Table 4. GRADE Evidence Profile: In children with mild to moderate COVID-19, does treatment with nirmatrelvir/ritonavir vs. no treatment result in better outcomes (e.g., time to symptom resolution, hospitalization, progression to severe or critical illness)?

Certainty assessment							№ of patients		Effect			
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirmatrelvir / ritonavir	no nirmatrelvir / ritonavir*	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Hospitalization (follow-up: 28 days)												
2[Hammond 2022, Hammond 2024]	randomized trials	not serious	not serious	serious[a]	serious[b]	none	13/1693 (0.8%)	0.5%	**RR 0.17** (0.10 to 0.31)	**4 fewer per 1,000** (from 5 fewer to 3 fewer)	⨁⨁◯◯ Low	CRITICAL
				serious[a]				3.0%		**25 fewer per 1,000** (from 27 fewer to 21 fewer)	⨁⨁◯◯ Low	
				not serious[a]				6.0%		**50 fewer per 1,000** (from 54 fewer to 41 fewer)	⨁⨁⨁◯ Moderate	
Serious adverse events												
3[Liu 2023, Hammond 2022, Hammond 2024]	randomized trials	not serious	not serious	not serious[a]	serious[b]	none	32/1895 (1.7%)	91/1881 (4.8%)	**RR 0.52** (0.20 to 1.35)	**23 fewer per 1,000** (from 39 fewer to 17 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events requiring discontinuation of treatment												
3[Liu 2023, Hammond 2022, Hammond 2024]	randomized trials	not serious	not serious	not serious[a]	serious[b]	none	24/1895 (1.3%)	9/1881 (0.5%)	**RR 0.75** (0.5 to 1.13)	**26 fewer per 1,000** (from 53 fewer to 14 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Symptom resolution for patients at high risk (follow-up: 28 days)[c]												
1[Hammond 2025]	randomized trials	not serious	not serious	not serious[a]	serious[d]	none	619/970 (63.8%)	566/986 (57.4%)	**HR 1.20** (1.07 to 1.35)	**67 more per 1,000** (from 25 more to 110 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Symptom resolution for all patients (follow-up: 28 days)[e]												
1[Hammond 2025]	randomized trials	not serious	not serious	not serious[a]	serious[d]	none	619/970 (63.8%)	566/986 (57.4%)	**HR 1.20** (1.07 to 1.35)	**67 more per 1,000** (from 25 more to 110 more)	⨁⨁⨁◯ Moderate	IMPORTANT

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

*For hospitalization, percentages represent illustrative baseline risks for patients without risk factors for progression to severe disease, patients at increased but not high risk, and patients at high risk.

Explanations

a. Most trial participants were adults and evidence in pediatric patients is limited, reducing applicability to children. In addition, key trials were conducted in the pre-Omicron era and largely among unvaccinated, high-risk outpatients; current baseline risks and hospitalization patterns have changed substantially, which may affect applicability—particularly for lower-risk populations where hospitalizations are now rarer and less specific to COVID-19. Because the trial populations closely match those at highest risk today, the panel did not further downgrade for baseline-risk differences in the highest-risk stratum but did downgrade for indirectness in lower-risk strata.

b. Few events do not meet the optimal information size and suggest fragility in the estimate (Guyatt 2011).

c. Median time to resolution: NMV/r 16 days (95% CI: 15, 18) vs. placebo 19 days (95% CI: 18, 20).

d. 95% CI crossing threshold of meaningful difference; median time to resolution: 95% CI not completely separated.

e. Median time to resolution: NMV/r 16 days (95% CI: 15, 18) vs. placebo 19 days (95% CI: 18, 20) for EPIC-HR; 12 days (95% CI: 11, 13) vs. 13 (95% CI: 12, 14) in EPIC-SR