Neurologic Disorders After Measles-Mumps-Rubella Vaccination

Annamari Mäkelä, MD*; J. Pekka Nuorti, MD‡; and Heikki Peltola, MD*

ABSTRACT. *Objective.* **The possibility of adverse neurologic events has fueled much concern about the safety of measles-mumps-rubella (MMR) vaccinations. The available evidence concerning several of the postulated complications is controversial. The aim of this study was to assess whether an association prevails between MMR vaccination and encephalitis, aseptic meningitis, and autism.**

Methods. **A retrospective study based on linkage of individual MMR vaccination data with a hospital discharge register was conducted among 535 544 1- to 7-year-old children who were vaccinated between November 1982 and June 1986 in Finland. For encephalitis and aseptic meningitis, the numbers of events observed within a 3-month risk interval after vaccination were compared with the expected numbers estimated on the basis of occurrence of encephalitis and aseptic meningitis during the subsequent 3-month intervals. Changes in the overall number of hospitalizations for autism after vaccination throughout the study period were searched for. In addition, hospitalizations because of inflammatory bowel diseases were checked for the children with autism.**

Results. **Of the 535 544 children who were vaccinated, 199 were hospitalized for encephalitis, 161 for aseptic meningitis, and 352 for autistic disorders. In 9 children with encephalitis and 10 with meningitis, the disease developed within 3 months of vaccination, revealing no increased occurrence within this designated risk period. We detected no clustering of hospitalizations for autism after vaccination. None of the autistic children made hospital visits for inflammatory bowel diseases.**

Conclusions. **We did not identify any association between MMR vaccination and encephalitis, aseptic meningitis, or autism.** *Pediatrics* **2002;110:957–963;** ***measles, mumps, rubella, MMR vaccine, immunization, adverse effects, encephalitis, aseptic meningitis, autism, autistic disorders.***

ABBREVIATIONS. MMR, measles-mumps-rubella; MIBE, measles inclusion body encephalitis; SSPE, subacute sclerosing panencephalitis; CSF, cerebrospinal fluid; *ICD, International Classification of Diseases*.

Immunizations have been described as the most effective health intervention after clean water and sewage disposal.[1] Worldwide, the incidences of measles, mumps, and rubella have been significantly reduced by measles-mumps-rubella (MMR) vaccination.[2,3] Concurrently, the severe complications of these diseases have become less apparent, and more attention has been focused on vaccine-related adverse events.[1]

Measles, mumps, and rubella viruses are neurotropic.[1] Involvement of the central nervous system is common in measles, and electroencephalographic changes have been reported in 50% of uncomplicated cases.[4] Measles virus causes a variety of central nervous system syndromes, including meningitis,[5] encephalitis,[5,6] measles inclusion body encephalitis (MIBE),[5,6] subacute sclerosing panencephalitis (SSPE),[5,6] and acute disseminated encephalomyelitis.[1] Acute encephalitis develops in 35 to 100 of 100 000 measles patients. The mortality rate is 10% to 20%, and neurologic damage occurs in 25% of survivors.[6–8]

Before the introduction of vaccination, mumps was the most common cause of viral encephalitis in children in several countries.[9] The reported incidence of mumps encephalitis averages 260 per 100 000 cases.[4,7] Estimates of the rate of clinical meningitis range from 0.1% to 15%, but 50% of mumps patients show pleocytosis of the cerebrospinal fluid (CSF).[4,7] With rubella, encephalitis develops in 13 of 100 000 patients.[7,10]

Electroencephalographic changes without neurologic symptoms have also been reported in children receiving live measles vaccine.[11] Cases of meningitis, encephalitis, MIBE, and acute disseminated encephalomyelitis have been reported after MMR vaccinations, but in most cases the link has remained unclear.[1,9,12–15] An association was suggested on the basis of clustering of cases of encephalitis after vaccination, but the reported rates were indistinguishable from the background rates.[8,16] However, MMR vaccines containing the Urabe or the Leningrad-3 strain of mumps virus have been shown to cause meningitis.[17–20] As a result, Urabe-containing MMR vaccines have been withdrawn from most countries.[21]

More recently, MMR vaccine has been suggested as 1 reason for the increasing incidence of autistic disorders.[22,23]

By linking data from hospital discharge and vaccination registers, we assessed whether an association prevails between MMR vaccination and encephalitis, aseptic meningitis, or autism.

METHODS

Subjects

In Finland, MMR vaccination of children aged 14 to 18 months and 6 years began in 1982. From November 1982 to June 1986,

From the *Hospital for Children and Adolescents, Helsinki University Central Hospital, Helsinki, Finland; and ‡Department of Infectious Disease Epidemiology, National Public Health Institute, Helsinki, Finland.
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Reprint requests to (A.M.) Hospital for Children and Adolescents, Helsinki University Central Hospital, Stenbäckinkatu 11, PL 281, 00029 HUS, Finland. E-mail: annamari.makela@hus.fi

TABLE 1. *ICD* Codes Used in Case Collection

ICD-8	Encephalitis, encephalopathies	
	065.99	Encephalitis virosa NUD
	066.01	Alterationes personae et characteris postencephaliticae
	066.02	Psychosis postencephalitica
	072.01	Parotitis epidemica cum meningoencephalitide/meningitis
	292.20	Psychoses cum encephalitide epidemica
	292.38	Psychoses cum encephalitide alia
	292.39	Psychoses cum encephalitide NUD
	323.00	Encephalitis postinfectiosa
	323.01	Encephalitis subacuta cum corporibus inclusionis
	323.08	Encephalitis alia definita
	323.09	Encephalitis NUD
	781.70	Encephalopathia
	999	Encephalitis, myelitis et encephalomyelitis post immunisationem
	999.10	Encephalitis, myelitis et encephalomyelitis post immunisationem
	Aseptic meningitis*	
	045.99	Meningitis NUD
	320.88	Meningitis alia definita
	320.99	Meningitis/meningoencephalitis NUD
	Autistic disorders	
	290–299	Psychoses
	295.8†	Infantile autism
	308.99	Gerendum abnorme infantum
	Inflammatory bowel disease	
	563.00	Morbus Crohn, enteritis regionalis
	563.10	Colitis ulcerosa
	563.98	Enterocolitis chronica et colitis ulcerosa alia definita
	563.99	Enterocolitis chronica et colitis ulcerosa NUD
	569.02	Proctitis haemorrhagica (ulcerosa)
	569.03	Periproctitis
	569.04	Perisigmoiditis
ICD-9	Autistic disorders	
	299	Psychoses ex origine infantia
	2990	Autismus infantilis
	2998	Developmental disorder
	2999	Developmental disorder
	Inflammatory bowel disease	
	555	Morbus Crohn
	5550A	Morbus Crohn, ilei
	5551A	Morbus Crohn, coli
	5552A	Morbus Crohn, ilei et coli
	5559X	Morbus Crohn NUD
	556	Colitis ulcerosa
	5560A	Colitis ulcerosa, proctitis
	5561A	Colitis ulcerosa, proctocolitis
	5562A	Colitis ulcerosa, totalis
	5563A	Colitis ulcerosa, fulminans
	5564A	Colitis ulcerosa, megacolon toxicum
	5568X	Enteritis et colitis chronica noninfectiosa alia definita
	5586X	Enterocolitis chronica et colitis ulcerosa NUD

NUD indicates nonultra descriptus.
* Codes used also for bacterial meningitis.
† Diagnosis number 295.8, which was used in Finland but not listed in the Finnish version of the *ICD*, was included in the study.

TABLE 2. Definitions

Disorder	Definition
Encephalitis	Acute or subacute onset of neurologic symptoms. Presence of neurologic symptoms or findings (clinical or laboratory, for example microbiological, electroencephalographic, computed tomographic) indicative of involvement of the brain parenchyma, such as coma, seizures, focal neurologic findings, or mental function impairment. Absence of evidence of other diagnoses, including non-inflammatory conditions and no microbiological or other laboratory findings suggestive of a nonviral infection. When pleocytosis in CSF is present, the term encephalitis is used, implying an inflammatory response within the brain. The presence of normal CSF findings does not preclude the diagnosis if the other criteria are satisfied.[26,27]
Encephalopathy	Clinically resembles encephalitis but no inflammatory response is evident. Chronic encephalopathy: persistence of acute findings usually over several months.[26]
Aseptic meningitis	Inflammation of the meninges. Usually a self-limiting disease of known or suspected viral cause consisting of fever, headache, signs of meningeal irritation, without evidence of brain parenchymal involvement and a lymphocytic and mononuclear pleocytosis of CSF. The term meningoencephalitis does not differentiate cases with prominent involvement of the brain parenchyma from those with meningeal involvement only.[26]
Autistic disorder	Severe qualitative impairment in reciprocal social interaction, in verbal and nonverbal communication and in imaginative activity and markedly restricted repertoire of activities and interests.[28]

561 089 vaccinees were enrolled in a surveillance study by the National Public Health Institute. The data collected on each vaccinated child included name and social security number of the vaccinee, age at vaccination, and timing (year and month) of the first MMR vaccination. Of the enrolled vaccinees, 535 544 (95%) were 1 to 7 years old at the time of vaccination and are included in the current analysis. The register represents ~86% of all children scheduled to be vaccinated between November 1982 and June 1986 in Finland.[24]

M-M-R_{II} (Merck & Co, West Point, PA) was the only vaccine in use in Finland during the enrollment. This vaccine contains the more attenuated Enders-Edmonston strain of measles virus, the Jeryl Lynn strain of mumps virus, and the Wistar RA 27/3 strain of rubella virus.

Hospital Discharge Register

The nationwide hospital discharge register includes data on all hospitalizations since 1972 and has a validated high coverage (over 95%).[25] Individual hospitalizations are identified from the register by using social security numbers and the *International Classification of Diseases* (*ICD*) codes of the World Health Organization. *ICD-8* (effective from 1969 through 1986) and *ICD-9* (effective from 1987 through 1995) codes listed in Table 1 were used for case collection.

Data Collection

Vaccination data of every 1- to 7-year-old child in the vaccination register was linked individually with data from the hospital discharge register. Hospitalizations because of encephalitis and

TABLE 3. Characteristics of the Vaccinees Hospitalized for Encephalitis or Aseptic Meningitis During the 3-Month Interval After MMR Vaccination and the Number of Hospitalizations During the Subsequent 3-Month Intervals

Encephalitis Time From Vaccination to Hospitalization	*n*	Gender	Age at Vaccination	Vaccination Dose
0–3 mo	9			
2 d		M	1 y 6 mo	I
13 d		F	1 y 5 mo	I
1 mo 17 d		M	3 y 1 mo	I
1 mo 21 d		M	5 y 2 mo	I
1 mo 23 d		M	1 y 3 mo	I
1 mo 24 d		F	1 y 6 mo	I
2 mo 7 d		M	3 y 8 mo	I
2 mo 16 d		M	6 y 10 mo	I
2 mo 22 d		M	5 y 11 mo	II
3–6 mo	20			
6–9 mo	14			
9–12 mo	13			
12–15 mo	11			
15–18 mo	14			
18–21 mo	5			
21–24 mo	11			
Aseptic Meningitis				
Time From Vaccination to Hospitalization	*n*	Gender	Age at Vaccination	Vaccination Dose
0–3 mo	10			
2 d		M	7 y	II
19 d		F	1 y 3 mo	I
25 d		M	1 y 8 mo	I
25 d		M	6 y	I
1 mo 2 d		M	7 y 1 mo	I
1 mo 12 d		M	4 y 1 mo	I
1 mo 23 d		M	3 y 4 mo	I
1 mo 26 d		F	3 y 1 mo	I
1 mo 27 d		M	3 y	I
1 mo 29 d		M	6 y 4 mo	I
3–6 mo	6			
6–9 mo	7			
9–12 mo	6			
12–15 mo	12			
15–18 mo	5			
18–21 mo	8			
21–24 mo	10			

encephalopathies (henceforth referred to as encephalitis) or aseptic meningitis were identified between November 1982 and September 1986 to allow 3 months of surveillance beyond the period of the vaccination register covered. Hospitalizations for autism between November 1982 and December 1995 were searched for. Patients hospitalized for encephalitis or meningitis with a defined cause unrelated to measles, mumps, or rubella infections or to MMR vaccination were excluded.

For calculation of the background incidences, hospitalizations among the 1- to 7-year-old children who were not vaccinated during the enrollment were also searched for. For autism, only the first hospital visit during the study period was included in the survey. If acute encephalitis or meningitis caused several hospitalizations in the same child, all visits were assessed. In addition, hospitalizations because of inflammatory bowel diseases during 1982–1995 were evaluated for the children with autism.

Of the patients hospitalized because of encephalitis or meningitis within 3 months of MMR vaccination, the exact dates of immunization were collected from the patients' medical records or personal vaccination cards filed at health centers. For verified other patients, the dates, based on the year and month of vaccination, could be estimated with an accuracy of 1 month. To assess the accuracy of the *ICD* coding and to evaluate the role of other causes for the events, we reviewed the medical records of all patients hospitalized for encephalitis or meningitis within 3 months of vaccination. Cases meeting the diagnostic criteria listed in Table 2 were further analyzed.

Definition of the Risk Interval

The incubation periods of measles (8–12 days), mumps, and rubella (both 16–18 days) are expected to be similar for the vaccine viruses.[4] To enable sufficient follow-up for encephalitis and aseptic meningitis, we used a 3-month period postvaccination as the risk interval. Because of the undefined latency until manifestation of the symptoms of autistic disorders, the follow-up was extended to the end of the study period for every vaccinee, irrespective of the date of immunization.

Statistical Methods

For encephalitis and aseptic meningitis, we compared the numbers of events observed within the 3-month risk intervals postvaccination with the numbers expected. The numbers expected were calculated on the basis of the numbers of events observed during the subsequent 3-month intervals until 24 months after vaccination. The data were analyzed using the χ^2 test with the Yates correction.[29] P values of $< .05$ were considered significant.

Because no risk period could be defined for autistic disorders, we evaluated whether there were changes in the overall number of hospitalizations for autism after MMR vaccination during the whole study period.

RESULTS

Of the 535 544 vaccinees, 199 were hospitalized for encephalitis, 161 for aseptic meningitis, and 352 for

autistic disorders. Vaccination data were missing for 7, 7, and 11 children enrolled in the register and hospitalized for encephalitis, meningitis, and autism, respectively.

Encephalitis

Of the 199 children, 9 were hospitalized for encephalitis within 3 months of vaccination (Table 3). MMR vaccine was administered to 80 children after the disease, and in 110 the interval between vaccination and hospitalization exceeded 3 months. In addition, 66 events were observed among unvaccinated 1- to 7-year-old children.

No excess of hospitalizations for encephalitis was detected within 3 months of vaccination ($P = .28$). Furthermore, in 8 of the 9 cases, a very short interval of 2 days or an interval exceeding 1 month between vaccination and hospitalization makes an association with immunization very unlikely.

The incidence of encephalitis of undefined cause among all 1- to 7-year-old children decreased by 35% from 19.90 per 100 000 in 1983 to 13.00 per 100 000 in 1985. The annual numbers of hospitalizations for encephalitis among children in the vaccination register are illustrated in Fig 1 and hospitalizations of unvaccinated 1- to 7-year-old children in Fig 2.

Aseptic Meningitis

In 10 vaccinees, aseptic meningitis developed within 3 months of MMR vaccination (Table 3). Forty-one children were vaccinated after hospitalization and in 110 the interval exceeded 3 months. Of the unvaccinated children, 30 were hospitalized for aseptic meningitis. No significant increase in the number of meningitis cases was observed within 3 months postvaccination ($P = .57$). As with encephalitis, an association between vaccination and meningitis occurring on day 2 or over 1 month after vaccination in 7 patients seems very unlikely.

The incidence of meningitis of undefined cause in 1- to 7-year-old children decreased by 24% during the study period from 10.17 per 100 000 in 1983 to 7.71 per 100 000 in 1985 (absolute numbers in Figs 1 and 2).

Autistic Disorders

Of the vaccinees, 309 were hospitalized for autism after vaccination. When the shortest possible intervals between MMR vaccination and the day of hospitalization were assessed, these ranged from 3 days to 12 years and 5 months. No distinguishable clustering was detected in the intervals from vaccination to the hospitalization. The number of hospital admissions remained relatively steady during the first 3 years and then gradually decreased, as was expected because of the increasing age of the vaccinees (Fig 3). Forty-three children were vaccinated after the first hospitalization and 31 were hospitalized but remained unvaccinated between November 1982 and June 1986.

Of the children hospitalized for autism, none made hospital visits because of inflammatory bowel diseases in 1982–1995.

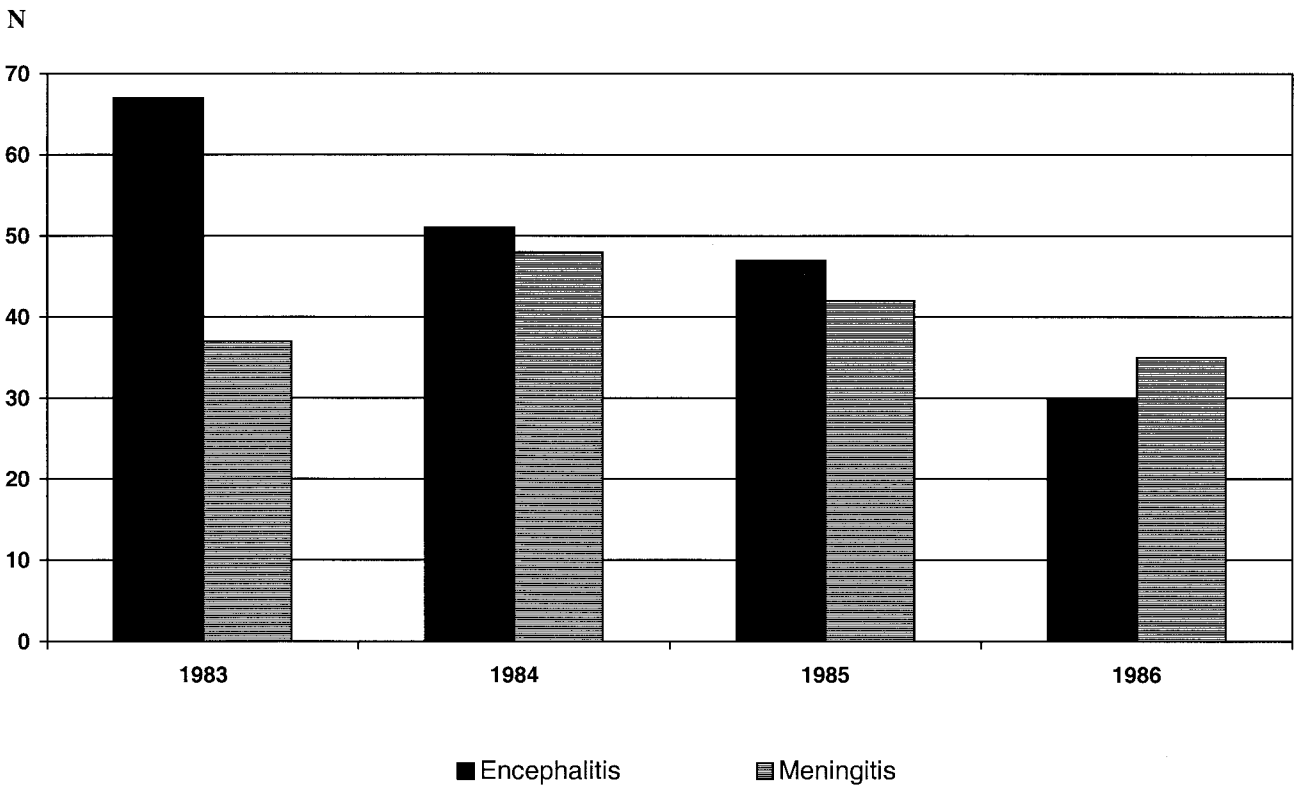

Fig 1. The annual number of hospitalizations for encephalitis and aseptic meningitis during 1983–1986 among children enrolled in the MMR vaccination register.

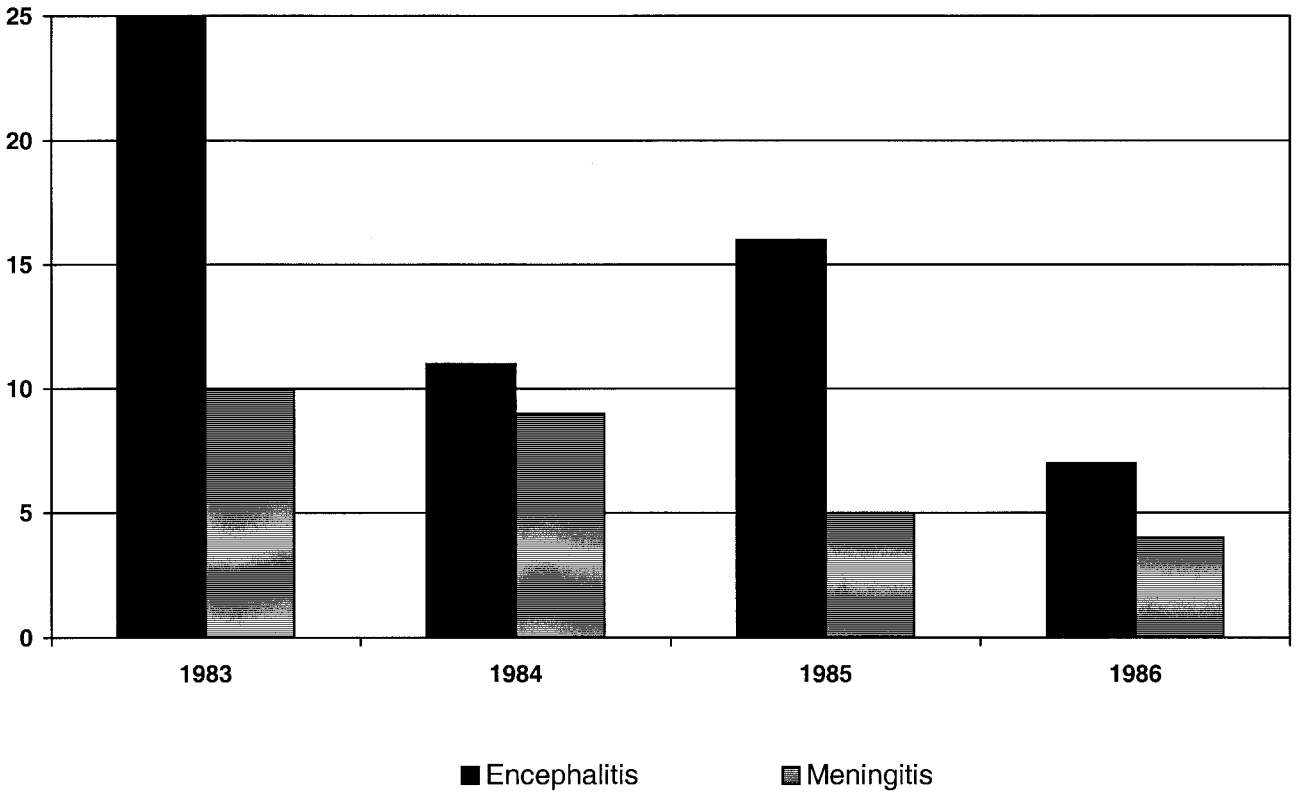

Fig 2. The annual number of hospitalizations for encephalitis and aseptic meningitis during 1983–1986 among unvaccinated 1- to 7-year-old children.

DISCUSSION

Linkage of vaccination records of over 500 000 children with a national hospital discharge register found no evidence of an increased risk of encephalitis or aseptic meningitis associated with MMR vaccination. On the contrary, during 1983–1985 the incidence of encephalitis of undefined cause among 1- to 7-year-old children decreased by 35% and the incidence of aseptic meningitis by 24%. This change is in concordance with the observed protective effect of MMR vaccination on encephalitis caused by measles, mumps, and rubella.[27] In addition, no evidence for the hypothesized link between MMR vaccination, autism, and inflammatory bowel disease was found.

Several other studies have evaluated the relation between live virus vaccinations and neurologic disorders. During 1963–1971 in the United States, a clustering of 45 cases of encephalitis was detected 6 to 15 days after measles vaccination. A definite link with the vaccine was not established in any of the cases, but was regarded possible. The incidence of neurologic disorders in the recipients of further attenuated vaccines was estimated as 0.08 per 100 000 doses.[16] A Canadian study found a rate of 0.18 cases of encephalitis per 100 000 doses of measles vaccine, which was very close to the background level of encephalitis of unspecified cause.[30] Weibel et al[8] reported a clustering of 17 cases of encephalopathy on days 8 and 9 after measles, measles-rubella, or MMR vaccination, but the authors stated that, with a denominator of 75 000 000 vaccinees throughout 23 years, encephalopathy would be an extremely rare complication (0.06 per 100 000 vaccinees).

In addition, several case reports of encephalitis occurring after monovalent or combination MMR vaccinations exist, but in most cases causality has not been proved.[1,9,12,13] However, the Urabe mumps vaccine strain has been shown to cause encephalitis,[31] and measles virus with a nucleotide sequence identical to the more attenuated Enders-Edmonston vaccine strain was isolated from the brain tissue of an immunodeficient patient developing fatal MIBE 8 months after MMR vaccination.[15] Development of SSPE has been described 3 weeks after live measles vaccination in a child with no history of measles.[32] This probably indicates mere concurrence, because only wild-type measles virus has been isolated from patients with SSPE.[1] Reassuringly, measles immunization has dramatically diminished the incidence of SSPE.[1]

The problem of vaccine-associated meningitis has been prominent with the Japanese MMR vaccines. In several cases, mumps virus has been isolated from CSF and identified by nucleotide sequencing analysis to be the Urabe vaccine strain.[31,33] The incidence of meningitis attributable to the Urabe vaccine varies from 3.5 to 166 per 100 000 doses.[19,34] A mass immunization campaign with the Urabe-containing MMR vaccine in Brazil resulted in 58 cases of aseptic meningitis. The relative risk 3 weeks' postvaccination as

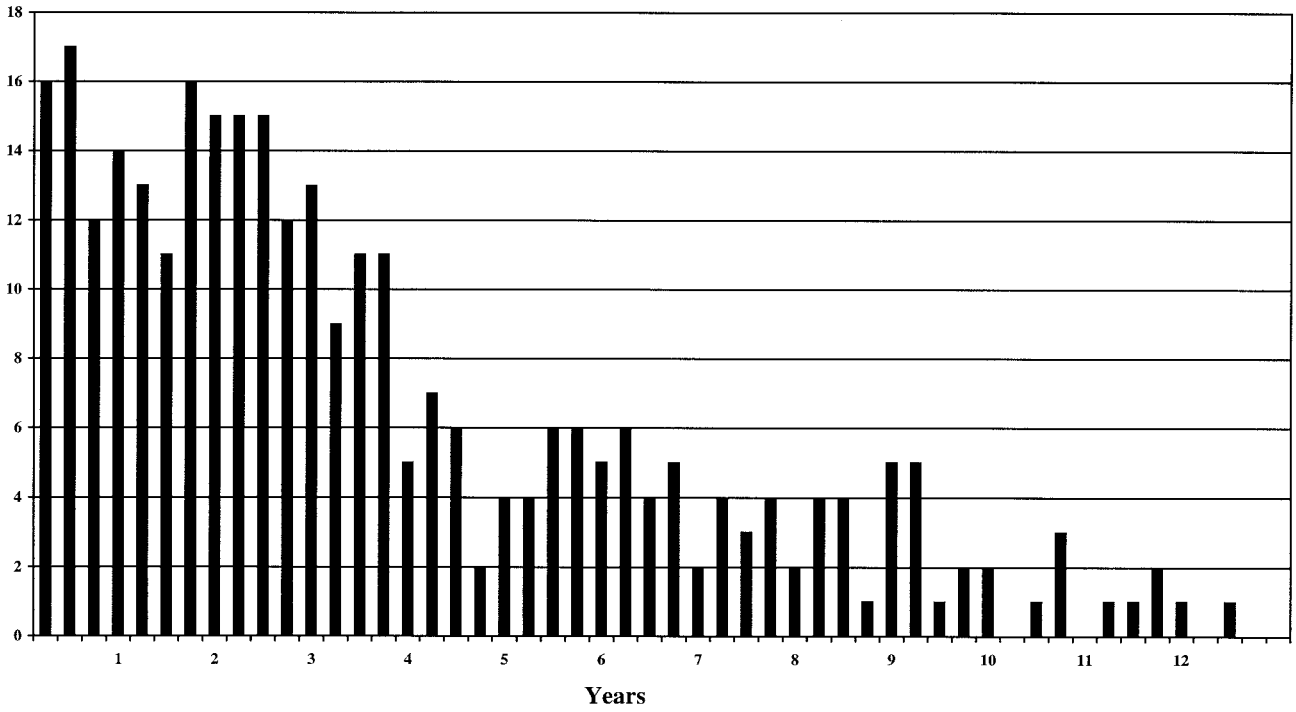

Fig 3. Interval from MMR vaccination to the first hospitalization for autistic disorder among 309 children (grouped in 3-month periods).

compared with the risk before the campaign was 14.3 (95% confidence interval: 7.9–25.7, 7.1 per 100 000 doses).[20] The Leningrad-3 strain of mumps has also been shown by virus isolation to cause meningitis in 90 to 100 per 100 000 vaccine recipients.[17]

Rare cases of meningitis have been reported after vaccination with the Jeryl Lynn mumps strain, but causality has not been proved in any of the cases.[1,13,14] Mumps virus was isolated from the CSF of a child with meningitis occurring 21 days after Jeryl Lynn vaccination, but the virus was not reliably identified as wild or vaccine virus.[1,13]

In 1998, Wakefield et al[22] suggested that MMR vaccine could cause enterocolitis leading to excessive absorption of peptides, disturbance of neurologic development, and autistic disorder within 14 days of immunization. This theory has been rebutted because of several methodological weaknesses, and the contradictory results of subsequent reports.[35–37] Taylor et al[35] investigated by the case series method whether clustering of autism occurred after MMR vaccination and found no support for the hypothesized link. A similar conclusion was reached in 2 time trend analyses from the United Kingdom and the United States.[36,37] The incidence of autism varies widely among studies, and the observed increase may reflect better case ascertainment and the use of different definitions for the disorders.[38] Although the first symptoms of autism are typically manifested at the age of MMR vaccination, there is no epidemiologic evidence that immunization causes autism.[35–37]

Reliable assessment of causality between immunization and rare disorders is extremely difficult. Therefore, the evidence of several of the suspected adverse effects of MMR vaccination has remained controversial or inconclusive.[1] Linkage of MMR vaccination and hospital discharge registers provided us with an opportunity to evaluate these complex issues further, but certain limitations were unavoidable. We had no access to data of outpatient visits. However, the occurrence of severe encephalitis and meningitis requiring hospitalization could be assessed reliably. For children with encephalitis and meningitis, the interval between vaccination and the day of hospitalization was calculated because the exact date of occurrence of symptoms was not always clear. Because these acute diseases usually lead to hospitalization within a few days of the onset of symptoms, excess of illness after immunization would have been detected.

The exact incidence of autism could not be defined with our approach, because autistic disorders develop insidiously over long periods of time, or the disorder is present at birth but not obvious until later, and the first hospitalization does not indicate the timing of the occurrence of symptoms. Furthermore, diagnosis of autism does not always involve hospitalization. However, in Finland it is common that these children are admitted to hospital for observation, in-depth neurobiological examinations, treatment, and rehabilitation. Thus, a significant clustering of hospital admissions for autistic disorders after MMR vaccination would have been detected in this study.

Furthermore, as the coverage of the MMR vaccination register was not complete, some children regarded as unvaccinated may actually have been immunized during the study period. Because the

number of unvaccinated children is minuscule as compared with the number of those vaccinated, this limitation is unlikely to influence the findings of this study.

Whether the cases of encephalitis and meningitis occurring within 2 days of vaccination should have been excluded from the analysis, because no viremia is to be expected within such a short interval, is debatable.[4] Correspondingly, the designated risk interval of 3 months exceeds the incubation periods of natural measles, mumps, and rubella,[4] but was chosen because of the suggestions that attenuation of viruses may prolong the usual incubation periods.[12]

Our results provide additional evidence of the safety of MMR vaccination. Nevertheless, significant public concern about adverse events of vaccines clearly exists, and continuous surveillance aiming at distinguishing true adverse events from unrelated, chance occurrences is crucial to maintain public confidence in immunization.

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