



COVID-19 Vaccine Compliance in Adolescents With Attention-Deficit/Hyperactivity Disorder

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Abstract

Objective: To compare the rate of the administration of the Pfizer–BioNTech COVID-19 vaccinations between adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD) and non-ADHD subjects.

Method: A retrospective chart review was performed on all adolescents aged 12–17 years registered at a central district in Israel from January 1st 2021 to October 31st 2021.

Results: Of the 46,544 subjects included in the study, 8241 (17.7%) were diagnosed with ADHD. Of them, 3% were PCR-COVID-19 positive. Among the patients with ADHD, the older adolescents were more likely to be vaccinated: 48.8% of those aged 12–15 years were vaccinated versus 59.6% of patients aged 16–17 years. The ultra-orthodox Jewish and Arab adolescents in the ADHD group were far less likely to be vaccinated (22.9% and 34.6%, respectively), compared to the adolescents with ADHD in the general population (60.5%). Girls were also somewhat more likely to be vaccinated.

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Conclusions: Adolescents diagnosed with ADHD had a higher COVID-19 vaccination rate compared to their non-ADHD counterparts. The vaccine uptake was lower amongst Arab and ultra-orthodox Jewish populations.

Keywords

COVID-19, vaccination, adolescents, ADHD

Introduction

COVID-19 has caused huge morbidity and mortality rates worldwide. On November 3, 2021, the World Health Organization (WHO) recorded 247,968,277 confirmed cases of COVID-19, including 5,020,204 deaths. As of November 4, 2021, a total of 7,027,377,238 vaccine doses have been administered worldwide.¹ Israel was one of the first countries to vaccinate a high proportion of the adult, and subsequently adolescent population. The national immunization program started on December 20, 2020, using Pfizer–BioNTech (BNT162b2).² Viral load in infected individuals was significantly lower in those who had been vaccinated than in unvaccinated individuals 12 days after vaccination.³

Children and adolescents usually present with milder symptoms than adults and are more likely to have an asymptomatic SARS-CoV-2 infection. The majority of children and adolescents in both hospital-based studies of acute infection and population-based seroprevalence studies developed symptoms of COVID-19.⁴ However, a study of national data from the USA on COVID-19 cases among children and adolescents in 2021 found they peaked in January, dropped in June and spiked in August. The weekly COVID-19 hospitalization rate followed a similar pattern.⁵ According to another study of 14 states in the USA during the week ending August 14, 2021, about 1.4 of every 100,000 children and adolescents were hospitalized for COVID-19, nearly five times the weekly rate in late June and close to the peak in January.⁶

In Israel, in mid-June 2021, after a month of extremely low SARS-CoV-2 activity, two local outbreaks erupted.^{7–9} These outbreaks marked the beginning of a new widespread SARS-CoV-2 outbreak in Israel, and the B.1.617.2 (Delta) variant accounted for 93%–99% of the sequenced viruses during July and August 2021.¹⁰

The reduction of asymptomatic transmission was essential to slow the spread of the virus, and growing evidence suggested that vaccination provides substantial public health benefits.¹¹ Fortunately, the Centers for Disease Control (CDC) in the United States approved the Pfizer–BioNTech COVID-19 vaccine for use in children and teens aged ≥ 12 years.¹² On June 21, 2021, the Israeli Health Ministry followed the CDC recommendation for the vaccination of teenagers aged 12 to 15 years (<https://www.gov.il/he/departments/news/21062021-02>).

Israel's population accounts for 9.41 million people: approximately 74% are Jews, 21% are Arabs and 5% belong to other ethnicities (<https://www.cbs.gov.il/he/pages/default.aspx>).

In the Jewish population, about 12% belong to a distinct subpopulation that is religiously ultra-orthodox.¹³ The Arab and ultra-orthodox Jewish populations are of lower socioeconomic status, have higher fertility rates, and are younger compared to the general Jewish population.¹³ The ultra-orthodox community in Israel has several unique characteristics. It is a very close-knit community, which has little contact with the general population. Many ultraorthodox men study in Yeshivas (religious schools), which are crowded, closed spaces. Additional characteristics include the central role of the Rabbi in community actions and behaviors, large families crowded in small apartments in overpopulated neighborhoods, and limited income.¹⁴

Attention-deficit/hyperactivity disorder (ADHD) has been found to be a risk factor for COVID-19 with poor outcomes. Two studies from Israel found that subjects with ADHD have a risk factor for COVID-19 infection and that drug therapy ameliorates this effect.^{15,16} ADHD was also found to be associated with more severe COVID-19 symptoms and hospitalizations.¹⁷ However, in a US study, recovery rates were found to rise with the prevalence of ADHD¹⁸ suggesting that ADHD may have a protective role against severe COVID-19 symptoms.

Patients with ADHD might have symptoms that tend to increase the risk for COVID-19 transmission: inattentive criteria (e.g. appearing not to listen to a caregiver or teacher, short attention span); hyperactive-impulsive criteria (e.g. squirming in a seat, taking risks); impulsivity (e.g. not thinking through decisions or long-term consequences, and restlessness).¹⁹ The basic requirements for the prevention of COVID-19, including social distancing, frequent hand washing, and face mask-wearing in public, as well as maintaining lockdown are all more difficult to follow for patients with ADHD. The aim of this study was to compare the characteristics of adolescents with ADHD versus non-ADHD with COVID-19 vaccine status.

We hypothesized that the COVID-19 vaccination rate is higher among adolescents in the ADHD group compared to adolescents in the non-ADHD group. We assumed that patients with ADHD and their parents would prefer to lower the risk of COVID-19 morbidity and mortality by vaccination.

Methods

Setting and Data Source

Clalit Health Services (CHS) is Israel's largest health fund, and serves as both insurer and health care provider, insuring 54% of Israel's population. CHS has a comprehensive computerized database, which is continuously updated with regard to a subject's demographics, community and outpatient visits, laboratory tests, hospitalizations, medication prescriptions, and purchases. During each physician visit, a diagnosis is established according to the International Classification of Diseases, ninth revision (ICD-9).²⁰

Data extracted from the CHS electronic medical records included demographics, diagnoses, and vaccination status. ADHD was diagnosed according to the Israeli Ministry

of Health criteria, which follows the international requirements for evaluation. The diagnosing physician was a senior physician with a specialty in the ADHD field (child or adult psychiatrist, child or adult neurologist, or pediatrician and family physician with certified ADHD training by the Israeli Ministry of Health). The diagnosis was established according to the criteria of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV or 5, depending on the year of diagnosis).²¹ Patients were determined as having ADHD on the basis of a written diagnosis in their medical files using the relevant ICD-9 codes in the CHS data warehouse during 2002-2021, or by the purchase of at least two ADHD medication prescriptions (as defined by *The Anatomical Therapeutic Chemical classification system*).

The study was conducted on all adolescents aged 12-17 years registered with Clalit from the region of Dan-Petach-Tikva district in Israel from January 1st, 2021 (the date when first vaccinations were introduced to the pediatric Israeli population) to October 31st, 2021. This central district comprises some 500,000 members, with a fairly large proportion of children and adolescents, large towns of mainly secular Jews, large cities of ultra-orthodox Jews, and some small Arab towns, with the majority from the general Jewish population. As Israelis tend to live within neighborhoods based on this grouping, clinic-level determination is very accurate.

In addition, gender and age, as well as PCR-COVID-19 information on the youths were collected, whether they had ever tested positive (and when), in which case they were not eligible for vaccination, and indeed their vaccination status (whether or not, and date). The Pfizer COVID-19 vaccine was the only vaccine approved in Israel for the 12-17-year-age group and was, therefore, the one included in our study. Data cutoff was August 31, 2021, by which time, the vaccination had already been available for all participants aged 12 years and older for approximately two months, with the recommendation to complete vaccinations before the beginning of the school year on September 1, 2021.

Statistical Analysis

The data were extracted into a central data table which was anonymized to allow statistical analysis. Proportions were compared by chi-squared test and proportion test as appropriate. Cox regression was performed to analyze the time-dependent proportional probability (hazard) as to vaccinating, adjusting for age, sex, ethnicity, ADHD status, and allowing for censoring (i.e. removing from analysis at the time of the event), due to infection prior to vaccination.

Results

A total of 46,544 subjects were included in the study, of whom, 8241 (17.7%) were diagnosed with ADHD. [Table 1](#) presents the COVID-19 infection status of the study population. One striking effect was the very high proportion (9.9%) of ultra-orthodox Jewish adolescents infected with COVID-19. A total of 3% (247/8421) of adolescents

Table 1. Characteristics and clinical details of COVID-19 infection status.

Characteristic	Total (% of total)	No. PCR-COVID-19 positive (%)	No. PCR-COVID-19 negative ^a (%)	p-value
N	46,544	1740	44,804	
Mean age, yr (SD)	14.4 (1.7)	14.5 (1.7)	14.4 (1.7)	.0002
Age (yr)				
12-15	32301 (69.4%)	1162 (3.6%)	31139 (96.4%)	.0169
16-17	14243 (30.6%)	578 (4.1%)	13665 (95.9%)	
Sector				
Ultraorthodox Jew	11481 (24.7%)	1137 (9.9%)	10344 (90.1%)	<.0001
Arab	4014 (8.6%)	103 (2.6%)	3911 (97.4%)	
General	31049 (66.7%)	500 (1.6%)	30549 (98.4%)	
Sex				
Female	22685 (48.7%)	863 (3.8%)	21822 (96.2%)	
Male	23859 (51.3%)	877 (3.7%)	22982 (96.3%)	
ADHD patients	8241 (17.7%)	247 (3.0%)	7994 (97.0%)	

ADHD, attention-deficit/hyperactivity disorder; COVID-19, Coronavirus disease.

^aNo PCR-COVID-19 negative includes adolescents who were tested for PCR-COVID-19 and found to be negative and adolescents who were not tested for PCR-COVID-19.

in the ADHD group and 3.9% (1493/38,303) of adolescents in the non-ADHD group were PCR-COVID-19 positive ($p < .0001$). Hence, it seems, that the adolescents in the ADHD group in our study were somewhat less prone to be infected with COVID-19.

Table 2 presents the demographic characteristics of vaccinated and unvaccinated ADHD patients aged 12-17 years. Among ADHD patients, the older adolescents were more likely to be vaccinated: 48.8% of ADHD patients aged 12-15 years were vaccinated, compared to 59.6% of ADHD patients aged 16-17 years were vaccinated ($p < .001$). The ultra-orthodox Jewish and Arab adolescents in the ADHD group were far less likely to be vaccinated (22.9% and 34.6%, respectively), compared to the adolescents with ADHD in the general population (60.5%), $p < .001$. Girls were also somewhat more likely to be vaccinated (55.4% girls vs. 50.9% boys).

We further studied the relative tendency of adolescents with ADHD versus adolescents without ADHD to receive the second vaccine and the booster administered in August 2021, as presented in **Table 3**. By the end of the process, many of the older adolescents had been vaccinated with at least two vaccinations by the end of August 2021, leaving the difference insignificant. However, the booster uptake was very different for the two groups: 1.2% (32/2652) of adolescents with ADHD aged 12-15 years received the booster dose, compared to 1.4% (164/11,854) of adolescents with non-ADHD aged 16-17 years ($p = .48$). A total of 45.8% (765/1671) of adolescents with ADHD aged 16-17 years received the booster dose, compared to 42.5% (2748/6468) of adolescents with non-ADHD aged 16-17 years ($p < .001$).

Table 2. Characteristics and clinical details of vaccinated and unvaccinated adolescents aged 12-17 years in the ADHD and non-ADHD groups.

	ADHD				Non ADHD				p
	Total	Vaccinated	%	Unvaccinated	Total	Vaccinated	%	Unvaccinated	
Total	8241	4323	52.5%	3918	38303	18322	47.8%	19981	52.2%
Mean age, yr (SD)	14.73 (1.69)	14.32 (1.68)			14.57 (1.71)	14.32 (1.68)			<0.001
12-15yr	5437	2652	48.8%	2785	26864	11854	44.1%	15010	55.9%
16-17yr	2804	1671	59.6%	1133	11439	6468	56.5%	4971	43.5%
Arab	295	102	34.6%	193	3719	1316	35.4%	2403	64.6%
Ultra-orthodox Jew	1609	369	22.9%	1240	9872	2321	23.5%	7551	76.5%
General	6337	3852	60.8%	2485	24712	14685	59.4%	10027	40.6%
Male	5380	2737	50.9%	2643	18479	8688	47.0%	9791	53.0%
Female	2861	1586	55.4%	1275	19824	9634	48.6%	10190	51.4%
PCR-COVID-19- positive	247	15	6.1%	232	1493	92	6.2%	1401	93.8%

ADHD, attention-deficit/hyperactivity disorder; COVID-19, Coronavirus disease.

Table 3. Vaccination status in adolescents in the ADHD and non-ADHD groups^a.

	Total	Adolescents In the ADHD group N (%)	Adolescents in the non-ADHD group N (%)	P-value
Ages 12–15 yr				
Total	32,301	5437 (16.8%)	26864 (83.2%)	
Vac1	16,060	2889 (18%)	13171 (82%)	.0016
Vac2	14,506	2652 (18.3%)	11854 (81.7%)	.0001
Booster	196	32 (16.3%)	164 (83.7%)	.9260
Ages 16–17 yr				
Total	14,243	2804 (19.7%)	11439 (80.3%)	
Vac1	8762	1801 (20.6%)	6961 (79.4%)	.1140
Vac2	8139	1671 (20.5%)	6468 (79.5%)	.1333
Booster	3513	765 (21.8%)	2748 (78.2%)	.0060

^aIn most cases, the 12–15-year-old group was not eligible for the booster vaccination.

To adjust for the bias associated with different COVID-19 infection rates, we performed survival analysis which allowed for censoring (that is removing from the study at independent event time while maintaining the contribution of their time in the study until the event) at end of the study, and also upon becoming infected before vaccination. The cumulative hazard results of vaccination (the overall uptake allowing for infection) are shown in [Figures 1 and 2](#) and Cox regression, in [Table 4](#).

Both the unadjusted Kaplan-Meier model, and the adjusted semi-parametric Cox regression demonstrate that the vaccination rate was higher in the adolescents in the ADHD group compared to the adolescents in the non-ADHD group. There were two peaks of vaccination coverage: the first was around 200 days since the beginning of the vaccination roll-out (at the beginning time point of adolescent vaccinations) and the second around 270 days since the start of the vaccination roll-out (September 2021, at the beginning of the new study year).

[Figure 3](#) depicts the reduction in vulnerability as determined by vaccination status among the various sectors. Initially, the COVID-19 vaccine was not released to the general youth population, but even when it was permitted for the 16-17-year-old age group, uptake was slow, possibly due to the lockdown when the vaccination was permitted also for the younger 12-15-year-old age group, uptake was considerable but with a striking contrast between sectors; the ultra-orthodox Jewish sector remained very hesitant to vaccination, as, to a lesser extent, did the Arab population.

Discussion

COVID-19 has had devastating consequences worldwide. Untreated subjects with ADHD seem to constitute a risk group for COVID-19 infection with poor outcomes.^{15–17} In our study, we found that older adolescents with ADHD, aged 16-17 years, were more likely to

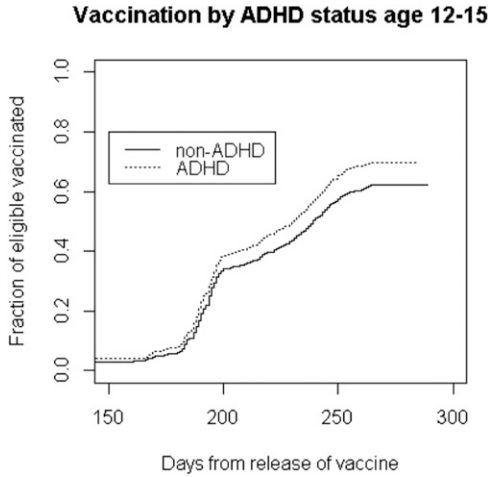


Figure 1. Vaccination by ADHD status for 12–15-year-olds. ADHD patients, dotted line. Non-ADHD, dashed

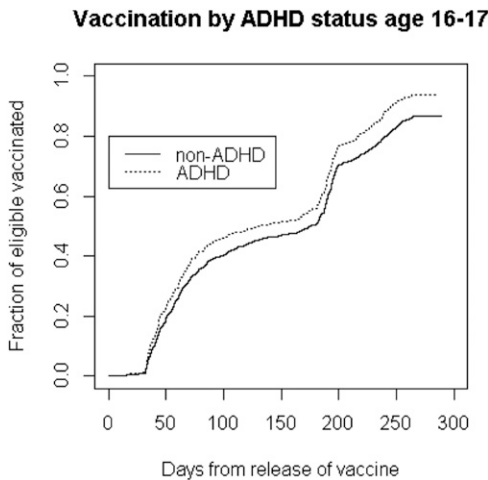


Figure 2. Vaccination by ADHD status for 16–17-year-olds. ADHD patients, dotted line. Non-ADHD, dashed

be vaccinated. The ultra-orthodox Jewish and Arab adolescents in the ADHD group were far less likely to be vaccinated (22.9% and 34.6%, respectively), compared to the adolescents with ADHD in the general population (60.5%).

Table 4. Proportional hazard results for vaccination by group

	Hazard ratio	CI lower 95%	CI upper 95%	P-value
ADHD	1.047618	1.013238	1.083165	.0063
Female	1.035326	1.008683	1.062672	.0091
Arab	0.454319	0.429861	0.480169	<.0001
Ultra-orthodox	0.383584	0.36939	0.398324	<.0001

ADHD, attention-deficit/hyperactivity disorder.

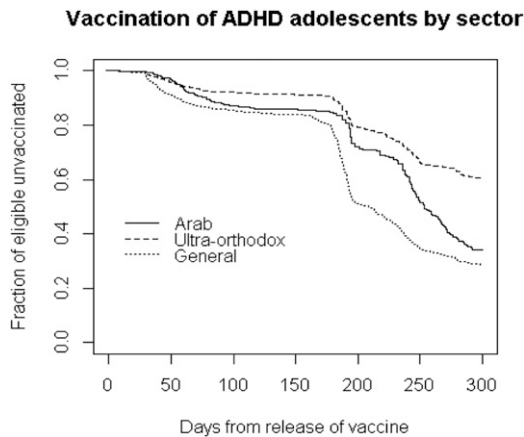


Figure 3. Vaccination of adolescents in the ADHD group by sector. Arabs, complete line. Ultra-orthodox Jews, dashed line. General Jews, dotted line

Merzon et al. reported their results regarding 1,416 subjects, aged 2 months-103 years in Israel who were COVID-19-positive between February 1st and April 30, 2020. They found that the risk for COVID-19-positive was higher in untreated subjects with ADHD compared to subjects without ADHD.¹⁵ In a separate study, Merzon et al. assessed 1,870 COVID-19 positive patients, aged 5-60 years, in Israel from February to June 2020. They concluded that ADHD is associated with poorer outcomes in COVID-19 infection.¹⁶

Cohen et al.¹⁷ reported 64,409 subjects aged 6-18 years in Israel, of whom 13,300 (20.65%) were diagnosed with ADHD. They found, that subjects with ADHD who were medically treated had a significantly lower likelihood to be infected with COVID-19 than untreated subjects.

The COVID-19 pandemic affected both children with ADHD and their parents. Children and adolescents with ADHD are more likely than those without ADHD to experience increased symptoms of inattention, hyperactivity/impulsivity, opposition

defiance, anger, anxiety, sluggish cognitive tempo, and depression during the COVID-19 pandemic.²²⁻²⁴

The COVID-19 pandemic disrupted the lifestyles and daily routines and deteriorated the behavioral problems in children with ADHD²⁵⁻²⁷; it also disrupted the social and medical support for parents.²⁸ Vaccine administration in adolescents in Israel requires formal consent from them as well as from their parents and therefore this might be a limiting or encouraging factor in COVID-19 vaccine uptake, depending on parental decisions.

There are multiple factors related to caregivers' hesitancy to vaccinate their children against COVID-19.^{24,29-35} Low vaccination compliance is linked to concern about the safety and efficacy of the COVID-19 vaccines^{29,31,34,35} and low confidence level in the knowledge about COVID-19 vaccines.³⁰ Research has found that caregiver concerns regarding COVID-19 infection are related to low hesitancy to vaccinate their children.^{34,35} A caregiver's exposure to negative information related to COVID-19 vaccination,²² a caregiver's lower education level,²⁹⁻³¹ and a younger age of the child^{30,32} are also related to increased hesitancy for caregivers to vaccinate their children.

Healthcare workers (including physicians and nurses) are considered reliable sources of information and have the opportunity to influence an individual's choice to accept the vaccine. For adolescents and adults who initially present as unwilling to be vaccinated, trying to persuade them with facts and scare tactics may cause more reluctance and resistance.³⁶ Motivational interviewing is a patient education or health coaching approach which is standardized and consistently demonstrated as causally and independently associated with positive behavioral outcomes.^{37,38} There is strong evidence that the use of motivational interviewing by health care workers in a wide range of challenging behaviors, including treatment adherence and vaccine hesitancy is a powerful tool.^{37,39}

The implications of COVID-19 morbidity and mortality on adolescents with ADHD and their parents may account for the higher vaccination rate of adolescents in the ADHD group compared to adolescents in the non-ADHD group in our study population.

Scherer et al.⁴⁰ evaluated the acceptability of adolescent COVID-19 vaccination and self-reported factors increasing vaccination. They found that obtaining more information about adolescent COVID-19 vaccine safety and efficacy, as well as school COVID-19 vaccination requirements, were the most commonly reported factors that would increase vaccination intentions among both parents and adolescents. Other potential factors that might increase vaccination included the prevention of spreading COVID-19 to family and friends, allowing resumption of or increase in social activities or traveling.⁴⁰ It is our opinion that massive publicity using different public and social media (school, TV, radio, Twitter, Facebook, and so on) on the safety and efficacy of COVID-19 vaccination for adolescents may help increase confidence in adolescents (in general, and ADHD patients, specifically) and vaccination coverage.

In our study, there was a very high proportion of ultra-orthodox Jewish adolescents who were infected with COVID-19 (9.9% of the participants were found positive); moreover, the ultra-orthodox Jewish adolescents diagnosed with ADHD were far less likely to be vaccinated (22.9%). These findings are similar to those reported by Muhsen et al.⁴¹ on a nationwide analysis of population group differences in the COVID-19 epidemic in the elderly population in Israel. Their results showed that vaccine uptake was lower amongst Arab and ultra-orthodox Jewish populations and low socioeconomic status communities.⁴¹

Several studies counted many other variables for the lower uptake of the COVID-19 vaccine amongst ultra-orthodox Jews and Arabs in Israel. These variables included hesitancy or lack of vaccine confidence, concerns about vaccine safety, concerns about fertility risks, their limited exposure to the media, mistrust of government, and insufficient transportation to vaccination sites.^{42–44}

We suggest performing targeted interventions specifically appropriate for the Jewish ultra-orthodox and Arab sectors, in order to overcome potential technical, linguistic, cultural, and religious barriers against vaccination in these minority groups. Tailored campaigns for these populations are obviously needed, especially through religious, health care, educational, and municipal leaders whom these populations trust.

Study Strengths and Limitations

The main strength of the study was its real-world, population-based nature. However, our study has a few limitations. First, our study included the adolescent population of a single Israeli district. Second, due to the retrospective nature of the study, we were unable to infer causality. Third, adolescents in our study were not comprehensively diagnosed with ADHD or evaluated for ADHD, rather the ADHD group was classified based on having had a prior diagnosis or if they had purchased at least two ADHD medication prescriptions. Fourth, we were unable to retrieve the data from the electronic database, such as the severity of ADHD symptoms, or its presentation (predominantly inattentive, predominantly hyperactive, or combined). We did not assess data regarding the COVID-19 presenting symptoms and severity, as well as adverse clinical outcomes (hospitalization, mechanical ventilation, and death). We did not include possible psychiatric comorbidities (such as oppositional defiant disorder, conduct disorders, alcohol, and drug abuse, autism spectrum disorder, etc.). We also did not analyze other medical comorbidities (such as asthma, obesity, diabetes mellitus, smoking, etc.), which might have influenced the decision to vaccinate or not vaccinate against COVID-19. Fifth, we did not consider the parental factor involved in the decision to vaccinate.

In conclusion, the general population of Jewish adolescents with ADHD achieved equivalent and indeed higher COVID-19 vaccination rates compared to their non-ADHD counterparts. The vaccine uptake was lower amongst Arab and ultra-orthodox Jewish populations. We suggest that large-ADHD population studies be performed in

order to evaluate the COVID-19 vaccination rate among adolescents in this patient population.

Author Contributions

Dr. Vered Shkalim Zemer conceptualized and designed the study and drafted the initial manuscript. Dr. Moshe Hoshen conceptualized and designed the study, analyzed data, and drafted the initial manuscript. Dr. Maya Gerstein conceptualized and designed the study and drafted the initial manuscript. Dr. Yael Richenberg conceptualized and designed the study and drafted the initial manuscript. Dr. Eyal Jacobson conceptualized and designed the study and drafted the initial manuscript. Cohen Moriya conceptualized and designed the study and drafted the initial manuscript. Prof. Avner Herman Cohen conceptualized and designed the study and drafted the initial manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: This study was approved by the community institutional review board which adheres to the Declaration of Helsinki and its amendments, and was exempt from individual informed consent.

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