half of infection-related deaths (figure 1): Plasmodium falciparum, Streptococcus pneumoniae, rotavirus, measles virus, and Haemophilus influenzae type b.

The value of presenting child mortality data by pathogen-specific cause is well illustrated by examining the relative contribution of P. falciparum to child mortality. Nearly all malaria deaths are due to P. falciparum. Malaria is typically ranked fourth after neonatal disorders, acute respiratory infections, and diarrheal diseases as a major cause of childhood mortality. However, when mortality is broken down according to pathogen-specific cause, P. falciparum is rivaled only by S. pneumoniae as the leading single cause of child mortality. Commercial vaccines are currently available for measles virus, rotavirus, S. pneumoniae, and H. influenzae type b and are being provided to developing countries through the Global Alliance for Vaccines and Immunization and other organizations. Increasing availability of these vaccines may result in an increase in the relative contribution of P. falciparum to child mortality. Issues such as this can only be appreciated when child mortality data are presented by pathogen-specific cause, which also highlights P. falciparum as the major pathogen for which a vaccine is not available.

Presenting child mortality estimates by pathogen-specific cause emphasizes the significant impact made by a small number of individual pathogens and could facilitate planning, implementation, and evaluation of preventative interventions and guide funding, training, and research priorities. Although there are major deficiencies in the data available on pathogen-specific causes of child death, available data sources (including vaccine and intervention studies) can be used to derive informative estimates. More complete data on pathogen-specific mortality, particularly in countries with high childhood mortality, are greatly needed.

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References


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The Importance of the Equivalence Trial Design for Comparison of Rectal Quinine Treatment with Other Quinine Applications

To the Editor—Achan et al. [1] reported on a randomized trial comparing intrarectal with intravenous quinine and found no difference in outcomes, such as coma recovery time and mortality, in the largest study (thus far) comparing rectal with other applications of quinine for treatment of cerebral malaria. The design and sample size calculation were based on the assumption that rectal quinine is superior to intravenous quinine with regard to parasite clearance time. However, in the treatment of cerebral malaria, parasite clearance is not a key outcome on which the design of such a comparison should be based. Mortality, coma recovery time, and neurological sequelae would be more important outcomes. Degree of parasitemia does not correlate with the amount of sequestration of parasites in the brain in cerebral malaria [2].

A previous systematic review [3] of data from 8 randomized, controlled trials found no difference in mortality and coma recovery time between rectal and other applications of quinine treatment. The comparison of a new with a traditional application of a drug should aim primarily at demonstration of equivalence for important primary outcomes and at comparison of safety, convenience, and cost implications [4]. For a sample size calculation for an equivalence trial with mortality as a primary outcome, with a difference in mortality of 2% as a range of equivalence and 8% mortality (as expected with standard quinine treatment of cerebral malaria), a sample size of at least 3863 persons in each treatment group would be required to demonstrate equivalence with a power of 80% and a 2-sided 95% CI for the difference in mortality [4]. For an equivalence trial with coma recovery time as a primary outcome, with a difference in coma recovery time of 4 h as a range of equivalence and 12 h as SD, at least 189 participants would be required in each group to demonstrate equivalence with 80% power and a 95% CI for the difference.

The trial by Achan et al. [1] was therefore underpowered to investigate equivalence, and this and previous trials [3] of rectal quinine for the treatment of severe malaria did not support a statement about equivalence of 2 applications of quinine. Future trials should investigate equivalence in an appropriately powered trial that takes into account power calculations for equivalence trials as a basis in their design.

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References

Reply to Eisenhut

To the Editor—Eisenhut [1] underlined the importance of the equivalence trial design for the comparison of rectal quinine treatment with other quinine applications. Very few cerebral malaria studies have been able to enroll a sufficient number of patients to answer the primary outcome of mortality among patients, and most studies have focused on secondary outcomes. Analysis of mortality can only be realized through costly multicenter studies, which are beyond the reach of many clinicians working in resource-constrained countries.

Although quinine remains the main treatment for severe malaria in Africa, alternative and simple techniques, such as the rectal route, have received little support. Since the first publications by Barrennes in 1989 and 1994 [2, 3], only 2 randomized studies evaluating rectal quinine for the treatment of cerebral malaria have been performed [4, 5]. We acknowledge that our recent study [4] had insufficient power to demonstrate equivalence between the 2 treatment groups; nonetheless, our study confirmed the efficacy of intrarectal quinine in the management of severe malaria.

Pooling data from similar studies allowed us to reach a sample size close to that suggested by Eisenhut [1]. Pooling the Niger and Ugandan data revealed an interesting but non–statistically significant trend toward higher mortality in the intravenous quinine group, compared with the rectal quinine group (15.4% [14 of 91 patients] vs. 8.4% [8 of 95 patients]; \( P = .1 \)). Furthermore, pooling data from similar studies in which intravenous quinine was administered to 327 patients in the same hospital from 2003 through 2007 [4, 6, 7] showed a trend of lower mortality in the intrarectal quinine group (8.4% [8 of 95 patients] vs. 15.9% [37 of 232 patients]; \( P = .07 \) [7, 8]).

However, we believe that the debate should focus on another topic. Less than 20% of deaths come to the attention of any formal health care system [8]. Therefore, hospital-based trials investigating severe malaria are affected by a survival bias, because only children who survive and seek care in a hospital can be evaluated. In our comparison of the 2 treatment modes, we noted that intravenous quinine is available only at hospitals and that intrarectal quinine could be available at the village level. Therefore, rectal quinine could be administered early, at the onset of illness, with a mean of 3.5 days before reaching the hospital [4]. In these situations, rectal quinine is likely to save more lives than intravenous quinine. Indeed, a study comparing the 2 routes should be performed at the community level, not at the hospital level.

Eisenhut [1] also commented on the need to focus on comparison of safety, convenience, and cost implications. However, a study performed since his review [9] provide this information. We previously evaluated drug tolerance among 898 patients in a randomized study in Burkina Faso; the feasibility and acceptability of treatment at the community level have recently been evaluated in Niger, Mali, and Senegal [10–12].

We acknowledge the comments by Eisenhut [1]; however, our results highlight the important role that rectal quinine could play as early treatment in settings where there are often insurmountable challenges associated with transferring patients to medical centers that are better equipped to handle such cases.

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Reference
9. Eisenhut M, Omari A, MacLehose HG. Intrarectal quinine for treating Plasmodium falc-