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Original Investigation

Vaccines and the Risk of Multiple Sclerosis and Other Central Nervous System Demyelinating Diseases

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IMPORTANCE Because vaccinations are common, even a small increased risk of multiple sclerosis (MS) or other acquired central nervous system demyelinating syndromes (CNS ADS) could have a significant effect on public health.

OBJECTIVE To determine whether vaccines, particularly those for hepatitis B (HepB) and human papillomavirus (HPV), increase the risk of MS or other CNS ADS.

DESIGN, SETTING, AND PARTICIPANTS A nested case-control study was conducted using data obtained from the complete electronic health records of Kaiser Permanente Southern California (KPSC) members. Cases were identified through the KPSC CNS ADS cohort between 2008 and 2011, which included extensive review of medical records by an MS specialist. Five controls per case were matched on age, sex, and zip code.

EXPOSURES Vaccination of any type (particularly HepB and HPV) identified through the electronic vaccination records system.

MAIN OUTCOMES AND MEASURES All forms of CNS ADS were analyzed using conditional logistic regression adjusted for race/ethnicity, health care utilization, comorbid diseases, and infectious illnesses before symptom onset.

RESULTS We identified 780 incident cases of CNS ADS and 3885 controls; 92 cases and 459 controls were females aged 9 to 26 years, which is the indicated age range for HPV vaccination. There were no associations between HepB vaccination (odds ratio [OR], 1.12; 95% CI, 0.72-1.73), HPV vaccination (OR, 1.05; 95% CI, 0.62-1.78), or any vaccination (OR, 1.03; 95% CI, 0.86-1.22) and the risk of CNS ADS up to 3 years later. Vaccination of any type was associated with an increased risk of CNS ADS onset within the first 30 days after vaccination only in younger (<50 years) individuals (OR, 2.32; 95% CI, 1.18-4.57).

CONCLUSIONS AND RELEVANCE We found no longer-term association of vaccines with MS or any other CNS ADS, which argues against a causal association. The short-term increase in risk suggests that vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease. Our findings support clinical anecdotes of CNS ADS symptom onset shortly after vaccination but do not suggest a need for a change in vaccine policy.

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The concern that vaccinations could induce a small increased risk of multiple sclerosis (MS) and other acquired central nervous system demyelinating syndromes (CNS ADS) remains controversial.

Most studies have focused on the risk of MS following hepatitis B (HepB) vaccine because of the potential for molecular mimicry of this vaccine with myelin basic protein,¹ a key immunodominant epitope in animal models of MS. The results of these studies are mixed; most show no effect,²⁻⁵ but one study showed a small increased risk of adult-onset MS⁶ and another of pediatric MS⁷ manifesting 3 or more years after HepB vaccination. The few published studies^{3,8-10} of other vaccines and MS have found no association. However, the studies are limited by the small number of vaccinated cases^{2-4,6-9}; incomplete case-finding methods^{2-6,8-10}; imprecise estimations or unknown time of symptom onset^{2-6,8-10}; inclusion of only individuals who developed MS^{2,4,6,8,9}; uncontrolled confounding factors, such as health care utilization²⁻¹⁰; and/or undefined delay between vaccination and symptom onset.^{2,3,10}

Several cases of young females presenting with fulminant onset of CNS ADS 2 to 4 weeks following the administration of human papillomavirus (HPV) vaccine have been reported.¹¹⁻¹⁵ Some of the patients had symptoms at the time of vaccination,^{11,15} raising the possibility that this vaccine may accelerate the transition from subclinical to clinical disease.

The purpose of this study was to examine in more detail the association between the first onset of CNS ADS and vaccines. The particular focus of the study was the most commonly observed clinical phenomenon of a short delay between vaccination and symptom onset.

Methods

Setting

The institutional review board at Kaiser Permanente Southern California (KPSC) approved this study. Informed consent was waived because this was a medical records review study without direct patient contact. A large, prepaid health maintenance organization, KPSC has more than 3.5 million members. It provides comprehensive health care coverage to approximately 20% of the population in the geographic area that it serves.¹⁶ The KPSC membership is representative of the general population in southern California with respect to race/ethnicity, age, sex, and socioeconomic status with the exception of underrepresentation of the lowest and highest ends of the socioeconomic spectrum.¹⁶ The cost of specialist consultations, hospitalizations, magnetic resonance imaging, other diagnostic tests, and medications are fully covered by KPSC. Data regarding demographics, services, and diagnoses are tracked in KPSC electronic health records from the outpatient, emergency department, and hospital settings. Data on care from non-KPSC providers are likely to be captured in KPSC databases, since documentation is required for reimbursement of such services. Vaccinations, regardless of whether administered within or outside KPSC, are tracked in the Kaiser

Immunization Tracking System (KITS). Vaccination records are back-entered into KITS when an individual becomes a member of KPSC.

Case Identification

To identify incident case individuals with MS or any other CNS ADS, we used the same methods as described in detail elsewhere.^{17,18} Briefly, we searched electronic medical records for first mention of *International Classification of Diseases, Ninth Revision (ICD-9)*, diagnostic codes (340, 341.0, 341.22, 341.8, 341.9, 377.30, 377.32, 377.39, and 336.39) for MS and other CNS ADS from January 1, 2008, to December 31, 2011, for persons of any age. All inpatient and outpatient encounters since enrollment into the health plan (N = 3556) were included. Diagnoses were confirmed and symptom onset date and additional clinical details were extracted through full medical records abstraction, including all inpatient and outpatient records, magnetic resonance imaging, and diagnostic test results, by an MS specialist (A.L.-G.) according to revised McDonald criteria for MS,¹⁹ the consensus definitions for pediatric acute disseminated encephalomyelitis (ADEM),²⁰ and the proposed consensus definitions for idiopathic transverse myelitis (TM).^{21,22} All patients with optic neuritis (ON) had been evaluated by ophthalmologists who confirmed the diagnosis. Patients with symptom onset prior to January 1, 2000; missing/imprecise symptom onset date; or without 6 months of continuous KPSC membership prior to symptom onset were excluded.

Control Selection

For each incident case, a maximum of 5 control individuals sampled without replacement from the KPSC population were matched to the case on date of birth (within 1 year), sex, and zip code (a surrogate measure for socioeconomic status) at the time of the case patient's symptom onset date. The control participants were assigned the same index date as their matched case (symptom onset date) and were also required to have 6 months of continuous KPSC membership prior to the index date for study inclusion. With this algorithm, 99% of the case patients had 5 matched controls and 90% of the matched case-control pairs had dates of birth within 34 days of each other.

Vaccination Records

Vaccination records within 3 years of the index date were obtained from the KITS. Any vaccination was considered to be an exposure. Single-antigen HepB vaccine is Engerix B (GlaxoSmithKline Biologics) or Recombivax HB (Merck Sharp & Dohme Corp). Any HepB-containing vaccine includes single-antigen HepB vaccines, Pediarix (GlaxoSmithKline), and HepB-containing vaccines not otherwise specified. Gardasil (Merck Sharp & Dohme Corp) was the only HPV vaccine in the study. All vaccines included any vaccination history that was recorded in the KITS. The most commonly reported other vaccines in adults were influenza; tetanus, pertussis, and diphtheria; and varicella-zoster. The most common other vaccines in children were measles, mumps, rubella, polio, and varicella. We were not able to distinguish between boosters or initial vaccinations owing to limited power.

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Covariates

Data extracted from the KPSC electronic medical records included race/ethnicity (white Hispanic, white non-Hispanic, black, Asian/Pacific Islander, Native American/Alaskan, and multiple/other/unknown), comorbid chronic diseases, history of infectious diseases, and health care utilization. Comorbid chronic diseases and history of infectious diseases (*ICD-9* codes 001-139) were defined as 1 or more *ICD-9* codes for the condition within 6 months before the index date. The *ICD-9* codes used for chronic diseases included diabetes mellitus (250), heart (411-414 and 428), lung (491 and 492), kidney (403, 581-583, and 585-588), and liver (571-573) disease. Health care utilization was defined as the number of hospitalizations, outpatient visits (only with physicians or nurse practitioners), or emergency department visits within 6 months before the index date.

Statistical Analysis

Conditional logistic regression was used to estimate the matched odds ratio (OR) and its corresponding 95% CI for the association between CNS ADS and vaccination. When 10 or more exposed individuals were identified, the models were adjusted for race/ethnicity, hospitalizations (0 or ≥ 1), outpatient visits (0 or ≥ 1), emergency department visits (0 or ≥ 1), comorbid chronic diseases (0 or ≥ 1), and infections (0 or ≥ 1) within 6 months before the symptom onset/index date. To examine both the immediate and long-term effects of vaccination on CNS ADS, the exposure (vaccination) was restricted to the following different time frames before the index date: 14 days, 30 days, 42 days, 90 days, 180 days, 1 year, and 3 years. To evaluate whether the association differed by disease severity or demyelinating disease subtype, the association of vaccines with MS, clinically isolated syndrome (CIS) (ON, TM, and monofocal or multifocal CIS), and ADEM were examined separately. First, all vaccines were examined as a combined exposure. To determine whether younger age was associated with any vaccine-associated CNS ADS, the study population was categorized according to age (<50 years and ≥ 50 years) at the index date because new-onset MS is rare in individuals older than 50 years. To understand whether a specific vaccine was associated with a higher risk for an outcome, analyses were further stratified by the type of vaccine for exposed cases and exposed controls when an increased OR was identified. Age cutoffs and exposure windows were selected so that the results could be compared with those of other vaccine safety and MS epidemiologic studies.

To assess the association between HPV vaccine and the outcomes, the analysis was restricted to females aged 9 to 26 years at symptom onset and after March 1, 2007, because this was the group that was initially targeted for HPV vaccination. Preplanned analyses for exposure to single-antigen HepB vaccine only or any HepB-containing vaccines combined were conducted in the entire study population. The means (SDs) of normally distributed variables were compared using 2-sample *t* tests; for binary or categorical variables, χ^2 analysis with the Fisher exact test was used. All analyses were conducted using SAS, version 9.2 (SAS Institute Inc).

Results

In all, 780 patients with newly diagnosed MS, CIS, or ADEM were included in the study after exclusion of 51 individuals (5.1%) because their symptoms began before January 1, 2000, or could not be precisely determined (10 [1.0%]) and 166 (16.6%) because they had less than 6 months of KPSC membership before symptom onset. The most common form of incident CNS ADS during the study period was MS (427 patients [54.7%]) followed by ON (177 [22.7%]), TM (122 [15.6%]), other forms of CIS (33 [4.2%]), and ADEM (21 [2.7%]). Most cases of CNS ADS were diagnosed within 300 days of symptom onset (median, 83.5 days; 25% by 13.0 days and 75% by 299.5 days). Correspondingly, most cases (718 [92.1%]) had an onset of symptoms between 2007 and 2011.

The baseline demographic and clinical characteristics of case patients and controls are presented in the **Table**. Case patients were more likely to have been hospitalized, been seen in the emergency department, and used outpatient services in the 6 months before symptom onset/index date than were the controls (**Table**). In addition, the cases were more likely to have had a visit for an infectious illness in the 6 months before symptom onset than were the controls.

Hepatitis B vaccination was uncommon in our study population, with only 3.3% of controls and 4.0% of cases receiving any HepB-containing vaccine in the 3 years before the index date or symptom onset, respectively (**Figure 1A**). There were no cases of ADS or ADEM onset within 42 days or 1 year following any HepB-containing vaccination, respectively. We did not find an association of new-onset MS or CIS in the 1 to 3 years after vaccination with either single-antigen or any type of HepB-containing vaccine in either adjusted (**Figure 1A**) or unadjusted (eTable in the Supplement) models.

In the 3 years prior to symptom onset (or the index date), HPV vaccination was common among females aged 9 to 26 years (controls, 38.1%; and cases, 39.1%) (**Figure 1B**), but the number of cases in this subgroup was small ($n = 92$). Based on these few cases and the 459 corresponding controls, we observed a statistically nonsignificant trend toward an increased risk of MS but not CIS or ADEM within the first 3 months after HPV vaccination (**Figure 1B**). The number of vaccinated individuals 30 days before symptom onset or before the index date for the controls was too low to draw any conclusions (**Figure 1B**). Although more than 10 individuals were exposed, an adjusted model for ADEM symptom onset within 3 years of HPV vaccination could not be calculated because all ADEM cases were exposed in the past 3 years, resulting in a zero cell for nonexposed cases.

Vaccination of any type in the 3 years before symptom onset was common in our study population (controls, 49.6%; and cases, 53.8%). There was no association between CNS ADS and any vaccination 3 years earlier in the total study population (adjusted OR, 1.03; 95% CI, 0.86-1.22). The risk of CNS ADS was increased 30 days after any type of vaccination in individuals younger than 50 years (**Figure 2A** and eTable in the Supplement). This trend toward an increased risk only shortly after

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Table. Distribution of Baseline Characteristics Between Cases and Controls

Characteristic	No. (%)		P Value
	Cases (n = 780)	Controls (n = 3885)	
Age at onset, y			
≤10	16 (2.1)	77 (2.0)	.97
11-18	52 (6.7)	260 (6.7)	
19-49	520 (66.7)	2590 (66.7)	
≥50	192 (24.6)	958 (24.7)	
Mean (range)	39.3 (2.2-85.8)	39.3 (2.2-85.9)	
Sex			
Male	239 (30.6)	1192 (30.7)	.98
Female	541 (69.4)	2693 (69.3)	
Race/ethnicity			
White	334 (42.8)	1227 (31.6)	<.01
Black	142 (18.2)	430 (11.1)	
Hispanic	233 (29.9)	1442 (37.1)	
Native American/Alaskan	2 (0.3)	10 (0.3)	
Asian/Pacific Islander	33 (4.2)	350 (9.0)	
Multiple/other/unknown	36 (4.6)	426 (11.0)	
No. of hospitalizations in 6 mo before index date			
0	703 (90.1)	3743 (96.3)	<.01
≥1	77 (9.9)	142 (3.7)	
No. of emergency department visits in 6 mo before the index date			
0	616 (79.0)	3546 (91.3)	<.01
≥1	164 (21.0)	339 (8.7)	
No. of physician or nurse practitioner visits in 6 mo before index date			
0	171 (21.9)	1513 (38.9)	<.01
1-4	464 (59.5)	1981 (51.0)	
≥5	145 (18.6)	391 (10.1)	
Infectious/parasitic diseases			
No	690 (88.5)	3546 (91.3)	.01
Yes	90 (11.5)	339 (8.7)	
Comorbidity ^a			
No	728 (93.3)	3643 (93.8)	.65
Yes	52 (6.7)	242 (6.2)	
Length of membership before onset of symptoms (index date), mean (range), y	7.72 (0.51-19.15)	7.23 (0.51-19.14)	.03

^a Comorbidities included diabetes mellitus, heart diseases, liver diseases, lung diseases, and kidney diseases.

any type of vaccination in younger individuals was similar for MS and CIS, although it did not reach statistical significance (Figure 2A). There was no association between any vaccination and CNS ADS in older individuals during any time interval (Figure 2B). Although more than 10 individuals were exposed, an adjusted model for ADEM symptom onset within 90 days of vaccination could not be calculated because all of the case patients were hospitalized, whereas none of the controls were.

Of the 24 younger individuals who developed their first symptoms of CNS ADS within 30 days following vaccination, 11 had MS. Among these 11 patients, 1 woman had 3 other MS risk factors: previously diagnosed radiologically isolated syndrome, a family history of MS, and comorbid ulcerative colitis. Nine individuals developed ON (including 1 woman who was 2 weeks post partum), 3 developed TM, and 1 child devel-

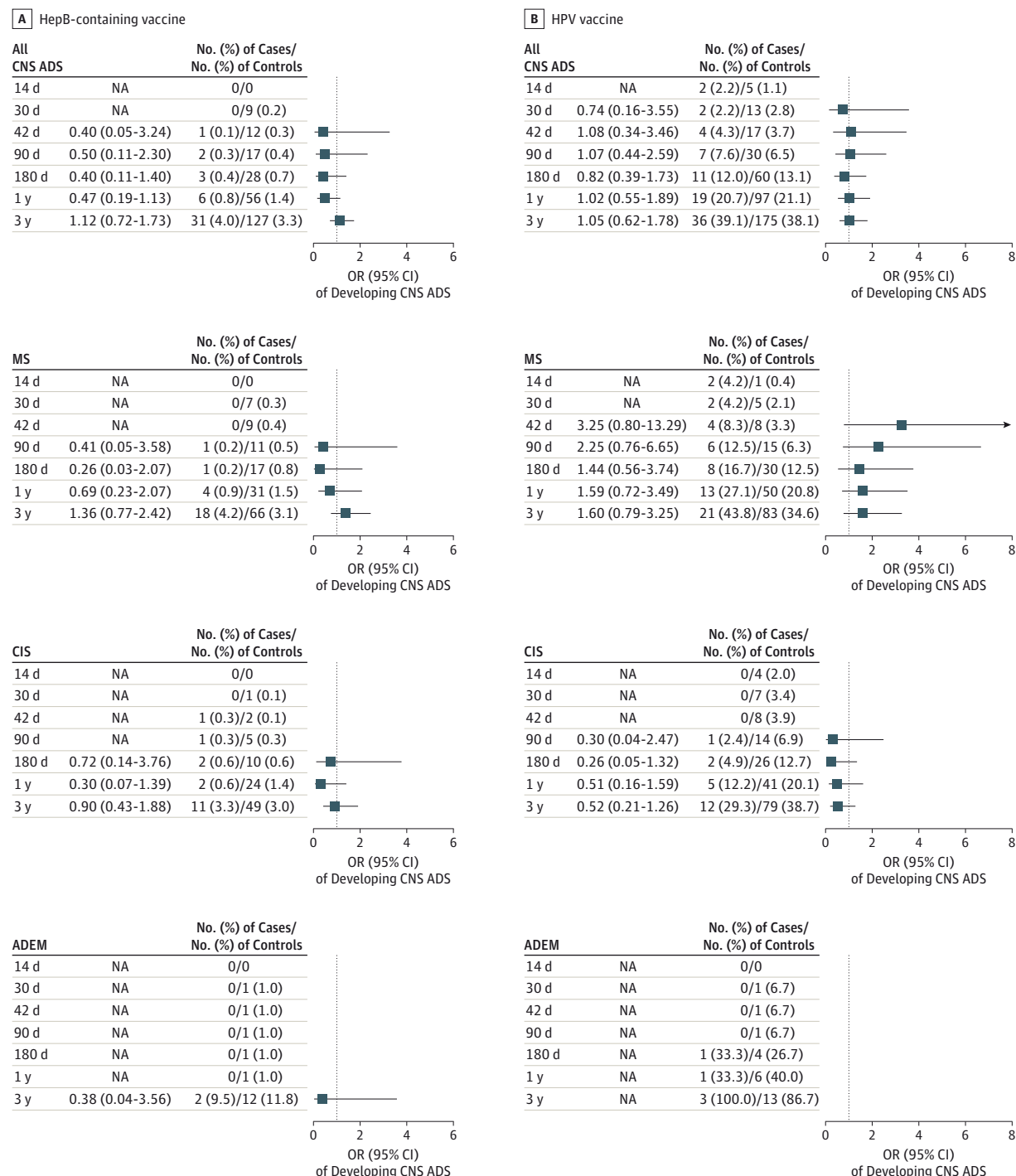
oped ADEM. All new-onset MS cases made a full recovery from their first attack, as did 8 of the patients with ON, 2 with TM, and the child with ADEM. Of the 12 patients with ON and TM, 9 did not have any asymptomatic lesions identified on brain magnetic resonance imaging, indicating a very low long-term risk of conversion to MS.²³ The most common type of vaccine received by these 24 cases and their 74 matched controls were influenza (14 cases and 36 controls) and tetanus, pertussis, and diphtheria (8 cases and 14 controls).

Discussion

In this nested case-control study, we found no long-term association between vaccines and MS or other CNS ADS. We found that younger patients had an increased risk of develop-

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Figure 1. Association Between Hepatitis B (HepB) and Human Papillomavirus (HPV) Vaccines and Acquired Central Nervous System Demyelinating Syndromes (CNS ADS) by Time Since Vaccination



Adjusted odds ratios (ORs) and 95% CIs of all CNS ADS and subtypes with increasing time since vaccination with any HepB vaccine (A) or HPV vaccine (B) are depicted. Human papillomavirus vaccine analyses were restricted to females aged 9 to 26 years. The cumulative number and percentage of

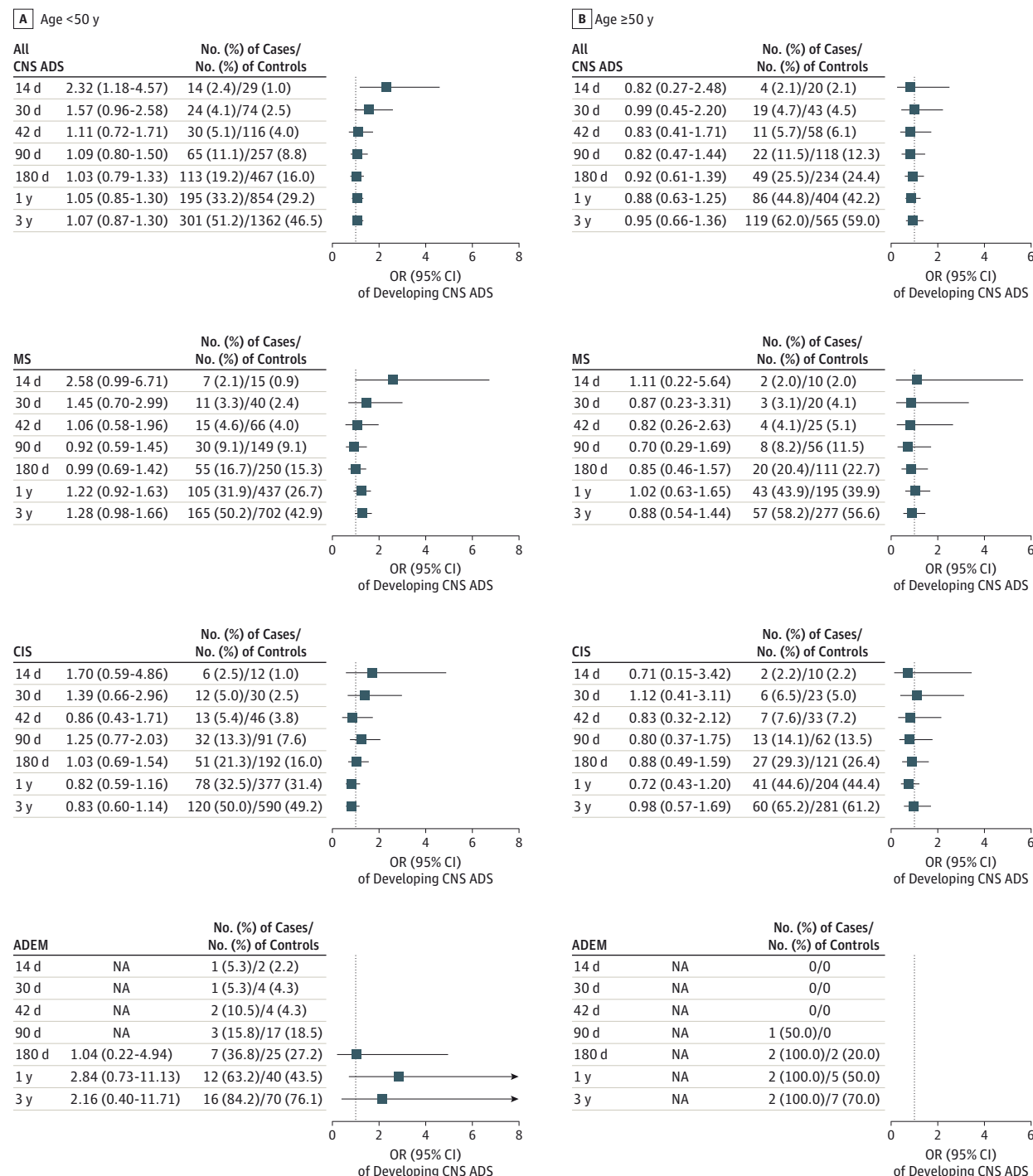
cases/controls vaccinated during each time interval are listed in the right column of each graph. ADEM indicates acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; MS, multiple sclerosis; and NA, not applicable. The vertical dashed line indicates an OR of 1.0.

ing their first symptoms of a CNS ADS up to 30 days following any type of vaccination. However, this association disappeared after 30 days, suggesting that, at most, vaccines are re-

dundant enhancers of preexisting autoimmunity. Our data do not support a causal link between current vaccines and the risk of MS or other CNS ADS.

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Figure 2. Association Between Any Vaccination and Acquired Central Nervous System Demyelinating Syndromes (CNS ADS) by Age and Time Since Vaccination



Depicted are the adjusted odds ratios (ORs) and 95% CIs of all CNS ADS and subtypes with increasing time since vaccination with any vaccine in individuals younger than 50 years (A) or 50 years or older (B) at the time of vaccination. The cumulative number and percentage of cases/controls vaccinated during

each time interval are listed in the right column. ADEM indicates acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; MS, multiple sclerosis; and NA, not applicable. Arrows indicate that the confidence limits exceed the x-axis.

Upper respiratory tract and other infections are well-known risk factors for MS relapses.²⁴ Vaccines could theoretically increase the risk of CNS ADS through mechanisms simi-

lar to those induced by infection. Infections are known to cause or enhance autoimmunity through expansion of autoreactive T-cell clones by molecular mimicry, later stimulation of

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autoreactive T-cell clones, or enhancement of antigen presentation by bystander activation, epitope spreading, adjuvant effect, and enhanced antigen presentation.²⁵ However, even in animal models,²⁵ these relationships are complex and depend on the timing of exposure, antigen type, genetic background, and coadministration of adjuvants. Under certain circumstances, infections and vaccines could just as likely lead to improved tolerance and decreased risk of autoimmunity.^{26,27} This is the central argument for the hygiene hypothesis: decreased exposure to infections increases the risk of autoimmunity.^{25,28}

Infections are known to accelerate the onset of overt CNS ADS in children.²⁹ We found that vaccines may have a similar effect, since we detected an increased risk of ADS symptoms shortly after vaccination in younger individuals. This effect was not vaccine specific, was similar for MS and CIS, was rare (4% of younger cases), and resulted in a monophasic, self-limited illness in almost half of the cases. In contrast, there was no increased risk of CNS ADS 30 days after vaccination. This argues against causality because the risk in the vaccinated group should remain elevated regardless of whether the time window between exposure and clinical disease expression is defined as 15 days or 3 years. However, our findings are consistent with vaccines acting as a proinflammatory cofactor in individuals with subclinical autoimmunity because this mechanism would be expected to hasten symptom onset but not change the long-term risk of developing MS or CIS.

We found no increased risk (and no trend of an increased risk) with HepB vaccine and the risk of MS or other CNS ADS 3 years following vaccination, which agrees with the results from most previous HepB vaccine and MS risk studies.²⁻⁵ Our results differ from the findings of 2 studies^{6,7} that showed a potential increased risk 3 years following vaccination. One study⁶ found an increased risk of MS among adults 3 years after administration of recombinant HepB vaccination (OR, 3.1; 95% CI, 1.5-6.3) but rested on a small number of vaccinated MS cases (n = 11) and did not account for differences in health care utilization. The other study⁷ reported an association between pediatric MS and Engerix B vaccine only 3 years after vaccination (OR, 2.8; 95% CI, 1.2-6.4) but was unable to account for differences in health care utilization. These findings are difficult to interpret because the study⁷ failed to find associations for other HepB vaccine brands or for the MS precursors (CIS and ADEM). It is hard to reconcile how a vaccine could increase the risk of MS only and not its potential precursors, suggesting that the MS findings may be due to chance.

The case reports¹¹⁻¹⁵ of young females presenting with fulminant onset of ADEM or MS 2 to 4 weeks following administration of HPV vaccine are difficult to interpret, since young

women are the highest MS risk group. Several of these women had mild symptoms of CNS ADS at the time of vaccination,¹¹⁻¹⁵ and several occurred after the second or third dose.^{11,12,15} An earlier study¹⁰ of HPV vaccine and MS, ADEM, and ON found no association, but only 11 cases were identified, making it difficult to draw conclusions. Our study, using more comprehensive and accurate case-finding methods, identified 92 women with incident CNS ADS. We found a small, nonsignificant increase in the risk of MS but not its potential precursors (CIS or ADEM), which suggests a spurious finding. Larger studies are needed to completely rule out an effect.

Our study overcomes many of the methodological limitations of previous MS vaccine safety studies with a larger sample size, rigorous case-finding methods, inclusion of MS precursors, prospectively recorded symptom onset dates, and complete vaccination records. However, our study remains underpowered, particularly for detecting associations with rare forms of CNS ADS (pediatric ADS and ADEM), uncommon exposures (single-antigen HepB vaccine), and small select subgroups (symptom onset within 180 days following HPV vaccine in young women). We were also underpowered to look at risk of CNS ADS following HepB vaccination in early childhood because this was not recommended in the United States until 1991 and most incident MS case patients were older than 20 years. In addition, the number of older individuals was relatively small. Other limitations include the inability to examine high-risk subgroups, such as those with a family history of MS or carriers of MS risk alleles, and the inability to examine the potential influence of vaccine preservatives.

Conclusions

Findings from the present study show no long-term association of vaccines with an increased risk of MS and other CNS ADS. In younger patients, we observed a short-term increase in risk after vaccination of any type, which suggests that vaccines (like infections) may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease. We found no association between HepB vaccination and an increased risk of MS or other CNS demyelination up to 3 years after vaccination, which is reassuring. Our results for HPV vaccine are inconclusive given the small number of cases and the paucity of previous studies on the topic. Our findings reconcile the anecdotal clinical reports of a CNS ADS onset shortly after vaccination with the larger body of epidemiologic literature showing no long-term increased risk of MS or other forms of CNS ADS following vaccination. Our findings do not warrant any change in vaccine policy.

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Study concept and design: Langer-Gould, Tseng.
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