Variables Associated With COVID-19 Vaccination Among Israeli Adolescents and the Need for Targeted Interventions

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Background: We aimed to elucidate variables associated with coronavirus disease 2019 (COVID-19) vaccine compliance in adolescents and devise targeted interventions. Our secondary aim was to compare the rates of severe acute respiratory syndrome coronavirus 2 infection, hospitalizations and deaths between vaccinated and unvaccinated adolescents.

Methods: A retrospective review of electronic medical records was performed on all adolescents 12–17 years of age registered at Clalit Health District in Israel during January 1, 2021, to November 18, 2021, with characterization by vaccination status against COVID-19. Univariate and multivariable analyses were employed to identify predictors of vaccination.

Results: Of the 43,919 subjects included in the study, 28,207 (64.2%) were vaccinated. Non–ultraorthodox Jewish adolescents had a higher vaccination rate than the minorities Arabs or ultraorthodox Jews (72.5%, 66.2% and 40.5%, respectively, $P < 0.001$). Adolescents of high socioeconomic status had nearly 2-fold higher vaccination rates than those of low socioeconomic status (80.4% vs 42.3%; $P < 0.0001$). Adolescents 16–17 years old had a higher rate of COVID-19 vaccination than those 12–15 years old (72.5% vs 60.6%, $P < 0.001$), as were girls versus boys (64.7% vs 63.8%, $P = 0.047$). Multivariate analysis identified 3 independent variables that were significantly ($P < 0.001$) associated with low vaccination: ultraorthodox sector, Arab population, and underlying obesity (hazard rations 0.42, 0.72 and 0.84, respectively). Vaccination was significantly associated with reduced severe acute respiratory syndrome coronavirus 2 infection, hospitalization and death ($P < 0.001$).

Conclusion: This study highlights several pediatric populations with low COVID-19 vaccine compliance. Targeted interventions aimed at these populations are suggested with consideration of their special cultural, social and societal characteristics.

Key Words: coronavirus-2019, COVID-19 vaccine, adolescents, comorbidity, vaccine hesitancy

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Coronavirus disease 2019 (COVID-19), caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a current worldwide pandemic with enormous morbidity and mortality.[1] In the initial stages of the pandemic, children and adolescents were infrequently affected and had a relatively mild course of the disease.[2–4] With the evolution of the epidemic and the appearance of new SARS-CoV-2 variants, children and adolescents were infected in increasing rates. Furthermore, as the rate of immunization against COVID-19 of adults increased, younger individuals accounted for an increased proportion of the infections.[5]

Two years into the pandemic, cumulative evidence demonstrates that adolescents and children can also present with a severe course of COVID-19 and develop complications, such as the pediatric inflammatory multisystem syndrome and long COVID.[6–8] Significant morbidity and, rarely, mortality are more prominent in children with underlying medical conditions, including smoking, obesity and attention-deficit hyperactivity disorder.[9,10] It has been also shown that adolescents and children infected with SARS-CoV-2 play an important role in the transmission of the virus.[11,12]

Vaccination is the major practice to decrease SARS-CoV-2 infection rates and COVID-19 disease. After the demonstration of the safety, immunogenicity and efficacy of the Pfizer–BioNTech COVID-19 vaccine in adolescents,[13] it was approved by the Centers for Disease Control and Prevention in the United States[14] and by the Israeli Health Ministry for use in adolescents 12–15 years old.[15] A campaign for adolescent vaccination was launched by health authorities, including the Israel Pediatric Association, emphasizing its safety and efficacy.[13,16] However, according to national data, as of the beginning of February 2022, only about 60% of adolescents had been vaccinated.[17]

The primary aim of the present study was to elucidate variables associated with acceptance of COVID-19 vaccine in adolescents, by comparing vaccinated and nonvaccinated individuals and the number of doses received, to improve targeted interventions in populations with low vaccination rates.

Israel's population accounts for 9.4079 million people and has diverse ethnic and cultural subpopulations. Approximately 74% are Jews, 21% are Arabs and 5% are of other ethnicities.[18] In the Jewish population, about 12% belong to a distinct subpopulation, which is religiously ultraorthodox.[19] In our study, we divided the population to 3 distinct demographic groups, which we referred to as "sectors": nonultra-orthodox Jews, ultraorthodox Jews and Arabs. These sectors differ in their cultural and societal characteristics. The Arab and ultraorthodox Jewish populations have high fertility rates, are younger compared with the nonultra-orthodox Jewish population and tend to live in close communities with

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limited access to the general media.[19,20] The ultraorthodox Jewish community in Israel is a very close community, which has, by choice, little contact with the general population. Many ultraorthodox Jewish men will choose full-time study in religious schools called Yeshivas, which are crowded, closed spaces. Additional characteristics include the central role of the Rabbi in community actions and behaviors, limited income, large families crowded in small apartments in overpopulated neighborhoods and strong community bonds.[19,20]

In addition, variables such as age, gender and socioeconomic status (SES), which affect vaccine acceptance,[21,22] were also studied. A secondary aim of the study was to compare the rates of SARS-CoV-2 infection, hospitalizations and deaths between vaccinated and unvaccinated adolescents.

METHODS

Setting and Data Source

Clalit Health Services insures about 5 million (54%) of the Israeli population. It maintains a comprehensive computerized database, continuously updated regarding subjects' demographics, community and outpatient visits, laboratory results, hospitalizations and medication prescribed and purchased. During each physician visit, diagnoses are recorded according to the International Classification of Diseases, Ninth Revision.

Study Population

The study population comprised all individuals 12–17 years old who were registered in Clalit Health Services during the study period from January 1, 2021, to November 18, 2021, in the Dan-Petach Tikva administrative district. This district comprises ~500,000 members, with a fairly large proportion of young persons, encompassing large towns of mainly Jewish origin, and a few Arab towns and villages.

The study period was chosen because the Pfizer–BioNTech 162b2 COVID-19 vaccine became available for adolescents ≥16 years in January 2021 and for those 12–15 years old in June 2021. The study population was divided to 2 groups: unvaccinated and vaccinated with at least 1 dose of the vaccine, with further subgrouping according to the number of doses received.

The data collected from the electronic database included demographic variables, including age, gender, sector, SES, vaccinations for COVID-19 (first, second and third doses) and influenza (as influenza vaccination was associated with reduced rates of SARS-CoV-2 infection), information regarding polymerase chain reaction (PCR) testing (sampling dates and results), comorbidities and the date of any COVID-19-related hospitalization and mortality. The chosen covariates were based on previous studies.[21] The study was approved by the Clalit Community Institutional Review Board (approval No. **0087-21**-COM).

Statistical Analysis

The data were extracted into a central data table, which was anonymized for the statistical analyses. Descriptive statistics were used to report demographic and clinical variables of the vaccinated and unvaccinated study groups. Proportions were compared by χ^2 or Fisher exact test, as appropriate, and continuous variables by Student *t* test or Mann-Whitney, as appropriate. Logistic regression was performed to analyze the adjusted odds ratio of vaccination as the dependent variable, based on known predictors of vaccination (age, gender, sector, SES, asthma, obesity and past influenza vaccination). Additional variables found significant using univariate analysis (such as smoking status and malignancy) were also introduced in the multivariate model and were left in the model only if they were found significant ($P < 0.05$) in the multivariate analysis. As sector in Israel was known to be a predictor of vaccination (as well as of infection), a survival curve of vaccination by sector was produced with adjustment for age and gender. Analysis was performed with R software (versions 4.1.0; R Core Team [2020]. R: A language and environment for statistical computing. The Foundation for Statistical Computing, Vienna, Austria), using "survival" and "survminer" packages.

RESULTS

All 43,919 adolescents 12–17 years old in the district were included in the study, of whom 69.5% were 12–15 years and 30.5% were 16–17 years old. There were 21,451 females (48.8%) and 22,468 males (51.2%). A total of 40,055 of the study group were Jews (91.2%) and 3864, Arabs (8.8 %).

Variables Associated With COVID-19 Vaccination Rates

Of the whole adolescent study group, 28,207 (64.2%) received at least 1 single dose of the vaccine. Table 1 presents the demographic details, status of COVID-19 and influenza vaccination, and high-risk populations for COVID-19 morbidity and mortality.

Adolescents 12–15 years old had a significantly lower vaccination rate than those 16–17 years old (60.6% vs 72.5%; $P < 0.001$). Females were more likely to be vaccinated than males (64.7% vs. 63.8%, P=0.047). Sectorial affiliation showed a highly significant effect on vaccination rates, which was 72.5% among nonultra-orthodox Jewish, but only 40.5% among ultraorthodox Jewish, and 66.2% among Arabs (P<0.001). Vaccination rates were also significantly related to SES, being 80.4% in adolescents of high SES compared with only 42.3% in low SES (P<0.001). Adolescents who had received previous vaccination against seasonal influenza were vaccinated against COVID-19 in higher rates than those not vaccinated against influenza (75.5% vs 60.4%; $P < 0.001$). Vaccination rates by underlying medical conditions are detailed in Table 1. Of note, smoking adolescents and those with obesity, factors with increased risk of severe COVID-19, had relatively low vaccination rates of 53.5% and 59.8%, respectively; as opposed, adolescents with asthma had a high vaccination rate of 72.3% ($P = 0.04$).

Figure 1 depicts the reduction with time of the number of nonvaccinated adolescents by sectorial association, adjusted for gender and age. The time presented is from the point at which vaccination was approved by Israeli Ministry of Health, initially for ages 16–17 and then for ages 12–15. As can be seen, the vaccination progress with time was slowest among ultraorthodox Jews, relatively slow in the Arab population and fastest among nonultraorthodox Jews.

Characteristics by Vaccine Doses Received

Of the 28,207 adolescents who were vaccinated against COVID-19, 3861 (13.7%) received only 1 dose of the vaccine, 20,224 (71.7%) received 2 doses and 4122 (14.6%) received 3 doses. Characterizations of the study group by the number of vaccine doses received are shown in Table 2. Compared with the whole population, a significantly higher number of vaccine doses were given to adolescents 16–17 years old ($P < 0.001$), females ($P = 0.007$) and to those previously vaccinated against influenza ($P < 0.001$). Ultraorthodox Jews, Arabs and adolescents of low SES had significantly lower relative rates of receiving 2 or 3 doses of the vaccine ($P < 0.001$). The number of vaccine doses given to adolescents with the various medical conditions is also described in detail in Table 2.

TABLE 1. Variables Associated With Adolescent Vaccination (≥1 dose) or No Vaccination Against COVID-19

Variable	Total	Vaccinated, N (%)	Unvaccinated, N (%)	*P* Value
Study cohort	43,919	28,207 (64.2)	15,712 (35.8)	
Age group, years				
12–15	30,510	18,492 (60.6)	12,018 (39.4)	<0.001
16–17	13,409	9715 (72.5)	3694 (27.5)	
Gender				
Male	22,468	14,330 (63.8)	8138 (36.2)	0.047
Female	21,451	13,877 (64.7)	7574 (35.3)	
Sector				
Non–ultraorthodox Jews	29,490	21,375 (72.5)	8115 (27.5)	<0.001
Ultraorthodox Jews	10,565	4275 (40.5)	6290 (59.5)	
Arabs	3864	2557 (66.2)	1307 (33.8)	
Socioeconomic status				
Low	10,709	4530 (42.3)	6179 (57.7)	<0.001
Middle	16,705	10,415 (62.3)	6290 (37.7)	
High	16,505	13,262 (80.4)	3243 (19.6)	
Influenza vaccination (past 3 years)				
Vaccinated	11,255	8492 (75.5)	2763 (24.5)	<0.001
Unvaccinated	32,664	19,715 (60.4)	12,949 (39.6)	
Underlying conditions				
Obesity (BMI >95 percentile)	17,380	10,400 (59.8)	6980 (40.2)	0.002
Type 1 diabetes	107	74 (69.2)	33 (30.8)	0.789
Type 2 diabetes	131	93 (71)	38 (29)	0.335
Asthma	2639	1907 (72.3)	732 (27.7)	0.040
Smoking	274	146 (53.3)	128 (46.7)	0.127
Former smoker	260	179 (68.8)	81 (31.2)	<0.001
Malignancy	144	111 (77.1)	33 (22.9)	0.468

[*]Socioeconomic status was defined according to the states Central Bureau of Statistics classification.
BMI indicates body mass index; COVID-19, coronavirus disease-19.

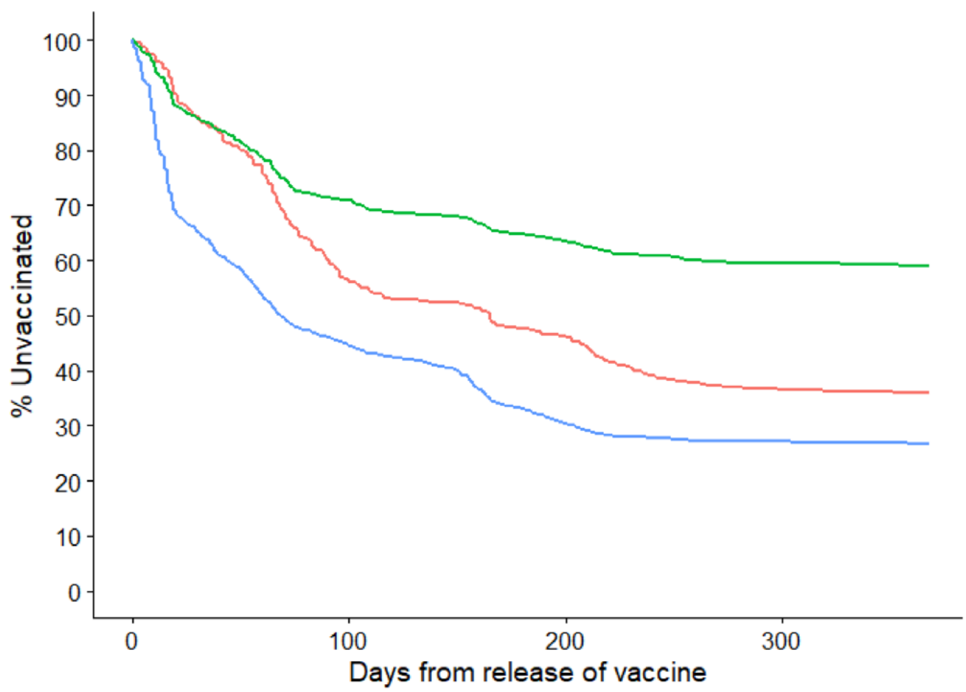

FIGURE 1. Kaplan-Meier-like adjusted survival curve showing the reduction with time of nonvaccinated adolescents by sector, after adjustment for gender and age. Blue line, non–ultraorthodox Jews; green line, ultraorthodox Jews; red line, Arab population. full color online

Multivariate Analysis

Table 3 presents the multivariate analysis of the factors related to vaccination in adolescents. Four variables were independently and significantly associated with COVID-19 vaccination rate. Belonging to the minority sectors of ultraorthodox Jewish or Arab, and being obese were negatively associated with being vaccinated (odds ratio = 0.42, 0.72, and 0.84, respectively; $P < 0.001$), whereas suffering from asthma was positively associated with being vaccinated (odds ratio = 1.09; $P < 0.001$).

TABLE 2. Characteristics of the Adolescent Study Group by the Number of COVID-19 Vaccine Doses Received

		Number of Vaccinations Received			
Variable	Total	1st Vaccine, N (%)	2nd Vaccine, N (%)	3rd Vaccine, N (%)	P
Study cohort	28,207	3861 (13.7)	20,224 (71.7)	4122 (14.6)	
Age group, years					
12–15	1842	2653 (14.3)	1570 (85.4)	49 (0.3)	<0.001
16–17	9715	1208 (12.4)	4434 (45.6)	4073 (41.9)	
Gender					
Male	14,330	2050 (14.3)	1044 (71.3)	2056 (14.3)	0.007
Female	13,877	1811 (13.1)	10,000 (72.1)	2066 (14.9)	
Sector					
Non–ultraorthodox Jews	21,375	1866 (8.7)	16,055 (75.1)	3454 (16.2)	<0.001
Ultraorthodox Jews	4275	1317 (30.8)	2488 (58.2)	470 (11)	
Arabs	2557	678(26.5)	1681 (65.7)	198 (7.7)	
Socioeconomic status*					
Low	4530	1231 (27.2)	2829 (62.5)	470 (0.4)	<0.001
Middle	10,415	1737 (16.7)	7281 (69.9)	1397 (13.4)	
High	13,262	893 (6.7)	10,114 (76.3)	2255 (17)	
Influenza vaccination (past 3 years)					
Vaccinated	8492	968 (11.4)	6424 (75.6)	1100 (13)	<0.001
Unvaccinated	19,715	2893 (14.7)	13,800 (70)	3022 (15.3)	
Underlying conditions					
Obesity (BMI >95 percentile)	10,400	1526 (14.7)	7846 (75.4)	1028 (9.9)	<0.001
Type 1 diabetes	74	7 (9.5)	52 (70.3)	15 (20.3)	0.270
Type 2 diabetes	93	9 (9.7)	65 (69.9)	19 (20.4)	0.192
Asthma	1907	192 (10.1)	1290 (67.6)	425 (22.3)	<0.001
Smoking	146	14 (9.6)	93 (63.7)	39 (26.7)	0.001
Former smoker	179	24 (13.4)	123 (68.7)	32 (17.9)	0.461
Malignancy	111	10 (9)	71 (64)	30 (27)	0.001

*Socioeconomic status was defined according to the states Central Bureau of Statistics classification.
BMI indicates body mass index; COVID-19, coronavirus disease-19.

TABLE 3. Multivariate Regression for the Likelihood of COVID-19 Vaccination Among Adolescents*

Variable	Odds Ratio (95% CI, Lower–Upper)	P
Ultraorthodox Jews	0.4247 (0.4105–0.4394)	<0.001
Arab sector	0.7271 (0.6974–0.7580)	<0.001
Obesity	0.8418 (0.8211–0.8630)	<0.001
Asthma	1.0935 (1.0422–1.1472)	<0.001

*The regression model analyzed the adjusted odds ratio of vaccination as the dependent variable. Predictors of vaccination that were significant by univariate analysis were introduced in the multivariate model and left in the model only if they were found significant ($P < 0.05$) in the multivariate analysis.
CI indicates confidence interval; COVID-19, coronavirus disease-19.

Outcomes of Vaccination

Of the 28,207 adolescents who were vaccinated against COVID-19, 2085 (7.4%) were PCR-positive for SARS-CoV-2 in the period after vaccination, compared with 3604/15,712 (22.9%) among unvaccinated adolescents ($P < 0.001$). The number of the vaccine doses received was important as well: PCR-positivity was noted in 1518/3861 (39.3%) of those receiving a single vaccine dose as opposed to 567/24,346 (2.3%) of those receiving 2 or 3 doses ($P < 0.001$). Hospitalization rates were 2/28,207 (0.007%) and 9/15,712 (0.057%) among vaccinated and unvaccinated adolescents, respectively ($P < 0.001$). No death was recorded among adolescents who were vaccinated against COVID-19 in our study group, compared with 7 adolescents (0.04%) in unvaccinated ($P < 0.001$), mostly in those with underlying medical conditions.

DISCUSSION

The present study elucidated variables associated with COVID-19 vaccination among adolescents and describes new findings in this age group that have practical implications for increasing vaccine acceptance and preventing the COVID-19-associated morbidity and mortality. The first findings are that 2 Israeli minority groups, who have also unique cultural characteristics—namely Israeli Arabs and ultraorthodox Jews—had substantially lower vaccination rates than the nonultra-orthodox Jews. In addition, a relatively high proportion (~30%) of these populations received only a single dose of the vaccine.

The Arab sector, which consists of ~21% of the Israeli population,[18] had a low vaccination rate of 66.2.5% with a high significance also in multivariate analysis. This is consistent with previous reports in Israeli adults ≥60 years and 20–39 years old during the initial phases of COVID-19 vaccination, in whom vaccination rates were generally higher than in adolescents.[21] Targeted interventions specifically appropriate for this sector are needed to overcome potential technical, linguistic, cultural and religious barriers against vaccination in this minority group. Cultural factors play a major role, for example, the fear of fertility problems associated with the COVID-19 vaccine.[22] Key messages should be distributed by local opinion and religious leaders that this sector trusts.

Another minority, the ultraorthodox Jewish sector, had the lowest vaccination rate of 40.5% with a high significance also in multivariate analysis. This is also in accordance with the findings related to COVID-19 vaccination in the adult population.[21,22] Many of the barriers that were described above regarding vaccination of the Arab sector apply also to the ultraorthodox Jews. In particular, this sector, which consists of ~12% of the Jewish population, has an independent education system with a central role of the Rabbi in community actions and behaviors and a very limited exposure to the mainstream media, with special concerns regarding the possible adverse effect of the COVID-19 vaccine on fertility.[19,20] Tailored campaign for this sector is obviously needed, especially through religious leaders whom this population trusts.

Adolescents of low SES had a very low COVID-19 vaccination rate of 42.3%, which was highly significant by univariate analysis. These results are similar to those published by Caspi et al[23] among individuals over 60 years old. Although vaccination against COVID-19 is available free of charge to all Israeli residents, they explained these results by lower accessibility of the low SES population to health care resources. However, in our study, SES did not reach significance in the multivariate analysis, whereas the minority sectors did. This implies that the effect of SES on vaccination rates was possibly secondary to the relatively low SES of the minority sectors, which is well documented,[24] in addition to other cultural and societal factors discussed above.

Regarding adolescents with underlying conditions, obesity was significantly associated with low COVID-19 vaccination rates in the univariate and the multivariate analysis. This finding is very unfortunate because obesity is a confirmed risk factor for complicated and even fatal course of COVID-19.[9,25–27] It probably reflects insufficient awareness of this risk factor and a difficulty of the obese adolescent and/or his parents to adhere to healthcare recommendations,[28] dictating the need for a targeted intervention in this population, highlighting its high vulnerability to severe COVID-19 morbidity and complications.

Multiple factors relate to caregivers' hesitancy to vaccinate their children against COVID-19.[29–36] These include concerns on the safety and efficacy of the vaccines,[29–32] low confidence in the knowledge about it,[33] exposure to negative information related to COVID-19 vaccination[34] and caregiver's lower education level.[30,35,36] These should be acknowledged in vaccine campaigns.

Although a secondary aim of the study, with the ~500,000 members in the district and the ~44,000 adolescents who were included in the study, some effectiveness parameters were noted. Namely, confirmed SARS-CoV-2 positivity by PCR was detected in lower rates in the vaccinated adolescents compared with unvaccinated individuals. Hospitalization rates were also lower in vaccinated compared with unvaccinated adolescents; no death was recorded among adolescents who were vaccinated against COVID-19, compared with 7 adolescents (0.04%) among unvaccinated. These findings highlight the current understanding that COVID-19 in children and adolescents can progress to severe disease,[9,37–41] with a potential of 2 significant consequences: pediatric inflammatory multisystem syndrome[8,39–41] and long COVID,[8] and even deaths, especially in high-risk populations.[9,37,38]

The main strength of this study is that it includes a high number of adolescents who were comprehensively followed with updated data regarding their demographics, vaccination and health. This study has several limitations. First, as vaccination rates were analyzed in a single district and not on a national level, generalization of the findings is limited. Nevertheless, the district included ~500,000 individuals of diverse sectors and living conditions. Second, there were unmeasured confounding factors (eg, wearing masks and close contact with persons with COVID-19), which may have biased the effectiveness results. Third, the relatively short follow-up duration did not allow conclusions about the long-term effect of the booster dose. Fourth, our observations were made before Omicron emerged as a leading variant of SARS-CoV-2, and therefore may not apply to that variant.

In conclusion, the present study examined adolescent vaccination against COVID-19 and demonstrated that the minority sectors and those with obesity have a significant low vaccine acceptance. Targeted interventions aimed at these populations are recommended with consideration of their special cultural, social and societal characteristics, as detailed above.

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