Effectiveness and safety of SAS-CoV-2 mRNA vaccines in children: a population-based study in Madrid # 398

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INTRODUCTION & AIMS

- COVID-19 vaccination decisions in children necessitate a meticulous benefit-risk assessment due to the relatively low incidence of severe complications from SAS-CoV-2 infection in this population group.
- Benefits encompass averting COVID-19 hospitalization and post-COVID multisystem inflammatory syndrome in children (MIS-C). Risks involve potential adverse events like myocarditis.
- Optimal assessment relies on evidence from randomized trials, requiring extensive follow-up on a large child population. Lacking such trials, we employ regionwide data from Madrid's health system to emulate a target trial for mRNA COVID-19 vaccines in children aged 6-11 years and 12-17 years.

METHODS

Target trial specification

- This study focuses on children aged 6-11 years (after 7 December 2021) and 12-17 years (after 31 May 2021) residing in the Madrid region.
- These unvaccinated children, without prior SARS-CoV-2 infection, are randomly assigned to receive an mRNA vaccine or no vaccination.
- The primary outcomes include COVID-19 hospitalization, MIS-C, and myocarditis.
- Participants are followed until the occurrence of the outcome, 240 days, or December 31, 2022, with both intention-to-treat (ITT) and per-protocol (PP) analyses conducted.
- ITT analysis employs Kaplan-Meier estimators to calculate cumulative incidences. Risks are compared between vaccine groups using differences and ratios, with vaccine effectiveness expressed as 1 minus the risk ratio.
- PP analysis mirrors ITT but censors unvaccinated individuals upon COVID-19 vaccination. Adjustments consider baseline prognostic factors if imbalanced post-censoring.
- Percentile-based bootstrapping yields 95% confidence intervals (CI). Analyses are stratified by age group.

Target trial emulation

- Our study utilized Madrid Health System Registry (SIP-CIBELES) data, encompassing 99.9% of the population as of December 31, 2019. This registry provided essential demo-graphic details, including date of birth, sex, residence district, date of death, and a unique identification code (CIPA).
- Linking CIPA with three Madrilenian Health Service (SERMAS) databases facilitated comprehensive analysis. The primary care database (AP-Madrid) detailed interactions and diagnostic test results, the hospital admissions database (CMBD) included admission details and comorbidities, and the Pharmacy database (Farmadrid) recorded prescription data.
- For analysis, children meeting eligibility criteria were identified daily from the start of the follow-up to December 31, 2022, and categorized as vaccinated or controls. Emulating sequential trials, we matched vaccinated and unvaccinated children based on calendar day, age, sex, and postal code in a 1:5 ratio.
- Balanced matching ensured emulated randomization. Standardized mean differences gauged balance, with a ≤0.1 difference deemed acceptable. To assess unmeasured confounding, we used SARS-CoV-2 infection in the first 10 days as a negative control outcome.
- Interest lay in the PP effect, considering many unvaccinated children received the vaccine during follow-up. Analysis mirrored the target trial, but matched sets were censored at un-vaccinated child vaccination.
- Additionally, we checked testing frequency similarity between vaccinated and unvaccinated groups due to the absence of a prespecified testing strategy in the real world.

RESULTS

- 183,430 children aged 6-11 years and 277,758 children aged 12-17 years received mRNA vaccinations, each matched to 5 controls (1,388,790 aged 12-17).
- Baseline characteristics were similar, with vaccinated children slightly more likely to be obese and have asthma (**Table 1**).
- In the age group 6-11 years, 76.9% of the vaccinated received a second vaccine dose and 24.8% of the controls received a first vaccine dose during the follow-up. In the age group 12-17 years, 90.4% of the vaccinated received a second vaccine dose, and 48.4% of the controls received a first dose during the follow-up.

Table 1. Baseline characteristics of children eligible for a target trial of mRNA COVID-19 vaccines, Madrid 2021-2022

	6-11 years			12-17 years		
	Vaccinated	Controls	SMD	Vaccinated	Controls	SMD
No.	183,273	916,365		277,561	1,387,805	
Age, years (SD)	9.6 (1.4)	9.6 (1.4)	0.00	15.1 (1.4)	15.1 (1.4)	0.00
Male sex	937,88 (51.2)	468,940 (51.2)	0.00	140,495 (50.6)	702,475 (50.6)	0.00
Asthma	22,801 (12.4)	94,731 (10.3)	0.07	52,322 (18.9)	20,8751 (15.0)	0.10
Chronic heart disease	133 (0.1)	493 (0.1)	0.01	464 (0.2)	1967 (0.1)	0.01
Diabetes	427 (0.2)	1,802 (0.2)	0.01	1,178 (0.4)	4,814 (0.3)	0.01
Obesity	4,984 (2.7)	22,746 (2.5)	0.02	12,503 (4.5)	52,889 (3.8)	0.04
Hematologic tumor	85 (0.0)	755 (0.1)	0.01	167 (0.1)	963 (0.1)	0.00
Solid tumor	181 (0.1)	776 (0.1)	0.01	292 (0.1)	1,061 (0.1)	0.01
HIV infection	55 (0.0)	362 (0.0)	0.01	124 (0.0)	766 (0.1)	0.01

*Numbers in parentheses are %, unless otherwise indicated; SMD: standardized mean difference.

RESULTS (Cont.)

Children aged 6-11 years:

COVID-19 hospitalization (Figure 1A)

- Hospitalization risk: 11.5 per 100,000 in vaccinated vs. 12.7 per 100,000 in controls.
- Vaccination effectiveness for hospitalization: 9.0% (95% CI -38 to 47).

MIS-C (Figure 2A)

- MIS-C risk: 3.8 per 100,000 in vaccinated vs. 5.2 per 100,000 in controls.
- Vaccination effectiveness for MIS-C: 27.0% (95% CI -54 to 76).

Myocarditis

- No myocarditis cases occurred.

Children aged 12-17 years:

COVID-19 hospitalization (Figure 1B)

- Hospitalization risk: 6.5 per 100,000 in vaccinated vs. 11.8 per 100,000 in controls.
- Vaccination effectiveness for hospitalization: 45% (95% CI 18 to 72).

MIS-C (Figure 2B)

- MIS-C risk: 1.8 per 100,000 in vaccinated vs. 3.1 per 100,000 in controls.
- Vaccination effectiveness for MIS-C: 42% (95% CI -31 to 83).

Myocarditis

- Myocarditis risk: 7.6 per 100,000 in vaccinated vs. 6.9 per 100,000 in controls.
- The myocarditis risk ratio for vaccinated vs. controls was 1.09 (95% CI 0.60 to 1.70) and was similar for males and females (**Table 2**).

Table 2. Estimated risk of acute myocarditis or pericarditis by sex in children aged 12-17 years eligible for a target trial of mRNA COVID-19 vaccines, Madrid 2021-2022*

	Vaccinated		Controls		Risk Ratio	Risk difference per 100,000
	Events	Risk per 100,000	Events	Risk per 100,000		
All	21	7.6 (4.5, 10.8)	96	6.9 (5.5, 8.3)	1.09 (0.60, 1.70)	0.7 (-3.0, 4.3)
Males	19	13.5 (7.8, 19.5)	85	12.1 (9.8, 14.8)	1.12 (0.62, 1.70)	1.4 (-5.0, 7.8)
Females	2	1.5 (0.0, 3.7)	11	1.6 (0.7, 2.6)	0.91 (0.00, 3.06)	-0.15 (-2.2, 2.3)

* Numbers in parentheses are 95% confidence intervals

DISCUSSION & CONCLUSIONS

- In this study encompassing the entire pediatric population of the Madrid region, the impact of mRNA vaccines on COVID-19-related outcomes was assessed over a 240-day period, involving over 460,000 vaccinated children and controls.
- Among 12–17-year-olds, vaccine effectiveness against COVID-19 hospitalization was estimated to be modest, ranging from 18% to 72%. For 6–11-year-olds, effectiveness was similarly imprecise but did not exceed 49%.
- The risk of MIS-C was small in both age groups, with vaccinated individuals showing smaller risks than controls, although estimates were imprecise.
- No cases of myocarditis/pericarditis were identified in the 6-11 age group, while in the 12-17 age group, both increases and decreases in risk after vaccination were plausible based on the data.

FIG 1A COVID-19 hospitalization Children 6-11 years

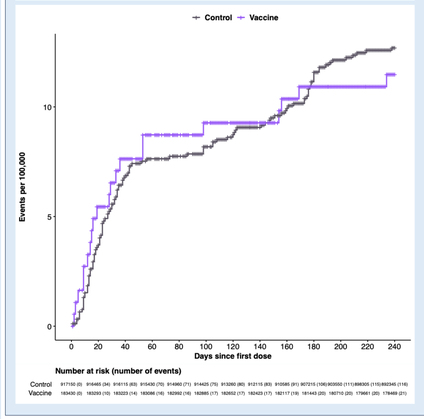


FIG 1B COVID-19 hospitalization Children 12-17 years

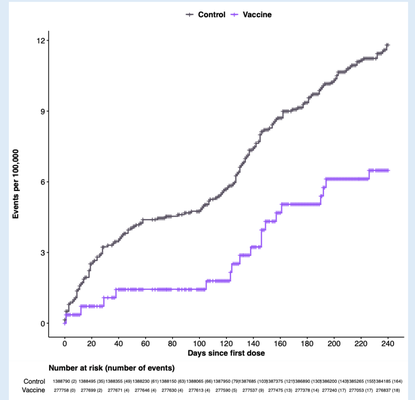


FIG 2A MIS-C Children 6-11 years

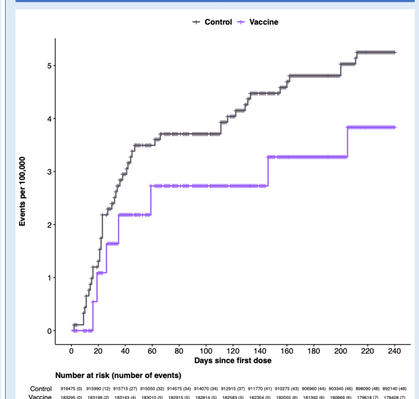
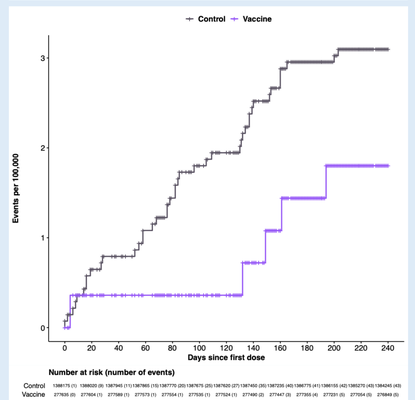


FIG 2B MIS-C Children 12-17 years



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