Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyramethamine for malaria in African infants: a pooled analysis of six randomized, placebo-controlled trials

Aponte JJ et al; Lancet 374: 1533-42, 2009

Introduction

Malaria due to *Plasmodium falciparum* causes a sizeable share of the disease burden and deaths of both children and adults in sub-Saharan Africa. Episodes of malaria also suppress appetite, impair growth, and contribute to low birth weight and anemia. Therefore, nutritionists need to be concerned with malaria control as one strategy for reducing the prevalence of malnutrition and anemia. Approaches to prevent malaria include disrupting transmission by mosquito control measures and insecticide-treated bed nets, chemoprophylaxis, and intermittent preventive therapy.

The World Health Organization (WHO) defines intermittent preventive therapy for infants (IPTi) as "the administration of a full course of an effective antimalarial treatment at the specified time points to infants at risk of malaria, regardless of whether or not they are parasitemic, with the objective of reducing the infant malaria burden" (WHO, 2007). WHO convened a meeting of technical experts in 2007 to review information on the use of sulfadoxine-pyramethamine for IPTi. Following that meeting, a consortium comprised of independent investigators and representatives of WHO and UNICEF was established to conduct a pooled analysis of the results of six existing trials of IPTi with sulfadoxine-pyramethamine (IPTi-SP). The results of the pooled analysis were recently published, as cited above, and are discussed in this month's NNA.

Methods

Six eligible trials were identified by soliciting information from the consortium members and by conducting a bibliographic search to identify other published studies. Trials that were considered suitable for inclusion in the analysis were those that enrolled asymptomatic infants who were randomly assigned to receive either IPTi with sulfadoxine-pyramethamine (IPTi-SP) or placebo. IPTi-SP was delivered to the children when they attended routine appointments scheduled through the Expanded Program for Immunization (EPI). Trials that employed different drugs, enrolled older children, or took place in areas of highly seasonal transmission were excluded. The primary outcomes that were compared were episodes of clinical malaria (using several different case definitions), hospital admissions, and the incidence of anemia following each round of IPTi, as well as any "rebound effect" of increased incidence of these outcomes during a period of 5 to 15 months after the last dose of IPTi.

Results and conclusions

The eligible trials were based in Tanzania (Schellenberg, 2001), Mozambique (Macete, 2006), Gabon (Grobusch, 2007), and Ghana, where three trials were conducted (Chandramohan, 2005; Kobbe, 2007; Mockenhaupt, 2007). The studies provided information from a total of 7930 infants who received IPTi-SP along with EPI at 3, 9 and 12 or 15 months of age. There were no significant differences between the treatment and placebo groups at baseline. IPTi-SP had a significant protective effect against episodes of clinical malaria (30.3% reduction in incidence, 95% CI = 19.8 - 39.4%, $p<0.0001$), hospital admissions associated with malaria (38.1% reduction; 95% CI = 12.5 - 56.2%, $p=0.007$) and anemia (21.3% reduction of first or only episodes, 95% CI = 8.2 - 32.5%, $p=0.002$). There were no significant differences in all-cause mortality, although the increased access to clinical services and intensive follow up provided by the research design may have obscured the ability to detect any differences that might otherwise occur under more typical program conditions.

The authors also explored for possible adverse effects of IPTi-SP, including possible interference with serological responses to the vaccines provided at the EPI contacts, dermatological reactions to S-P, and possible

"rebound effects" of increased incidence of malaria or anemia during the period following the last dose of IPTi-SP. Overall, no adverse events were significantly related to IPTi-SP. The authors concluded that the IPTi-SP provided at the time of routine EPI contacts is safe and efficacious, and rapid, large-scale deployment of IPTi is feasible. This intervention could make an important contribution to reducing the burden of malaria in infants and should be considered along with other effective control methods in countries with continuous transmission of malaria and a high incidence among infants.

NNA Editors' comments*

Malaria control is generally not a prominent topic of discussion within the nutrition community, but there are several reasons why nutritionists should be concerned with and supportive of malaria control programs. Firstly, there is considerable evidence that malaria causes impaired fetal (Schantz-Dunn, 2009) and child growth (Holding, 2004), thereby contributing to childhood malnutrition. Unfortunately, only one of the current studies reported results for weight gain, so the possible growth effects of IPTi-SP remain unknown. Malaria is also an important cause of anemia, as was demonstrated by the present studies. Because of the known effects of malaria on nutritional status, nutritionists should be strong advocates for malaria control programs.

The current review also illustrates the value of collaboration among different sub-sectors within the health domain, both to maximize the potential impact of service delivery platforms and to permit cost-sharing among different programs. In the present example, the service delivery platform was designed and primarily supported by the EPI program and utilized by the malaria control program to the advantage of nutrition. This type of integrated service delivery obviously provides benefits to each of the programmatic areas. Provision of bed nets, vitamin A supplements, and selected immunizations during child health days is another example of such integrated service delivery. Each of these examples argues for the need for closer communication among professionals working in distinct programmatic realms to explore how best to maximize the health benefits and cost-effectiveness of the respective interventions.

* These comments have been added by the editorial team and are not part of the cited publication.

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Documents received for diffusion this month:

Integration of IYCF Support into CMAM. Produced by the Emergency Nutrition Network (ENN) in partnership with Nutrition Policy and Practice, LLC, in consultation with the IFE Core Group, individual collaborators, and funded by the Global Nutrition Cluster (GNC). The materials comprise a Facilitators Guide and a set of Handouts, which are available e-versions at: http://www.ennonline.net/resources/722).

Dietary Diversity as a Measure of the Micronutrient Adequacy of Women's Diets in Resource-Poor Areas: Results from Five Countries. Submitted by The Food and Nutrition Technical Assistance II Project (FANTA-2). The documents report the results of analyses of the relationship between simple indicators of diet diversity–such as those that could be derived from the Demographic and Health Surveys–and the micronutrient adequacy of women's diets. Results include data sets from three African countries: Burkina Faso, Mali, and Mozambique. Country reports are available at: http://www.fantaproject.org/publications/wddp_countries2009.shtml.

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