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Long-term immunoprotection after live attenuated measles-mumps-rubella booster vaccination in children with juvenile idiopathic arthritis

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ABSTRACT

Introduction: Vaccines, especially live attenuated vaccines, in children with JIA pose a great challenge due to both potential lower immunogenicity and safety as a result of immunosuppressive treatment. For many years, in the Netherlands, JIA patients receive a measles-mumps-rubella (MMR) booster vaccine at the age of nine years as part of the national immunization program.

Objectives: To study long-term humoral immunoprotection in a large cohort of JIA patients who received the MMR booster vaccine while being treated with immunomodulatory therapies at the Wilhelmina Children's Hospital in Utrecht, the Netherlands.

Methods: MMR-specific IgG antibody concentrations in stored serum samples of vaccinated JIA patients were determined with chemiluminescent microparticle immunoassays (CMIA). Samples were analyzed five years after MMR booster vaccination and at last available follow-up visit using both crude and adjusted analyses. Additional clinical data were collected from electronic medical records.

Results: In total, 236 samples from 182 patients were analyzed, including 67 samples that were available five years post-vaccination, and an additional 169 samples available from last visits with a median duration after vaccination of 6.9 years (IQR: 2.8–8.8). Twenty-eight patients were using biologic disease-modifying antirheumatic drugs (bDMARDS) of whom 96% anti-TNF agents and 4% tocilizumab. Percentages of protective antibody levels against measles after five years were significantly lower for patients who used bDMARD therapy at vaccination compared to patients who did not: 60% versus 86% ($P = 0.03$). For mumps (80% versus 94%) and rubella (60% versus 83%) this difference did not reach statistical significance ($P = 0.11$ and $P = 0.07$, respectively). Antibody levels post-vaccination decreased over time, albeit not significantly different between bDMARD users and non-bDMARD users.

Conclusion: The MMR booster vaccine demonstrated long-term immunogenicity in the majority of children with JIA from a large cohort, although lower percentages of protective measles antibody levels were observed in bDMARD users. Hence, it might be indicated to measure antibody levels at least five years after MMR booster vaccination in the latter group and advice an extra booster accordingly.

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood (1,2). Clinical outcomes have dramatically improved over the last two decades, and clinical inactive disease can be obtained in most patients by treating them with immunomodulatory agents. Commonly used drugs in the treatment of JIA are conventional synthetic disease-modifying antirheumatic drugs

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(csDMARDs), particularly methotrexate, and biologic disease-modifying antirheumatic drugs (bDMARDs), most commonly anti-TNF agents [1–5].

JIA patients both have an increased risk for infections due to their underlying disease and due to the use of immunomodulatory or immunosuppressive drugs. Therefore, safe and effective immunization is crucial in the management of these groups of patients [6–9]. However, vaccine immunogenicity might be impaired due to treatment [10–12].

In the Netherlands, the live attenuated measles-mumps-rubella (MMR) booster vaccination is routinely administered via the National Immunization Program at the age of nine years. At the Wilhelmina Children's Hospital in Utrecht, the Netherlands, JIA patients are advised to take the booster MMR vaccine, also when receiving immunomodulatory drug therapy, which is in line with the recently updated PRES and EULAR recommendations for vaccination of paediatric patients with autoimmune inflammatory rheumatic diseases [13,14].

Long-term follow up data on immunoprotection after MMR booster vaccination in children with JIA is limited in the current era of bDMARD therapy. In this study, we describe long-term immunoprotection in a large cohort of JIA patients who received the live attenuated MMR booster vaccine, and were simultaneously treated with csDMARD and/or bDMARD therapy.

2. Methods

2.1. Study design and participants

A monocenter observational cohort study was performed at the Pediatric Rheumatology department of the Wilhelmina Children's Hospital. All JIA patients born between 2002 and 2012 that met the International League of Associations for Rheumatology (ILAR) criteria for JIA [15] at the time of MMR booster vaccination and were enrolled in the international Pharmachild register [16] were included into the current study. Clinical and drug therapy data were collected from electronic medical records for the time of MMR booster vaccination, which was defined as the 9th birthday for all patients. The cut-off date for data collection was 17 September 2022.

Pharmachild obtained approval from the Institutional Review Board of the University Medical Center Utrecht (11-499c) and is carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent.

2.2. Outcome measure

The primary outcome measure of the current study was long-term humoral immunoprotection, as determined from stored serum samples. If available, MMR antibodies were measured five years after booster vaccination (range 5–6 years) and in the most recent sample, for which the time from MMR booster vaccination varied per patient. Since the incidence of naturally occurring MMR infections is low in the Netherlands [17], immunoprotective concentrations were used as a surrogate measure of vaccine efficacy, a reflection of the immune response that substitutes for the true immunologic correlate of protection [18]. MMR-specific immunoglobulin class G (IgG) concentrations in stored serum samples were determined with chemiluminescent microparticle immunoassays (CMIA). Antibodies against mumps and measles were analyzed using Vircia IgG monotest (Vircell, Granada, Spain). Results were expressed as indices, where an index > 1.1 is considered protective. Previous carried in-house evaluation showed that an IgG anti-measles index > 1.1 corresponded with > 150 international units (IU)/l. Antibodies against rubella were analyzed using Alinity i Rubella IgG (Abbott Laboratories, Ireland). Results were given in IU/ml, where results of $\geq$10 IU/ml were considered protective.

2.3. Statistical analysis

Characteristics of included patients were presented as frequency and percentage for categorical variables and median and interquartile range (IQR) for numerical variables. To study the effect of bDMARD use at the time of MMR booster vaccination (either bDMARD monotherapy or combination therapy of a bDMARD and csDMARD) on antibody levels after five years (both absolute and protective levels), we performed univariable (crude) and multivariable (adjusted) linear and logistic regression analyses. Multivariable analyses were adjusted for JIA subtype, age at JIA diagnosis and sex. Additionally, we performed the same analyses on samples from last available visits – disregarding samples five years post-vaccination – to study the effect of time after vaccination on antibody levels, and whether or not this effect is different for bDMARD and non-bDMARD users. For the latter analysis, an interaction term between bDMARD use and time after vaccination in years was added to the regression models. For all analyses, absolute rubella-specific IgG antibody levels – but not IgG anti-measles and IgG anti-mumps indices – were log-transformed. All analyses were performed with R version 4.0.3 and a *P*-value of 0.05 was considered statistically significant.

3. Results

3.1. Cohort characteristics

In total, 182 patients with a diagnosis of JIA at the time of MMR booster vaccination were included. The majority of these patients were girls (67%) and had oligoarthritis (57%) (Table 1). Median age at JIA

Table 1
Characteristics of included patients.

Characteristic	Total cohort (n = 182)	Patients with serological sample 5 years post-vaccination (n = 67)
Girls, n (%)	121 (66.5%)	47 (70.1%)
JIA subtype, n (%)		
Oligoarthritis	103 (56.6%)	34 (50.7%)
Persistent oligoarthritis	28 (15.4%)	8 (11.9%)
Extended oligoarthritis	25 (13.7%)	10 (14.9%)
Unknown	50 (27.5%)	16 (23.9%)
Polyarthritis	46 (25.3%)	21 (31.3%)
RF + polyarthritis	1 (0.5%)	1 (1.5%)
RF- polyarthritis	40 (22.0%)	15 (22.4%)
Unknown	5 (2.7%)	5 (7.5%)
Psoriatic arthritis	8 (4.4%)	4 (6.0%)
Enthesitis-related arthritis	1 (0.5%)	0 (0.0%)
Systemic arthritis	24 (13.2%)	8 (11.9%)
Age at JIA diagnosis, median (IQR)	5.1 (3.0–7.0)	4.9 (2.3–6.5)
Drug therapy at MMR booster vaccination, n (%)		
No immunosuppressive therapy/NSAIDs	92 (50.5%)	24 (35.8%)
Systemic corticosteroids	6 (3.3%)	1 (1.5%)
csDMARDs		
Methotrexate monotherapy	50 (27.5%)	26 (38.8%)
Azathioprine monotherapy	1 (0.5%)	0 (0.0%)
Leflunomide monotherapy	1 (0.5%)	1 (1.5%)
bDMARDs		
Adalimumab monotherapy	1 (0.5%)	0 (0.0%)
Etanercept monotherapy	10 (5.5%)	6 (9.0%)
csDMARD and bDMARD combination therapy	17 (9.3%)[1]	8 (11.9%)[2]

[1] bDMARDs: ADA (n = 13), ETN (n = 3) and tocilizumab (n = 1).
[2] bDMARDs: ADA (n = 6) and ETN (n = 2)IQR: interquartile range, JIA: juvenile idiopathic arthritis, MMR: measles mumps rubella, NSAID: non-steroidal anti-inflammatory drug, RF: rheumatoid factor.

diagnosis was 5.1 years (IQR: 3.0–7.0). Fifty patients (28%) used MTX monotherapy at the time of MMR booster vaccination and 11 (6%) used bDMARD monotherapy, which were all anti-TNF agents. Seventeen patients (9%) used a combination of csDMARD and bDMARD monotherapy, of whom 96% used anti-TNF agents. Fifty-one percent of the patients used no immunosuppressive therapy or NSAIDs.

3.2. Long-term humoral immunoprotection

For 67 patients, a serological sample was available five years post-vaccination (Table 1). In these samples, mean indices for measles and mumps, and geometric mean concentrations for rubella, were lower for patients who used bDMARDs at the time of vaccination compared to patients who did not (Fig. 1). Percentages of protective antibody levels after five years were also lower in bDMARD users compared to non-bDMARD users for both measles (60% vs. 86%), mumps (80% vs. 94%) and rubella (60% vs. 83%). The difference in absolute antibody levels between patients who used bDMARDs and patients who did not was statistically significant on both univariable and multivariable analysis for measles ($P = 0.02$ and P = 0.02, respectively), but not for mumps and rubella (Table 2). Similarly, on univariable analysis, the odds ratio for a protective antibody level between bDMARD users and non-bDMARD users was statistically significant for measles (0.23, 95% CI: 0.06–0.87), but not for mumps and rubella (Table 3). On multivariable analysis, odds ratios did not reach statistical significance.

In addition, antibody levels were analyzed for 169 patients from samples obtained at last available visit, with a median follow-up time of 6.9 years after vaccination (IQR: 2.8 – 8.8). For these analyses, samples obtained five years post-vaccination were disregarded. Here, MMR antibody levels decreased over time (Fig. 2), but the rate of decrease was not significantly different between bDMARD and non-bDMARD users (Table 4).

Table 2
Univariable (crude) and multivariable (adjusted) linear regression analyses for the association between bDMARD therapy at the time of MMR booster vaccination and IgG antibody levels after five years.

Virus	Analysis	Mean difference for bDMARD use vs. no bDMARD use (95% CI)	*P*-value
Measles (index)	Crude	−0.45 (-0.83 – 0.08)*	0.02*
	Adjusted[1]	−0.49 (-0.89 – −0.09)*	0.02*
Mumps (index)	Crude	−0.30 (-1.12 – 0.51)	0.47
	Adjusted[1]	−0.34 (-1.22 – 0.55)	0.46
Rubella (IU/ml)[2]	Crude	−0.14 (-1.14 – 0.85)	0.78
	Adjusted[1]	−0.37 (-1.46 – 0.72)	0.51

* Statistically significant effect.
[1] Adjusted for gender, JIA subtype and age at JIA diagnosis.
[2] Antibody levels were log-transformed.

4. Discussion

In the current study, we evaluated long-term immunogenicity of the MMR booster vaccine as a surrogate outcome for vaccine efficacy in children with JIA [18]. We observed that antibody concentrations post-vaccination were above the protective threshold in the majority of included patients and tended to decline over time. Five years post-vaccination, antibody levels against measles were significantly lower in patients who used bDMARDs at vaccination, of which 96% were anti-TNF agents. Antibody levels against mumps and rubella were also lower in bDMARD users, but this difference did not reach statistical

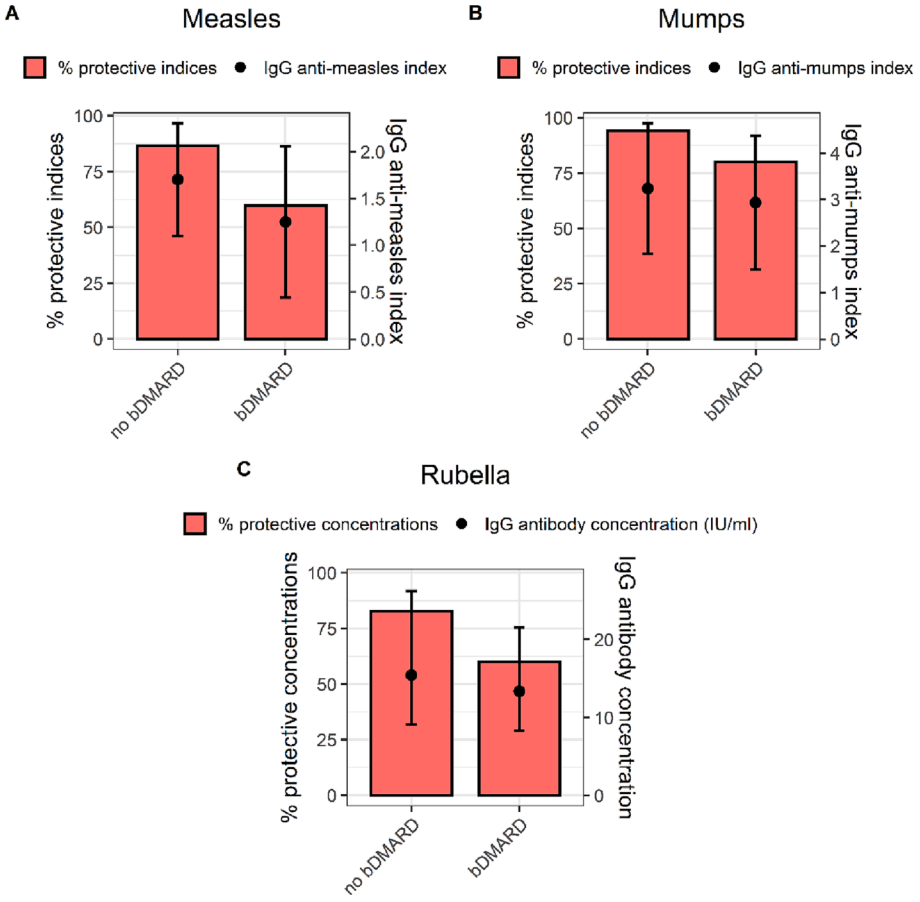

Fig. 1. MMR-specific IgG antibody assays five years post-booster vaccination (n = 67). Data are presented separately for JIA patients who did and did not receive bDMARD therapy at the time of booster vaccination. A & B: red bars indicate % protective indices >1.1 (considered protective). Black dots indicate mean indices with standard deviation. C: red bars indicate % protective concentrations ≥10 IU/ml (considered protective). Black dots indicate geometric mean concentrations with 95% confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Univariable (crude) and multivariable (adjusted) logistic regression analyses for the association between bDMARD therapy at the time of MMR booster vaccination and a protective IgG antibody concentration after five years.

Virus	Analysis	Odds ratio for bDMARD use vs. no bDMARD use (95% CI)	*P*-value
Measles	Crude	0.23 (0.06–0.87)*	0.03*
	Adjusted[1]	0.25 (0.05–1.07)	0.06
Mumps	Crude	0.24 (0.04–1.46)	0.11
	Adjusted[1]	0.18 (0.02–1.50)	0.11
Rubella	Crude	0.31 (0.09–1.13)	0.07
	Adjusted[1]	0.32 (0.07–1.38)	0.12

* Statistically significant effect.
[1] Adjusted for gender, JIA subtype and age at JIA diagnosis.

significance. The rate of antibody waning after vaccination was also not significantly different between bDMARD and non-bDMARD users.

A randomized trial published in 2013 reported no effect of MTX and bDMARDs on humoral response against measles, mumps and rubella in JIA patients 12 months after booster vaccination, although low patient numbers for the bDMARD group precluded definite conclusions [13]. Furthermore, a cross-sectional study concluded that JIA patients had lower antibody concentrations and seroprotection rates compared to healthy controls against mumps and rubella, but not measles. In JIA patients, the use of glucocorticosteroids and MTX did not influence antibody concentrations and seroprotection rates [19]. Other studies in patients with JIA and other pediatric rheumatic diseases also concluded that bDMARDs did not interfere with levels of MMR virus-specific IgG antibodies following booster vaccination [20,21]. One study in children with enthesitis-related arthritis (ERA) using adalimumab investigated the persistence of measles and rubella-specific IgG antibodies one and three years after booster vaccination and compared these with healthy age-matched children [22]. At both time points, the response was lower in ERA patients on adalimumab therapy compared with healthy children. In this study, no difference was found between children with adalimumab therapy only and children who received a combination therapy [22]. A study of 30 children and adolescents with SLE reported similar measles-specific antibody levels compared to a healthy age-matched control group, despite use of glucocorticosteroids and/or other immunosuppressive drugs [23].

Safety of the MMR booster vaccine in JIA patients is confirmed by the available literature. A large retrospective study of 186 JIA patients – of which 51% of the patients used csDMARD and 28% used bDMARD therapy – found that disease activity scores after MMR booster vaccination were not significantly different compared to pre-vaccination. Mild adverse events related to the MMR booster were reported for 7% of the patients and no serious adverse events were reported [24]. In a multicenter retrospective study of 211 booster vaccinated JIA patients – of which 124 patients received csDMARDs and/or bDMARDs – none of the patients developed a disease flare, including those with high disease activity [25]. Two systematic literature reviews also concluded that disease activity does not worsen following MMR booster vaccination in children with autoimmune rheumatic diseases [8,26]. Furthermore, the 2021 PRES and EULAR recommendations for vaccination of pediatric patients with autoimmune inflammatory rheumatic diseases indicate that the MMR booster vaccine can be safely administered in patients on MTX, and can be considered in patients treated with low-dose glucocorticosteroids, TNF-inhibitors, anti-IL1 and anti-IL6 therapy [14]. Other studies in children with rheumatic diseases also conclude that the MMR vaccine is generally well-tolerated and rarely associated with serious adverse events, and that postponing the MMR booster vaccination is often not required [11,13,20,25,27,28].

Waning of vaccine-induced immunity is considered to play a central role in the re-emergence of infections, especially among

Table 4
Linear regression analyses for the adjusted rate of antibody waning after MMR booster vaccination and the effect of bDMARD use.

Virus	Variable[1]	β (95% CI)	*P*-value
Measles ((index)	Follow-up time (years)	−0.02 (−0.05–0.01)[2]	0.13
	Follow-up time (years) *bDMARD use	−0.04 (−0.11–0.04)[3]	0.32
Mumps (index)	Follow-up time (years)	−0.02 (−0.08–0.04)[2]	0.51
	Follow-up time (years) *bDMARD use	0.06 (−0.12–0.23)[3]	0.53
Rubella (UI/ml)[4]	Follow-up time (years)	−0.04 (−0.11–0.04)[2]	0.33
	Follow-up time (years) *bDMARD use	−0.10 (−0.30–0.11)[3]	0.36

[1] Adjusted for gender, JIA subtype and age at JIA diagnosis.
[2] Represents the average decrease in antibody level unit per year.
[3] Represents the difference in rate of antibody waning between patients who used bDMARDs at the time of MMR booster vaccination and patients who did not.
[4] Antibody levels were log-transformed.

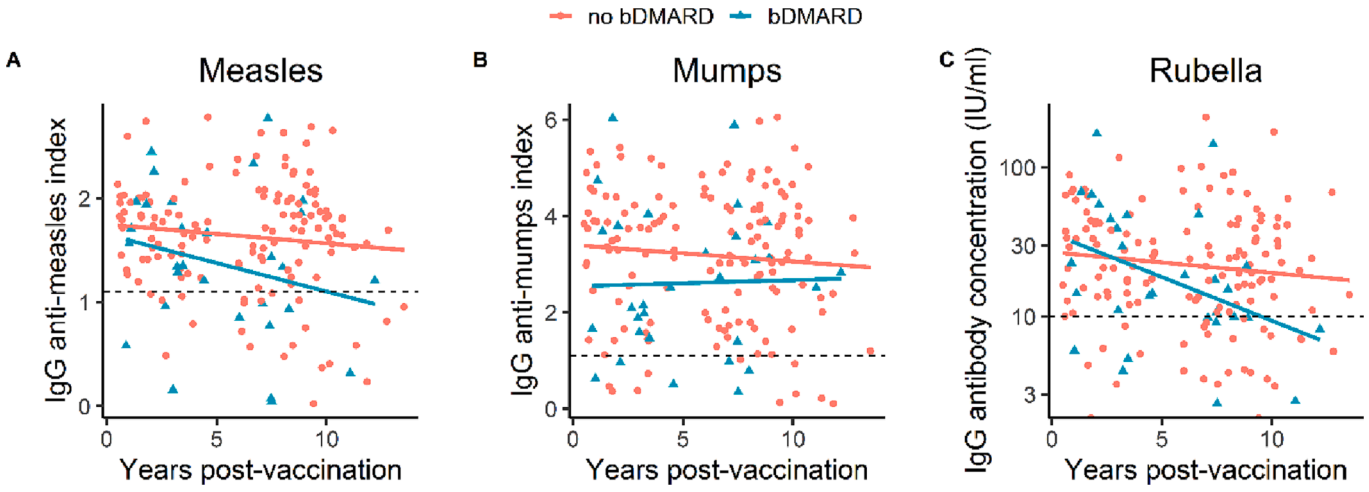

Fig. 2. Scatter plot with linear trend of MMR antibody levels in last collected samples (n = 169) over time as a function of bDMARD use at the time of booster vaccination. Horizontal dotted line indicates protective threshold.

immunosuppressed patients with rheumatic or other diseases. In the last few years, an increasing number of measles and mumps outbreaks has been registered worldwide [29–31]. A study of healthy adults who received two doses of the measles vaccine found that neutralizing antibody titers tended to decline over time, with inverse correlation between neutralizing antibody titers and the time elapsed between the two vaccinations [32]. Furthermore, a third dose of the MMR vaccine was found to improve immunity against mumps in young adults and is expected to be a good and safe intervention for controlling outbreaks [33]. A third MMR vaccine dose is also recommended in the United States for persons at increased risk for mumps during outbreaks, and has demonstrated to be safe and well tolerated [34]. These results may indicate that periodic vaccination against MMR is required to prevent sporadic infections, especially in patients whose antibody concentrations have decreased below the protective threshold years after vaccination. In the current study, although none of the included patients had reported measles, mumps or rubella infection, we also observed decreasing MMR antibody levels over time, with 40% of bDMARD users not being protected against measles and rubella already five years after booster vaccination.

This study has a few limitations. Due to its retrospective nature, time between MMR booster vaccination and last hospital visit varied per patient. Furthermore, it was not possible to retrieve exact dates of MMR booster vaccination for all patients, although all children in the Netherlands are vaccinated around their ninth birthday. Finally, there is still limited evidence about the correlation between vaccine-induced antibody titers and cell-mediated responses, because of the large number of samples and prolonged periods of follow-up, we could not analyze vaccine-induced T-cell responses in addition to humoral responses, which may also be important in conferring viral immunity.

In the current study we only included patients with JIA. Recently, there is sufficient data to assume that MMR booster vaccination is also safe and immunogenic in patients with other pediatric rheumatic diseases and in children receiving MTX, low dose glucocorticoids, anti-TNF, anti-IL-1 and anti-IL-6 therapy [8,14,26,35,36]. Further large multicenter studies are needed to shed light on these groups of patients and on patients with a primary immunodeficiency. Larger studies should also be performed in order to increase the strength of future recommendations for vaccination, and to obtain more knowledge on vaccine efficacy and safety in patients receiving bDMARDs.

In conclusion, the MMR booster vaccine demonstrated long-term immunogenicity in the majority of JIA patients included in the current study, although lower percentages of protective measles antibody levels were observed in bDMARD users. Clinicians should therefore consider to measure antibody levels at least five years after MMR booster vaccination, especially in bDMARD users, and advice an extra booster accordingly.

Funding

No funding was received for this research.

Ethics statement

Patients were included from the ongoing observational Pharmachild register. Pharmachild obtained approval from the institutional review board of University Medical Center Utrecht (11-499c) and is carried out in accordance with the Declaration of Helsinki. All patients provided written informed consent/assent.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All relevant data are reported in the article. Additional details can be provided by the corresponding author upon reasonable request.

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