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Since publication of their article, the authors report no further potential conflict of interest.

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# Therapy for Tuberculous Meningitis

**TO THE EDITOR:** Heemskerk et al. (Jan. 14 issue)[1] report no survival benefit for intensified antituberculosis treatment for patients with tuberculous meningitis in Vietnam, a finding that was contrary to the results of our study in Indonesia.[2] Our unblinded study was smaller and had a higher proportion of patients with advanced tuberculous meningitis. However, we think that the contrasting results are explained by the dose of rifampin that was administered. The Vietnam study compared 10 mg of rifampin per kilogram of body weight per day with an increased dose of 15 mg of rifampin per kilogram, whereas we evaluated 13 mg of rifampin per kilogram administered intravenously. The high dose used in our study resulted in an increase in rifampin exposure in blood and cerebrospinal fluid by a factor of 3, with a relationship between the drug level and the therapeutic response.[3] In our study, 38% of patients who were receiving 13 mg of rifampin per kilogram had drug exposure that was lower than the target exposure, which suggests that the dose was not high enough.

Recent trial data for pulmonary tuberculosis also support higher doses of rifampin than that used in the Vietnam study. Regimens consisting of doses of less than 35 mg of rifampin per kilogram did not reduce the time to culture conversion.[4] We are currently evaluating similarly increased rifampin doses for the treatment of tuberculous meningitis to prepare for a phase 3 trial. Pharmacokinetic and pharmacodynamic analyses may show how many patients in the Vietnam trial with its modest dose increase reached target exposures of rifampin.[3]

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** Heemskerk et al. investigated an "intensified" treatment for tuberculous meningitis and did not find a higher survival rate than that with standard treatment. We think that the dose of rifampin was too low. We have shown that doses up to 35 mg per kilogram are tolerated.[1,2] The authors suggest that the benefits of rifampin may be modest. Our data show that higher doses of rifampin were associated with a faster decline in the bacterial load, which suggests that enhanced efficacy can occur with higher doses. Thus, it is difficult to draw conclusions about the failure of the experimental regimen when the trial regimen was possibly suboptimal.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** The study by Heemskerk et al. raises important questions about the approach to the treatment of tuberculous meningitis. The Kaplan–Meier curve for mortality in the subgroup with grade 3 disease according to British Medical Research Council criteria appeared to favor the intensified-treatment regimen until it began to converge with that of the standard-treatment regimen around day 150. A brief, but less substantial, divergence of the curves was seen early on in other subgroups as well. This raises the question as to whether a more prolonged intensive-treatment strategy might be beneficial. This approach is not without precedent, as described by Donald et al. in the editorial accompanying the article[1] and in a study of intensive therapy.[2] Although most new regimens that are evaluated have focused on reducing the duration of treatment or modifying the intensive phase in patients with pulmonary tuberculosis,[3] perhaps the use of multiple drugs for longer periods may have an effect on mortality in patients with tuberculous meningitis.

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**THE AUTHORS REPLY:** We agree with all three groups of correspondents that higher doses of rifampin, perhaps given throughout treatment after initial intravenous administration, may yet improve outcomes for patients with tuberculous meningitis. This effect, however, is predicated on the hypothesis that enhanced intracerebral killing of *Mycobacterium tuberculosis* by "intensified" antituberculosis treatment will increase survival from tuberculous meningitis.

There are good reasons to question this hypothesis. First, our trial tested the addition of higher-dose rifampin and levofloxacin to standard four-drug treatment for the first 2 months of therapy. Leaving aside the chosen rifampin dose, levofloxacin is highly active against *M. tuberculosis*, and oral administration of the dose used in the trial achieves high concentrations in the cerebrospinal fluid.[1] Yet the addition of levofloxacin to treatment had no discernible effect on survival from tuberculous meningitis.

Unlike pulmonary tuberculosis, tuberculous meningitis is caused by a small number of bacteria. This fact hampers both the microbiologic diagnosis and investigations linking drug exposures with destruction of bacteria and clinical outcomes, but neither the bacterial load in cerebrospinal fluid nor the time to its sterility has ever been clearly linked with survival among patients with tuberculous meningitis.[2] Instead, the clinical outcome has been much more closely associated with the intracerebral inflammatory response, which may explain why the use of adjunctive glucocorticoids improves survival[3] and why intensifying antituberculosis treatment has so far met with limited success.

In addition, increased doses of antituberculosis drugs increase the risk of drug-induced hepatic toxicity. In patients with pulmonary tuberculosis, this complication can usually be managed safely by stopping the drugs and reintroducing them slowly. But in patients with tuberculous meningitis, any interruption in treatment with antituberculosis drugs is an independent risk factor for death.[3] This suggests that any potential survival benefit of intensified regimens may be offset by even moderately increased toxicity and consequent reductions in dose or withdrawal of drugs.

In patients with tuberculous meningitis, survival depends on controlling inflammation and killing bacteria before the development of complications of advanced disease: hydrocephalus,

infarction, tuberculomas, and coma. Diagnostic delay and the failure to start antituberculosis drugs before the onset of coma is the strongest predictor of death from tuberculous meningitis.[4] The extent to which enhanced killing of bacteria through intensified antituberculosis regimens might improve outcomes remains a question worth asking, but it should not detract from the need to find better diagnostic tests and to better understand and control the immunopathology of the disease.

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# Planned Out-of-Hospital Birth and Birth Outcomes

**TO THE EDITOR:** Snowden et al. (Dec. 31 issue)[1] report increased mortality among neonates in Oregon whose mothers had planned out-of-hospital births and therefore corroborate our previous findings of significantly increased risks of perinatal deaths and neonatal seizures among neonates whose mothers had out-of-hospital births in the United States.[2-4] Snowden et al. undeniably underestimate the absolute and relative neonatal risks associated with out-of-hospital births, specifically with home births. First, they lump together the outcomes for infants born in birthing centers (which are associated with better outcomes and have a better selection of patients) with the outcomes for those whose mothers had planned home births.[2] Second, they excluded deliveries associated with higher risk (twins, breech births, and anomalous births).[1] Both the absolute risk and the relative risk of death for infants whose mothers have home births are therefore likely to be even greater than the authors report. Reducing the risks of childbirth is an ethical imperative for professionals in perinatal care who are committed to increasing the safety and improving the quality of childbirth.[5] Women planning an out-of-hospital birth should be informed of the modern perinatal interventions available in the hospital that are often lifesaving and can prevent the increased neonatal risks associated with planned out-of-hospital births.

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No potential conflict of interest relevant to this letter was reported.

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**TO THE EDITOR:** Snowden et al. report higher rates of perinatal death, depressed 5-minute Apgar scores, neonatal seizures, and maternal blood transfusions among births that occur out