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Withdrawal of a mumps vaccine

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Sir: We would like to comment on some points in your annotation by Schmitt et al. [5] about the replacement of the Urabe Am-9 mumps vaccine strain in the United Kingdom and to correct some factual inaccuracies it contained.

The licences for the Urabe Am-9 mumps strain containing vaccines were not withdrawn in the United Kingdom. Vaccines containing this strain are not longer purchased in the national measles mumps rubella (MMR) vaccination programme. The decision to change vaccine supply was taken by the Department of Health after considering data from a number of sources including Nottingham [1] and a multicentre confirmatory study coordinated by the Public Health Laboratory Service [4]. The multicentre study showed a meningitis rate of 1:11000, not significantly different from Nottingham, and confirming that the Nottingham cases were not an isolated cluster. It is also consistent with findings from Japan [2, 6].

We agree that criteria for lumbar puncture are important particularly following febrile convulsions. Paediatricians in Nottingham follow the guidelines of the Research Unit of the Royal College of Physicians and the British Paediatric Association [3]. The lumbar puncture rate is similar to that in another teaching centre [4]. All the children in our study were acute medical admissions in whom meningitis was considered a possibility, and the absence of meningism does not exclude this diagnosis. We know that the clinicians did not consider MMR vaccine as a factor in their patients illness prior to performing lumbar puncture, and the temporal relationship with MMR vaccine was only established in retrospect. All the cases identified by national surveillance are being followed up to asses long-term outcome.

It has been suggested that a subclinical CSF lymphocytosis occurs in many children who receive the Urabe strain [7]. If this is so then some children who have lumbar puncture for other reasons in the period after receiving vaccine will be found to have lymphocytic CSF. This possibility is considered in our paper [4] and is under investigation.

Our experience shows that laboratory data co-ordinated with clinical information can reveal adverse events not detected by other surveillance methods. In view of its proven value, this method is being included in the prospective surveillance of the Jeryl Lynn vaccine in the United Kingdom.

National decisions about which MMR vaccine to use must take into account all aspects of vaccine performance, not just meningitis. The releative risk of other adverse events such as idiopathic thrombocytopenic purpura should be assessed as should the relative immunogenicity.

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Reply

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Sir: We are most pleased to read that Drs. Colville et al. now agree that not just laboratory date, but "... laboratory data coordinated with clinical information..." should be used to reveal adverse events. We would like to add that e.g. "fever > 37°C [1] is not a useful clinical parameter on definition of abnormal body temperature.

In a case control study like the one presented [1] it is the obligation of the authors to convince the readers that the results cannot be explained by one or several forms of bias or simply by chance. It is helpful that in their letter printed above, the authors – now – reveal some more details on the study methods used, making bias less likely. Nevertheless, a case control study based on retrospectively collected data is always subject to bias and the results should be interpreted with caution.

At the time we wrote our annotation [3], we had no other information but the data mentioned [1]. It borders cynicism to say that the licence of the vaccine was not withdrawn, but only the purchasing of a vaccine for a national programme. The results of the action taken are the same: in many countries Urabe Am-9 is no longer available.

This – and not the quality of the study by Colville et al. [1] – was our main point: health decisions in one country influence health decisions and thus moribidity in other countries. It would have been fair, if physicians outside the United Kingdom would have been able to review additional available data, to judge their validity and to then make the correct decisions for their individual countries.

We still believe that the action taken was not justified. Even with the data available today [2], for various reasons (including efficacy *and* adverse effects) we would prefer using the Urabe Am-9 strain over the Jeryl Lynn strain. A strain with a somewhat higher rate of side-effects but with a higher rate of vaccine efficacy may still have the advantage of a reduced overall incidence of adverse events (e.g. prevention of meningitis due to the wild virus *and* due to the vaccine-virus). The fact

that the Jeryl Lynn strain may be associated with thrombocytopenic purpura further strengthens our view that the decision made was premature.

In 1993 physicians everywhere should think of ways to avoid tragedies to vaccination programmes wordwilde.

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Methylmalonic acidaemia: haplotype analysis of the methylmalonyl-CoA-mutase gene in Europe

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Abbreviations *MCM* methylmalonyl-CoA-mutase · *MMA* methylmalonic acidaemia

Table 1. Definition of the 4 haplotypes at the human MCM gene and frequencies of the haplotypes found in normal and mutant genes

Haplotype	*Taq*I-fragment	*Hin*dIII-fragment	Frequency in MMA gene ($n = 5$)	Frequency in normal gene ($n = 24$)
1	4.4 kb	1.8 kb	0.00	0.00
2	4.4 kb	4.3 kb	0.40	0.14
3	*x* kb	1.8 kb	0.30	0.40
4	*x* kb	4.3 kb	0.30	0.46

Sir: Methylmalonic acidaemia (MMA) is an autosomal recessive disorder caused by deficiency of methylmalonyl-CoA-mutase (MCM) or by a lack of vitamin B_{12}. The clinical course varies and is often characterized by severe mental retardation. Cloning and sequencing of the complete human MCM cDNA offered the possibility to investigate MMA on the molecular level. Ledley et al. [1–3] described a restriction fragment length polymorphism after DNA-digestion with the endonucleases *Hin*dIII and *Taq*I.

We investigated the MCM gene in 17 European families with at least one affected child and in 59 healthy individuals. In seven families a deficiency of MCM was proven. After digestion with *Hin*dIII we found in the normal and in the mutant chromosome a frequency of 0.6 of the polymorphous 4.3 kb fragment and of 0.4 of the polymorphous 1.8 kb fragment. In contrast, the *Taq*I-digest revealed only one DNA-marker at 4.4 kb; the second band (fragment *x*) was not detectable. The question of homo- or heterozygosity could only be answered because of the intensity of the 4.4 kb fragment. On the normal gene there was a frequency of 0.23 of the polymorphous 4.4 kb fragment. On the MMA gene we found a frequency of 0.28.

Our results from haplotype analysis showed linkage disequilibrium: haplotype 2 had a frequency of 40% on the MMA gene and of 14% on the normal gene. Haplotypes 3 and 4 which showed on the mutant gene a frequency of 60%, constitute 86% of the normal gene. The clinical course in patients with haplotype 2 was more severe than in patients with haplotypes 3 or 4. We conclude that there is a close association between haplotype 2 and a specific mutation on the MCM gene which causes a severe clinical course of the disease.

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