

Varicella in Infants After Implementation of the US Varicella Vaccination Program

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KEY WORDS

varicella, chickenpox, infant varicella, active surveillance, neonatal varicella

ABBREVIATIONS

VZV—varicella-zoster virus

CI—confidence interval

The views in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, US Department of Health and Human Services.

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www.pediatrics.org/cgi/doi/10.1542/peds.2011-0017

doi:10.1542/peds.2011-0017

Accepted for publication Aug 15, 2011

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*



WHAT'S KNOWN ON THIS SUBJECT: Risk of severe varicella disease in infants might not be uniform throughout the first year of life, because maternal antibodies decline over time. The risk of infant exposure to varicella can be decreased by indirect vaccination (or herd immunity) effects.



WHAT THIS STUDY ADDS: Tremendous indirect benefits of the US varicella vaccination program were demonstrated by a 90% decrease in varicella incidence among infants. Clinical disease was milder in younger (0–5 months) versus older (6–11 months) infants, possibly because of the presence of maternal antibodies to varicella-zoster virus.

abstract

FREE

OBJECTIVE: To describe varicella disease in infants since implementation of the varicella vaccination program in the United States.

PATIENTS AND METHODS: From 1995 to 2008, demographic, clinical, and epidemiologic data on cases of varicella in infants were collected prospectively through a community-based active surveillance project. We examined disease patterns for infants in 2 age groups: 0 to 5 and 6 to 11 months.

RESULTS: Infant varicella disease incidence declined 89.7% from 1995 to 2008. Infants aged 0 to 5 months had milder clinical disease than those aged 6 to 11 months: ≥ 50 lesions, 49% vs 58% ($P = .038$); fever (body temperature $> 38^{\circ}\text{C}$), 12% vs 21% ($P = .014$); and varicella-related complications, 6% vs 14% ($P = .009$), respectively. Age was an independent predictor of the occurrence of complications.

CONCLUSIONS: The varicella vaccination program has resulted in substantial indirect benefits for infants, who are not eligible for vaccination. Presence of maternal varicella-zoster virus antibodies might explain attenuated disease in very young infants likely born to mothers with history of varicella. Although varicella disease incidence has declined, exposure to varicella-zoster virus continues to occur. Improving varicella vaccination coverage in all age groups will further reduce the risk of varicella exposure and protect those not eligible for varicella vaccination. *Pediatrics* 2011;128:1071–1077

Varicella has been described as a serious health condition in infants younger than 12 months, who are at increased risk for varicella-related hospitalizations and death compared with older children.^{1–4} During the prevaccine era, the estimated varicella case fatality ratio for infants was 4 times higher than among children aged 1 to 14 years (~8 vs 2 per 100 000, respectively).⁵ Varicella acquired in utero with onset of illness during the first 10 days of life can be especially severe; the estimated case-fatality ratio was ~30% in the prevaccine era.⁴ Detailed descriptions of the epidemiology and clinical severity of varicella in the postneonatal period of infancy are scarce and mostly limited to cases for which infants were hospitalized.⁶ A study conducted 3 decades ago during varicella outbreaks in a domiciliary institution for infants in Osaka, Japan, correlated varicella disease presentation in infants with preexisting maternal antibody titers, which suggested that the risk of severe varicella might not be uniform throughout the first year of life. Infants born to mothers with a history of varicella developed milder disease if infected in the first few months of life compared with later in infancy, probably because of passively acquired maternal antibodies to varicella-zoster virus (VZV).⁷ Subsequent serologic studies confirmed that VZV antibodies in newborns are strongly correlated with maternal values and that titers decline exponentially after birth.^{8–12}

Varicella vaccine is a live, attenuated vaccine. The vaccine currently licensed in the United States (Varivax [Merck and Co, West Point, PA]) is indicated for children aged 12 months and older. Therefore, the only way infants can be protected from varicella is by indirect vaccination (or herd immunity) effects that lower their risk of exposure. After

implementation of the varicella vaccination program in the United States in 1995, a remarkable decline in varicella morbidity and mortality was documented.^{13–16} By 2000–2005, reduction in varicella disease incidence had occurred in all age groups, including infants.^{13,14} A community-based varicella active surveillance project in the United States provided investigators with the opportunity to examine 14 years of data (1995–2008) that could be used to better describe the epidemiology and clinical presentation of varicella disease in infants.

PATIENTS AND METHODS

Setting

Active surveillance for varicella disease has been conducted in Antelope Valley, Los Angeles County, CA, and West Philadelphia, PA, since 1995.¹³ The total population for both surveillance sites comprises more than 600 000 people, of whom ~2% are younger than 12 months. Over 300 reporting units per site, including child care centers, physicians, and health maintenance organizations, report every 2 weeks whether a varicella case is identified. A structured telephone interview was conducted with each parent/guardian of infant case-patients to collect detailed demographic, clinical, and epidemiologic data. Specific data on the mothers of infant case-patients (eg, age, history of varicella disease or vaccination) were not collected as part of this surveillance.

Definitions

For surveillance purposes, varicella was defined as an illness with acute onset of a diffuse maculopapulovesicular rash without other apparent cause. We defined an immunosuppressive condition as any chronic medical condition that was diagnosed by a physician and that depresses the immune system, such as AIDS or cancer. We de-

finied a complication as an illness recognized as varicella-related that occurred within 14 days of rash onset. Medical and/or hospital records were reviewed for all serious complications and hospitalizations.

Analysis

Data from 1995 through 2008 were used to calculate annual age-specific varicella incidence rates per 1000 infant population on the basis of population estimates from the US Census Bureau. Because questionnaires were not fully standardized between sites in the first few years of surveillance, we included only data from 1997 through 2008 for the clinical description of varicella in infants. Clinical presentation of varicella disease was evaluated on the basis of the number of skin lesions (<50, 50–500, >500), fever (>38°C), and the presence of complications. Because levels of passively acquired maternal antibodies against VZV decline sharply after 5 to 6 months of life,^{8–12} we examined disease patterns for 2 age groups: 0 to 5 and 6 to 11 months. We used a logistic regression model to investigate independent predictors of varicella-related complications. We calculated rates of specific complications per 1000 infant cases and estimated 95% confidence intervals (CIs) for rates by using the continuity-corrected scores statistical method.¹⁷ We also estimated rate ratios and derived respective 95% CIs by using the δ method. To compare proportions, we used χ^2 and Fisher's exact tests as appropriate. All *P* values were calculated by use of a 2-sided test. Data were analyzed by using SAS 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Incidence

Varicella incidence among infants younger than 12 months declined 89.7%, from 15.6 (95% CI: 13.5–18.2)

cases per 1000 infants in 1995 to 1.6 (95% CI: 1.0–2.6) cases per 1000 infants in 2008. The decline inversely followed an increase in varicella vaccination coverage observed in both study sites (Fig 1A). Distribution of varicella disease incidence according to age group changed after implementation of the varicella vaccination program. In 1995, the year of varicella vaccination program implementation in the United States, disease incidence was highest among children aged 1 to 10 years, followed by infants and then adolescents aged 10 to 14 years. By 2008, however, disease incidence was similar in all age groups (Fig 1B).

General Characteristics

From 1997 through 2008, a total of 11 336 varicella cases were reported in both active surveillance sites, of which 519 (4.6%) occurred in infants younger than 12 months. Among infant case-patients with varicella, 175 (34%) were aged 0 to 5 months and 344 (66%) were aged 6 to 11 months; 266 (51%) were girls. Distribution of case-patients on the basis of race/ethnicity reflected the population composition of each surveillance site: in Antelope Valley, 314 (80%) of case-patients were white, of which 192 (48%) were of Hispanic ethnicity; in West Philadelphia, 100 (81%) of the case-patients were black, and Hispanic infants constituted only 8 (6.5%) of the overall number of case-patients.

Clinical Aspects and Varicella-Related Complications

From 1997 through 2008, statistically significant differences were seen in the clinical presentation of varicella disease among infants according to age group. Infants aged 0 to 5 months generally had milder clinical disease compared with infants aged 6 to 11 months; a lower proportion had ≥ 50 lesions (49% vs 58%; $P = .036$), fewer

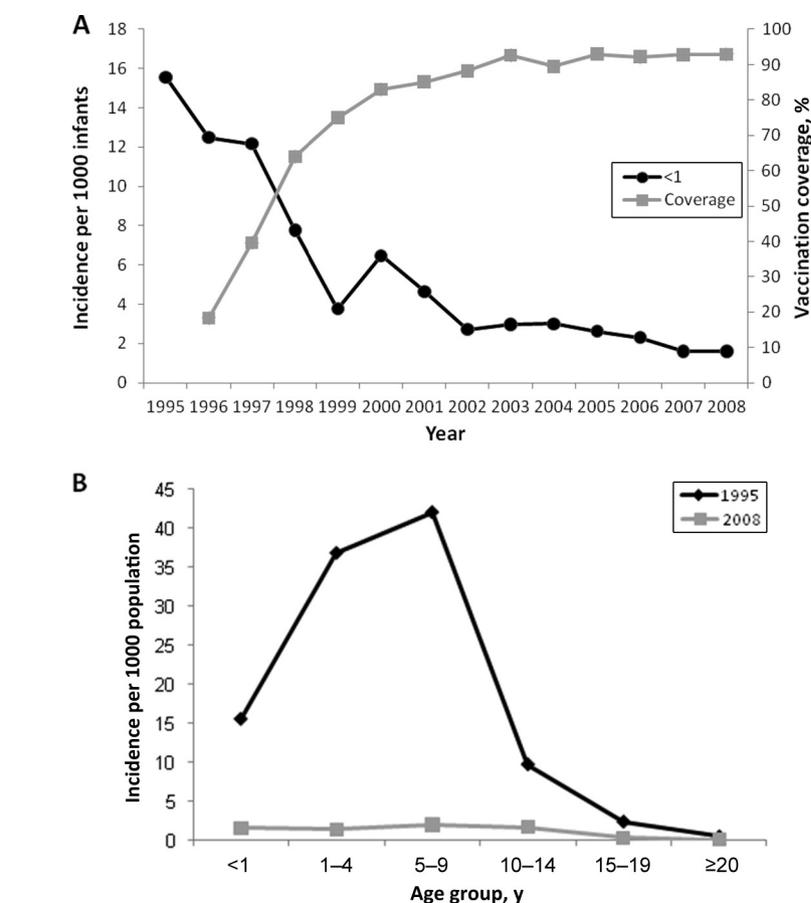


FIGURE 1 A, Varicella incidence among infants from 1995 through 2008 and varicella vaccination coverage among children aged 19 to 35 months in West Philadelphia and Los Angeles County. B, Varicella disease incidence according to age group in 1995 and 2008, West Philadelphia and Los Angeles County.

had fever of $>38^{\circ}\text{C}$ (12% vs 21%; $P = .012$), fewer had varicella-related complications (6% vs 14%; $P = .01$) and fewer were prescribed antibiotics (8% vs 14%; $P = .044$) (Table 1). Eight infants were younger than 1 month at the time of varicella onset, but disease

in these patients was generally mild. All of them had <50 lesions; 1 infant was hospitalized and 1 infant, although not hospitalized, had a varicella-related complication (unspecified). Only 1 of these very young infants had disease onset within 10 to 12 days af-

TABLE 1 Clinical Characteristics of Cases of Varicella Disease Among Infants According to Age Group, 1997–2008

Clinical Characteristic	Total, N ^a	0–5 mo, n (%)	6–11 mo, n (%)	P ^b
<50 lesions	509	89 (51)	140 (42)	.096
50–500 lesions		74 (43)	168 (50)	
>500 lesions		10 (6)	28 (8)	
>50 lesions (2 groups)	509	84 (49)	196 (58)	.036
Presence of fever ($>38^{\circ}\text{C}$)	519	21 (12)	72 (21)	.012
Fever >2 d	519	15 (9)	38 (11)	.379
Rash >5 d	519	34 (19)	65 (19)	.884
Complication	514	11 (6)	48 (14)	.01
Prescribed antibiotic	496	13 (8)	46 (14)	.044

^a Number of subjects with complete information for each clinical characteristic.

^b χ^2 test for difference in proportions.

TABLE 2 Varicella-Related Complications According to Age Group, 1997–2008

Complication	0–5 mo		6–11 mo		Rate Ratio (95% CI) ^b	P
	No. (n = 175)	Rate (95% CI) ^a	No. (n = 343)	Rate (95% CI) ^a		
Skin superinfection	6	34.3 (15.4–76.3)	15	43.7 (26.4–72.5)	1.3 (0.5–3.3)	.308
Otitis media	3	17.1 (5.5–53.2)	14	40.8 (24.2–68.9)	2.4 (0.7–8.3)	.086
Diarrhea	1	5.7 (0.8–40.6)	9	26.2 (13.7–50.4)	4.6 (0.6–36.2)	.074
Pneumonia	0	—	3	8.7 (2.8–27.1)	—	—
Neurologic ^c	1	5.7 (0.8–40.6)	1	2.9 (0.4–20.7)	0.5 (0.0–8.2)	.319
Miscellaneous ^d	0	—	6	17.5 (7.9–38.9)	—	—
Total	11	62.9 (34.8–113.5)	48	139.9 (105.5–185.7)	2.2 (1.2–4.3)	.008

^a Rate per 1000 infant varicella cases. 95% CIs are based on continuity-corrected score methods.

^b 95% CIs for rate ratios were derived by using the δ method.

^c Neurologic outcomes include 1 case of aseptic meningitis and 1 case of encephalitis.

^d Miscellaneous cases include pharyngitis, asthma exacerbation, scarring, and swollen lymph nodes.

ter birth, but this infant had a mild disease presentation.

A total of 59 infants (11%) (48 [81%] aged 6 to 11 months) presented with varicella-related complications. The most frequently reported complications were skin superinfection (36%), followed by otitis media (29%) and diarrhea (17%). Rates of complications were higher among older infants (Table 2). In general, infants aged 6 to 11 months were more than twice as likely to have complications (rate ratio: 2.2; $P = .008$) compared with infants aged 0 to 5 months.

Hospitalization

A total of 15 infants were hospitalized for varicella from 1997 through 2008. Most hospitalized cases (10 of 15 [67%]) occurred in infants aged 6 to 11 months. The median duration of hospitalization was 2 days (range: 1–12 days). The rate of hospitalization among infants was 28.9 per 1000 infant case-patients with varicella (95% CI: 17.5–48.0), and this rate did not differ according to age group (28.6 of 1000 infant case-patients with varicella among infants aged 0 to 5 months versus 29 of 1000 infant case-patients with varicella among infants aged 6 to 11 months).

Thirteen (86.7%) of the hospitalized infants were hospitalized because of varicella-related complications and all received treatment with third-generation cephalosporin, glycopepe-

tide, lincosamide, and/or penicillinase-resistant β -lactam antibiotics. The main reason for hospitalization of case-patients was skin superinfection (ie, staphylococcus/streptococcus, impetigo, or cellulitis) accompanied by sepsis and/or dehydration in 6 infants (2 of 6 were admitted to the ICU); neurologic complications in 3 infants (2 infants aged 0–5 months with aseptic meningitis [1 treated with intravenous acyclovir], and 1 infant aged 6 to 11 months with encephalitis complicated with dehydration and cellulitis); pneumonia in 3 infants (all aged 6–11 months; 1 case was described as varicella pneumonia and treated with intravenous acyclovir, and in the other 2 cases pneumonia types were not specified); and otitis media and dehydration in 1 infant. The remaining 2 hospitalized infants were admitted for observation and intravenous acyclovir treatment (1 infant was 19 days old, and 1 infant was HIV-positive).

Risk Factors for Complications

Age at primary VZV infection, having an illness that suppresses the immune system, or having >500 lesions were all independent predictors of varicella-related complications (Table 3). Infants aged 6 to 11 months were twice as likely to have complications compared with those aged 0 to 5 months (adjusted odds ratio: 2.3; 95% CI: 1.1–4.5; $P = .0216$).

VZV Exposure History

Overall, among the 443 infant case-patients with varicella with information about day care attendance, 32 (7%) were reported to be attending day care, and 3 of these infants were aged 0 to 5 months. More detailed information on exposure to VZV was collected beginning in 2000. Among the 243 case-patients from 2000 through 2008 with information on VZV exposure, 137 (56%) had a known source of

TABLE 3 Predictors of Varicella-Related Complications, 1997–2008

Variable	Complication, n (%)	Adjusted OR (95% CI) ^a	P ^b
Age group, mo			
0–5	11 (6)	Reference	—
6–11	48 (14)	2.3 (1.1–4.5)	.0216
Immunosuppressive illness			
No	50 (86)	Reference	—
Yes	8 (14)	4.2 (1.6–10.6)	.0026
No. of lesions			
<50	23 (40)	Reference	—
50–500	25 (43)	0.97 (0.53–1.8)	.9226
>500	10 (17)	2.9 (1.2–6.9)	.0168

^a Adjusted odds ratios (ORs) were calculated by using logistic regression. Variables were mutually adjusted.

^b P values were estimated by using maximum-likelihood estimates.

exposure. Of those, 97 (71%) reported VZV exposure in the household, 9 (7%) reported exposure in child care, 11 (8%) reported exposure to a friend/neighbor, and 19 (14%) had other reported exposure (not specified). Overall, of infant case-patients with a reported household exposure to VZV, the majority (67 [73%]) were exposed to a case of varicella in an unvaccinated person; 25 (27%) were exposed to a case in a vaccinated person (ie, breakthrough varicella); and 14% (14 of 97) were exposed to a herpes zoster case. Exposure patterns changed over time, such that during the latter part of the study period, 2004–2008, 50% (11 of 22) of case-patients with household exposures were exposed to case of varicella in an unvaccinated person compared with 84% (48 of 57) during 2000–2003 ($P = .003$). The proportion of infant case-patients with varicella exposed to a herpes zoster case increased from 14% (14 of 97) in 2000–2003 to 28% (9 of 32) during the late study period ($P = .01$).

DISCUSSION

This study is the first community-based investigation of the detailed epidemiology and clinical characteristics of varicella among infants after implementation of a national varicella vaccination program. Between 1995 and 2008, varicella incidence among infants declined almost 90%, which demonstrated the tremendous indirect benefits of the varicella vaccination program in protecting infants through lowered risk of exposure as a result of high population immunity. This benefit reinforces the importance of maintaining high rates of varicella vaccination in the community to protect individuals who cannot be vaccinated because of age or medical contraindications.

Our results confirm and expand existing knowledge on the clinical presentation and severity of varicella among infants.^{2–4,18,19} Overall, 11% of the in-

fants developed varicella-related complications, and of them, 25% were hospitalized. Our findings are not directly comparable to those from studies performed before the vaccine era, because those investigations were limited to more severe cases (ie, hospitalizations or deaths).^{1,18,19} Being 6 to 11 months of age was an independent predictor of more severe disease in infants even after adjustment for preexisting immunosuppressive illness and number of lesions. Rates of varicella-related complications among infants aged 6 to 11 months from our community-based assessment were twice that of infants aged 0 to 5 months, a finding that is consistent with previous reports of complication rates among infants hospitalized with varicella.^{18,19} These findings that rates of complications are 2 to 3 times higher among older infants are likely attributable to decline in passively acquired maternal VZV antibodies after the first few months of life.^{7–12}

In our study, the risk of hospitalization was similar in both age groups, possibly because of a low threshold for hospital admission among very young infants. The overall rate of varicella hospitalization for infants in our study was ~4 times higher than that previously reported (30 of 1000 vs ~7 of 1000 varicella cases, respectively).²⁰ The latter rate, however, was based on administrative codes for discharge diagnoses, which likely underestimate the contribution of varicella as a cause for hospitalization. Among hospitalized infants, bacterial complications such as sepsis after skin superinfection, such as cellulitis, were the most common reason for admission, and most were aggravated by dehydration and/or febrile seizures. However, 2 infants had neurologic complications and 3 had pneumonia, conditions that are well-described viral-mediated complications of vari-

cella. In our study, 4 (26%) of the hospitalized infant case-patients were treated with acyclovir and 2 of the 5 infants with neurologic complications or pneumonia received acyclovir treatment. Acyclovir is not licensed for children younger than 2 years. Nevertheless, it has been used safely to treat severe herpesvirus infections in this age group, including neonatal varicella and herpes simplex virus infections.^{21–23} Thus, physicians should consider prompt antiviral therapy for infants with varicella, principally when the mother's varicella immune status is unknown or in-existent.

Since 2006, recommendations for prenatal assessment of VZV immunity and postpartum varicella vaccination have been in place to prevent women from reaching childbearing age without either natural or vaccine-induced immunity.²⁴ The amount and persistence of VZV maternal antibodies transferred to infants of vaccinated women, however, are likely to be less than those transferred from naturally infected women. Women vaccinated for measles have significantly lower titers to measles than women naturally immune to the disease.²⁵ Maternal measles antibody levels are correlated with neonatal values, and infants of mothers with vaccine-induced measles immunity have been shown to lose passively acquired measles antibodies earlier than infants of naturally infected mothers.^{25–27} As the varicella vaccination program further matures, a higher proportion of infants will be born to mothers with vaccine-induced varicella immunity, and therefore these infants will have lower or more rapidly waning levels of maternal antibody and may be at increased risk of varicella-related complications if infected during the early months of infancy. This situation further highlights the importance of maintaining high vaccination coverage among unvacci-

nated age groups likely to expose infants such as care givers and household members.

Despite reduction in varicella disease, exposure to VZV continues to occur. In our study, exposure to another varicella case accounted for most of the known sources of VZV infection among infants, and half of those exposures continued to result from unvaccinated household members during the latter part of the study period. Breakthrough varicella (ie, VZV infection in previously vaccinated persons) also contributed to household exposures. Moreover, the proportion of reported herpes zoster exposures increased during the late period of our study. From 2004 through 2008, 28% of infant case-patients with varicella for whom the household was reported as the source of infection had varicella that resulted from exposure to a case of herpes zoster disease. Such exposures could be reduced by wider implementation of existing vaccination policy recommendations. In June 2006, the Advisory Committee on Immunization Practices recommended a universal 2-dose varicella immunization policy.²⁴ The new recommendations also place high emphasis

on catch-up vaccination among those who previously received only 1 dose of the vaccine. The current 2-dose varicella vaccine schedule is expected to further reduce the number of varicella cases and exposures in vaccinated persons.^{28,29} To further mitigate VZV exposure, persons with herpes zoster who have direct contact with infants should be advised to cover their rash until lesions are completely healed. For persons aged 60 years and older, herpes zoster vaccine is recommended to reduce the likelihood of VZV reactivation.^{30,31}

Our study had some limitations. We did not collect information on age and immune status of mothers. Moving forward, this information would be important for determining changes in susceptibility among infants born to vaccinated mothers. However, because the varicella vaccination program was initiated in 1995, most of the infants in our study were likely born to mothers with history of varicella disease and not vaccination.³²

CONCLUSIONS

Through reducing varicella disease and exposures, the varicella vaccina-

tion program in the United States has provided substantial benefits to infants who are too young to be vaccinated. Catch-up varicella vaccination and high uptake of the herpes zoster vaccine among older age groups will further reduce infection risk and protect those persons who are not eligible for varicella vaccination. Continued monitoring of the epidemiology of varicella will be important to ensure that infants born to mothers with vaccine-induced varicella immunity are not at increased risk of severe varicella disease.

ACKNOWLEDGMENTS

We thank all the surveillance sites in the Antelope Valley and West Philadelphia communities for their continued reporting and involvement in the Varicella Active Surveillance Project. We also acknowledge the important contributions of Ms Mia Renwick, Ms Dana Perella, Ms Bernadette Porter, Ms Tina Carbajal, and Ms Christina Jackson for thorough investigation of varicella cases and coordination of the varicella-zoster virus disease surveillance activities in the field.

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Pediatrics 2011;128;1071

DOI: 10.1542/peds.2011-0017 originally published online November 28, 2011;

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Varicella in Infants After Implementation of the US Varicella Vaccination Program

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Pediatrics 2011;128;1071

DOI: 10.1542/peds.2011-0017 originally published online November 28, 2011;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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