Objective: To assess the postulated causal association between measles-mumps-rubella (MMR) vaccination and Guillain-Barré syndrome (GBS).

Study design: Active retrospective study based on linkage of the nationwide hospital discharge register with individual vaccination records. All patients hospitalized for treatment of GBS in Finland between November 1982 and December 1986 were included in the study.

Results: During the study period, 189 patients were hospitalized for treatment of GBS, and ~630,000 vaccine recipients received 900,000 doses of MMR vaccine; 24 of the 189 patients represented the prevailing target population for MMR vaccination, of whom 20 were vaccinated. MMR vaccination did not cause any increase over the background incidence of GBS, and no clustering of cases of GBS occurred at any time point after administration of MMR vaccine. The interval between vaccination and onset of symptoms of GBS exceeded the designated risk period of 6 weeks in all cases, varying from 80 days to years. MMR vaccination after recovery from GBS did not cause relapses of the illness. Respiratory or gastrointestinal tract infection predated the onset of GBS by 3 to 30 days in 20 (83%) of the 24 patients.

Conclusions: No causal association seems to prevail between MMR vaccination and GBS. (J Pediatr 2001;138:250-4)

Since the elimination of poliomyelitis from most of the world, Guillain-Barré syndrome, an autoimmune polyneuropathy, has become the most common cause of acute generalized paralysis. GBS affects individuals of all ages but is rare in infancy. The annual incidence of GBS in children <15 years of age is 0.38 per 100,000 in Finland and 0.91 per 100,000 in Latin America. In adults, the annual incidence is somewhat higher, varying from 0.4 to 2 cases per 100,000 population.

The pathogenesis of GBS is unclear, but the involvement of various viral and bacterial infections in the etiology has been acknowledged, with the most frequent antecedent event being Campylobacter jejuni gastroenteritis. Because of the postinfectious nature of the illness, GBS has also been attributed to immunizations. The results of studies on GBS in relation to monovalent or combination measles, mumps, and rubella vaccines, influenza vaccine, oral polio vaccine, or diphtheria and tetanus toxoids remain controversial. A committee of the US Institute of Medicine concluded that there was insufficient evidence to accept or reject a causal relationship between measles-mumps-rubella vaccination and GBS.

Recent years have shown that any implication of adverse events of vaccination—even without establishment of causality—may cause public concern and decrease vaccination coverage and therefore requires attention. The aim of this active retrospective study linking data from a nationwide hospital discharge register with individual vaccination records was to provide further information about the postulated causal relation between MMR vaccination and GBS.

Methods

Subjects

To increase the efficiency of prevention of measles, mumps, and rubella in Finland, monovalent vaccines were replaced by a combined MMR vaccine in November 1982. Since then, 2 doses of MMR vaccine, the first given at 14 to 18 months of age and the second at
6 years of age, have been part of the schedule of voluntary and free-of-charge childhood immunization. Children are vaccinated at special well-child clinics at municipal health centers.

In addition to these main target groups, children were immunized at intermediate ages and at 7 to 11 years of age in catch-up projects carried out during the early years of the national program. Since 1986, MMR vaccination has been routine for men called up for military service, and the target population was further extended in 1988.

During the study period from November 1982 to December 1986, the mean population of Finland was 4.89 million, and vaccination coverage exceeded 95%.

In all, 900,000 doses of MMR vaccine were administered to approximately 630,000 individuals. During those years, the only MMR vaccine used in Finland was M-M-R II (Merck & Co, Inc, West Point, Pa), distributed in Scandinavia as Virivac. It contains Wistar RA 27/3 strain of rubella virus.

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The national hospital discharge register comprises all hospitalizations in the whole of Finland since 1972, and its good coverage has been validated. All patients, both children and adults, hospitalized with a diagnosis of polyradiculitis during the study period were identified from this register, according to the codes of the International Classification of Diseases. Because virtually all patients with GBS in Finland are hospitalized, no other measures were considered necessary for the case collection.

To obtain detailed case histories, including the findings of microbiologic tests, and to exclude inappropriately coded cases, individual medical records were reviewed by 2 of the authors (E.K., senior neurologist, and O.J., trainee in neurology), who were unaware of the patients’ MMR vaccination data.

The exact dates of MMR vaccination were obtained from the patients’ personal vaccination cards filed at health centers. Details of the vaccination of all pediatric patients between the ages of 1 and 12 years were collected. Because MMR vaccine has been administered to men performing military service only since 1986, vaccination details were checked only for those 17- to 28-year-old (age of call-up) male patients who were hospitalized during 1986.

To disclose any vaccine-related relapses of GBS, the outcome of MMR vaccinations given after recovery from the disease were checked from the vaccination cards and medical records or by interviewing the local nurses.

**Definition of Guillain-Barré Syndrome**

GBS is an acute, usually self-limited, inflammatory polyneuropathy, characterized by progressive symmetrical limb weakness, loss of tendon reflexes, absent or mild sensory signs, and variable autonomic dysfunctions. An increased protein concentration (above 0.55 g/L) in the cerebrospinal fluid and evidence of slowing or block of nerve conduction in electrophysiologic examination were considered strongly supportive of the diagnosis.

**Definition of the Risk Interval**

The interval between a preceding event and the onset of GBS symptoms usually varies from 1 to 3 weeks, the average being 11 days, but latencies of 8 to 10 weeks have been proposed. In this study the onset of GBS within a 6-week period after MMR vaccination was considered suggestive of a causal association. This relevant risk interval was defined according to the US Institute of Medicine, which judged 6 weeks to be the maximum time between vaccination and the onset of symptoms of GBS if any causal relation existed. This definition is based on experience with the swine influenza vaccine and GBS and has been used in previous studies.

According to a survey conducted in Finland before and during the early years of the MMR vaccination program, the mean annual incidence of GBS in children <15 years of age is 0.38 per 100,000. Studies in several countries give annual incidence rates ranging from 0.4 to 2 cases per 100,000 in adults. With an average birth cohort of 65,000 in Finland, 0.34 cases of GBS were expected to occur within every 6-week period by chance alone among 1- to 12-year-old children, and 0.56 to 1.8 cases among 17- to 28-year-old men.

**RESULTS**

After evaluation of the medical records of all 218 patients with a diagnosis of polyradiculitis, 189 children and adults fulfilled the criteria for GBS, amounting to a mean annual incidence of 0.93 per 100,000 population. During the years 1982 through 1986, 20 children (9 boys and 11 girls) aged 1 to 12 years (median age, 5 years 5.5 months) were hospitalized for treatment of GBS. Four 21- to 25-year-old (median age, 25 years 11.5 months) male patients were hospitalized in 1986.

The details of MMR vaccination were confirmed in all cases, except for the exact date of vaccination of a 21-year-old man, who was vaccinated after the illness (Table). Four patients had not received MMR vaccination by the time of the check-up in 1999: a 12-year-old girl and 3 young men who had been called up for military service before 1986.

Of the 20 patients who had received MMR vaccination, none had onset of GBS symptoms within 6 weeks of the vaccination. The shortest lapse of time between the administration of MMR vaccine and the onset of GBS was 80 days in a 5-year-old boy, who had had...
gastroenteritis and respiratory tract infection complicated by otitis media 1 month preceding the onset of GBS symptoms.

In 13 cases the interval varied from 10 months to 3 years and 10 months, and 6 individuals received MMR vaccine only after the illness. In these 6 patients, MMR vaccination 13 months to 7 years after GBS did not cause a recurrence of the symptoms of polyneuropathy. Furthermore, of those 14 subjects who had received the first dose of MMR vaccine before the onset of GBS, 11 were re-vaccinated within 6 months to 4 years of recovery without relapses.

Of these 24 patients, 20 (83%) had had an antecedent respiratory or gastrointestinal tract infection during the preceding 42-day risk interval; respiratory symptoms predated the polyneuropathy by 3 to 30 days in 14 patients, and gastroenteritis by 6 to 14 days in 2 patients. Four individuals had had both respiratory and gastrointestinal tract infection 7 to 30 days before onset of GBS.

Comprehensive laboratory examinations were performed in 23 patients. Elevated titers in paired sera suggested that cytomegalovirus infection might have triggered the polyneuropathy in 2 patients. Respiratory syncytial virus was isolated from a bronchial swab obtained from one child while he was receiving ventilatory assistance. No specific etiology was identified in the others.

One of the 24 patients had sequelae: an 18-month-old girl was diagnosed with GBS in 1985, and 14 years later in November 1999, she still had severe sensory polyneuropathy. All the other patients recovered uneventfully, in keeping with the natural course of GBS.

### DISCUSSION

MMR vaccination programs have been highly successful in several countries, and indigenous measles, mumps, and rubella have been eliminated from Finland. With the disappearance of complications caused by vaccine-preventable diseases, adverse effects of immunization have become more apparent.

During recent years, public concern has been caused by the attribution of several disorders, including meningitis, inflammatory bowel disease, autism, and GBS to MMR vaccination. All such allegations must be evaluated thoroughly, and if warranted, the current vaccination policy must be changed, as in the case of vaccine-associated meningitis and paralytic poliomyelitis. If no evidence of a causal relation can be found, the public must be informed of the confirmed safety and continuing importance of immunization. This is a prerequisite for maintenance of sufficient vaccination coverage, which is especially important in the prevention of such highly infectious diseases as measles.

Information about possible causality between MMR vaccination and GBS has been contradictory, and the US Institute of Medicine considered the data insufficient to conclude that a causal relationship exists. Cases of GBS have been reported after administration of MMR or its component vaccines from the United States, Sweden, Germany, the United Kingdom, and Denmark; but more recent studies from the United Kingdom and Latin America have not supported a causal association. A 14-year follow-up of adverse events associated with MMR vaccination in

### Table. Characteristics of the study subjects

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>MMR vaccination Before onset of GBS</th>
<th>After onset of GBS</th>
<th>Preceding infection/No. of days before</th>
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<tbody>
<tr>
<td>1 y</td>
<td>F</td>
<td>—</td>
<td>1 y 1 mo</td>
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<td>5 y</td>
<td>M</td>
<td>1 y 7 mo</td>
<td>4 y</td>
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<td>5 y 2 mo</td>
<td>M</td>
<td>1 y 10 mo</td>
<td>2 y 11 mo</td>
<td>URI/15</td>
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<td>5 y 8 mo</td>
<td>M</td>
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<td>2 y 4 mo</td>
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<tr>
<td>4 y</td>
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<tr>
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*GEA, Acute gastroenteritis; URI, upper respiratory tract infection.*

with GBS in 1985, and 14 years later in November 1999, she still had severe sensory polyneuropathy. All the other patients recovered uneventfully, in keeping with the natural course of GBS.
Finland detected 2 cases of GBS within the 6-week risk period. These cases in 18-month-old boys yielded an incidence of 0.07 per 100,000 vaccine doses. The annual incidence during the follow-up period was 0.22 per 100,000 18-month-olds, showing no increase over the background incidence.

This study provides further evidence against the postulated causal relation between MMR vaccination and GBS. Not a single MMR vaccine-attributable case occurred among more than 600,000 vaccine recipients during more than 4 years. The greater than 95% coverage of the Finnish hospital discharge register, reliable case ascertainment, and meticulously filed vaccination data guarantee the high credibility of the results. Since all patients with GBS require hospital admission because respiration may be affected, omission of patients is extremely unlikely.

The concern that vaccinations might cause relapses of GBS is also addressed in this study. MMR vaccination also proved safe in those children who were immunized or re-immunized after recovery from polyneuropathy.

Our study is limited by the relatively small number of patients with GBS (the syndrome is rare in childhood). The set-up could be extended to older vaccine recipients with a higher background incidence who were immunized during later years, such as women who have recently given birth, or a larger number of men performing military service. Nevertheless, this active approach, with access to the individual vaccination data of every patient with GBS, ascertains the absence of an increased risk of GBS after MMR vaccination in children.

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**References**


50 Years Ago in The Journal of Pediatrics

THYMECTOMY AND ACTH IN LYMPHATIC LEUKEMIA
Earle AM, Reilly WA, Dean GO. J Pediatr 1951;38:63-8

The late 1940s and early 1950s were exciting times for physicians caring for children with leukemia. This disease, for which there had been no prior therapy, was being shown to be responsive to a variety of newly discovered anti-metabolites including aminopterin, methotrexate, and 6-mercaptopurine. At about this same time, ACTH (corticotropin) and oral corticosteroid preparations were being studied, and they too were effective in destroying leukemia cells, at least in the short term.

The series reported here by investigators at the University of Arkansas included 4 children with newly diagnosed acute lymphoblastic leukemia (ALL). They were treated with what was perhaps one of the first examples of “combination therapy,” receiving more than a single modality as treatment of their malignancy. Each of these children had a surgical thymectomy in addition to receiving ACTH, and each had a temporary response caused by one or both of these treatments. Although all 4 children died, the temporary clinical and hematologic remissions were dramatic. Although thymectomy is no longer used to treat leukemia, the observation of combining medical and surgical treatment approaches was novel.

Now virtually every child with cancer receives multi-modal therapy consisting of surgery, multiple chemotherapeutic agents, and (in some cases) radiation therapy. The results have been spectacular, with over 75% of children with ALL now cured and leading normal lives. The remaining 25% of patients with ALL, as well as children with diverse other forms of malignancy, will continue to present challenges to clinician researchers of today and tomorrow.

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