The Risk of Guillain-Barré Syndrome after Tetanus-Toxoid–Containing Vaccines in Adults and Children in the United States

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ABSTRACT

Objectives. This study examined whether there is a risk that tetanus-toxoid–containing vaccines could cause Guillain-Barré syndrome and, if so, how large the risk is.

Methods. This study was based on previous active surveillance epidemiological studies of Guillain-Barré syndrome and vaccination history.

Results. A background rate of 0.3 cases of Guillain-Barré syndrome per million person-weeks has been estimated. By chance, 2.2 people with the syndrome would have received tetanus-toxoid–containing vaccine within the 6 weeks before onset, yet only 1 person had done so. Data on children show similar results.

Conclusions. If an association exists, it must be extremely rare and not of public health significance. (*Am J Public Health.* 1997;87:2045–2048)

Introduction

The National Childhood Vaccine Injury Act of 1986 mandated that the US government conduct a scientific review of the possible adverse consequences of all childhood vaccines.[1] The Vaccine Safety Committee of the Institute of Medicine published its conclusions about adverse reactions of pertussis and rubella vaccines in 1991[2] and about the other childhood vaccines in 1993.[3] In the 1993 report, the Institute of Medicine concluded that "the evidence favored acceptance of a causal relation between tetanus toxoid (and therefore tetanus-toxoid–containing vaccines (TTCV)) and Guillain-Barré syndrome (GBS)."[3] This conclusion was based on biological plausibility and a striking case report, from 1978, of a 42-year-old man who received tetanus toxoid on three occasions during a 13-year period and developed a self-limited episode of Guillain-Barré syndrome after each vaccination. This man also experienced multiple subsequent episodes of Guillain-Barré syndrome following acute viral illnesses. Several other case reports of Guillain-Barré syndrome following tetanus-toxoid–containing vaccines among adult patients exist, as does a single report of Guillain-Barré syndrome following diptheria, tetanus, and pertussis (DTP) vaccination in a child with exacerbation following tetanus-diptheria (Td) vaccination as an adolescent (National Vaccine Injury Compensation Program, Geoffrey Evans, MD, oral communication), but these reports do not establish causality. Because no controlled studies were done, however, the Institute of Medicine was unable to quantify the magnitude of this potential risk.

Over 36 million doses of tetanus-toxoid–containing vaccines are administered to children and adults annually as DTP, diptheria–tetanus (DT) and Td, and tetanus vaccine.[4] It is therefore important to estimate the risk of Guillain-Barré syndrome after administration of tetanus-toxoid–containing vaccines.

In this study, we examined whether such an epidemiological association exists for adults and children and attempted to quantify this risk. We reviewed the findings of two large, active surveillance studies for Guillain-Barré syndrome in adults and children and compared the number of cases observed after tetanus-toxoid–containing vaccine with the number that would be expected to occur by chance alone, on the basis of the estimated number of doses of tetanus-toxoid–containing vaccine given in these two populations.

Methods

Adults

Data from a 1991 study conducted by the CDC were reviewed to evaluate a possible association between receipt of influenza vaccine and Guillain-Barré syndrome[5] (Table 1). In this study, active surveillance was conducted for a 7-month period to detect all new cases of Guillain-Barré syndrome among 23.2 million adults older than 17 years of age. Cases were sought via neurologists, hospitals, and plasmapheresis centers at 13 sites. Physician-diagnosed cases of Guillain-Barré syndrome were accepted if they met a case definition based on criteria established by the American Academy of Neurology.[6] Recent history of vaccination against all antigens, including tetanus-toxoid–containing vaccine, was independently ascertained and verified for each case.

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To estimate the tetanus-toxoid vaccination coverage for this study population, we used data from two national sources (Table 1). The CDC Biologics Surveillance compiles information on the net doses distributed by manufacturers for each tetanus-toxoid–containing vaccine during 1991, including Td toxoid formulation and tetanus toxoid alone.[4] Because these data include an unknown number of doses of these vaccines given to adolescents, we also used data from the 1991 National Health Interview Survey (NHIS),[7] which assessed the frequency with which a representative sample of adults aged 18 years and older had received a tetanus-toxoid–containing vaccine during the preceding 10 years. The total US population above the age of 17 years (183.2×10^6 adults) was derived from 1990 census data (Table 1, Section A).[8]

On the basis of association between swine influenza vaccine and Guillain-Barré syndrome noted in the National Influenza Immunization Program for 1976 through 1977,[9] we defined the possible risk interval for Guillain-Barré syndrome after vaccination as 6 weeks. On the basis of data from this study, we also calculated a background rate of 0.3 cases of Guillain-Barré syndrome per million (10^6) person-weeks, using the number of cases of Guillain-Barré syndrome not attributed to influenza vaccination and total person-time outside the defined 6-week risk interval following influenza vaccination. The number of cases of Guillain-Barré syndrome expected in this study population within 6 weeks of tetanus-toxoid vaccine by chance was then determined (Table 1).

TABLE 1—Calculation of the Number of Guillain-Barré Syndrome (GBS) Cases Expected to Occur In Adults Within 6 Weeks of Receipt of Tetanus-Toxoid–Containing Vaccine (TTCV) by Chance Alone

Given:
- Study population = 23.2 million adults > 17 y of age (Chen et al.[5])
- 213 GBS cases observed; 1 case within 6 wk of TTCV
- 16.5 million doses of tetanus–diptheria and tetanus vaccines distributed in United States in 1991 (Centers for Disease Control, Biologics Surveillance)[4]
- 9 million doses of tetanus-toxoid–containing vaccines administered to adults in 1991 (National Health Interview Survey)[7]

Calculations:

Background rate of GBS

$$= \frac{\text{cases of GBS not attributed to influenza vaccination}}{\text{total person-time outside 6-wk risk interval following influenza vaccination}}$$

$$= \frac{\text{no. cases GBS not within 6 wk of influenza vaccination}}{(\text{no. persons without influenza vaccine} \times 28\text{ wk}) + (\text{no. persons with influenza vaccine} \times 22\text{ wk})}$$

$= 0.3$ cases/10^6 person-wk

Risk based on tetanus-toxoid–containing vaccine doses distributed

Estimated TTCV coverage in the study population

$$= 16.5 \times 10^6 \text{ doses} \times \frac{23.2 \times 10^6 \text{ adults}}{183.2 \times 10^6 \text{ adults}} \times \frac{7\text{ mo}}{12\text{ mo}}$$

$= 1.2 \times 10^6$ doses

Estimated no. Guillain-Barré syndrome cases within 6 wk of TTCV by chance alone

$= 1.2 \times 10^6$ doses $\times$ 6 wk $\times$ 0.3 cases/10^6 person-wk
$= 2.16$ cases expected
1 case observed

Estimated relative risk (95% CI) = 0.46 (0.01, 2.57)

Estimate using 1991 coverage data

Estimated TTCV coverage in the study population

$$= 9.0 \times 10^6 \text{ doses} \times \frac{23.2 \times 10^6 \text{ adults}}{183.2 \times 10^6 \text{ adults}} \times \frac{7\text{ mo}}{12\text{ mo}}$$

$= 0.7 \times 10^6$ doses

Estimated no. GBS cases within 6 wk of TTCV by chance alone

$= 0.7 \times 10^6$ doses $\times$ 6 wk $\times$ 0.3 cases/10^6 person-wk
$= 1.3$ cases expected
1 case observed

Estimated relative risk (95% CI) = 0.79 (0.02, 4.47)

Note. CI = confidence interval.

Children

We examined data from a previous study conducted by two of us (H.R., J.D.C.), which investigated the relationship between the administration of oral polio vaccine (OPV) and Guillain-Barré syndrome in children in Southern California[10] (Table 2). During a 7-year period, from 1980 through 1986, a search for cases of Guillain-Barré syndrome among 2.2 million children below 15 years of age was conducted. The medical records of all children discharged with a diagnosis of any type of neuropathy from the 22 hospitals that care for children in Los Angeles and Orange counties, California, were reviewed. All cases of Guillain-Barré syndrome were verified by a pediatric neurologist (H.R.), and vaccination histories were ascertained for them.

To estimate the risk of Guillain-Barré syndrome following DTP, DT, or tetanus toxoid alone on the basis of these data, we stratified the preschool population in these counties into two groups: children below 2 years of age and those 2 through 5 years of age. The recommended number of doses of DTP for each group currently endorsed by the Advisory Committee on Immunization Practices and the American Academy of Pediatrics is four doses of DTP vaccine in the first 2 years of life, followed by a booster dose at school entry.[11] The vaccination coverage rate for each group was estimated from the 1991 data from the NHIS, which included a survey of immunization coverage among a representative sample of US children from birth through age 5.[12] On the basis of these data, it was estimated that children under 2 years of age had received an average of 3.1 doses of DTP, while those 2 through 5 years of age had received an average of 0.8 doses. A uniform age distribution in the study population was assumed, and again, the possible risk interval for Guillain-Barré syndrome after vaccination was defined as 6 weeks. Age-specific background rates for Guillain-Barré syndrome were calculated for each group on the basis of the California study.[10]

Two relative rates for adults were calculated on the basis of two different estimates of vaccine coverage. An overall relative rate for children was estimated with age controlled. By means of the exact method as provided by the StatXact software program,[13] 95% confidence intervals for the relative rates were computed.

Results

Adults

According to the Biologics Surveillance data, approximately 12.5 million

doses of Td and 4 million doses of tetanus toxoid were distributed in the United States in 1991. The NHIS estimated that about 9 million doses of tetanus-toxoid–containing vaccine were administered to adults. Extrapolating these data to the Guillain-Barré syndrome study population of 23 million persons, we estimated that between 0.7 million (NHIS) and 1.2 million (CDC) doses of tetanus-toxoid–containing vaccine were administered over the 7-month period in this study population (Table 1).

During the CDC Guillain-Barré syndrome and influenza vaccine study, 213 cases of Guillain-Barré syndrome were observed in the study population, of which 12 occurred within 6 weeks of influenza vaccination. None of the 12 people with these cases had simultaneously received a tetanus-toxoid–containing vaccine, and all were excluded from the calculation of the Guillain-Barré syndrome background rate of 0.3 cases per million person-weeks (Table 1).

On the basis of NHIS and Biologics Surveillance data, 1.3 to 2 cases, respectively, of Guillain-Barré syndrome could be expected to occur within 6 weeks of tetanus-toxoid vaccine by chance alone. In contrast, 1 case of Guillain-Barré syndrome was actually observed within 6 weeks of tetanus-toxoid vaccination in the Guillain-Barré syndrome and influenza study.

TABLE 2—Calculation of the Number of Guillain-Barré Syndrome (GBS) Cases Expected to Occur in Children Within 6 Weeks of Receipt of DTP Vaccine by Chance Alone

Given:
- Study population = 2.2 million children < 15 y of age (Rantala et al.[10])
- 93 cases of Guillain-Barré syndrome observed; 2 cases within 6 wk of DTP
- For stratified age groups:

	Children < 2 y	Children aged 2–5 y
Recommended DTP doses	4	1
Age-specific coverage rates (CDC[12])	3.1 doses/child	0.8 doses/child
No. at risk	290 000	440 000
Risk window	6 wk	6 wk
Age-specific background rate of GBS (Rantala et al.[10])	0.39/100 000/y	1.1/100 000/y

Calculations:

Expected number of GBS cases within 6 wk of DTP in children <2 y by chance alone
$= 0.145 \times 10^6$ persons $\times$ 7 y $\times$ 3.06 doses per child $\times$ 6 wk
$\times \frac{3.9 \text{ cases}}{10^6 \text{ person-y}} \times \frac{1 \text{ person-y}}{52 \text{ person-wk}}$
= 1.4 cases expected

Expected number of GBS cases within 6 wk of DTP in children aged 2–5 y by chance alone
$= 0.145 \times 10^6$ persons $\times$ 7 y $\times$ 0.8 doses per child $\times$ 6 wk
$\times \frac{11 \text{ cases}}{10^6 \text{ person-y}} \times \frac{1 \text{ person-y}}{52 \text{ person-wk}}$
= 1.03 cases expected

Overall expected number of GBS cases within 6 wk of DTP in children ≤ 5 y by chance alone
= 2.4 cases expected
2 cases observed

Overall estimated relative risk (95% CI) = 0.81 (0.09, 3.32)

Note. DTP = diptheria, tetanus, and pertussis vaccination; CDC = Centers for Disease Control and Prevention; CI = confidence interval.

Children

Ninety-three children fulfilled the diagnostic criteria for acute Guillain-Barré syndrome in this study population. Of these, only four had received vaccinations within the preceding 6 weeks. Two of these children, approximately 2.5 and 3 years old, had received DTP (simultaneously with other vaccines.

If we apply the estimated age-specific background rates of Guillain-Barré syndrome in the population to the estimated number of DTP vaccine doses delivered in this population, 1.4 cases of Guillain-Barré syndrome would be expected to occur within 6 weeks of DTP vaccination by chance alone in children less than 2 years of age (Table 2). In the 2- through 5-year-old age group, 1.07 cases of Guillain-Barré syndrome would be expected to occur within 6 weeks of DTP vaccination by chance.

Overall, 2.4 cases of Guillain-Barré syndrome would be expected for all children aged 5 years or younger. Only 2 cases of Guillain-Barré syndrome within 6 weeks of DTP vaccination were observed in the study.

Discussion

Acute inflammatory demyelinating polyneuritis, or Guillain-Barré syndrome, is characterized by the rapid onset of flaccid motor weakness with hyporeflexia and elevation of protein levels in the cerebrospinal fluid without pleocytosis.[3] Its occurrence after viral and some bacterial infections has been well known. Except for the influenza vaccine, vaccinations have been an infrequent antecedent event in patients with Guillain-Barré syndrome, as evidenced by the lack of a history of recent vaccination in most large case series of Guillain-Barré syndrome.[5,9,14,15]

Our analysis of studies of both children and adults failed to demonstrate an enhanced risk of Guillain-Barré syndrome within 6 weeks following administration of tetanus-toxoid–containing vaccine. Underascertainment of cases of Guillain-Barré syndrome and overestimation of vaccine coverage, which is based on national data for 1991, in the study populations are potential weaknesses in this study. However, national DTP coverage among children in 1991 was similar to the coverage measured in 1980 through 1986 by the US Immunization Survey. Among adults, we used a range of coverages based on two separate data sources. Furthermore, our data are robust, so that even if true vaccination coverage rates were 20% lower than those used here, the result would still be a greater number of expected cases than were observed in each study.

The only prior well-demonstrated association between Guillain-Barré syndrome and vaccination was that shown with swine influenza vaccine in 1976 with a relative risk of approximately 8 for onset of Guillain-Barré syndrome within 6 weeks of vaccination and an attributable risk of slightly less than 1 case per 100 000 vaccinations.[9,16] Our study had 85% power to detect a relative risk half of this[5] among both children and adults (high-coverage assumption) and 60% power for adults (low-coverage assumption). The upper 95% confidence limits for our relative risk estimates for each of these categories were 3.32 (children), 2.57 (adult high coverage), and 4.47 (adult low coverage), respectively. Clearly, a substantially larger study would be required to bring these limits closer to 1.

Whether this would be a prudent use of resources given the rarity of the potential association is debatable. Irrespective of this question, our analyses show that if an association between Guillain-Barré syndrome and tetanus-toxoid–containing vaccine exists, it is unlikely to be large enough to be of significant public health importance.

Guillain-Barré syndrome after swine influenza vaccination[16] was found to have an attributable risk of 1 in 100 000 doses. At the other extreme, vaccine-associated paralytic polio on the order of 1 in 2.5 million doses[17] is enough to push for a change to the inactivated polio vaccine/oral polio vaccine schedule. These associated risks are of sufficient magnitude to cause public concern.

The Institute of Medicine's conclusion that tetanus-toxoid–containing vaccines can cause Guillain-Barré syndrome was based on limited data, primarily a single case report of an individual with apparently unusual susceptibility to Guillain-Barré syndrome. Using data from two large, active surveillance studies in which adult and child populations received an estimated 0.7 million to 1.2 million and 8.1 million doses, respectively, of tetanus-toxoid–containing vaccine, we have shown that the number of cases of Guillain-Barré syndrome observed after administration of such vaccines in both adults and children is less than the number expected by chance alone. We therefore conclude that on the basis of available data, no association of public health significance exists between tetanus-toxoid–containing vaccine and Guillain-Barré syndrome. □

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