

of antigen formulation, should be considered in post-exposure vaccination, always in association with HAART.

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#### Authors' reply

Sir—Christian Fiala and Gordon Stewart comment on the design of our recent trial of rgp160. As we clearly stated, this trial was initiated before HAART was available and did not evaluate this combination. Very few individuals dropped out from the clinical follow-up. Clinical data were missing for only three individuals out of 835 at the end of the trial. It is true that no attempt was made to account for continued risk behaviour. If these behaviours indeed accelerate disease progression they should be equally distributed between the arms in a placebo controlled trial of this size.

We point out that the trial was not commercially sponsored. MicroGeneSys donated vaccine and placebo and contributed the equivalent of about US\$20 000 to support on-site monitoring, but the main burden of the trial was carried by The Swedish Institute of Infectious Disease Control, the participating clinics, and academic grants. The conduct of the trial was determined by the researchers without company involvement.

That therapeutic immunisation with HIV-derived immunogens alone are not sufficient to alter the clinical progression in the absence of

antiretroviral therapy is well known. However, these interventions are known to be safe. In this we completely agree with Oscar Pontesilli and Fernando Aiuti. Clearly, at least zidovudine treatment does not reduce the development of immune responses during HIV therapy. Their observation that the combination of the 2-week interventions, zidovudine and rpg160 immunisations, did not alter the clinical course, does not invalidate the idea of active immunisation during HAART.<sup>1</sup>

We agree that our study did not attempt to show an effect on viral load or the contribution of adjunctive antiretroviral treatment. In samples from a pilot trial we analysed the effect on viral load over 6 months of continued immunisations and within 2 weeks of an immunisation with signs of neither long-term decline of plasma HIV RNA nor an immediate activation of HIV.<sup>2</sup> At the time of the initiation of the trial there was no clinical ground for systematic antiretroviral treatment of patients with the characteristics suitable for the trial; consequently, only retrospective data on the use of antiretroviral treatment could be obtained. These data do not allow an analysis of the effect of the combination of antiretrovirals and rgp160 immunisation.

We also agree that current thinking mandates that therapeutic immunisation should only be contemplated in the presence of effective HAART—in our view to undetectable viral concentrations (<50 copies/mL) for more than 3 months and CD4-cell counts above 400/ $\mu$ L—and that a combination of immunogens should be included, including Tat. Alternative immunisation technologies should also be explored—for example, DNA or other vectors. We have recently initiated such a trial, but foresee that a combination of immunisation schedules will be required to ensure that both arms of the immune system are duly addressed.

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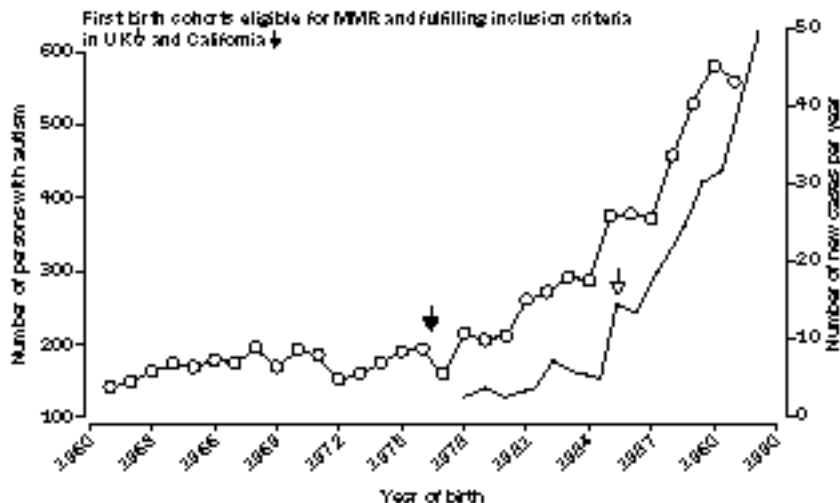
## MMR vaccination and autism

Sir—Hypothesis testing and presentation of the outcome—either positive or negative—is a fundamental part of the scientific process. Accordingly we have published studies that both do,<sup>1</sup> and do not<sup>2</sup> support a role for measles virus in chronic intestinal inflammation: this is called integrity. The latest of these studies was strongly positive,<sup>3</sup> and was accepted by the MRC Review in February, 1998. By contrast, Brent Taylor and colleagues (June 12, p 2026)<sup>4</sup> have ignored the rules. They are inappropriately didactic in their conclusions, despite the weakness of their method and the contradictions in their data. A case-series analysis is unlikely to identify a relation between exposure and disease, in which the onset is insidious and in which, very often, there is diagnostic delay.

Taylor et al tested the hypothesis that there should be no temporal clustering of first parenteral concerns with measles, mumps, and rubella (MMR) vaccination. They identified a statistically significant excess risk by 6 months after MMR, which they dismiss, post hoc, as indicating parental recall bias. Had this been the case it should have been seen in both of their vaccine groups—those receiving MMR and those receiving any measles-containing vaccine. The excess risk was seen only in the MMR group; this is a fundamental flaw.

However, it pales into insignificance compared with their failure to declare the fact of an MMR catch-up campaign that was initiated in 1988 with the introduction of this vaccine. This campaign was targeted at children, whatever their age, who presumably had not received either monovalent mumps or rubella vaccine whatever their exposure status. As such it was a novel and, in terms of safety, untested policy. On the basis of Taylor and colleagues' inclusion criteria, and taking account of the catch-up campaign, then those first birth cohorts who actually received MMR (circa 1986) were precisely those in whom a doubling of the numbers of cases of autism were seen. Thereafter these numbers continue to increase strikingly. Omission of this essential fact—the catch-up campaign—requires explanation lest it be misconstrued.

Can the dramatic increase in autism be ascribed to change in diagnostic practice? Data from the recent California report from the Office of Developmental Services belie this contention. The figure juxtaposes the data from California with those from



Temporal trends for autism in the USA (California\*) and the UK (north-west London)

In 1998 the expected numbers of newly diagnosed autistic children in California should have been 105–263 cases, according to DSM-IV; the actual figure was 1685 new cases. The temporal trend in north-west London is almost identical, although the rise is delayed by about 10 years. The two countries use the same diagnostic criteria. The sequential trends are consistent with the timing of introduction of MMR to both regions.

\*Data from Department of Developmental Services, Sacramento, 1987–98 ([www.dds.ca.gov](http://www.dds.ca.gov)).

north-west London. Identical temporal trends are shown, with the rise in autism from a steady baseline value, coinciding with the introduction of MMR vaccine as the single strategy in both countries that use the same diagnostic criteria for autism.

These data expose the danger of not only setting out to prove, rather than to test, hypotheses but also presenting the data whether they are supportive or not. The full story has yet to unfold. In a timely *BMJ* newspeice,<sup>5</sup> Begg who is described as a leading virologist, calls for MMR research to be terminated on the basis of Taylor and co-workers' report and a non-peer-reviewed so-called analysis in *Current Problems of Pharmacovigilance*. Clearly there are some things that may end-up being terminated as a consequence of these events: research into the possible link between MMR, autism, and bowel disease is not one of them.

Andrew J Wakefield

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#### Authors' reply

Sir—Andrew Wakefield criticises our study on three counts. We restrict our response to the scientific aspects of his letter. He states that the case-series methodology lacks power for detecting temporal associations between vaccination and conditions of insidious onset or subject to diagnostic delay. The method is well suited to test the hypothesis that he generated and which was the basis of our study. Wakefield et al<sup>1</sup> reported autistic spectrum disorders occurring in close temporal association with MMR, the interval from vaccine to onset of behavioural problems ranging from a few hours to a few weeks, and suggested that this association might be causal. Case series analysis methods are very appropriate to investigate such relations. We assessed several endpoints with a range of risk periods. For the analysis of autism diagnosis we allowed for possible delays in diagnosis by extending the risk period to 1 and 2 years after vaccine, similar non-significant results were obtained when the risk period was extended still further. The power of the method in all these analyses is shown by the narrowness of the 95% CIs, the highest upper limit being 2.56.

Wakefield then takes us to task for describing as an artifact a single marginally significant raised incidence of first parental concern 0–5 months after MMR, out of a total 14 statistical tests in this section of the analysis. One might have expected one such

significant result by chance. However, as we discussed at length in our report, this association was restricted to first parental concern occurring exactly 5 months after MMR. Such a fixed interval is not biologically plausible. We concluded that the observed association was induced by the combined effect of approximate recording of parental concern at 18 months of age and a peak in MMR vaccinations at 13 months of age. Wakefield regards this interpretation as “fundamentally flawed” because the association disappears when other measles-containing vaccines are included in the analysis. We disagree: the reason for the difference is that measles-containing vaccines other than MMR were given over a much broader age range.

Finally, Wakefield reprimands us for misinterpreting our graph of autism prevalence by birth cohort by “concealing” the fact that children born earlier than 1987 might have been vaccinated in the MMR catch-up programme. We are indeed aware of the catch-up programme. However, it is not relevant: we reviewed the details of all 36 children in our dataset born before 1987 who received MMR; 29 of these had age at first parental concern recorded; in all instances this was before MMR was given. We chose the 1987 breakpoint because this corresponds to the first birth cohort exposed to MMR in the second year of life. This cohort is therefore the first one in whom a substantial proportion would have been exposed to MMR before the median age at first parental concern (19 months). In reality, little can be learned about causal relations by looking in isolation at time series such as those Wakefield presents. However, as we showed in our report, the hypothesis that the rise in autism in successive birth cohorts is due to MMR is incompatible with the fact that MMR coverage was constant in these cohorts.

In short, Wakefield's critique of our work rests on a selective and inaccurate interpretation of our data and results. We stand by our findings: the epidemiological evidence from this large study does not support a causal association between MMR and autism.

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