

## EDITORIAL

# Vaccinating children and adolescents against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—The Israeli experience

The coronavirus disease 2019 (COVID-19) pandemic has spread to almost all countries, with many severely affected. Vaccines, in general, have proven their profound value in preventing illnesses and terminating epidemics, as seen for example in measles, polio and smallpox. Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are already showing a significant positive impact on the number of COVID-19 cases in countries with a rapid and effective roll-out of vaccinations. Israel is among world leaders, with an effective vaccination campaign that began at the end of December 2020. Vaccines are free of charge and given to all adults. Indeed, as of 13 May 2021, 63% of the population have received at least one dose and 59% are fully vaccinated.<sup>1</sup> Vaccine coverage is lower in minorities in Israel but steadily increasing, as seen for example in the Arab population: in mid-February 2021, 19% were vaccinated with at least one dose, while by May 2021, 54% were already fully vaccinated. Accordingly, the daily number of new COVID-19 cases in Israel has declined from 10 000 at the peak of the third wave in January 2021 to less than 100 in May this year.<sup>1</sup>

SARS-CoV-2 infects all ages. Although childhood morbidity rates are low compared with their relative proportion of the population, severe cases, the need for admission to the paediatric intensive care unit (PICU) and mortality have been reported worldwide.<sup>2</sup> Additionally, since April 2020, a novel hyperinflammatory condition with severe multisystem involvement has been described in children and adolescents, typically 2–4 weeks after SARS-CoV-2 infection, and named paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C).<sup>3</sup>

As regards children, Israel is a country with a young population, where, of 9.3 million people, one third are children under 18 and only 12% are adults over 65. Data on COVID-19 morbidity and mortality among children in Israel, as reported by the Israeli Ministry of Health (IMOH) and a recently published prospective national surveillance, demonstrate that by the middle of March 2021, a year after the identification of the first COVID-19 patient in Israel, of 813 742 SARS-CoV-2-infected patients, 291 628 were children under 18 years of age (36%).<sup>4,5</sup> During the same period, in the Israeli prospective surveillance network of 20/26 hospitals caring for children, 1007 children were brought to emergency departments with COVID-19

(0.35% of all infected children) of whom 568 were hospitalised (56% of emergency department visits and 0.2% of all infected children). Of hospitalised children, 82% had a mild disease but 8% had moderate-severe COVID-19, and 10% had MIS-C necessitating admission to the PICU in many instances.<sup>5</sup> According to the IMOH, overall 7 children died due to COVID-19.<sup>4</sup> Interestingly, as vaccine roll-out progressed, the epidemiology of newly infected patients has shifted; the ratio of children up to 19 years of age among newly diagnosed patients has increased from 36% before the vaccination campaign to 46% during February–April 2021.<sup>4</sup> These data demonstrate that in Israel, where the proportion of the young in the population is high, over one third of the COVID-19 cases occurred in children. Although most of cases were mild, a significant number of children had moderate-to-severe disease or MIS-C, required PICU admission, and unfortunately, some died. These adverse results of COVID-19, as well as the possibility of children experiencing 'long COVID' symptoms, similar to adults, could be prevented by vaccines against SARS-CoV-2.

The COVID-19 vaccination campaign in Israel is based mainly on the BNT162b2 mRNA vaccine (Pfizer-BioNTech) and includes adolescents aged 16–18 years. In January 2021, a month after the beginning of the campaign, 16- to 18-year-olds were included in the priority groups for vaccine eligibility, in view of the importance of keeping the higher classes of high schools open, facilitating learning for matriculation examinations, and as a countermeasure against the severe psychosocial effects of COVID-19 in this age group.<sup>6</sup> In fact, many adolescents in Israel express a strong desire to receive the vaccine in order to feel safe, be able to resume social activities and 'be like everybody else'. Rapid roll-out of vaccination ensued; according to IMOH data, 200 000 adolescents were fully immunised within 10 weeks (69% of Israeli adolescents aged 16–18 years).<sup>4</sup>

Effectiveness of the vaccine against COVID-19 is high, similar to the results of the BNT162b2 phase 3 trial.<sup>7</sup> The effectiveness was assessed in a large, observational, pragmatic study in Israel during the vaccination campaign, comparing 1:1 matched, vaccinated and unvaccinated people according to demographic and clinical characteristics.<sup>8</sup> Overall, data on almost 1.2 million people were analysed, including over 426 000 persons in the 16–39 years group. In this age group, vaccine effectiveness against documented infection was 94% (95% confidence interval [CI], 87–97) and 99% against symptomatic

illness (95% CI, 96–100) 7 days after the second dose. In an interim analysis, performed by the IMOH, vaccine effectiveness in 16- to 18-year-olds against symptomatic COVID-19 was 98% (95% CI, 96–99) and against hospitalisation 98% (95% CI, 83–100). No cases of severe or critical morbidity or mortality were reported among vaccinated 16- to 18-year-olds during mid-January-mid-May 2021, whereas during the same period, 15 non-vaccinated adolescents were hospitalised in severe condition, 2 in critical condition and one died of COVID-19. Short-term safety of the vaccine (2–3 months after vaccination) was evaluated in the large BNT162b2 phase 3 trial and showed the incidence of serious adverse events to be low and similar in the vaccine and placebo groups.<sup>7</sup> Similar findings were reported by the Centers for Disease Control and Prevention (CDC) safety profile monitoring of over 13 700 000 COVID-19 vaccine doses (BNT162b2 and mRNA-1273-ModernaTX, Inc.) administered in the United States (US) during December 2020-January 2021.<sup>9</sup>

Shortly after the inclusion of adolescents aged 16–18 years in the priority groups for vaccination in Israel, in view of the successful vaccine roll-out and demonstration of high efficacy with no major safety issues, and concomitant with the announcement of Pfizer-BioNTech on enrolment of children 12–15 years old in vaccine trials, vaccination of 12- to 15-year-olds with predisposing conditions for severe COVID-19 has commenced in Israel. In an orderly process in January 2021, the Israeli Pediatric Association and the Israeli Pediatric Infectious Diseases Society, after literature review and discussions, prepared a position paper for vaccinating members of this age group who have major risk factors for severe COVID-19, as well as an indication when a household member suffers from severe immunosuppression. Risk factors included morbid obesity, severe chronic pulmonary disease with low pulmonary reserve or chronic mechanical ventilation, heart failure, renal failure, sickle cell anaemia, malignancy, severe immunosuppression and severe neurodevelopmental or neuromuscular disorders. Following the approval of the IMOH, a designated committee examined data submitted by the primary physician on each vaccine candidate. As of 1 April 2021, 1028 doses of BNT162b2 were administered to 618 children aged 12–15 years. Active assessment of adverse events in this population, by the health maintenance organisations of the patients, did not find serious or severe adverse events.

On May 10 this year, the US Food and Drug Administration authorised the BNT162b2 vaccine for emergency use in adolescents aged 12–15 years, based on an ongoing randomised, placebo-controlled trial in the US of 2260 participants of this age group. Interim results demonstrated the immune response of adolescents to the vaccine was non-inferior to the immune response of young adults, effectiveness in preventing symptomatic COVID-19 was 100%, and during a 2-month follow-up adverse events were consistent with those reported earlier in the BNT162b2 phase 3 trial.<sup>7</sup> The American Academy of Pediatrics issued a policy statement 2 days later recommending the COVID-19 vaccine to all children and adolescents aged 12 years and older. The Academy also stated that given the importance of routine vaccination and the need for rapid uptake of COVID-19 vaccines, co-administration of routine childhood and adolescent immunisations with COVID-19 vaccines is recommended for children and

adolescents who are behind on or due for immunisations. In Israel, after lifting the social distancing limitations and the re-opening of the commerce and schools in March-April 2021, an increase in the weekly numbers of new COVID-19 cases was evident only in the 12–15 age group. Given the advantages of vaccination against COVID-19, the experience with vaccines in Israel and the interim results of the BNT162b2 vaccine in children and adolescents aged 12–15 years, the Israeli Pediatric Association and the Israeli Pediatric Infectious Diseases Society issued a statement supporting the vaccination of this population in Israel. On 2 June 2021, the IMOH approved the vaccine for this population. In the approval process, the IMOH reviewed data regarding peri-myocarditis temporally associated with vaccination. Peri-myocarditis cases occurred mainly after the second dose and in young male adolescents (16–19 years old), and in 95% of cases were mild in clinical nature and resolved in a matter of days.<sup>10</sup> The IMOH concluded that an association possibly exists between vaccination and peri-myocarditis and that the risks of COVID-19 outweigh the possible risk of peri-myocarditis. On 27 May 2021, the CDC published a similar statement concluding that the known and potential benefits of COVID-19 vaccination outweigh the known and potential risks, including the possible risk of myocarditis or pericarditis. The CDC added that most patients with myocarditis and pericarditis who received care responded well to medicine and rest and quickly felt better.

At the beginning of the COVID-19 pandemic, some expert opinions and hopeful thinking leaned towards a rapid termination of the pandemic with the disappearance of the virus, similar to SARS-CoV-1. Almost a year and a half later, it seems the virus is here to stay, either in the current wave dynamics or in the seasonal epidemics, similar to the influenza virus and the respiratory syncytial virus. In our opinion, vaccinating children and adolescents against SARS-CoV-2 is the way to go forward to reduce COVID-19 morbidity and mortality, as an ounce of prevention is worth a pound of cure.

#### CONFLICT OF INTEREST

None.

Daniel Glikman<sup>1,2</sup> 

Michal Stein<sup>3,4</sup> 

Eric S. Shinwell<sup>2,5</sup>

<sup>1</sup>Infectious Diseases Unit, Padeh Poriya Medical Center, Tiberias, Israel

<sup>2</sup>Azrieli Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel

<sup>3</sup>Infectious Diseases and Infection Control Unit, Hillel Yaffe Medical Center, Hadera, Israel

<sup>4</sup>Rappaport Faculty of Medicine, Technion, Haifa, Israel

<sup>5</sup>Department of Neonatology, Ziv Medical Center, Safed, Israel

#### Correspondence

Daniel Glikman, Infectious Diseases Unit, Padeh Poriya Medical Center, 768 Road, Lower Galilee, 15208, Israel.

Email: daniel.glikman@biu.ac.il

## ORCID

Daniel Glikman  <https://orcid.org/0000-0002-8006-5845>

Michal Stein  <https://orcid.org/0000-0002-0765-7326>

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