Factors associated with COVID-19 non-vaccination in adolescents hospitalized without COVID-19

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Abstract

Background: Pfizer-BioNTech COVID-19 vaccine received emergency use authorization for persons ≥16 years in December 2020 and for adolescents 12-15 years in May 2021. Despite the clear benefits and favorable safety profile, vaccine uptake in adolescents has been suboptimal. We sought to assess factors associated with COVID-19 non-vaccination in adolescents 12-18 years of age.

Methods: Between June 1, 2021 and April 29, 2022, we assessed factors associated with COVID-19 non-vaccination in hospitalized adolescents ages 12-18 years enrolled in the Overcoming COVID-19 vaccine effectiveness network. Demographic characteristics and clinical information were captured through parent interview and/or electronic medical record abstraction; COVID-19 vaccination was assessed through documented sources. We assessed associations between receipt of COVID-19 vaccine and demographic and clinical factors using univariate and multivariable logistic regression and estimated adjusted odds ratios (aOR) for each factor associated with non-vaccination.

Results: Among 1,665 hospitalized adolescents without COVID-19, 56% were unvaccinated. Unvaccinated adolescents were younger (median age 15.1 years vs. 15.4 years, p<0.01) and resided in areas with higher social vulnerability index (SVI) scores (median 0.6 vs 0.5, p<0.001) than vaccinated adolescents. Residence in the Midwest [aOR 2.60 (95% CI: 1.80, 3.79)] or South [aOR 2.49 (95% CI: 1.77, 3.54)] US census regions, rarely or never receiving influenza vaccine [aOR 5.31 (95% CI: 3.81, 7.47)], and rarely or never taking precautions against COVID-19 [aOR 3.17 (95% CI: 1.94, 5.31)] were associated with non-vaccination against COVID-19.

Conclusions: Efforts to increase COVID-19 vaccination of adolescents should focus on persons with geographic, socioeconomic, and medical risk factors associated with non-vaccination.

Keywords: COVID-19 vaccine, risk factors, adolescent

Background

Throughout the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, pediatric coronavirus disease 2019 (COVID-19) has been largely overshadowed by adult illness. Despite being generally characterized as mild, pediatric COVID-19 has resulted in >15 million infections, >150,000 hospitalizations, and >1,700 child and adolescent deaths in the US.[1,2] Racial and ethnic minority children and those with underlying medical conditions such as obesity, lung disease, and immunosuppression are at increased risk for hospitalization and death.[3,4] Among US children and adolescents, adolescents ages 12-17 years experienced the highest proportion of cases during the first three waves of the COVID-19 pandemic.[5] Pfizer-BioNTech COVID-19 (BNT162b2) vaccine received initial emergency use authorization (EUA) from the Food and Drug Administration for persons ≥16 years in December 2020, and this was expanded in May 2021 to include adolescents 12-15 years of age.[6] These EUAs were quickly followed by interim recommendations for administration from the Advisory Committee on Immunization Practices (ACIP).[7] Real-world observational vaccine effectiveness studies have demonstrated the Pfizer-BioNTech vaccine to be highly effective against hospitalization and ICU admission for adolescents.[8] Although rare cases of myocarditis/pericarditis have been linked to vaccination, especially in adolescent and young adult males, Pfizer-BioNTech COVID-19 vaccine is safe and well-tolerated.[9,10] Despite the clear benefits and favorable safety profile, vaccine uptake in adolescents has been suboptimal, and hospitalizations due to COVID-19 are ten times higher in unvaccinated adolescents.[11,12] As of April 30, 2022, only 59% of US adolescents have received ≥2 doses of Pfizer-BioNTech COVID-19 vaccine.[13] We sought to assess factors associated with COVID-19 non-vaccination in adolescents 12-18 years of age, using persons hospitalized for non-COVID-19 illness, who are anticipated to be generally representative of the population of adolescents in each institution's catchment area, as a proxy for the source population.

Methods

We analyzed data from the Overcoming COVID-19 pediatric vaccine effectiveness (VE) network, a network of 31 children's hospitals in 23 states conducting active surveillance for pediatric hospitalizations. Details of the Overcoming COVID-19 VE investigation have been previously published; in brief, adolescents 12-18 years of age hospitalized with acute COVID-19 as the primary admission diagnosis or a clinical syndrome consistent with COVID-19 or multi-system inflammatory syndrome in children (MIS-C) were identified and enrolled as case-patients.[14,15] Due to potential biases related to the selection of controls initially, two groups of control-patients were enrolled: children hospitalized with COVID-19-like illness with a negative SARS-CoV-2 RT-PCR or antigen test ("test-negative" control-patients) and children with no COVID-19 symptoms who may or may not have been tested for SARS-CoV-2 ("syndrome-negative" control-patients).[8] Sites attempted to enroll all patients hospitalized with COVID-19; control-patients without COVID-19 were identified after case enrollment, and were matched by age, hospital, and calendar week (within 3 weeks) of case-patient hospitalization. Prior analyses demonstrated that vaccine effectiveness results did not vary by type of control-patient, so enrollment of syndrome-negative control-patients was halted in December 2021, only traditional test-negative control-patients were enrolled for the remainder of the study, and both control types were combined in subsequent analyses.[8,16] As our primary interest was to identify factors associated with COVID-19 non-vaccination in the source population for hospitals in the Overcoming COVID-19 network, we restricted analyses to hospital-based controls without COVID-19 enrolled between June 1, 2021 and April 29, 2022. Cases with COVID-19 were excluded because vaccines are highly effective against preventing hospitalization with COVID-19 and thus cases were less likely to be vaccinated.[8]

Demographic characteristics, clinical information, SARS-CoV-2 testing history, influenza vaccination history (parent reported receipt of influenza vaccine in the preceding 12 months and frequency of receipt; every year, most years, some years, rarely, never), and frequency of precautions taken to protect against COVID-19 in the 14 days prior to

hospitalization (e.g., social distancing, mask wearing, hand washing; precautions not taken, rarely taken, often taken, always taken) were captured through parent interview and/or electronic medical record abstraction by trained study personnel. All case- and control-patients were enrolled irrespective of their COVID-19 vaccination status, which was not assessed until after completion of the parent/guardian interview and/or medical record abstraction. COVID-19 vaccination status was determined through documented sources only, including searches of state immunization information systems (IIS), electronic medical records, or documentation from patient immunization cards. We categorized participants as unvaccinated if they had received no doses of COVID-19 vaccine prior to hospitalization and vaccinated if they had received 2 doses. We excluded patients with 1 dose of vaccine and those without documented vaccination history. This activity was reviewed by CDC and participating institutions and was conducted consistent with applicable federal law and CDC policy (45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq).

We calculated unweighted estimates of COVID-19 vaccination coverage by age group (12-15 years vs. 16-18 years) and by study month. We compared characteristics of vaccinated and unvaccinated controls using chi-squared, Kruskal-Wallis, and Wilcoxon rank sum tests. We assessed associations between non-receipt of COVID-19 vaccine and demographic and clinical factors using univariate and multivariable logistic regression. We estimated adjusted odds ratios (aOR) for each predictor associated with non-vaccination. We assessed two adjusted models: 1) adjusting for a priori variables of age, sex, race/ethnicity and census region, and 2) adjusting for a priori variables and additional variables associated with COVID-19 non-vaccination in bivariate analysis with $p<0.20$ (Table 1). Since the adjusted model including a priori and additional variables associated with COVID-19 non-vaccination reduced the sample size by 45%, the a priori model was selected as the final model.

Results

A total of 1,665 SARS-CoV-2-negative control-patients were enrolled from 31 pediatric hospitals during June 2021 through April 2022, including 1,072 (64%) test-negative and 593 (36%) syndrome-negative control-patients. The two control types enrolled before December 2021 did not differ by age, race/ethnicity, sex, or region but differed by social vulnerability index and underlying conditions (Supplemental Table 1). Among all control-patients, 56% (n=933) were unvaccinated, 50% (n=831) were female, 43% (n=715) were non-Hispanic white, and 68% (n=1,135) had ≥1 underlying medical conditions (Table 1). The plurality (40%, n=669) were enrolled from the South US census region, reflecting matching of control-patients with COVID-19 case-patient enrollment.

COVID-19 vaccine uptake increased in early months in the study period (June through October 2021), but plateaued in later months (November 2021 through April 2022, Figure 1). Unvaccinated adolescents were younger (median age 15.1 years vs. 15.4 years, $p<0.01$) and resided in areas with higher social vulnerability index (SVI) scores (median 0.6 vs 0.5, $p<0.001$) compared to vaccinated adolescents. No differences were observed between unvaccinated and vaccinated patients by sex, presence of underlying medical conditions, or prior hospitalization in the preceding 12 months (Figure 2, Table 1). Although race/ethnicity was independently associated with non-vaccination in univariate analyses, no association was observed in adjusted analyses. In adjusted analyses, residence in the Midwest [aOR 2.60 (95% CI: 1.80, 3.79)] or South [aOR 2.49 (95% CI: 1.77, 3.54)] census regions was associated with non-receipt of COVID-19 vaccine, compared to residence in the Northeast.

Parental report of prior season influenza vaccination of adolescents was most strongly associated with COVID-19 vaccination. The odds of COVID-19 non-vaccination were 5 times higher [aOR 5.31 (95% CI: 3.81, 7.47)] among adolescents who rarely or never were vaccinated against influenza compared to adolescents who were vaccinated every year. Similarly, parental report of non-receipt of current season influenza vaccination of their adolescents was associated with greater odds of COVID-19 non-vaccination [aOR 3.21

(95% CI: 2.48, 4.15)]. Adolescents whose parents reported they rarely or never took precautions to protect themselves against COVID-19 had greater odds of non-vaccination compared to adolescents who always took precautions [aOR 3.17 (95% CI: 1.94, 5.31)]. Finally, compared to in-person school attendance, adolescents who attended school virtually had greater odds of non-receipt of COVID-19 vaccine [aOR 1.68 (95% CI: 1.27, 2.22)].

Discussion

In this multi-state assessment of factors associated with COVID-19 non-vaccination in adolescents, the majority of adolescents (56%) were unvaccinated, which is higher than national estimates (38%).[13] Multiple factors have hindered COVID-19 vaccine uptake in adolescents, including widespread misinformation about vaccine safety, parental vaccine hesitancy, and lack of perceived need for COVID-19 vaccination in this population. Our study population was composed of hospitalized adolescents without COVID-19, one-fifth of whom reported ≥1 hospitalization in the prior 12 months and two-thirds of whom reported ≥1 underlying medical condition. We did not specifically assess reasons for non-vaccination in this population, but suspect that the low vaccine uptake observed in our assessment might be due to lack of routine well-child care and vaccine hesitancy triggered by perception of medical fragility, concerns about vaccine side effects, and low perception of risk among some parents of adolescents with complex medical needs.[17,18] In a pre-vaccine assessment of parental intent, Goldman et al found that parents of children with chronic illness were less willing to vaccinate their children against COVID-19 compared with parents of healthy children.[20] This is unfortunate as adolescents with chronic illness face increased risk of severe COVID-19 disease, hospitalization, and death.[21] Conversely, parents of adolescents with complex medical needs with high health literacy who closely follow evidence-based recommendations may be more likely to vaccinate their adolescents.[22] We also noted that unvaccinated adolescents were slightly younger than vaccinated adolescents. This is not surprising as the EUA for older adolescents ≥16 years predated authorization for younger adolescents 12-15 years by 5 months. Thus, parents of older adolescents have had more

time to weigh the risks and benefits of vaccination and opt-in to COVID-19 vaccine for their teens. As observed with other adolescent vaccines, vaccine coverage increases slowly over time following vaccine introduction.[23] In addition, other assessments of COVID-19 vaccine have demonstrated that parents of older adolescents have expressed greater intent to vaccinate than parents of younger adolescents.[20,24]

Early assessments of COVID-19 vaccine uptake suggested that non-Hispanic Black and Hispanic/Latino individuals were less likely to be vaccinated than non-Hispanic white individuals.[25,26] In our adolescent population, race/ethnicity did not predict COVID-19 non-vaccination. This is consistent with more recent analyses suggesting that racial and ethnic disparities in vaccine uptake have narrowed.[26-28] Instead of racial and ethnic differences, we found that geographic location (living in the South or Midwest US census regions) was associated with lower COVID-19 vaccine uptake. Our findings are similar to other assessments, which noted low COVID-19 vaccination in adults residing in Southern states.[28-32] Furthermore, unvaccinated adolescents resided in areas with higher SVI, which has been previously associated with low COVID-19 vaccine uptake.[33]

In our population of adolescents, parental report of influenza vaccination, both current and past season, was strongly associated with COVID-19 vaccine uptake. Other adult and pediatric assessments examining history of influenza vaccine and COVID-19 vaccine acceptance had similar findings.[19,34,35] Studies of influenza vaccine acceptance have shown that absence of a strong provider recommendation, low perceived risk of disease, lack of perceived benefit of vaccination, and low perceived vaccine effectiveness are associated with non-receipt of influenza vaccine.[36] We believe that many of these factors likely apply to COVID-19 vaccine acceptance for adolescents. Beyond this, children and adolescents who are regularly vaccinated against influenza are more likely to receive routine preventive care, and, therefore, have increased opportunities to receive a recommendation for vaccines, including COVID-19 vaccine.[37,38]

Finally, consistent with other studies of COVID-19 vaccine acceptance,[39-41] we noted that adolescents who less frequently adopted COVID-19 precautionary measures were less

likely to be vaccinated against COVID-19 than adolescents who frequently or always used these measures. Adolescent acceptance of COVID-19 precautions is heavily influenced by parental attitudes and behaviors and parental norms play a key role in COVID-19 vaccine uptake.[24] Although we did not measure parent vaccination status, we believe the contribution of parental influence should not be overlooked when considering factors that contribute to adolescent COVID-19 vaccination. In addition, some adolescents may hold strong beliefs regarding COVID-19 vaccination and might seek vaccination without parental guidance, as permitted in some states. Efforts to promote acceptance of adolescent COVID-19 vaccination should focus on strategies previously demonstrated to be successful in improving uptake of other vaccines, such as strong provider recommendations for vaccination, convenient access, and coordinated and consistent messaging dispelling myths and combatting misinformation.[42]

Our findings are subject to several limitations. First, our assessment contains a relatively small number of participants and is confined to adolescents only, thus we were unable to assess factors associated with COVID-19 vaccination in younger children. Additionally, because control-patients were identified only after enrollment of an eligible case-patient, sites with large numbers of COVID-19 hospitalizations in geographic regions where the burden of COVID-19 was high are over-represented in our analyses. In some cases, these areas may have had lower COVID-19 vaccination rates than corresponding areas with fewer pediatric COVID-19 hospitalizations. Furthermore, because control-patients were matched by age and week of admission to case-patients with COVID-19, the adolescent population included in this assessment and the factors identified as being associated with COVID-19 non-vaccination may differ from the true source population; the relatively high prevalence of underlying medical conditions among case-patients and control-patients suggests this might be the case. The primary objective of the Overcoming COVID-19 network is to evaluate severe pediatric COVID-19; therefore, this assessment includes only hospitalized adolescents and our findings may not be generalizable across the full spectrum of pediatric COVID-19 if adolescents with milder disease differed in vaccination

behavior. Additionally, because each of the participating institutions are tertiary care facilities and care for patients from large geographic areas, location of care might not represent true geographic location of residence. However, this difference is unlikely to be large enough to result in misclassification of census region of residence. Minimal collection of information not directly related to risk for and treatment of COVID-19 facilitated rapid and large patient enrollment but precluded the examination of risk factors known to be associated with acceptability and uptake of COVID-19 vaccines and other vaccines (e.g., parental COVID-19 vaccination status and sociodemographic factors). Finally, some information was self-reported (e.g., influenza vaccination status) and available for only a subset of participants.

In conclusion, factors negatively impacting COVID-19 vaccine uptake are multifactorial and have resulted in suboptimal vaccination of adolescents. Our assessment identifies potential persons for intervention, including adolescents residing in specific geographic regions of the U.S., those with higher SVI scores, those with underlying medical conditions, and those less likely to adhere to evidence-based recommendations.

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Table 1. Risk factors associated with non-vaccination among control patients aged 12-18 years 31 pediatric hospitals in 23 states, June 2021 – April 2022, United States

Figure 1. COVID-19 vaccine coverage among control patients by age group (12-15 years vs. 16-18 years) and month of enrollment

Figure 2. Demographic factors and COVID-19 vaccination status among control patients aged 12-18 years 31 pediatric hospitals in 23 states, June 2021 – April 2022, United States

Characteristic	Unvaccinated (N=933)	Vaccinated (N=732)	p-value	OR	95 % CI	aOR†	95 % CI
Age in Years, Median (IQR)	15.1 (13.7, 16.8)	15.4 (13.9, 16.8)	<0.01				
Age Category, No. (%)							
12-15 years	591 (63.3)	443 (60.5)	0.24	1.13	0.92 - 1.38	1.18	0.96 - 1.45
16-18 years	342 (36.7)	289 (39.5)		REF	REF	REF	REF
Sex, No. (%)							
Female	464 (49.7)	367 (50.1)	0.87	REF	REF	REF	REF
Male	468 (50.2)	365 (49.9)		1.01	0.84 - 1.23	0.99	0.82 - 1.21
Race/Ethnicity, No. (%)							
White, non-Hispanic	423 (45.3)	292 (39.9)	<0.01	1.52	1.18 - 1.95	1.32	1.01 - 1.72
Black, non-Hispanic	219 (23.5)	146 (19.9)		1.57	1.18 - 2.10	1.31	0.96 - 1.79
Hispanic, any race	188 (20.2)	197 (26.9)		REF	REF	REF	REF
Other, non-Hispanic	61 (6.5)	67 (9.2)		0.95	0.64 - 1.42	0.92	0.61 - 1.38
Unknown	42 (4.5)	30 (4.1)		1.47	0.88 - 2.46	1.42	0.84 - 2.41
Social Vulnerability Index¥, Median (IQR)	0.6 (0.3, 0.8)	0.5 (0.2, 0.8)	<0.01				
U.S. Census Region, No. (%)							
Northeast	67 (7.2)	103 (14.1)	<0.01	REF	REF	REF	REF
Midwest	257 (27.5)	146 (19.9)		2.71	1.88 - 3.93	2.60	1.80 - 3.79
South	413 (44.3)	256 (35.0)		2.48	1.76 - 3.51	2.49	1.77 - 3.54
West	196 (21.0)	227 (31.0)		1.33	0.93 - 1.91	1.45	1.00 - 2.10
Underlying Health Conditions - no./total no. (%)							
No underlying conditions	307/931 (33.0)	219/730 (30.0)	0.20	1.15	0.93 - 1.42	1.21	0.97 - 1.50
At least one underlying condition	624/931 (67.0)	511/730 (70.0)		REF	REF	REF	REF
Respiratory, including asthma	251/928 (27.0)	195/728 (26.8)	0.91				
Cardiovascular	72/929 (7.8)	67/726 (9.2)	0.28				

Neurologic/Neuromuscular	173/928 (18.6)	157/728 (21.6)	0.14				
Immunosuppression or autoimmune	101/931 (10.8)	81/729 (11.1)	0.87				
Endocrine, including diabetes	97/930 (10.4)	77/728 (10.6)	0.92				
Obesity‡	264/929 (36.2)	190/732 (26.0)	0.14				
Other chronic conditions¶	361/929 (38.9)	314/729 (43.2)	0.08				
Other Characteristics – no./total no. (%)							
Prior Hospitalizations in past year¶¶							
Yes	191/553 (34.5)	168/492 (34.1)	0.89	1.02	0.79 - 1.31	1.01	0.78 - 1.32
No	362/533 (65.5)	324/492 (65.9)		REF	REF	REF	REF
History of influenza vaccine¶¶							
Every Year	159/550 (28.9)	290/504 (57.5)	<0.01	REF	REF	REF	REF
Most Years	82/550 (14.9)	78/504 (15.5)		1.92	1.33 - 2.77	2.12	1.45 - 3.12
Some Years	93/550 (16.9)	55/504 (10.9)		3.08	2.10 - 4.56	3.69	2.46 - 5.59
Rarely or Never	216/550 (39.3)	81/504 (16.1)		4.86	3.54 - 6.73	5.31	3.81 - 7.47
Receipt of current season influenza vaccine¶¶							
Yes	201/571 (35.2)	322/505 (63.8)	<0.01	REF	REF	REF	REF
No	370/571 (64.8)	183/505 (36.2)		3.24	2.53 - 4.16	3.21	2.48 - 4.15
Adoption of COVID-19 precautions¶¶							
Always	271/483 (56.1)	334/459 (72.8)	<0.01	REF	REF	REF	REF
Often	142/483 (29.4)	99/459 (21.6)		1.77	1.31 - 2.40	1.91	1.38 - 2.64
Rarely or Never	70/483 (14.5)	26/459 (5.7)		3.32	2.08 - 5.44	3.17	1.94 - 5.31
School Attendance¶¶							
In-person school attendance	337/526 (64.1)	358/486 (73.7)	<0.01	REF	REF	REF	REF
No in-person school attendance	189/526 (35.9)	128/486 (26.3)		1.57	1.20 - 2.06	1.68	1.27 - 2.22

Abbreviations: IQR = Interquartile Range, SVI = Social Vulnerability Index

* COVID-19 vaccination status included the following two categories: 1) unvaccinated, defined as no receipt of any SARS-CoV-2 vaccine before hospitalization and 2) fully vaccinated, defined as receipt of 2 doses of mRNA vaccine before hospitalization.

† Models adjusted for age (continuous), sex, race/ethnicity, and census region.

¥ Scores on the Social Vulnerability Index range from 0 to 1.0, with higher scores indicating greater social vulnerability. Details regarding this index are available on the website of the Agency for Toxic Substances and Disease Registry of the Centers for Disease Control and Prevention at https://www.atsdr.cdc.gov/placeandhealth/svi/index.html. opens in new tab. The median scores on the Social Vulnerability Index for case patients and controls are based on 2018 data.

‡ Obesity is defined as clinician documented obesity in the medical record or BMI >= 95th percentile for those with height and weight available (for those without height available weight-for-age percentile >=90th percentile identified obese children.[19]

¶ Other chronic conditions included, but not limited to, obesity, rheumatologic/autoimmune disorder, hematologic disorder, renal or urologic dysfunction, gastrointestinal/hepatic disorder, metabolic or confirmed or suspected genetic disorder, or atopic or allergic condition.

¶¶ In-person school attendance, prior hospitalization, history of influenza vaccine, and COVID-19 precautions in the past year were based on self-reported data from parent or guardian.

Figure 1

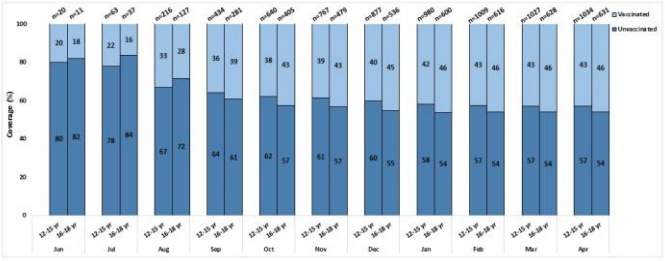

Figure 2