

Overall health effects of mRNA COVID-19 vaccines in children and adolescents

## **Overall Health Effects of mRNA COVID-19 Vaccines in Children and Adolescents:**

### **A Systematic Review and Meta-Analysis**

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## **Question, Findings, and Meaning**

### **Question**

What is the overall health effect of mRNA COVID-19 vaccines in children?

### **Findings**

In this systematic review and meta-analysis of phase 3 trials, mRNA vaccine vs. placebo was not associated with increased risk of serious adverse events. The mRNA vaccines were associated with higher risk of severe adverse events in children aged 5 years and older. In children younger than 5 years, mRNA vaccines were associated with a 3-fold higher risk of lower respiratory tract infections.

### **Meaning**

The results suggest that mRNA vaccines are associated with increased risk of severe adverse events and increased risk of LRTI. Given the low risk of severe COVID-19 infection in children, it is not clear that the benefits of COVID-19 vaccines in children outweigh the harms.

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## Abstract

**Importance:** Phase 3 randomized controlled trials (RCTs) of mRNA COVID-19 vaccines in children and adolescents showed efficacy in preventing COVID-19 infections. Vaccines may have non-specific effects; this is not assessed within the current regulatory framework.

**Objective:** Conduct a systematic review and meta-analysis of the phase 3 trials to assess overall and non-specific health effects of the mRNA COVID-19 vaccines in children.

**Data Sources:** PubMed, Embase, Clinical Trials, Web of Science, and regulatory websites were searched for RCTs of mRNA vaccines. The latest trial data was included.

**Study Selection:** All RCTs conducted with mRNA vaccines BNT162b2 and mRNA-1237 in children and adolescents below 18 years of age, with placebo, adjuvant, or other vaccines as controls. Two authors independently screened 1199 studies, six were included in the analysis.

**Data Extraction and Synthesis:** Data on serious adverse events (SAEs) and severe adverse events (AEs) as well as organ-specific diseases was extracted following the PRISMA reporting guideline, with a focus on non-specific infectious events. Risk Ratios (RRs) comparing vaccine and placebo cohorts were calculated separately for each vaccine and combined in Mantel-Haenszel estimates.

**Main Outcomes and Measures:** The primary outcome was SAEs, overall and infectious. Secondary outcomes were severe AEs and lower respiratory tract infection (LRTI) including RSV.

**Results:** The analyses included 25,549 individuals (17,538 mRNA vaccine recipients and 8,011 placebo recipients). The risk of SAEs was similar for vaccine and placebo recipients. Both mRNA vaccines were associated with increased risk of severe AEs in older children. In a combined analysis, the RR was 3.77 (1.56-9.13[0.4% vs 0.1% in vaccine vs placebo recipients]) in above 5 year-olds, and 0.82 (0.53-1.29)[0.8% vs 0.9%] in younger children ( $p=0.003$  for same effect in older and younger children). In the younger children, mRNA vaccines were associated with higher risk of LRTI (RR=3.03 (1.29-7.09)[0.6% vs 0.2%]).

**Conclusions and Relevance:** mRNA vaccines did not increase the risk of SAEs but were associated with an increased risk of severe AEs in older children, and an increased risk of LRTI in the young. Further research into the overall and non-specific health effects of mRNA vaccines is warranted.

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### INTRODUCTION

COVID-19 vaccines were developed and implemented at an unprecedented speed. As of September 2023, 11 COVID-19 vaccines had received licensure or emergency use authorization (EUA). All COVID-19 vaccines were tested in phase 3 randomized clinical trials (RCTs) in adults and showed efficacy in preventing COVID-19 infections. Subsequent phase 3 trials included progressively younger populations. The most administered vaccine types in children and adolescents are the messenger RNA (mRNA) vaccines (Pfizer/BioNTech (BNT162B2) and Moderna (mRNA-1273)). Both have received full approval or emergency/conditional authorization in the United States and the European Union in children 6 months of age and older.

Children have biological differences from adults that gradually diminish with age.<sup>1</sup> Most children with a COVID-19 infection are asymptomatic or have influenza-like symptoms.<sup>2,3</sup> Given the age-related differences in COVID-19 morbidity, COVID-19 mRNA vaccine benefit-risk assessments may differ in children vs. adults.

Safety data collected during vaccine trials are reported as either “solicited” adverse reactions, i.e., events related to reactogenicity, or as “unsolicited” adverse events (AEs) that are spontaneously reported unexpected events. AEs are divided by severity. Serious AEs (SAEs) are outcomes leading to death, life-threatening events, hospitalization, or disability/permanent damage, also defined as Grade 4 and/or 5 AEs.<sup>4</sup> Severe AEs are medically significant but not immediately life-threatening events, also known as Grade 3 adverse events. In vaccine trials, Severe AEs are usually collected up to 1 month after vaccination, whereas information on SAEs, (all-cause deaths, and hospitalizations) and AEs of special interest (AESIs) should be observed in all study participants for at least 6 months after the last vaccination dose.<sup>5</sup>

Since the implementation of COVID-19 vaccines in children, several AEs have been detected in post-authorization safety monitoring.<sup>6-10</sup> These include encephalitis,<sup>11</sup> nephritis,<sup>12</sup> neurological complications,<sup>13</sup> and myocarditis.<sup>14</sup>

Vaccines may have non-specific (off-target) effects, i.e., an ability to affect the risk of other diseases by either reducing or increasing the susceptibility to other infections. In general, live vaccines reduce susceptibility to a broad range of other infections, whereas non-live vaccines may increase susceptibility to other infections.<sup>15</sup> The existence of non-specific effects was not taken into consideration when the current framework for testing vaccine efficacy and safety was established.<sup>16</sup>

In this review, as previously performed for the adults’ phase 2-3-trials,<sup>17</sup> the available phase 3 trial reports were used to examine the overall health effect of COVID-19 mRNA vaccines in children, with a particular focus on non-COVID-19 infectious disease outcomes.

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## **METHODS**

The systematic review was conducted under the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and registered in PROSPERO before initiating the search.<sup>18,19</sup>

### *Search strategy*

Randomized controlled trials (RCTs) with participants under 18 years old meeting the following criteria were included: phase 2/3 studies of randomized placebo-controlled trials of COVID-19 mRNA vaccines published in a peer-reviewed journal or in the process of applying for regulatory approval.

### *Search for published literature*

In March 2023, we searched PubMed, Embase, Clinical Trials, and Web of Science for RCTs of mRNA vaccines. The search string is available in Supplementary Material. All identified studies were exported into Covidence. The search was rerun in September 2023 to ensure that the review was up to date. All included trials are ongoing; data on long-term safety will, according to protocols, be available from 2024.

All RCTs with original data, comparing Pfizer and Moderna mRNA vaccines as interventions, with placebo, adjuvant, or other vaccines as controls. After removing duplicates, two review authors (SH and CSB) independently assessed titles and abstracts of all records and conducted a full-text review.

### *Search for regulatory reports*

Next, trial data was found on *The United States Food and Drug Administration* (FDA) and *The European Medicines Agency* (EMA) websites, for both advisory committee meeting material and sponsor presentations. For each study, we obtained the newest vaccine trial data published by the FDA and EMA matching on clinical trial number, local trial number, and number of participants in each age group.<sup>20–27</sup>

### *Data extraction*

Relevant data was extracted from the most comprehensive report. The following data were extracted (where possible): study characteristics (including author, publication year, local Pfizer/Moderna trial number and Clinical Trial number), age and sex of participants, enrollment period and location, trial phase, type of vaccine and placebo, number of vaccines and antigen dose per injection. Furthermore, health outcome data was extracted.

### *Health outcome data*

The primary outcome was SAEs (overall, excluding accidents, and infectious SAEs). Additional outcomes were Infectious disease deaths; Infectious disease hospitalization; Severe AEs (overall and infectious);

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AESIs, and other health outcomes where reporting and numbers allow for meaningful analysis, with a focus on non-COVID infectious diseases.

For efficacy estimates and the safety outcomes SAEs, AESIs, and death, participants had been followed for the full duration of the study (Table 1). The less severe outcomes, Severe AEs and other health outcomes, were only registered for one month after each vaccine dose.

Details on other health outcomes defined by System Organ Class (SOC) group are described in Supplementary materials.

Lastly, the trials in the younger children reported specific data on respiratory infections, including pneumonia, and pathogen-specific disease such as RSV. As non-specific effects of vaccines have been shown to be most pronounced for lower respiratory infections (LRTIs),<sup>28</sup> we analyzed the effect of the vaccines on “RSV infection”, as well as LRTI which we defined as pneumonia, lower tract infection, and/or RSV. “Upper respiratory tract infections” (URTI), defined as upper respiratory infections (URIs), viral URI, and croup, were also analyzed.

Data on vaccine efficacy against COVID-19 was extracted from each trial’s main publications plus supplementary material. We chose the local trial definition of COVID-19.

All health outcomes are presented in Supplementary Tables 1 and 2, where details on data extraction are also presented. Cochrane Risk of Bias tool (RoB) for RCTs was used to assess the quality of the included publications (Supplementary Table 3).

### *Data analysis*

The absolute risks for vaccine and placebo groups were presented as [X% vs X%]. Risk ratios (RRs) were calculated using the *metan* command in Stata BE version 18 providing Mantel-Haenszel (MH) estimates. All MH estimates were stratified for vaccine type and age group, whenever combining across these strata. The *metan* command in Stata was used to produce forest plots and test of homogeneity of RRs across strata. All analyses were done by age group (6-23 months, 2-4(5)-years, 5(6)-11 years, 12-15(17) years) and vaccine manufacturer. Events in children older and younger than 5(6) years of age were analyzed, stratified for age group (older vs younger children) and vaccine type. There was insufficient information to analyze data by sex.

We compared the Number Needed to Treat (NNT) separately for the four age groups, for preventing a case of COVID-19 to the risk of different adverse event outcomes, by using the *bci* command in Stata. A positive NNT indicates the number of children that need to be vaccinated to prevent one event (hereafter the

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number needed to treat to benefit (NNTB)). A negative NNT implies that the vaccine is more likely to harm than benefit and the absolute value may also be interpreted as number needed to treat to harm (NNTH).<sup>29</sup>

All RRs were reported with 95% confidence intervals (95% CI).

### RESULTS

The main search for published literature resulted in 1864 records. After removing duplicates, 1199 studies were screened, 1135 of these were excluded by title or abstracts and 64 full texts were assessed. Of these, six studies were included in the analysis.<sup>30–35</sup> (Supplementary Figure 1). For each of the two mRNA COVID-19 vaccines, three main publications were published according to age groups: 12-15 years,<sup>30</sup> 5-11 years,<sup>31</sup> and 6 months to 4 years for Pfizer (presenting safety data for the 6 to 23 months and 2-4 year old groups separately),<sup>32</sup> and for Moderna 12-17 years,<sup>33</sup> 6-11 years,<sup>34</sup> and 6 months to 5 years (presenting safety data for the 6-23 months and 2-5 year old groups separately).<sup>35</sup> Table 1 presents background information on the included phase 3 studies. Table 2 presents the number of participants with outcomes, for both vaccines combined, overall and across age groups. Supplementary Tables 4a (Pfizer trials) and 4b (Moderna trials) present the data extracted from each of the vaccine trials along with our RR calculations.

#### *Primary outcome: SAEs (overall, excluding accidents, and infectious only)*

There were no reported deaths in any of the trials. The combined RR for SAEs for mRNA vaccine vs placebo recipients was 1.12 (0.74-1.70) (Table 2). For the Pfizer vaccine, the RR tended to be highest in the older children (3.49 (0.73-16.78[0.6% vs 0.2% in vaccine vs placebo recipients]) and declined with lower age. For Moderna vaccines, the highest RR was seen among the youngest population (5.02 (0.66-37.90[0.9% vs 0.2%])), but overall numbers were small (Figure 1, Supplementary tables 4a+b). Splitting data by above and below 5(6) years of age, the combined estimates were 1.84 (0.81-4.20[0.2% vs 0.1%]) for the oldest children and 0.93 (0.57-1.51[0.7% vs 0.8%]) for the youngest ( $p$  for homogeneity of effects=0.20) (Figure 1). The results were similar when excluding accidents (1.11 (0.72-1.72)) and when focusing on SAEs due to infections (1.08 (0.41-2.83)) (Table 2, Supplementary Tables 4a+b).

#### *Severe AEs*

Severe AEs were not reported as narratives, so it was not possible to distinguish between overall and infectious Severe AEs. For both vaccines there was higher risk of Severe AEs in vaccine vs placebo recipients in the two oldest populations, but not in the two youngest populations. For the 12-15(17)-year-olds, the combined RR was 3.76 (1.24-11.39[0.6% vs 0.2%]) (Table 2). In the 5(6)-12-year-olds, the same tendency was observed (Figure 2, Supplementary tables 4a+b), though not statistically significant. The overall risk of Severe AEs for younger children was lower in vaccine recipients (Table 2). Splitting data by above and below

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5(6) years of age, the estimates were significantly different for the oldest (3.77 (1.56-9.13)[0.4% vs 0.1%]) and the youngest children (0.82 (0.53-1.29)[0.8% vs 0.9%]),  $p$  for homogeneity of effect=0.003 (Figure 2).

### *AESIs*

All RCT studies presented AESIs adapted from the Brighton Collaboration judged to be relevant to COVID-19 vaccines. Numbers of events per age group were lower than for SAEs and Severe AEs (Supplementary tables 4a+b). The combined RR was 0.97 (0.48-1.95[0.2% vs 0.1%]) (Table 2).

### *Respiratory tract infections*

In the 6-23 months and 2-4(5) year age groups, trials reported data on respiratory tract infections. The risk of LRTI was higher in vaccine recipients (3.03 (1.29-7.09[0.6% vs 0.2%]) (Table 2 and Figure 3). For RSV, the risk tended to be higher in vaccine recipients (2.09 (0.92-4.74 [0.4% vs. 0.2%]) (Table 2, Figure 3). For the youngest, the RR was significantly higher in Moderna recipients vs placebo: 2.91 (1.04-8.19[0.4% vs 0.2%]) for the 2–5-year-olds, 3.25 (1.16-9.08[0.8% vs. 0.2%]) for the 6-23-months-olds. There was no difference in the risk of URTI (1.01 (0.87-1.16[3.8% vs. 2.8%]).

### *Other health outcomes defined by System Organ Class, and COVID-19 infections*

There were no clear patterns in the presented System Organ Class systems. However, “skin and tissue disorders” had a combined RR of 1.33 (1.06-1.67[1.8% vs. 1.2%])(Table 2).

As expected, the risk of COVID-19 infections was significantly lower in vaccine recipients with overall RRs of 0.15 (0.08-0.27[0.5% vs.2.7%]) for Pfizer and 0.55 (0.41-0.74[1.2% vs.2.1%]) for Moderna. However, analyzed by age group, only the RR for the 2–5-year-olds in Moderna trials was statistically significant (RR 0.55, 0.38-0.79[2.7% vs 5.0%])(Supplementary tables 4a+b).

### *Number needed to treat*

For COVID-19 infections, the combined NNTB ranged from 37 to 103. For SAEs and Severe AEs, the NNT range included both possibilities of benefit and harm, with a range from -2219 to 630. For LRTI in young children, the NNTH ranged from 183 to 271 (Supplementary table 5).

## **DISCUSSION**

From the RCTs in children aged 6 months to 15(17) years, neither of the mRNA vaccines had a beneficial effect on overall health, assessed as the incidence of SAEs, Severe AEs, RTIs, and other organ-specific diseases. mRNA vaccines were not associated with an increased risk of SAEs, but the risk of Severe AEs was more than 3.5-fold higher in the older children. In younger children, information on respiratory infections



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was provided, and mRNA vaccines were associated with a 3-fold increased risk of LRTI and a 2-fold increased risk of RSV. As expected, the vaccines reduced the risk of COVID-19 infection.

### *Strengths and limitations*

The review was based on placebo controlled RCTs and represents the best available estimates of the overall health effect of COVID-19 vaccines in children.

Our analyses also have several limitations, which are largely a consequence of the data availability.

First, the included trials were designed to collect and analyze safety and efficacy of vaccines, not overall health effects. Only SAEs and AESI were collected for the full duration. All health outcomes ought to be investigated to include non-specific effects of vaccines.<sup>16,36</sup> The occurrence (or absence) of e.g., another respiratory infection several months after randomization may well be the result of the vaccination.<sup>15</sup> While it is not customary to collect all health outcomes for the full duration of vaccine trials, the results on respiratory infections presented here suggest this data can provide important insights.

Second, vaccine efficacy in the younger populations has primarily been assessed by "immunobridging", where antibody responses in children receiving the vaccine are compared to antibody responses in older age groups, in which efficacy was demonstrated. Hence, clinical trial populations including children were much smaller than in adults. This led to several limitations regarding safety analysis, as also highlighted in the EMA report: *"The study size did not allow detection of rare adverse events, or to evaluate whether the characteristics of identified, but rarer risks differ compared with the adolescent and adult populations."*<sup>21</sup>

Third, data comparison and counting of unsolicited SAEs, Severe AEs, and AESIs was challenging due to inconsistencies in the reported number of events between the main texts, supplementary data, and trial reports: a problem that has been previously addressed.<sup>37,38</sup> Furthermore, AEs could be registered as both Severe AEs and SAEs according to event definition in each trial's supplementary material, AESIs could also be SAEs, and respiratory infections could also be registered as Severe AEs or SAEs confounding composite outcome analysis as cases could have counted twice or thrice.

Fourth, there were considerable differences between the two vaccine types regarding the incidence of reported events. For example, the incidences of some SOC groups differed markedly (Supplementary Tables 4a+b), e.g., "infections and infestations" (incidence 13.5% vs 2.8% for Moderna vs Pfizer vaccinees), "nervous system disorders" (2.2% vs 0.7%), and "respiratory disorders" (5.6% vs. 0.5%). The difference in infections and respiratory disorders could be related to Fall dates for the Moderna trial versus Summer dates for the Pfizer trials. However, different dosing and reporting standards might complicate combined analyses.

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Fifth, data was not reported by sex. Non-specific effects have been shown to be sex-differential, and in several instances, an overall null-effect has been shown to be a result of a positive effect in one sex but a negative effect in another.<sup>39,40</sup> As it pertains to COVID-19 mRNA vaccines and adults, there is a striking female predominance in severe allergic reactions.<sup>41</sup> Many journals require data be broken down by biological sex.<sup>42</sup> It is a serious omission that this is still not done consistently.<sup>16</sup>

### *Interpretation*

For SAEs and Severe AEs, the oldest populations generally had the highest risk of events compared to the youngest. The observed risk difference could be an effect of the vaccine dose. The youngest children received a lower dose than the 5-11-year-olds who again received a lower than adolescents (Pfizer 3 vs 10 vs. 30 µg, Moderna 25 vs 50 vs 100 µg). The Pfizer dose for the youngest children is 10 times lower than for the oldest group, whereas the Moderna dose was only 4 times lower, which might help explain the stronger dose-response in Severe AEs and SAEs in the Pfizer trials. During the open-label dose-level finding part of the studies, children 2 to 5 years of age in the Pfizer trials had a higher frequency and greater severity of adverse reactions to the 10 µg dose compared with the 3 µg dose, which contributed to the selection of the lower dose.<sup>21</sup>

Our finding of a higher rate of LRTI after mRNA vaccination lines with other studies showing negative non-specific effects of non-live vaccines for respiratory infections. Sørup et al found a higher risk of both RSV-related and other non-targeted infections in children after receiving a non-live vaccine compared to the live vaccine against Measles, Mumps, and Rubella.<sup>43,44</sup> Two small immunological studies, one in adults and one in children, have found mRNA vaccines to be associated with a decrease in cytokine responses to viral stimulants for 6 months.<sup>45,46</sup> Similar immunological effects have been observed for other non-live vaccines.<sup>47,48</sup> Taken together, the results suggest that mRNA vaccines may have negative non-specific immunologic effects, lasting at least some months.

Regarding the increased overall risk of “skin and tissue disorders”, this apparent association could be a chance finding as many outcomes were assessed. Nevertheless, various skin reactions from COVID-19 mRNA-vaccines have previously been described.<sup>49</sup>

### *Number needed to treat to benefit or harm*

Only COVID-19, SAEs, and AESIs were captured for more than four weeks post-vaccination. Thus, there would inherently be a lower baseline risk for other health outcomes, which would bias towards higher NNTB/H for other health outcomes. Nonetheless, the data indicates that for the 12–15-year-olds receiving either vaccine, the NNTB for preventing one additional case of COVID-19 was 103, and the NNTH for

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developing one additional Severe AE was 260. Thus, there would be roughly one Severe AE for each 3 cases of COVID-19 prevented (260 NNTH/103 NNTB $\approx$ 2.52). In the youngest age group, the data suggest that for each 3 prevented COVID-19 cases, one child would develop an LRTI (NNTB for COVID-19 60 and NNTH for LTRI 183), and for each 12 COVID-19 cases prevented, one child would get an RSV infection (NNTH for RSV 709). LRTI including RSV infections in infants and small children are usually more severe than COVID-19 infections.<sup>50</sup>

### **CONCLUSION**

Both mRNA vaccines approved to children were associated with reductions in the risk of COVID-19 and showed no difference in the risk of SAEs. Among the older children, the vaccines were associated with a 3.5-fold higher risk of Severe AEs. Among children younger than 5 years of age, the mRNA vaccines were associated with a 3-fold higher risk of LRTI and a 2-fold higher risk of RSV. Given the low risk of severe COVID-19 infections in children, the RCTs call for a renewed assessment of the value of COVID-19 vaccination of children and adolescents.

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All authors affirm that the manuscript is an accurate and transparent presentation of the studies being reported, no important aspects has been omitted, and all relevant data has been published.

*Author contributions:*

The study was conceptualized by CSB and SMT. SSH wrote the first draft with input from the other authors. SN provided statistical advice. All authors commented and approved the final version.

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**Table 1. Background information on the included phase 3 studies of COVID-19 vaccination of children.**

First author	Publication date	Clinical trial/ local trial	Age	Enrolment	Data cut-off	% vaccine efficacy (VE) (95% CI)*	Median follow-up time for SAE and AESI	Median follow-up time for other health outcomes	Doses	µg/ dose	Ratio
<b>Pfizer (BNT162b2) versus placebo (saline)</b>											
Freneck	July 15, 2021	NCT04368728/ C4591001	12-15 years	October 15, 2020, to January 12, 2021	March 13, 2021	VE 100 (75.3-100)	>2 months after dose 2	From dose 1 to 1 months after dose 2	2	30	1:1
Walter	November 9, 2021	NCT04816643/ C4591007	5-11 years	June 7 to June 19, 2021	September 6, 2021	VE 90.7 (67.7-98.3)	3.3 months (0.0- 3.5) after dose 2	From dose 1 to 1 month after dose 2	2	10	2:1
EMA/FDA <sup>a</sup>	November 25, 2021	NCT04816643/ C4591007	5-11 years	August to September 2021	October 8, 2021	Not evaluated	2.4 weeks (0.0-3.7) after dose 2	From dose 1 to data cut-off.	2	10	2:1
Muñoz <sup>b</sup>	February 16, 2023	NCT04816643/ C4591007	2-4 years	June 21, 2021, to January 2022	April 29, 2022	VE 71.8 (28.6-89.4)	2.1 months (0.0- 3.2) after dose 3	From dose 1 to 1 month after dose 3.	3	3	2:1
Muñoz <sup>b</sup>	February 16, 2023	NCT04816643/ C4591007	6 to 23 months	June 21, 2021, to January 2022	April 29, 2022	VE 75.8 (9.7-94.7)	2.1 months (0.0- 3.2) after dose 3	From dose 1 to 1 month after dose 3.	3	3	2:1
<b>Moderna (mRNA-1273) versus placebo (saline)</b>											
Ali	August 11, 2021	NCT04649151/ P203	12-17 years	December 9, 2020, to February 28, 2021	May 8, 2021	VE 100.0 (28.9 to NE)	53 days (0-121) after dose 2	Within 28 days after any injection	2	100	2:1
Creech	May 11, 2022	NCT04796896/ P204	6-11 years	March to August 2021	November 10, 2021	VE 69.0 (-131.4-95.8)	51 days (0-65) after dose 2	Within 28 days after any injection	2	50	3:1
Anderson <sup>c</sup>	October 19, 2022	NCT04796896/ P204	2-5 years	October 2021 to January 2022	February 21, 2022	VE 46.4 (19.8-63.8)	71 days (0-99) after dose 2	Within 28 days after any injection	2	25	3:1
Anderson <sup>c</sup>	October 19, 2022	NCT04796896 P204	6 to 23 months	October 2021, ongoing at data cut off <sup>d</sup>	February 21, 2022	VE 31.5 (-27.7-62.0)	68 days (0-99) after dose 2	Within 28 days after any injection	2	25	3:1

\* COVID-19 data extracted from the main paper from each trial, focusing on participants with no prior infection, with onset of follow up after the last recommended dose

<sup>a</sup>The FDA and EMA report describe an additional expansion group along with the initial group described in the Walter study, this expansion group is included in the analysis.

<sup>b,c</sup>Same publication presenting data on two age groups.

<sup>d</sup>Email correspondence with corresponding author Dr. Schnyder Ghamloush.

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**Table 2. Risk ratio calculations for all outcomes, combining Pfizer and Moderna versus placebo. All analyses stratified by both age group and vaccine type. Trials with no information on event (marked with -) not included in overall RR calculations.**

<b>Pfizer+Moderna</b>										
	<b>12 to 15(17) years</b>		<b>5(6) to 11 years</b>		<b>2 to 4(5) years</b>		<b>6 to 23 months</b>		<b>Overall</b>	
	Vaccine (3617)	Placebo (2369)	Vaccine (6116)	Placebo (2533)	Vaccine (4866)	Placebo (1922)	Vaccine (2939)	Placebo (1187)	mRNA-1273 (N=17538)	Placebo (N=8011)
<b>Subjects with outcome in % (n)</b>										
Serious AE overall	0.4 (13)	0.2 (4)	0.2 (10)	0.1 (3)	0.4 (21)	0.5 (10)	1.1 (32)	1.3 (15)	0.4 (76)	0.4 (32)
RR (95% CI)	2.35 (0.79-7.04)		1.30 (0.36-4.65)		0.91 (0.43-1.96)		0.95 (0.50-1.77)		1.12 (0.74-1.70)	
Serious AE ex. accidents	0.3 (11)	0.2 (4)	0.1 (7)	0.1 (3)	0.4 (20)	0.5 (9)	1.0 (30)	1.1 (13)	0.4 (68)	0.4 (29)
RR (95% CI)	2.07 (0.69-6.23)		0.84 (0.21-3.30)		0.97 (0.44-2.14)		1.02 (0.52-1.99)		1.11 (0.72-1.72)	
Serious AE - infectious	0.0 (1)	0.0 (0)	0.1 (4)	0.0 (1)	0.3 (15)	0.3 (6)	0.9 (25)	0.7 (8)	0.3 (45)	0.2 (15)
RR (95% CI)	2.99 (0.12-73.43)		1.43 (0.17-12.23)		1.08 (0.41-2.83)		1.39 (0.62-3.12)		1.08 (0.41-2.83)	
Severe AE	0.6 (20)	0.2 (4)	0.3 (19)	0.1 (2)	0.6 (30)	0.8 (15)	1.0 (30)	1.2 (14)	0.6 (99)	0.4 (35)
RR (95% CI)	<b>3.76 (1.24-11.39)</b>		3.79 (0.88-16.28)		0.77 (0.41-1.42)		0.89 (0.47-1.69)		1.26 (0.86-1.85)	
AESI	0.0 (0)	0.1 (2)	0.1 (8)	0.1 (2)	0.2 (11)	0.3 (6)	0.3 (8)	0.2 (2)	0.2 (27)	0.1 (12)
RR (95% CI)	0.20 (0.01-4.15)		1.49 (0.33-6.67)		0.78 (0.29-2.11)		1.66 (0.36-7.77)		0.97 (0.48-1.95)	
<b>System Organ Class (SOC) groups in % (n)</b>										
GI disorders	1.2 (42)	1.0 (23)	1.9 (118)	1.9 (48)	4.4 (216)	5.2 (100)	9.4 (275)	9.4 (112)	3.7 (651)	3.5 (283)
RR (95% CI)	1.10 (0.68-1.78)		0.94 (0.67-1.31)		0.86 (0.68-1.09)		0.98 (0.80-1.21)		0.94 (0.82-1.08)	
Infections/infestations	2.2 (78)	1.9 (46)	5.1 (314)	3.6 (91)	12.7 (620)	10.4 (199)	19.7 (580)	17.9 (212)	9.1 (1592)	6.8 (548)
RR (95% CI)	0.92 (0.64-1.33)		1.22 (0.97-1.53)		1.07 (0.92-1.24)		1.01 (0.88-1.16)		1.07 (0.92-1.24)	
Musculoskeletal disorders	1.9 (67)	1.7 (40)	1.0 (61)	1.0 (26)	0.1 (7)	0.2 (4)	<0.1 (1)	0.1 (1)	0.8 (136)	0.9 (71)
RR (95% CI)	0.94 (0.64-1.38)		0.86 (0.54-1.36)		0.87 (0.26-2.97)		0.51 (0.03-8.10)		0.83 (0.67-1.03)	
Nervous system disorders	2.2 (81)	1.6 (38)	1.7 (103)	1.6 (40)	0.8 (39)	1.0 (19)	1.8 (52)	1.5 (18)	1.6 (275)	1.4 (115)
RR (95% CI)	1.20 (0.82-1.76)		0.92 (0.64-1.32)		0.74 (0.43-1.29)		1.08 (0.64-1.82)		1.00 (0.81-1.24)	
Respiratory disorders	1.0 (36)	0.7 (16)	3.6 (221)	3.5 (89)	6.3 (305)	5.9 (114)	6.9 (202)	5.6 (67)	4.4 (764)	3.6 (286)
RR (95% CI)	1.23 (0.67-2.24)		0.89 (0.70-1.13)		0.99 (0.80-1.22)		1.15 (0.88-1.50)		1.01 (0.88-1.15)	
Skin and tissue disorders	1.0 (35)	0.8 (20)	1.8 (109)	0.8 (20)	1.7 (82)	1.1 (21)	3.0 (87)	3.2 (38)	1.8 (313)	1.2 (99)
RR (95% CI)	1.15 (0.64-2.05)		<b>2.13 (1.32-3.43)</b>		1.46 (0.90-2.35)		0.92 (0.63-1.34)		<b>1.33 (1.06-1.67)</b>	

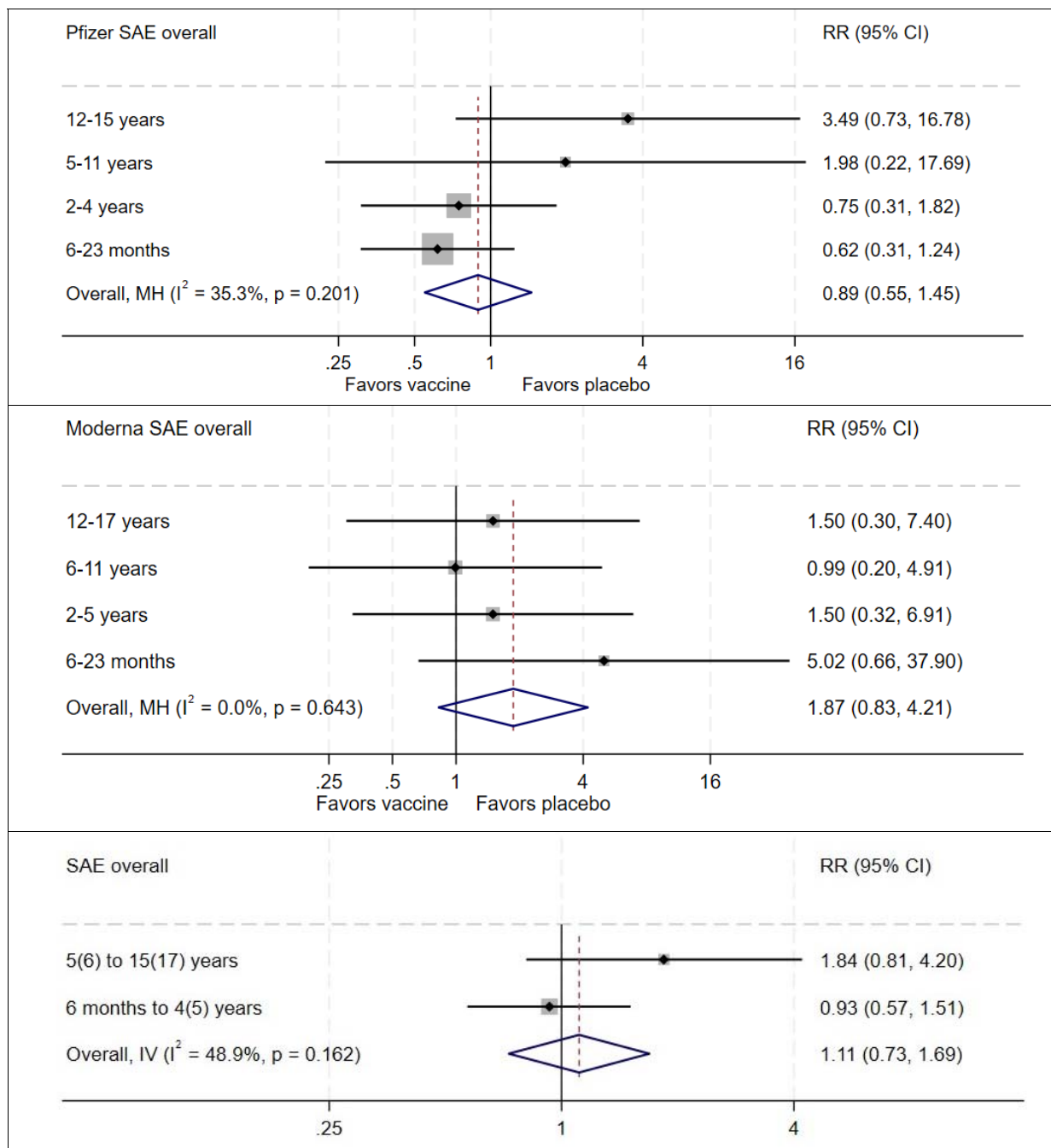
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<b>Respiratory infection groups in % (n)</b>										
COVID-19 infection <sup>a</sup>	0.0 (0/3168)	1.0 (20/2051)	0.2 (6/3949)	1.3 (19/1516)	2.6 (80/3092)	5.0 (53/1062)	2.3 (41/1807)	3.9 (26/660)	1.1 (127/12016)	2.3 (121/5289)
RR (95% CI)	<b>0.04 (0.00-0.29)</b>		<b>0.14 (0.05-0.35)</b>		<b>0.49 (0.35-0.68)</b>		<b>0.57 (0.35-0.93)</b>		<b>0.39 (0.30-0.50)</b>	
Upper RTI	-	-	1.9 (117)	1.0 (26)	6.6 (320)	6.0 (115)	8.1 (238)	6.8 (84)	3.8 (675)	2.8 (222)
Relative Risk (95% CI)	-		1.50 (0.99-2.28)		0.93 (0.76-1.14)		0.96 (0.76-1.21)		1.01 (0.87-1.16)	
RSV <sup>b</sup>	-	-	0.3 (9)	0 (0)	0.4 (12)	<0.1 (1)	0.6 (19)	0.5 (6)	0.4 (40)	0.2 (7)
Relative Risk (95% CI)	-		6.29 (0.37-107.99)		3.99 (0.52-30.62)		1.23 (0.48-3.11)		2.09 (0.92-4.74)	
Lower RTI	-	-	-	-	0.5 (23)	0.1 (2)	0.9 (26)	0.3 (4)	0.6 (49)	<0.1 (6)
Relative Risk (95% CI)	-		-		4.10 (0.93-18.14)		2.50 (0.89-7.08)		<b>3.03 (1.29-7.09)</b>	

<sup>a</sup>COVID-19 data extracted from the main paper from each trial, focusing on participants with no prior infection, with onset of follow up after the last recommended dose (see also Supplementary tables 4a and 4b). Significant results in bold.

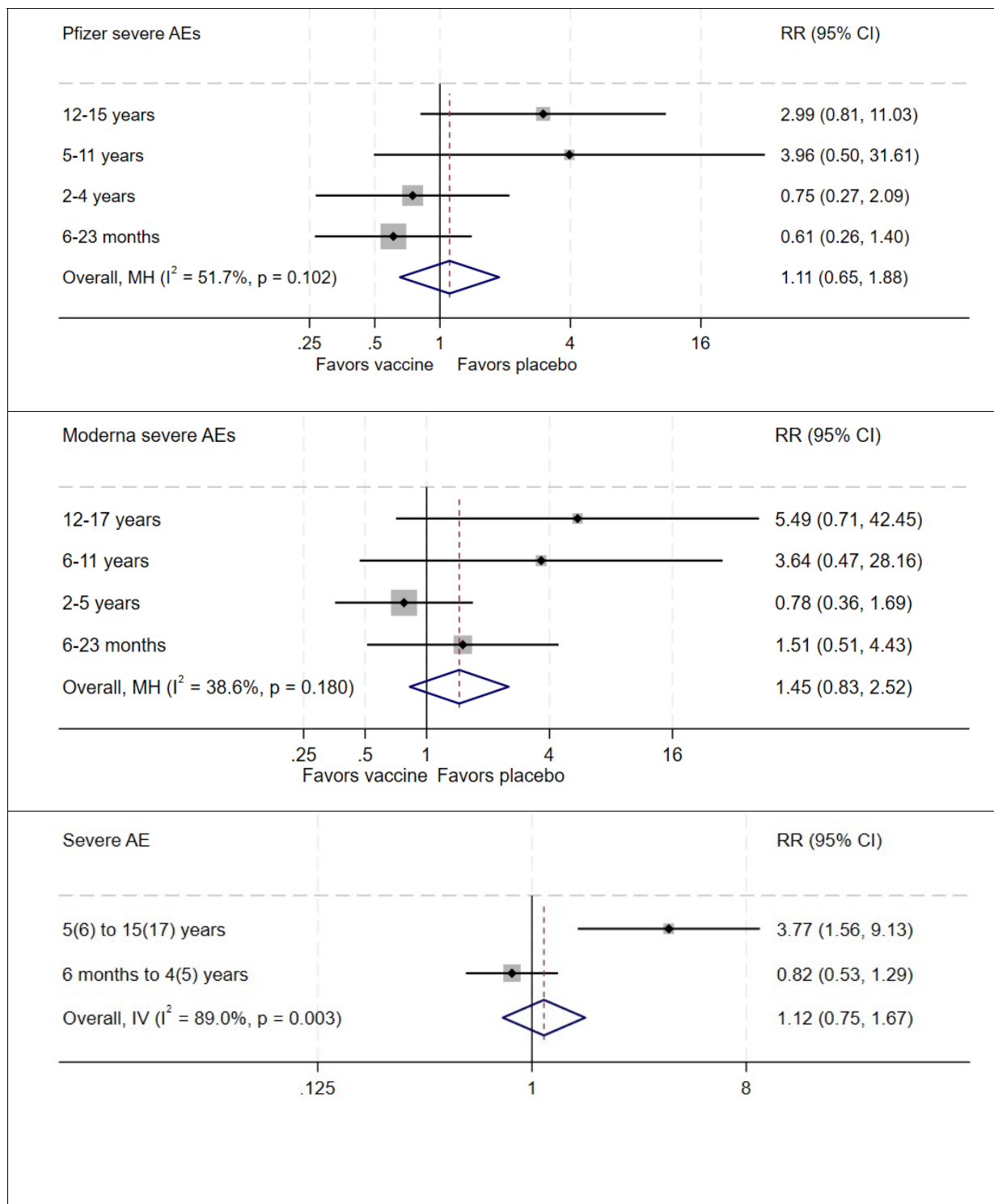
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**Figure 1. The risk of Overall SAEs in the mRNA phase 3 trials. Analysis done by vaccine type as well as combined, comparing children by age group, and children older and younger than 5(6) years of age, presenting RR (95% CI) and p for homogeneity of effects across age groups.**



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**Figure 2. The risk of severe AEs in the mRNA phase 3 trials. Analysis done by vaccine type as well as combined, comparing children by age group, and children older and younger than 5(6) years of age, presenting RR (95% CI) and p for homogeneity of effects across age groups.**



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**Figure 3. LRTI, RSV and URTI for vaccines versus placebo recipients, according to the age groups where trials had available data. Analysis done by vaccine type as well as combined, presenting RR (95% CI), overall RR and p for homogeneity of effects.**

