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ORIGINAL ARTICLE

# Seroprotection against measles in previously vaccinated children with difficult-to-treat nephrotic syndrome

**Jiten Kumar Sahoo[1] · Soumya Tiwari[1] · Viswas Chhapola[1] · Manoj Jais[2]**

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## Abstract

**Background** Children with nephrotic syndrome (NS) are vulnerable to infections. Measles infection is an important cause of morbidity and mortality in immunosuppressed children. A suboptimal seroprotection against measles has been shown in immunocompromised children. There is limited published literature on measles immunity in children with difficult-to-treat nephrotic syndrome (DTNS). We compared the proportions of children with DTNS and healthy controls who were seroprotected against measles.

**Methods** This was a cross-sectional study. Measles-specific IgG antibodies of 108 children with DTNS (3 to 10 years of age) and an equal number of age-matched healthy controls were measured. All children had received two doses of measles-containing vaccine at 9–12 and 16–24 months of age under routine immunisation programme. Serum measles IgG antibody titres were measured by indirect ELISA. The assay results were interpreted as (1) > 11 NTU (NovaTec Units), positive/seroprotective titres; (2) 9–11, equivocal; and (3) < 9 NTU, negative. Inter- and intra-group comparisons were made to identify the disease characteristics related to seroprotection status.

**Results** The proportion of children with protective anti-measles antibodies ($n = 70$, 65%) was significantly lower in DTNS as compared to controls ($n = 88$, 81.48%) ($p = 0.005$). Their median [IQR] antibody titres were also significantly lower than those in controls (14.1 [14] NTU vs. 18.3 [15.2] NTU ($p = 0.001$). The age, gender, clinical subtype, duration of disease, and type of immunosuppressive therapy were not significantly different between seroprotected and non-seroprotected children with DTNS.

**Conclusion** A significantly lower percentage of fully vaccinated children with DTNS were seroprotected against measles compared to healthy controls.

**Keywords** Measles · Seroprotection · Steroid-sensitive nephrotic syndrome · Steroid-resistant nephrotic syndrome

## Introduction

Children with nephrotic syndrome (NS) are vulnerable to infections due to weak defences attributable to factors such as altered humoral and cell-mediated immunity, urinary loss of immunoglobulins and complement proteins, and treatment with immunosuppressive agents. The likelihood of infections is even greater in frequently relapsing/steroid-dependent and steroid-resistant NS (SRNS), grouped as difficult-to-treat nephrotic syndrome (DTNS). Infections often trigger a relapse of NS and are associated with higher hospitalisation and mortality rates [1–4]. About half of infections among children with primary NS are upper respiratory tract infections (URTI) [3].

Measles is a common cause of URTI in children in developing nations. The world has witnessed a resurgence

✉ Soumya Tiwari
soumyaakshay@gmail.com

Jiten Kumar Sahoo
sahoo.jitenkumar@gmail.com

Viswas Chhapola
viswaschhapola@gmail.com

Manoj Jais
drmanojjais@yahoo.co.in

[1] Department of Pediatrics, Kalawati Saran Children's Hospital & Lady Hardinge Medical College, Bangla Sahib Road, New Delhi 110001, India

[2] Department of Microbiology, Lady Hardinge Medical College, Bangla Sahib Road, New Delhi 110001, India

of measles recently, with approximately 869,770 confirmed cases of measles in 2019 with an estimated 207,500 deaths [5]. In 2020, India reported 5614 cases of measles, corresponding to an incidence rate of 4 cases per million [6]. Measles infection may present with atypical clinical pictures, and complications such as giant-cell pneumonia, encephalopathy, and death in immunosuppressed children [7–9]. The literature backs high case fatality of measles in immunocompromised patients with HIV infection and malignancy [10]. Apart from a few case reports, there is not enough data on measles morbidity and mortality in children with NS [8]. These children, however, are expected to have a more complicated measles illness due to their immunosuppressed condition. Measles can be prevented with an effective live viral vaccine, which is given as a two-dose schedule in routine immunisation programmes in many countries. The seroconversion rate after two doses of the vaccine is around 96%, but there is a slow decline in seroprotection even in healthy children [11]. A greater degree of reduced immunity against measles has been documented in children with malignancies, kidney transplantation, and HIV infection [12–15]. However, there is little evidence for the same in children with DTNS. We hypothesise that a lower percentage of fully immunised children with DTNS are seroprotected against measles. The aim of our study was to compare the proportions of children with DTNS and healthy controls who were seroprotected against measles following a two-dose routine immunisation schedule.

## Materials and methods

This was a cross-sectional study undertaken from November 2018 to March 2020 at a tertiary care hospital in New Delhi. The research was approved by the institutional ethics committee.

### Study population

Children with DTNS between 3 and 10 years were eligible for inclusion as cases. NS was defined as the presence of heavy proteinuria (early morning urine protein 3 + /4 + on dipstick, or spot urine protein: creatinine > 2 mg/mg, or urine albumin excretion > 40 mg/m$^2$/h), hypoalbuminemia (< 2.5 g/dl), and oedema. DTNS was labelled if a child had frequently relapsing (two or more relapses in initial 6 months or more than three relapses in any 12 months); steroid-dependent (two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation); or steroid-resistant (absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg per day for 4 weeks) course. Remission of the nephrotic state was defined as nil or trace urinary albumin (or proteinuria < 4 mg/m$^2$/h) in early morning samples for three consecutive days. Relapse was defined as urine albumin 3 + or 4 + (or proteinuria > 40 mg/m$^2$/h) in early morning samples for three consecutive days, in a child who was in remission previously [16]. Steroid-dependent and frequently relapsing NS were jointly labelled as steroid-sensitive NS (SSNS).

Children were included as:

Cases: If they were diagnosed as DTNS for a minimum of 6 months.
Controls: If they were healthy age-matched children visiting the outpatient department for vaccination and well-child visits.

*And* both cases and controls had received two doses of measles-containing vaccine (MCV), subcutaneously in the right upper arm, at 9–12 and 16–24 months of age under the Universal Immunisation Programme of India [17].

Children were excluded if they had any one of the following: (i) a past history of clinical illness compatible with measles; (ii) pre-existing primary immunodeficiency disorder; (iii) chronic illnesses such as chronic liver disease, diabetes mellitus, connective tissue disorder, malabsorption syndromes; (iv) active tuberculosis; (v) HIV infection; (vi) critically sick child; (vii) malignancy, transplant recipient; and (viii) recipient of blood transfusion and plasmapheresis in the last 6 months.

### Patient recruitment

We obtained written informed consent/assent for both cases and controls. Children with DTNS were enrolled during routine follow-up visits to the paediatric nephrology clinic. Epidemiological and clinical features were documented. Information on disease course and treatment, including drug-type and duration, was collected. A blood sample (3 ml venous blood) was taken from both cases and controls, centrifuged, and stored at –70 °C for measles antibody titre measurement.

### Analytical methods

Serum titres for measles IgG antibody were measured by indirect enzyme-linked immunosorbent assay (NovaLisa, Measles Virus IgG, NovaTec, Immunodiagnostica $G_{MB}H$, Germany). The results were interpreted according to the manufacturer's recommendations – values of > 11 NTU (NovaTec Units) were considered positive (seroprotective titres), 9–11 as equivocal, and < 9 NTU negative.

### Sample size

The primary outcome variable was the proportion of children with seroprotective measles antibody titres (> 11 NTU). We calculated the sample size using the results of a previous study by Han et al. [18]. The authors demonstrated that measles seroprotection was 72% in children with NS and 90% in controls. With an alpha error of 0.05 and power of 0.9, the sample size was 98 children with DTNS. We included 108 children considering a 10% drop-out rate. Healthy controls were included in the 1:1 ratio.

### Statistical analysis

We examined the data for normality distribution. Descriptive statistics were expressed as percentages and mean/median. Hypothesis testing was done using the independent sample *t* test, the Mann–Whitney *U* test, the Chi-square/Fisher exact test, and the Kruskal–Wallis H test. The Spearman's rho was used to analyse the correlation. A $p$ value of $<0.05$ was considered significant. STATA and Minitab were used for statistical analysis.

## Results

One hundred and seventeen children met the inclusion criteria, out of which one hundred and eight were included as cases. Nine children were excluded (active tuberculosis [$n=2$], systemic lupus erythematosus [$n=1$], past history of measles [$n=2$], critical illness [$n=4$]). An equal number of healthy children were selected as a control group. The cases and controls were comparable with respect to age (mean age cases: 78.4 ± 26 months, controls 72.8 ± 24 months, $p=0.1$) and gender (cases M:F 78:30, controls M:F 68:40, $p=0.15$). Supplementary Table 1 shows the demographic profile of children with DTNS. Seventy-one children had SSNS, and thirty-seven had SRNS.

The proportion of children with protective anti-measles antibodies ($n=70$, 65%) was significantly lower in DTNS as compared to controls ($n=88$, 81.48%) ($p=0.005$) (Table 1). Their median [IQR] antibody titres were also significantly lower than those in controls (14.1 [14] NTU vs. 18.3 [15.2] NTU ($p=0.001$). Patients had lower antibody titres than controls across the entire age spectrum (Supplementary Fig. 1).

Among children with DTNS, seroprotection status did not differ between boys and girls ($p=0.18$). There was no significant difference in the median [IQR] antibody titres among patients in relapse ($n=12$) compared to those in remission ($n=96$) (17.5 [19.1] vs. 13.9 [12.4], $p = 0.57$). Antibody titres were not significantly different for SSNS and SRNS patients (14.2 [14.4] vs. 14 [12.9], $p = 0.9$).

Antibody titres were not significantly different between children receiving steroids only compared to those receiving steroids with an additional immunosuppressive agent ($p=0.89$) (Fig. 1). Nine children received rituximab late in the course of disease, with the mean time gap between second dose of vaccine and rituximab being 53.8 (±25.6) months. The age, duration of disease, and age at diagnosis of NS were not significantly different between seroprotected and non-seroprotected children with DTNS (Table 2). The data for the number of relapses was available in ninety-seven children. There was a weak correlation (Spearman rho 0.235, $p=0.02$) between antibody titres and the number of relapses.

**Table 1** Comparison of measles-seroprotection status of children with difficult-to-treat nephrotic syndrome and controls

| Measles IgG titre NTU (Nova Tec units) | Cases ($n=108$) | Controls ($n=108$) | $p$-value |
|---|---|---|---|
| <9 | 28 (26%) | 10 (9%) | 0.005 |
| 9–11 | 10 (9%) | 10 (9%) | |
| >11 | 70 (65%) | 88 (82%) | |

## Discussion

We observed a much lower proportion of seroprotection against measles in DTNS as compared to that reported in other studies in children with NS [18, 19]. The overall proportion of children seroprotected against measles in our study was only 81% in healthy children and 65% in children with DTNS. It is lower than what can be explained by an estimated overall annual waning rate of 0·009 in healthy children [11]. We did not observe any significant differences in antibody titres among various clinical subtypes of DTNS

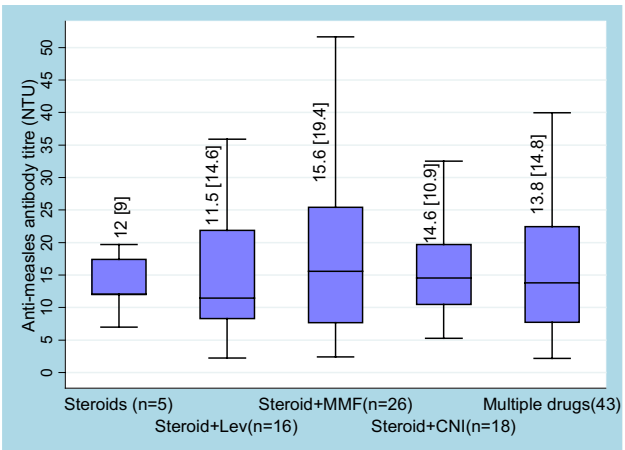


**Fig. 1** Box plots of anti-measles antibody titres in various immunosuppressive treatment categories

**Table 2** Comparison of disease-characteristics between seroprotected and non-seroprotected children with difficult-to-treat nephrotic syndrome

| Variable | Anti-measles IgG titres > 11 NTU (mean ± SD) | Anti-measles IgG titres < 11 NTU (mean ± SD) | *p*-value |
|---|---|---|---|
| Age (months) | 81.9 ± 26 | 71.95 ± 24.6 | 0.57 |
| Age at diagnosis of NS (months) | 37.9 ± 19.1 | 35.3 ± 18.7 | 0.48 |
| Duration of disease (months) | 43.7 ± 25.8 | 36.4 ± 21.4 | 0.14 |

(SDNS, FRNS, SRNS). In addition, we did not find any significant difference across treatment categories (Fig. 1). This is contrary to the observation by Ajay et al. who showed that a higher proportion of children on steroids alone were seroprotected compared to those receiving additional immunosuppressive medications. However, they did not test the statistical significance of this difference [19].

We did not witness any change in measles antibody titres with age, in cases as well as in controls (Supplementary Fig. 1). A serial measurement of antibody titres in the same child at different ages can provide insight into age- and disease-related variations in antibody titres.

We did not find significant difference between median anti-measles antibody titres in relapse as compared to remission states of DTNS. Han et al. reviewed the antibody status of 18 children with SSNS who received routine immunisation with diphtheria-pertussis-tetanus and measles-mumps-rubella vaccines [18]. Vaccine-specific antibodies were low during relapse, and immune recovery occurred rapidly during remission. The low anti-measles antibody titres in children with DTNS might be reflective of generalised hypogammaglobulinemia due to urinary losses of IgG [20, 21].

Kemper et al. made a different observation in children with SSNS, wherein they found that even children in remission had significantly lower titres of serum IgG than controls ($p < 0.001$) [22]. Therefore, generalised hypogammaglobulinemia in NS cannot be attributed entirely to urinary leak of IgG. We did not check serum IgG levels in our study children; therefore, we cannot comment upon this aspect.

Prolonged immunosuppression could also interfere with vaccine-derived immunity. Baris et al. showed that corticosteroid therapy leads to B and T cell reduction in NS, and the reduction in memory cells persists even after 3 months following stoppage of corticosteroids [23]. Kemper et al. observed that alterations in B and T lymphocytes in SSNS were more evident in remission than relapse and steroid treatment further reduces CD4 + T lymphocyte levels [24].

Unlike measles, specific antibody titres against other vaccines were demonstrated to be satisfactory in children with NS. Ulinski et al. showed that the seroconversion response to pneumococcal polysaccharide vaccine did not vary with prednisolone dosage and remained significantly higher than baseline levels even at eighteen months [25]. Antibody titres after influenza vaccination were maintained at 6 months, possibly due to boosting effects of subclinical infections [26]. Persistent seroprotection after varicella vaccine was observed in 91% even after 2 years, and low-dose steroids at vaccination did not affect antibody titres [27].

The incidence of measles has increased from 2017 to 2019, with outbreaks reported from both developing and developed countries [5]. Immunity gaps caused by failure to vaccinate children were primarily responsible for resurgence of measles [5]. The COVID pandemic has worsened the situation due to fewer children reaching vaccination centres as well as poor surveillance.

Seroconversion following measles vaccination is higher in children who receive the first dose at or after 12 months of age [28, 29]. The endemicity and a high childhood mortality of measles in India led to the recommendation of an early first dose of MCV (between 9 and 12 months) in the national immunisation schedule [17]. Also, the schedule recommends the second dose earlier (at 16–24 months of age) as compared to ACIP recommendation (second dose of MCV at 4–6 years) [30]. The above factors might have contributed to low anti-measles antibody titres in both cases and controls in our study and other studies from India [31, 32]. Therefore, additional doses of MCV in both unprotected patients with DTNS and healthy children should be considered. An evidence-based vaccination guideline for patients with immune-mediated disorders strongly recommends assessment of immunisation status and administration of age- and condition-appropriate vaccines prior to initiation of immunosuppressive therapy [33]. Although the guideline does not specifically mention NS, the recommendation can be extrapolated to this subset of immunosuppressed children also.

Our study had a few limitations. There was a chance of Berkson's bias while selecting controls. We did not perform a serial assessment of antibody titres in both relapse and remission in the same child, which is required to reliably associate low antibody titres with proteinuria. An adequate sample size and inclusion of a control group are the strengths of our study over earlier studies.

To conclude, we observed significantly lower measles antibody titres in children with DTNS. Based on our results, we recommend an individualised measles vaccination schedule for children with DTNS according to seroprotection status.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00467-021-05290-7.

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**Author contribution** ST, VC, MJ, and JKS were involved in the study design and data acquisition. ST and VC were involved in data analysis and interpretation. ST, VC, MJ, and JKS drafted the manuscript, performed critical revisions, and gave final approval for submission.

**Data availability** Data will be made available upon request.

**Code availability** Not applicable.

## Declarations

**Ethics approval** The study was approved by the Institutional Ethics Committee (LHMC/ECHR/2018/791), and conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

**Consent to participate** Written informed consent was obtained from the parents or legal guardians of all children. When possible, consent from the patients themselves was also obtained.

**Consent for publication** Study participants gave written informed consent for publication of the results of the study before their enrolment in the study.

**Conflict of interest/Competing interests** The authors declare no competing interests.

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