LETTERS TO THE EDITOR

Pitfalls of meta-analysis

EDITOR,—The article by Lacy and Ohlsson clearly shows how statistical manipulation of figures can produce differing results from the same basic data.[1] The authors with their 'cautious use of meta-analysis' find insubstantial evidence of the benefit of IVIG in either prevention or treatment of neonatal sepsis. Using similar data, Weisman *et al*[2] found the relative risk of infection if IVIG prophylaxis was not given to neonates to be 2·6 (3·2) (mean (SD)), and a relative risk of death in infected neonates not treated with IVIG to be 3·0 (0·7). The authors explain this difference by suggesting use of 'inappropriate statistical methods' by Weisman *et al.*

Lacy and Ohlsson have heavily pruned published data in search of 'good quality' and 'homogeneity'. In the field of IVIG nothing thus far has been homogenous. All the published data – good or poor quality – have not only differed in entry and outcome criteria but also in basic definitions of variables such as the definition of sepsis and mortality from sepsis. Nor have the authors differentiated between mortality from sepsis and that from unrelated causes or weight groups. Babies that weigh 800 g have a higher mortality from causes other than sepsis than those weighing 2500 g. The authors have also failed to discriminate between studies in which a placebo was used for the control group and studies in which there was no intervention in the control group.

Another bias in this analysis was the uncritical use of the large study by Fanaroff[3] which accounts for 46% of the total sample. This study was blinded only in phase I and open in phase II.

As the authors themselves pointed out, the studies differed in dose regimen, duration of treatment, and the IVIG preparation used. However, they fail to point out two crucially important differences between preparations: bioavailability which depends on the method of preparation,[4] and variability in IgG subclass distribution. IgG subclass distribution in the preparations is of greatest relevance, taking into account the organisms which cause infection in the neonatal period.

Second, Clapp *et al*[5] and ourselves have clearly shown how important it is to attain and maintain serum IgG above at least 400 mg/dl to be protective – very few studies report or measure serum IgG, thus making any comparison extremely difficult, if not impossible.

It may make statistical sense to reject studies which are not prospective, blinded, and controlled, but it makes a nonsense to compare studies without taking into consideration the very principles on which the whole concept of IVIG is based. Information such as bioavailability of the product, serum concentrations obtained, and well defined outcome measure are crucial principles missing from this meta-analysis. Any conclusions drawn on this basis are therefore questionable to say the least. No clinician would use a subtherapeutic dose of antibiotic, for example, and expect it to be effective. It is clear, however, that well designed, large studies with appropriate IVIG are required.

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1 Lacy JB, Ohlsson A. Administration of intravenous immunoglobulins for prophylaxis or treatment of infection in preterm infants: meta-analyses. *Arch Dis Child* 1995; **72:** F151–5.
2 Weisman LE, Cruess DF, Fischer GW. Current status of intravenous immunoglobulin in preventing or treating neonatal bacterial infections. *Clin Perinatol* 1993; **20:** 211–24.
3 Fanaroff A, Wright E, Korones S, *et al.* A controlled trial of prophylactic intravenous immunoglobulins to reduce nosocomial infections in VLBW infants. *Ped Res* 1992; **31:** 202(A).
4 Morell A. Characterization and safety aspects of intravenous immunoglobulin preparations. In: Koch C, ed. *Clinical use of intravenous immunoglobulin.* Copenhagen: FADL Publishers, 1988: 9–15.
5 Clapp DW, Baley JE, Kliegman RM, *et al.* Use of intravenously administered immunoglobulin to prevent nosocomial sepsis in low birth weight infants: Report of a pilot study. *J Pediatr* 1989; **115:** 973–8.

Drs Lacy and Ohlsson comment:

Dr Haque compares our meta-analysis with the review by Weisman *et al.* In our paper we used generally accepted methods for a systematic overview.[1] Our statistical synthesis included a different set of data than those of Weisman *et al.* We stand by our original statement that Weisman *et al* used inappropriate statistical methods to combine study results – that is, they appear to have combined individual study results by using an arithmetic mean of the relative risks, and thus do not account for study variance which depends on sample size and number of outcomes.

To avoid bias, we used explicit criteria for the inclusion of studies and definitions of outcomes. Regarding Dr Haque's criticism of our use of mortality from all causes other than death from sepsis, we believe that the outcome of death from all causes is less subject to bias than disease specific mortality. Feinsten has recently written that: 'An important scientific advance can occur in meta-analysis ... if the outcomes become confined to total deaths, rather than the inconsistencies and occasional fantasies cited as disease-specific causes of death'.[2]

Our use of the random effects model for pooling of data gave less weight to studies with large sample size than if we had used the fixed effects model.

In our discussion we emphasised that the lack of benefit for the prophylactic use of IVIG is based on preparations used to date and that 'new preparations of IVIG with other antibodies or other combinations of antibodies might be effective'.

1 Ohlsson A. Systematic reviews – theory and practice. *Scand J Clin Lab Invest* 1994; **54** (suppl 219): 25–32.
2 Feinstein AR. Meta-analysis: statistical alchemy for the 21st century. *J Clin Epidemiol* 1995; **48:** 71–9.

Neonatal meningitis with human parvovirus B19 infection

EDITOR,—We were interested to read two recent papers by Okumura and Watanabe, on the infection of the central nervous system by human parvovirus B19 (B19) infection.[1 2] In these cases, the disease manifest at around school age and not during the neonatal period. Three years ago, we encountered a newborn infant who presented with meningitis and persistent anaemia, presumably related to B19 infection.

Case report

A 20 day old girl was admitted with high fever (39·8°C). She had been born by normal vaginal delivery, and showed uneventful growth until poor feeding developed on the 17th day of life. On the day of admission, the infant's mother had had low grade fever, joint pains, a rash on all four limbs and headache. Both the infant and the mother had had close contact with the infant's 5 year old brother, who had had erythema infectiosum 17 days previously. Her peripheral leucocyte count was $10{\cdot}2\times10^9$/l, erythrocyte count $3{\cdot}91\times10^{12}$/l, and haemoglobin 127 g/l. A cerebrospinal fluid (CSF) sample indicated severe pleocytosis (861×10^3 leucocytes/ml, with 57% lymphocytes and 43% neutrophils), along with 23×10^3 red cells/ml, protein 0·54 g/l, and glucose 2·7 mmol/l. Serum anti-B19 IgG and IgM tested by enzyme linked immunosorbent assays (SRL commercial assay) were positive in both the infant and the mother. Routine cultures of CSF, blood, and throat swabs yielded no pathogenic growth. Aseptic meningitis were diagnosed, and antibiotics (imipenem, cefotaxime, and amikacin) and gamma globulin were started. Her fever

Correction

Please note that figure 2 of the paper by Lacy and Ohlsson (*Arch Dis Child* 1995; **72:** F151–5) was incorrectly reproduced and should have looked like this:

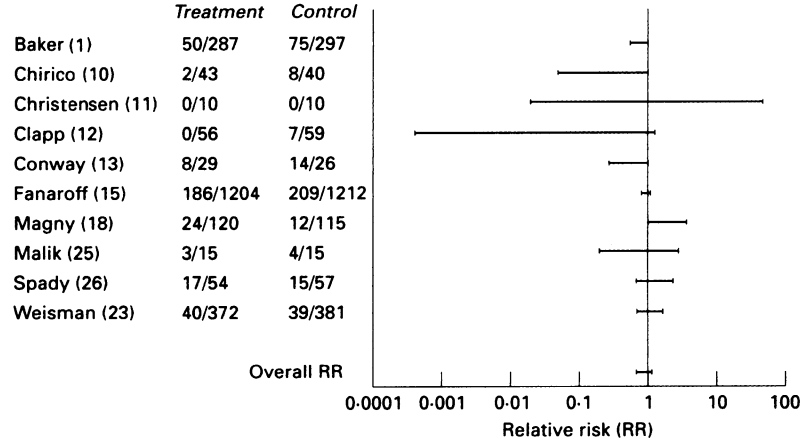

Figure 2 IVIG prophylaxis: effect on sepsis.