Risk of aseptic meningitis after measles, mumps,and rubella vaccine in UK children

ELIZABETH MILLER MICHAEL GOLDACRE SIMON PUGH
ALARIC COLVILLE PADDY FARRINGTON AUDREY FLOWER
JAMES NASH LORNA MACFARLANE RICHARD TETTMAR

Cases of aseptic meningitis associated with measles/mumps/rubella vaccine were sought in thirteen UK health districts following a reported cluster in Nottingham which suggested a risk of 1 in 4000 doses, substantially higher than previous estimates based on cases reported by paediatricians (4 per million). Cases were ascertained by obtaining vaccination records of children with aseptic meningitis diagnosed from cerebrospinal fluid samples submitted to Public Health Laboratories or discharged from hospital with a diagnosis of viral meningitis. Both methods identified vaccination 15–35 days before onset as a significant risk factor and therefore indicative of a causal association. With both, half the aseptic meningitis cases identified in children aged 12–24 months were vaccine-associated with onset 15–35 days after vaccine. The study confirmed that the true risk was substantially higher than suggested by case reports from paediatricians, probably about 1 in 11 000 doses. However, the possibility that the aseptic meningitis induced by vaccination was largely asymptomatic and a chance laboratory finding in children investigated for other clinical conditions, particularly febrile convulsions, could not be excluded.

Comparison of national reports of virus-positive mumps meningitis cases before and after the introduction of this vaccine indicated that the risk from wild mumps was about 4-fold higher than from vaccine. Altogether, 28 vaccine-associated cases were identified, all in recipients of vaccines containing the Urabe mumps strain. The absence of cases in recipients of vaccine containing the Jeryl Lynn strain, despite its 14% market share, suggested a higher risk from Urabe vaccine.

A prospective adverse event surveillance system using the study methods is currently being established to assess the risk, if any, from the Jeryl Lynn strain which is now the only mumps vaccine used in the UK.

Lancet 1993; **341**: 979–82.

Introduction

Aseptic meningitis is a well-recognised complication of mumps vaccine[1] typically occurring 2–4 weeks after immunisation and resolving without sequelae. The diagnosis can be confirmed in about one-third of temporally associated cases by isolating mumps virus from cerebrospinal fluid (CSF).[2,3] North American studies have shown a risk of between 0·4 and 10 per million doses[4,5] although work from Japan suggests that the true risk may be much higher.[2,3] This disparity may be due in part to differences in the methods used to ascertain and define cases but may also reflect differences in the neurotropism of vaccine virus strains or in host susceptibility.

To assess the risk in the UK, where both Urabe and Jeryl Lynn strains have been used, paediatricians were asked to report to the British Paediatric Surveillance Unit (BPSU) all confirmed and suspected cases diagnosed during 1990–91. The risk based on confirmed cases was estimated to be 4 per million doses distributed; all were in Urabe vaccine recipients.[6] However, data from one district, based on 2 confirmed and 4 suspected cases identified by Nottingham Public Health Laboratory, suggested a much higher risk, about 1 in 4000 doses.[7] To investigate whether the risk observed in Nottingham was atypical or indicative of substantial under-reporting elsewhere, cases were actively sought in thirteen other districts by obtaining vaccination histories for children with laboratory evidence or a hospital discharge diagnosis of aseptic meningitis. In addition, national reports of virus positive mumps meningitis cases before and after the introduction of the combined measles, mumps, and rubella (abbreviated generically to MMR here) vaccine were compared. The findings have been used to assess the true risk of vaccine-associated meningitis in the UK and the risk from vaccine relative to wild mumps virus.

Methods

Laboratory study

CSF samples sent to Ashford, Chelmsford, Leicester, or Preston Public Health Laboratories (PHL) from children aged 12–24 months, without a CSF shunt, who had been admitted to hospitals exclusively within the catchment areas of those laboratories were identified retrospectively for a period of at least 2 years after the introduction of MMR vaccine. Second episodes in the same child were included. CSF samples from children resident in the Nottingham health district were identified as previously described.[7] Samples with <5 leucocytes/μL corrected for red blood cells and with no bacterial isolate were considered normal. Lymphocytic samples (≥ 5 leucocytes/μL, predominantly lymphocytes with no bacterial isolate) were considered indicative of aseptic meningitis. Dates of MMR vaccination and batch numbers were sought for all study children from health authority and general practice records. The temporal association with vaccination was investigated by survival methods[8] with interval from vaccination as a time-dependent variable. Aseptic meningitis 15–35 days after vaccine was defined as vaccine-associated. Denominator information on the number of doses and types of MMR vaccine given in the study

ADDRESSES: **Immunisation Division, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ** (E. Miller, MFPHM, P. Farrington, PhD); **Unit of Health Care Epidemiology, Department of Public Health Medicine, University of Oxford, Headington, Oxford OX3 7LE** (M. Goldacre, FFPHM); **and Public Health Laboratories, Nottingham** (S. Pugh, MRCPath, A. Colville, MRCPath); **Leicester** (A. Flower, MD), **Ashford, Kent** (J. Nash, MRCPath), **Preston** (L. Macfarlane, MB), **and Chelmsford** (R. Tettmar, FRCPath). Correspondence to Dr Elizabeth Miller.

TABLE I—CSF SAMPLES FROM 432* CHILDREN AGED 12–24 MONTHS SUBMITTED TO FIVE PHLS LABORATORIES

Laboratory (district)	Study period	Total children aged 12–24 mo	CSF samples submitted (and rate/10 000)	Laboratory diagnosis (no [and rate/10 000])		
				Normal CSF	Bacterial meningitis	Lymphocytic CSF
Leicester (Leicestershire)	Oct 88–June 92	47 150	226 *(48)*	192 *(41)*	20 *(4·2)*	14 *(3·0)*
Nottingham (Nottingham)	Oct 88–Dec 91	26 650	120 *(45)*	92 *(35)*	18 *(6·8)*	10 *(3·8)*
Preston (Preston; Chorley and Ribble)	April 89–June 92	14 900	42 *(28)*	29 *(19)*	9 *(6·0)*	4 *(2·7)*
Ashford (South East Kent)	Jan 89–Mar 92	11 450	28 *(24)*	17 *(15)*	9 *(7·9)*	2 *(1·7)*
Chelmsford (Mid-Essex)	Apr 90–Mar 92	7700	24 *(31)*	18 *(23)*	4 *(5·2)*	2 *(2·6)*
Total	..	107 850	440 *(41)*	348 *(32)*	60 *(5·6)*	32 *(3·0)*

*8 children had a second illness resulting in lumbar puncture.

districts was obtained from official statistics[9] and health authority records. Proportions were compared by Fisher's exact test (two-tailed) and lymphocyte counts were compared by the Mann-Whitney test.

Hospital study

Statistical records of children aged under 6 years discharged from hospitals in the eight districts in the Oxford region between October, 1988, and December, 1991, with a diagnosis of aseptic meningitis were identified in hospital systems on ICD codes 072·1 (mumps meningitis), 047 (aseptic meningitis), or 321 (meningitis due to unspecified viruses) and then linked to immunisation data held in child health systems. Evidence of temporal clustering after vaccination was sought and denominator data were obtained, as described above.

National reports

All children aged 12–24 months with mumps virus isolated from CSF and reported to the PHLS Communicable Disease Surveillance Centre (CDSC) by a laboratory in England and Wales between January, 1980, and September, 1992, were identified and MMR vaccination histories sought for those diagnosed since January, 1989. The incidence of natural mumps in children aged 12–24 months before the introduction of vaccination was estimated from age-specific antibody prevalence data in a national serological survey during 1987.[10] The number of doses of MMR vaccine given in England and Wales to children aged 12–24 months was estimated from official statistics and the national distribution of Urabe and Jeryl Lynn containing vaccines was obtained from the Department of Health.

Results

Laboratory study

440 CSF samples from 432 children aged 12–24 months admitted to district hospitals were identified by the five laboratories during the study period; 348 samples (79%) were normal (table I). The lumbar puncture rate per 10 000 children was significantly higher in Nottingham and Leicester, the two laboratories serving teaching hospitals ($p < 0·001$), largely because of 2-fold higher rates for normal CSF; there was no significant difference in the rates for aseptic and bacterial meningitis. MMR vaccination histories were obtained for 418 (97%) children; of the 380 (91%) who were vaccinated, 303 had received Urabe and 62 Jeryl Lynn vaccine (15 strain not known). The proportion of Urabe recipients among study children (83%) was similar to the proportion of Urabe vaccine distributed in the study districts (81%).

Vaccination histories were obtained for all 32 children with laboratory evidence of aseptic meningitis. Of the 27 vaccinated before 24 months of age, 13 (48%) had received Urabe vaccine 15–35 days before lumbar puncture. Vaccination in this period was a significant risk factor ($p < 0·001$). The median interval to onset was 23 days (range 18–34). Mumps virus was isolated in 2 Nottingham and 2 Leicester cases; no other viruses were isolated. The median lymphocyte count in the 9 virus-negative vaccine-associated cases was 225 (range 16–800) compared with 10·5 (range 5–1250)/μL in non-vaccine-associated cases ($p < 0·001$). All 13 vaccine-associated cases presented with a febrile convulsion usually accompanied by vomiting, drowsiness, or irritability; only 2 had meningism and none had parotitis.

The risk of vaccine-associated aseptic meningitis per 10 000 doses of vaccine (table II) was higher in Nottingham than in the other four laboratories—2·6 and 0·95, respectively, for all vaccine types and 3·2 and 1·2 for Urabe vaccines—though these differences were not significant ($p = 0·09$ for both comparisons). The difference in risk between Urabe and Jeryl Lynn vaccines (13/78 300 and 0/18 400 doses) was not significant ($p = 0·15$), but a substantial risk difference cannot be excluded in view of the low study power.

Among children with normal CSF, 13 (5%) of the 275 vaccinated before 24 months of age had a lumbar puncture 6–11 days after vaccination, the expected time of onset of convulsions attributable to the measles component of the vaccine.[11] Vaccination in this period was a significant risk factor ($p = 0·021$) for first episodes. The risk per 10 000 doses of vaccine was 0·88 in Nottingham and 1·5 elsewhere ($p = 0·75$). 1 of the 13 vaccine-associated cases had received Jeryl Lynn vaccine.

12 of the children with normal CSF had a lumbar puncture 15–35 days after vaccination, about half the number expected on the basis of the rate of occurrence of such episodes in the control period. When cases with normal and lymphocytic CSF in the 15–35 day post-vaccination period were combined, there was no evidence of a significant excess of events relative to the control period ($p = 0·6$)

Hospital study

10 children aged 12–24 months with a discharge diagnosis of viral meningitis were identified in the Oxford region and their vaccination status ascertained. 9 had received MMR vaccine by 24 months of age of whom 5 (56%) were

TABLE II—RISK OF VACCINE-ASSOCIATED ASEPTIC MENINGITIS IN VACCINATED CHILDREN AGED 12–24 MONTHS

Laboratory	Total vaccinated children	% Urabe vaccine distributed	Aseptic meningitis cases 15–35 days after vaccination*	Risk in 15–35 day period (95% CI) per 10 000 doses
Leicester	42 300	92	5	1·2 (0·15–2·2)
Nottingham	22 800	82	6	2·6 (0·53–4·7)
Preston	13 550	100	1	0·74 (0·00–2·2)
Ashford	10 650	0	0	0·00 (0·00–2·8)
Chelmsford	7400	100	1	1·4 (0·00–4·0)
Total	96 700	81	13	1·3 (0·61–2·1)

*All cases in this period were in Urabe vaccine recipients.

TABLE III—FREQUENCY OF VACCINE-ASSOCIATED ASEPTIC MENINGITIS IN VACCINATED CHILDREN AGED 12–24 MONTHS ACCORDING TO SOURCE AND CASE DEFINITION

Source of case	Virus positive		All cases	
	No	Frequency: doses	No	Frequency: doses
Laboratory study				
Nottingham PHL	2	1:11 000	6	1:4000
Other PHLs	2	1:37 000	7	1:11 000
Hospital study	1	1:107 000	5	1:21 000
CDSC reports	16*	1:143 000	(all cases virus positive)	

*Includes 5 cases also identified in laboratory and hospital studies

admitted 15–35 days after vaccination (significant risk factor, $p = 0{\cdot}003$). The estimated risk per 100 000 doses was 4·7 (95% CI 0–8·8). Mumps virus, identified as Urabe-like by nucleotide sequencing,[12] was isolated from the CSF in 1 child; 3 others had received a Urabe-containing vaccine (vaccine type in the remaining child was not known).

National reports

During 1980–87, 19 children aged 12–24 months with mumps virus isolated from CSF were reported to CDSC, giving an estimated risk per 100 000 cases of wild mumps in this age group of 2·7. During January, 1989, to September, 1992, 18 children aged 12–24 months were reported of whom 16 had been vaccinated 15–35 days before onset (median interval to sample 21 days, range 17–33), giving an estimated risk per 100 000 doses in this age group of 0·7 (95% CI 0·36–1·0). All had received a Urabe vaccine as evidenced by the batch number and/or strain characterised by nucleotide sequencing. The proportion of Urabe cases (16/16) is not significantly different from that expected on the basis of UK vaccine distribution figures (86%) ($p = 0{\cdot}18$; 2 × one-tail binomial probability). An excess of males was found both among vaccine-associated (10/16) and wild cases (12/18; 1 sex not known).

The different estimates of the risk of vaccine-associated aseptic meningitis (expressed as frequencies) are summarised in table III, according to source and case definition. Combining all cases of known vaccine type from the various sources, a total of 28/28 were identified in Urabe recipients, a higher proportion than expected from the national share ($p = 0{\cdot}03$).

Discussion

The active ascertainment methods used in the five study laboratories identified 13 cases of vaccine-associated aseptic meningitis in children aged 1–2 years. Although mumps virus was identified in only one-third, the characteristically high lymphocyte counts in the remainder, together with the significantly increased risk 15–35 days after vaccination, provides evidence in favour of causal association. The study therefore confirms that the risk of aseptic meningitis after MMR vaccine is substantially higher than previously supposed in the UK. The risk estimate of 1 per 11 000 doses, based on the results from four independent laboratories, shows that the cases reported by Nottingham PHL were not a chance cluster. The slightly higher risk found in Nottingham than elsewhere may reflect local policy differences in investigating children presenting with a convulsion but no meningism, as evidenced by the higher lumbar puncture rates in the two districts with teaching hospitals. However, the risk of adverse neurological events associated with the measles component of MMR vaccine was not higher in Nottingham, suggesting no major difference in the likelihood of conducting lumbar punctures in recently vaccinated children.

The findings of the laboratory study were supported by the hospital study. In both, half the aseptic meningitis cases in vaccinated children aged 12–24 months were vaccine-associated and most had not previously been recognised as such. The lower risk estimated from hospital discharge data may reflect imprecision in ICD coding and suggests that more complete ascertainment of cases would require the selection of a wider range of ICD codes and study of hospital notes.

The risk estimate for virus-positive cases based on national reports was the lowest and is consistent with the incomplete reporting to CDSC, especially by laboratories in the London area. Comparison with national reports before the introduction of vaccination indicated a risk of virus-positive meningitis from vaccine relative to wild mumps of about 1 to 4. However, this comparison may overestimate the neurotropism of vaccine virus because of the greater likelihood of a lumbar puncture being done in vaccine-attributable cases. Children with wild mumps meningitis, unlike vaccine-associated meningitis, will usually have parotitis, permitting diagnosis on clinical grounds alone. Both vaccine-attributable and wild cases showed a 2-fold excess in males, confirming other observations[2,3] and suggesting that host factors influence neurotropism.

Lymphocytic CSF without clinical evidence of meningitis has been reported in over 80% of children infected with wild mumps virus[13] and it has been suggested that this frequently happens with vaccine virus, the laboratory diagnosis of aseptic meningitis being made by chance if the child has a lumbar puncture for other clinical reasons in the 15–35 day post-vaccination period.[14] If the aseptic meningitis induced by the vaccine is largely asymptomatic, no overall excess of neurological events should be found in this time period. Our observation that the excess of lymphocytic CSF 15–35 days after vaccination was compensated by a deficit of normal CSF is consistent with this prediction. A further study to test this hypothesis is now underway.

The absence of proven cases of meningitis associated with Jeryl-Lynn-containing vaccine in our investigation, together with the low risk of vaccine-associated meningitis reported in countries exclusively using this strain, led to the decision to replace Urabe with Jeryl Lynn vaccine in the UK.[15] However, neither the laboratory study nor the analysis of CDSC reports showed a significantly higher risk of meningitis after Urabe than Jeryl Lynn vaccines. The absence of cases in Jeryl Lynn recipients was consistent with the low market share of this vaccine in the UK. Although evidence of a significant difference in risk between vaccines emerged when confirmed and suspected cases ascertained from all sources were combined, this finding should be interpreted with caution because of the different methods and case definitions used. The risk reported in the US with Jeryl Lynn vaccine of 1 per million doses[4] should not be compared with the risks for Urabe vaccine found in our study because of the different methods used to ascertain cases. The true relative risk of meningitis from Urabe as compared with Jeryl Lynn vaccine remains uncertain. However, the reported reduction in vaccine-associated aseptic meningitis in Canada which followed the change from Urabe to Jeryl Lynn-containing MMR vaccine in 1989 supports the recent UK decision.[16]

National decisions about which MMR vaccine to use must take account of relative immunogenicity as well as

safety.[17] Immediate seroconversion rates to the mumps component are generally higher (about 4%) with Urabe than with Jeryl Lynn[17] but comparative data on longer-term antibody persistence and protective efficacy are lacking. The relative immunogenicity of the different measles components of Urabe and Jeryl Lynn-containing vaccines must also be considered. A serological follow-up of a cohort of children who received Urabe and Jeryl Lynn containing MMR vaccines in 1988, before the launch of the national programme in the UK,[11] is in progress and a similar study is underway in Canada. Information on the relative risk of other adverse events, such as idiopathic thrombocytopenic purpura,[18] is also required for a full assessment of the relative merits of different MMR vaccines.

The study demonstrates the importance of using active case ascertainment methods for adverse event surveillance. Although audit of the reporting system operated through the British Paediatric Surveillance Unit has shown high levels of case ascertainment for other disorders (S. M. Hall, personal communication), reporting of vaccine-associated meningitis cases was incomplete, probably due to failure to inquire routinely about the date of vaccination in children with relevant symptoms. Development of an adverse event surveillance system which allows automatic linkage of vaccination records held on local child health computer systems with computerised hospital discharge data is being explored and extension of the laboratory-based system is in progress. Following the decision to change to Jeryl Lynn-containing vaccine in the UK, these systems will allow the risk of meningitis associated with this mumps strain to be assessed.

We thank the paediatricians and general practitioners who provided information on their patients and Dr P. Morgan-Capner (Preston PHL) and Mrs J. Vurdien (CDSC) for their help.

REFERENCES

1. Anon. Mumps meningitis and MMR vaccination. *Lancet* 1989; ii: 1015–16.
2. Fujinaga T, Motegi Y, Tamura H, Kuroume T. A prefecture-wide survey of mumps meningitis associated with measles, mumps and rubella vaccine. *Pediatr Infect Dis J* 1991; **10:** 204–09.
3. Sugiura A, Yamada A. Aseptic meningitis as a complication of mumps vaccination. *Pediatr Infect Dis J* 1991; **10:** 209–13.
4. Anon. Mumps prevention. Recommendations of the Immunisation Practices Advisory Committee (ACIP). *MMWR* 1989; **38:** 388–40.
5. Hockin JC, Furesz J. Mumps meningitis, possibly vaccine-related—Ontario: comment. *Can Dis Wkly Rep* 1988; **14:** 210.
6. Maguire HC, Begg NT, Handford SG. Meningoencephalitis associated with MMR vaccine. *CDR* 1991; Review no 6: 1: R60–61.
7. Colville A, Pugh S. Mumps meningitis and measles, mumps and rubella vaccine. *Lancet* 1992; **340:** 786.
8. Prentice RL, Vollmer WM, Kalbfleisch JD. On the use of case series to identify disease risk factors. *Biometrics* 1984; **40:** 445–58.
9. Begg NT, Gill ON, White JM. COVER (Cover of Vaccination evaluated Rapidly): description of the England and Wales scheme. *Publ Hlth* 1989; **103:** 81–89.
10. Morgan-Capner P, Wright J, Miller CL, Miller E. Surveillance of antibody to measles, mumps, and rubella by age. *BMJ* 1988; **297:** 770–72.
11. Miller CL, Miller E, Rowe K, Bowie C, Judd M, Walker D. Surveillance of symptoms following MMR vaccine in children. *Practitioner* 1989; **233:** 69–73.
12. Forsey T, Mawn JA, Yates PJ, Bentley ML, Minor PD. Differentiation of vaccine and wild mumps viruses using the polymerase chain reaction and dideoxynucleotide sequencing. *J Gen Virol* 1990; **71:** 987–90.
13. Ocklitz HW, Schmitz B. Die mumps-meningitis-ein Mumps-komplikation? *Kinderarztl Prax* 1976; **44:** 145–56.
14. Weirsbitzky S, Bruus R. Safety of vaccines in childhood. *Lancet* 1993; **341:** 379.
15. PL/CMO (92) 11. London: Department of Health, 1992.
16. Ahronheim GA, Allard M, Forsey T, Rydbeck R, Teuwen DE, Yamada A. Mumps associated with the trivalent vaccine containing Urabe Am 9 strain. *Pediatr Res* 1991; **29:** A166.
17. Nokes DJ, Anderson RM. Vaccine safety versus vaccine efficacy in mass immunisation programmes. *Lancet* 1991; **338:** 1309–12.
18. Bottiger M, Christenson B, Romanus V, Taranger J, Strandel A. Swedish experience of two dose vaccination programmes aiming at elimination of measles, mumps and rubella. *BMJ* 1987; **295:** 1264–67.

Recessive inheritance of von Willebrand's disease type I

JEROEN C. J. EIKENBOOM PIETER H. REITSMA
KATHELIJNE M. J. PEERLINCK ERNEST BRIËT

The inheritance of type I von Willebrand's disease is thought to be autosomally dominant. The laboratory profile may, however, vary between affected people, even within a single family. There is also a large variation in the severity of clinical symptoms. To see if there is an association between the von Willebrand factor genotype, the laboratory profile, and the severity of the clinical symptoms we did a genetic analysis of four families with type I von Willebrand's disease.

The proband of each family proved to be a compound heterozygote for defects in the von Willebrand factor gene. Simple heterozygotes in these families were either symptomless or only mildly affected. One of the identified mutations, which was shared by the probands of three of the four families, may have a carrier prevalence of 1:50 in the general population.

These results suggest that the inheritance of von Willebrand's disease is often recessive rather than dominant and so have important implications for diagnosis and genetic counselling.

Lancet 1993; **341**: 982–86.

Introduction

Von Willebrand's disease (vWD) is the most common hereditary bleeding disorder,[1] and results from a qualitative or quantitative defect in the von Willebrand factor (vWF). The vWF is a multimeric plasma protein[2] that is required for normal primary haemostasis since it mediates the adhesion and aggregation of platelets. The vWF is also needed for secondary haemostasis because it is a carrier

ADDRESSES: **Department of Haematology, Haemostasis and Thrombosis Research Centre, University Hospital Leiden, Netherlands** (J. C J Eikenboom, MD, P. H. Reitsma, PhD, E. Briet, MD) **and Centre for Thrombosis and Vascular Research, University of Leuven, Belgium** (K. M. J. Peerlinck, MD). Correspondence to Dr Jeroen C. J. Eikenboom, Department of Haematology, Building 1: C2-R, Haemostasis and Thrombosis Research Centre, University Hospital Leiden, PO Box 9600, 2300 RC Leiden, Netherlands