LETTERS TO THE EDITOR

RSV prevention

EDITOR,—I recently saw the UK guidance for the use of synagis (Palivizumab) brought out by the manufacturer and contributed to (?endorsed) by a number of UK experts. My interpretation of the IMpact-RSV (respiratory syncytial virus) study[1] appears to be at variance to the conclusions drawn and the recommendations of the "guidance".

To me, in the above mentioned study,[1] compared to placebo, Palivizumab: (a) did not (the trial lacked the power to demonstrate) reduce death or need for mechanical ventilation; (b) reduce RSV related hospitalisation by 55%—the primary outcome of interest.

Based on (b), the "guidance" recommends Palivizumab for premature infants of < 36 weeks' gestation who are < 6 months old at the start of RSV season as well as those with bronchopulmonary dysplasia < 2 years old who have required medical treatment within six months of the RSV season beginning.

Looking at the data in another way, one would need to treat 16 suggested "at risk" babies (20 for babies with bronchopulmonary dysplasia) to prevent one RSV related hospitalisation. Is it worth it in clinical or economic costs?

Clinical—There was no evidence that RSV illness was less severe among hospitalised Palivizumab recipients than among hospitalised placebo recipients. (The paper provides figures for secondary efficacy end points as per 100 treated children. I suppose they are clinically more relevant than for per 100 hospitalised children.) Although statistically insignificant, both the RSV related deaths occurred in the Palivizumab recipients. Three per cent of placebo recipients (but 15 of 53 hospitalised placebo recipients) and 1.3% of Palivizumab recipients (but 13 of 48 hospitalised Palivizumab recipients) had RSV intensive care unit admissions. Only 0.2% (one of 500 treated or 53 hospitalised) placebo recipients and 0.7% (seven of 1002 treated or 48 hospitalised) Palivizumab recipients required mechanical ventilation. Similar conclusions can be drawn for total ventilator days. In other words, reduction in hospitalisation rates does not necessarily equate with reduction in severity of illness.

Economic—As 16 at risk infants need to be treated to prevent one hospitalisation, and as the infants would receive five monthly injections of the antibody costing between £424 (US$680) and £706 (US$1130) per injection (depending on their weight), the cost of preventing one hospitalisation from RSV related illness is at least £32 000 (US£51 000). I do not know the latest figures for a paediatric inpatient stay but analogies from neonatal "special care" category days would suggest that a six to eight day admission (calculated figures from the IMpact-RSV trial) should not cost more than £1800 to £2500 (US$2880–4000).

So I see very little clinical benefit to those "at risk" children who receive Palivizumab and get RSV illness nor do I see any economic advantage to prevention of RSV related hospitalisations. Indeed both the PREVENT[2] and Impact-RSV[1] studies show much lower rates of hospitalisation among the placebo infants than for historic data, which has been attributed among other things to "extensive education". The valid conclusion then should be that education is the most important tool for prophylaxis against RSV hospitalisation.

The "guidance" suggests drawing conclusions from local RSV hospitalisation rates but these are affected by geographic and social factors as much as clinical ones. Moreover, would local figures have any meaningful value if a large multinational study fails conclusively to prove clinical or economical benefits of the treatment? I do not dispute that there will be an occasional baby with such severe lung disease that any help, however proved, would be welcome. But a generalised preventive measure such as this will be difficult to justify.

Have I got it all wrong?

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1 The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;**102**:531–7.
2 The PREVENT Study Group. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. *Pediatrics* 1997;**99**:93–9.

EDITOR,—Palivizumab, a monoclonal respiratory syncytial virus (RSV) antibody that may reduce the need for hospital admission because of infection with RSV has recently received a licence for use in the UK. Guidelines for its use have already been published in the USA,[1] and there are early indications that some paediatricians in this country plan to use this product.[2]

The USA guidelines are based on the results of a multicentre, randomised, double blind, placebo controlled trial (n = 1502) of Palivizumab[3] conducted at 139 centres in the USA, Canada, and the UK. Treatment or placebo was administered by intramuscular injection at monthly intervals for five months during the RSV season, to infants considered at risk for hospital admission (the primary end point). This paper ends by stating that "prophylaxis with this monoclonal antibody results in a significant (55%) reduction in RSV hospitalization in children at high risk for severe RSV infection".

We have appraised the evidence on which this and other conclusions are drawn in the paper and feel it important to bring our comments to the attention of UK colleagues who may be considering this treatment as we approach the start of another RSV season.

- The study group was heterogeneous in terms of baseline risk for acquiring RSV. Some were less than 35 weeks' gestation but had not been ventilated, others were of extreme low birthweight and had had severe bronchopulmonary dysplasia (BPD). Whether the study group was truly "high risk" could be debated. Only 1% of the entire study population required intensive care. Mortality was similar in both placebo (1%) and Palivizumab groups (0.4%).
- The baseline risk for the primary outcome (hospital admission) was just 10.6% in the placebo control group. This is important as the reduction in hospital admission rates are expressed as relative risk reduction (RRR) with 95% confidence intervals (CI) and p values rather than absolute risk reduction (ARR), and number needed to treat (NNT)[4] with 95% CI.[5]
- The use of RRR in the paper flatters the results, as table 1 illustrates. Data in **bold** have been extracted by us from the paper. Expenditure data is based on the number of babies needed to treat in each group to prevent one extra hospital admission and assuming the baby weighs 3 kg. Dose regimen is 15 mg/kg per dose for five doses; the cost of a 50 mg ampoule is £424 (US$680).

While prevention of hospital admission is clearly desirable, many may feel the cost to be prohibitive. A UK clinical trial of Palivizumab in infants at high risk of needing intensive care because of RSV (for example, babies discharged from neonatal units and in home oxygen at the start of winter) might be more informative.

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Table 1 RSV antibody: clinically useful measures of effect

Event	*CER*	*EER*	*RRR*	*ARR (95% CI)*	*NNT (95% CI)*	*Expenditure (£) to prevent one hospital admission (95% CI)*
Hospital admission (all)	10.6%	4.8%	55%	**5.8% (3 to 9)**	**17 (11 to 33)**	**25500 (16500 to 49500)**
Premature (no BPD)	8.1%	1.8%	78%	**6.3% (3 to 10)**	**16 (10 to 39)**	**24000 (15000 to 58500)**
Previous BPD	12.8%	7.9%	39%	**5.1% (0.4 to 9.8)**	**20 (10 to 250)**	**30000 (15000 to 375000)**

CER, control event rate; EER, experimental event rate.

Interhospital transfer of sick children: proposal for a unified approach

EDITOR,—We read with interest the personal practice described by Rashid *et al* discussing their model of the regionalised transport service in New South Wales, Australia.[1] They rightly stated that the success in the centralisation of resources and expertise in the care of critically ill children is dependent on a reliable and effective transport service.

Systems that work well in other countries may not be appropriate for the UK, but there are lessons to be learned from North America and Australia. The need for adequate and appropriate intensive care services for children in UK has been discussed recently.[2] Implicit in centralisation of intensive care service is the provision of a coherent transport structure,[3] which is crucial for the provision of a high quality service across the whole country.

The size of the country and the population distribution in Australia and North America have forced considerations of transport on health care planners that has never been a high priority in the UK. The features of the New South Wales retrieval service that ought to be incorporated into the UK include: regional centralisation, integration of neonatal and paediatric retrievals, a central point of reference, telephone triage, and access to specialist advice.

The model for the transport team is a doctor (usually an experienced training grade doctor) and trained transport nurse, but there is experience of nurse led[4] or nurse–nurse teams (for example, Hospital for Sick Children, Toronto, Canada) supported by central coordination staff (usually a clinical fellow).

Separation of the service from the hospital system in terms of funding and staffing also has advantages. It facilitates care of the sick child by establishing a standardised, safe, and reliable service, backed up by audit and research with potential to provide systematic training.

The present paediatric transport system in the UK is ad hoc, fragmented, and centre dependent (neonatal or paediatric) with no plans for its integrated development. It is left to the individual intensive care units to arrange transport by diverting funds and staff from other clinical areas, resulting in a patchy, often intermittent service with wide regional differences and inadequacies. Neonatal and paediatric transport is sometimes integrated but more often separate, and the administrative task of identifying available beds and coordinating the response is largely borne by busy on call nursing and medical staff.

The message from the Australian and Canadian experience is that a specialised transport system for children can work. Transport services need to cover a large population to be economic in terms of resources and manpower. This means cooperation between acute trusts on a regional basis, and amalgamation of neonatal and paediatric transport teams, with central telephone triaging and a central record of available neonatal and paediatric beds. This would provide opportunities for a seamless service by streamlining the administrative process (reducing response time and coordinating specialist advice), standardising equipment, and enhancing staff training and research. We hope that the issues will be resolved at a national level rather than left to the individual units to sort out local transport services for critically ill children.

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Definitive diagnosis of nut allergy

EDITOR,—We are concerned that the general readership of *Archives of Disease in Childhood* may be misled by a paper based on results of non-standardised or obsolete tests used in the diagnosis of children with potentially severe allergies to peanut and tree nuts.[1] The implicit confidence of the paper's title is not supported by the experimental approaches.

We would like to express our serious concern about the following specific points.

It cannot be assumed a nut is "the only possible allergen" in a composite food. Any allergenic food can cross contaminate a "safe food."

Intradermal testing is not considered standard practice and has no place in the modern diagnosis or management of food allergy.[2] Rubbing the forearm until erythema is induced makes distinction from dermographism impossible. Skin contacts that cause allergic reactions are usually minimal and non-traumatising. Percutaneous skin prick testing (SPT) with negative and positive controls—neither of which was performed in this study—is easy to perform, causes minimal discomfort compared to blood sampling, and is considered safe. It also provides an immediately available and graphic result for parents. A history of significant reaction to an allergen is not generally considered an absolute contraindication to skin prick testing.[3]

Interpretation of SPT and serum allergen specific IgE depends entirely on the quality of the allergen extracts employed. Genuine allergy may be missed if concentrations of particular allergenic proteins are low. Negative skin tests with standardised solutions of food allergens usually (> 95% negative predictive value) predict absence of disease and are therefore usually easy to interpret.[3] Positive skin tests need to be interpreted with more caution. For instance a peanut SPT of < 6 mm may not be associated with clinical reactivity, irrespective of history.[4 5] It appears from the data presented that the authors found this to be true, with a positive IgE against nuts being associated with a positive challenge. A χ^2 test of categories of negative and positive IgE in 62 challenged subjects shows a significant association ($\chi^2 = 5.81$, 3 df, $p = 0.001$).

The gold standard for diagnosis of food allergy is an adequately performed double blind, placebo controlled food challenge, but an open challenge is acceptable in most children. A challenge cannot be considered negative until a dose has been consumed that would cause a reaction in most affected individuals. A figure of 8 g has been widely adopted.[3 6] The maximum dose in this study (about 2 g) is far too low and might have led to (potentially serious) false negative results. The negative responders may have had genuine severe allergy to a higher dose of the nut tested, to another nut, or to another food not tested. The challenge dose interval can only be dictated by clinical history and 10 minutes may be too short an interval for some subjects.

Good clinical practice requires the application of state of the art techniques. We agree with the authors when they state that to do otherwise is a disservice to families. We suggest that non-standardised practice in the field of investigating anaphylaxis is playing with fire and does nothing to reassure patients.

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Urinary glycosaminoglycan excretion in urolithiasis

EDITOR,—Akçay *et al* reported urinary glycosaminoglycan (GAG) excretion to be significantly diminished in children with idiopathic urolithiasis compared with controls, and proposed that urinary GAG may play an important role in the prevention and reduction of calculi in children.[1] Our findings do not fully support this hypothesis.[2] We evaluated urinary GAG excretion in 22 children with calcium oxalate stones (eight with absorptive hypercalciuria, six with renal hypercalciuria, eight with normocalciuria) and in 20 age matched controls. There was no significant difference in total urinary GAG between the two groups. In terms of the various GAG fractions, patients with renal hyper-

calciuria excreted considerably less keratan sulphate and considerably more dermatan sulphate than the other patients and healthy controls. There was no difference between the two groups in chondroitin sulphate, heparan sulphate, and hyaluronic acid excretion. We conclude that there is no significant correlation between the formation of calcium oxalate stones and urinary GAG excretion.

These conflicting data can be reconciled if the degree of sulphation (that is, the number of negatively charged sites on the surface) is of primary importance in the prevention of stone formation rather than the amount of total or individual GAGs.[3] Although we did not investigate this in our study, it is likely to influence the inhibitory potency of GAGs, and may explains the finding of Suzuki *et al* that heparan sulphate, which is highly sulphated, is incorporated into calcium oxalate crystals precipitated from urine in preference to chondroitin sulphate, despite the fact the urinary concentration of chondroitin sulphate is many times greater than that of heparan sulphate.[4] With the exception of our paper, no study has ever examined in detail individual GAGs in children's urine and attempted to relate them to the occurrence of stones; the routine measurement of total GAG excretion in the investigation of children with idiopathic urolithiasis is irrational and should be discontinued.[5]

In summary, we were unable to detect any difference in the urinary GAG excretion of children with idiopathic urolithiasis and healthy subjects. On the basis of these and similar findings, as well as the lack of any unequivocal experimental evidence that urinary GAGs are significant inhibitors of calcium oxalate crystallisation in vitro, the role of urinary GAGs in the formation of renal calculi is a matter for debate requiring further study.

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Varicella: to vaccinate or not vaccinate?

EDITOR,—I am in complete agreement with Dr Aebi that strategies for delivering varicella vaccine effectively are critical to the success of immunisation programmes.[1] In the USA great efforts are being made in this direction. Nevertheless, despite the licensure of varicella vaccine for routine use in the United States in March 1995, deaths from varicella continue in children and adults.[2] (At my hospital, a 37 year old, previously healthy man died recently of varicella pneumonia.) The US Centers for Disease Control and Prevention has set goals for eventual vaccine coverage rates of over 90% within the next decade. Since morbidity and mortality continue to occur in the USA, it is very difficult for me to believe that there is little problem with varicella in Europe. It may be that studies so far have not been large enough or have not been truly representative sampling. Varicella is clearly a disease associated with many complications.[3] It should also be remembered that varicella vaccine provides protection against herpes zoster as well as against chickenpox.

In the USA, the best approach to ensure vaccine delivery has been to require immunisation before school entry. This rationale may or may not be useful for all countries. As the efficacy of antimicrobials continues to decrease due to resistant organisms, it is likely that the world will become more dependent on vaccines to protect the populace from infections. Society must be prepared to develop effective means and strategies to protect its children from infectious diseases.

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1 Aebi C. Varicella: to vaccinate or not vaccinate? [letter] *Arch Dis Child* 1999;**81**:278.
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A randomised controlled trial of specialist health visitor intervention for failure to thrive

EDITOR,—I was surprised to read in Raynor *et al*'s recent paper[1] the statement that their study was "the largest randomised controlled trial on children with failure to thrive in this country". Our trial studied nearly three times as many children and was published four months before their paper was accepted.[2]

Did they think that it was not a true trial? It conformed to CONSORT guidelines,[3] with random allocations to treatment, and all patients recruited prospectively (not retrospectively as they suggest). Did they feel the children did not have true failure to thrive? They suggest that our study included "many children who . . .proved to be small or to have temporary growth faltering". Eighty per cent of the cases identified in our study had persistent failure to thrive and, as they were identified solely on the basis of slow postnatal weight gain, the contribution of constitutional short stature will have been much less than in Raynor *et al*'s study where low centile position alone was used as one of the entry criteria.

Much of Raynor *et al*'s paper and Blair's accompanying commentary dwells on the "mystery" of why the intervention did not show a significant effect. In fact, with only about 40 children in each arm they had little hope of detecting anything other than a very large treatment effect (80% power, $p = 0.05$ to detect difference of 0.85 SD score). This which would be unlikely when both groups were offered some sort of active treatment. In our study, with subjects followed up for twice as long and up to half of the control children completely untreated, we had only a 40% chance of detecting the significant treatment effect (0.28 SD) that we in fact found.

If the condition of interest is failure to thrive, where referral reflects concern about growth or weight gain, the main outcome must be a measure of growth, whoever is delivering the intervention. The solution to the problem of measuring the effectiveness of health visiting is not to argue for some new measure but to conduct trials of sufficient size to have some realistic hope of success.

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Dr Rudolf comments:

At the time of writing our article Wright *et al*'s study had not yet been published. The reference to our study being the largest in this country was inadvertently left in when we subsequently revised the article for publication. However, Wright's comments do allow us to highlight the differences between these two studies on health visitor intervention for failure to thrive.

The first relates to the two populations of children studied. The Newcastle children were selected by weight screening alone, whereas the Leeds children were included only on receiving a clinical diagnosis of failure to thrive. We contend that "weight faltering" is a more appropriate term for those showing poor growth alone, and that "failure to thrive" should be reserved for children where there are associated psychosocial or emotional issues. This is of course not just semantics. Wright's own recently published work[1] suggests that the intellectual and growth risks are low in children identified by weight screening alone.

The second difference regards the intervention itself. The Leeds children received intensive individualised help from a highly experienced health visitor with special training in assessment, counselling, and nutrition. In comparison, the Newcastle health visitors' training consisted of only a few hours and the intervention was often only one or two visits. Why there is such a discrepancy in the results, given the relative difference in intensity of the interventions, is not entirely clear.

We noted that our study numbers were small, although 83 children is a sizeable sample from any single clinic. It is unlikely that any one centre can enrol enough patients using the strict clinical diagnosis outlined above, and I fully support Wright's contention that larger (almost definitely multicentre) studies are required to produce definitive results.

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