LETTERS

Response to the article by Baird et al.

The report by Baird et al., published in this issue of *Archives of Disease in Childhood* was examined and the following conclusions have been drawn from the evidence presented.

1. The choice of participants in the study appears to have been chosen on the basis of established diagnostic criteria. However, and more importantly, the authors have not examined the aetiology of the children’s autism spectrum disorder (ASD). Furthermore, given that all MMR vaccine manufacturers advise in their fact sheets that in rare cases encephalitic fevers may result from administration of the vaccine, none of the children were identified as having had an adverse reaction to the vaccine.

2. There is a growing body of evidence to suggest that ASD may be the result of genetic mutations occurring in utero, triggered by ingested exogenous agents which cross the placenta to insult the developing fetus. The resultant damage to the central nervous system of the fetus in the first trimester of pregnancy inevitably results in a miscarriage or, at around 7–8 months’ gestation, in premature delivery. Damage to the central nervous system of a fetus gives rise to traumatic birth procedures and in many cases the need for assisted birth or caesarean section delivery. The resulting unnatural birth further exacerbates an already damaged central nervous system.

3. The study is clearly compromised when comparisons are made with the work undertaken by Dr Wakefield and the Royal Free Hospital team. The conclusions drawn are misleading given the limited investigation of blood samples many years after the initiating events. Likewise, to undertake a study to test a hypothesis that measles vaccination was or was not involved in the pathogenesis of ASD is invalid if the study cohort of ASD individuals only contains children already neurologically dysfunctional at birth, immediately after birth or before vaccination.

4. While the study is valid, the report’s conclusions have been presented by the authors to show “no association between measles vaccination and ASD”. This, of course, will be sold by many health professionals as being further proof of the safety of the MMR vaccine. However, others will construe it as an attempt by the Department of Health to sway public opinion on the “benefits” of MMR vaccination without accepting any downsides.

5. The final point is that all children in the study group (ASD with special educational needs (SEN), ASD but no SEN, and no ASD but SEN) can be considered neurologically dysfunctional as a consequence of brain injury resulting from similar aetiology.

R Burn
Correspondence to: Robin Burn, The Autism Centre, 26 Gwiscwm Park, Bury Port, Llanelli, Carmarthenshire SA16 0DX, UK; robin.burn@theautismcentre.co.uk

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What does this study test, and why?

Of the original 1770 children with special educational needs (SEN) in the study by Baird et al., 255 had autistic spectrum disorder (ASD). Of the 1770, a total of 735 dropped out and then a further 780 were excluded for reasons which are not transparent. This left 255 children (not the 255 with ASD): some had ASD and some just SEN, but we do not know in what proportion. Then, exactly 100 were excluded because of inadequate blood tests. Of the remaining children, 101 had ASD (less than 40% of the original 255 children with autism). None is reported to have bowel disease (the subgroup of Wakefield’s study) or an adverse reaction to MMR.

It is not clear what the scientific purpose of this study is. The study states: “We did not obtain gut mucusal samples for ethical reasons”. It would, of course, be unethical to obtain gut biopsies from patients without gut symptoms, and since none of the patients in the study had gut symptoms there would be no grounds for subjecting them to such invasive treatment. This, of course, makes this a distinct group from the children referred to Andrew Wakefield and his colleagues at the Department of Paediatric Gastroenterology of the Royal Free Hospital in the 1990s and slightly later.

In this regard it is worth noting the recent warning of the National Autistic Society (NAS):

> The National Autistic Society is keenly aware of the concerns of parents surrounding suggested links between autism and the MMR vaccine. The charity is concerned that the GMC hearing, and surrounding media coverage, will create further confusion and make it even more difficult for parents to access appropriate medical advice for their children.

Getting it wrong

In a case-control study of 10–12-year-old children with either autism, special educational needs or normal development, Baird et al. examined measles antibody responses (plaque reduction neutralisation assay) and the presence of measles virus in peripheral cases their concerns have been dismissed as hysteria following previous publicity around the MMR vaccine. It is crucial that health professionals listen to parents’ concerns and respect their views as the experts on their individual children.

There is an urgent need for further, authoritative research into the causes of autism, to improve our understanding of the condition, to respond to parents’ concerns and to enable us to ensure that there are appropriate services and support in place to meet people’s needs.

J Stone
Correspondence to: John Stone, parent of a son with autism; johnstanstone@gmail.com

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blood mononuclear cells (reverse transcriptase polymerase chain reaction). The study apparently sought to identify autistic children relevant to the original MMR/autism hypothesis, that is, those with both regression and significant gastrointestinal symptoms. The study is severely limited by case definition in the context of the crucial “possible enterocolitis” group. For inclusion in this group the child had to have two or more of the following five current gastrointestinal symptoms (plus past persistent diarrhoea of >14 days’ duration excluding current constipation):

- current persistent diarrhoea (defined as watery/loose stools three or more times per day >14 days),
- current persistent vomiting (occurring at least once per day, or more than five times per week),
- current weight loss,
- current persistent abdominal pain (three or more episodes (frequency not specified by the authors) severe enough to interfere with activity),
- current blood in stool.

Over the last 10 years we have evaluated several thousand children on the autistic spectrum who have significant gastrointestinal symptoms. Upper and lower endoscopy and surgical histology have identified mucosal inflammation in more than 80% of these children. Very few of these children with biopsy-proven enterocolitis would fit the criteria set out above. Firstly, these children rarely have vomiting, current weight loss (as opposed to failure to gain weight in an age-appropriate manner) or passage of blood per rectum. The requirement is thus narrowed to a child having two of two relevant symptoms – current persistent diarrhoea and current persistent abdominal pain according to their criteria, plus a past history of persistent diarrhoea excluding current constipation.

The requirement for the current presence of these symptoms, for 14 or more days continuously, shows a singular lack of understanding of the episodic, fluctuating and alternating (eg, diarrhoea/constipation) symptom profile experienced by these children. In our experience, autism spectrum disorder children with histologically proven enterocolitis typically have one to two unformed stools per day that are very malodorous and usually contain a variety of undigested foodstuffs. This pattern alternates with that of constipation, in which the unformed stool is passed after many days of no bowel movements at all, and with excessive straining. This group is entirely overlooked by the arbitrary criteria set forth in this paper. With respect to diarrhoea and constipation, a detailed discussion of stool pattern in these children is available, which further highlights the shortcomings of the above criteria. Moreover, the interpretation of pain as a symptom in non-verbal children, as it often manifests as self-injury, aggressive outbursts, sleep disturbances and abnormal posturing, is notoriously difficult. Recognition of the presence of pain requires an insight based upon the correlation of symptoms, histological findings and response of symptoms to anti-inflammatory treatment. There is no evidence in the Baird et al paper that these crucial factors were taken into account. This study’s inappropriate symptom criteria would explain the discordance with other reports that have revealed a high prevalence of significant gastrointestinal symptoms in general autism populations.1,4

It is surprising that Dr Peter Sullivan, a co-author of the paper who presumably provided the above gastrointestinal criteria, was not aware of the aforementioned limitations. In his role as a defendant’s expert in the UK MMR litigation, he would have had access to the clinical records of autistic children with the relevant intestinal symptoms and biopsy-proven intestinal inflammation.

We suggest that the authors might wish to reflect on the ethical implications of setting the bar too high for the investigation of such children by ileo-colonoscopy, with the attendant risk of missing symptomatic, treatable inflammation.

Since the relevant MMR/autism children are considered to be those with regression and significant gastrointestinal symptoms, the appropriate stratification for between-group analyses of measles virus antibody levels has not been conducted and therefore the paper is difficult to interpret, adding little if anything to the issue of causation. Moreover, it is a major error to have presumed that peripheral blood mononuclear cells are a valid proxy for gut mucosal lymphoid tissues when searching for persistent viral genetic material.

A further major problem in this study is the number of children who dropped out or who were unable to provide adequate blood samples. We know nothing about the 735 children who were lost at stage two or the 100 children for whom blood samples were not available. At the very least, we should be told whether the children who dropped out were likely to be representative of those who stayed in as regards the key issues of interest.

For reasons that will emerge in the near future, it would be of interest to know whether siblings of autistic children were included in either of the two control groups. This information is not provided.

As a general observation, this paper contributes nothing to the issue of causation, one way or another. Case definition alone is likely to have obscured the relevant group of autistic children. The study tells us nothing about what actually happened to the children at the time of exposure. We are of the growing opinion that measuring blood components many years down the line tells us very little about events in what is, in effect, a static (non-progressive) encephalopathy unlike, for example, subacute sclerosing panencephalitis, which is a progressive measles encephalopathy. The gut is a different matter, and analysis of mucosal tissues has been very informative in the relevant children, demonstrating active ongoing, possibly progressive,1 inflammation.

A J Wakefield, C Stott, A Krigsman
Thoughtful House Center for Children, Austin, TX, USA.
Correspondence to: Andrew J Wakefield, Thoughtful House Center for Children, 3001 Bee Caves Road, Austin, TX 78746, USA; andy.wi@thoughtfulhouse.org

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Letters by Burn, Stone and Wakefield: author’s response

In our paper we specifically explored the hypothesis linking autism spectrum disorder (ASD) to MMR vaccination. Our cohort is approximately 9 years from their MMR vaccination but our findings are identical to those of D’Souza et al whose subjects were 26–30 months from vaccination.

Singh’s paper on measles antibody levels in autism compared with controls reports on a wide age range of children.5

Two correspondents refer to 735 “lost” children. This is a misunderstanding. As described in Baird et al,1 the original study design intended that only a subsample of those screened would be assessed in depth and these were selected at random within strata formed by Social Communication Questionnaire (SCQ) screen score and local ASD diagnosis. It would certainly have been better if all the children with special educational needs (SEN) and ASD had been able to give satisfactory blood samples, but this was a study with informed consent. It will not surprise experienced clinicians that many of the young people refused and some samples were found unsuitable after transit. Further analysis indicated that while those for whom we had satisfactory samples had an average IQ seven points higher than those who did not, differences on the ADI-R and