Case Report of Subcutaneous Nodules and Sterile Abscesses Due to Delayed Type Hypersensitivity to Aluminum-Containing Vaccines

Christine T. Lauren, MD,[a,b] Donald V. Belsito, MD,[a] Kimberly D. Morel, MD,[a,b] Philip LaRussa, MD[b]

Routine childhood immunizations have resulted in great reductions in vaccine-preventable infectious diseases. Vaccine-related adverse events, albeit rare, can be of significant consequence. Although anaphylaxis, or type I hypersensitivity, is recognized as a potential reaction after vaccination, delayed type hypersensitivity or type IV reactions are less so. We present a case of persistent subcutaneous nodules and sterile abscesses in the setting of delayed type hypersensitivity to aluminum, confirmed by patch testing and recurrence on re-exposure. We review sources of aluminum in common immunizations, principles for treatment, and strategies for management of future vaccinations for this patient.

Although anaphylaxis is recognized as a rare side effect of vaccination with rates of 0.0001 to 0.002% or less,[1,2] delayed type hypersensitivity (DTH) reactions are less well known, with reported frequencies of 0.35% to 1.18%.[3] We present a case of persistent subcutaneous nodules and sterile abscesses due to DTH to aluminum to increase awareness of this reaction and resources for vaccine safety expert consultation.

PATIENT PRESENTATION

A 7-month-old healthy boy presented with a 3-month history of subcutaneous nodules at sites of previous immunizations. Vaccinations at 2 months of age (Prevnar 13 [pneumococcal 13-valent conjugate vaccine], ActHib [*Haemophilus* b conjugate vaccine]), and Pediarix (diphtheria-tetanus-acellular pertussis [DTaP]-hepatitis B [hep B]-inactivated polio vaccine [IPV]) at 3 months of age occurred without incident. At 4 months of age, he received second doses of Prevnar 13 and *Haemophilus influenzae b* vaccine (PedvaxHIB) in the right and left thighs, respectively. Within 3 to 5 days, his mother reported a right thigh nodule and an erythematous left thigh nodule. At 5 months of age, he received Pediarix in his left arm and 3 to 5 days later, developed erythema and swelling that persisted for 5 weeks. Culture-negative purulent material was drained after incision, suggesting a sterile abscess. Violaceous subcutaneous nodules were still present at all 3 sites when the child was seen at 7 months of age (Fig 1). He had no history of hives, respiratory distress, mucosal swelling, or fever. Ultrasound examination of these nodules demonstrated teardrop-shaped echogenic areas extending from the skin to the subcutis, the largest measuring 1.1 cm in diameter (Fig 2).

Aluminum was the only component common to the vaccinations that

Departments of [a]Dermatology, and [b]Pediatrics, Columbia University Medical Center, New York, New York

Dr Lauren drafted the initial manuscript and critically reviewed the manuscript; Drs Morel, Belsito, and LaRussa critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2014-1690

Accepted for publication Jun 16, 2016

Address correspondence to Christine T. Lauren, MD, Departments of Dermatology and Pediatrics, Columbia University Medical Center, 161 Fort Washington Ave, 12th Floor New York, NY 10032. E-mail: cat35@cumc.columbia.edu

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

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

POTENTIAL CONFLICTS OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

FUNDING: This work was supported in part by the Clinical Immunization Safety Assessment Network through a subcontract with America's Health Insurance Plans under contract 200-2002-00732 and in part by contract U50 CU220700 from the Centers

To cite: Lauren CT, Belsito DV, Morel KD, et al. Case Report of Subcutaneous Nodules and Sterile Abscesses Due to Delayed Type Hypersensitivity to Aluminum-Containing Vaccines. *Pediatrics.* 2016; 138(4):e20141690

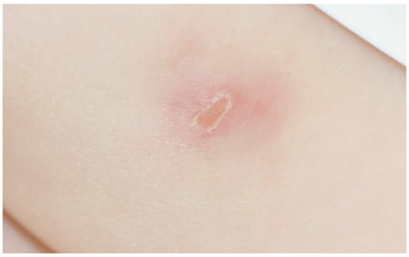

FIGURE 1
Representative nodule when the patient was 7 months of age at time of initial evaluation.

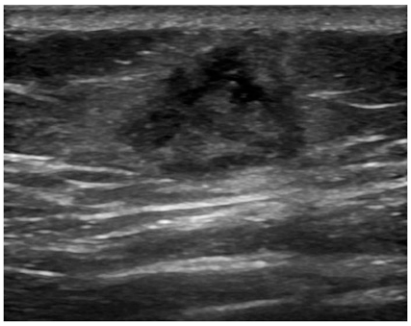

FIGURE 2
Ultrasound examination of subcutaneous nodule at time of initial examination when the patient was 7 months of age.

TABLE 1 Ingredients in Vaccinations, Only Common Component in Vaccinations Received at Sites of Nodules was Aluminum[4]

	Pediarix (DTaP, Hep B, IPV)	PedvaxHIB (*Haemophilus influenzae b*)	Prevnar 13 (Pneumococcal)
Aluminum	X	X	X
Glutaraldehyde	X	—	—
Latex	X	X	—
Neomycin	X	—	—
Polymyxin B	X	—	—
Polysorbate	X	—	X
Soy	—	—	X
Yeast protein	X	—	—

X, present; —, not present.

resulted in nodule formation (Table 1).[4] Patch testing was performed by using empty Finn chambers (SmartPractice, Phoenix, AZ) on Scanpor tape (Actavis Norway) applied to the back for 48 hours. Readings at 48 and 96 hours demonstrated 1+ and 2+ reactions, respectively (Fig 2).

The history and clinical findings supported our impression of DTH to aluminum. Subsequent vaccination with IPOL (aluminum-free IPV) was well-tolerated. The patient's case was reviewed by the Centers for Disease Control and Prevention (CDC)-funded Clinical Immunization Safety Assessment (CISA) Network, which provides expert consultation on the evaluation, management, and assessment of causality of adverse events after licensed vaccines.[5–7] The review concurred with the diagnosis of aluminum hypersensitivity and assisted with the development of a vaccination plan to minimize subsequent aluminum exposure. The recommendation was that future vaccinations be aluminum-free when available (eg, *H. influenzae b*: ActHib, inactivated trivalent polio: IPol, and trivalent influenza: Fluzone). Although aluminum-free alternatives were not available for subsequent DTaP, conjugate pneumococcal, and Hep B immunizations, the benefits of vaccination were felt to outweigh the potential of an adverse reaction. It was recommended that pneumococcus and DTaP vaccinations were first priorities, with the stipulation that topical steroid preparations could be used to mitigate the severity of the expected reactions. Live viral vaccines (measles-mumps-rubella, Varicella) do not contain aluminum and should be given according to the recommended schedule. Hepatitis A vaccine (aluminum-containing) was deferred until higher priority vaccinations were completed.

Subsequent vaccinations included a third Prevnar 13 (aluminum-containing) in the right deltoid and influenza (aluminum-free) in the left deltoid at 12 months of age, followed by a second aluminum-free influenza vaccine in his left deltoid. He then inadvertently received an aluminum-containing PedvaxHIB vaccine in his right deltoid at 13 months. Two weeks later, redness was noted on the skin of the right arm with a palpable 2.5 × 1.8 cm subcutaneous nodule (Fig 4) at the site of his Prevnar 13 and PedvaxHIB vaccinations. Topical steroids under occlusion resulted in subsequent improvement. Six weeks later, the nodule spontaneously drained purulent material, followed by resolution. At the time of manuscript preparation, measles-mumps-rubella, Varicella, IPV, and influenza vaccines, all of which are aluminum-free, were received without incident.

DISCUSSION

Aluminum hypersensitivity, a DTH reaction, is a rare, underrecognized entity.[8,9] Local erythema and induration are more common after aluminum-containing vaccines compared with aluminum-free vaccines.[10] Although mild vaccination site reactions are most commonly reported,[11] persistence of erythema, sterile abscess,[12] or subcutaneous nodules weeks to months after vaccination can also occur.[10,13–27] Lesions and severe pruritus may develop within days to months after vaccination, may last for years, and may be recalcitrant to treatment. Cutaneous changes include dermatitis, hyperpigmentation, lichenification, and hypertrichosis. It is not clear how many cases of sterile abscesses are secondary to DTH, but the association with this reaction pattern and aluminum has been reported.[21] Nonencapsulated granulomatous infiltrates in subcutaneous nodules[22] and sterile abscesses[21] have been described with evidence of aluminum within macrophages.[23,28]

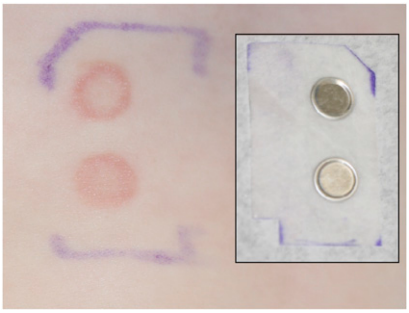

FIGURE 3
Patch testing to empty aluminum Finn Chambers revealed a 2+ papulovesicular reaction with accentuation at the margin along the point of maximal contact with the chamber rim. Finn chamber, *inset*.

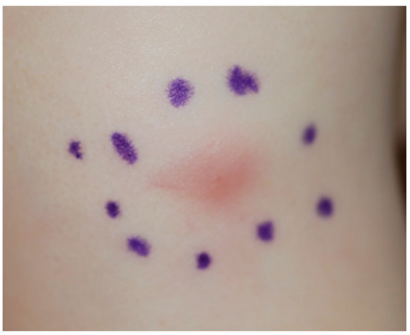

FIGURE 4
Site of re-exposure to aluminum containing vaccine when the patient was 13 months of age. Pen markings outline the border of the palpable subepidermal nodule.

Intramuscular injection of aluminum, a common adjuvant in inactivated vaccines and in allergen immunotherapy leaves a "depot" of antigen, prolonging exposure to antigen presenting cells and improving host immunologic response. Common vaccinations given within the first year of life, including DTaP, Pediarix, hepatitis A, Hep B, pneumococcal conjugate (Prevnar), and some *H. influenzae b* vaccines contain aluminum. Live virus vaccines are aluminum-free, as are some inactivated vaccines, including meningococcal, seasonal influenza, IPV, and certain *H. influenzae b* vaccines. Other excipients and preservatives used in the immunization manufacturing process have also been reported to cause DTH reactions. The package insert[4] should be reviewed because ingredients may change. A list of excipients can be found at http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf[29]

There are various aluminum formulations, including: -hydroxyphosphate sulfate, -hydroxide, -phosphate, or -potassium sulfate. Aluminum-hydroxide has become more widely used and has been implicated in the increased incidence of DTH reactions.[14–16,24] Our patient received immunizations containing the hydroxide and phosphate forms.

Improper placement of vaccine in the dermis or subcutis, as opposed to intramuscularly, has been proposed as a trigger for development of aluminum hypersensitivity.[17,26,27] Epidermal Langerhans cells have been implicated in the pathogenesis of this reaction.[14] In some reports, the rate of hypersensitivity reaction decreased by adjusting the route of administration to intramuscular injection.[26] In our case, ultrasonography showed a tract from the skin surface, suggesting deposition of vaccine along the path of the injection to the subcutaneous space, which may have allowed priming of antigen presenting cells.

Treatment of symptomatic nodules may be ineffective. Topical steroids may be unsuccessful given the depth of the reaction pattern. Occlusion may increase the potency of the topical steroid and limit scratching; hydrocolloid dressings alone have also been reported with variable effect.[15,16] Intralesional steroids and topical capsaicin have been used with varying success[18]; side effects include atrophy and absorption. The effect of these treatments on the immune response is not clear.

Patch testing to evaluate allergen-induced eruptions has been described.[30] Plastic or aluminum wells (Finn chambers) containing small amounts of suspected allergens are placed on the skin and left undisturbed for 48 hours or longer. Skin eruptions present at 72 to 96 hours after application are graded on a severity scale of 1+ to 3+ and signify a DTH to the suspected allergen.

Empty Finn chambers, which are generally considered inert and nonreactive,[31] contain aluminum. Testing with the Finn chamber alone induced a DTH reaction in our patient. A negative result to a Finn chamber test does not exclude aluminum hypersensitivity. Aluminum chloride hexahydrate (2%) in petrolatum is a standard preparation for patch testing. Previous studies[14–16,24] suggested that the higher concentration of aluminum in this preparation results in more positive test results. Other studies used diluted aluminum chloride.[12] Given our patient's positive reaction to the empty Finn chamber, we did not proceed to testing with the standard preparation, however many reports test both chamber and reagent simultaneously to limit the number of potential office visits.

As with other DTH reactions, recurrence can be anticipated with repeat exposure. Patch testing[14,24] and intercurrent illness[14–16] have been reported to result in progression or recurrence of previous subcutaneous nodules. Symptoms include increasing pruritus, enlargement of existing nodules or development of new nodules. In our patient, reexposure to aluminum-containing vaccines resulted in a similar reaction at the injection site, but without flare of previous nodules in the remaining extremities.

Delayed reaction to aluminum has been previously classified as an irritant reaction rather than the more fitting immunologically mediated DTH reaction.[2] DTH may manifest days to weeks after the inciting agent. Sensitization after initial exposure is

necessary for development of a DTH. Our patient's initial vaccinations at age 2 and 3 months likely sensitized him to aluminum with a resultant hypersensitivity reaction on reexposure at age 4, 5, 12, and 13 months. Aluminum has been reported to be responsible for 77% to 85% of all DTH to vaccinations.[3,15] Other reported ingredients include polysorbate,[32] thimerosal,[33,34] phenoxyethanol,[35] formaldehyde,[36] and polymyxin B[37]. Although neomycin and others are known causes of DTH, there have been no reports of vaccine DTH to date.

Although severe vaccine-associated allergic reactions are a contraindication to reexposure,[38] there are no reports of life threatening reactions to aluminum-containing vaccines in a sensitized patient. Alternative preparations that do not contain, or contain less of, the suspected allergen should always be selected when available. For immunizations without an aluminum-free alternative, a risk/benefit discussion on a case-by-case basis is important, because the risk of reaction should be weighed against the risk of exposure and potential consequences of vaccine-preventable disease(s). Consultation with a pediatric allergist-immunologist or infectious disease specialist with vaccine expertise is suggested. The CDC-funded CISA network[7] was able to provide the necessary vaccine safety expertise in this case. US healthcare providers with a vaccine safety question about a specific patient residing in the United States can contact CISA at CISAeval@cdc.gov to request a case evaluation; this service is free of charge, but not all cases are accepted. Any unexpected or clinically significant suspected immunization reaction should be reported to the Vaccine Adverse Event Reporting System (http://vaers.hhs.gov/index[39]) to allow for proper signal detection of this reaction within the US population. Additional information regarding vaccines and vaccine safety may be found at http://www.cdc.gov/vaccinesafety/index.html.[40]

ACKNOWLEDGMENTS

The CISA Hypersensitivity Working Group members were: Jane Gidudu, MD, (CDC), Neal Halsey, MD, and Robert Wood, MD (Johns Hopkins University), Cornelia Dekker, MD, (Stanford University), Nicola Klein, MD, PhD, and Roger Baxter, MD, (Kaiser Permanente of Northern California), Kathryn Edwards, MD (Vanderbilt University), Renata Engler, MD, (Walter Read Army Medical Center), Melvin Berger, MD, PhD (Case Western Reserve University) and Steven Dreskin, MD, PhD (University of Colorado Denver).

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
CISA: Clinical Immunization Safety Assessment
DTaP: diphtheria-tetanus-acellular pertussis
DTH: delayed type hypersensitivity
IPV: inactivated polio vaccine

for Disease Control and Prevention. The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

REFERENCES

1. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol*. 2016;137(3):868–878
2. Wood RA, Berger M, Dreskin SC, et al; Hypersensitivity Working Group of the Clinical Immunization Safety Assessment (CISA) Network. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics*. 2008;122(3). Available at: http://pediatrics.aappublications.org/content/122/3/e771
3. Bergfors E, Hermansson G, Nyström Kronander U, Falk L, Valter L, Trollfors B. How common are long-lasting, intensely itching vaccination granulomas and contact allergy to aluminium induced by currently used pediatric vaccines? A prospective cohort study. *Eur J Pediatr*. 2014;173(10):1297–1307
4. US Food and Drug Administration. Vaccines licensed for immunization and distribution in the US with supporting documents. Available at www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093830.htm. Accessed May 15, 2016
5. Halsey NA, Edwards KM, Dekker CL, et al; Causality Working Group of the Clinical Immunization Safety Assessment network. Algorithm to assess causality after individual adverse events following immunizations. *Vaccine*. 2012;30(39):5791–5798
6. Loughlin AM, Marchant CD, Adams W, et al. Causality assessment of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*. 2012;30(50):7253–7259
7. Centers for Disease Control and Prevention. Clinical Immunization Safety Assessment (CISA) Project. Available at www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/cisa/index.html. Accessed May 15, 2016
8. Veien NK, Hattel T, Justesen O, Nørholm A. Aluminium allergy. *Contact Dermat*. 1986;15(5):295–297
9. Böhler-Sommeregger K, Lindemayr H. Contact sensitivity to aluminium. *Contact Dermat*. 1986;15(5):278–281
10. Jefferson T, Rudin M, Di Pietrantonj C. Adverse events after immunisation with aluminium-containing DTP

vaccines: systematic review of the evidence. *Lancet Infect Dis*. 2004;4(2):84–90

11. Fritsche PJ, Helbling A, Ballmer-Weber BK. Vaccine hypersensitivity--update and overview. *Swiss Med Wkly*. 2010;140(17-18):238–246
12. Beveridge MG, Polcari IC, Burns JL, Adler A, Hendrickson B, Stein SL. Local vaccine site reactions and contact allergy to aluminum. *Pediatr Dermatol*. 2012;29(1):68–72
13. Avcin S, Jazbec J, Jancar J. Subcutaneous nodule after vaccination with an aluminum-containing vaccine. *Acta Dermatovenerol Alp Panonica Adriat*. 2008;17(4):182–184
14. Bergfors E, Trollfors B. Sixty-four children with persistent itching nodules and contact allergy to aluminium after vaccination with aluminium-adsorbed vaccines-prognosis and outcome after booster vaccination. *Eur J Pediatr*. 2013;172(2):171–177
15. Bergfors E, Trollfors B, Inerot A. Unexpectedly high incidence of persistent itching nodules and delayed hypersensitivity to aluminium in children after the use of adsorbed vaccines from a single manufacturer. *Vaccine*. 2003;22(1):64–69
16. Bergfors E, Björkelund C, Trollfors B. Nineteen cases of persistent pruritic nodules and contact allergy to aluminium after injection of commonly used aluminium-adsorbed vaccines. *Eur J Pediatr*. 2005;164(11):691–697
17. Frederiksen MS, Tofte H. Immunisation with aluminium-containing vaccine of a child with itching nodule following previous vaccination. *Vaccine*. 2004;23(1):1–2
18. García-Patos V, Pujol RM, Alomar A, et al. Persistent subcutaneous nodules in patients hyposensitized with aluminum-containing allergen extracts. *Arch Dermatol*. 1995;131(12):1421–1424
19. Klein NP, Edwards KM, Sparks RC, Dekker CL; Clinical Immunization Safety Assessment Network. Recurrent sterile abscesses following aluminium adjuvant-containing vaccines [published ahead of print March 17, 2009]. *BMJ Case Rep*. 2009. doi:10.1136/bcr.09.2008.0951
20. Kaaber K, Nielsen AO, Veien NK. Vaccination granulomas and aluminium allergy: course and prognostic factors. *Contact Dermat*. 1992;26(5):304–306
21. Lehman HK, Faden HS, Fang YV, Ballow M. A case of recurrent sterile abscesses following vaccination: delayed hypersensitivity to aluminum. *J Pediatr*. 2008;152(1):133–135
22. Lopez S, Pelaez A, Navarro LA, Montesinos E, Morales C, Carda C. Aluminium allergy in patients hyposensitized with aluminium-precipitated antigen extracts. *Contact Dermat*. 1994;31(1):37–40
23. Nagore E, Martínez-Escribano JA, Tato A, Sabater V, Vilata JJ. Subcutaneous nodules following treatment with aluminium-containing allergen extracts. *Eur J Dermatol*. 2001;11(2):138–140
24. Netterlid E, Hindsén M, Björk J, et al. There is an association between contact allergy to aluminium and persistent subcutaneous nodules in children undergoing hyposensitization therapy. *Contact Dermat*. 2009;60(1):41–49
25. Skowron F, Grézard P, Bérard F, Balme B, Perrot H. Persistent nodules at sites of hepatitis B vaccination due to aluminium sensitization. *Contact Dermat*. 1998;39(3):135–136
26. Thierry-Carstensen B, Stellfeld M. Itching nodules and hypersensitivity to aluminium after the use of adsorbed vaccines from SSI. *Vaccine*. 2004;22(15-16):1845
27. Vogelbruch M, Nuss B, Körner M, Kapp A, Kiehl P, Bohm W. Aluminium-induced granulomas after inaccurate intradermal hyposensitization injections of aluminium-adsorbed depot preparations. *Allergy*. 2000;55(9):883–887
28. Pineau A, Durand C, Guillard O, Bureau B, Stalder JF. Role of aluminium in skin reactions after diphtheria-tetanus-pertussis-poliomyelitis vaccination: an experimental study in rabbits. *Toxicology*. 1992;73(1):117–125
29. Centers for Disease Control and Prevention. Vaccine excipient & media summary excipients included in U.S. vaccines, by vaccine. Available at: www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf. Accessed May 14, 2016
30. Jacob SE, Brod B, Crawford GH. Clinically relevant patch test reactions in children--a United States based study. *Pediatr Dermatol*. 2008;25(5):520–527
31. Tosti A, Vincenzi C, Peluso AM. Accidental diagnosis of aluminium sensitivity with Finn Chambers. *Contact Dermat*. 1990;23(1):48–49
32. Badiu I, Geuna M, Heffler E, Rolla G. Hypersensitivity reaction to human papillomavirus vaccine due to polysorbate 80. *BMJ Case Rep*. 2012;bcr022012579
33. Audicana MT, Muñoz D, del Pozo MD, Fernández E, Gastaminza G, Fernández de Corres L. Allergic contact dermatitis from mercury antiseptics and derivatives: study protocol of tolerance to intramuscular injections of thimerosal. *Am J Contact Dermat*. 2002;13(1):3–9
34. Lee-Wong M, Resnick D, Chong K. A generalized reaction to thimerosal from an influenza vaccine. *Ann Allergy Asthma Immunol*. 2005;94(1):90–94
35. Vogt T, Landthaler M, Stolz W. Generalized eczema in an 18-month-old boy due to phenoxyethanol in DPT vaccine. *Contact Dermat*. 1998;38(1):50–51
36. Kuritzky LA, Pratt M. Systemic Allergic Contact Dermatitis After Formaldehyde-Containing Influenza Vaccination. *J Cutan Med Surg*. 2015;19(5):504–506
37. Leventhal JS, Berger EM, Brauer JA, Cohen DE. Hypersensitivity reactions to vaccine constituents: a case series and review of the literature. *Dermatitis*. 2012;23(3):102–109
38. Centers for Disease Control and Prevention. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm?s_cid=rr6002a1_e. Accessed May 15, 2016
39. Centers for Disease Control and Prevention; Food and Drug Administration. Vaccine adverse event reporting system. Available at: https://vaers.hhs.gov/index.
40. Centers for Disease Control and Prevention. Vaccine safety. Available at: www.cdc.gov/vaccinesafety/index.html.

Case Report of Subcutaneous Nodules and Sterile Abscesses Due to Delayed Type Hypersensitivity to Aluminum-Containing Vaccines

Christine T. Lauren, Donald V. Belsito, Kimberly D. Morel and Philip LaRussa

Pediatrics 2016;138;
DOI: 10.1542/peds.2014-1690 originally published online September 27, 2016;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Case Report of Subcutaneous Nodules and Sterile Abscesses Due to Delayed Type Hypersensitivity to Aluminum-Containing Vaccines

Christine T. Lauren, Donald V. Belsito, Kimberly D. Morel and Philip LaRussa

Pediatrics 2016;138;
DOI: 10.1542/peds.2014-1690 originally published online September 27, 2016;