Waiting for intermittent preventive treatment treatment of infants to go live

Even though there has been nearly a decade of positive research results, countries and international organisations have been reluctant to adopt this life-saving tool. Prof William Brieger reports

While our tools for controlling and eventually eliminating malaria are greater than the days of the first malaria eradication efforts, they are not limitless. Strides have been made in reducing the burden of malaria disease using insecticide treated nets (ITNs) for prevention and artemisinin-based combination therapy (ACT) for treatment. Indoor residual spraying (IRS), once the prime tool in the fight to eradicate the disease, is now used somewhat sparingly taking into consideration costs, logistics, and local epidemiological and ecological conditions. Vaccines are under development and new vector management technologies are being explored, but one other available tool, intermittent preventive treatment (IPT) has not been deployed to its full potential.

IPT is different from traditional prophylaxis. 'IPT is based on the use of antimalarial drugs given in treatment doses at predefined intervals,'[1] for the express purpose of clearing malaria parasites from asymptomatic individuals. Countries in regions of stable and intense malaria transmission have adopted a policy of IPT for pregnant women (IPTp) using the drug sulphadoxine-pyrimethamine (SP) twice during pregnancy after quickening.

SP has a one-dose malaria regimen and thus, is ideal for administration as directly observed treatment (DOT) during antenatal care (ANC) visits. IPTp uptake in endemic countries has been poor, with few coming near the Roll Back Malaria 2010 target of 80% coverage with two doses, which can be blamed in part on community factors such registration for ANC services late in pregnancy and health systems factors such as frequent stock-outs of IPTp. Although the medical community has been reluctant to deliver IPTp through volunteer community health workers, this approach has been found safe and successful, without deterring seeking of other ANC services, and it addresses some of the barriers to care seeking.[2]

The first IPTi research trial was conducted in Ifakara, Tanzania by Schellenburg and colleagues of IPTi with SP, delivered at the time of the second and third doses of Diptheria-Tetanus-Pertussis/Oral Poliovirus Vaccine (DTP/OPV) and measles vaccination, at approximately 2, 3, and 9 months of age. This resulted in a 59% reduction in the incidence of clinical malaria and a 50% reduction in the incidence of severe anaemia (a PCV < 25%) in the first year of life.[3] This resulted in fewer clinic visits for fever and was found to be safe. Based on these results, the IPTi Consortium[4] was funded in 2004 by the Bill and Melinda Gates Foundation to conduct research on IPTi in different African Settings.

The early IPTi Consortium results encouraged the World Health Organization in 2005 to observe the life-saving potential of IPTi in early research trials in Tanzania and Ghana delivered in conjunction with regular child health clinic visits for the Expanded Program on Immunization (EPI). WHO indicated that full support of an IPTi policy guidance would rest on further research in other countries in the region. Specifically WHO explained that, 'It is anticipated that, by mid-2006, the Consortium will have generated sufficient evidence on the safety and efficacy of IPTi with SP to support a possible WHO policy recommendation.'[5]

The IPTi Consortium conducted a variety of randomized, double-blinded, placebo-controlled efficacy trials in Mozambique, Gabon, Kenya, Tanzania, and Papua New Guinea (PNG) using SP and other drug combinations. Further implementation studies of IPTi with SP by

Ghana pharmacy shop: SP is still sold in shops in many clinics, threatening the efficacy of the drug for IPT

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the Consortium in the aforementioned countries. The Consortium collaborated with UNICEF in Benin, Mali, Senegal, Ghana, Malawi, and Madagascar for further implementation research on IPTi. This work generated over 30 scientific publications in the Consortium's first 5 years of operation.

Even though there has been nearly a decade of positive research results on IPT for infant (IPTi), countries and international organisations have been reluctant to adopt this life-saving tool. The increasing resistance of malaria parasites to SP is one factor, but cannot explain the potential benefit of including this additional tool in the fight against malaria in some of the highest burden countries in Africa.

It was not until March 2010 that WHO issued an actual recommendation on IPTi[6] stating that, 'WHO is now recommending a new intervention against Plasmodium falciparum malaria: Intermittent Preventive Treatment for infants (IPTi).' The basic recommendation addressed the co-administration of SP-IPTi with DTP2, DTP3 and measles immunisation to infants, through routine EPI in countries in sub-Saharan Africa, in areas:

- with moderate-to-high malaria transmission (Annual Entomological Inoculation Rates ≥10), and
- where parasite resistance to SP is not high – defined as a prevalence of the 'pfdhps 540' genetic mutation of #50%.

Just recently WHO's Global Malaria Program issued a field guide for 'Intermittent Preventive Treatment for Infants Using Sulfadoxine-Pyrimethamine (SP-IPTI) For Malaria Control in Africa.'[7] It defines IPTi as 'the administration of a full therapeutic course of SP delivered through the Expanded Programme on Immunization (EPI) at intervals corresponding to routine vaccination schedules for the second and third doses of DTP/Penta3, and measles vaccination – usually at 8-10 weeks, 12-14 weeks, and ~9 months of age – to infants at risk of malaria.'

The guide reiterates the benefits of IPTi with SP as found in the IPTi Consortium studies, to wit, 'SP-IPTi reduces clinical malaria, anaemia, and severe malaria in infants in the first year of life. EPI provides a ready-made and generally well-functioning delivery system that reaches a high number of infants. Through EPI the scale-up of IPTi coverage can be rapidly achieved and its impact accelerated.' The importance of an existing healthcare platform such as EPI is in keeping with using ANC as a platform for delivery of IPTp – in short, IPT interventions should be easier to deliver if they are integrated into existing services.

To date Ghana is possibly the only original IPTi test site that has considered incorporating the intervention into its national malaria strategy. Countries in East Africa are very concerned about SP resistance. Ghana's own IPTi research[8–11] points out both positive…

- ✔ SP-based IPTi mainly works through a therapeutic and prophylactic effect over 30 to 60 days after drug application
- ✔ Intermittent preventive treatment provides considerable protection against malaria and anaemia for short periods
- ✔ IPTi may work best if focused in an areas and times of intense seasonal transmission

… and negative aspects of adopting the IPTi strategy.

- ✘ A possible rebound of severe malaria
- ✘ A sustained effect beyond post-treatment prophylaxis might be very low
- ✘ IPTi was not helpful in malnourished children

In response to some of the concerns, one can see that shorter protective periods may be associated with reduced half-life of SP as drug resistance increases, leading to the need for more frequent administrations of IPTi. Concerning IPTp, recent studies report that 'Even when there is substantial resistance, SP may be used in modified IPTp regimens as a component of comprehensive antenatal care,' and in such cases IPTp with SP is NOT associated with any increase in malaria in pregnancy.[12] Similar work is needed for IPTi.

Mothers attending a child health clinic in Akwa Ibom State, Nigeria

Another major health systems factor related to SP resistance is the continued availability and us of SP for treatment even though all endemic countries in Africa have adopted ACTs as their frontline malaria treatment. SP persists in the generally unregulated private sector, and there, because of its low price, continues to out sell ACTs. Even in the public sector, when stock-outs of ACTs occur, health staff resort to using the IPT stocks of SP for case management.

The resistance issue is being addressed by researchers. Recently the Pharmaceutical manufacturer Pfizer has been testing an azithromycin-chloroquine (AZ-CQ) combination for IPT.[13] This research has found

that AZ-CQ creates a synergistic effect overcoming any problems associated with chloroquine resistance alone.

Malaria in Pregnancy Consortium (MIPc) is currently researching other candidates to replace SP in IPTp, and this should have implications for IPTi.[14] One study is examining the use of mefloquine in pregnant women in Mozambique, Benin, Tanzania and Gabon. Another is looking at mefloquine for HIV-positive pregnant women on cotrimoxizole who cannot take SP in Kenya, Tanzania, and Mozambique. Hopefully these studies will also have lessons for IPTi.

The challenge with other combinations will be the need to extend administration of IPT up to 3 days, a major compliance challenge compared with the one-dose SP regimen. Thus, it is important to implement IPTi with SP now while it remains efficacious.

Though Burkina Faso was not one of the field sites for the IPTi Consortium's work it did express interest in piloting the concept though its application for the now defunct Global Fund Round 11.[15] The proposal did not spell out details of how IPTi would be implemented other than mentioning educational materials for IPTi. Of interest though, the Round 7 Global Fund grant application indicated that 'The cost for IPT (for pregnant women) is born by the State and is not included in this funding proposal.'[16] Subsequently in the application for the transitional funding, IPTi was not mentioned,[17] but as with the Round 7 grant, it is possible that the government intends to fund its own IPTi piloting efforts because relatively speaking, SP is quite cheap.

In the meantime IPTi research results continue to be shared. In Mali Dicko and colleagues in a large-scale intervention involving over 5000 children during a 2-year period report that, 'The implementation of the IPTi-SP resulted in a substantial reduction in all-cause mortality in children. The results of this study support the adoption and the implementation of IPTi-SP as malaria control strategy.'[18]

In the context of malaria control and elimination, no one intervention is applied alone but in combination with others including ITNs and proper case management with ACTs. Now that the tools and guidance are available for implementing IPTi, it is up countries, or even provinces or states within countries that have high and stable malaria transmission, to adopt and roll out this strategy and save children's lives.

Mozambique: health workers assess immunisation status of small children and could also determine if the child needed IPTi

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