Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

application of preventive measures such as facemask wearing, hand hygiene, cleaning, and ventilation of indoor spaces.

We declare no competing interests. The findings and conclusions in this Comment are those of the authors and do not necessarily represent the official position of the US Centres for Disease Control and Prevention.

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When vaccine adverse event reporting generates hope, not fear

Children have not been spared from the significant morbidity of the COVID-19 pandemic. As of Jan 22, 2022, in the USA alone, there have been 94 COVID-19-associated hospitalisations per 100 000 children (aged <18 years), 883 childhood deaths (aged <19 years) due to COVID-19, and 6431 reported cases of multisystem inflammatory syndrome in children (MIS-C), of which 55 resulted in death. With the development of vaccines against SARS-CoV-2, a crucially important public health endeavour for infection prevention, two questions arose regarding MIS-C: is vaccination associated with development of MIS-C, and can vaccination prevent MIS-C?

In *The Lancet Child & Adolescent Health*, Anna Yousaf and colleagues offer evidence to answer the first question, with rigorously adjudicated US surveillance data on reported cases of MIS-C after at least one dose of COVID-19 vaccine.[1] The authors investigated potential cases of MIS-C after COVID-19 vaccination reported to the MIS-C national surveillance system of the US Centers for Disease Control and Prevention (CDC), the Vaccine Adverse Event Reporting System, and CDC's Clinical Immunization Safety Assessment Project from Dec 14, 2020, to Aug 31, 2021. A multidisciplinary team adjudicated cases, and the authors describe the demographic and clinical features of cases, stratified by laboratory evidence of SARS-CoV-2 infection.

Yousaf and colleagues identified 21 individuals (median age 16 years, range 12–20) with MIS-C after COVID-19 vaccination. Their findings overall are quite reassuring. Reports of MIS-C after COVID-19 vaccination occurred in only 1 per million individuals aged 12–20 years who received one or more doses of a COVID-19 vaccine, and 15 (71%) of 21 individuals with MIS-C had laboratory evidence of antecedent SARS-CoV-2 infection, casting doubt about attribution. This timely report is of special interest to health-care providers, scientists, and policy makers given ongoing, widespread transmission of the omicron (B.1.1.529) variant.

Few health interventions undergo the same level of scrutiny as vaccines. As COVID-19 vaccines were being introduced to the paediatric population, there were fears that vaccination could induce a hyperinflammatory response akin to MIS-C.[2] No cases resembling MIS-C had yet been described in vaccine trials of BNT162b2 (tozinameran; Pfizer–BioNTech), but rare adverse events were bound to arise as millions of individuals became exposed. Concerns about post-vaccination MIS-C stemmed from uncertainties surrounding MIS-C's immunopathogenesis. Early reports suggesting that higher anti-spike antibody levels were associated with MIS-C[3] led to speculation that inducing neutralising

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For the **COVID data tracker in the USA** see https://covid.cdc.gov/covid-data-tracker

For **data on COVID-19-associated hospitalisations** see https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html

For **data on childhood COVID-19 deaths** see https://data.cdc.gov/NCHS/Provisional-COVID-19-Deaths-Focus-on-Ages-0-18-Yea/nr4s-juj3

antibodies with spike-protein mRNA vaccines could cause or worsen MIS-C. This association was later refuted by Weisberg and colleagues, who showed that children with or without MIS-C had similar anti-spike antibody titres and neutralising activity after SARS-CoV-2 infection.[4] Higher avidity antibodies have been associated with decreased severity of MIS-C.[5] To date, no direct evidence exists that neutralising anti-spike antibodies contribute to MIS-C pathogenesis. The exceeding rarity of MIS-C after COVID-19 vaccination reported by Yousaf and colleagues should further alleviate these fears and bolster vaccine uptake in children.

Other safety signals arose in post-marketing surveillance concerning post-vaccination myocarditis, predominantly in young men (median age 25 years). Subsequent estimates of the excess risk of myocarditis after vaccination (1–5 per 100 000 individuals) remained well below the excess risk of myocarditis due to SARS-CoV-2 infection (5–15 per 100 000), offering further reassurance regarding the risk–benefit ratio of vaccination.[6]

Evaluation of vaccine effectiveness is also important when considering MIS-C. Much of the argument for vaccinating children rests on herd immunity and preventing severe illness. Fortunately, real-world data support that the BNT162b2 vaccine is effective at preventing critical COVID-19 illness in adolescents.[7] Regarding MIS-C, some investigators have suggested that the reduced neutralising activity of antibodies generated by children compared with those of adults in native infection contributes to delayed SARS-CoV-2 clearance and concomitant susceptibility to MIS-C.[4] This might be compounded by genetic risk factors for immune dysregulation.[8] As a result, vaccines that generate neutralising antibodies could presumably protect against MIS-C. Additionally, because MIS-C is a post-infectious complication of COVID-19, vaccines that are effective at preventing COVID-19 should also reduce MIS-C rates. Indeed, a recent report estimated that two doses of BNT162b2 were 91% effective against the development of MIS-C among adolescents aged 12–18 years when the delta (B.1.617.2) variant was predominant.[9] Together with the report by Yousaf and colleagues, these data offer hope that vaccination will reduce morbidity and mortality due to MIS-C.

Unanswered questions remain. It is unclear whether currently available vaccines will offer similar protection against MIS-C due to different SARS-CoV-2 variants. Additionally, as the usefulness of serological testing declines among rising rates of seropositivity, we will need better diagnostic tools for MIS-C. The data presented by Yousaf and colleagues show that alternative diagnoses need to be carefully considered among vaccinated children presenting with clinical syndromes mimicking MIS-C. Lastly, there has been vigorous debate as to whether children who have fully recovered from MIS-C should be vaccinated, due to concerns about triggering an aberrant immune response in individuals susceptible to hyper-inflammation. As with previous speculation about vaccines inducing MIS-C in healthy children, further investigation will determine whether this theoretical risk outweighs the risk of reinfection with new SARS-CoV-2 variants.

As the pandemic continues to challenge our global community and intense scrutiny of COVID-19 vaccines persists, Yousaf and colleagues' report is a welcome addition to the growing literature supporting the safety and efficacy of vaccination against SARS-CoV-2.

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