Clinical opinions in general medicine

This issue of *The Journal* brings us a timely overview of the current controversy in the UK surrounding possible links between the triple measles, mumps and rubella (MMR) vaccine and the development of autism and bowel disorders in young children. This is a major public health issue that has resulted in considerable and often heated debate. Stewart and Nelson critically review four of the key papers in this area, providing the reader with a clear exploration of the issues. While obviously of interest to our paediatric Fellows and Members we believe this is of much wider interest, not least to those of us who are parents and grandparents. A further, more detailed, review of the evidence in this area has been commissioned and this paper will be published shortly in *The Journal*.

Hepatocellular carcinoma normally carries a dismal prognosis. College President, Niall Finlayson, summarises a paper, of relevance to all physicians, which suggests that a surveillance programme for high-risk patients may improve survival.

Advances in our knowledge of genetics have raised expectations both within the profession and among the public at large. Genetic screening, particularly for treatable disease, is frequently cited as one such possible benefit. Not necessarily so, as Hayes points out in his review of a recent *Lancet* paper on the subject.

As part of the continuing development of our educational content we are pleased to report that the College has approved two CPD points for each opinion piece published in *The Journal* and we would welcome contributions from our Fellows and Members around the world.

As always any comments should be sent by e-mail to cme_editor@rcpe.ac.uk.

Study 1

TITLE: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children.

KEYWORDS: MMR vaccination, inflammatory bowel disease, autism.

AUTHORS: Wakefield AJ, Murch SH, Anthony A *et al.*

JOURNAL: *Lancet* 1998; **351:**637–41.

SUMMARY:
Twelve children (of whom 11 were boys) who had both a history of developmental regression (nine with autism, two with post-viral encephalitis and one with disintegrative psychosis) and bowel symptoms were assessed. Investigations showed intestinal abnormalities in all 12 (chronic non-specific colitis). No common gut pathogens were identified and anti-endomyseal antibodies were negative. Five children had early adverse reactions to immunisation (rash and fever), and three had convulsions. The onset of behavioural problems was felt to be associated with the MMR vaccine by parents of eight of the children. No focal neurological abnormalities were found clinically, and further investigations (including MRI, LP, EEG, Fragile X DNA testing) were negative. The paper could not identify a definite link between the MMR vaccine and features of inflammatory bowel disease or autism, and suggested further investigations were needed.

Study 2

TITLE: Autism and measles, mumps and rubella vaccine: no epidemiological evidence for a causal association.

KEYWORDS: Autism, MMR vaccine, immunisation rates, epidemiological associations

AUTHORS: Taylor B, Miller E, Farrington CP *et al.*

JOURNAL: *Lancet* 1999; **353:**2026–9.

SUMMARY:
This study looks specifically at MMR vaccination and autism. There were 498 cases of autism in children born since 1979 in the North Thames region, and of these 82% were confirmed by the ICD-10 criteria. The researchers found a steady increase in autism by year of birth, but no sudden increase after the introduction of the MMR vaccine in 1988. There was no difference in the age at diagnosis between MMR vaccinated and unvaccinated children; no difference in the MMR immunisation rates between those children with autism and the general population; and no link between the timing of the MMR vaccination and the onset of autism. Developmental regression was not clustered in the months after vaccination. The analyses do not support the hypothesis that MMR vaccination is causally related to autism.

Study 3

TITLE: Measles, mumps, rubella vaccine: through a glass, darkly.

KEYWORDS: Safety of MMR vaccine, pre-licensing studies, adverse events.

AUTHORS: Wakefield AJ, Montgomery SM.

JOURNAL: *Adverse Drug React Toxicol Rev* 2000; **19(4):**265–83.

SUMMARY:
This paper alleges that early studies of the MMR vaccine indicated a safety problem, and the licensure was premature. It focuses on pre-licensing studies of the MMR vaccine and the documentation of subsequent adverse events. Six pre-licensing studies are quoted (four from the US, one from Japan, one from the UK) prior to licensing of MMR in the UK (1988). They criticise the small patient sample sizes (174 to 10,000) and short follow-up time (max. 28 days) to detect adverse events. The authors argue that gastrointestinal (GI) symptoms reported from these trials were ignored or overlooked, and suggest that GI symptoms are worse with the combined MMR vaccine rather than the single antigen measles vaccine alone. They highlight concerns over the potential for interference between the components of vaccines, particularly in view of the immunosupressive properties of the wild measles virus. In conclusion, they state 'a significant index of suspicion exists for MMR, autism and inflammatory bowel disease, without adequate evidence of safety'.

Study 4

TITLE: Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up.

KEYWORDS: MMR vaccination, serious adverse events.

AUTHORS: Patja A, Davidkin I, Kurki T *et al.*

JOURNAL: *Paediatr Infect Dis J* 2000; **19(12):**1127–34.

SUMMARY:
This is a 14-year prospective study from Finland which has monitored all patients who received the MMR vaccine since its introduction there in 1982, through to 1996. A total of 1·8 million children were given almost three million vaccine doses, and 173 potentially serious adverse reactions (n=77 neurological, n=73 allergic and n=22 miscellaneous) were reported within 80 days of receiving the vaccine. In 45% of these events the authors attributed a causal association other than the MMR vaccine (e.g. intercurrent infection). Febrile seizures were most commonly reported (n=52), and there was one reported death (eight days post vaccine in a 13-month-old boy with gastritis whose autopsy confirmed death from aspiration). Thirty-one children were reported to have developed mild GI symptoms after vaccination (commonly diarrhoea, vomiting, abdominal pain and gingivostomatitis). In the subsequent follow-up of an average of nine years there were no reports of a direct association between the MMR vaccine and autistic spectrum disorder. The background morbidity of chronic disease in this cohort of children is not described in the paper. The incidence of serious adverse events with MMR vaccination was 5·3 per 100,000 vaccines.

OPINION:

These four studies highlight important aspects of both measles infection and MMR vaccination programmes, which have been of recent concern among professionals, parents and the general public.

Measles is not a mild disease, and has not disappeared. Complications include otitis media (one in 20), pneumonia (one in 25), febrile convulsion (one in 200), meningitis/encephalitis (one in 1,000), death from acute infection (one in 2,500–5,000) and late onset subacute sclerosing panencephalitis (SSPE) (one in 8,000).[1] The recent outbreaks of measles in Ireland in 1994/95 and in 2000 after poor vaccine uptake emphasises the necessity of maintaining good herd immunity to provide sufficient levels of protection in the community.[2,3] Vaccination has been shown to prevent measles in over 90% of immunised children following a single dose, and over 99% with a second dose.[4]

Wakefield's very small heterogeneous study in 1998 triggered concerns in relation to a putative association between MMR, Crohn's disease and behavioural problems (Study 1). He later highlighted further valid concerns (Study 3) on the long-term safety of the MMR vaccination. However, the authors have been selective in their reporting and their statistical interpretation has been questioned and rejected (Public Health Laboratory Service (PHLS) and Medicines Control Agency (MCA) reports). Important negative studies (e.g. Study 2) were not discussed. Taylor *et al.* (Study 2) strongly and scientifically refutes a causal association between the MMR vaccine and autism. Other studies have supported this.[5]

A postulated link between Crohn's disease and the MMR vaccine[6] has been scientifically investigated and refuted.[7] However, it does not appear that other forms of chronic GI problems, such as 'non-specific colitis' in association with the vaccine, have been investigated within longer term studies. We would welcome further research in this area.

Current anecdotal evidence suggests that there is an epidemic of autism.[5] The perception that it is increasing is of real concern, but difficult to quantify. There is a global increase in awareness of autistic spectrum disorders,[8] perhaps leading to earlier and increased referral for further assessment. Methods of diagnostic labelling however are diverse, as there is no single standard national diagnostic tool. Some professionals use the DSM-IV or ICD-10 criteria. Others use criteria as broad as the 'triad' of autistic features – namely the impairment of social interaction, social communication and social integration.[9] Irrespective of whether the increase in autistic spectrum disorder is real or perceived the aetiology remains undetermined and needs to be elucidated.

In keeping with organisations such as the Joint Committee on Vaccination and Immunisation (JCVI), the Committee on Safety of Medicines (CSM), the Medical Research Council (MRC), PHLS, MCA and the World Health Organisation (WHO) we strongly endorse the use of the MMR vaccine on the grounds of its convincing record of safety and efficacy. However, as with wild measles virus and the longer term sequelae of SSPE, the possible long-term morbidity of the MMR vaccination programme is not yet clear, and safety studies need to address this. Papers such as Study 4 have attempted to examine longer term complications, but still only comprehensively address the time period 80 days post-vaccination. It is important to cross reference all reported adverse events with background childhood morbidity, and surveillance studies should incorporate a longer term monitoring facility reporting possible adverse and chronic complications, even occurring many years afterwards.

In the UK, every child currently receives 17 doses of vaccine before the age of six months, even before the MMR vaccination is given. The infant immune system is constantly triggered from eight weeks of age. Parents must be vigilant and professionals must not become complacent in their ongoing reporting of all adverse effects of all vaccines administered.

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TITLE: Surveillance programme of cirrhotic patients for the early diagnosis and treatment of hepatocellular carcinoma: a cost-effectiveness analysis.

KEYWORDS: Hepatocellular carcinoma, cirrhosis, prophylaxis.

AUTHORS: Bolondi L, Sofia S, Siringo S *et al.*

JOURNAL: *Gut* 2001; **48:**251–9.

SUMMARY:

Three hundred and thirteen Italian patients with liver cirrhosis were followed six-monthly by ultrasonography and plasma α-fetoprotein over a mean of 56 months. Sixty-one patients (19·5%) developed hepatocellular carcinoma (4·1% annually), 42 (68·9%) could be treated by transplantation, resection or local therapy, the median survival of screened patients (30 months) was significantly lower (p=0·02) than unscreened patients (15 months) and the cost per treatable screened patient was US $17,934.

OPINION:

Patients presenting with hepatocellular carcinoma have a very poor prognosis as their tumours have usually progressed to a stage at which they are no longer amenable to resection or transplantation. Most patients, however, have underlying hepatic cirrhosis, raising the possibility that surveillance could lead to early diagnosis and better treatment. Ultrasonography and plasma α-fetoprotein measurement are the most widely available means for surveillance and this study shows that about two-thirds of tumours – detected by repeating these investigations six-monthly – can be treated. There is a statistically significant survival improvement for these patients, though the improvement is limited and the cost of a surveillance programme high. However, physicians should consider this surveillance scheme for individual cirrhotic patients who would be suitable for resection or more likely liver transplantation (single tumour ≤5 cm diameter or ≤3 nodules each ≤3 cm diameter).

Dr Niall Finlayson, Consultant Gastroenterologist, Edinburgh

TITLE: Penetrance of 845G→A (C282Y) HFE hereditary haemochromatosis mutation in the USA.

KEYWORDS: Genotype, phenotype, haemochromatosis.

AUTHORS: Beutler E, Felitti VJ, Koziol JA *et al.*

JOURNAL: *Lancet* 2002; **359:**211–18.

SUMMARY:

The prevalence of homozygotes for the main genetic mutation in haemochromatosis is 0·5%. How many of these patients develop phenotypic changes of haemochromatosis is unknown. In this study 41,038 individuals attending a health appraisal clinic were screened for homozygosity for the haemochromatosis mutation. Of the 152 homozygotes identified only one had signs and symptoms that would suggest a diagnosis of haemochromatosis. The authors conclude that if 1% of homozygotes develop frank clinical haemochromatosis this calls into question the potential of screening for this disorder.

OPINION:

The huge potential of modern genetics is greatly emphasised, particularly in academic circles, and it is the human genome that is increasingly analysed and frequently results in science fiction-type scenarios where the illnesses patients are likely to develop are predicted years before their development. Screening is clearly a cornerstone. For this approach to screening to be effective the prevalence, effectiveness of treatment and penetrance of the disorder should be known. Haemochromatosis would certainly appear to be a classical condition for screening since it is common (homozygosity of the gene mutation is one

in 200), the disorder can be effectively treated by venesection and penetrance has supposedly been high. This paper raises major questions, not only about haemochromatosis, but about genetic screening in general. Although the individuals identified to be homozygotes do not undergo a liver biopsy, the authors persuasively suggest that they are not missing a large group of patients with the clinical disease and were able to identify only one of the 152 homozygotes who they believe had clinical haemochromatosis. Such low penetrance of phenotype could be a major handicap in screening for this condition and clearly emphasises the problem in our appreciation of the cause and effect, even for what at first sight would seem to be a fairly straightforward single gene disease. The main lesson of this study is that any genetic analysis of disease must be accompanied by a rigorous determination of the penetrance phenotype in large unselected control populations.

Professor Peter Hayes, Consultant Gastroenterologist, Edinburgh

REFERENCES

1 *Measles Mumps Rubella Vaccine*. London: HEA; 1997.
2 Payne D. Ireland's measles outbreak kills two. *BMJ* 2000; **321:**197.
3 McBrien J *et al.* Outbreak of measles: 2000. *Arch Dis Child* 2001; **84(suppl I):**A1–A10 (abstract).
4 CDR review 1994.
5 Kaye J, Adel Mar Melero-Montes M, Jick H. Mumps, measles and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ* 2001; **322:**460–3.
6 Wakefield AJ, Pittilo RM, Sim R *et al*. Evidence of Persistent Measles Virus Infection in Crohn's disease. *J Med Virol* 1993; **39:**345–53.
7 Chadwick N, Bruce IJ, Schepelmann S *et al*. Measles virus RNA is not detected in inflammatory bowel disease using hybrid capture and reverse transcription followed by the polymerase chain reaction. *J Med Virol* 1998; **55:**305–11.
8 Fombonne E. Is there an epidemic of Autism? *Paediatrics*. 2001; **107:**411–12.
9 Cumine V, Leach J, Stevenson G *et al*. *Asperger Syndrome: A practical guide for teachers*. London: Fulton; 1998.