Estimating the Burden of Global Mortality in Children Aged <5 Years by Pathogen-Specific Causes

To the Editor—Globally, infectious diseases account for more than one-half of all deaths among children aged <5 years. Knowledge of the burden of mortality associated with individual pathogens is important for targeting interventions, managing and planning health care services, and guiding research and training priorities. A limitation of the current approach to estimating and reporting global mortality among children aged <5 years is that major causes of deaths are typically presented as a mixture of both pathogen-specific causes (e.g., tuberculosis or HIV infection) and clinical syndromes (e.g., respiratory infections or diarrheal diseases). Although the reporting of mortality statistics from developing countries by clinical syndrome is often pragmatic given the lack of diagnostic tools and vital registration data, it means that the health impact of individual pathogens may not be fully appreciated and the contribution of specific pathogens to global or regional mortality is not specified.

To highlight this issue, we present estimates of global mortality among children aged <5 years by pathogen-specific causes (figure 1), using available World Health Organization Global Burden of Disease data from 2002 (compiled from vital registration data, epidemiological studies, verbal autopsies, disease surveillance systems, and analyses from World Health Organization technical programs) [1–3]. Most deaths among children aged <5 years were due to infectious diseases; infectious diseases accounted for 64% of deaths globally and 81% in the Africa region [1]. More than one-half of these deaths were attributed to “respiratory infections” (26%) and “diarrheal diseases” (24%). However, when data are presented by specific etiology, the following 5 pathogens account for nearly one-

Figure 1. Infection-related global mortality among children aged <5 years by pathogen-specific cause, based on figures from the World Health Organization Global Burden of Disease 2002 estimates [1, 2]. Infection-related deaths accounted for 64% of all deaths in children aged <5 years [1]. Of child deaths from respiratory infection, 41% were attributed to Streptococcus pneumoniae, and 22% were attributed to Haemophilus influenzae type b (Hib). The estimated proportion of diarrheal deaths caused by rotavirus was 25% [2].
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.

**Acknowledgments**

We thank Jack Richards and Katherine Howell for engaging in helpful discussions.

**Financial support.** Financial support was provided by the National Health and Medical Research Council of Australia and the Miller Fellowship of the Walter and Eliza Hall Institute of Medical Research.

**Potential conflicts of interest.** S.R.E. and J.G.B.: no conflicts.

Salenna R. Elliott and James G. Beeson
The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia

**References**


Reprints or correspondence: Dr. James Beeson, The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Victoria 3050, Australia (beeson@wehi.edu.au).

Clinical Infectious Diseases 2008; 46:1794–5 © 2008 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2008/4611-0030$15.00 DOI: 10.1086/588049

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.

**Acknowledgments**

Potential conflicts of interest. M.E.: no conflicts.