

Safety of Live Viral Vaccines in Patients With Chromosome 22q11.2 Deletion Syndrome (DiGeorge Syndrome/Velocardiofacial Syndrome)

Elena E. Perez, MD, PhD*; Aleksandra Bokszczanin, MD§; Donna McDonald-McGinn, MS‡; Elaine H. Zackai, MD§; and Kathleen E. Sullivan, MD, PhD*

ABSTRACT. The package inserts of live viral vaccines include immunodeficiency as a contraindication. Nevertheless, patients with mild forms of immunodeficiency may benefit from vaccination. No published guidelines exist for the administration of these vaccines specifically to patients with chromosome 22q11.2 deletion syndrome. This syndrome is also sometimes called DiGeorge syndrome and is associated with thymic hypoplasia and diminished T-cell numbers and has a wide spectrum of phenotypic features that include cardiac anomalies, dysmorphic facial features, and hypocalcemia. Patients generally exhibit a mild to moderate decrement in T-cell numbers with preservation of T-cell function. The aims of this study were to investigate the incidence of side effects after live viral vaccine administration in a population with chromosome 22q11.2 deletion syndrome. The high frequency of this syndrome in the population (1:3000 children) mandates a greater understanding of the risks and benefits related to live viral vaccine administration. A retrospective analysis of vaccine adverse events was performed. The data acquisition form evaluated the frequency of live vaccine administration and the consequences of both vaccination and withholding the vaccine. Flow cytometric enumeration of T cells was performed as part of an immunologic evaluation. Thirty-two of 59 responders were vaccinated with the varicella vaccine. Only 9% of patients reported adverse events. However, 63% of unvaccinated children developed chickenpox. Comparison of patients who tolerated the vaccine with those who reported adverse events showed no statistically significant differences in current age (7 vs 5.7 years), age at vaccination (3 vs 2.5 years), or T-cell subset counts: CD3 (1951 vs 2083 cells/ μ L), CD4 (1283 vs 1463 cells/ μ L), and CD8 (530 vs 502 cells/ μ L). Fifty-two of 59 responders were vaccinated with measles-mumps-rubella (MMR). Twelve (23%) of 52 reported mild side effects, including fever, rash, and constitutional symptoms. No severe adverse reactions were reported. No patient reported natural disease with measles, mumps, or rubella. There were no statistically significant differences between the T-cell counts in the vaccinated group reporting side effects versus the vaccinated group without side effects (mean CD3 counts: 1928 vs 1736 cells/ μ L; CD4 counts: 1250 vs 1127 cells/ μ L; and CD8 counts: 528 vs

483 cells/ μ L). In our study, patients with chromosome 22q11.2 deletion syndrome had a similar incidence of adverse effects with varicella and MMR vaccines compared with that reported in the general population. All side effects were mild. However, in patients who did not receive the varicella vaccine, an overwhelming 63% contracted the disease. Patients who were not vaccinated against MMR did not develop natural disease. The data suggest that this is a cohort of patients with 22q11.2 deletion syndrome who have tolerated live viral vaccinations without evidence of significant side effects. A prospective study could address whether there are T-cell thresholds below which vaccination is unsafe; however, the information that we present suggests that vaccinating children with chromosome 22q11.2 deletion with live viral vaccines does not carry a significantly higher risk of adverse reactions compared with the general population, provided that they have no evidence of severe immunocompromise. *Pediatrics* 2003;112:e325–e327. URL: <http://www.pediatrics.org/cgi/content/full/112/4/e325>; *immunodeficiency, T lymphocytes, adverse events, varicella, MMR*.

ABBREVIATION. MMR, measles-mumps-rubella.

Live attenuated viral vaccines are a part of routine childhood immunizations and over the years have proved their safety and efficacy in the general population. Mild adverse effects of measles-mumps-rubella (MMR) vaccination include fever, rash, and lymphadenopathy and occur in approximately 5% to 15% of vaccine recipients.^{1,2} Similarly, side effects of the varicella vaccine include injection site reactions, fever, and rash, which occur in 5% to 30% of individuals.^{3–5} Severe side effects are exceedingly rare with both vaccinations.^{5,6}

The package inserts for both the varicella and MMR vaccines warn against use in patients with any form of cellular or humoral immunodeficiency. However, the most recent Advisory Committee on Immunization Practices allows the use of varicella vaccine in patients with a humoral immunodeficiency as well as in patients with human immunodeficiency virus with age-specific CD4 count \geq 25%.⁴ No published guidelines exist for the administration of these vaccines to patients with chromosome 22q11.2 deletion syndrome.⁷ This syndrome is associated with thymic hypoplasia and diminished T-cell numbers and has a wide spectrum of phenotypic features that include cardiac anomalies, dysmorphic facial features, and hypocalcemia.^{8,9} Patients gener-

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Received for publication Apr 16, 2003; accepted Jun 13, 2003.

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TABLE 1. Side Effects Reported

	Varicella Recipients (%)	MMR Recipients (%)
No. of patients immunized	32	52
Side effect frequency	3 (9)	12 (23)
Fever	3 (9)	11 (21)
Rash	0	3 (6)
Constitutional	0	4 (8)
Systemic disease	0	0
Other	0	0
Hospitalization	0	0

ally exhibit a mild to moderate decrement in T-cell numbers with preservation of T-cell function.¹⁰ Thus, patients with chromosome 22q11.2 deletion syndrome are at risk for disease from attenuated vaccine-strain virus and from wild-type viral infection. The aims of this study were to investigate the incidence of side effects after live viral vaccine administration in a population with chromosome 22q11.2 deletion syndrome. The high frequency of this syndrome in the population (1:3000 children) mandates a greater understanding of the risks and benefits related to live viral vaccine administration in this population.¹¹

METHODS

A total of 174 patients who had a genetically confirmed diagnosis of chromosome 22q11.2 deletion and were seen at Children’s Hospital of Philadelphia between 1994 and 2002 constituted the study population. A retrospective analysis of vaccine adverse events was performed. Institutional review board approval was granted for this study.

The data acquisition form was designed to evaluate the frequency of live vaccine administration and the consequences of both vaccination and withholding the vaccine. Many of the patients received the vaccine before the diagnosis of chromosome 22q11.2 deletion syndrome. Flow cytometric enumeration of T cells was performed in the Clinical Immunology Laboratory of the

Children’s Hospital of Philadelphia using standard techniques as part of an immunologic evaluation.

RESULTS

Fifty-nine responses were received from 174 directed mailings. T-cell numbers from survey responders were no different from T-cell numbers from people who enrolled in the cohort but failed to respond to the survey (CD3: 1759 vs 1669 cells/ μ L; CD4: 1142 vs 1076 cells/ μ L; CD8: 489 vs 503 cells/ μ L). Thirty-two of 59 responders were vaccinated with the varicella vaccine. Only 9% of patients reported adverse events (Table 1). However, 63% of unvaccinated children developed chickenpox. Comparison of patients who tolerated the vaccine with those who reported adverse events showed no statistically significant differences in current age (7 vs 5.7 years), age at vaccination (3 vs 2.5 years), or T-cell subset counts: CD3 (1951 vs 2083 cells/ μ L), CD4 (1283 vs 1463 cells/ μ L), and CD8 (530 vs 502 cells/ μ L; Fig 1). Comparison of vaccinated and unvaccinated patients showed statistically significant differences in CD3 counts (1963 vs 1339 cells/ μ L; $P < .05$), CD4 counts (1300 vs 893 cells/ μ L; $P < .05$), and CD8 counts (527 vs 404 cells/ μ L; $P < .05$). This presumably reflects intentional withholding of the varicella vaccine from the more T-cell-compromised patients. None of the patients who developed wild-type varicella had a severe course requiring hospitalization. None of the vaccinated people developed wild-type disease.

Fifty-two of 59 responders were vaccinated with MMR. Twelve (23%) of 52 reported mild side effects, including fever, rash, and constitutional symptoms (Table 1). No severe adverse reactions were reported. No patient (vaccinated or unvaccinated) reported natural disease with measles, mumps, or rubella.

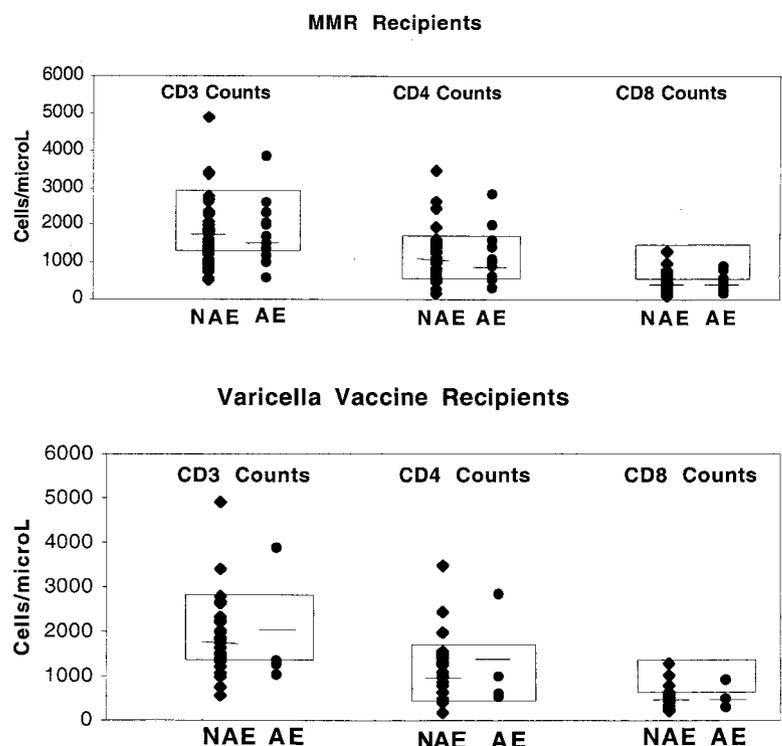


Fig 1. Low T-cell counts are not associated with adverse events in vaccine recipients. CD3, CD4, and CD8 T-cell counts are displayed for both MMR and varicella vaccine recipients. ●, individuals who reported an adverse event (AE); ◆, individuals who had no adverse events (NAE). Horizontal lines indicate the mean for the group and the boxes indicate the normal range for ages 1 to 77 years.

There were no statistically significant differences between the T-cell counts in the vaccinated group reporting side effects versus the vaccinated group without side effects (mean CD3 counts: 1928 vs 1736 cells/ μ L, $P = .795$; CD4 counts 1250 vs 1127 cells/ μ L, $P = .863$; and CD8 counts 528 vs 483 cells/ μ L, $P = .798$; Fig 1). Comparison of vaccinated and unvaccinated groups showed significant differences only for age at time of study (8.9 vs 6 years; $P = .04$). Comparison of vaccinated and unvaccinated patients showed no significant differences in CD3 counts (1759 vs 1315 cells/ μ L; $P = .14$), CD4 counts (1142 vs 914 cells/ μ L; $P = .22$), and CD8 counts (489 vs 340 cells/ μ L; $P = .15$).

Unfortunately, low T-cell counts were not an indicator of adverse events. We also examined whether poor response to phytohemagglutinin was associated with adverse reactions to immunizations. MMR recipients who did not have an adverse reaction had a mean stimulation index of 383 ± 335 , whereas those who had adverse reactions had a mean stimulation index of 381 ± 343 ($P = .99$). Similarly, there were no significant differences between varicella immunization recipients with and without adverse reactions (430 vs 360; $P = .36$).

DISCUSSION

In our study, patients with chromosome 22q11.2 deletion syndrome had a similar incidence of adverse effects with varicella and MMR vaccines compared with that reported in the general population. Nine percent of patients who received the varicella vaccine reported side effects compared with 5% to 30% in the general population. Twenty-three percent of patients who received the MMR vaccine reported side effects compared with 5% to 15% in the general population. All side effects were mild. However, in patients who did not receive the varicella vaccine, an overwhelming 63% contracted the disease. Patients who were not vaccinated against MMR did not develop natural disease. The discrepancy between the 2 groups of unvaccinated patients is probably attributable to differences in the prevalence of these diseases in the United States.

The data suggest that this is a cohort of patients with 22q11.2 deletion syndrome who have tolerated live viral vaccinations without evidence of significant side effects. Study limitations include the use of published comparative data, a limited number of participants, and a retrospective design that relies on parental recollection. In addition, T-cell counts were not available for every patient at the time immediately preceding vaccination; therefore, counts closest to vaccination were used. For the MMR group, the average difference between the age at which cell counts were obtained and the vaccine was adminis-

tered was 55 months. For the varicella vaccine group, the mean difference in age between vaccination and the age at which the T-cell studies were obtained was 19.3 months.

A prospective study could address whether there are T-cell thresholds below which vaccination is unsafe; however, the information that we present suggests that vaccinating children with chromosome 22q11.2 deletion with live viral vaccines does not carry a significantly higher risk of adverse reactions compared with the general population, provided that they have no evidence of severe immunocompromise. On the contrary, withholding vaccination, especially in the case of more prevalent infections such as varicella, can result in a high frequency of wild-type disease. Prospective studies to confirm the findings presented here are necessary to be able to guide families and caregivers in the risk-benefit analysis of live viral vaccine administration.

ACKNOWLEDGMENTS

This work was supported in part by the Wallace Chair of Pediatrics, the General Research Center (M01-RR00240), and the Immunodeficiency Foundation.

We thank the parents and patients who took the time to provide the information necessary for this study.

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Pediatrics 2003;112;e325

DOI: 10.1542/peds.112.4.e325

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