REVIEW Open Access

Protective efficacy of malaria case management for preventing malaria mortality in children: a systematic review for the Lives Saved Tool

[illegible][1*], [illegible][2], [illegible][3]

Abstract

Background: [illegible]

highly effective at preventing death [6-8]. More recently, a large scale trial of intravenous artemisinin has been shown to reduce mortality compared to quinine in African children with severe malaria [9]. However, the impact of prompt and effective treatment of uncomplicated malaria and case management of severe malaria on reducing child malaria deaths has not been quantified with placebo-randomized controlled trials for obvious ethical reasons.

In the absence of sufficient systems to monitor real-time trends in cause-specific child mortality in many developing countries, mathematical models are increasingly being used to estimate the impact of the scale-up of child survival interventions on child mortality. The Lives Saved Tool (LiST) is one such model developed by WHO and UNICEF's Child Health Epidemiology Reference Group (CHERG) and based on the earlier work on effectiveness of interventions [10]. The model estimates child deaths prevented (within specific cause of death categories) due to intervention scale-up within a specified country as a function of three primary parameters: 1) the number of child deaths by cause projected to occur in each year (including population growth parameters over time); 2) the protective efficacy (PE) on cause-specific mortality (PE = 1 - relative risk (RR) * 100) for each intervention being scaled-up; and 3) increases in population coverage of each intervention [11].

We performed systematic literature reviews to identify studies that could be used to estimate the effect of prompt effective treatment of uncomplicated malaria and effective case management of severe malaria for preventing post-neonatal child malaria deaths, defined here as mortality directly following a clinical episode of malaria (within a 28 day follow up period for uncomplicated and during hospitalization for severe) in children 1-59 months (assuming no malaria deaths occur or could be accurately attributed during the neonatal period). We chose to focus on sub-Saharan Africa, given the vast majority of childhood deaths due to malaria

P. falciparum malaria endemic settings. Uncomplicated malaria was defined as illness, febrile or otherwise, for which treatment was sought, with confirmation of a *P. falciparum* infection, either by microscopy or rapid diagnostic test. Given the absence of placebo-controlled trials of treatment of uncomplicated malaria, we adopted the following approach to estimate a relative risk for ACT versus no treatment of uncomplicated malaria for preventing malaria mortality, which requires the rate of malaria death (observed) in those treated with ACT and the rate of death in those untreated (natural history). A comprehensive and thorough review of comparative effectiveness studies of ACTs against other antimalarials for uncomplicated malaria was published in 2009 [3]. We retrieved the articles included in this review and abstracted mortality from each trial to determine case fatality ratios (CFR) despite prompt and effective treatment of uncomplicated malaria. The mean CFR across all trials used in this analysis was weighted by the sample size reported in each study. While literature searches to determine natural history of untreated uncomplicated falciparum malaria in children were fruitless, Sudre and Breman conducted a study using the Delphi method to garner expert opinion on the proportion of otherwise healthy children who would die from uncomplicated malaria if left untreated, within an area of stable *P. falciparum* transmission in Africa [14]. They found that experts estimated mortality in untreated children <2 years old with uncomplicated *P. falciparum* malaria to be 5%, and in untreated 2-5 year olds to be 2%. We used these estimates as proxies for mortality of untreated uncomplicated malaria (natural history). We estimated uncertainty using a sensitivity analysis. For the lower bound, the CFR among treated children was assumed double the observed estimate and the CFR among untreated children was assumed to be half the Delphi estimate. For the upper bound, the CFR among treated children was assumed half the observed estimate and the CFR among untreated children was assumed to be double the Delphi estimate.

Effective case management of children hospitalized with malaria

We sought to estimate the PE of effective case management with intravenous quil1(ui.0142Tc0-1210022TDd[(g)--360(53)-358(ot)ldre(,)-n)-334(52spital(t)-4(i)-1e(,)-d)-33.0248Tc0--1

hospitalized children estimated by this method is very similar to that found by other authors [71,81,82], and the CFR of 13.6% for strictly defined malaria is slightly higher than the AQUAMAT trial [9], not surprising for observational studies compared to clinical trial conditions. As a proxy for mortality of untreated hospitalized malaria (natural history), we used mortality data from observational studies in the setting of chloroquine failure, during the era when chloroquine resistance was being established and chloroquine was still in widespread use. This resulted in the estimated CFR of untreated hospitalized malaria ranging from 13-21%. The higher bound (21%) is problematic, as the majority of the children in this sample who died had received chloroquine, and died despite respite receiving intravenous quinine after being admitted in critical condition, thus it may be a major underestimation. A qualitative study in Mali found that mortality for severe malaria (by maternal definition during interview) was 17.0% regardless of treatment-seeking [83], which falls in the middle of this range and lends some credence to its accuracy. Thus we believe that a PE of 82% for protective efficacy of effective case management with intravenous quinine is reasonable. Given that these studies all used intravenous quinine, the PE of intravenous artesunate for preventing mortality would be expected to be even higher.

The currently recommended coverage indicator for prompt effective treatment is the proportion of children <5 years old with fever in the past two weeks who received an ACT within 24 hours from the onset of

Author details

[1] [illegible]

01210 [illegible]

Authors' contributions

[illegible]

artemether-lumefantrine versus mefloquine-artesunate for the treatment of uncomplicated multi-drug resistant Plasmodium falciparum on the western border of Thailand. Malaria journal 2005, **4**:46.

33. [illegible]: A randomized open study to assess the efficacy and tolerability of dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria in Cambodia. Trop Med Int Health 2007, **12(2)**:251-259.

34. [illegible], et al: Artemether-lumefantrine versus dihydroartemisinin-piperaquine for treatment of malaria: a randomized trial. PLoS Clin Trials 2007, **2(5)**: 20.

35. [illegible]: Safety and efficacy of dihydroartemisinin/piperaquine (Artekin) for the treatment of uncomplicated Plasmodium falciparum malaria in Rwandan children. Trans R Soc Trop Med Hyg 2006, **100(12)**:1105-1111.

36. [illegible], et al: A trial of combination antimalarial therapies in children from Papua New Guinea. The New England journal of medicine 2008, **359(24)**:2545-2557.

37. [illegible]

falciparum malaria in Burkina Faso: a randomised non-inferiority trial. Lancet 2007, **369(9560)**:491-498.

62. [illegible]: Randomized comparison of amodiaquine plus sulfadoxine-pyrimethamine, artemether-lumefantrine, and dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria in Burkina Faso. Clin Infect Dis 2007, **45(11)**:1453-1461.
63. [illegible], et al: An open, randomized comparison of artesunate plus mefloquine vs. dihydroartemisinin-piperaquine for the treatment of uncomplicated Plasmodium falciparum malaria in the Lao People's Democratic Republic (Laos). Trop Med Int Health 2006, **11(8)**:1157-1165.
64. [illegible]: Severe malaria in children in Togo. Arch Pediatr 1998, **5(12)**:1310-1315.
65. [illegible], et al: Malaria in rural Mozambique. Part II: children admitted to hospital. Malaria journal 2008, **7**:37.
66. [illegible]: The causes of hospital admission and death among children in Bamako, Mali. Journal of tropical pediatrics 2004, **50(3)**:158-163.
67. [illegible]: Hospital-based surveillance of malaria-related paediatric morbidity and mortality in Kinshasa, Zaire. Bull World Health Organ 1989, **67(2)**:189-196.
68. [illegible]: Differences in presentation of severe malaria in urban and rural Gabon. The American journal of tropical medicine and hygiene 2007, **77(6)**:1015-1019.
69. [illegible], et al: Indicators of life-threatening malaria in African children. The New England journal of medicine 1995, **332(21)**:1399-1404.
70. [illegible], et al: Manifestation and outcome of severe malaria in children in northern Ghana. The American journal of tropical medicine and hygiene 2004, **71(2)**:167-172.
71. [illegible], et al: African children with malaria in an area of intense Plasmodium falciparum transmission: features on admission to the hospital and risk factors for death. The American journal of tropical medicine and hygiene 1999, **61(3)**:431-438.
72. [illegible]