designing future studies to evaluate the use of dexamethasone in bacterial meningitis, were it not for the immense practical difficulties in recruitment for, and conduct of, such studies, which will be made immensely more difficult by the virtual disappearance of meningitis caused by Haemophilus influenzae type b in developed countries.

I think that Prasad and Haines, while giving a complete picture of the characteristics of the perfect study, contribute very little to the readers' ability to use the available, if imperfect, data in the most clinically useful manner. The sensitivity analysis shown in Table 3 is inappropriate and misleading, even as a worse case scenario. The number of subjects withdrawn from the analysis includes both children who are excluded because of diagnoses other than bacterial meningitis, primarily aseptic meningitis, and children with bacterial meningitis who were lost to follow up. It is clearly unreasonable to equally assign patients with aseptic meningitis to the treatment and control group and then assign all such patients in the treatment group as having had an adverse outcome and all patients in the control group as having a favourable outcome as it is known that aseptic meningitis is rarely, if ever, associated with adverse sequelae. The other only work presented by the authors is a stratified analysis of the study by age group which only confirms that their overall findings of reduced mortality remained after stratification.

In summary, I think that only the most dramatic of treatment benefits in the most rigorous of trials could survive sensitivity analysis as exacting as that tabulated by Prasad and Haines. I do not consider that the results of this sensitivity analysis can reasonably be interpreted as showing lack of demonstrable benefit from dexamethasone in bacterial meningitis. In addition to the concern which the authors rightly have for demonstrating a favourable risk-benefit ratio in a real life clinical setting, there is also the concern that patients may be denied the benefit of an effective treatment which has been shown to be inappropriate and misleading handling of the data.

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Prasad replies:

I read with interest the letter by McIntyre. He raises three points: (1) future studies will be difficult because of the virtual disappearance of meningitis in developed countries; (2) our sensitivity analysis is based on “unreasonable” assignment of adverse outcome to the treatment group, particularly for patients with meningitis and it cannot reasonably be interpreted as showing lack of demonstrable benefit from dexamethasone in bacterial meningitis; (3) the “primary data” is not appropriate and misleading handling of the data”. I take each point in turn.

If bacterial meningitis has virtually disappeared from the developed countries, future studies can and should be undertaken in developing countries where it is still a major public health problem. This is all the more necessary because maximum use of dexamethasone will occur where meningitis occurs. As we have shown in our paper, the studies to date have limited internal validity and generalisability.

Our sensitivity analysis is appropriate and revealing because it shows the weakness of the evidence available on the subject. This is what other authors have also reported.3 McIntyre has an incorrect notion about the place and purpose of a sensitivity analysis. Firstly, this kind of analysis is required when authors do not report intention to treat (ITT) analysis or do not provide enough information to allow such an analysis and do not report steps taken to protect their analysis from bias. Most trials of treatments (whether dramatic or otherwise) do carry ITT analysis and therefore, sensitivity analysis is not required. If it is required, its purpose, as reported in our paper, is to assess the robustness of conclusions based on inadequate data and it is not to show the presence or lack of benefit. The inadequacy may be in terms of poor recording of risks or excessive losses to follow up. Almost any drug can be proved beneficial, if patients with adverse effects of the drug are withdrawn from the analysis or adverse effects are not counted. Although patients with aseptic meningitis rarely have a poor outcome, they are not immune to adverse effects of dexamethasone. Certainly, it is not reasonable to assume that all patients with aseptic meningitis given dexamethasone will have an adverse outcome, but to this extent, all sensitivity analyses with worst case scenarios are unreasonable. But it serves its purpose by showing that the published evidence is not strong and that it has not been proved beyond doubt that dexamethasone does more good than harm. However, “absence of proof” is not the “proof of absence”. If we wish to base our practice on stronger evidence—as we should—we need more studies and proper analysis of the primary data collected from the investigators of the primary studies. Studies are proceeding in both directions. We and some investigators in Holland are conducting randomised trials of dexamethasone in adults with bacterial meningitis and a Cochrane review of the primary data is planned.

The third point by McIntyre is more profound. It has at its heart questions such as: “is it unethical to withhold a potentially effective treatment the risk-benefit profile of which is not studied adequately?”; “when are randomised trials of a treatment unethical?”; “when is the evidence good enough to make strong recommendations?” and so on. These are issues about the science and ethics of practice of medicine. The available space will not allow me to do justice to the issues involved. I will simply state that until we have shown “a favourable risk-benefit ratio of a drug in real life clinical setting,” there is no justification to subject all our patients to risk of adverse effects of the drug except in randomised trials. It is true that “ways of science” and evidence (randomised trials being the best method) do require some patients what may turn out to be beneficial, but the other way—policies advocating clinical use of a drug without proper evaluation of the risk-benefit ratio—is far too dangerous to be acceptable.

1 Guyatt GH, Sackett DL, for the Evidence-Based Medicine Working Group. Users guides to the medical literature, II: How to use an article about therapy or prevention, A: Are the results of the study valid? JAMA 1993;270:2598-601.
Aicardi thinks provides suggest that all is not well in the cor-

brain might merely function and are no


early feature. Instead there are parox-
mymotor attacks apparently associated with dis-

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