cost in the United Kingdom is just over £500 for the recommended three-day course.

In our opinion the only way to resolve our doubts is a multicentre, double blind, placebo controlled trial of nebulised ribavirin for infants with pre-existing cardiopulmonary disease and babies under 6 weeks old who develop proved respiratory syncytial virus infection. The main hypotheses to be tested are that nebulised ribavirin reduces the need for artificial ventilation, shortens hospital stay, and reduces mortality in one or both of these two groups. Pending the results of such a trial we would respectfully urge paediatricians to be circumspect in the use of an expensive drug that we do not feel has been proved to be of undoubted benefit. Our efforts in the interim would be better directed towards prevention of nosocomial respiratory syncytial virus infection, particularly of high risk patients, by improved handwashing and other infection control measures, and towards early identification and supportive treatment.

References
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D Isaacs, E R Moxon, D Harvey, I Kovar, C R Madeley, R J Richardson, M Levin, A Whitelaw, and N Modi
Correspondence to Dr D Isaacs, Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU.

Reply from Dr Snell:

I am grateful for the opportunity to respond to the thoughtful article from Dr Isaacs and his coauthors regarding the use of nebulised ribavirin in respiratory syncytial virus infection. In essence, they express doubts regarding the value of ribavirin and feel that a further large scale clinical trial should be carried out, in infants with pre-existing cardiopulmonary disease and neonates ("high risk infants"), in order to convince them of the efficacy of ribavirin in this situation.

The authors review only four published studies, including 62 treated infants, implying that no other data are available. This is not the case, as published data are available which document at least 175 infants treated with ribavirin, 128 in double blind, controlled clinical trials, and all these papers were made available to Dr Isaacs. In addition, further studies have been carried out which are not yet published.

The United States and the United Kingdom licensing authorities, who had access to all the existing data, published and unpublished, have granted product licenses for nebulised ribavirin in the treatment of infants and children with severe infection by respiratory syncytial virus. In so doing they have accepted the efficacy of the drug (in comparison with placebo) and its safety (as judged on a risk/benefit basis). The trials completed to date have shown statistically significant improvements in comparison with controls, in severity of illness,1 3 5–7 resolution rate,1 7 oxygen saturation,1 3 5–7 need for supplemental oxygen,8 days requiring assisted ventilation,8 need for therapeutic interventions,7 duration of viral shedding,1 7 and IgE response to infection.10 No serious toxicity was ascribed to ribavirin in any of the published reports, controlled1–10 or open,11–14 and none has been reported to the United States Food and Drug Administration, although some 30 000 infants have now received nebulised ribavirin treatment.

To clarify one specific point that has been raised;
Ribavirin in respiratory syncytial virus infection

in the study of Hall et al of ‘high-risk’ infants, those infants considered to be at highest risk were not entered into the placebo controlled study (this was not considered acceptable), but treated openly with ribavirin. Thus the study population was not analogous to the group in which a 37% mortality had previously been shown. It may be noteworthy, however, that all these infants most at risk, who all received ribavirin, survived, in contrast with previous experience.

Dr Isaacs and his coauthors consider that a further placebo controlled study should be carried out in ‘high-risk’ infants to assess effects on need for assisted ventilation, duration of hospital stay, and mortality. Beneficial effects on the first two of these parameters have already been shown (unpublished data) and are being addressed again in a large scale study which is planned to take place in the United Kingdom (not in high risk infants) in the next winter season. This study includes a one year follow up to assess both long term benefit and any long term adverse effects; again, Dr Isaacs was made aware of this planned study before finalising the article for the Archives.

Beneficial effects on mortality can only be shown, by definition, if a number of infants in the placebo group die. For this reason, I cannot accept that it is ethical to carry out a placebo controlled study in high risk infants, where half the patients would be denied a treatment whose beneficial effects have already been shown (and accepted by several very critical licensing authorities) in the expectation that some would die. I very much doubt that such a study design would be acceptable to any local ethical committee, nor can I believe that any parent could give a truly informed consent for their sick child to participate in such a study under these circumstances. The feeling that further placebo controlled trials would not be ethical has been expressed by other experienced researchers in this field, and recent informed opinion appears to support the view that the efficacy of ribavirin in infants with cardiopulmonary disease is proved and that all such infants hospitalised because of respiratory syncytial virus infection should receive ribavirin treatment.

I see no ethical dilemma, however, in carrying out randomised, placebo controlled studies in subjects who are not severely ill and do not fall into one of the ‘high risk’ categories, in whom morbidity will be low and mortality should be zero, provided these are designed to address sufficiently important questions relevant to the mode of action of the drug, its safety and efficacy.

Future research approaches could usefully include studies of modified dosage regimens; animal data suggest that increasing the dose of ribavirin in the aerosol and shortening the duration of administration may produce equivalent therapeutic benefit to the currently recommended schedule.

No one could argue with the author’s final statement that efforts should be directed towards prevention of nosocomial infection by respiratory syncytial virus, but the real question is whether effective treatment should be withheld from those infants who, despite all control measures, contract severe disease. Here, I would fully agree with the opinion recently expressed by Dr Isaacs himself: ‘... In infants with cardiopulmonary disease and respiratory syncytial virus infection, there is clear evidence of clinical benefit and minimal toxicity... I believe nebulised ribavirin is indicated in such children.’

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References

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**Randomised trials and ribavirin**

‘Uncertainty’ about whether to use a treatment is the basis of all randomised controlled trials. Indeed, it can be argued that it is unethical not to randomise when there is uncertainty because this ensures that only 50% of current patients will receive whichever turns out to be the worse management, quite apart from the benefits which accrue to those who have the illness in the future.

Should paediatricians be uncertain whether or not to use ribavirin? The articles on the previous pages certainly suggest that there are widely varying beliefs about the place of this new drug in everyday practice, and variations in practice are a measure of ‘collective’ uncertainty. Individually, paediatricians should decide by critically appraising the evidence which is ‘in the public domain’ for themselves. (There are understandable commercial and other reasons why a company may choose not to publish data about a new product, but Dr Snell must recognise that these data cannot then be used as ‘public’ support for the product). Most weight should be given to the *randomised* controlled trials. The weakness of using historical controls is illustrated by the apparent change over time in the risk of death due to respiratory syncytial virus in infants with congenital heart disease treated conservatively.

Comparisons using concurrent but non-randomised controls are also highly prone to bias. The five properly reported randomised controlled trials included only 76 children treated with ribavirin. They are ‘efficacy’ or ‘explanatory’ (*can it work?*) trials. That is to say, small numbers of patients were investigated in a tightly controlled environment and outcome was assessed by short term surrogate measures such as illness severity scores and arterial oxygen concentrations. These trials do suggest a benefit in these respects, but the clinical significance of this is unclear, particularly in the longer term. Dr Isaacs and his colleagues (p 986) call for a much larger ‘effectiveness’ or ‘pragmatic’ (*does it work?*) trial to assess ribavirin in everyday practice in terms of clinically more meaningful outcomes such as length of time on a ventilator and length of stay in hospital. Improvement in these terms could offset the high financial cost of treatment.

The possibility of unanticipated adverse effects of ribavirin must also be included in the appraisal. It is reassuring that licensing authorities in the United Kingdom and the United States have given ribavirin a (limited) licence, because these authorities are primarily concerned with drug safety. Nevertheless, the Committee on Safety of Medicines has made special reporting a requirement for ribavirin and the marketing data sheet does mention the possibility of serious side effects in the short term. Furthermore, larger numbers of children must be followed up for much longer before rare, but serious, long term adverse effects can be ruled out with any confidence.

On the basis of the limited evidence currently available paediatricians are likely to come to differing conclusions about the effectiveness and safety of ribavirin. Some may feel that ribavirin must be used in some clinical situations; others may conclude that on present evidence, it has no place in everyday practice. But I suspect that many will be uncertain whether they should use ribavirin for respiratory syncytial virus infection, even for children who are most severely affected or most at risk. If so, this uncertainty can only be resolved by large ‘pragmatic’ randomised controlled trials as called for by Dr Isaacs and his colleagues.

**Adrian Grant**

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**Response**

Dr Snell reaches different figures from us on the number of children who have received ribavirin in controlled trials because of our different interpretation of what constitutes a quotable controlled trial. But this is quibbling: our point was that thousands have been treated on the basis of relatively little controlled data. To use the granting of a product licence by licensing authorities as evidence of efficacy is novel but scientifically unacceptable.

We do not believe that Dr Snell has refuted our three main points, namely that there is no evidence