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Pneumonia vaccine response in individuals with Down syndrome at three specialty clinics

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Abstract

Individuals with Down syndrome (DS) have been particularly impacted by respiratory conditions, such as pneumonia. However, the description of co-occurring recurrent infections, the response to pneumococcal immunization, and the association of these was previously unknown. We screened individuals with DS using an 11-item screener and prospectively collected pneumococcal titers and laboratory results. We found that the screener did not successfully predict which individuals with DS who would have inadequate pneumococcal titers. Thirty four of the 55 individuals with DS (62%) had abnormal pneumococcal titers demonstrating an inadequate response to routine immunization. In the absence of a valid screener, clinicians should consider screening all individuals with DS through the use of pneumococcal titers to 23 serotypes to assess vaccine response.

KEYWORDS
Down syndrome, pneumonia, trisomy 21, vaccination

1 | INTRODUCTION

Inborn errors of immunity (IEIs), monogenetic causes of a deficient or dysregulated immune system, have impacted 1 in 1000 to 1 in 5000 individuals (Bonilla et al., 2015; Tangye et al., 2020). In 1993, a group of experts generated the only screening tool in existence for IEIs, the "10 warning signs." (Modell et al., 2011) This tool, combined with physician education and public awareness, has increased identification of patients with IEIs (Modell et al., 2011). No such screening tools have been developed for patients who may have a secondary immune deficiency or genetic syndromes which place them at increased risk of infections, such as Down syndrome (DS).

The laboratory evaluation has been shown to play a key role in assessing for IEI (Khan & Williams, 2022). A complete blood count (CBC) with differential may be one of the easiest tests to use, due to its wide availability. The absolute lymphocyte count (ALC) values in healthy children, defined as the exact number of lymphocytes in a sample of whole blood, have shown age-based differences in normative ranges (Shearer et al., 2003). Patients with immunodeficiencies involving T and B lymphocytes have abnormal ALC values, but a normal ALC does not exclude IEI. Laboratory evaluation has also typically

Abbreviation: DS, Down syndrome.

included an immunoglobulin profile (IgG, IgA, and IgM levels) and vaccine titers (IgG to tetanus, diphtheria, and *Streptococcus pneumoniae*). Normal ranges IgG, IgA, and IgM vary by age and must be interpreted according to age-related norms (Buckley et al., 1968). Vaccine titers assess the body's response to receiving a vaccine—that is, IgG specific to the vaccine should be produced to create the immune protective response that vaccines confer. Low specific IgG titers after receiving a vaccine could indicate immune deficiency.

Patients who have received the pneumococcal vaccine were protected from infection due to the *S. pneumoniae* bacteria. Multiple types of pneumococcal vaccine have been developed, including the pneumococcal conjugate vaccine (PCV13) and the pneumococcal polysaccharide vaccine (PPSV23). These two vaccines differed in the serotypes of *S. pneumoniae* that they were developed to protect against, and the mechanism by which the immune system is stimulated to make specific IgG. The Centers for Disease Control and Prevention (CDC) has recommended that all children younger than 5 years old receive PCV13. The CDC has also advised that children with "certain medical conditions" that increase their risk of pneumococcal disease should receive PCV13 at age 5 through 18 years, and should also receive PPSV23 at age 2 through 18 years (Centers for Disease Control and Prevention, 2023).

Children with DS have been shown to be at increased risk of severe pneumococcal infections (Blake et al., 2021). Pneumonia has been found to be the most common cause of hospital admissions, and the most common indication for the pediatric intensive care unit (ICU) admission for children with DS (Hilton et al., 1999; Santoro et al., 2021). Respiratory infections, like respiratory syncytial virus pneumonia, in children with DS has resulted in a higher risk of mortality, increased risk for hospitalization, and greater need for mechanical ventilation support than otherwise healthy children (Beckhaus & Castro-Rodriguez, 2018; Santoro et al., 2021). The 2022 American Academy of Pediatrics' *Health Supervision for Children and Adolescents with Down syndrome* suggested administering immunizations as recommended for all children, unless there are specific contraindications, and that children with "chronic cardiac or pulmonary disease" should be given the 23-valent PPSV at 2 years of age or older (Bull et al., 2022). However, DS, as a diagnosis, per se, has not been listed as one of the "certain medical conditions" identified by the CDC; patients with DS would need a co-occurring condition to qualify for the PPSV23.

To date, few studies have evaluated the response to pneumococcal vaccine in individuals with DS (Kusters et al., 2013; Nurmi et al., 1982; Valentini et al., 2015). Studies assessing vaccine response have significant limitations including small sample sizes, <23 serotypes assessed, and lack of additional immune evaluation (Kusters et al., 2013; Nurmi et al., 1982; Valentini et al., 2015). A generalization of the studies to date: children with DS are able to generate an antibody response that has been deemed "adequate" but lower than otherwise healthy children without DS. We do not know, however, if "adequate" levels are clinically protective and whether they are sustained over time. Data on pneumococcal vaccine response in adults with DS have been even more limited.

We began this study to identify which children with DS may be more likely to have an insufficient immune response when given vaccines. Specifically, in three specialty clinics for DS, we aimed to (1) characterize the immune response to pneumococcal vaccine at various intervals post-routine vaccination with PCV13 and/or PPSV23, and (2) correlate vaccine response with basic immunologic studies and clinical history to identify risk factors for poor vaccine response.

2 | METHODS

2.1 | Population

An experienced, international DS clinic consortium, the International Down Syndrome Patient Database, with a track record of clinical research and publication (Lavigne et al., 2015, 2017; Santoro et al., 2020, 2022; Sharr et al., 2016), informed this project. Three sites from this consortium (Massachusetts General Hospital, Duke University Medical Center, and Children's Mercy Hospital) participated in this study from April 2021 to April 2022. The three corresponding institutional review boards approved this study. Database consent was obtained during or following a visit to each site's specialty clinic. Each site collected and maintained data in REDCap® (Harris et al., 2009). Inclusion criteria were: (1) a clinical diagnosis of DS, (2) consent to participate in the international database, (3) a clinic visit to a participating site, (4) age 12 months or older, and (5) who answered "yes" to at least 1 of the 11-item immunodeficiency screening questions based on an existing 10-item screener (Bjelac et al., 2019) with an added question regarding recurrent upper respiratory tract infections. Patients were also excluded if they had incomplete data, defined as having fewer than 20 of 23 serotypes completed.

2.2 | Data collection

Two sources of data were used: (1) parent-reported clinical history information obtained through an 11-item IEI screening survey (Modell et al., 2011), and (2) laboratory evaluation including ALC from CBC with differential, immunoglobulin levels (IgG, IgA, and IgM), and titers to diphtheria, tetanus, and pneumococcus. All data were shared between sites in de-identified aggregate form.

2.3 | Data analysis

Data were summarized using means, standard deviations, and frequencies. Raw values of ALC and immunoglobulins were converted to *Z*-scores using age-based means and standard deviations in healthy children (Buckley et al., 1968; Shearer et al., 2003).

To assess which variables might predict nonresponse to child vaccines in our total cohort with DS, logistic regression for the binary outcome of abnormal pneumonia titers was performed. Presence of

abnormal pneumonia titers was defined by age as: if <6 years of age, consider abnormal if <50% of serotypes are ≥1.3 μg/mL and if ≥6 years of age, consider abnormal if <70% of serotypes are ≥1.3 μg/mL. We considered explanatory factors including demographic variables and relevant clinical history. If less than five patients had a given characteristic, we did not analyze the characteristic because we are unlikely to get stable/reliable estimates for these variables. As such, abscess development, deep-seated infections, history of immunodeficiency, malignancy, receipt of PPSV/Pneumovax were excluded from the analyses based on this criterion. Similarly, there was inadequate variability in number of prior doses of PCV13 and age at last dose of PCV13 for inclusion in the models, but this was by design as we wanted participants to be at least 12 months of age. We fit univariate models for each analyzable variable. A multivariable model was derived using backwards selection, retaining variables significant at $p < 0.05$. In addition, based on our a priori suspicion that history of pneumonia would be associated with abnormal titers, we fit a model including pneumonia history with adjustment for age, sex, and race/ethnicity. We also analyzed a subset of patients with DS who were vaccinated by standard protocol, by excluding those whose vaccination timing was unknown and excluding those who had received the Pneumovax vaccination.

Pearson's correlation coefficient was calculated for each serotype against all other serotypes. Positive correlations indicate that higher values for one serotype correlate with higher values for the other, while negative correlations suggest that higher values for one serotype correlate with lower values for the other.

The de-identified, aggregate data that support the findings of this study are available on request from the corresponding author.

3 | RESULTS

From April 2021 to April 2022, we identified 55 individuals with DS with sufficient data from our three sites (Table 1). These individuals with DS screened positive for at least one screening indicator and had blood work with an adequate number of pneumococcal serotypes. Participants ranged in age from 1 to 52 years of age with a mean age of 10.8 (±8.6) years with a median age of 8 years (Figure S1). Many participants were missing ethnicity information, but of those with race and ethnicity information available, most were White and not Hispanic/Spanish/Latino (Table 1).

3.1 | IEI screening survey

Among the screening results from these 55 individuals with DS, 21 (40%) screened positive for recurrent ear infections, and 22 (41%) for recurrent sinus infections (Table 2). All 11 items on the screening survey for recurrent infections were seen in at least one individual with DS. On average, individuals with DS screened positive for 2.2 symptoms, range 1–6.

TABLE 1 Demographic traits of 55 individuals with Down syndrome.

Trait		N (%)
Sex: male		28 (51)
Race		
White		31 (56)
Black or African American		1 (2)
Other (White and Portuguese)		1 (2)
Unknown		3 (5)
Missing		19 (35)
Ethnicity: Spanish/Hispanic/Latino		6 (11)
Site		
Massachusetts General Hospital		46 (84)
Duke Medical Center		5 (9)
Children's Mercy Hospital		4 (7)
Gestation		
Preterm (<37 weeks)		12 (22)
Full term (≥37 weeks)		39 (71)
Unknown		4 (7)
Co-occurring medical conditions for individual with Down syndrome		
Congenital heart malformation		42 (76)
GERD		20 (36)
Seizure disorder		6 (11)
Autoimmune diagnosis		7 (13)
Malignancy		1 (2)
Age (years)	Mean (std. dev)	10.8 (8.6)
	Median	8
	Range	1–52

Abbreviation: GERD, gastroesophageal reflux disease.

3.2 | Immune assessment

In obtaining *S. pneumoniae* vaccine history, most (90%) individuals had received four PVCs, and most (89%) had received the last dose at 12–15 months (Table 3). Only three individuals had ever received the PPSV (PPSV23, Pneumovax). Three individuals with DS had pneumonia known to be caused by *S. pneumoniae*.

Thirty-four participants with DS (62%) had overall abnormal pneumococcal titers using standard definitions used by practicing immunologists (Table 3). Of the 13 serotypes of *S. pneumoniae* in the PCV13 vaccine (routinely given in childhood), more than 50% of participants had adequate titers to serotypes 1, 3, 5, 6b, 7f, 9v, 19a, 19f, and 23f (Table 4). Less than 50% of participants had adequate titers to serotypes 4, 14, and 18c. Serotype 6a is included in PCV13 but is not assessed in laboratory testing. Response to serotypes not included in PCV13 was variable with the majority of patients mounting adequate response to serotypes 8, 10a, 15b, 17f, and 22f; the minority responded to serotypes 2, 11a, 12f, 20, and 33f (Table 4). Too few participants had titers for serotype 9n to make conclusions. Of the

TABLE 2 Eleven screening questions and number of positive responses for 55 individuals with Down syndrome.

Items	"Yes" responses: *N* (%[a])
1. Over the period of any 1 year, has the participant had recurrent ear infections? If <18 years old: ≥4 ear infections considering years from birth to current age If ≥18 years old >2 ear infections considering years 18 and up	21 (40)
2. Over the period of any 1 year, has the participant received antibiotics for ≥2 sinus infections?	22 (41)
3. Has the participant ever required antibiotics for ≥2 months with little improvement or persistent symptoms such as cough, trouble breathing, fever, or congestion in spite of treatment?	12 (22)
4. Over the period of any 1 year, has the participant had ≥2 documented episodes of pneumonia, based on clinical exam or x-ray?	8 (15)
5. Over the period of any 1 year, has the participant had ≥1 recurrent upper respiratory infection per month? If they are <18 years old, consider years from birth to current age If they are ≥18 years old, consider years 18 and up	14 (26)
6. If the participant is of pediatric age, has the participant displayed insufficient growth OR failure to gain weight in the last 2 years?[b]	10 (19)
7. Has the participant ever developed deep skin or organ abscesses in liver, spleen, lungs, bone, lymph nodes, or other organs?	3 (6)
8. In participants over 12 months of age, has the participant ever had persistent fungal infections involving skin, mouth (thrush), nail beds, or mucous membranes?	14 (25)
9. Has the participant ever had infections that did not respond to oral antibiotics and required i.v. antibiotics to resolve?	13 (24)
10. Has the participant ever had ≥2 deep-seated infections such as sepsis, meningitis, empyema, peritonitis, or septic arthritis in his/her lifetime?	1 (2)
11. Does the participant have a family history of a primary (genetic) immunodeficiency?[c]	3 (6)

Abbreviation: i.v., intravenous.

[a]% Calculated by dividing the number of "yes" responses by the number of completed responses. If response missing, this was not included in denominator.

[b]Defined as: (1) weight for length < 5th percentile on the Down Syndrome growth curve for boys/girls up to 36 months of age; (2) body max index (BMI) for age < 5th percentile on the standard pediatric growth curve for boys/girls over 36 months of age; (3) OR a sustained decrease in growth velocity, in which BMI on the standard pediatric growth curve or weight for length on the Down Syndrome growth curve falls by two major percentiles (percentile markers 95, 90, 75, 50, 25, 10, and 5) over time.

[c](1) Family should be defined as: a parent(s), sibling(s), aunt(s), uncle(s). (2) Primary immunodeficiency diseases are caused by a genetic mutation leading to deficiency of part or all of the immune system and leading to recurrent and sometimes severe infections. Infections should be the defining symptoms of the disease. Some examples include: severe combined immune deficiency, DiGeorge syndrome, common variable immune deficiency, IgA deficiency, hyper IgE syndromes. (3) Primary immunodeficiency does not include autoimmune diseases (lupus, inflammatory bowel disease [IBD], rheumatoid arthritis, etc). (4) Primary immunodeficiency does not include atopic diseases (asthma, atopic dermatitis, and food allergy etc.).

TABLE 3 Pneumonia vaccination and infection history for 55 individuals with Down syndrome.

Question	Answer	*N* (%)
How many doses of the pneumococcal conjugate vaccine (PCV13) has the participant received prior to today's clinic visit? (choose one)	4	49 (90)
	3	1 (2)
	1	1 (2)
	Unknown	4 (7)
At what age did the participant last receive a PCV13 vaccine? (choose one)	12–15 months	49 (89)
	Other	2 (4)
	Unknown	4 (7)
In addition to routine immunizations, has the participant ever received the vaccine PPSV23 (Pneumovax)?[a]	No	50 (94)
	Yes	3 (5)
	Unknown	2 (4)
Has the participant ever had any of the following infections that were known to be caused by *Streptococcus pneumoniae*? (choose all that apply)	Pneumonia	3 (5)
	Meningitis	0 (0)
	Sepsis	0 (0)
Did the patient have:		
Abnormal streptococcal titers?[b]	Yes, abnormal	34 (62)
Abnormal diphtheria titers?	Yes, abnormal	0 (0)
Abnormal tetanus titers?	Yes, abnormal	0 (0)
Additional labs		
Absolute lymphocyte count (ALC)	Below 10th percentile	23 (42)
	Missing	4 (7)
IgG	Below 10th percentile	3 (5)
	Missing	1 (2)
IgM	Below 10th percentile	7 (13)
	Missing	1 (2)
IgA	Below 10th percentile	8 (15)
	Missing	2 (4)

[a]In the United States, it is given if a child is 2 years of age or older if he/she is at high risk of pneumococcal disease including having congenital heart disease and asthma.

[b]Abnormal defined by age: Interpret results of pneumococcal titers 23 serotypes according to age of participant. If <6 years of age, consider abnormal if <50% of serotypes are ≥1.3 μg/mL. If ≥6 years of age, consider abnormal if <70% of serotypes are ≥1.3 μg/mL.

TABLE 4 Vaccine response in 55 individuals with Down syndrome (DS) receiving pneumococcal conjugate vaccine (PCV13+/−) pneumococcal polysaccharide vaccine (PPSV13) on pneumococcal titers.

		Inadequate titers defined as <1.3		Adequate titers defined as ≥1.3		Joshi et al. studying post-PPSV13 response in Down syndrome
Pneumococcal serotype	Individuals with missing titers, *N*	Individuals with DS, *N*	% of those with titers available	Individuals with DS, *N*	% of those with titers available	*N* with adequate titers, %
Serotype_1[a,b]	1	5	9%	49	91%	6 (54%)
Serotype_2[b]	0	30	55%	25	45%	4 (36%)
Serotype_3[a,b]	0	23	42%	32	58%	6 (54%)
Serotype_4[a,b]	0	40	73%	15	27%	8 (72%)
Serotype_5[a,b]	0	28	51%	27	49%	1 (9%)
Serotype_6b[a,b]	3	17	32%	36	68%	4 (36%)
Serotype_7f[a,b]	1	12	22%	43	78%	0
Serotype_8[b]	0	26	47%	29	53%	3 (27%)
Serotype_9n[b]	44	5	100%	0	0%	7 (63%)
Serotype_9v[a,b]	0	14	25%	41	75%	7 (63%)
Serotype_10a[b]	2	21	39%	33	61%	0
Serotype_11a[b]	0	41	75%	14	25%	5 (45%)
Serotype_12f[b]	0	48	87%	7	13%	0
Serotype_14[a,b]	0	33	60%	22	40%	9 (81%)
Serotype_15b[b]	1	23	43%	31	57%	6 (54%)
Serotype_17f[b]	0	16	29%	39	71%	0
Serotype_18c[a,b]	0	47	85%	8	15%	8 (72%)
Serotype_19a[a,b]	1	14	26%	40	74%	2 (18%)
Serotype_19f[a,b]	0	4	7%	51	93%	4 (36%)
Serotype_20[b]	0	37	67%	18	33%	3 (27%)
Serotype_22f[b]	0	5	9%	50	91%	0
Serotype_23f[a,b]	0	3	5%	52	95%	3 (27%)
Serotype_33f[b]	0	45	82%	10	18%	4 (36%)

[a]Serotype in the PCV13 vaccine.
[b]Serotype included in the PPSV23 vaccine.

three individuals who had received a PPSV23, two had adequate titers, and one individual had inadequate titers responding to 5 of 22 pneumococcal serotypes. Several serotypes were significantly correlated (Table S3).

In our cohort, diphtheria and tetanus titers were not abnormal (Table 3), based on reference lab values at our three sites (Table S4). Additional labs, including ALC, IgG, IgM, and IgA were abnormally low, below the 10th percentile, in some individuals with DS (42%, 5%, 13%, and 15%, respectively; Table 3).

3.3 | Regression analysis

In univariate models, positive screen for history of fungal infections and history of ear infections were significantly associated ($p < 0.05$) with *lower* odds of abnormal titers (Table 5). The univariate odds ratio (OR) for fungal infections was 0.23 (95% confidence interval [CI]: 0.06–0.83, $p = 0.025$), indicating that the odds of abnormal titers for a patient with prior fungal infections are *lower*, 0.23 times the odds of abnormal titers for a patient without prior fungal infections. The univariate OR for ear infections was 0.29 (95% CI: 0.09–0.93, $p = 0.038$; Table 5).

Multivariate logistic regression models were obtained using backward selection among all variables. Fungal infections and ear infections remained significantly associated with lower odds of abnormal titers on multivariable analysis (adjusted $p = 0.021$ and 0.024, respectively; Table 5 and Figure S2). Repeating this analysis in the subset of individuals with DS with confirmed up-to-date pneumococcal titers and excluding those who received Pneumovax (PPSV23) did not change regression results (Table S1). A third regression analysis using pneumonia history and demographic factors did not find the warning sign of history of episodes of pneumonia to be associated with inadequate streptococcal titers (Table S2).

Co-occurring conditions that could increase risk of infections—including gastroesophageal reflux disease (GERD), congenital heart disease, and prematurity—were not correlated

TABLE 5 Association between patient characteristics and abnormal pneumococcal serotype titers.

Variable	Comparison	Unadjusted odds ratio (OR)[a]	Lower 95% conf limit	Upper 95% conf limit	Unadjusted *p*-value	Adjusted OR[b]	Lower 95% conf limit	Upper 95% conf limit	Adjusted *p*-value
Fungal infections	Yes vs. no	0.23	0.06	0.83	0.025*	0.19	0.05	0.78	0.021
Ear infections	Yes vs. no	0.29	0.09	0.93	0.038*	0.23	0.06	0.82	0.024
ALC below 10th percentile	Yes vs. no	0.31	0.09	1	0.05	–	–	–	–
IgA Z-score below 10th percentile	Yes vs. no	5.6	0.64	49.35	0.121	–	–	–	–
IgM Z-score below 10th percentile	Yes vs. no	4.44	0.5	39.87	0.183	–	–	–	–
Number of warning signs	3+ warning signs vs. 1 warning sign	0.47	0.13	1.71	0.252	–	–	–	–
Seizure disorder	Yes vs. no	3.57	0.39	32.96	0.262	–	–	–	–
Race/ethnicity	Unknown vs. White	0.58	0.18	1.91	0.374	–	–	–	–
Hispanic ethnicity	Spanish/Hispanic/Latino vs. not Spanish/Hispanic/Latino	2.78	0.28	27.21	0.38	–	–	–	–
Pneumonia	Yes vs. no	0.53	0.12	2.42	0.415	–	–	–	–
Age	1-unit increase	0.98	0.92	1.04	0.444	–	–	–	–
GERD	Yes vs. no	0.67	0.22	2.06	0.481	–	–	–	–
Sinus infections	Yes vs. no	1.47	0.47	4.59	0.511	–	–	–	–
Gestational age	Preterm vs. term	1.55	0.4	6	0.53	–	–	–	–
i.v. Antibiotics	Yes vs. no	1.53	0.4	5.78	0.531	–	–	–	–
Insufficient growth	Yes vs. no	1.53	0.35	6.73	0.577	–	–	–	–
White race	Yes vs. no	2.1	0.12	37.12	0.613	–	–	–	–
Race/ethnicity	Black/Hispanic/other vs. White	1.32	0.22	8.04	0.766	–	–	–	–
Antibiotics ≥2 months	Yes vs. no	0.83	0.23	3.06	0.779	–	–	–	–
Upper respiratory infections	Yes vs. no	0.8	0.23	3.06	0.779	–	–	–	–
Number of warning signs	2 warning signs vs. 1 warning sign	0.85	0.21	3.36	0.814	–	–	–	–
Autoimmune disease	Yes vs. no	0.83	0.17	4.13	0.818	–	–	–	–
Congenital cardiac malformation	Yes vs. no	1.16	0.31	4.28	0.823	–	–	–	–
Sex	Male vs. female	0.97	0.32	2.89	0.951	–	–	–	–

Abbreviations: ALC, absolute lymphocyte count; i.v., intravenous; GERD, gastroesophageal reflux disease.

[a]Unadjusted results are obtained from univariate logistic regression models.

[b]Adjusted results are obtained from a multivariable logistic regression model.

*$p < 0.05$.

with abnormal pneumococcal titers and therefore not included in the model (Table 5).

4 | DISCUSSION

Children with DS are at an increased risk of severe pneumococcal infections (Blake et al., 2021); lower respiratory tract infections are the leading cause of acute hospital admission, and the predominant cause of ICU admissions in children with DS is pneumonia (Ram & Chinen, 2011). Children with DS have a 12 times increased risk of mortality when infected with pneumonia compared to children without DS (Ram & Chinen, 2011). Patients with DS are known to have several abnormalities of their immune system that likely contribute to this risk including mild to moderate T lymphocytopenia with decreased T cell function in vitro, mild to moderate B cell lymphocytopenia, IgA deficiency, and decreased neutrophil functionality (Ram & Chinen, 2011). In general, children with DS have been shown to generate an "adequate" titer response to various vaccines by normal ranges; however, their absolute titer levels have been lower than controls (Kusters et al., 2013; Nurmi et al., 1982; Valentini et al., 2015). Yet the immune response to vaccines for *S. pneumoniae* was not previously well characterized, and no studies had examined the impact of routine pneumococcal vaccination on etiologies of pneumonia in children with DS. Using an existing immunodeficiency screener (Modell et al., 2011) of "10 warning signs" of primary immunodeficiency diseases (McCusker et al., 2018; Bjelac et al., 2019) and an additional question regarding recurrent upper respiratory tract infections, we identified 55 individuals with DS who screened positive for at least once warning sign and had sufficient laboratory data for inclusion in our analysis.

Our cohort with DS screened positive on different questions from the same screener used in the general pediatric and adult population (Bjelac et al., 2019). In our cohort, we found that the most positive screening questions were to recurrent ear infections and sinus infections (Table 2). In contrast, among pediatric patients without DS, Subbarayan et al. (2011) found that among those with a primary immunodeficiency, the most prevalent positive screening questions were for use of intravenous (i.v.) antibiotics, positive family history, and failure to thrive. In another study of pediatric subjects, those with primary immunodeficiency had a significantly elevated frequency of recurrent pneumonia (OR 2.9, $p < 0.001$), failure to thrive (OR 2.1, $p < 0.001$), need for i.v. antibiotics (OR 2.1, $p < 0.001$), serious bacterial infection ($p < 0.001$), and recurrent otitis media (OR 1.5, $p = 0.027$) compared to controls (Bjelac et al., 2019). These differences in frequency of responses might be due to the underlying anatomy of individuals with DS or to the co-occurring conditions which are more prevalent in DS. For example, otitis media with effusion impacts 50%–70% of children and adolescents with DS (Bull et al., 2022), but it is possible that the underlying cause of this could be related to anatomical reasons rather than IEI. Anatomic factors contributing to infection risk include laryngomalacia, tracheomalacia, pulmonary hypoplasia, midface hypoplasia, macroglossia, mandibular hypoplasia, enlarged tonsils and adenoids, external ear canal stenosis, small Eustachian tube, and GERD (Ram & Chinen, 2011).

In characterizing the immune response to pneumococcal vaccine at various intervals post-routine vaccination with PCV13 and/or PPSV23, we found that many (62%) children with DS had abnormally low pneumococcal titers indicating an inadequate response to routine vaccination. The previous literature has been mixed, showing both adequate (Kusters et al., 2013) and inadequate (Joshi et al., 2011; Kusters et al., 2009) responses to vaccination in individuals with DS. Kusters et al. found no defects in response to the conjugated (routine childhood vaccine) or unconjugated (PPSV23, elderly vaccine) pneumococcal vaccine in a study of 18 participants, 6–24 years of age, with DS based on both antibody titers and in vitro opsonophagocytosis (Kusters et al., 2013). Also, in comparing response to conjugated (routine childhood vaccine, PCV13) pneumococcal response in 15 children with DS to 15 children without DS, similar increases in pneumococcal-specific IgG antibodies and memory B cells were seen (Valentini et al., 2015). All children had completed a routine vaccine series with PCV13 prior to the booster administered in this study. However, the children with DS had fewer pneumococcal-specific memory B cells in response to their routine vaccine series with PCV13, which may reflect exhaustion of the memory B cells in children with DS (Valentini et al., 2015). Joshi et al. (2011) found that children with DS specifically had suboptimal response to certain serotypes (7F, 10A, 12F, 17F, and 22F) of *S. pneumoniae*. In our cohort, we also found suboptimal response, but to different serotypes (only 9N had no participants with an adequate immune response; Table 4).

When determining which screener questions would best correlate with abnormal pneumococcal titers, regression analysis found two screening questions that were associated with *lower* risk for abnormal titers. Both history of recurrent ear infections and history of persistent fungal infections in our cohort with DS were significantly associated with lower odds for abnormal titers indicating an inadequately low immune response ($p < 0.01$; Table 5). Typically, a positive response to an IEI screening survey question would indicate immunodeficiency and predisposition to an abnormally low response to vaccination. We hypothesized that screening indicators would be associated with greater odds of abnormal pneumococcal titers; however, we did not find any of the screening questions to predict this. Our findings that history of ear infections and fungal infections were associated with lower odds for abnormal titers was counterintuitive to our hypothesis, but could be explained in a number of ways. As our screening questions asked about history broadly, without pathologic confirmation through culture for microbial source, it is possible that our cohort with DS had higher rates of non-pneumococcal acute otitis media, which led to positive IEI screening survey response but did not impact pneumococcal titer levels. Further, the prevalence of co-occurring conditions in individuals with DS, such as high incidence for recurrent ear infections among all individuals with DS (Bull, 2020; Bull et al., 2022), may yield the screener ineffective to detect those individuals with DS with IEI. Additionally, future studies could evaluate the link between history of persistent fungal infection or of recurrent

ear infections and lower odds of abnormal titer of anti-pneumococcal antibody. It is possible that immune defects could predispose to fungal infection or ear infections, and those defects could be linked to better pneumococcal vaccine response in people with DS. Alternatively, one would generally expect an antibody defect if a T cell defect leading to fungal infections is present, but not always. For pneumococcal serotypes not included in the vaccine, we know that people obtain protective titers through exposure. Therefore, it is possible that frequent infections represent an adjuvant that improves pneumococcal vaccine response in people with DS. Regardless, knowing that the IEI screening survey was not predictive of pneumococcal response is useful information for those clinicians wishing to identify which, of up to 62%, among their patients with DS are inadequately responding to routine PCV13 immunization.

Our project used a multi-site clinical cohort to assess the use of an existing screener questionnaire to detect immunodeficiency in individuals with DS. In assessing pneumococcal vaccine titers, we found that many had inadequate immune response despite vaccination, but this was not predicted from the IEI screening survey questions. Without a useful screening, this finding suggests that clinicians might consider screening all children with DS for vaccine response. Additional research among a cohort of individuals with DS who screen negative on this screener would strengthen this recommendation. In our methodology, we found it useful to screen for all 23 pneumococcal, and we describe the use of a scoring system used by practicing immunologists (Orange et al., 2012) rather than following standard laboratory reference ranges.

Previous studies suggest it may be more common for families of children with DS to express suggested vaccine hesitancy and have found parent-reported rates of only 58% of children with DS being up-to-date on routine childhood vaccines (Langkamp et al., 2020). Yet, overall, most of our cohort had received the full pneumococcal vaccination, and several had even received the PPSV23. Our three DS clinics may not represent the broader population of children with DS, or previously reported parent-report survey may have reflected a different cohort than that of our clinics. This study is limited by its reliance on a clinic-based cohort with its inherent recruitment bias and lack of generalizability to the broader population with DS; however, our cohort is larger than existing studies of pneumococcal vaccine response which have included 15–18 individuals with DS (Kusters et al., 2013; Valentini et al., 2015). We also obtained clinical information through parent report to the immunodeficiency screener, which may have recall bias due to reliance on recall and estimation of number of infections in a given time frame. We asked the age at which a patient had last received an immunization, but there may be differences based on time since that last vaccination as an older teen or adult would have received their last PCV13 years ago while a younger child would be closer to their routine vaccinations. However, we did not see any age-related differences in our results to suggest that timing from vaccination predicted inadequate pneumococcal titer values.

Our cohort all had at least one positive screening symptom, and thus, does not provide data on those individuals with DS without an IEI symptom which were not included in our study. Further, as all individuals in the cohort in this study screened positive to at least one screening question, the individuals may be experiencing frequent infections, and parents in this group may be more interested to seek out all options to prevent infection and may be less vaccine hesitant. Analyses of those individuals with DS who had not received the PPSV23 did not differ, suggesting that our results were not impacted by the limited number of individuals who had received additional immunization through PPSV23. However, our sample size limits the ability to draw conclusions regarding the efficacy of the PPSV23 at improving pneumococcal immunity gaps identified.

Future study could build on this project in a variety of directions. Continued tracking of this cohort of patients with DS to determine if there is a clinical benefit and response to receiving PPSV23 through repeat of pneumococcal titers could build on the outcomes of the data described here. Also, obtaining additional laboratory data to fully describe the cellular response to vaccination, or obtaining titers on those patients with DS who screened negative for IEI symptoms could provide more information to characterize the vaccine response. Future study could also include increased sample size from more clinics, or from a population-based cohort. Given the high rates of inadequate pneumococcal vaccine response and morbidity and mortality associated with pneumonia in individuals with DS, adding "Down syndrome" to the CDC list of "certain medical conditions" which could receive PPSV23 is another reasonable consideration to increase physician awareness and insurance coverage of this vaccine.

5 | CONCLUSIONS

A screener used to detect IEI did not successfully identify which patients with DS would have abnormally low pneumococcal titers indicating an inadequate pneumonia vaccine response. Clinicians might consider universally measuring the 23-serotype pneumonia titers in all individuals with DS given the high rate of abnormal pneumococcal titers in our cohort.

AUTHOR CONTRIBUTIONS

Stephanie L. Santoro: Conceptualization, data curation, methodology, writing—original draft, writing—review and editing. **Carolyn H. Baloh**: Conceptualization, methodology, writing—review and editing. **Sarah J. Hart**: Conceptualization, data curation, methodology, writing—review and editing. **Nora Horick**: Formal analysis, writing—review and editing. **Priya S. Kishnani**: Conceptualization, methodology, writing—review and editing. **Kavita Krell**: Conceptualization, data curation, methodology, writing—review and editing. **Nicolas M. Oreskovic**: Conceptualization, methodology, writing—review and editing. **Mikayla Shaffer**: Data curation, writing—review and editing. **Nasreen Talib**: Conceptualization, data curation, methodology, writing—review and editing. **Amy Torres**: Conceptualization, data curation, methodology, project administration, writing—review and editing. **Gail A. Spiridigliozzi**: Conceptualization, data curation, methodology, writing—review and editing. **Brian G. Skotko**: Conceptualization, methodology, project administration, writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

Stephanie L. Santoro has received research funding from LuMind IDSC Down Syndrome Foundation to conduct clinical trials for people with Down syndrome (DS) within the past 2 years. She serves in a nonpaid capacity on the Board of Directors of the Massachusetts Down Syndrome Congress, the Board of Directors of the Down Syndrome Medical Interest Group (DSMIG-USA), and the Executive Committee of the American Academy of Pediatrics Council on Genetics. Brian G. Skotko occasionally consults on the topic of DS through Gerson Lehrman Group. He receives remuneration from DS nonprofit organizations for speaking engagements and associated travel expenses. Within the past 2 years, Dr. Skotko received annual royalties from Woodbine House, Inc., for the publication of his book, *Fasten Your Seatbelt: A Crash Course on Down Syndrome for Brothers and Sisters*. In the past 2 years, he has also received research funding from AC Immune and LuMind IDSC Down Syndrome Foundation to conduct clinical trials for people with DS. Dr. Skotko is occasionally asked to serve as an expert witness for legal cases where DS is discussed. Dr. Skotko serves in a nonpaid capacity on the Honorary Board of Directors for the Massachusetts Down Syndrome Congress and the Professional Advisory Committee for the National Center for Prenatal and Postnatal Down Syndrome Resources. Dr. Skotko has a sister with DS. The other authors do not have any conflicts to disclose.

DATA AVAILABILITY STATEMENT

The de-identified, aggregate data that support the findings of this study are available on request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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