Effectiveness of the BNT162b2 mRNA COVID-19 vaccine among adolescents with juvenile-onset inflammatory rheumatic diseases

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Abstract

Objectives. The effectiveness of the BNT162b2 mRNA COVID-19 vaccine for adolescents with juvenile-onset inflammatory or immune rheumatic diseases (IRDs) is unknown. Several studies have suggested attenuated immunogenicity in patients with IRD. This study evaluated the effectiveness of the BNT162b2 mRNA COVID-19 vaccine in preventing COVID-19 infection in adolescents with juvenile-onset IRD compared with controls without immune rheumatic disease.

Methods. We used data from Clalit Health Services, the largest health-care organization in Israel, to conduct an observational cohort study from February to December 2021, involving 12–18-year-old adolescents diagnosed with IRD. Study outcomes included documented COVID-19 infection in relation to vaccination status and immunomodulatory therapy. We estimated vaccine effectiveness as one minus the risk ratio. Adolescents aged 12–18 years without immune rheumatic disease served as controls.

Results. A total of 1639 adolescents with IRD (juvenile idiopathic arthritis, SLE, or familial Mediterranean fever) were included and compared with 524,471 adolescents in the same age range without IRD. There was no difference in COVID-19 infection rates after the second dose of vaccine between those with IRD and controls (2.1% vs 2.1% respectively, \( P = 0.99 \)). The estimated vaccine effectiveness for adolescents with IRD was 76.3% after the first dose, 94.8% after the second and 99.2% after the third dose.

Conclusion. We found that the BNT162b2 mRNA vaccine was similarly effective against COVID-19 infection in adolescents with and without IRD. Immunomodulatory therapy did not affect its effectiveness. These results can encourage adolescents with IRD to get vaccinated against COVID-19.

Key words: adolescent rheumatology, COVID-19 vaccine, effectiveness, immunomodulatory therapy

Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to significant morbidity and mortality worldwide [1]. Children and adolescents typically have milder COVID-19 infections compared with adults [2]. Nevertheless, severe illness can occur in these age groups [3–4]. Liguoro et al. reported that among 1475 cases of children hospitalized with COVID-19, 615 (42%) had moderate or severe
disease [5]. In a recent prospective study that included 20 hospitals in Israel, 17.8% of children hospitalized due to COVID-19 or multisystem inflammatory syndrome in children (MIS-C) had moderate or severe disease [6]. Furthermore, long COVID or post-COVID syndrome has been described in both children and adults [7]. The incidence of this condition in children varies from 0 to 40% [7, 8]. Young adolescents and children are significant vectors in SARS-CoV-2 transmission and can infect the elderly, who are susceptible to severe disease [9].

Due to the above, preventing COVID-19 transmission is of paramount importance. The BNT162b2 (Pfizer–BioNTech, New York, NY, USA) vaccine, an mRNA-based vaccine, was shown to have a favourable safety profile, with 95% efficacy in preventing COVID-19 infection in healthy participants over 16 years of age [10] and in healthy adolescents aged 12–15 years [11], leading to FDA approval in these age groups. The Centers for Disease Control have issued guidelines for use in children aged 5–11 [12]. In June 2021, the B.1.617.2 (delta) variant of SARS-CoV-2 became the dominant strain in Israel and went on to cause a major resurgence of COVID-19 infection [13]. Studies conducted during this period found vaccine effectiveness against SARS-CoV-2 severe infection to be around 96% and 92% after the second vaccine dose for persons 16–39 years of age and for adolescents 12–15 years of age, respectively [14–15].

Children with autoimmune inflammatory rheumatic diseases (IRDs) may have an increased risk of infections due to the disease itself or due to treatment with immunomodulating or immunosuppressive drugs [16–17]. Patients with paediatric-onset IRD require a personalized vaccination schedule that considers many factors, including disease activity, treatment, infection risk, and vaccine safety and efficacy [18]. Most studies have evaluated the immunogenicity (ability to induce humoral and cellular immune responses) of vaccines, rather than the effect of vaccination on infection rates (i.e., vaccine efficacy or effectiveness) [19]. The ongoing COVID-19 pandemic is an opportunity to examine the immunogenicity and the efficacy of the COVID-19 vaccine among different populations, including adolescents with IRD.

This study estimated the effectiveness of the BNT162b2 mRNA vaccine in adolescents with IRD compared with controls without immune rheumatic disease.

Methods

Study design and population

This observational cohort study was designed to estimate the effectiveness of the BNT162b2 mRNA COVID-19 vaccine in adolescents with IRD. Eligibility criteria were adolescents aged 12–18 years, who were members of Clalit Health Services (CHS) and had a documented diagnosis of JIA, SLE or FMF [according to International Classification of Diseases, ninth edition (ICD-9) codes or Clalit diagnostic criteria] during the 6 months preceding data extraction.

We extracted data regarding vaccination status and current treatment, including treatment with conventional DMARDs (c-DMARDs) and biologic DMARDs (b-DMARDs). The pharmaceutical data was based on the CHS prescription system if the regimen was issued during the 3 months before the study period. The control group consisted of adolescents without IRD of the same ages who were members of CHS.

The primary outcome was documented SARS-CoV-2 infection based on a positive PCR test. The secondary outcome was hospitalization due to COVID-19.

Data source

CHS is the largest health-care organization in Israel and insures 4.7 million patients (53% of the population). The CHS membership is generally representative of the Israeli population. The present study was based on CHS data covering adolescent patients vaccinated between February 2021 and December 2021. CHS data are integrated daily with data collected centrally by the Israeli Ministry of Health regarding COVID-19 vaccines, SARS-CoV-2 tests, and COVID-19–related hospitalizations and deaths.

Patient and public involvement

Patients took part in the data research analysis, broadening the scope of the research question, and providing information that would help dispel parents’ fears of the vaccination, and encourage them to vaccinate their children. Patients also reviewed and commented on the research paper and will take an important and active part in disseminating the outcomes of the study through European Network for Children with Arthritis (ENCA) and other parents’ organizations, locally and abroad.

Ethics

This study was approved by the CHS Community Institutional Review Board on 21 September 2021, (no. COM2-0139–21). Since the study was an observational, non-interventional study, it was exempt from the requirement for informed consent.

Data analysis

Data were analysed using SPSS, version 27. Descriptive statistics were produced using frequencies (n and %) for all variables. The rates of adolescents who were infected by COVID-19 in both cohorts were compared using χ² tests. The level of significance (P-value) was set at <.05.

We calculated risk ratios for vaccination, compared with no vaccination, and estimated the vaccine effectiveness as one minus the risk ratio. We validated the results using the formula: VE = (NVAC – VAC)/NVAC, where VE is vaccine effectiveness, NVAC is the attack rate among the unvaccinated and VAC is the attack rate among vaccinated individuals.
Results

The cohort

The study cohort included 1639 adolescents with IRD, aged 12–18 years. We collected data on the three most prevalent diagnoses of adolescents with IRD in Israel: FMF, JIA and SLE. Patients with FMF (n = 1168) comprised 71.3% of the study cohort, followed by JIA at 23.2% (n = 380) and SLE at 5.5% (n = 91).

Table 1 presents the data regarding vaccination status and COVID-19 infection among the entire cohort. A total of 1188 (72.5%) adolescents with IRD were vaccinated: 179 (10.9%) had received one dose, 745 (45.5%) of the patient cohort had received two doses of vaccine and 264 (16.1%) had received three doses. The remaining 451 (27.5%) adolescents with IRD were not vaccinated at all.

COVID-19 infection was diagnosed among 16.9% (n = 277) of the adolescents with IRD and 51.9% (n = 234) of the non-vaccinated adolescents with IRD. Among the adolescents with IRD who received at least two vaccine doses, 21/1009 (2.1%) were infected with COVID-19 after receiving their second or third dose of vaccine.

The median follow-up times after receiving vaccination for the study cohort were 21.6 weeks [interquartile range (IQR) 14.3–38.7], 18.6 weeks (IQR 13.6–36.9) and 21.3 weeks (IQR 14.3–38.7) after one, two and three doses, respectively. The infection rates were not significantly different between these two groups ($\chi^2 = 0.01, P = 0.99$).

Effectiveness of COVID-19 vaccination among patients with IRD vs controls

Table 3 and Fig. 1 present the comparison between patients with IRD (FMF, JIA and SLE) and controls. Among the 380 adolescents with JIA who were evaluated in the study, 235 (61.8%) were vaccinated at least twice. Five adolescents (5/235, 2.1%) were infected with COVID-19 after receiving a second vaccine dose. The time span of infection from the second dose was 22–28 weeks. None of these 5 received immunomodulating drugs on a regular basis. None of the adolescents who received three doses of the vaccine was infected with COVID-19.

The results showed a significant difference in the rates of COVID-19 infection between JIA patients and controls following one dose of vaccine (0% vs 12.6%, respectively, $P < 0.01$). There was no significant difference in the rates of COVID-19 between unvaccinated adolescents with JIA and controls ($P = 0.36$), and for those who received two ($P = 0.14$) or three doses ($P = 0.53$) of the vaccine.

Overall, 47 (12.4%) of patients with JIA were treated with MTX, 84 (22.1%) with anti-TNF, and 7 (1.8%) with tocilizumab (Table 4). None of the adolescents with JIA receiving immunomodulation were infected with COVID-19 after the second dose of vaccine.

Among 91 adolescents with SLE, 62 (68.1%) received at least two doses of vaccine and 2 were infected after

Table 1 Vaccination status and COVID-19 infection among adolescents with IRD

| Vaccine doses               | Total | 0     | 1     | 2     | 3     |
|-----------------------------|-------|-------|-------|-------|-------|
| Adolescents with IRD        | 1639  | 451(27.5%) | 179(10.9%) | 745(45.5%) | 264(16.1%) |
| COVID-19 infection          | 277   | 234   | 22    | 20    | 1     |
| Infections/vaccinated$^a$   | 16.9% | 51.9% | 12.3% | 2.7%  | 0.4%  |
| Vaccine effectiveness$^b$   | 76.3% | 94.8% | 99.2% |

$^a$Percentage of COVID-19 infection per vaccine dose. $^b$Vaccine effectiveness calculated according to the formula: $VE = (NVAC – VAC)/NVAC$. IRD: inflammatory rheumatic disease; VE: vaccine effectiveness; NVAC: attack rate among the unvaccinated; VAC: attack rate among the vaccinated.
one dose. None of the patients with SLE who received two or three doses of the vaccine were infected with COVID-19 after completing the series of vaccinations.

There were no significant differences in the post-vaccination COVID-19 rates among adolescents with SLE compared with controls, for any of the time points—one dose ($P = 0.38$), two doses ($P = 0.33$) or three doses ($P = 0.25$)—or between non-vaccinated adolescents with SLE and controls ($P = 0.79$).

Among the 23 (25.3%) of adolescents with SLE who were treated with MMF, none were infected with COVID-19. Similarly, no infections with COVID-19 were documented for adolescents with SLE treated with AZA ($n = 3$) or MTX ($n = 1$) (Table 4).

A total of 1168 adolescents with FMF were evaluated in this study. Among them, 712 (61%) were vaccinated at least twice, of whom 16/712 (2.2%) became infected with COVID-19.

Significantly more non-vaccinated adolescents with FMF contracted COVID-19 compared with non-vaccinated controls (54.7% vs 37.2%, respectively, $P = 0.001$). There was no significant difference in infection rates with COVID-19 between adolescents with FMF and controls after one dose ($P = 0.46$), two doses ($P = 0.18$) or three doses ($P = 0.34$) of vaccine.

Among the adolescents with FMF, 793 (67.9%) were treated with colchicine, 31 (2.6%) with canakinumab and 9 (0.8%) with anakinra. None of the adolescents treated with canakinumab or anakinra were infected with COVID-19 after the second dose of vaccine.

**Hospitalizations**

Four patients with IRD (0.2%) were hospitalized due to COVID-19 infection, 3 with SLE and 1 with JIA. All were unvaccinated and had mild disease. There were no hospitalizations due to MIS-C. No deaths due to COVID-19 infection or MIS-C were reported among adolescents with IRD. Among the control group, 420 (0.08%) were hospitalized due to COVID-19 infection or MIS-C: 74% with mild disease and 14% with moderate/severe disease. Disease severity during hospitalization was not documented in 12%. The only death was that of an obese, but otherwise healthy, 16-year-old boy who died due to MIS-C.

**Discussion**

This study compared the effectiveness of the BNT162b2 mRNA COVID-19 vaccine for adolescents with an IRD vs controls without IRD. The estimated vaccine effectiveness was very high for both groups. Among adolescents with IRD, it was 76.3% after the first dose, 94.8% after the second dose and 99.2% after the third dose.

Data from adults with IRD receiving the BNT162b2 vaccine demonstrate safety and immunogenicity in most patients with IRD, with 86% seropositivity. However, antibody levels to the S1/S2 spike protein were significantly lower among patients with IRD compared with controls [20]. Information on the safety and immunogenicity of COVID vaccines for adolescents with IRD is limited. Heshin-Bekenstein et al. [21] recently reported a study on 91 adolescents with IRD and 42 healthy controls from four centres in Israel and Slovenia. The results demonstrated that the BNT162b2 COVID-19 vaccine has a good safety profile. IRD patients had an adequate immunogenic response, but significantly lower antibody titres, when compared with healthy controls.

In the past decade, knowledge about the safety and immunogenicity of vaccines in paediatric patients with IRD has increased significantly. Evidence has accumulated that vaccines, including live-attenuated vaccines, are safe for paediatric patients with IRD on immunosuppression [22–24]. Regarding immunogenicity,
Numerous studies have found that vaccinations were immunogenic in paediatric patients with IRD, including those receiving CSs, MTX or TNF inhibitors [25–26].

Data on effectiveness remains scarce. No studies were powered to assess the effectiveness of vaccinations in paediatric patients with IRD. These studies are difficult to perform because the risk of infection is low, due to high herd immunity. Most of the vaccines included in national immunization programs have resulted in the elimination of these diseases, making current studies regarding their effectiveness impossible [27]. The ongoing COVID-19 pandemic is a rare opportunity to examine the immunogenicity and effectiveness of a vaccine among different populations, including adolescents with IRD, and to compare the data with that for adolescents without IRD.

Randomized clinical trials of mRNA-based vaccines reported that the efficacy for preventing COVID-19 is 94% to 95% in persons 16 years of age or older [11]. Follow-up research evaluating adolescents ages 12–15 years found that the BNT162b2 vaccine was safe, immunogenic and resulted in an observed efficacy of 100% against COVID-19 infection [12]. Our study found that the estimated vaccine effectiveness for documented COVID-19 infection for adolescents with IRD was almost 95% after the second dose of vaccine and above 99% after the third dose.

The current study demonstrates that immunomodulatory drug treatment did not affect the effectiveness of the vaccine. No COVID-19 infections were documented for adolescents treated with c-DMARDS or b-DMARDS who received two or three doses of vaccine. Recent studies evaluating the immunogenicity of the COVID-19 vaccine in adults and adolescents with IRD found reduced humoral response in patients treated with MMF [21, 28]. We found that the effectiveness of the vaccine for adolescents treated with MMF was 100% after the second dose.

Another finding of our study was that only about 60% of the adolescents with IRD received two or three doses of vaccine. Although vaccination coverage

| Vaccine doses | Total | 0 | 1 | 2 | 3 |
|---------------|-------|---|---|---|---|
|                | N (%) | P-value | N (%) | P-value | N (%) | P-value | N (%) | P-value |
| Subjects       |       |       |     |     |     |       |     |       |
| Controls       |       |       |     |     |     |       |     |       |
| JIA            | 380   | 0.01  | 34  | 0.01 | 91  | 0.01  | 13  | 0.01 |
| SLE            | 46    | 0.01  | 4   | 0.01 | 21  | 0.01  | 3   | 0.01 |
| FMF            | 111   | 0.01  | 11  | 0.01 | 17  | 0.01  | 2   | 0.01 |
| JIA            | 34    | 0.01  | 3   | 0.01 | 9   | 0.01  | 1   | 0.01 |
| SLE            | 4    | 0.01  | 0.42| 0.01 | 2   | 0.01  | 0.22| 0.01 |
| FMF            | 11   | 0.01  | 1   | 0.01 | 1   | 0.01  | 0.07| 0.01 |
| JIA            | 91   | 0.01  | 9   | 0.01 | 2   | 0.01  | 1   | 0.01 |
| SLE            | 21   | 0.01  | 3   | 0.01 | 2   | 0.01  | 1   | 0.01 |
| FMF            | 1    | 0.01  | 0.54| 0.01 | 0.14| 0.01  | 0.07| 0.01 |
| JIA            | 13   | 0.01  | 2   | 0.01 | 1   | 0.01  | 0.14| 0.01 |
| SLE            | 2   | 0.01  | 0.14| 0.01 | 0.14| 0.01  | 0.07| 0.01 |
| FMF            | 1   | 0.01  | 0.07| 0.01 | 0.07| 0.01  | 0.07| 0.01 |
| JIA            | 1   | 0.01  | 0.07| 0.01 | 0.07| 0.01  | 0.07| 0.01 |
| SLE            | 1   | 0.01  | 0.07| 0.01 | 0.07| 0.01  | 0.07| 0.01 |
| FMF            | 1   | 0.01  | 0.07| 0.01 | 0.07| 0.01  | 0.07| 0.01 |

IRD: inflammatory rheumatic disease.

Table 3 COVID-19 infection following vaccination among paediatric patients with IRD compared with controls without IRD.
was slightly better among patients with IRD compared with controls, we should aim for higher vaccination rates for all adolescents and especially those with IRD, due to their increased risk for disease flare if infected and increased risk for a more severe clinical course of COVID-19 infection.

The findings presented here can reassure families and patients with IRD who are being treated with immunomodulation regarding the effectiveness of the COVID-19 vaccine. This might improve the sub-optimal vaccination coverage for this population.

Our study has some limitations to take into consideration. This is a retrospective nationwide study that relies on medical data gathered from the electronic medical records of patients with IRD. Due to security and privacy reasons, we could not validate the ICD-9 codes for this cohort. Another limitation was the absence of data regarding glucocorticoid use in our study. We decided not to include glucocorticoid use in our study due to our inability to validate the accurate dosage prescribed. Moreover, we could not confirm whether it had been prescribed for a rheumatologic condition (rather than other concomitant conditions, e.g. asthma). Another limitation was that infection rates of adolescents with IRD, especially individuals taking immunomodulatory drugs, might be influenced by better health-promoting behaviour in this group, e.g. a higher tendency to wear masks and stay at home. Our analysis could not be fully controlled for aspects related to human behaviour. Nonetheless, the data size, consistency of the results, and valid outcomes such as PCR positivity and hospitalization rates are reassuring about the effect of the vaccination.

This is the first study to evaluate the effectiveness of the COVID-19 vaccine in adolescents with IRD. Access to the database from the largest health-care organization in Israel enabled us to analyse a large cohort of adolescents with IRD and compare it with a large control group.

In conclusion, this nationwide observational study conducted during the COVID-19 pandemic demonstrated that the effectiveness of the BNT162b2 mRNA vaccine was excellent among patients with IRD treated with immunomodulatory drugs, and similar to the effectiveness among controls without IRD. Our results can encourage adolescents with IRD to get vaccinated against COVID-19 and, thus, improve the suboptimal vaccination coverage for this population.

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Data availability statement

All the data relevant to this study are included in the manuscript, tables, and figures. Additional data will be provided upon request.

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