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Myocarditis in Adolescents (12-17 years) Associated with the Pfizer-BioNTech (BNT162b2) Vaccine: A Systematic Review and Meta-analysis

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Abstract

Purpose: Data on the incidence rate of myocarditis associated with mRNA COVID-19 vaccines in adolescents is limited. The research estimated the incidence of myocarditis associated with the Pfizer- BioNTech COVID-19 vaccine (BNT162b2) in adolescents (12-17 years).

Methodology: This study was conducted as per the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Incidence rates were estimated after generating a random effects model.

Findings: The Incidence rate in males after the first dose was 2.4 per 100,000 persons (0.8- 6.8 per 100,000; I^2: 17.17%). The IR in females after the first dose was 1.9 per 100,000 persons (0.5-6.5 per 100,000; I^2: 0.00). After the second dose, the IR in males was 15.7 per 100,000 persons (3.2-78.1 per 100,000; I^2: 96.45%), while in females the IR after the second dose was 6.1 per 100,000 persons (2.9-12.1 per 100,000; I^2: 0.00). The Incidence Rate Ratio (IRR) after the first dose between males and females was 1.86 (0.40-8.5; I^2: 0.00) and 6.35 (2.98-13.49; I^2: 0.00) after the second dose. Among individuals between 12- 17 years of age, myocarditis is a rare side effect associated with Pfizer- BioNTech COVID-19 vaccine (BNT162b2) vaccination. The incidence in males were about two times greater than females following the first dose and six times greater following the second dose.

Recommendation: Vaccination strategy in adolescent males needs to be revisited to mitigate risk of myocarditis.

Keywords: *Myocarditis, BNT162b2, adolescent*

INTRODUCTION

The development of mRNA vaccines has been a game changer in the COVID-19 pandemic. On August 23, 2021, the Food and Drug Administration (FDA) announced the first approval of a COVID-19 vaccine when it approved the Pfizer-BioNTech Covid vaccine/BNT162b2 (now marketed as Comirnaty) for individuals 16 years and older. The BNT162b2 vaccine has also been approved for individuals 12 through 15 and has emergency use authorization for children older than 6 months [1]. The Moderna COVID-19 vaccine/mRNA-1273 (now marketed as Spikevax) was approved on January 31, 2022, for individuals 18 years and older[2] and was given emergency use authorization on June 17, 2022 for individuals 6 months up to 18 years of age.

With wide scale dissemination of these vaccines, rare side effects that were previously unreported in phase-3 trials were reported, including myocarditis. Historically, vaccine associated myocarditis was linked to the smallpox vaccine[3]. However, several studies have found an association between Covid vaccination and myocarditis[4-14], mostly with mRNA vaccines. They were mostly seen in young males. With adult studies reporting a preponderance of this side effect in the younger population, it is imperative that we study its incidence in adolescents. While we have several studies on mRNA Covid vaccine associated myocarditis in adults, data in adolescents is limited. To bridge this knowledge gap, we undertook a systematic review of literature and meta-analysis. As the BNT162b2 was the only available vaccine for individuals under 18 years until recently in the U.S, we estimated the incidence of myocarditis in adolescents (12-17 years of age) with the BNT162b2 vaccine. The advantage with performing a meta-analysis is that it produces a pooled estimate from a larger sample size with more events, allowing a greater precision of the estimate.

METHODS

This study was conducted as per the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[15]. Literature search was conducted on MEDLINE/PubMed, EMBASE, Scopus and Cochrane Library from inception until May 3, 2022, for eligible observational studies using MeSH words, “COVID-19”, “SARS-CoV2”, “COVID Vaccine” or “mRNA Covid vaccine” and “myocarditis”, “myopericarditis”. Studies on myocarditis and/or myopericarditis associated with mRNA vaccination in adolescents were included in review. Studies that included cases with isolated pericarditis were excluded from meta-analysis. Adolescent age group was defined as ages between 12 and 17 years. Due to rarity of the disease, we screened letters to the editor, conference abstracts and presentations. The search was supplemented by screening bibliographies of the retrieved articles. Review articles, editorials, case reports and case series were not included. Articles not available in English and studies with subgroup categories outside of our reference age group were not included. Study selection was conducted by two independent authors (S.A and A.S). Initial screening was done by title and abstract review. This was followed by full text review of relevant articles. Disagreements were resolved by discussion and achieving consensus.

Quality of included studies were assessed based on the Newcastle-Ottawa scale for cohort studies[16]. The scale assigns a maximum of four points for selection (representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at the start of the study), two points for comparability (comparability of cohorts on the basis of the design or analysis controlled for confounders), and three points for exposure or outcome (appropriate assessment of outcome, sufficient period, and

adequacy of follow-up period). A score of 0-2 was considered poor quality, 3-5 Fair, and 6-9 good. As this is a review and meta-analysis, IRB approval was not required.

Incidence rates were estimated after generating a random effects model. Incidence was estimated at 4 weeks following COVID-19 mRNA vaccination weeks, as cases diagnosed beyond 4 weeks of vaccination is usually attributed to other causes. Incidence rate was calculated using the formula: Incidence rate= Number of cases * 28 days/total person days. Stratified incidence rates were obtained based on dose and sex. Incidence rate ratios (IRR) between males and females were calculated after each dose using the formula: IRR= Incidence Rate in Males/Incidence Rate in Females. Data analysis was conducted in R version 4.1.2 using the statistical package "metafor"[17]. Study heterogeneity was quantified using Higgins I^2 statistic[18]. A I^2 =0 was considered to indicate no heterogeneity, values of I^2 as < 25 %, 25-75 %, and > 75% to indicate mild, moderate, and high degrees of heterogeneity, respectively. Results are reported in 95% Confidence Intervals.

RESULTS

Initial literature search yielded 527 citations. Following removal of duplicates, 362 articles were screened by reviewing title and abstract. Full text was reviewed in 59 articles. Four articles were included in quantitative analysis[6,8,9,19] and 16 articles for qualitative review[6-10,12,19-28]. The flow diagram is given in Figure 1. Included studies for meta-analysis with its characteristics are listed in table 1. Quality of studies was assessed using the Newcastle- Ottawa scale as described above. All included studies were of good quality.

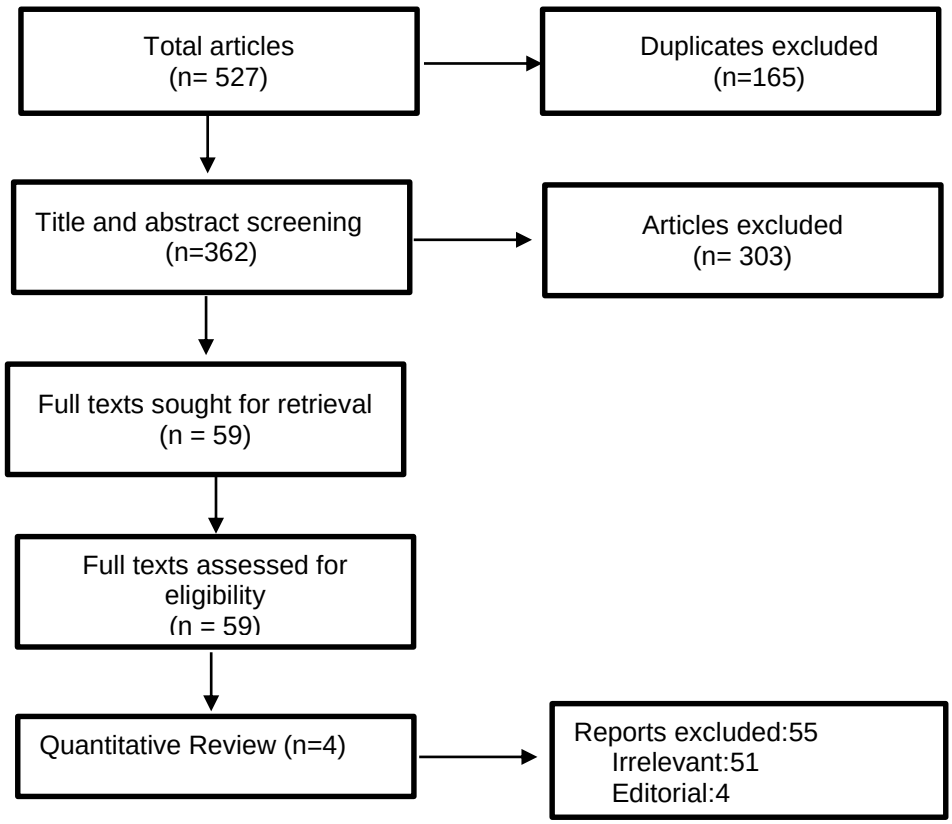

Figure 1: Flow diagram showing study selection.

Table 1: Study characteristics

Author	Country	Events after 1st dose		Person days follow up after 1st dose	Events after 2nd dose		Person days follow up after 2nd dose
		Male	Female		Male	Female	
Block	U.S. A	3.3	2	2,100,000	26.7	5.4	2,100,000
Karlstad	Nordic Countries	0.49	N.A	2,800,000	1.16	N.A	2,800,000
Mevorach	Israel	0.56	0	2,100,000	8.09	0.69	2,100,000
Oster	U.S.A	0.716		700,000		8.09	700,000

The Incidence rate in males after the first dose of vaccination was 2.4 per 100,000 persons (0.8-6.8 per 100,000; I^2: 17.17%) (Figure 2). The IR in females after the first dose was 1.9 per 100,000 persons (0.5-6.5 per 100,000; I^2: 0.00) (Figure 3). After the second dose, the IR in males was 15.7 per 100,000 persons (3.2-78.1 per 100,000; I^2: 96.45%) (Figure 4), while in females the IR after the second dose was 6.1 per 100,000 persons (2.9-12.1 per 100,000; I^2: 0.00) (Figure 5). The Incidence Rate Ratio (IRR) after the first dose between males and females was 1.86 (0.40-8.5; I^2: 0.00) and 6.35 (2.98-13.49; I^2: 0.00) after the second dose. Testing for publication bias were not conducted as the number of studies were less than 10.

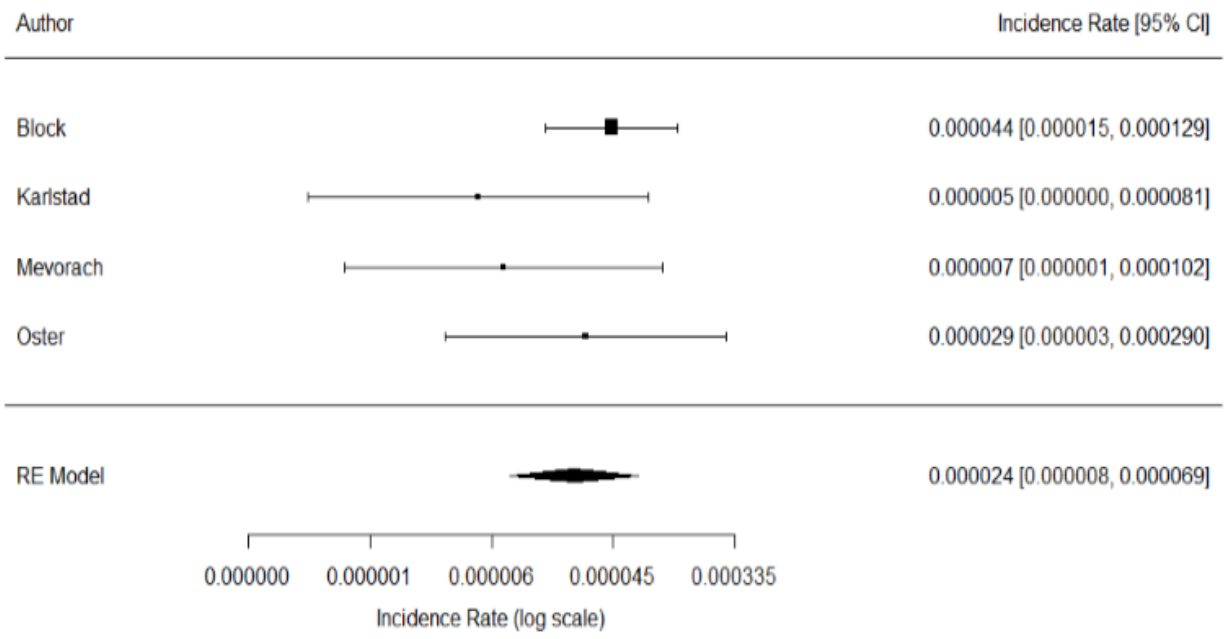

Figure 2: Incidence rate of myocarditis in adolescent males after first dose of the Pfizer BioNTech vaccine

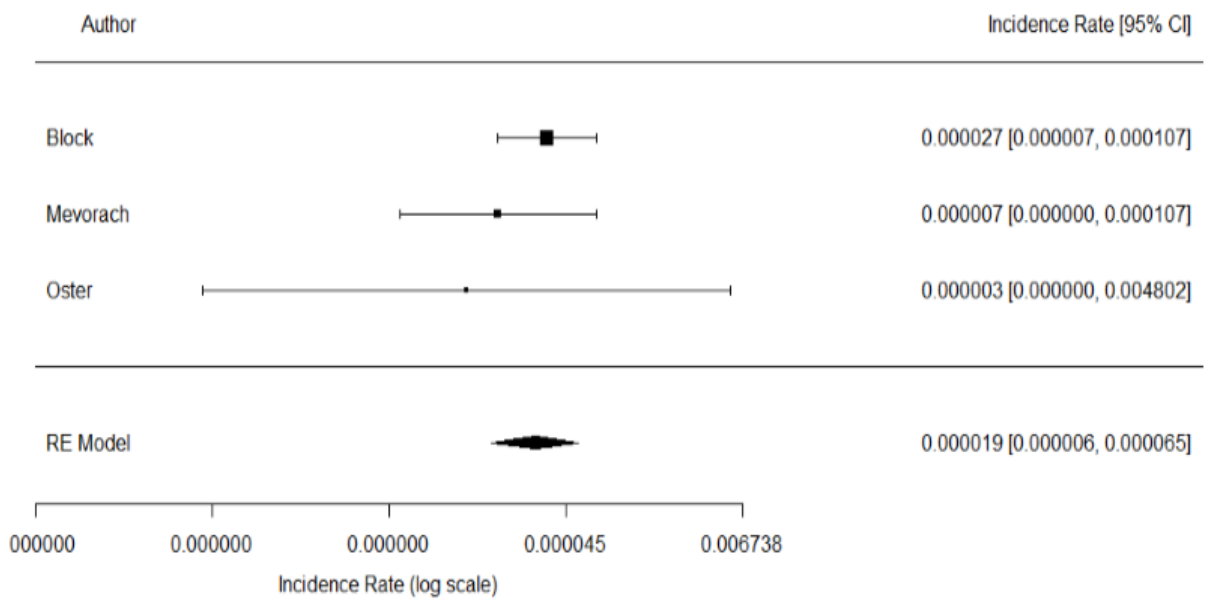

Figure 3: Incidence rate of myocarditis in adolescent females after first dose of the Pfizer-BioNTech vaccine

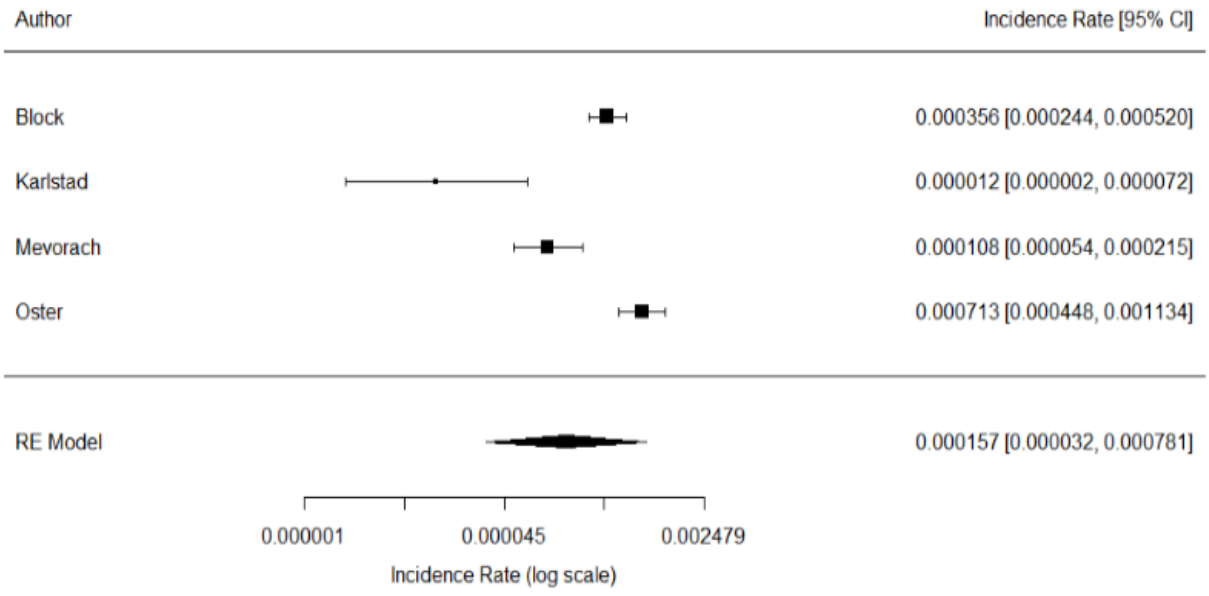

Figure 4: Incidence rate of myocarditis in adolescent males after second dose of the Pfizer-BioNTech vaccine

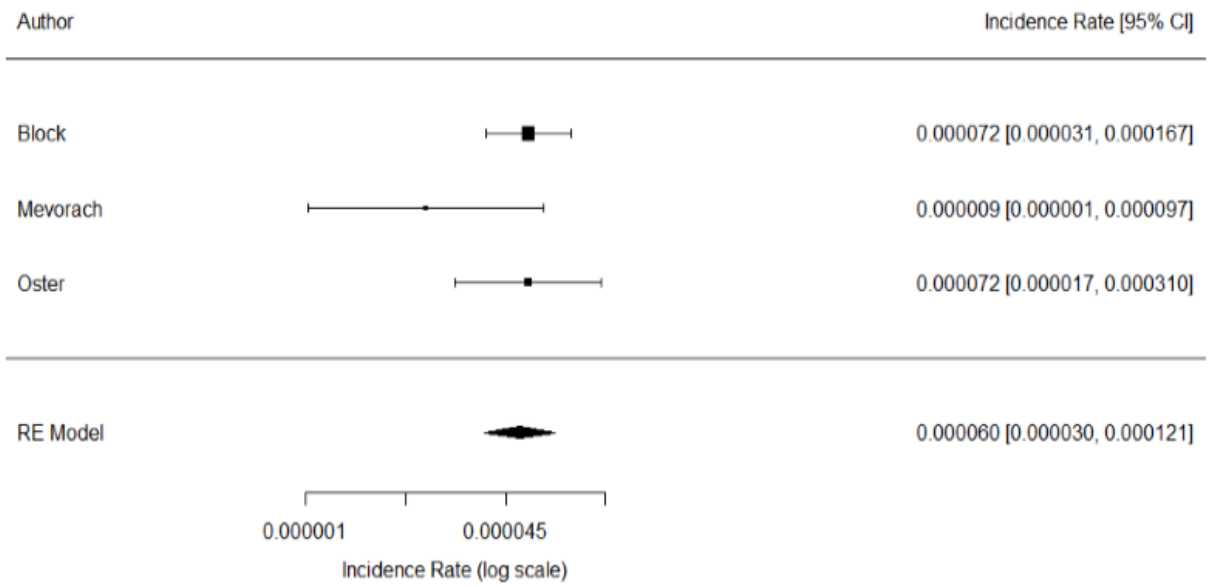

Figure 5: Incidence rate of myocarditis in adolescent females after second dose of the Pfizer-BioNTech vaccine

DISCUSSION

Myocarditis has been associated with mRNA COVID-19 vaccination but the data in adolescents is limited. This study was an effort to bridge this knowledge gap by conducting a systematic review and meta-analysis of myocarditis/myopericarditis associated with the Pfizer-BioNTech COVID-19 vaccine (BNT162b2) in adolescents (12-17 years). The study demonstrates that while the incidence rate is low, the incidence in males were about two times greater than females with first dose and six times greater with the second dose. Significant heterogeneity was found between studies, which is likely due to variations in study design and population characteristics between studies, but the results were consistent across all studies.

While myocarditis/myopericarditis is associated with mRNA COVID-19 vaccination, studies have reported higher incidence rates following SARS-CoV2 infection. Among males 12-17 years of age, Block et al reported a 21- day risk ratio of 18 (5.4-60.6) and 2.2 (1.2-4.0) with SARS-CoV2 infection compared to the first and second dose of BNT162b2 vaccine respectively. In females 12-17 years, the 21-day risk ratio between SARS-CoV 2 infection and the first and second dose of BNT162b2 was 35.4(4.6-270.5) and 11.1 (3.2-39.0) respectively[6]. Patone et al. reported an Incidence Rate Ratio (IRR) of 2.83 (1.14-7.03) for myocarditis following SARS-CoV2 infection, 1.11 (0.56-2.21) following first dose of BNT162b2 and 2.88(1.24-6.72) following second dose of BNT162b2 in individuals aged 16-29.

The mechanisms by which mRNA COVID-19 vaccines induce myocarditis is unclear. It has been postulated that vaccine mediated expression of SARS-CoV-2 surface spike protein on the surface of cardiomyocytes could trigger an immunologic response resulting in organ specific cell death[29]. It is likely that multiple mechanisms are involved in the disease process as there are major differences in mRNA vaccination induced myocarditis not only clinically but also histologically[30,31]. The major limiting factor in elucidating mechanisms is the scarcity of

endomyocardial tissue sampling as the clinical course is mild in majority of patients. It is also unclear why the risk of myocarditis/pericarditis with mRNA vaccination is higher in young males. In adolescents and young adults, males had a higher incidence of myocarditis, even prior to COVID-19 pandemic. It might be due to the effect of sex hormones on the immune system[32].

As most cases were seen in young males, the timing, and interval of vaccination in this population might have to be re-evaluated[20, 22]. The clinical course of vaccine associated myocarditis in adolescents is mild in majority of cases with excellent outcomes[24]. However, the Center for Disease Control and Prevention (CDC) guidelines recommend that no further doses of any COVID-19 vaccine be given to those who developed myocarditis/pericarditis following COVID-19 mRNA vaccination[33]. The major limitation of this study is the significant heterogeneity between studies that arose from varying methodologies employed to gather data. Studies on COVID-19 vaccine related side effects may also suffer from potential surveillance bias arising from closer scrutiny of recently vaccinated individuals.

CONCLUSION

Among individuals between 12- 17 years of age, myocarditis is a rare side effect associated with BNT162b2 vaccination. The incidence in males were about two times greater than females following the first dose and six times greater following the second dose. Vaccination strategy in adolescent males needs to be revisited to mitigate risk of myocarditis.

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Disclosures

None of the authors have anything to disclose

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