Can intermittent preventive treatment for malaria reduce child mortality?

Dicko A, Konare M, Traore D, Testa J, Salamon R, Doumbo O, Rogier C. (Malaria Research and Training Center, Faculty of Medicine Pharmacy and Dentistry; and Department of Public Health, Faculty of Medicine Pharmacy and Dentistry, University of Bamako, Bamako, Mali; Institut de Santé Publique, d’Épidémiologie et de Développement, Université Victor Segalen Bordeaux; Institut de Recherche Biomédicale des Armées IRBA-ex-IMTSSA & UMR6236-URMITE, Allée du Médecin colonel Jamot, Parc du Pharo, Marseille, Cedex, France; Institut Pasteur de Madagascar, Antananarivo, Madagascar.) The implementation of malaria intermittent preventive trial treatment with sulphadoxine–pyrimethamine in infants reduced all-cause mortality in the district of Kolokani, Mali: Results from a cluster randomized control. Malar J 2012;11:73. doi:10.1186/1475-2875-11-73.

SUMMARY
This cluster randomized trial was done in Mali to study the impact of intermittent preventive treatment for malaria in infancy (IPTi) using sulphadoxine and pyrimethamine (SP) on all-cause mortality in children aged 4–12 months. IPTi is the administration of two doses of SP along with the second and third doses of dihydropteroate synthase (DHPS) 540, is very low (9.7%).10 An IMF in areas where resistance to SP is malaria in pregnancy. Malaria in pregnancy may lead to high prevalence zones.

The Indian scenario
The estimation of true burden of malaria prevalence in India is fraught with under-reporting because of scattered occurrence in remote/tribal areas and inaccuracies in reporting. Malaria is endemic with 26% of the population living in high (>1 case/1000 population) and 56% in low transmission zones (0–1 case/1000 population). In 2010, there were 1.49 million confirmed cases of malaria with an annual parasite incidence of 1.3%.6 The bulk of malaria cases occur in the flood plains of northern India and coastal plains of the East and West. The north-eastern region and the forests and forest fringes on the hill ranges of peninsular India are highly endemic to malaria. Orissa, Jharkhand, Chhattisgarh, West Bengal and Madhya Pradesh contribute >60% of reported (confirmed) malaria cases in India.7 The inaccuracy in reporting could be due to variability between clusters than due to intervention. The final mortality rate observed in the control zone (40.8 per 1000) was lesser than what they have assumed (106 per 1000). This could have reduced the power of the study and resulted in wider confidence intervals.

COMMENT
The authors have studied all-cause mortality as an outcome rather than malaria-specific mortality, since the latter would require a larger sample size and it is difficult to assign the cause of death retrospectively, even if verbal autopsy is used. The authors have not mentioned if the intervention and outcome are at an individual or cluster level. However, it is clear that both are at cluster level, in which case it is not necessary to account for clustering in calculation of sample size and in analysis.8 Another problem in the interpretation of the results is the absence of baseline description of the two zones except for gender, which would imply that the results observed could be due to variability between clusters than due to intervention. The final mortality rate observed in the control zone (40.8 per 1000) was lesser than what they have assumed (106 per 1000). This could have reduced the power of the study and resulted in wider confidence intervals.

The authors have studied all-cause mortality as an outcome rather than malaria-specific mortality, since the latter would require a larger sample size and it is difficult to assign the cause of death retrospectively, even if verbal autopsy is used. The authors have not mentioned if the intervention and outcome are at an individual or cluster level. However, it is clear that both are at cluster level, in which case it is not necessary to account for clustering in calculation of sample size and in analysis.8 Another problem in the interpretation of the results is the absence of baseline description of the two zones except for gender, which would imply that the results observed could be due to variability between clusters than due to intervention. The final mortality rate observed in the control zone (40.8 per 1000) was lesser than what they have assumed (106 per 1000). This could have reduced the power of the study and resulted in wider confidence intervals.

According to the Malaria Atlas project, the EIR for 2010, in most regions of India is <1. However, in certain regions it could exceed 10% because of the uncertainty in the process involved in calculating the EIR. Also, the available literature on resistance to SP suggests that drug resistance is within acceptable limits.7 The resistance to SP, as measured by mutations in genes of the enzyme dihydrofolate reductase synthase (DHPS) 540, is very low (9,7%).10 An EIR <1 suggests that IPTi need not be implemented in India except in the high prevalence zones.

Another situation which requires intermittent prophylaxis with SP is malaria in pregnancy. Malaria in pregnancy may lead...
to a fatal outcome in the mother or stillbirth, abortion, or low-birth weight (LBW) babies. A study from rural Madhya Pradesh estimates that per year there were 220 000 women with malaria in pregnancy, 95 800 lost foetuses and 1000 died. According to the strategic plan for malaria control in 2007–12 in India, there is scope for introduction of chemoprophylaxis in pregnancy in areas with a high burden of malaria in pregnancy. However, this would require an estimation of the true burden of disease in these areas and a documentation of the safety and benefits of ITP in Indian settings.

REFERENCES

An effective dengue vaccine: A glass half full or half empty?


SUMMARY
This study was a randomised, controlled, single-centre phase 2b trial of the efficacy of an investigational dengue vaccine, CYD-TDV. This is a recombinant, live-attenuated, tetravalent dengue vaccine (TDV). It is based on the yellow fever 17D vaccine strain, produced using Vero cells.

The study was conducted in the Muang district of Ratchaburi province of Thailand. This site was found suitable for the trial during an epidemiological study done earlier. Four thousand and two healthy schoolchildren aged 4–11 years were recruited from 35 schools. Those with an acute febrile illness or an immunodeficiency disease were excluded. Children were randomly assigned to receive either three doses of the dengue vaccine (n=2669) or a saline placebo (n=1333) subcutaneously at months 0, 6 and 12. The first 50 children randomized to the placebo arm received one dose of the rabies vaccine as placebo. However, the use of rabies vaccine in the placebo arm was stopped following the advice of the independent data monitoring committee.

All children were followed up for at least 13 months after the third dose of injection. Acute febrile illnesses were detected using school records, phone calls and home visits. In case of a febrile illness, parents were asked to take their child to the Ratchaburi Regional Hospital. Paired serum samples were collected at presentation and 7–14 days later. Acute samples were screened at a central laboratory. Virologically confirmed dengue was defined as a positive dengue serotype-specific polymerase chain reaction (PCR) or detection of NS1 dengue antigen by enzyme-linked immunosorbent assay (ELISA). Serious adverse effects were monitored until the sixth month after the last injection. Dengue immune responses were assessed in the first 300 enrolled children using sera collected at enrolment, and before and 4 weeks after each injection. Neutralizing antibody titres against each dengue serotype were also assessed.

Of the 4002 children enrolled over a period of one year, 3839 (96%) received three injections and 3673 (2452 in the vaccine group and 1221 in the placebo group) were included in the per-protocol analysis. At baseline, over 90% of the 300 children tested for immunogenicity were seropositive against dengue virus (DENV) or