RAPID REVIEW

Malaria intermittent preventive treatment in infants, chemoprophylaxis, and childhood vaccinations

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Context Malaria accounts for 1–3 million deaths yearly worldwide, mostly in children under 5 years of age in sub-Saharan Africa. Laboratory and clinical studies show an association between acute malaria and a decreased response to diphtheria and tetanus toxoids and to meningococcal, salmonella, and *Haemophilus influenzae* type b vaccines. Malaria treatment, chemoprophylaxis, or other forms of parasite suppression might improve the immune response to childhood vaccinations. However, the anti-malarial 4-aminoquinolones are immunodepressive, such that antimalarial drugs might depress the vaccine response.

Starting point Last year, Julius Massaga and colleagues reported a randomised double-blinded placebo-controlled study in 291 infants aged 12–16 weeks in Tanzania (Lancet 2003; 361: 1853–60). At enrolment, children received their third dose of combined diphtheria-tetanus-pertussis-polio vaccine and poliomyelitis expanded vaccines with the first of three daily doses of amodiaquine intermittent preventive treatment (IPTi) or placebo. After 60 days, children receiving amodiaquine had significantly fewer malaria fevers than controls.

Where next The increasing concordance of malaria control and vaccination, movement toward co-administration of IPTi with immunisation, and the increase in travellers to malarial areas who receive concurrent vaccinations and chemoprophylaxis warrant further study.

Malaria accounts for 1–3 million deaths yearly worldwide, with most of this burden occurring in children under 5 years of age in sub-Saharan Africa. Intermittent preventive treatment in infants (IPTi), a treatment dose given generally at the time of infant and early childhood vaccinations, might revolutionise the treatment and prevention of malaria. Large populations of at-risk children born in endemic areas would be enrolled in antimalaria and expanded programmes of immunisation (EPI), practically at birth. In view of the large number of children that will be affected by IPTi, any effect of IPTi and the response to childhood vaccines would have enormous implications. Organisations planning IPTi programmes alongside EPI need to be aware of the associations between antimalarial use and vaccine response. These potential associations could have an important role in the timing, drug, dose, and other components of the IPTi strategy.

To elucidate the potential impact of IPTi on vaccine response, we reviewed nine published clinical studies on associations between IPTi and malaria chemoprophylaxis (usually daily or weekly administration of a suppressive dose of drug) and the serological response to childhood vaccinations in populations exposed to malaria. We searched MEDLINE with the terms malaria, vaccinations, and chemoprophylaxis. We included all studies in malarious areas that analysed the serological effect of vaccine response in IPTi or chemoprophylaxis (CH+) versus non-IPTi or non-chemoprophylaxis (CH−) groups. Two studies used IPTi with vaccinations and the remaining seven used chemoprophylaxis. Four of the studies were randomised placebo-controlled trials and, in the two IPTi studies, vaccine response was measured as a secondary endpoint.

Study design, IPTi and chemoprophylaxis regimens, vaccines, and vaccine responses are shown in the table. The studies are grouped by estimated quality of the study design on the basis of whether randomisation and controls were used and the statistical power of the results (p values) reflected, in part, by number of participants. The studies varied greatly in design, methodology (including laboratory tests), and analysis. Each vaccine type (ie, live, toxoid, killed, polysaccharide) elicits a specific immune response. As a result, antimalarial drugs might affect the response to one vaccine type and not another. All studies involved children and *Plasmodium falciparum* was sensitive to the drugs used.

In the most recent IPTi report, Julius Massaga and colleagues did a randomised double-blinded placebo-controlled study in 291 infants aged 12–16 weeks in Tanzania. At enrolment, children received their third dose of combined diphtheria-tetanus-pertussis (DTP) and poliomyelitis vaccines simultaneously with the first of three daily doses of amodiaquine IPTi or placebo. After 60 days, children receiving amodiaquine had significantly fewer cases of malaria fevers than controls. As part of a secondary analysis, antitoxin levels were measured for tetanus, and antibodies were assayed for diphtheria and poliomyelitis at recruitment and after 60 days.

Humoral immunity For live-attenuated viral vaccines (poliomyelitis, measles), Masaga’s IPTi study and one CH+ study showed that drug use had no effect on the response to poliomyelitis vaccine. In the CH+ study, the serological response to the poliomyelitis vaccine was only measured in 48 vaccinated children, limiting the power of the study. Response to measles vaccine was not associated with drug administration in five studies. Schellenberg et al did a randomised placebo-controlled study in which children received the measles vaccination at the time of their third (and final) dose of sulphadoxine-pyrimethamine IPTi.

In a randomised double-blinded placebo-controlled study by Faucher et al, the rate of seroconversion to live atten-
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<table>
<thead>
<tr>
<th>Country (ages) and year</th>
<th>Study design</th>
<th>% with parasitaemia (Rx/No Rx)</th>
<th>Drug used</th>
<th>Drug dose</th>
<th>Vaccine: type, doses (n)</th>
<th>% Seroconversion (Rx/No Rx)</th>
<th>GMT or post-vaccination GMT (Rx/No Rx)</th>
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</thead>
<tbody>
<tr>
<td>Tanzania (12–16 weeks) 1999–2000</td>
<td>Randomised, placebo-controlled, double-blinded</td>
<td>Baseline: 32/24 During 6-month intervention phase: malaria incidence rate per year (malaria episodes for &gt;5000 parasite per µL): 0.48–1.74</td>
<td>Amodiaquine IPTi</td>
<td>3 doses over 3 days (10 mg/kg d1+ d2, 5 mg/kg d3)</td>
<td>Polio: live, 3 (140)</td>
<td>Not reported</td>
<td>Post-Vx antibody concentration (IU/mL): IgG: 652/717† IgM: 201/147† IgG: 12–7/10–4† IgM: 0.02/0.02† IgG: 1.3–1.2†</td>
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<td>Tanzania (2–12 months) 1999–2000</td>
<td>Randomised, placebo-controlled, double-blinded</td>
<td>Acute malaria rate during first year of life (events/person-year-at-risk): 0.15/0.36*</td>
<td>Pyrimethamine + sulphadoxine IPTi</td>
<td>3 doses (at 2, 3, 9 months of age): 1/4 tab, 1/2 tab, 1 tab for children &lt;5 kg, 5–10 kg, &gt;10 kg, respectively</td>
<td>Tetanus: toxoid, 3 (140) Diptheria: toxoid, 3 (140) Measles: live, 1 (322) Tetanus: toxoid, 3 (322) Diptheria: toxoid, 3 (322)</td>
<td>Not reported</td>
<td>&gt;98/&gt;98 &gt;98/&gt;98</td>
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<tr>
<td>Gabon (4–16 years) 2000</td>
<td>Randomised, placebo-controlled, double-blinded</td>
<td>At baseline: 34 in all children Week 12: Incidence density proguanil 125, or 187.5 mg+ live, 3 (275) IgA: 45/33</td>
<td>Atovaquine+ Atovaquine 50 mg base</td>
<td>Cholera: killed, 1 (275)</td>
<td>IgG: 74/67† IgA: 45/33†</td>
<td>27/22†</td>
<td>IgG: 9.63/9.33† IgA: 2.33/1.91† 1.7–1.6†</td>
</tr>
<tr>
<td>Nigeria (0–2 years) 1976–83</td>
<td>Randomised, placebo-controlled, part-blinded</td>
<td>At any point during study: 9/41*</td>
<td>Chloroquine prophylaxis</td>
<td>&lt;1 year: 100 mg base per week; 1–2 years: 200 mg base per week from shortly after birth until age 1 or 2 years</td>
<td>Measles: live, 1 (259) Polio: live, 3 (48)</td>
<td>95/98†</td>
<td>IgG: 1.71/0.97*</td>
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<tr>
<td>Republic of Niger (9–18 months) 1985</td>
<td>Randomised, placebo-controlled, not double-blinded, Day 28: 27/54*</td>
<td>Baseline: 60/56†</td>
<td>Chloroquine prophylaxis</td>
<td>1 dose, 10 mg/kg</td>
<td>Measles: live, 1 (580)</td>
<td>76/82†</td>
<td>Not reported</td>
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<td>Nigeria (3–17 months) Before 1981</td>
<td>Randomised, placebo-controlled, not double-blinded</td>
<td>At Vx: 7/59</td>
<td>Chloroquine prophylaxis</td>
<td>50 mg base×2 doses</td>
<td>Measles: live, 1 (175)</td>
<td>Not reported</td>
<td>Post-Vx GMT at: 1 month: 4.4–2† 6 month: 3.5–2.9† 1 month: 6.6–6.7† 6 month: 5.7–5.9† Meningitis A: polysaccharide, 1 (385) Meningitis C: polysaccharide, 1 (385)</td>
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<td>Burkina Faso (1–3 years) Before 1985</td>
<td>Not randomised, placebo-controlled, not double-blinded</td>
<td>Baseline: 100/0 Post-Vx: 100/0</td>
<td>Amodiaquine prophylaxis</td>
<td>200 mg per week×4 weeks</td>
<td>Measles: live, 1 (113)</td>
<td>92/90†</td>
<td>Meningitis A at: 1 month: 2.7–1.9* 6 month: 1.8–1.6* Meningitis C at: 1 month: 3.0–2.4* 6 month: 1.6–1.6† Not reported</td>
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<td>Burkina Faso (1–3 years) Before 1982</td>
<td>Not randomised, placebo-controlled, not double-blinded</td>
<td>Post-Vx: 44 of all children</td>
<td>Chloroquine + amodiaquine prophylaxis</td>
<td>100 mg per week×3 months=200 mg per week×6 weeks Tetanus: toxoid, 1 or 2 (414)</td>
<td>99 (of all children)</td>
<td>Not reported</td>
<td>Post-Vx GMT (in responders): 0.19–0.18 U/mL</td>
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<td>Gambia (0–3 years) 1958–59†</td>
<td>Not placebo-controlled, not double-blinded</td>
<td>Post-Vx: % γ-globulins greater in no-treatment group* Chloroquine or pyrimethamine prophylaxis</td>
<td>Cholera: killed, 2 (66)</td>
<td>Not reported</td>
<td>Responders, 87/73*</td>
<td>Post-Vx GMT: 1.02/0.97</td>
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† p<0.05, ‡ p=0.05.

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uated Ty21a and cholera vaccines was not significantly different in CH+ children receiving atovaquone/proguanil prophylaxis daily for 12 weeks and CH– children. Seroconversion to cholera vaccine was low in both groups, probably due to high baseline titres of vibriocidal antibody.

Seroconversion rates of those receiving oral whole-cell killed salmonella vaccine were poor (67% vs 44% in CH+...
and CH+ children, respectively); neither the differences in these rates nor in the change in geometric mean titre (GMT) were statistically significant.

Five studies found that the seroconversion rate, change in GMT, and/or post-vaccination GMT after tetanus toxoid vaccine was not associated with IPTi or prophylaxis. Schellenberg et al administered the second and third doses of DTP vaccine (spread 4 weeks apart) with the first and second of three doses of sulphadoxine-pyrimethamine IPTi. In one study without placebo control, the proportion of children with post-vaccination titres greater than a threshold level increased with prophylaxis; the proportion of individuals with parasitaemia was not known at vaccination. No association has been found between diphtheria vaccine response, IPTi, and chemoprophylaxis.

Two studies found the response to unconjugated meningococcal vaccines was improved with prophylaxis. In one study, two weekly doses of chloroquine were given at the time of vaccination; the 1-month post-vaccination GMT for meningococcal A and C was greater in CH+ than in CH− children, but these differences disappeared after 6 months. There was a greater change in GMT in parasitaemic than in non-parasitaemic children for meningococcal A and C vaccines. In the other study, weekly chloroquine prophylaxis was given from birth to age 1–2 years. Compared with CH− children, seroconversion rates in children without antibody at the time of vaccination and change in GMT were greater in CH+ children for meningococcal C but not for meningococcal A. The number of children with antibody levels likely to be associated with protective immunity (cut-off titre 1:8) after vaccination was greater in CH+ than in CH− children for both meningococcal A and meningococcal C. The GMT at a month after vaccination was greater in CH+ than CH− children for meningococcal A and C. The importance of this finding for meningococcal A is unclear given that the titres before vaccination were also greater in CH+ than CH− children. The higher prevaccination titres in the CH+ group could be due to greater meningococcal exposure or to a suppressive effect of malaria on nasopharyngeal colonisation by meningococcal A.

Cellular immunity
No significant differences were found between Mantoux-negative CH+ and CH− children in rates of conversion or in mean diameter of skin induration after BCG vaccination, a live-attenuated bacterial vaccine. There were no differences between CH+ and CH− children or between children with acute malaria and healthy controls in the response to skin testing with Candida albicans, Mycobacterium tuberculosis, mixed streptococcal antigens, and dinitrochlorobenzene.

Conclusions
The studies are of variable quality in that not all were randomised or placebo-controlled and few were double-blind, which makes interpretation difficult. However, it is difficult and ethically problematic to give some children efficacious vaccines, treatments, or prophylaxis and deny others in the same village or community, even if all children receive the same benefits at the end of the study. Children were vaccinated at different ages. The proportion of individuals with parasitaemia at baseline differed between studies; the presence of parasites, number of parasites in the blood, and proportion with parasitaemia were not always measured. The type, dose, and duration of drug use varied between studies and the number of vaccination doses provided was not necessarily the number recommended by the WHO EPI. Not all studies measured rates of seroconversion, and different assays and definitions of vaccine response were used.

Malaria chemoprophylaxis does not enhance or impair the cellular or humoral immune response to most vaccines, as illustrated by the responses to live measles, poliovaccinlitis, and salmonella, tetanus and diphtheria toxoids, and killed salmonella and cholera vaccines. Several studies show that children with acute malaria have impaired vaccine responses compared with healthy children; we excluded them because they did not use IPTi or chemoprophylaxis. By decreasing rates and, presumably, the number of parasites in the blood, chemoprophylaxis seems to improve the response to unconjugated polysaccharide vaccine. The poor immunogenicity of unconjugated polysaccharide vaccines in young children might be because these vaccines are type-2 T-cell-independent and only activate mature B cells, increasing the immunodepressive effect of parasitaemia on humoral immunity.

The EPI, Global Alliance for Vaccines and Immunisations, and other initiatives have promoted greatly the expansion of vaccination programmes in malarious areas. IPTi shows great promise as a new public-health initiative, as has IPT for pregnant women living in malarious zones. Further, more and carefully controlled studies are needed. Further elucidation of the immunological response to additional vaccines, to malaria treatment and prophylaxis with different drugs and regimens, and to acute malaria is crucial. Of special focus must be children aged up to 2 years, who are the most vulnerable to malaria in heavily endemic areas.

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References