Rejoinder to Eigenmann PA, Haenggeli CA, Food colourings and preservatives—allergy and hyperactivity (Lancet 2004;364:823–4) and an erratum

Eigemann and Haenggeli have commented on a paper we recently published examining the effects of artificial food colourings and hyperactivity in children.1–4 This commentary gives a seriously misleading account of the findings of the study. Eigemann and Haenggeli claim that ‘‘the hyperactivity that seems to be used synonymously to ADHD’’. We deliberately did not use the term ADHD as a criterion for recruitment into the study. This is a diagnostic term requiring a set of explicit criteria to be met and is of doubtful value when applied to 3 year olds. The definition of hyperactivity we used for this study was one based on the risk of subsequent behaviour difficulties in middle childhood which we had established previously in a longitudinal study of an epidemiologically ascertained sample of 3 years olds.1–4

The study used screens for atopy (AT) and for hyperactivity (HA) applied to a total population through schools to identify cases. The following design: ‘‘Children were entered into the four group randomised, placebo controlled, double blind crossover challenge study. The four groups were in a 2×2 between group design with the following groups: HA/AT, non-HA/AT, HA/non-AT, and non-HA/non-AT.’’5 Eigemann and Haenggeli observe that ‘‘…families interested in hyperactivity seem to be over-represented’’ and on this basis conclude that ‘‘…results from this study should not lead to recommendations for the general population’’. The presence of hyperactivity was one of the inclusion criteria of the food challenge phase of the study and consequently occurs in about half of the cases. A substantial proportion of children were included in the food challenge phase by design. Full details of participant flow were given in a diagram (fig 1 in our paper) as recommended in the CONSORT statement for reporting randomised trials.5

The separate issue of sample attrition through the stages of the study was considered carefully and we concluded that the findings from the group completing the food challenge phase would indeed hold for the general population.

The study found significantly greater increases in hyperactive behaviour reported by parents when the children were given the active compared to the placebo challenge. The statement by Eigenmann and Haenggeli that ‘‘parents’ observations can be easily explained by their expectations’’ is puzzling. The parents, children, and the person collecting the behaviour ratings were blind as to the food challenge being taken by the child over these periods. Consequently, ‘‘expectations’’ cannot account for the effects we identified based on changes during the active and placebo periods. This does not hold for the reduction in hyperactivity we observed during the withdrawal phase which, as we discussed in the paper, was not blinded and was greater than that for the placebo versus active periods. This would be expected if the withdrawal effect alone was influenced by parental expectations.

The final part of the Eigemann and Haenggeli commentary is concerned with the use of diet changes as treatments for hyperactivity. Our study showed that the effects of food colourings and the benzoate preservative were not restricted to or more strongly present for children with atopy or hyperactivity. Consequently our conclusions did not relate to the treatment of children with hyperactivity but rather to the preventive public health issue of whether food additives are having a general detrimental effect on children’s behaviour. The final conclusion from the paper was ‘‘...if additives have an effect at all, it is via a pharmacological effect which is best exemplified by the non- IGE dependent histamine release. We believe that this suggests that benefit would accru for all children if artificial food colours and benzoate preservatives were removed from their diet. These findings are sufficiently strong to warrant attempts at replication in other general population samples and to examine whether similar benefits of the removal of artificial colourings and sodium benzoate from the diet could be in identified community samples at older ages.’’ We are now conducting just such a replication.

Erratum

While preparing this rejoinder, we have discovered an error in the reporting of the composition of the above mix in the paper. The sentence reads:

“The active drink included 20 mg in total of artificial food colourings (sunset yellow, tartrazine, carminosine, and ponceau 4R; 5 mg of each) [Forrester Wood, Oldham, UK] and 45 mg of sodium benzoate [J Loveridge, Southampt., UK].”

should have read:

“The active drink included 20 mg in total of artificial food colourings [sunset yellow, tartrazine, carminosine, and ponceau 4R; 5 mg of each] [Forrester Wood, Oldham, UK] and 45 mg of sodium benzoate [J Loveridge, Southampton, UK].”

References


Developmental delay versus developmental impairment

The use of the term delay should be replaced by impairment because of parental perception of the meaning of delay as applied to development. I would like to draw attention to my experience of parents’ perception of the language we use in describing children and their ability.

It is common practice to refer to children who are detected to be significantly behind in achieving developmental milestones to be developmentally delayed. In talking to prospective adoptive parents I have become aware of how misleading this phrase is in describing to prospective adopters what we mean.

The general population has a perception of delay to mean something that will get there in the end, rather like a train being delayed, but reaching its destination eventually. It has taught me to use the term impairment rather than delay so that I do transmit to prospective adopters the true meaning of what I am trying to describe.

I wonder if as a profession we would consider examining our use of this term delay and possibly re-educating our profession to use the term impairment because it does not suggest that the child will be normal eventually.

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Palivizumab prophylaxis in haemodynamically significant congenital heart disease

Patients with congenital heart disease (CHD) have been reported by many authors to have high rates of hospitalisation, morbidity, and mortality associated with respiratory syncytial virus (RSV) lower respiratory tract illness.1–4 However, in a recent paper in Archives of Disease in Childhood, Duppenthaler et al reported a substantially lower incidence of
RSV hospitalisation in patients with “haemodynamically significant” CHD.

They suggest that the rate of hospitalisation in their population of patients from the Canton of Bern, Switzerland was as much as four times lower than rates previously reported in the United States. Based on these results they concluded that the unrestricted use of palivizumab to prevent RSV hospitalisation would not be cost-effective in their study.

There are several possible methodological reasons for the disparity in RSV hospitalisation rates in the calculations of both the numerator and denominator. With respect to the former, traditional Duppenthaler’s methods would miss all of the nosocomial RSV disease. Furthermore, ascertaining the true incidence of RSV hospitalisation would require that all CHD patients admitted to the hospital undergo RSV screening, as was done in the international multicentre trial, not just those with symptoms judged typical of RSV.

Finally, in a previous paper by the same authors in the first four years of the study (1997/98–2000/01), 12 of 497 patients studied aged <5 years were identified with CHD compared to 6 of 449 aged <2 years in this study. This previous study encompassed children under the age of 5, the difference of six patients between the first study and this one would imply that children who were hospitalised were between the ages of 2 and 5 (making a strong case for palivizumab prophylaxis in that age group), or they were deemed to have haemodynamically insignificant heart disease (making a case for prophylaxis in this group or questioning the definition of haemodynamically significant heart disease). With respect to the denominator, the author used the International Classification of Diseases (ICD) coding as a screen for patients with haemodynamically significant CHD. However, the ICD system does not allow for severity adjustment and therefore does not distinguish between haemodynamically significant and insignificant disease. In our recent multicentre trial, we defined haemodynamically significant CHD as patients with cyanotic CHD, single ventricle physiology, or those with acyanotic CHD that required hospitalisation. This would account for only about 35–40% of all the CHD patients. This would have significantly reduced the number of patients in the denominator, increasing RSV hospitalisation incidence. Secondly, no attempt was made to verify the accuracy of screening utilizing the ICD system, which might have resulted in an underestimation of the relative risk in a lower direct comparison. Our recent group would be the low risk group as was done by Boyce and colleagues.

We would agree with the authors that unrestricted use of palivizumab in CHD patients is not warranted. The intervention was never to use the drug indiscriminately in CHD patients as evidenced in the cardiac trial that restricted its use in truly haemodynamically significant young CHD patients. We disagree with the use of an NNT analysis to justify this statement. An NNT analysis only factors in the cost from a single RSV hospitalisation. But the CHD infant with RSV is likely to incur additional morbidity and mortality related to future hospitalisations and/or treatment, especially when it comes to surgical correction, and thus raises the cost of care. Second, NNT analysis takes only a payer’s perspective and ignores the societal component of pharmacoeconomics. As healthcare providers, it is our responsibility to use costly drugs in a responsible manner, while also ensuring that these patients receive the treatment/prevention from which they would clearly benefit.

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References

Authors’ reply

We greatly appreciate the interest of Feltes and Simoes in our study, but we are somewhat surprised by the intensity of their allegations. The large number of unrelated flaws they claim to find in the methods we used suggests that Feltes and Simoes have a fundamentally different view of what the data should be interpreted. In our opinion, their critique is mostly unjustified and requires a firm rebuttal.

It is true that nosocomial infections were not included in our study. We did not claim otherwise. However, adding for instance a 14% rate of nosocomial RSV infections as reported for the placebo arm in their study (9 of 63 cases), would not translate into a major change in the calculated RSV hospitalisation incidence.

It is also correct that RSV tests were not conducted in CHD patients admitted for reasons other than respiratory tract disease, but the CHD infant with RSV is likely to incur additional morbidity and mortality related to future hospitalisations and/or treatment, especially when it comes to surgical correction, and thus raises the cost of care. Secondly, no attempt was made to verify the accuracy of screening utilizing the ICD system, which might have resulted in a more complete case catchment, but may not reflect real life a well known limitation of RCT. It would have been more appropriate to compare our study with the Tennessee Medicaid Study by Boyce and colleagues, which we used as the comparator study. In this study, however, only 6% of cases were specifically coded as RSV infection; 94% were coded as "bronchiolitis". Thus, it appears obvious that our case catchment was not inappropriately insensitive. It is also worth mentioning here that our method of diagnosing RSV had undergone in-house validation. In our previous study, we did not focus on CHD cases. During the entire six year period described in the present study, there were 21 hospitalisations among CHD patients <24 months of age, 11 of which were considered by the cardiologist as haemodynamically insignificant CHD cases. During the entire six year of the study period covered also by our previous study, there were 12 hospitalisations among CHD cases <24 months of age, all haemodynamically significant. During the first four years of the study period, the registry was available, so we only considered three cases in children >24 months of age, which we used as the comparator study. During the subsequent two years, there were 12 cases. Of these, nine cases occurred in children <24 months of age and were haemodynamically significant in four.

We did not—as Feltes and Simoes apparently assume—use ICD codes for case catchment. As stated in the method section, the ICD-10 codes Q20–Q26 describe CHD patients included in the database. The large groups of haemodynamically insignificant VSD, ASD, and PDA are not included. All cases included in the registry were “CHD requiring medical therapy”. It follows that the definition of haemodynamically significant CHD used in our study to create the denominator is quite similar to the definition used by them. Their claim that the true denominator of CHD in our population was only about 35% is therefore based on an ICD code that was never used in our study. Again, our main comparator study used a less stringent definition of CHD (ICD-9 codes 743–747) which did not address the issue of haemodynamically significant, and was thus more likely to report estimates of low precision.
Feltes and Simoes also claim that we got it wrong with the “child-years” and thus overestimated that denominator by a factor 2. Objection! We agree that RSV exposure only occurs in approximately half of the child-years, and that total child-years should be divided by factor 2 for calculation of incidence per child-year of RSV season. However, we compared our incidence rates with those of Boyce and colleagues,1 which were already corrected for this discrepancy (that is, our data in table 3 were compared to the column entitled “Hospitalisations per 1000 child-years in table 1 of Boyce’s paper, p. 867,” which were multiplied by factor 2). Had we truly committed the mistake claimed by Feltes and Simoes, we would have compared our data with the preceding column in the said table, which is entitled “Incidence” (meaning: hospitalisations per 1000 child-years of RSV season).

Reduction of our denominator by factor 2 was indeed necessary, when children <6 months of age only were investigated. This, however, we did for calculation of the figures in table 3 and we explicitly stated that we did so in the text on page 963. Thus, this allegation again is incorrect in our opinion.

It is true that we used the entire population of non-CHD patients as referent, because we did not have data of sufficient quality for analysis of other individual risk factors. This was clearly stated in the manuscript. However, to claim that such a comparison is “unfair” is difficult to understand, because (1) for comparison we used Boyce’s raw data2 to calculate non-CHD rates in their population, and (2) in Switzerland, palivizumab has been recommended for children with severe BPD only.

Thus, we believe that it does make sense to compare CHD patients to all others who do not receive palivizumab. The very small group of children with severe BPD makes no substantial difference here.

We agree with Feltes and Simoes that NNT should not play a major role when it comes to providing optimal care for children with CHD. The reason why the new 2004 Swiss recommendations for the administration of palivizumab include children <1 year of age with surgically uncorrected, haemodynamically significant CHD and cyanotic CHD or severe hypertension or cardiac failure2, as soon as the distributor of palivizumab successfully applies for mandatory coverage by the health insurance companies. If, however, resources are limited, and they increasingly are in many European countries, cost-effectiveness analyses including NNT do play a role when authorities have to weigh different new interventions against each other.

In summary, we believe that Feltes and Simoes create a largely incorrect worst case scenario of what could have gone wrong with our study. As elaborated above, we believe that our data are correct and—with the limitations described in the paper—reflect the current epidemiology in the study area.

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References
1 Duppenthaler A, Ammann RA, Gorgievski-Hrisoho M, et al. Low incidence of respiratory syncytial virus hospitalizations in

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If the RCPCH is serious about campaigning for a greater number of junior attendees at the Spring Meeting then it must follow the example of most other major paediatric meetings worldwide and offer financial concessions to the future paediatricians they are hoping to train.

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Competing interests: none declared

References

Reply by the RCPCH
I am pleased to have the opportunity to respond on behalf of the Academic Board. The trainee representatives on the Academic Board have taken soundings from their peers and formal approaches have been made to regional advisers, to inform our extensive discussions of these same data. The data above show a fall in attendance, but do not provide any evidence that the reducing attendance is because the meeting is too expensive. Indeed, during inquiries many other factors were identified—European Working Time Directive, the introduction of shift systems at middle grade, shorter training attachments at Specialist Registrar year level are some—which not only have the effect of reducing and availability for visits to the Spring Meeting, but mitigated against research activities by trainees, so reducing their chance of presenting at the Spring Meeting. The growth of sub-speciality training may also be attracting trainees to specialty groups in the UK and Europe instead of the RCPCH Spring Meeting. The Academic Board Executive has written to RCPCH college tutors and the chairman and members of the National Association of Clinical Tutors to ensure that trainees are encouraged to attend and given study leave and funding to do so. Contrary to popular belief, the Spring Meeting does not make money for the College, even when profits from the trade exhibition are included (these latter are far smaller than abroad, because of rules about sponsorship). Indeed, the meeting runs without a very narrow margin of making a loss. The figures are published in the annual accounts. Concessions for any group would mean an increase in costs for another.

Finally, the venue of the Spring Meeting is regularly reviewed, but there are few alternative venues, when the requirements for simultaneous sessions, technical support, accommodation, and provender are taken into account. Currently, York University offers good value and a fine setting where paediatricians, senior and junior, from the UK and abroad can meet, make and renew
Meningitis is a common cause of convulsive status epilepticus

With the benefit of hindsight from this study, which refuted the perception that convulsive status epilepticus is atypical of acute bacterial meningitis (ABM), cerebrospinal fluid (CSF) sampling might have been more readily undertaken, and perhaps more blood cultures done, given the fact that the latter modality sometimes tests positive even when the former is negative.

The crux of the matter is how the index of suspicion for meningitis is “packaged”, and the bottom line is that, given the fact that both ABM and tuberculous meningitis (TBM) are eminently amenable to treatment, and without treatment death is an almost invariable outcome for both, common ground must be found in the “packaging” in order to optimise diagnostic potential. A package which does not acknowledge the true prevalence of disease manifestations risks relegating those stigmata to oblivion, the latter being the fate of the blanching maculopapular rash which, notwithstanding its prevalence of 13% in meningococcaemia,1 nevertheless totally escaped mention in the section on ABM in a leading textbook.2 With a prevalence of 6.5–9.7% in ABM, the CSF which is characterised by normal cellularity and biochemistry3 is another parameter that deserves greater recognition than is usually the case, especially because this is a feature which may characterise TBM as well.4 One view is that, in the latter context coexisting HIV/AIDS is the operative factor for this manifestation of TBM.5

What is also evident from the HIV/AIDS epidemic is that tuberculous patients who harbour this virus are more likely to have extrapulmonary tuberculosis than their counterparts who do not have HIV/AIDS.6 The paradigm shift dictated by the HIV/AIDS era is that the index of suspicion for meningitis has to, hence, TBM, should be correspondingly higher, and that parallels between ABM and TBM should be more readily recognised. For example, like the four patients reported with ABM in the absence of meningococcal disease and outcomes in meningococcal disease presenting with maculopapular rash. Arch Dis Child 1991; 66:485–7.8


And it’s only £18, including postage! But how does one review a book like this, a collection of twelve dozen editorials spanning four decades? I thought of the late Ronnie Mac Keith (“I am not your boss, I am your colleague”) whose evocative personal memories by Martin rounds off this book, and looked for a bottle of Madeira to accompany my morning coffee and sweet biscuit. All I could find was port, and at once I was thinking of watching Ronnie standing on the college dining room table between the silver giving a dinner speech, while Martin, already an editor since 1961, sat beaming below. But before I continue, I should explain about the editor date. The year 1961 is when Martin first became co-editor (with Ronnie Mac Keith) of Developmental Medicine and Child Neurology. Martin had already been editor of Ambit (the literary and artistic magazine with poetry and visual arts side by side http://www.3ammagazine.com/archive/2002_jun/interview_martin_bax.html) since 1959. That may give a clue as to why the present collections of editorials are so fascinating to paediatricians, and not just to paediatric neurologists or students of developmental medicine. These editorials are well written (as befits a literary man), wide ranging, and a delight to dip into, delightful enough to find a place on the bedside table or even—and this is a compliment—in the loo.

Martin’s first editorial was on animal behaviour, summarising the work of Harry Harlow on infant Macaque monkeys and the contrasting effects of cloth and wire “inmantes” (surrogate mothers) on early life experiences and behaviour affectionation. He was then fresh from Guy’s, having previously been up at New College, Oxford. In a later editorial, he tells us that at his first paediatric unit two elderly paediatricians took him aside and advised him not to continue in that specialty, which they saw as declining and coming to an end, what with the eradication of tuberculous meningitis and other infectious diseases of childhood. But, he writes (p. 141) “There were two straws blowing in the wind: one was the developing interest in neonatology, the second was that people were beginning to wonder about the fate of the many children treated with congenital disabilities who at that time were often fated to be placed in institutions and to spend the rest of their lives there.” As Martin’s mentor (if not boss) Ronnie Mac Keith predicted, paediatrics did not disappear, and Martin’s new specialty was making “a plea for not too many more paediatric specialties. A paediatrician is a doctor who looks after the child, intending both to promote health and development and to care for the child who becomes ill. This is a species that should not be endangered by too much fragmentation.”

Nonetheless, in this travel through the academic life of Martin Bax, I sometimes sense a whiff of conflict between paediatric specialties whole, in one piece, and dividing up even into subsections of paediatric neurology, so that rare disorders may be properly dealt with, so that doctors know more than the internet learned parents. Another conflict is between the role of paediatric neurologists in centres for handicapped children (p. 56) and the Aciard view that the prime task or skill of paediatric neurologists is to make parents feel happy. Did it happen, will it happen again, and can it be treated, rather than can the child be managed, for the answer to the latter is always yes. The solution may lie in the various skills as doctors that each of us has, fortunately as doctors we have, and to spend the rest of their lives there.” As

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A PAR is a different trajectory of development that the fetus takes as a result of its intrauterine (or perhaps early postnatal) environment, with the aim of maximising chances of survival to reproductive maturity, in a particular expected postnatal environment. For example, in the pregnant snowshoe hare, stress (due to predation, cold, or starvation, for example) may lead to increased maternal cortisol levels. Cortisol may cross the placenta, and the fetus may detect, via signalling from the mother and placenta, that the external environment is a harsh one. The cortisol levels may enhance maturation of fetal organs, such as the lungs, and prepare the fetus for the rigours of postnatal life. However, it appears that exposure to such high cortisol levels in utero may alter the sensitivity of the hypothalamo-pituitary-adrenal axis, making it hyper-responsive after birth. So the offspring of hares that have been stressed during pregnancy, may be hyper-alert—a predictive adaptive response to the expected postnatal environment. One wonders what the effects of an analogous human PAR might be.

Gluckman and Hanson propose that while we have reached a stage in the 150 000 year history of Homo sapiens where Darwinian evolution is no longer active or has slowed dramatically, the predictive adaptive responses we have evolved now threaten our post-reproductive health, in terms of obesity, type 2 diabetes, atherosclerosis, and hypertension. These responses could be initiated soon after conception, mediated by DNA methylation. What is unclear is the extent to which PARs may play a role in human disease outside the context of birth weight (or rather suboptimal fetal growth) and the metabolic “syndrome X”. Gluckman and Hanson make a case for other diseases such as osteoporosis, cognitive decline, psychosis, and polycystic ovarian syndrome, with varying degrees of persuasiveness.

The message from the book appears to be twofold: that the evidence for PARs playing a role in human disease is a persuasive one, which should not be overlooked in favour of “sexy” genome research; and secondly, that if these hypotheses are correct then this has significant implications for society, and how we try to reduce the burden of disease in later life. Unfortunately, there appear to be few recommendations we can make for optimising the intrauterine, and postnatal, environment to minimise the potentially harmful effects of inappropriate PARs.

The fetal matrix concludes with a call for an increased emphasis on the importance of female health before and during pregnancy, with improved female literacy and education (and therefore, hopefully, avoidance of teenage pregnancy), and nutrition. It therefore sends a message to research funding councils of the potential importance of this area of research, and to politicians about priorities. The book should however be of interest (and thought provoking) to anyone with an interest in perinatal care, human nutrition, and fetal physiology.

A C Breeze

Reference