trial results was already difficult, and sponsors and investigators alike ran into difficulties for not disclosing these considerations and results right away.

The above findings were not widely known until well after the hearings.[7,8] In the meantime, several (sponsored and unsponsored) reviews and meta-analyses of the available data were hastily written or performed with conflicting results—eg, those of Mukherjee et al[9] and Konstam et al.[10] Despite significant problems in design, execution, and interpretation, these reviews appeared in respected journals and were subsequently used in marketing campaigns. The result was to further confuse the issues.[11]

There are other concerns. One is the overall quality of reporting of adverse events, which lags seriously behind the reporting of benefits of intervention. The second is the sometimes unreasonable requirements imposed by regulatory agencies for choice of endpoints and analysis strategy (eg, the absolute FDA rule that a trial has a negative result when the treatment target of the primary endpoint is not met at the $p<0{\cdot}05$ level). The third is the invisible influence of peer reviewers and journal editors, which can substantially alter the published report. Comprehensiveness is sometimes sacrificed for readability and conciseness. Finally, the barriers to accessing the full dataset, often encountered by the principal investigator, make verification hard or impossible.

The professional and public trust in pharmaceutical clinical research is under threat. If the validity of the trial analysis and report is corrupted, all parties involved lose, but current and future patients lose most.[12] A fierce discussion is underway over the place of industry-sponsored research,[4] and editors have made the requirements for authorship more stringent;[13] however, imposing this strategy may be insufficient. All parties involved in pivotal trials (sponsor, investigator, regulator, reviewer, and editor) have specific interests at heart that may hinder dispassionate analysis and reporting. Therefore I propose that guidelines be added to the good clinical practice requirements for trials that better deal with these issues. A possibility would be to require completely independent and preferably masked analysis and draft first report of the primary outcome for pivotal trials. Such an approach, which is briefly mentioned in the CONSORT requirements for reporting randomised trials but not widely implemented,[14] would further reduce the potential for bias.[15] This approach would work best in trials that are already masked. On inspection of this first analysis, parties could (in agreement with the other parties) request additional analyses for clarification. Only when all are agreed on the interpretation of these analyses would the masked allocation be removed—in other words, not double-masking but triple-masking or even quadruple-masking. These results and interpretations would then form the core of the scientific publication and the regulatory submission file.

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Treatment for bronchiolitis: the story continues

For over 40 years, respiratory syncytial virus (RSV) has been recognised as the primary pathogen of respiratory-tract infections in infants and young children.[1] Annual outbreaks with a peak each winter cause a serious burden on health-care budgets in the west, where RSV is the leading cause of hospitalisation for bronchiolitis and other forms of lower respiratory-tract infections among children. In addition, the number of hospitalisations for bronchiolitis has substantially increased in different parts of the world.[2,3]

Despite decades of effort, no effective treatment is available for RSV bronchiolitis. This lack was recently once again confirmed by A Abul-Ainine and colleagues.[4] Although previously, adrenaline nebulisation was considered to be better than other bronchodilators, the investigators showed in a well-designed trial that adrenaline nebulisation is not superior to placebo or general supportive care. The available evidence on the efficacy of bronchodilator therapy in both ambulatory and hospitalised patients with bronchiolitis is conflicting. In part, this may be explained by great variability in design and intervention in the previous studies, as well as biased enrolment of subjects. These shortcomings have hampered the reliability of two meta-analyses on the efficacy of bronchodilators in patients with bronchiolitis. Both meta-analyses demonstrated a statistically significant but clinically irrelevant beneficial effect.[5,6]

A large amount of evidence has shown that immunopathological mechanisms are, in part, responsible for the symptoms of RSV bronchiolitis.[7] Therefore corticosteroids may be an effective treatment. This idea has been the subject of studies since the 1960s, but is controversial. Most of the well-designed studies were unable to show a benefit with either inhaled or systemic corticosteroids. However, a meta-analysis of systemic corticosteroids in infant bronchiolitis suggested a statistically significant benefit in clinical symptoms.[8]

Why are bronchodilators and corticosteroids, which are

the cornerstone in the treatment of childhood asthma, at best marginally effective in bronchiolitis in infants despite the pathological, inflammatory, and clinical similarities between these two diseases? There might be several explanations.

First, other factors, besides bronchial constriction and airway inflammation, that are related to the anatomy and immature physiology of the respiratory system in infants likely play a role in the pathogenesis of bronchiolitis. Indeed the risk for a severe course of RSV infection is increased in younger and smaller infants.

Second, RSV infections are mild and self-limiting in most cases. Severe respiratory insufficiency, necessitating admission for supportive therapy and monitoring, develops in only a few patients with their first RSV infection. Most of the benefit of bronchodilators or corticosteroids probably occurs in patients in a severe course of RSV infection. In a randomised trial, corticosteroids seemed to be most effective in those patients who needed mechanical ventilation.[9]

Finally, potentially effective treatment for bronchiolitis may be obscured by the heterogeneity of the investigated populations. There is little uniformity in the definition of bronchiolitis.[6] In the UK and Australia bronchiolitis is strictly reserved to an acute upper-respiratory-tract infection preceding tachypnoea and (non-obligate) wheezing with widespread fine crepitations and sometimes expiratory ronchi on auscultation.[10] In US publications, however, the definition of bronchiolitis tends to be broader since all first-time wheezing associated with a respiratory-tract infection in infants is included.[10] The distinction, based on the clinical presentation, that can be made between RSV bronchiolitis and RSV pneumonia, where wheezing may also occur, complicates the situation. It is questionable if these old definitions are still sufficient for the description of patients in intervention trials.

Apart from the entangling definitions, it is likely that lower respiratory-tract infection with RSV is not a uniform disease and that interindividual differences in the balance between viral cytotoxic and disease-augmenting immunological phenomena strongly determine the pathogenesis and therefore the response to certain forms of treatment. This may explain why bronchodilators and corticosteroids seem to be helpful only in limited groups of patients, which still need to be defined more precisely.

In the treatment for bronchiolitis, the story has not ended. Only precise and more differentiated description of patients in future intervention studies may help to identify the patient that will benefit from different treatments. In addition, not enough is known about the differences of pathophysiology resulting in different clinical patterns of RSV infection in the lower respiratory tract.

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Rapid reviews in *The Lancet*—and beyond

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What is a general medical journal for? To inform and to reform medical thought and practice was the aim of the first Editor of *The Lancet*—a goal that remains true today. A major role for the editorial staff is to select or to seek out the best research for publication to a general medical audience. In July, 2000,[1] we laid out our publication priorities for research submitted to the journal. We stated that *The Lancet*'s aims were: to be the natural home for rapid publication of randomised controlled trials and systematic reviews of diseases that have a major impact on human health; to report substantial advances in understanding causal pathways of disease and treatment effects across the major threats to human health; and to be a leading voice in coverage of global public-health and health-policy research.

These three aims continue to underpin our selection criteria for original research. But what about our other important role—that of interpreting research that either we or other journals publish? Clinical practice is rarely altered by the findings of one study but more usually by a gradual process of informed comment and review of the evidence, and then further comment and review as more evidence emerges. A good starting point is to provide Commentaries, often on original research in the same issue of *The Lancet*, to put the new data into context, to highlight the clinical or research relevance of the paper, or to comment on aspects of the study's design. Sometimes, though, 700 words are not enough for this task, which is one reason why we are introducing in this week's issue a new section, called Rapid reviews. In three pages, these reviews will allow greater discussion of the context of recent research that we judge of special relevance to our readers. Our aim is to publish Rapid reviews within 3 months of publication of the new research findings.

But what of comprehensive, state-of-the-art overviews? We aim to increase our provision of such overviews by commissioning Seminars on common diseases, especially those that are the major threats to human health and are of international relevance. Seminars are clinically focused, disease-based overviews, which cover epidemiology, prevention, pathophysiology, diagnosis, and treatment. Where there are areas of controversy, or international differences in practice, we will cover these to ensure that our Seminars have global relevance. *Lancet* Reviews will continue to cover a narrower aspect of a complex medical topic, which occasionally may warrant a Series of four or more commissioned papers on different aspects of a disease or specialty.

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