Effect of intermittent preventive treatment for malaria during infancy on serological responses to measles and other vaccines used in the Expanded Programme on Immunization: results from five randomised controlled trials

*Jane Crawley, Charalambos Sismanidis, Tracey Goodman, Paul Milligan, WHO Advisory Committee on serological responses to vaccines used in the Expanded Programme on Immunization in infants receiving Intermittent Preventive Treatment for malaria**

Summary

Background Intermittent preventive treatment for malaria during infancy (IPTi) is the administration of a full therapeutic course of antimalarial drugs to infants living in settings where malaria is endemic, at the time of routine vaccination in the first year of life. We investigated whether IPTi with sulfadoxine-pyrimethamine or other antimalarial drug combinations adversely affected serological responses to vaccines used in the Expanded Programme on Immunization (EPI).

Methods The study was done in a subset of children enrolled in five randomised controlled trials in Navrongo, Ghana; Kilimanjaro, Tanzania; Manhica, Mozambique; Kisumu, Kenya; and Bungoma, Kenya. All infants presenting for the second dose of the diphtheria-tetanus-pertussis vaccination (given at 8–10 weeks of age) were eligible, and analyses included all children who had received measles vaccination (at 9 months of age) and at least one dose of IPTi or placebo. Blood samples were collected before and after vaccination, and antibody titres were measured by plaque reduction neutralisation (measles, yellow fever), microneutralisation (polio serotypes 1 and 3), and ELISA (all other EPI antigens). Laboratory personnel were unaware of the randomisation groups. We compared the proportion of infants in the IPTi and placebo groups who did not attain protective antibody titres after vaccination, using a one-sided significance non-inferiority margin of 5% for measles (the primary endpoint) and 10% for other EPI antigens.

Findings Between September, 2000, and May, 2008, 8416 children were enrolled in the five studies. Paired samples from 2368 children from sites where sulfadoxine-pyrimethamine was compared with placebo were analysed for measles antibodies. 464 children with detectable measles antibody in their sample before vaccination were excluded, leaving 1904 individuals (934 placebo and 970 sulfadoxine-pyrimethamine) in the study. IPTi with sulfadoxine-pyrimethamine did not have a clinically significant effect on immune responses to measles vaccine; 61 of 970 (6·3%) children who received IPTi did not develop a protective antibody response after measles vaccination compared with 60 of 934 (6·4%) who received placebo, a difference of –0·14% (95% CI –2·3 to 2·1). When other antimalarial drugs were used for IPTi the results were much the same. Among 2396 children from whom serological response data for other EPI antigens were available, we identified no evidence of an adverse effect of IPTi with sulfadoxine-pyrimethamine or other antimalarial drugs on the proportion achieving protective antibody concentrations.

Interpretation IPTi with sulfadoxine-pyrimethamine does not affect serological responses to EPI vaccines. This analysis, therefore, supports the WHO recommendation for coadministration of IPTi with sulfadoxine-pyrimethamine to infants at the time of the second and third doses of DTP and measles vaccination, in areas of sub-Saharan Africa with moderate to high malaria transmission and where malaria parasites are sensitive to these drugs. It also suggests that treatment of clinical malaria at or around the time of vaccination does not compromise vaccine responsiveness.

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Introduction

Malaria caused an estimated 216 million cases of clinical malaria (defined as fever with malaria parasitaemia) and 655 000 deaths in 2010.[1] More than 85% of malaria cases and 90% of malaria deaths occur in sub-Saharan Africa, where the greatest burden of disease falls on young children.

In regions of moderate to high transmission of malaria, intermittent preventive treatment during infancy (IPTi) with sulfadoxine-pyrimethamine reduced the incidence of clinical *Plasmodium falciparum* malaria in the first year of life by 30·3% (95% CI 19·8–39·4), anaemia by 21·3% (8·2–32·5), hospital admissions associated with malaria parasitaemia by 38·1% (12·5–56·2), and all-cause hospital admissions by 22·9% (10·0–34·0%).[2] At an individual level, this treatment provided personal protection against clinical malaria for about 35 days.[2]

In early trials,[2] IPTi with sulfadoxine-pyrimethamine was delivered through WHO's Expanded Programme on Immunization (EPI) at the time of the second and third

doses of the diphtheria-tetanus-pertussis (DTP2 and DTP3) vaccine (usually given at 8–10 and 12–14 weeks of age), and with measles vaccination at 9 months of age. According to WHO and UNICEF estimates, coverage of the DTP3 vaccine in Africa was 77% in 2010.[3]

The purpose of our study was to compare serological responses to EPI vaccines with and without concurrent IPTi. Confirmation that IPTi does not adversely affect vaccination is a prerequisite for EPI to be safely recommended as the delivery platform for coadministration. The integration of IPTi with vaccination would be unacceptable if it inadvertently increased rates of vaccine-preventable diseases. Furthermore, if the receipt of IPTi compromised immune responses of vaccinated individuals, it could adversely affect herd immunity, whereby non-vaccinated susceptible individuals are indirectly protected from disease.

Methods

Study design and participants

WHO used the opportunity provided by the IPTi Consortium (a collaboration between 17 research institutions, WHO, and UNICEF, established in 2002 with funding from the Bill & Melinda Gates Foundation), to coordinate a study to investigate the effect of IPTi on serological responses to EPI vaccines in infants.

The study was done in a subset of children enrolled in five randomised trials of IPTi in Navrongo, Ghana;[4] Kilimanjaro, Tanzania;[5] Manhica, Mozambique;[6] Kisumu, Kenya;[7] and Bungoma, Kenya (Menya D, Department of Epidemiology and Nutrition, School of Public Health Moi University, Eldoret, Kenya, unpublished). All children presenting for the DTP2 vaccination were eligible. Exclusion criteria were known history of allergy to sulfa drugs, illness requiring hospital admission (all trials); co-trimoxazole prophylaxis for HIV infection (Kisumu); and weight less than 4·5 kg with HIV infection (Kilimanjaro). All trials were approved by their national ethics committees, and by ethics committees of the collaborating institutions. Written informed consent was obtained from parents or guardians.

To oversee and guide this work, WHO established an independent advisory committee that assisted with the design of the project, selected the subcontractors, reviewed data from the five EPI serology studies, and made recommendations to WHO. To assure the quality of data collection, all trials were subject to either audit or clinical monitoring. An independent post-study audit of the laboratory data was done before the advisory committee reached its final conclusions.

Procedures

See Online for appendix

IPTi was administered on three occasions, immediately after DTP2, DTP3, and measles vaccination. In three of the trials (Navrongo, Manhica, Bungoma) children received placebo or IPTi with sulfadoxine-pyrimethamine. In Kisumu, infants received placebo or IPTi (with sulfadoxine-pyrimethamine plus artesunate, amodiaquine-artesunate, or chlorproguanil-dapsone), and in Kilimanjaro placebo or IPTi (with sulfadoxine-pyrimethamine, mefloquine, or chlorproguanil-dapsone). In Navrongo, a fourth dose of IPTi was given at 12 months without concurrent vaccination. Table 1 provides the full immunisation schedule. At all sites, infants received oral polio and hepatitis B vaccination with all three doses of DTP. Infants in Mozambique and Tanzania received a tetravalent DTP-hepatitis B combination vaccine, whereas infants in Ghana and Kenya additionally received *Haemophilus influenzae* type b vaccination as a component of the newly introduced pentavalent DTP-hepatitis B-*H influenzae* type b combination vaccine. Measles vaccine was administered at 9 months at all sites, with additional yellow fever vaccination in Ghana.

Whole blood (0·5 mL) was taken by finger prick or venous sampling at the timepoints indicated in table 1. To assess serological response to measles vaccination, samples were collected immediately before vaccination and one month after vaccination in Kilimanjaro and Bungoma or 3 months after vaccination in Navrongo, Manhica, and Kisumu. Samples collected before and after yellow fever vaccination in Navrongo were used to assess serological response to the co-administered measles and yellow fever antigens. For all other serological investigations, blood samples were collected a month after DTP3 vaccination from three sites. Varying immunisation schedules meant that this was at 18 weeks of age in Kisumu and Bungoma, and at 20 weeks of age in Manhica. In Kisumu, blood samples were taken before and after vaccination from all randomised children. At the other sites, blood samples were taken from a subset of children in each treatment group: in Manhica, infants who attended the immunisation clinic were selected consecutively for blood sampling until the required sample size was achieved; in Kilimanjaro and in Bungoma a subset of infants were sampled from each treatment group. In Navrongo, stored blood samples were selected retrospectively.

This sampling strategy permitted assessment of responses to measles vaccination across all five sites; to diphtheria, pertussis, tetanus, hepatitis B, oral polio vaccination in Manhica, Kisumu and Bungoma; to *H influenzae* type b vaccine in Kisumu and Bungoma; and to yellow fever vaccination in Navrongo.

For serological assays, clotted whole blood samples were centrifuged; the serum was separated and frozen at –20°C, then transferred to the Health Protection Agency, UK. Antibody titres were measured by the plaque reduction neutralisation test (measles and yellow fever), microneutralisation (polio serotypes 1 and 3), and ELISA (all other EPI antigens). All assays were run in duplicate, with standardised reagents or validated test kits (appendix p 1). For measles and yellow fever, blood samples taken before vaccination were assayed to check whether participants had been exposed to these diseases