

Polyarteritis Nodosa Reports to the Vaccine Adverse Event Reporting System (VAERS): Implications for Assessment of Suspected Vaccine-Provoked Vasculitis

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ABSTRACT. *Objective.* To examine polyarteritis nodosa (PAN) reports to the Vaccine Adverse Event Reporting System (VAERS) as the initial stage in investigating the hypothesis that vaccination can very rarely cause PAN.

Methods. We reviewed PAN reports submitted from 1990 through 2001 using a causal inference framework to evaluate the consistency of the reports' clinical details with this hypothesis. We also reviewed published literature relating to the hypothesized association's biological plausibility.

Results. VAERS received 25 PAN reports. Ten met our case definition for definite or possible PAN and had no alternative etiology for PAN identified. Nine of these 10 followed hepatitis B vaccine with a modal peak (4 definite cases) in time to symptom onset 2 weeks after vaccination. However, all potential triggering infections were not excluded, and identification of vaccine antigens in clinical specimens was not attempted. Also, 14 of 25 reports were European, with 11 from France. All 9 French reports with a known diagnosis date began during 1994-97, when autoimmune and rheumatologic events following hepatitis B vaccine were a focus of public concern in France.

Conclusion. While we identified some supportive evidence, overall, current adverse event reports do not support a causal link between vaccination and PAN. Appropriate prospective evaluation of future post-vaccination PAN cases could add to current knowledge with rigorous confirmation of diagnosis, appropriate testing for possible triggering infections including polymerase chain reaction testing for latent hepatitis B infection, and an attempt to link the vaccine antigen to pathology such as by immunohistochemical staining or immune complex identification. (J Rheumatol 2004;31:2181-8)

Key Indexing Terms:

VASCULITIS POLYARTERITIS NODOSA VACCINATION HEPATITIS B VACCINE

Rheumatologic events following hepatitis B and other vaccines have been an area of public and scientific concern in recent years^{1,2}. Polyarteritis nodosa (PAN) is a rare life-threatening form of necrotizing vasculitis affecting medium-size arteries, with a well documented association with hepatitis B virus (HBV) infection³⁻⁵. Multiple case reports have suggested a link between PAN and hepatitis B vaccination⁶⁻¹¹. The second most frequently administered vaccine

in the United States¹², hepatitis B vaccine is universally recommended for infants as well as selected high risk adults¹³. Current hepatitis B vaccines contain hepatitis B surface antigen (HBsAg) produced in yeast cells using recombinant DNA techniques¹³, and the series usually involves 3 vaccinations with followup doses one and 6 months after the first¹³.

While assuming causality simply because a disease temporally follows a vaccine or drug is the logical fallacy of "post hoc ergo propter hoc" ("after this, therefore, because of this"), case reports have generated the initial sentinel hypothesis for vaccine-disease associations^{14,15}. Specifically, careful analysis of spontaneous adverse event reports from the Vaccine Adverse Event Reporting System (VAERS) has identified rare, potentially serious vaccine side effects in the post-licensure period^{16,17}.

Miller, *et al* proposed a framework to evaluate case reports as the first stage of identifying and defining environmentally associated rheumatic disorders¹⁴. Using this framework, we investigated PAN's proposed association with hepatitis B vaccination and vaccination generally by

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systematically reviewing all PAN reports to VAERS. This methodology is similar to the Institute of Medicine's (IOM) approach to case reports in its evaluation of proposed vaccine-adverse event relationships¹⁵.

MATERIALS AND METHODS

VAERS is a passive surveillance system jointly administered by the US Food and Drug Administration and Centers for Disease Control for post-licensure vaccine safety surveillance (see <http://www.VAERS.org>). Important limitations of VAERS include underreporting, incomplete clinical information, and difficulty in determining whether a vaccine caused the reported adverse event^{12,18}.

Case identification and classification. We searched the entire VAERS database using coding terms (arteritis, polyarteritis nodosa, vasculitis, and vasculitis kidney) and text searches ("polyarter," "nodosa," and "arterit") to identify clinician-diagnosed PAN cases received from the inception of VAERS in 1990 through 2001. We applied a case definition based on the 1993 Chapel Hill Consensus Conference (CHCC) vasculitis nomenclature¹⁹ to categorize the reports by diagnostic certainty (definite, possible, or indeterminate) and to identify reports of PAN that were more likely other vasculitides.

CHCC defined PAN as "necrotizing inflammation of medium-size or small arteries *without* glomerulonephritis or vasculitis in arterioles, capillaries or venules."¹⁹ We classified reports as "definite" PAN cases if the report described a tissue biopsy with medium-size vessel vasculitis or an angiogram documenting microaneurysms. "Possible" cases reported biopsy or angiogram results as consistent with PAN but without adequate additional detail. "Indeterminate" cases had a diagnosis of PAN without documentation of whether a tissue biopsy or angiogram was done. PAN reports with serum eosinophilia and a history of asthma were classified as indeterminate since Churg-Strauss disease was more likely the diagnosis¹⁹. PAN reports noting glomerulonephritis, an exclusion criterion for PAN, were reclassified as microscopic polyangiitis (MPA)¹⁹. Diagnostic concerns for definite and possible cases, including the presence of hematuria, which is common in MPA but can be seen in PAN, are described in Tables 1 and 2. Information sources included the initial VAERS reports, routine followup correspondence, and any associated publications. We did not attempt to recontact reporters for additional information, since many reports were from outside the US and were received more than 5 years ago.

Case evaluation. We reviewed all definite or possible PAN cases, with no other documented etiology, for evidence of the primary and secondary attribution elements proposed by Miller, *et al*¹⁴. Primary elements include temporal association (timing consistent with biologic knowledge of disease and pharmacology of vaccine), alternative explanations (exclusion of other known causes), dechallenge (evidence that the adverse event diminished, as would be expected if the vaccine caused the event), rechallenge (if the vaccine was readministered, did the adverse event worsen or recur?), and biologic plausibility (consistency of proposed relationship with biological knowledge of vaccine and disease). The secondary elements are analogy (evidence of vaccination's relationship with related disorders), dose responsiveness (evidence that the vaccine dose or number of doses is related to likelihood or severity of disease), and specificity (consistency of clinical syndrome across cases). Results for analogy and biological plausibility are based on review of published literature and were focused on hepatitis B vaccine, due to HBV infection's known association with PAN and the large proportion of reported cases that followed this vaccine. The use of dechallenge as a consideration for vaccine-provoked disease has been questioned, since complete elimination of the vaccine and its effects is not possible¹⁴. However, the IOM has used this element in its reviews¹⁵, and for immune complex-mediated diseases like PAN, dechallenge evaluation is appropriate, as vaccine antigens would not circulate indefinitely.

Regarding alternative etiologic explanations, the available case information was reviewed for evidence of preceding or concurrent infectious ill-

ness, in particular HBV infection, as well as other infections for which an association with PAN has been postulated: hepatitis C, human immunodeficiency virus (HIV), and β -hemolytic Group A streptococcus⁴. To calculate the median time to onset, the midpoint of the reported range was used if a case lacked exact information.

RESULTS

Overall, 25 reports of PAN were submitted to VAERS from 1990 through 2001. Two reports were reclassified as MPA due to presence of glomerulonephritis. Among the remaining 23 PAN reports, 9 definite, 6 possible, and 8 indeterminate cases were identified (Figure 1). Case 7 (Table 2) had detailed appropriate biopsy results but was classified as possible due to a clinical inconsistency, a pulmonary infiltrate, that is unusual in PAN²⁰. One report with a neuromuscular biopsy reported as consistent with PAN was classified as indeterminate, due to a history of asthma and serum eosinophilia. Six of the 25 reports had been previously published^{6-8,10,20}.

Figure 2 depicts all 25 clinician-diagnosed PAN reports by year of onset and hepatitis B vaccine exposure status. A peak is seen during years 1995 through 1997. Fourteen reports were European, with 11 from France. All 9 French PAN reports with a known date of onset began during 1994-97.

Five reports had evidence of another possible etiology for PAN (Figure 1). Two definite cases were diagnosed with chronic active hepatitis B after vaccination^{6,7} and 3 cases had evidence of recent Group A streptococcus infection. A possible case had a history of sinusitis with a high anti-streptodornase count (200; suggesting recent streptococcal infection) 4 days prior to vaccination and 11 days prior to diagnosis of PAN. This case was previously published without mention of the prior streptococcal infection¹⁰. A definite case that died from a PAN-related myocardial infarction was found to have elevated antistreptolysin O titers (200-400 IU/ml) on autopsy, consistent with recent streptococcal infection. Another definite case experienced sore throat and cervical lymphadenopathy a week prior to symptom onset (one week after vaccination), although no throat culture results were provided. No case reported a history of hepatitis C, HIV, or other infectious illness.

Ten cases, 5 definite (Cases 1-5; Table 1) and 5 possible (Cases 6-10; Table 2), had no other documented etiology for PAN. A summary of the attribution elements for these 10 cases is presented in the following text and Tables 1 and 2.

Temporal association. A modal peak (4 definite hepatitis B vaccine cases) in time to onset of symptoms was noted 2 weeks after vaccination (Cases 1, 2, 4, 5), and median time to onset for the 10 definite or possible cases was 2.8 weeks (range 1-32 weeks).

Alternative etiologic agents. While these 10 case reports did not note alternative etiologic agents, no single report documented negative serologies for all of the potentially asymptomatic associated infections (hepatitis C, HIV, and hepati-

Table 1. Definite cases of polyarteritis nodosa reported after vaccination to VAERS with no other described etiology for the disease, 1990–2001.

Case*	Age, yrs	Sex	Country	Vaccine	Weeks Until Onset	Clinical Features	Diagnosis	Serology Results	Dechallenge/Clinical Course	Diagnostic Concerns
1 ⁸	45	M	Belgium	1 dose Hep B	2.1	Myalgia, arthralgia, morning stiffness, leg ulcer, digital ischemia; ANCA (+) 1:64 (homogeneous); ANA (+) 1:40, serum immune complexes slightly elevated	Skin biopsy: medium-size vessels with concentric fibrosis of muscle wall accompanied by infiltrating inflammatory cells; humeral artery angiogram: vasculitis	2 mo after last dose anti-HBs, HBs Ag, anti-HBc (–)	Hospitalized. Out of work for 6 months. Amputation of right distal phalanx. 3 yrs afterwards still symptomatic	
2	33	F	USA	3 doses Hep B	2.1	Fever, vomiting, abdominal pain, headache, weight loss, rash, hematuria, back pain, visual disturbances, fatigue, myalgias, hypertension, “fluid in lungs”	Diagnosed with “kidney and liver aneurysms”	Not reported	Hospitalized for 21 days. Considered life-threatening and resulted in permanent disability. 6+ years after vaccination still symptomatic	“Fluid in lungs” and hematuria raise question of MPA. Data on arteriogram limited and no biopsy provided
3	41	F	France	5 doses Hep B	1.5 to 5.5	Arthralgia, myalgia, digital ischemia, ANA (+), ANCA (–); also diagnosed with rheumatoid arthritis 4 yrs after 5th dose	Arteriogram: occlusion of right cubital artery and interdigital arteritis, microaneurysm of renal arteries	4 mo after 5th dose anti-HBs (–); 2 years after 6th dose anti-HBs (+) 14 MU/ml; Hep C antibody (–)	Hospitalized. 5+ years after onset still “not recovered”	Atypical course with improvement despite no mention of treatment with immunosuppressives
4	56	F	Canada	3 doses Hep B	2.0	“Cutaneous vasculitis”, hematuria, malaise, ESR 100, ANA (+) 1:160	Skin biopsy: vasculitis of medium-size vessels and PAN	Not reported	Considered life-threatening. No designation of level of care. 4 mo after vaccination all signs and symptoms resolved, but pt still on prednisone and cyclophosphamide	Presence of hematuria raises question of MPA
5 ⁸	35	F	Belgium	4 doses Hep B (primary series and booster 5 yrs later)	2.0	Relapsing fever, myalgia, dry cough, rash, dyspnea, ANA (–), ANCA (+)	Skin biopsy: medium-size blood vessels with complete destruction of vessel wall, fibrinoid necrosis, infiltration of neutrophils	HBs Ag & HBe Ag (–); anti-HBs strongly (+); anti-HBc & anti-HBe (–) 2 mo after last dose	Outpatient treatment. Out of work for several months. “Gradual relief of symptoms with prednisone treatment”, no timeline given	

ANCA: antineutrophil cytoplasmic antibody, ANA: antinuclear antibody, ESR: erythrocyte sedimentation rate, PAN: polyarteritis nodosa, MPA: microscopic polyangiitis. * Cases ordered by onset-year within case category.

tis B), nor did any report describe testing to rule out streptococcal infection. For 5 cases, hepatitis B antigen testing was noted to be negative after vaccination, ruling out chronic active hepatitis B. For one additional case (Case 3), negative hepatitis B surface antibody results were noted 3 months after symptom onset.

Dechallenge. Four case reports described several years of symptoms due to PAN. Five patients had experienced only months of illness at last followup but were not documented as symptom-free off medication at last contact. Case 3 did exhibit an atypically mild course with remission without report of immunosuppressive treatment, suggesting a rela-

Table 2. Possible cases of polyarteritis nodosa reported after vaccination to VAERS with no other described etiology for the disease, 1990–2001.

Case*	Age, yrs	Sex	Country	Vaccine	Weeks Until Onset	Clinical Features	Diagnosis	Serology Results	Dechallenge/Clinical Course	Diagnostic Concerns
6	50	M	USA	2 doses Hep B	3 to 6	Subcutaneous nodules on pretibial region bilaterally	Skin biopsy: consistent with PAN	Not reported	Outpatient treatment. 5 months after vaccination no change in macules noted	Cutaneous symptoms only; skin biopsy with no reference to vessel size
7 ²⁰	60	M	Canada	Flu	1.0	Fever, rigors, fatigue, bilateral calf pain, migratory maculopapular rash, dry cough with right upper lobe infiltrate; ESR 140; ANA (–)	Skin biopsy, perivascular mononuclear infiltrate and fibroid necrosis of medium-size vessels	HBs Ag and anti-HBs “undetectable” days to weeks after event onset; HIV (–)	Multiple hospitalizations. 11 weeks after vaccination symptom-free on low dose prednisone	Lung infiltrate atypical for PAN [bronchoalveolar lavage (–)]. Possibility MPA but no hematuria; no ANCA performed
8	NA	M	USA	Hep B (dose no. not given)	21 to 32	Fever, weight loss	Muscle biopsy: PAN	Not reported	Outpatient treatment. At least 5 months of illness	Muscle biopsy listed as PAN only, with no reference to vessel size
9	18	F	USA	3 doses Hep B	18 to 20	Rash	Skin biopsy: “mid artery vasculitis resembling cutaneous PAN”	Not reported	Outpatient treatment. Duration and clinical course not reported	Cutaneous symptoms only. Unclear if “mid” means “medium” in biopsy description
10	44	F	France	2 doses Hep B	5.4	Fever, weight loss, myalgia, arthralgia, focal weakness/paresthesias with disseminated neuritis by EMG; ANA (–); ESR 96; Raynaud’s also diagnosed	Neuromuscular biopsy: “compatible with panarteritis”	HBs Ag (–) days after event onset; HIV (–)	Hospitalized. 3+ yrs after vaccination recovered except for persistent muscle weakness	Muscle biopsy with no reference to vessel size

* Cases ordered by onset year within case category. ANCA: antineutrophil cytoplasmic antibody, ANA: antinuclear antibody, ESR: erythrocyte sedimentation rate, PAN: polyarteritis nodosa, MPA: microscopic polyangiitis. NA: not available.

tive dechallenge compared to the usual aggressive natural history. However, the patient went on to have relapsing symptoms for several years, long after last vaccination.

Rechallenge. Three case reports had information on the patient’s response to vaccine rechallenge. Case 1 developed myalgia, arthralgia, and morning stiffness 2 weeks after his first dose of vaccine, and these symptoms noticeably worsened following the administration of his second dose a month after the first, when he also developed several ischemic lesions⁸. However, he had no clear recovery period after initial symptoms. Case 3 received a 6th dose of hepatitis B vaccine one year after PAN symptom onset and finally seroconverted. Her symptoms continued afterwards for at least 4 years, and no disease exacerbation was specifically noted to have followed this last vaccine dose. A week after influenza vaccination (Fluogen, Fall 1990), Case 7 developed 10 days of nonspecific influenza-like symptoms, fever, dry cough, myalgia, and fatigue, and then was well for a year²⁰. He then received another dose of influenza vac-

cine (Fluogen, Fall 1991) and one week later developed similar symptoms that were subsequently diagnosed as PAN²⁰.

Biological plausibility. HBV-associated PAN is generally considered to be part of the subset of systemic vasculitides whose pathogenesis involves immune complex deposition in vessel walls²¹. Hepatitis B surface antigen has long been held to be the antigen responsible for the pathogenic immune complex formation in HBV-associated PAN²². Hepatitis B surface antigenemia has been documented to frequently follow hepatitis B vaccine and has been detected up to 18 days after the 20 µg vaccine²³, increasing the biological plausibility of related immune complex-mediated disease.

However, several lines of evidence have challenged the role of hepatitis B surface antigen-antibody immune complexes in mediating PAN, suggesting that hepatitis B proteins other than surface antigen may be involved^{5,22}. First, hepatitis B surface antigen-antibody immune complexes

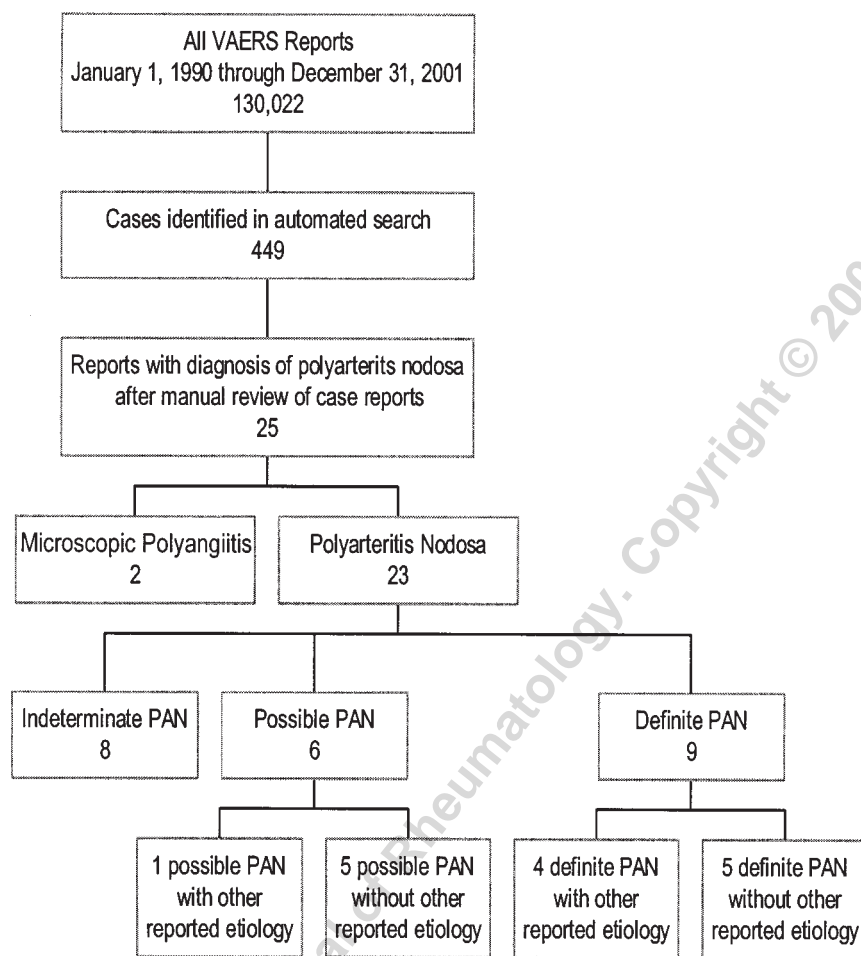


Figure 1. Case identification and classification.

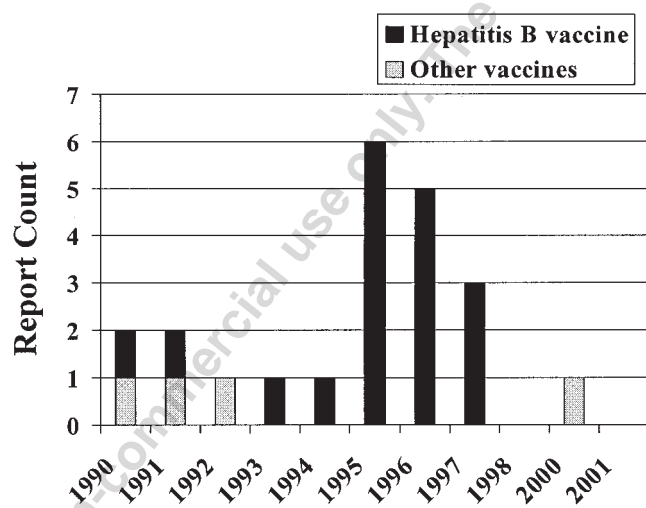


Figure 2. Counts of polyarteritis nodosa reports to the Vaccine Adverse Event Reporting System by onset year and vaccine type, 1990-2001. For 2 reports with missing onset date, vaccination date was substituted. Three reports were excluded: 2 hepatitis B vaccine reports without onset or vaccination dates and one rubella vaccine report with onset in 1986.

can be found in infected patients who do not have vasculitis²⁴. Second, disease activity and clearance of symptoms have been better correlated with HBV replication as measured by HBV DNA levels and hepatitis E antigen/antibody seroconversion than with HBV surface antigen levels^{5,22}. Finally, recurrence of PAN is rare in patients who have undergone hepatitis E antigen/antibody seroconversion despite continued hepatitis B surface antigenemia^{3,5}.

Analogy. Other immune complex-mediated illnesses have been anecdotally associated with the hepatitis B vaccine. A "serum-sickness-like" hypersensitivity syndrome of delayed onset occurring days to weeks after vaccination has been reported to follow the 20 µg vaccine in passive post-marketing surveillance²⁵. Case reports and case series of other immune complex diseases^{26,27} including glomerulonephritis^{26,28} have been published. One glomerulonephritis case report described hepatitis B surface antigen in the kidney's tubular and peritubular areas using immunohistochemical staining, but no antigen was noted in the glomeruli, the site of pathology²⁸. Of note, immune complex deposition is not thought to mediate the pathology of

rheumatoid arthritis and multiple sclerosis, other autoimmune illnesses that have been reported in association with hepatitis B vaccine^{2,27}.

Dose responsiveness. All cases with documented dose-number information received at least 2 doses of vaccine prior to symptom onset (Tables 1 and 2), except for Case 1 described above in the rechallenge section. Case 3 received 5 doses, due to repeated failure to seroconvert. Nine cases occurred after hepatitis B vaccines, the 20 µg Engerix-B® (GlaxoSmithKline) or the 10 µg Recombivax HB® (Merck). Among these, 7 cases (5 definite) followed the 20 µg dose, while 2 possible cases received 10 µg.

Specificity. Median age for definite and possible cases was 45 years (range 18–60 yrs). Cases 6 and 8 reported only cutaneous symptoms. The remaining cases described a variety of systemic symptoms (Tables 1 and 2). Five cases reported hospitalization.

DISCUSSION

Case reports have suggested a link between PAN and vaccination, particularly hepatitis B vaccination^{6–11,20}. We examined reports of clinician-diagnosed PAN submitted to the Vaccine Adverse Event Reporting System using a framework proposed by Miller, *et al*¹⁴ to assess consistency with a causal association. Case series analyses are not appropriate for hypothesis testing, but case reports have generated the initial hypothesis for many known drug-disease associations^{14,15}. In evaluating Miller's attribution elements, we found partial support for a plausible temporal association, biologic plausibility, analogy, and dose responsiveness, but little convincing evidence of dechallenge, rechallenge, or specificity. Most important, the cases lacked documentation to conclusively rule out previously established provoking infections. We found evidence of reporting bias, based on a high proportion of reports originating from France during a time of heightened community concern about rheumatologic and autoimmune adverse events following hepatitis B vaccination. Also, no case report directly linked the vaccine antigen to the patient's pathology.

The modal peak in time to onset 2 weeks post-vaccination differs from most vaccine adverse event case series, since the peak is not within a few days of vaccination¹². This suggests a more plausible temporal association than onset immediately after vaccination. However, in one series of 18 hepatitis B-associated PAN cases with known date of infection or acute hepatitis onset, the mode for time to onset was one month after onset of clinical hepatitis or infection³, suggesting that most of these PAN cases presented months after HBV infection, given the 2–3 month incubation period. Yet in the setting of previous antigen exposure (vaccination), no viral replication and less antibody production lead-time would be required after vaccine reexposure prior to immune complex formation. PAN, therefore, might rea-

sonably occur more rapidly if the vaccine was truly a provoking factor.

We found partial support for biologic plausibility, analogy, and dose responsiveness, specifically for hepatitis B vaccine and PAN. Hepatitis B vaccine has been linked to other immune complex disease, although only through case reports. The long-standing hypothesis that hepatitis B surface antigen-antibody immunocomplexes mediate PAN's pathology in HBV-associated disease²² is consistent with a hepatitis B surface antigen-based vaccine causing PAN, and we found evidence that antigenemia can persist for weeks after vaccination²³. However, hepatitis B surface antigen's role in mediating PAN has been questioned recently^{5,22}. Further work to clarify which hepatitis B antigen-antibody complex mediates pathology, if any, could help in evaluating whether the vaccine might rarely provoke this disease. Regarding dose responsiveness, more cases followed the higher dose vaccine, and nearly all cases followed multiple vaccinations (in one case, 5 doses), but differential market distribution and coincidence could explain these findings. More specifically, with respect to the possibility of coincidence regarding the history of multiple vaccinations, the usual brief one-month interval between the first and the second dose of hepatitis B vaccine provides less time to develop the disease by chance after a single dose and would result in fewer cases reported after the first dose, even if the temporal association between the vaccine and disease is purely coincidental and cases were merely randomly distributed across time.

Overall, evidence was not sufficient in any reported case to rule out all other alternative etiologic agents for PAN: hepatitis B, Group A streptococcus, HIV, and hepatitis C⁴. Additionally, some PAN patients with negative hepatitis B serologies by commercial testing have been found to have evidence of latent HBV infection by Southern blotting for viral DNA and radioimmunoassay for hepatitis B surface antigen using monoclonal antibodies²⁹. Such latent hepatitis B is a recently recognized entity in the pathology of idiopathic chronic hepatitis and treatment-resistant hepatitis C liver disease³⁰. In other patient populations, polymerase chain reaction (PCR) testing for hepatitis B virus DNA had been used to identify chronic hepatitis B infection despite negative hepatitis B antigen testing³⁰. Such testing would be warranted before concluding that a PAN case was vaccine-provoked.

We found the wide range of clinical presentations and severity not supportive of specificity. No case provided convincing evidence of rechallenge or dechallenge. For the 2 potential rechallenge cases, one case may have had a self-limited viral illness following his first vaccination, and the other had no clear recovery period after initial symptoms. Regarding dechallenge, no reported case is documented symptom-free off medication at last contact. PAN disease activity is best correlated with HBV replication via HBV

DNA levels, suggesting that ongoing antigen excess drives disease activity^{5,22}. Permanent tissue damage from the initial insult might be expected to produce continued symptoms, but exacerbations years after the event without additional antigen to form immune complexes would be difficult to explain. Similarly, when an IOM panel examined the hypothesis that hepatitis B vaccine might provoke PAN, in their consideration of arthritis as an adverse event, it concluded that such a causal association seemed implausible in the absence of continuing antigen production after vaccination¹⁵.

A concern for passive surveillance systems with substantial underreporting such as VAERS is that reporting bias can be an important determinant of what is received¹². In this review, we saw a large proportion of cases from France diagnosed during 1994-97. In 1994, a universal hepatitis B immunization campaign targeting newborns and adolescents (10-11 yrs) began in France. In response to reports of post-vaccinal demyelinating disorders and autoimmune illness that generated widespread public concern, the French government suspended school-based adolescent hepatitis B vaccination in 1998³¹. VAERS has not received reports of post-hepatitis B vaccine PAN cases diagnosed during 1998-2001 despite continued widespread adult hepatitis B vaccination, further supporting the hypothesis that public and media attention played a role in linking the disease to the vaccine in the minds of reporters. Indeed, France has experienced a decline in PAN incidence coinciding with increased hepatitis B vaccination of at-risk populations⁵.

While other etiologies for PAN might potentially interact with a vaccination to increase risk for the illness, it is generally not possible to distinguish among potential competing causes from case reports alone. As outlined by Miller, *et al*¹⁴ and others¹⁵, lack of alternative explanations is generally considered a prerequisite for postulating that an environmental agent is causing an illness. For that reason, we excluded cases with another explanation for the illness

based on existing knowledge. Characteristics of cases with no other identified etiologies best serve as the basis for specific hypothesis generation from case series. If the initial hypothesis is confirmed after further research, a more compelling argument can be made to conduct the more difficult studies to evaluate potential interactions with other etiologies.

Given the rarity of this illness, controlled studies are logistically difficult, but this analysis suggests that further investigation of cases alleged to be vaccine-provoked might add to our knowledge regarding this hypothesized association. Three key components of prospective evaluation of future cases should include rigorous confirmation of diagnosis, ruling out of potential provoking infections, and an attempt to link the vaccine antigen to patient pathology. Detailed suggestions are outlined in Table 3. Future publication of case reports of PAN following vaccination are unlikely to add to current knowledge without some or all of this additional testing and a detailed description of the evolution of the clinical course.

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Table 3. Suggested evaluation for suspected vaccine-provoked PAN.

I. Rigorously confirm diagnosis
A. Obtain tissue biopsy with medium-size artery (s) and/or angiogram
B. Rule out glomerulonephritis if hematuria present
II. Rule out other provoking agents
A. Rule out hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and Group A streptococcus* infections with appropriate serologic testing
B. Consider polymerase chain reaction testing for hepatitis B DNA (using a nested approach if possible) if hepatitis B antigen testing is negative ³⁰
C. Rule out other infections anecdotally associated with PAN ⁴
i. Detailed history and physical for signs and symptoms of infection
ii. Additional investigation as clinically indicated
III. Attempt to link vaccine antigen to pathology
A. Immunohistochemical staining of tissue samples for vaccine antigens ²⁸
B. Immune complex testing and identification ²⁴

* Antistreptolysin O antibodies and antideoxyribonuclease B (anti-DNAse B) testing are options for ruling out Group A streptococcus infections as well as culture of clinically suspicious sites.

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