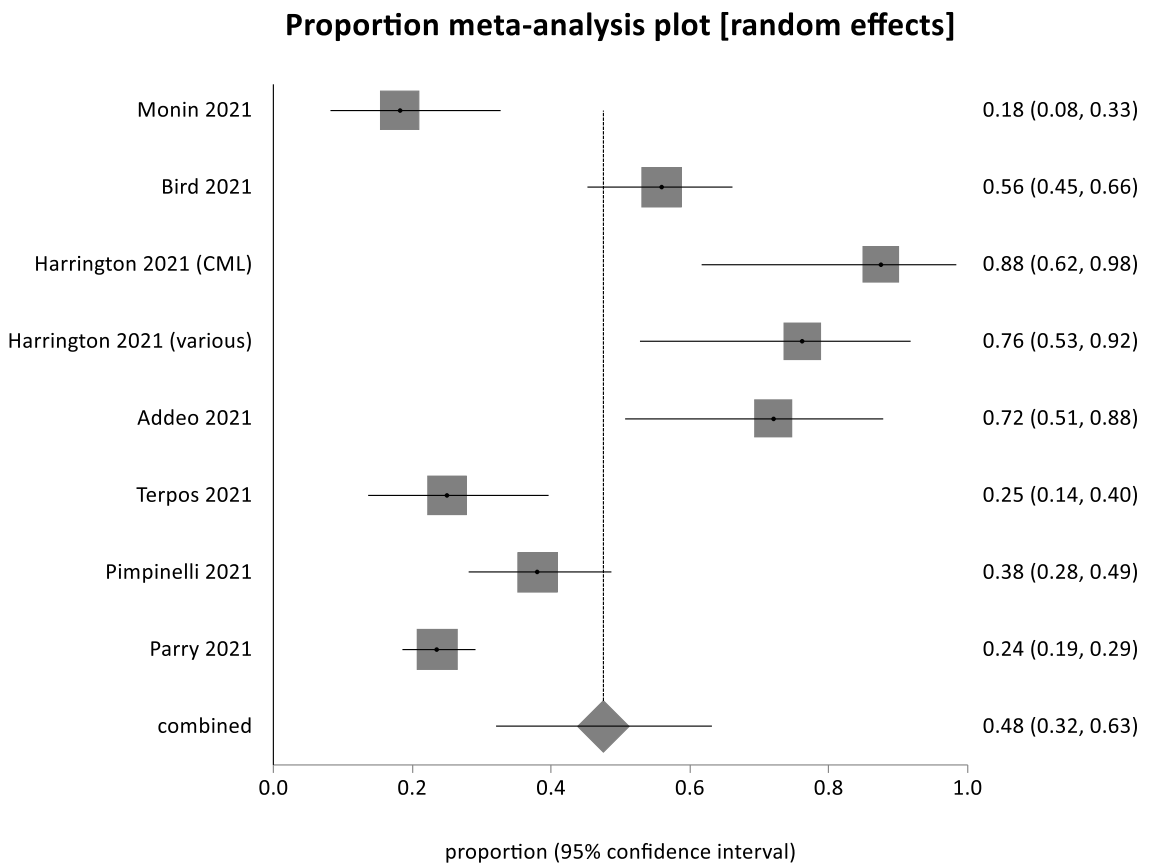
Solid malignancy: proportion seroconverting after 1st vaccine



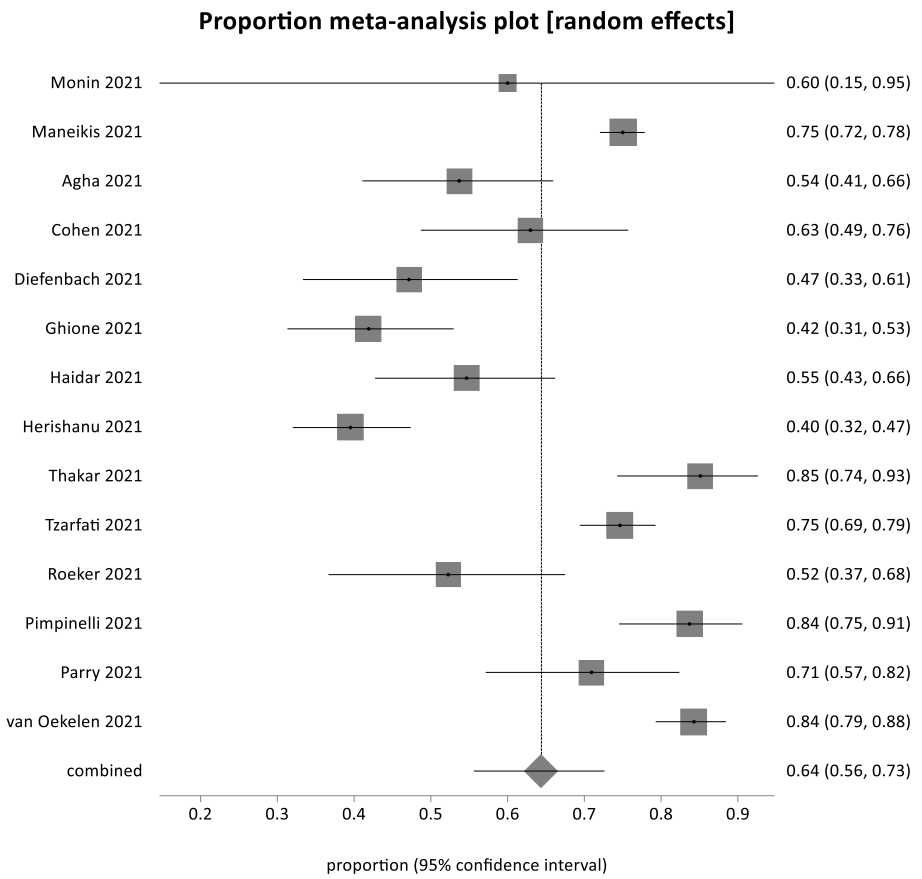
Solid malignancy: proportion seroconverting after 2nd vaccine



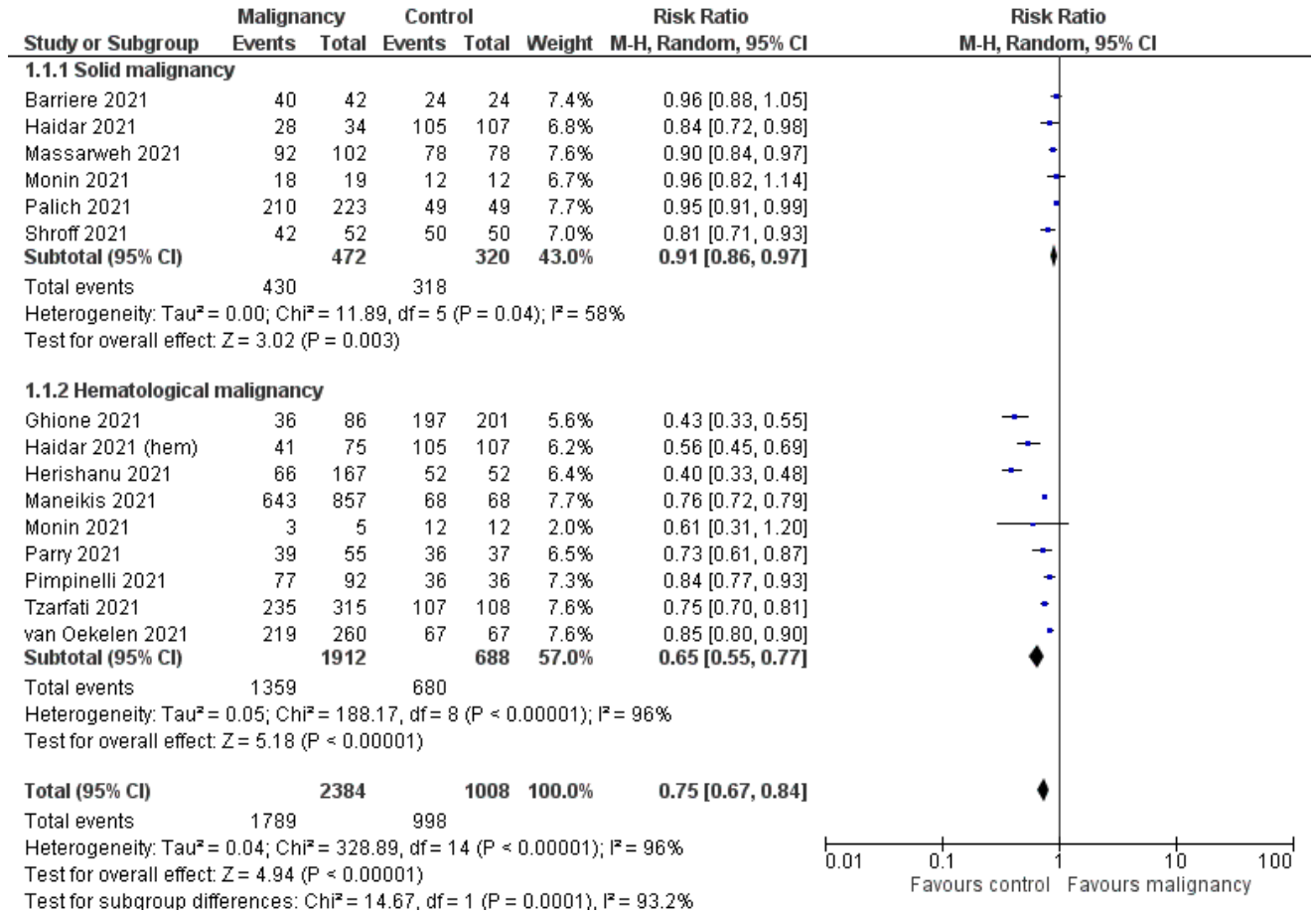
Hematological malignancy: proportion seroconverting after 1st vaccine



Hematological malignancy: proportion seroconverting after 2nd vaccine

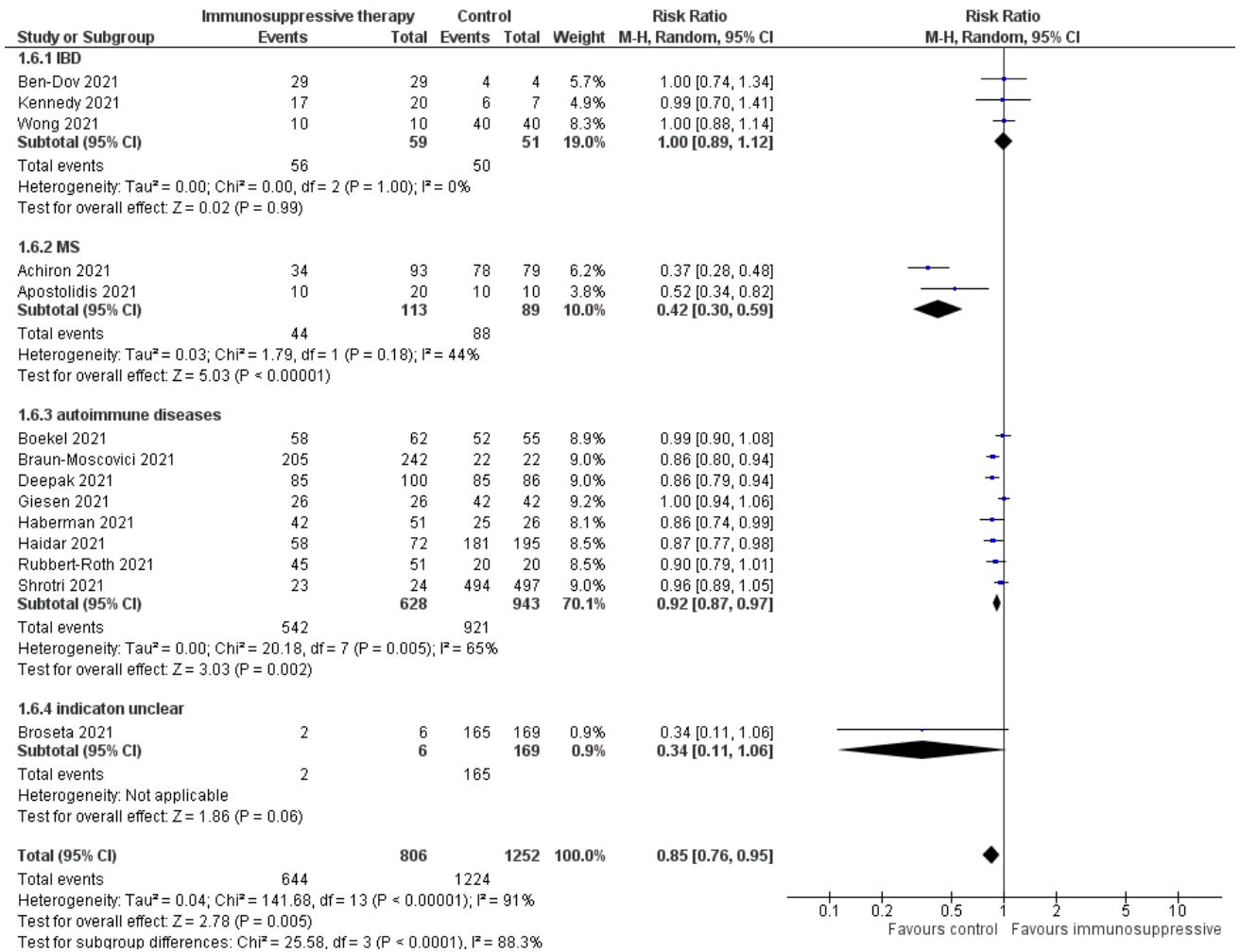


Comparison of malignancy with healthy controls after second vaccine



Study or Subgroup	Malignancy Events	Malignancy Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Solid malignancy						
Barriere 2021	40	42	24	24	7.4%	0.96 [0.88, 1.05]
Haidar 2021	28	34	105	107	6.8%	0.84 [0.72, 0.98]
Massarweh 2021	92	102	78	78	7.6%	0.90 [0.84, 0.97]
Monin 2021	18	19	12	12	6.7%	0.96 [0.82, 1.14]
Palich 2021	210	223	49	49	7.7%	0.95 [0.91, 0.99]
Shroff 2021	42	52	50	50	7.0%	0.81 [0.71, 0.93]
Subtotal (95% CI)		**472**		**320**	**43.0%**	**0.91 [0.86, 0.97]**
Total events	430		318			
Heterogeneity: Tau² = 0.00; Chi² = 11.89, df = 5 (P = 0.04); I² = 58%						
Test for overall effect: Z = 3.02 (P = 0.003)						
1.1.2 Hematological malignancy						
Ghione 2021	36	86	197	201	5.6%	0.43 [0.33, 0.55]
Haidar 2021 (hem)	41	75	105	107	6.2%	0.56 [0.45, 0.69]
Herishanu 2021	66	167	52	52	6.4%	0.40 [0.33, 0.48]
Maneikis 2021	643	857	68	68	7.7%	0.76 [0.72, 0.79]
Monin 2021	3	5	12	12	2.0%	0.61 [0.31, 1.20]
Parry 2021	39	55	36	37	6.5%	0.73 [0.61, 0.87]
Pimpinelli 2021	77	92	36	36	7.3%	0.84 [0.77, 0.93]
Tzarfati 2021	235	315	107	108	7.6%	0.75 [0.70, 0.81]
van Oekelen 2021	219	260	67	67	7.6%	0.85 [0.80, 0.90]
Subtotal (95% CI)		**1912**		**688**	**57.0%**	**0.65 [0.55, 0.77]**
Total events	1359		680			
Heterogeneity: Tau² = 0.05; Chi² = 188.17, df = 8 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 5.18 (P < 0.00001)						
Total (95% CI)		**2384**		**1008**	**100.0%**	**0.75 [0.67, 0.84]**
Total events	1789		998			
Heterogeneity: Tau² = 0.04; Chi² = 328.89, df = 14 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 4.94 (P < 0.00001)						
Test for subgroup differences: Chi² = 14.67, df = 1 (P = 0.0001), I² = 93.2%						

Immunogenicity after 2nd vaccine in those on immunosuppressive therapy compared to controls



Adverse events in immunocompromised compared to healthy controls

	Immunocompromised		Control			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
Botwin 2021	100	186	41	50	13.9%	0.66 [0.54, 0.79]
Chevallier 2021	45	94	16	24	12.1%	0.72 [0.50, 1.02]
Frater 2021	22	51	32	49	11.8%	0.66 [0.45, 0.96]
Giesen 2021	11	26	12	38	8.5%	1.34 [0.70, 2.56]
Mahil 2021	63	80	16	17	14.1%	0.84 [0.71, 0.99]
Monnin 2021	9	31	11	16	8.6%	0.42 [0.22, 0.80]
Rabinowich 2021	18	71	18	21	11.1%	0.30 [0.19, 0.46]
Schmidt 2021	11	38	34	70	9.6%	0.60 [0.34, 1.04]
Simon 2021	14	81	53	80	10.2%	0.26 [0.16, 0.43]
Total (95% CI)		**658**		**365**	**100.0%**	**0.58 [0.43, 0.77]**
Total events	293		233			

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 50.00$, $df = 8$ ($P < 0.00001$); $I^2 = 84\%$

Test for overall effect: $Z = 3.69$ ($P = 0.0002$)