Anti-Malarial Drugs for Prevention of Malaria

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WHAT IS THE ISSUE?

The 'decision question' is whether anti-malarial drugs could be used for preventing malaria in children. The 'clinical question' is: "*In healthy children* (population), *is the use of anti-malarial drugs* (intervention), *efficacious and safe for the prevention of malaria* (outcome) *as compared to no drugs* (comparison)"

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RELEVANCE

Malaria is a significant problem in India, with potential for severe complications and mortality. Global estimates suggest that almost a million children die of malaria annually, second only to pneumonia and diarrhea(1). It is believed that in endemic areas, some degree of immunity is acquired by the age of seven to ten years(2); therefore children under five are at the greatest risk(3). Although strategies for primary prevention such as vector control, personal protection through insecticide-coated mosquito-nets etc. are useful(4), they are sometimes not feasible, cumbersome and expensive to implement on a large scale. Since the likelihood of an affordable vaccine in the near future is remote, the use of anti-malarial drugs for prevention could be a useful option, if found to be efficacious and safe. Thus the disease and intervention under consideration are relevant in the Indian context.

CURRENT BEST EVIDENCE WITH CRITICAL APPRAISAL

The Cochrane Library published a systematic review(5) on 16 April 2008 that included trials till August 2007. An updated search from 1 August 2007 to 24 June 2008, with the terms (*malaria prevention*) and limits (*Humans, Meta-Analysis, Randomized Controlled Trial, All Child: 0-18 years*) yielded 18 citations; five were considered relevant. Of these, one trial had data that could be included in meta-analysis(6), two publications were further analyses of trials already included in the Cochrane review(7,8) and two trials were conducted in pregnant women(9,10). BestBETs, InfoPOEMs and TRIP Database did not yield any further data. Thus data from the Cochrane review(5) and an additional trial(6) comprise current best evidence.

The Cochrane review included 21 randomized trials (including 6 cluster RCT) conducted in malaria-endemic areas. Together, these included almost 20,000 under-five children; all except 6 trials had more than 500 participants each. The trials compared anti-malarial drugs given either in prophylactic doses at regular intervals or therapeutic courses administered intermittently, against a placebo or no drug. The reviewers combined the results into 12 outcomes reflecting efficacy and safety of the intervention. The most relevant - prevention of (clinical) malaria and development of anemia were chosen as primary outcomes. The authors also reported outcomes that could not be combined in meta-analysis.

Ten trials evaluated a combination of pyrimethamine-dapsone, eight assessed sulfadoxine-pyrimethamine, two evaluated chloroquine prophylaxis and one amodiaquine. Most trials had a follow-up of at least 1 year; only 5 had shorter follow-up. Eleven trials administered anti-malarials as weekly or fortnightly prophylaxis for variable

EURECA CONCLUSIONS IN THE INDIAN CONTEXT

- Anti-malarial drugs used in regular prophylactic and intermittent therapeutic regimens prevent the development of clinical malaria and severe anemia.
- These effects are evident with pyrimethamine-dapsone and sulfadoxine-pyrimethamine, but not chloroquine prophylaxis.

durations upto two years; the remainder administered three therapeutic courses over periods ranging from 6 to 15 months.

The systematic review incorporated the usual exacting methodology characteristic of Cochrane reviews. Although the authors stated that intention-to-treat analysis was performed, in effect they performed only 'complete case analysis'; therefore the impact of participants randomized but not followed up, is indeterminable.

The review showed that prior administration of anti-malarial drugs significantly reduced the risk of developing clinical malaria and severe anemia. This was evident in methodologically higher quality trials also, suggesting that the results are robust. However, a beneficial effect on all-cause mortality could not be clearly established, although there was a significant reduction in hospitalization for any cause. Detailed analysis showed that the favorable effect on prevention of clinical malaria was more marked among trials that used intermittent therapeutic courses, rather than regular prophylactic doses. Interestingly, the opposite effect was seen on prevention of severe anemia; the lone trial using prophylactic doses showed clear benefit, whereas intermittent therapy showed only a trend towards benefit. However, it should be noted that these results were reported using the more conservative random-effects model; re-analysis using the more popular but scientifically less rigorous fixed-effect model showed that the intervention had even greater benefit for both outcomes, irrespective of the type of regimen used. The single cluster RCT where data could be analyzed showed similar findings as trials with individual participants. The impact on prevention of clinical malaria was evident with all drugs/combinations, except chloroquine (5 mg/kg) prophylaxis. However, meta-analysis of trials evaluating impact on the primary outcomes after cessation of the intervention, failed to show a clear effect. Most adverse events appeared to be equally distributed in both intervention and control arms; some relatively minor events such as vomiting and development of hyperpigmented macules, were more common with anti-malarial drugs.

The new trial identified(6) was a methodologically sound double-blind, placebo-controlled RCT that administered sulfadoxine-pyrimethamine intermittently; about 85% of 1189 enrolled children were available at follow-up. Fresh meta-analysis adding data from this trial to those in the Cochrane review also confirmed a beneficial effect on prevention of clinical malaria (RR=0.56, 95% CI 0.41-0.76); however the effect on severe anemia was marginally altered (RR=0.76, 95% CI 0.57-1.01, random-effects model).

EXTENDIBILITY

All the 22 trials were conducted in African countries where *P. falciparum* malaria is endemic and a major cause of under-five mortality. Although this may not be the case all over India, in the absence of methodologically robust local trials, the results from current best evidence can be extended to our setting. This is especially relevant since a survey in India showed that about 12% under-five children received presumptive anti-malarial therapy, during the fortnight preceding the survey(11); suggesting that the clinical suspicion of malaria in febrile children is so high as to warrant presumptive therapy. Although the impact of using preventive anti-malarial drugs on the dynamics of acquiring natural immunity in Indian children is not clear, it may be an option worth considering. It may be even better to use the intervention in entire districts (endemic and non-enedemic), with other similar districts serving as controls; and assessing short and long-term outcomes through a large-scale study. In the absence of a

national primary prevention strategy, this may contribute towards the National Rural Health Mission goal of 50% reduction in malaria mortality by 2010(12).

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