

PYRIMETHAMINE (Commentary)

Malaria: intermittent pre-emptive treatment can reduce the risk of overt illness

While pneumonia and diarrhoea (compounded by malnutrition) cause most of the ten million deaths currently seen in the world every year in children less than five years old (Brice *et al.*, 2005), malaria remains endemic in much of Africa, and is probably responsible for a fifth of all such death in this continent. While strategies for reducing this toll have been well studied they have, as yet, only been adopted by a minority of countries.

In pregnancy: It has been known for at least a decade that intermittent pre-emptive (or 'presumptive') treatment with sulphadoxine-pyrimethamine (Fansidar[®]) in pregnancy can reduce the incidence of maternal anaemia and improve fetal growth in countries like Malawi and Kenya where malaria is endemic (Schultz *et al.*, 1994; Shulman *et al.*, 1999). Treatment was given three times in the latter study if the woman was seen early enough in pregnancy for this to be possible (at 16–19, 20–26 and 27–30 weeks gestation). However, benefit was seen even in women only seen in time to receive the last of these three three-tablet doses. It was also seen in women who were using insecticide-treated bed nets as well as those who were not. There was even a strong trend for treatment to reduce the risk of neonatal death in the 1200 women in Shulman's study (Protective efficacy 38% [95% CI -8 to 65%]). Cot and Deloron (2003) point to the fact that infection during pregnancy can be particularly damaging if it occurs in an area where episodes of infection are relatively infrequent – complicated infection (with cerebral malaria or pulmonary oedema) is particularly likely in women with low levels of immunity, and infection in these women is particularly likely to cause miscarriage or stillbirth. A recent randomised trial in Ghana that compared intermittent preventive treatment with sulfadoxidine-pyrimethamine, or amodiaquine, or both drugs because of concern that parasites are increasingly becoming resistant to Fansidar (Clerk *et al.*, 2008) found all three strategies to be of comparable efficacy and commented that there were more side effects in women given amodiaquine.

In young children: A controlled trial in Ghana published in the *BMJ* in 2005 showed that giving children living in an area where malaria is endemic half a crushed tablet of sulfadoxidine-pyrimethamine in water on each of the three occasions when the child was seen for immunisation during the first nine months of life and then once more at a year, caused a modest but significant 25% reduction in the number of children presenting with evidence of overt malaria during that time (Chandramohan, *et al.*, 2005). Anaemia was also 35% less common. There was, however, an excess of overt infection in children so treated in the second year of life after intermittent pre-emptive treatment was stopped. Schellenberg *et al.* reported similar findings from Tanzania in a paper published in the *Lancet* in the same year, (a 59% drop in the incidence of clinical malaria) and in this study there was *no* excess overt infection in children so treated during the following 12 months. In both these studies all the children were also offered a month's supply of an oral iron supplement (15 mg of elemental iron twice a week for four weeks) each time they were seen.

More recently a pooled analysis of the results from six trials has been published (Aponte *et al.*, 2009). Children given just half a tablet of Fansidar[®] (i.e. 250 mg of sulfadoxine and 12.5 mg of pyrimethamine) once when 3, 9 and 15 months old had fewer overt episodes of malaria, were less likely to become anaemic and less likely to require hospital admission. Unfortunately such a strategy does not work in areas where parasites have now become very resistant to this combination of drugs. Luckily, however, there is some evidence (Gosling *et al.*, 2009) that, in these areas, intermittent prophylaxis using mefloquine (q.v.) rather than sulfadoxine and pyrimethamine may well deliver similar benefit. A monthly dose of artesunate and amodiaquine (q.v.) in children less than a year old proved equally effective in another recent large trial in Ghana (Kweku *et al.*, 2008).

Importantly, the evidence from studies to date is that, although *continuous* prophylaxis offers considerable protection while it is being given, its use in young children seems to interfere with the development of natural immunity. *Intermittent* chemoprophylaxis, on the other hand, by just ameliorating rather than preventing infection, does not do this (or only does this to a limited extent). Strategies for increasing insecticide-treated bed-net usage can have a further major impact on survival in the first three years of life in countries where malaria is endemic (Fegan *et al.*, 2007; Hanson *et al.*, 2009).

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