

Live Vaccine Use and Safety in DiGeorge Syndrome



WHAT'S KNOWN ON THIS SUBJECT: Individuals with DiGeorge syndrome (DGS) have varying degrees of immunodeficiency. All are susceptible to vaccine-preventable infections with serious complications. Although live vaccines are generally contraindicated in this population, limited evidence suggests that they may be effective and safe for select individuals.



WHAT THIS STUDY ADDS: Many individuals with DGS received live vaccines despite having a known diagnosis. Adverse events following live immunizations were typically minor and self-limited, suggesting that live vaccines may be considered for patients with DGS who exhibit mild-to-moderate immunosuppression.

abstract



OBJECTIVE: Live vaccines are generally contraindicated in patients with DiGeorge syndrome (DGS), a congenital disorder characterized by cellular immune deficiency. Vaccine utilization and safety in this population are not well described. This study examined vaccination patterns and adverse events following live immunization (AEFLI) in these individuals.

METHODS: A multicenter retrospective cohort study was conducted in subjects with DGS confirmed by fluorescence in situ hybridization assay (chromosome 22q11.2 microdeletion). Live vaccine-preventable illnesses, vaccination coverage and timeliness, and AEFLIs in the 56-day window after live vaccination were examined. Bivariate and multivariable analyses assessed the impact of demographics, medical history, timing of diagnostic confirmation, and preceding immune function on vaccination patterns and AEFLIs.

RESULTS: Of 194 subjects, 77% and 75% received measles-mumps-rubella (MMR) and varicella vaccines, respectively; 58% completed recommended vaccinations by age 19 to 35 months. Adverse events occurred after 14% and 20% of MMR and varicella vaccine doses, respectively. Most events were minor, few were serious, and no deaths were reported in post-live vaccination windows. Although early diagnostic confirmation negatively affected live vaccination coverage and timeliness ($P < .001$), baseline CD4% did not differ between subjects who did or did not receive live vaccines by 12 to 18 months. Among varicella vaccine recipients, those with a subsequent adverse event had a lower preceding CD4% ($24.8\% \pm 7.3\%$) than those without ($35.5\% \pm 11.7\%$) ($P < .05$); no CD4% differences were observed with MMR vaccination. Fourteen unvaccinated subjects experienced live vaccine-preventable illnesses.

CONCLUSIONS: Live vaccines were frequently given and generally well-tolerated among patients with DGS with mild-to-moderate immunosuppression.

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KEY WORDS

DiGeorge syndrome, chromosome 22q11.2 microdeletion syndrome, live vaccines, adverse events, vaccination

ABBREVIATIONS

AE—adverse event
AEFLI—adverse event following live immunization
CISA—Clinical Immunization Safety Assessment Network
DGS—DiGeorge syndrome
DTP/DTaP—diphtheria-tetanus-pertussis (whole-cell or acellular)
ED—emergency department
FISH—fluorescence in situ hybridization
IPV—inactivated poliovirus vaccine
MMR—measles-mumps-rubella
MMRV—measles-mumps-rubella-varicella
OPV—oral poliovirus vaccine
WHO—World Health Organization

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DiGeorge syndrome (DGS) is most commonly caused by a chromosome 22q11.2 microdeletion that occurs in 1:3000 to 1:6000 births, making it one of the most prevalent chromosomal abnormalities affecting children.^{1–4} Thus, it is of particular public health importance.⁵ Most patients with DGS have mild-to-moderate immunosuppression (ie, partial DGS); ~1% have thymic aplasia with severe T-cell deficiency (ie, complete DGS) that may necessitate thymus or bone marrow transplantation.^{6–9} Patients with DGS are at increased risk of recurrent and/or prolonged viral infections, including vaccine-preventable infections (eg, varicella),^{10,11} and secondary bacterial infections.⁷

Live vaccines are generally contraindicated in individuals with severe cell-mediated immunodeficiency, such as complete DGS, yet may be considered in those with less-severe T-cell immunodeficiencies, such as partial DGS.^{12,13} Earlier small retrospective studies revealed that many patients with DGS received measles-mumps-rubella (MMR) and varicella vaccines.^{10,11} No serious adverse events (AEs) were reported after vaccination, although power was limited; 9% to 23% experienced minor AEs, comparable to rates seen in the general population.^{13–15} Two small prospective studies similarly demonstrated that 7% to 21% of patients with DGS experienced minor AEs after MMR vaccination.^{16,17} Further characterization of vaccination patterns in this population, including differences in coverage and timeliness based on demographic characteristics, vaccine type (live versus inactivated), timing of diagnostic confirmation, and preceding immune function, is needed. A comprehensive investigation of live vaccine safety, including more recently introduced vaccines (ie, rotavirus), among patients with DGS is also warranted and may be enhanced using new causality assessment algorithms.^{18–20}

This study from the Clinical Immunization Safety Assessment (CISA) Network

describes live vaccine-preventable illnesses, vaccination patterns, and adverse events following live immunization (AEFLIs) among 194 individuals with a documented chromosome 22q11.2 microdeletion.

METHODS

This retrospective cohort study was conducted by the CISA Network, a collaboration between the Centers for Disease Control and Prevention and select academic medical centers that conduct immunization safety assessments and research.²¹ Individuals were eligible for inclusion if they had a chromosome 22q11.2 microdeletion detected by fluorescence in situ hybridization (FISH) assay, which was typically performed at initial diagnosis or to confirm a clinical diagnosis in those born before FISH assay became available (1993).²² Subjects were identified by *International Classification of Diseases, Ninth Revision* searches, clinical data repository queries, and lists from subspecialists caring for patients with DGS. At 4 study sites, eligible individuals or their parents (if <18 years old) gave informed consent and identified all providers from whom medical records were then requested. The fifth site received a waiver of informed consent for medical record abstraction. This study was approved by each site's institutional review board.

Medical record abstractions were performed by trained study personnel by using standardized abstraction forms. Collected data included demographic characteristics (eg, gender, race/ethnicity), medical history (eg, FISH testing, cardiac history), laboratory studies (eg, all available lymphocyte subsets, lymphocyte proliferation responses to mitogens and specific antigens), immunization history, provider-documented live vaccine-preventable illnesses, and AEFLIs. Sites 1 and 3 (Table 1) abstracted AEFLI data from all 56-day postvaccination windows (eg, comprehensive approach).

For feasibility reasons, sites 2, 4, and 5 were limited to using a targeted approach, abstracting data only from the 56-day postvaccination windows identified by families during the enrollment process or providers during medical record ascertainment (“did [subject] have any AEFLIs? If yes, please describe [including approximate dates]”).

The primary outcome measure was a medically attended AE occurring 0 to 56 days after live immunization. AEFLIs were broadly defined as any constellation of signs, symptoms, and/or diagnoses. AEFLIs resulting in emergency department (ED) visits or hospitalizations were analyzed separately. Live vaccines included MMR and varicella-containing (MMR, varicella, MMRV), oral poliovirus (OPV), BCG, and rotavirus vaccines. Only 1 BCG and 4 MMRV doses were received. MMRV was included in the separate MMR and varicella vaccine analyses. No live-attenuated influenza, oral typhoid, or yellow fever vaccinations were recorded.

Secondary outcomes included (1) live vaccine-preventable illnesses, defined as measles, mumps, rubella, varicella, or rotavirus illnesses based on history, examination, and/or laboratory confirmation (required of rotavirus infection); (2) vaccination coverage, described as MMR and varicella vaccination by 12 to 18 months and per the 4:3:1:3:3:1 schedule²³ for 19- to 35-month-olds with ≥ 1 health care encounter in the abstracted record after 18 months of age; and (3) vaccination timeliness, determined by age(s) at MMR and varicella vaccination (first dose) and diphtheria-tetanus-pertussis (whole-cell or acellular) (DTP/DTaP) vaccination (fourth dose).²⁴ Analyses of *Haemophilus influenzae*, hepatitis B, and varicella vaccinations included only children for whom these vaccines were available and recommended for similarly aged healthy children.²⁵

Key independent variables included demographic characteristics, study site, abstraction procedure (ie, comprehensive

TABLE 1 Study Population Characteristics

Demographics (<i>n</i> = 194)	
Gender, % (<i>n</i>)	
Female	51 (99)
Male	49 (95)
Ethnicity, % (<i>n</i>)	
Non-Latino	72 (140)
Latino	24 (47)
Unknown	4 (7)
Race, % (<i>n</i>)	
White	66 (128)
Asian	15 (28)
Black	8 (16)
Unknown	11 (22)
Study site enrollment, % (<i>n</i>)	
Site 1	45 (87)
Site 2	27 (53)
Site 3	14 (27)
Site 4	11 (22)
Site 5	3 (5)
Medical history (<i>n</i> = 194)	
Chromosome 22q11.2 microdeletion, % (<i>n</i>)	100 (194)
Timing of FISH confirmation, % (<i>n</i>)	
Prenatal	2 (4)
Postnatal	98 (190)
Age, y, at FISH confirmation ^a	
Mean (SD)	2.9 (5.0)
Range	0–24.5
Cardiac disease, % (<i>n</i>) ^b	
Cyanotic heart disease	40 (77)
Congestive heart failure	23 (45)
Pulmonary hypertension	10 (20)
Cardiac surgery, % (<i>n</i>)	62 (121)
Deaths, % (<i>n</i>)	3 (5)
Immune function	
CD4%, % (<i>n</i>) (total <i>n</i> = 121) ^c	
≥25% (no immunosuppression)	66 (80)
15% to 24% (moderate immunosuppression)	29 (35)
<15% (severe immunosuppression)	5 (6)
Mitogen response, % (<i>n</i>) (total <i>n</i> = 29)	
Any abnormal ^d	31 (9)
Only normal	69 (20)
Specific antigen response, % (<i>n</i>) (total <i>n</i> = 27)	
Any abnormal ^d	74 (20)
Only normal	26 (7)

^a For subjects with prenatal FISH confirmation of a chromosome 22q11.2 microdeletion, age was defined as day 0.

^b Hemodynamically significant. Some subjects fulfilled criteria for ≥1 category.

^c Evidence of immunosuppression on at least 1 occasion during the observation period. Subjects were assigned according to the greatest level of immunosuppression.

^d Any abnormal response that was reported as low, decreased, or negative.

versus targeted), timing of FISH confirmation, hemodynamically significant cardiac disease, history of cardiac surgery, and CD4% before live vaccination or by age 12 to 18 months, if unvaccinated. Although all subjects had FISH confirmation at some time point, bivariate and multivariable analyses examining timing of FISH confirmation, dichotomized into early (<1 year of age) and late (≥1 year of age), were limited to those born after this assay became available (1993) (*n* = 160).²² CD4% were categorized as <15% (severe immunosuppression), 15% to 24% (moderate immunosuppression), and ≥25% (no evidence of immunosuppression).²⁶ Lymphocyte proliferative responses to mitogens and specific antigens were categorized as normal (ie, positive, adequate) or abnormal (ie, low, decreased, negative).

Descriptive analyses were performed for demographics, timing of FISH confirmation, cardiac history, immune function, live vaccine-preventable illnesses, vaccination coverage, and AEFLIs. The causal relationships between live vaccination and rash or pneumonia, 2 commonly described complications of live vaccination in immunocompromised patients,^{13–15} were assessed by using World Health Organization (WHO) criteria modified by CISA investigators²⁰ and a novel algorithm developed by the CISA Network.¹⁸ If a subject died, cause of death provided in the medical record was accepted; previous live vaccine-preventable illnesses and vaccinations were reviewed.

The relationships between AEFLI and demographic characteristics, study site, abstraction procedure, timing of FISH confirmation, and cardiac history were assessed by using χ^2 and Fisher's exact tests. Similar analyses were performed for vaccination coverage. Factors found to be significant at $P < .10$ were added to the multivariable logistic regression models. CD4% results were compared between (1) live vaccinated and unvaccinated subjects

and (2) subjects with and without AEFLIs using Wilcoxon-Mann-Whitney test. Timeliness of MMR, varicella, and DTP/DtP vaccination was examined by using survival analyses.^{27,28} Individuals were censored when they received the vaccine of interest or at the time of last provider documentation in the abstracted record. Analyses were performed by using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Study Population

The study included 194 individuals born between 1974 and 2008 (Table 1). The mean observation period was 8.3 years; subjects ranged in age between 0 and 31.5 years. All underwent FISH diagnostic confirmation, most (*n* = 120/194) before 1 year of age. Most (*n* = 121/194) had hemodynamically significant cardiac disease and underwent cardiac surgery. Many exhibited lymphocyte subsets below or in the low-normal range for healthy individuals (Supplemental Information Table 6).²⁹ One-third of subjects with available CD4% results (*n* = 41/121) had evidence of immunosuppression (CD4% <25%); the proportion who were immunosuppressed did not differ based on timing of FISH confirmation. Among the 5% (*n* = 6/121) with documented severe immunosuppression (CD4% <15%), total lymphocyte counts ranged from low (*n* = 1) to normal (*n* = 3), CD3/CD3% ranged from low (*n* = 4) to normal (*n* = 1), and CD8/CD8% ranged from low (*n* = 5) to normal (*n* = 1).²⁹ Most subjects with lymphocyte proliferation testing had normal mitogenic, but abnormal specific antigenic responses. Three of 25 subjects had an abnormal response to tetanus antigen: 1 previously unvaccinated, 1 vaccinated 20 years before testing, and 1 with booster vaccination <1 month before testing; none had a CD4% <25% around the time of testing. Five subjects died; no death was assessed to be related to live vaccination. No differences in timing of FISH confirmation, cardiac

history, or immunosuppression were noted between study sites or based on abstraction procedure.

Live Vaccine–Preventable Illnesses

Fourteen subjects experienced a live vaccine–preventable illness (Table 2). Of subjects unvaccinated against varicella ($n = 59$), 11 (19%) experienced varicella infection; none required ED visits or hospitalizations. Of subjects unvaccinated against rotavirus ($n = 182$), 3 (2%) were hospitalized with laboratory-confirmed rotavirus infection.

Vaccination Coverage and Timeliness

All subjects received at least 1 vaccine, 90% received at least 1 live vaccine, and 58% completed the 4:3:1:3:3:1 vaccination series by 19 to 35 months (Table 3). Up-to-date 4:3:1:3:3:1 coverage differed by gender (boys: 68%, girls: 48%, $P < .05$) and ethnicity (Latino 73%; non-Latino: 52%, $P < .05$).

Differences in vaccination coverage and/or timeliness were noted between

select live and inactivated vaccines. Only 52 subjects received OPV, whereas 157 received inactivated poliovirus vaccine (IPV) (19 received both). Half of subjects born when only OPV was available (before 1988) received 3 doses by 19 to 35 months of age, whereas 85% of those born on or after an all-IPV vaccination schedule was recommended (January 2000)³⁰ received 3 IPV doses by that time ($P < .01$). No differences were observed in MMR, varicella, and DTP/DTaP coverage or timeliness. Most received MMR (62%) and/or varicella (59%) vaccine between 12 and 18 months of age; an additional 24% and 22%, respectively, received subsequent doses in the observation period. Although MMR and varicella vaccination coverage did not differ by decade of birth, DTP/DTaP vaccination coverage varied over time (1974–1990: 59%; 1990–2000: 84%; 2000–2008: 82%; $P < .05$).

One-quarter (27%) received a live vaccine before FISH confirmation (among those for whom FISH testing was available at birth, $n = 160$). Only 2 cases

occurred before 1 year of age: 1 received rotavirus vaccine, the other received OPV: both without subsequent AEs. Early FISH confirmation was associated with lower MMR and varicella vaccination coverage and delayed timeliness (Fig 1). Of those with early FISH confirmation ($n = 119$), 56% had documented CD4% screening by age 12 to 18 months. Approximately one-third had evidence of immunosuppression ($CD4\% < 25\%$) ($n = 23/67$ MMR vaccine-eligible; $n = 19/60$ varicella vaccine-eligible). More than one-third of these received MMR ($n = 9/23$) and varicella ($n = 7/19$) vaccines by 18 months. Mean CD4% did not differ between those who were vaccinated or unvaccinated against MMR ($32.6\% \pm 12.5\%$ vs $32.8\% \pm 16.6\%$, $P = .66$) or varicella ($33.6\% \pm 11.9\%$ vs $32.3\% \pm 16.8\%$, $P = .36$). Two subjects exhibited severe immunosuppression ($CD4\% < 15\%$) before 12 to 18 months: 1 received MMR and varicella vaccines at 21 months and 3.5 years, respectively; the other received neither vaccine. Of the 4 additional subjects with severe

TABLE 2 Live Vaccine–Preventable Illnesses

Site-Subject No.	Year of Illness	Laboratory-Confirmed Illness	Physician-Confirmed Illness	ED Visit	Hospitalization	Prior FISH	Prior CD4%	Interval: Prior CD4% and Illness (days)	Existing ACIP Recommendation ^a	Prior Vaccine Receipt
Varicella ($n = 11$)										
1–114	2001	No	Yes ^b	No	No	Yes	26	293	Yes	No ^c
1–111	2000	No	Yes	No	No	No	N/A	N/A	Yes	No ^d
2–29	1998	No	Yes	No	No	Yes	N/A	N/A	Yes	No
1–11	1995	No	No	No	No	No	N/A	N/A	No	No
1–175	1995	No	No	No	No	No	N/A	N/A	No	No
1–174	1994	No	No	No	No	No	N/A	N/A	No	No
1–164	1993	No	Yes	No	No	No ^e	N/A	N/A	No	No
1–139	1990	No	No	No	No	No ^e	N/A	N/A	No	No
1–52	1988	No	Yes	No	No	No ^e	N/A	N/A	No	No
1–84	1987	No	Yes	No	No	No ^e	N/A	N/A	No	No
2–39	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No
Rotavirus ($n = 3$)										
3–74	2007	Yes	Yes	No	Yes	Yes	19	95	Yes	No
3–55	2004	Yes	Yes	Yes	Yes	Yes	19	73	No	No
1–4	2001	Yes	Yes	No	Yes	Yes	42	28	No	No

N/A, not available.

^a ACIP recommendations for varicella vaccination were published in 1996 and rotavirus vaccination in 2006. Annual ACIP recommendations for influenza vaccination were published in the 1996, 1998, and 2008 seasons when these cases occurred.²⁵

^b Subject received varicella zoster immune globulin (VZIG) after physician confirmation of varicella illness.

^c Received varicella vaccine 5 mo after varicella illness. Had an unspecified rash at injection site on day 11 and then fever and possible pharyngitis on day 14 after varicella vaccination.

^d Received varicella vaccine, along with MMR, DTaP, *Haemophilus influenzae* type B, and pneumococcal conjugate vaccines, 3 months after varicella illness. Had acute gastroenteritis on day 56 after vaccination.

^e Date of illness preceded development of FISH testing for chromosome 22q11.2 microdeletion (1993).²²

TABLE 3 Vaccination Coverage of 19- to 35-month-old Children With DGS

Vaccine(s)	No. Doses	Completion, % (n) ^a
DTP/DTaP	4	80 (146/183)
OPV/IPV	3	84 (153/183)
MMR	1	77 (141/183)
Hib	3	94 (149/159)
HepB	3	85 (133/156)
Varicella	1	75 (98/130)
4:3:1:3:3:1		58 (75/130)

HepB, hepatitis B virus vaccine; Hib, *Haemophilus influenzae* type B vaccine.

^a The denominator includes children with at least 1 health care encounter in the abstracted record after 18 months of age ($n = 183$) and those for whom the given vaccine was available and recommended for similarly aged healthy children.²⁵

immunosuppression at any point during the observation period, 2 ultimately received MMR and varicella vaccines; the others received no live vaccines.

Subjects with cardiac disease were more likely to have early FISH confirmation than those without (92% vs 41%; $P < .001$) and less likely to receive MMR (54% vs 74%, $P < .01$) and varicella (45% vs 82%, $P < .001$) vaccines by 12–18 months. After adjusting for cardiac disease, early FISH confirmation remained a significant negative predictor of MMR (adjusted odds ratio

0.28, 95% confidence interval 0.10–0.82), but not varicella (adjusted odds ratio 0.30, 95% confidence interval 0.11–1.21) vaccination.

AEFLI

Forty-four of 175 live-vaccine recipients experienced an AEFLI. There were 91 events, resulting in 72 outpatient sick visits, 13 ED visits, 6 hospitalizations, and no deaths. Outpatient visits were typically for minor illnesses (eg, otitis media, upper respiratory infections) except for pneumonia (4), bronchospasm (4), anaphylaxis (1), and thrombocytopenia (1), all were self-limited, none requiring an ED visit/hospitalization. All hospitalizations were secondary to respiratory illness (Table 4). By using causality assessment tools,^{18–20} CISA investigators found sufficient evidence to support a causal relationship between live vaccination and 4 of 15 rashes, but none of 13 pneumonias (Table 5).

The 91 events occurred after 14% of MMR, 20% of varicella, 8% of OPV, and 5% of rotavirus doses. Receipt of multiple vaccines preceding an event was common (30% received >1 live vaccine; 66%

also received an inactivated vaccine). There were no differences in AEFLIs by age, gender, race, ethnicity, cardiac disease, or cardiac surgery. AEFLIs were detected in 43 of 114 individuals (442 live-vaccine doses) at sites using the comprehensive abstraction procedure and in 1 of 80 subjects (198 live-vaccine doses) at sites using the targeted approach ($P < .001$). ED visits and hospitalizations were detected only at sites using the comprehensive approach.

CD4% before live vaccination was available for 44 of the 91 AEFLIs (mean: $32.5\% \pm 8.9\%$; range: 17% to 48%; mean interval before vaccination: 283 days). Previous CD4% was similar among 12- to 18-month-olds who experienced or did not experience an AE after MMR vaccination ($29.3\% \pm 9.6\%$ [$n = 8$] vs $33.8\% \pm 13.6\%$ [$n = 23$], $P = .48$), but lower among those with versus without an AE after varicella vaccination ($24.8\% \pm 7.3\%$ [$n = 5$] vs $35.5\% \pm 11.7\%$ [$n = 2$], $P < .05$). When stratifying subjects by preceding CD4% (<25% vs $\geq 25\%$), no significant difference in AEs after MMR or varicella vaccination was observed.

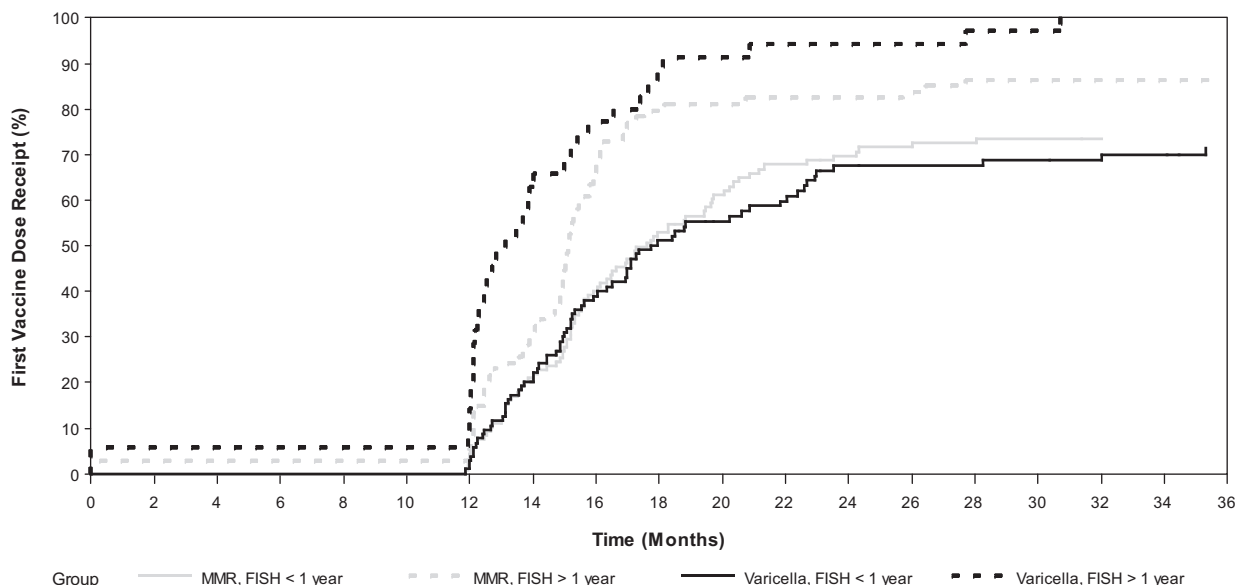


FIGURE 1

Live vaccination patterns according to timing of FISH diagnostic confirmation. Timeliness of MMR vaccination (gray) and varicella vaccination (black) between 0 and 36 months of age differed between those with FISH confirmation of a chromosome 22q11.2 microdeletion before 1 year of age (solid line) compared with those with FISH confirmation after 1 year of age (dashed line) (Kaplan Meier, $P < .001$).

TABLE 4 Description of AEs in the 56-day Windows After Live Vaccination Resulting in ED Visits Only or Hospitalizations

Site-Subject No.	Vaccine(s)	Interval, d	Presentation
ED visits only			
1–124	MMR, OPV, DTaP	1	Otitis media
1–167	MMR, Varicella, DTaP, Hib	5	Seizure, fever
1–22	MMR, Varicella, Hib	5	Seizure, fever, thrombocytopenia, viral illness
1–167	MMR, Varicella, DTaP, Hib	10	Otitis media, fever
1–143	MMR, Varicella, DTaP	10	Rash (unspecified), fever
3–79	MMR, Varicella	14	Pneumonia, fever, conjunctivitis, viral illness
1–68	OPV, DTaP, Hib, HepB, Study Vaccine ^a	19	Bronchospasm, fever
3–12	MMR	20	Pneumonia, fever
3–79	OPV, DTaP, Hib, HepB	36	URI, fever
3–29	MMR, IPV, DTaP	39	Croup, fever, lymphadenopathy
3–79	OPV, DTaP, Hib, HepB	43	Tracheostomy discharge (<i>Pseudomonas</i>)
3–79	MMR	47	Pneumonia, fever, otitis media, pharyngitis, conjunctivitis
1–15	MMR, Varicella, Influenza	56	URI, fever
Hospitalizations			
1–85	IPV, DTaP, Hib, HepB, Rotavirus	0	RSV bronchiolitis, bronchospasm
1–176	OPV, DTP	17	Pneumonia, fever
1–55	OPV, DTP	31	Pneumonia, fever, RSV bronchiolitis
1–119	OPV, DTP, Hib	47	Pneumonia, fever
3–79	OPV, DTaP, Hib, HepB	50	Pneumonia, fever
3–42	Varicella	53	Pneumonia, fever bronchospasm, lymphadenopathy

HepB, hepatitis B virus vaccine; Hib, *Haemophilus influenzae* type B vaccine; RSV, respiratory syncytial virus; URI, upper respiratory infection.

^a Received either pneumococcal conjugate vaccine or meningococcal serogroup C conjugate vaccine.

Only 1 of 3 subjects with CD4% <15% before live vaccination experienced an AEFLI (tonsillitis 1 month after MMR/varicella vaccination). Mitogen testing was performed before MMR and varicella vaccination in 12 and 10 subjects, respectively. None had an AE after MMR vaccination. Three had minor AEs after varicella vaccination (eg, 1–114 and 1–191 in Table 5); only 1 of these had abnormal mitogen responses and evidence of immunosuppression (CD4% = 24%) between 2 and 6 years before vaccination.

DISCUSSION

Our study of 194 subjects with FISH-confirmed DGS is the largest to date describing live vaccine-preventable illnesses, vaccination patterns, and AEFLIs among patients with DGS. Contrary to American Academy of Pediatrics and Advisory Committee on Immunization

Practices recommendations,^{12,13} many received live vaccines despite having a confirmed chromosome 22q11.2 microdeletion and evidence of preceding immunosuppression. Although most had FISH confirmation before 1 year of age, only half had documented lymphocyte screening by 12 to 18 months and one-third of these had a CD4% <25%. Of the latter, nearly 40% received MMR and/or varicella vaccines by 18 months of age. Nonetheless, AEFLIs were typically minor, as shown in smaller studies of subjects with DGS^{10,11,16,17} and the general population.^{13–15} Few serious events were temporally associated with live vaccination, and none were assessed to be causally associated with live vaccination. These data are consistent with earlier studies^{10,11,16,17} and suggest that live vaccines may be given safely to some patients with DGS. The benefits of MMR and varicella vaccination, in particular, appear to outweigh the potential risks

for patients with DGS with mild-to-moderate immunosuppression. Further investigation of MMRV vaccine, which may have a different safety profile than separate MMR and varicella vaccines,³¹ and live vaccination of severely immunosuppressed patients with DGS is warranted given the small numbers included here.

The immune profile of our study population is consistent with mild-to-moderate immune deficiency and, thus, representative of the general DGS population (ie, partial DGS).^{6–8,32} Few unvaccinated individuals experienced severe live vaccine-preventable illnesses, as shown in a smaller cohort of patients with DGS with mild-to-moderate immunosuppression.¹⁰ Another study reported higher rates of varicella illness among unvaccinated patients with DGS, which could reflect greater disease exposure, lower vaccine uptake, or less herd immunity.^{11,33} In our study, the paucity of severely immunosuppressed subjects could explain why there were relatively few AEFLIs despite high vaccination coverage. In support of this, patients with an AE after varicella vaccination had lower preceding CD4% (24.8%) versus those who did not (35.5%). These data, although limited, suggest that CD4 levels may be useful for predicting when live vaccines may be administered safely and could help guide provider vaccination decisions, as done in other immunocompromised populations.¹² Although no live vaccine-preventable illnesses and only 1 AEFLI (tonsillitis) were observed among the 6 subjects with severe immunosuppression (CD4% <15%), additional retrospective data on this small subset of patients with DGS (estimated 1% nationally) are needed.

Overall, most subjects were up-to-date with inactivated vaccines and received them at appropriate ages. With respect to live vaccines, MMR vaccination coverage was high (77%), similar to that reported previously among patients

TABLE 5 Causality Assessment of Live Vaccination and Pneumonias and Rashes Using a CISA Causality Assessment Algorithm^a and Modified WHO Causality Assessment Criteria^b

Site-Subject No.	Vaccine(s)	Interval, d	Algorithm	Modified WHO Criteria
Pneumonias				
1-176	OPV, DTP	17	Indeterminate	Unlikely
3-79	MMR ^c	0	Indeterminate	Unlikely
3-12	MMR	20	Indeterminate	Unlikely
3-79	MMR	47	Indeterminate	Unlikely
1-111	MMR, DTaP, IPV	15	Indeterminate	Unlikely
1-15	MMR, Varicella, Influenza	20	Indeterminate	Unlikely
3-47	Varicella, Influenza	54	Indeterminate	Unlikely
3-42	Varicella	53	Indeterminate	Unlikely
3-78	Varicella	55	Indeterminate	Unlikely
3-79	Varicella ^c	14	Indeterminate/ Inconsistent	Unlikely
3-79	OPV, DTaP, Hib, HepB	50	Inconsistent	Unrelated
1-55	OPV, DTP	31	Inconsistent	Unrelated
1-119	OPV, DTP, Hib	47	Indeterminate/ Other diagnosis	Unrelated
Rashes				
3-47	MMR	9	Consistent	Probable
1-91	MMR, Hib	11	Consistent	Probable
1-114	Varicella	9	Consistent	Probable
1-107	MMR, varicella, DTaP, Hib, IPV, Influenza	6	Consistent (MMR) Indeterminate (varicella)	Possible (MMR) Unlikely/Possible (varicella)
1-91	Varicella	5	Indeterminate	Unlikely
2-25	MMR	6	Indeterminate	Unlikely
1-164	MMR	31	Indeterminate	Unlikely
1-35	MMR, Varicella	41	Indeterminate (MMR) Inconsistent (varicella)	Unrelated
3-42	MMR	21	Indeterminate	Unrelated
1-66	MMR, Hib, IPV	3	Inconsistent	Unlikely/Unrelated
1-60	MMR	3	Inconsistent	Unrelated
3-68	MMR, HepA, HepB, Hib	28	Inconsistent	Unrelated
1-143	MMR, Varicella, DTaP	10	Inconsistent	Unrelated
3-79	Varicella, DTaP, Menactra, HPV	34	Inconsistent	Unrelated
1-191	Varicella	1	Inconsistent	Unrelated

^a Halsey et al (2012).¹⁸

^b Rosenberg et al (2009).¹⁹

^c These vaccine doses preceded the same pneumonia event.

with DGS (47%–88%),^{10,11} but lower than the ~90% of US children aged 19 to 35 months who receive MMR vaccine.^{10,11,23} Varicella vaccination coverage in our DGS cohort (75%) was higher than previously described (25%–54%),^{10,11} which may reflect lower varicella vaccine safety concerns among providers of our patients with DGS. Consistent with what has been shown in other high-risk populations,²⁸ our subjects exhibited no difference in timeliness of MMR, varicella, and DTP/DTaP vaccination overall. We did observe delayed live vaccination among those with early FISH confirma-

tion (ie, <1 year of age), many of whom may have had a more severe clinical presentation, as evidenced by a higher frequency of cardiac disease. After adjusting for cardiac disease, early FISH confirmation remained a negative predictor of MMR, but not varicella, vaccination. This could reflect MMR's more limited licensing history and safety profile among immunocompromised patients compared with varicella vaccine^{34–38} and lower measles versus varicella prevalence.²⁴ No difference in preceding CD4% was noted between vaccinated and unvaccinated subjects. This is

consistent with existing data,¹⁰ although potential withholding of varicella vaccine for more immunocompromised subjects has been described.¹¹

This study has some important limitations. It was a retrospective study of patients with complex health care needs and multiple providers. Medical management, including lymphocyte screening and vaccination practices, varied widely. The lack of CD4% data for many subjects may have resulted in an underestimation of immunosuppression. Medical care received at multiple sites also made record collection challenging, although few incomplete records were identified through internal review and external queries. Different approaches for abstracting AEFLI data (ie, comprehensive versus targeted) likely explain the differential prevalence between sites, as no other site-based differences were detected. By introducing recall bias, the targeted approach may have resulted in fewer AEFLIs, especially minor ones, being detected. The lack of more serious AEFLIs at sites using the targeted approach also could be explained in part by the low incidence of such events. Although 69% of live vaccine doses were given at sites using the comprehensive approach, serious events at those sites were rare and not found to be causally associated with vaccination. Last, FISH testing was developed after some subjects were born, and age at the time of clinical DGS diagnosis was not available. For these individuals, the impact of diagnostic timing on vaccination decisions could not be assessed.

CONCLUSIONS

Our data expand the findings of smaller studies,^{10,11,16,17} indicating that live vaccination of patients with DGS with mild-to-moderate immunosuppression is well-tolerated. Prospective studies are needed to confirm our findings and offer guidance for live vaccination, as

done previously for individuals with HIV given varicella vaccine.^{12,15,39,40} Lymphocyte screening before all live immunizations should be encouraged because our data indicate that this is not universally done and that the level of immunodeficiency varies over time in individual patients with DGS. Because this study included few patients with DGS with severe immunosuppression, further retrospective investigation of this population is warranted.

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