Table 4. GRADE Evidence Profile: Should Influenza vaccination vs. no vaccination be used in immunocompromised patients (adults and children)?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Influenza vaccination	no vaccination	Relative (95% CI)	Absolute (95% CI)		
Influenza-associated hospitalization (Immunocompromised adults)												
1[11]	non-randomised studies (case-control studies)	serious[a]	not serious	not serious	not serious[b]	none	212 cases 1639 controls		**VE: 32%** (7-50%) Note: OR 0.68 (0.50 to 0.93)	-	⨁⨁⨁◯ Moderate[a,b]	CRITICAL
							-	2.0%[c]		631 fewer per 100,000 (from 990 fewer to 137 fewer)		
Influenza-associated hospitalization (Overall adults ≥ 65 yrs; test negative case-control studies)												
11[11, 16, 17, 18, 19, 20, 21, 22, 23, 24]	non-randomised studies (case-control studies)	serious[a]	not serious[d]	not serious	not serious	none	18277 cases 139,627 controls		**VE: 42%** (39-44%) Note: OR 0.58 (0.56 to 0.61)	-	⨁⨁⨁◯ Moderate[a,d]	CRITICAL
							-	0.5%		209 fewer per 100,000 (from 219 fewer to 194 fewer)		
All-cause mortality (Overall adults ≥ 60 years)												
1[25]	non-randomised studies (cohort studies)	serious[a]	not serious	serious[e]	serious[f]	none	68/7372 (0.9%)	1765/59172 (3.0%)	**VE: 53%** (41-63%) Note: HR 0.47 (0.37 to 0.59)	1,570 fewer per 100,000 (from 1,869 fewer to 1,212 fewer)	⨁◯◯◯ Very low[a,e,f]	CRITICAL
Severe Disease (ICU admission; in overall adults >18 years)												
1[24]	non-randomised studies (case-control studies)	serious[a]	not serious	serious[e]	not serious	none	824 cases 12644 controls		**VE: 41%** (31-50%) Note: OR 0.59 (0.50 to 0.69)	-	⨁⨁◯◯ Low[a,e]	CRITICAL
							-	20.0%		71 fewer per 1,000 (from 89 fewer to 53 fewer)		
Guillian Barre Syndrome (in overall adults ≥ 65 years)												
2[26, 27]	non-randomised studies (other design)	serious[a]	not serious	not serious	not serious	none	163/31234097 (0.0%)	186/312340 97 (0.0%)	**IRR 0.96** (0.73 to 1.27)	0 fewer per 1,000,000 (from 2 fewer to 2 more)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Severe adverse events (in overall adults/older adults)												
2[27, 28]	non-randomised studies (case-control + other combined)	serious[a]	not serious	not serious	serious[g]	none	An SCCS including people on Medicare found no increased risk of ischemic or hemorrhagic stroke following various influenza vaccines overall, but identified a statistically significant increased risk of a composite of ischemic stroke or TIA occurring 22-42 days after influenza vaccination (i.e. Medicare Advantage population, IRR 1.10, 95% CI, 1.02 to 1.17)[27]. However, this translates into approximately 1 additional endpoint in 10,000 vaccinated Medicare Advantage enrollees. In addition, a Canadian cohort study found influenza vaccine within 30 days was *associated with reduced risk of* stroke (aHR 0.66, 95% CI, 0.65 to 0.68)[28].				⨁⨁◯◯ Low[a,g]	CRITICAL
Exacerbation of immunocompromising or autoimmune condition												
4[12, 13, 14, 30]	non-randomised studies (cohort studies)	very serious[h]	not serious	not serious	not serious	none	A study evaluating safety of vaccination in 450 kidney transplant recipients found no significant difference between vaccinated and no-vaccinated groups in changes of eGFR, Serum creatinine (sCr) and occurrence of clinically significant proteinuria. None amongst the vaccinated group experienced leucopenia, neutropenia, or thrombocytopenia after vaccination. One study evaluating multiple sclerosis showed no increased risk of flares (OR 0.9, 95% CI 0.88 to 1.09). Conversely, another study showed no increased risk of flu vaccine and excess inflammatory bowel disease flares (aIRR 0.68, 95% CI 0.46 to 1.02). Another study of 1,777 patients with autoimmune diseases showed no cases of disease flare or exacerbation of underlying conditions among influenza vaccine recipients or unvaccinated individuals (Soe 2025).				⨁⨁◯◯ Low[h]	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Possibility of unknown and potential residual confounding warrants rating down in ROBINS-I. Although some studies were rates as higher risk of bias in the VIP SR, sensitivity analysis comparing low risk of bias studies to higher risk of bias studies did not show an effect difference strengthening our assessment of moderate certainty evidence.

b. Given a large body of indirect evidence of VE in older, presumable immunocompetent adults (42% 95% CI 36-47%), the panel decided to not rate down for imprecision

c. CDC estimates an influenza hospitalization rate of around 600/100,000 for the elderly (O'Halloran A, Habeck JW, Gilmer M, et al. Influenza-Associated Hospitalizations During a High Severity Season — Influenza Hospitalization Surveillance Network, United States, 2024–25 Influenza Season. MMWR Morb Mortal Wkly Rep 2025;74:529–537. DOI: http://dx.doi.org/10.15585/mmwr.mm7434a1.). Correcting for influenza vaccine status (rate: 32%) and increased risk due to immunocompromised conditions (RR: 4.4 (PMID: 33252189)), the displayed rate facilitates visualizing the population effects of the flu vaccination.

d. Although statistically significant heterogeneity was observed (I squared of 81%), 9 out of 10 studies revealed a clinically meaningful vaccination effectiveness - not rated down

e. Indirect evidence of VE in overall adult population

f. Given the relative low number of deaths in the cases, fragility of the estimate could not be ruled out

g. Some outcomes with few events

h. Potential unknown and residual confounding