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Is the Expanded Programme on Immunisation the most appropriate delivery system for intermittent preventive treatment of malaria in West Africa?

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Summary

OBJECTIVE To investigate the coverage and equity of the Expanded Programme on Immunisation (EPI) and its effect on age schedule, seasonality of malaria risk, and linked intermittent preventive treatment (IPT) in West Africa.
METHOD Secondary analyses of data from a trial of IPT in Ghana. The potential effectiveness and impact of EPI-linked IPT in West Africa was calculated using the coverage of Diptheria Pertussis Tetanus vaccination obtained from national surveys and the reported protective efficacies of IPT.
RESULTS In West Africa, where the transmission of malaria is highly seasonal, only 10% of malaria episodes in infants would be averted with the current coverage of EPI.
CONCLUSION In this setting, the EPI-linked IPT is not necessarily the most appropriate approach and alternative IPT schedules and delivery systems are needed.

keywords Expanded Programme on Immunisation, intermittent preventive treatment, malaria, seasonality, coverage, Ghana

Introduction

It was estimated that, in 2002, 400 million episodes of clinical malaria occurred in sub-Saharan Africa (Snow *et al.* 2005), and 94% of global deaths attributable to malaria occurred in this region (Bryce *et al.* 2003). Insecticide treated nets (ITN) have been shown to reduce the incidence of malaria by 50% (Lengeler 2004), and there are concerted national and international efforts to increase the use of ITNs. Another promising approach is the administration of intermittent preventive treatment for malaria (IPT) to infants (IPTi) or to children under five years old (IPTc), which involves administration of a predefined number of treatment courses of antimalarial drugs at specified time intervals.

Impact upon malaria incidence has varied widely in the IPT efficacy studies undertaken to date. Administration of sulfadoxine/pyrimethamine (SP) to infants at the time of the second and third DPT (Diptheria Pertussis Tetanus) and measles vaccinations reduced the incidence of malaria by 50% in an area with perennial transmission in Tanzania (Schellenberg *et al.* 2001). However, in areas with highly seasonal transmission of malaria in Ghana(Chandramohan *et al.* 2005) and Mozambique (Macete *et al.* 2006), SP–IPTi, delivered together with DPT and measles vaccinations, as in Tanzania, reduced the incidence of malaria by only 25% and 22%, respectively Amodiaquine-IPTi delivered through Mother and Child Health Clinics (MCHs) at 6, 8 and 10 months of age reduced malaria incidence by 65% in an area of Tanzania with perennial transmission (Massaga *et al.* 2003). In Senegal, three courses of SP and artesunate during the high transmission season to children under 5 years old reduced the incidence of malaria by 86% (Cisse *et al.* 2006). The IPTi trials delivered the drugs to infants at EPI and growth monitoring clinics (two along with childhood vaccinations and one not linked to vaccination), and the IPTc trials delivered the drugs by visiting the children at home.

The Expanded Programme on Immunisation (EPI) was seen as an opportunistic delivery system for IPTi, in trials in Tanzania (Schellenberg *et al.* 2001), Ghana (Chandramohan *et al.* 2005), and Mozambique (Macete *et al.* 2006). The frequency and timing of administration of IPTi was designed to link directly with the EPI vaccine schedule. EPI is now seen as a system through which sustained delivery of ITPi could be achieved (Egan *et al.* 2005). The following are necessary assumptions underpinning the approach of linking IPT with the existing EPI vaccination schedule: (1)

the average age at the time of administration of DPT2, DPT3 and measles vaccinations is optimal for protecting against malaria; (2) the seasonality of malaria transmission will not affect the protective efficacy of IPTi given throughout the year; (3) linking IPTi with the EPI vaccination schedule will maximise the coverage, equity and sustainability of IPTi programmes; (4) there are no adverse interactions between the drugs used for IPTi and EPI vaccines; (5) communities' perception of IPTi will not have a negative impact on utilisation of EPI services or *vice versa*.

Empirical evidence supporting these assumptions should be examined before adopting this strategy, particularly in the context of widely differing results from the Tanzania, Ghana, Mozambique and Senegal trials. Review of current evidence and empirical data collection are underway by the IPTi Consortium, a collaboration between most of the groups undertaking research into IPTi in Africa in relation to several of these assumptions (Egan *et al.* 2005). In this paper, we discuss whether linking IPT to the existing EPI schedule is necessarily the best option for maximising the impact of IPT, or whether in the context of West Africa this may need some adaptation to account for the much wider seasonal variations seen in the region than some of the sites for the initial IPTi trials.

Effect of age and season on protective efficacy of intermittent preventive treatment for malaria to infants

To assess the effect of age and seasonality of malaria transmission, we re-analysed the data from a recent, cluster randomised trial of IPTi in Navrongo Ghana (Chandramohan *et al.* 2005). In Navrongo, the prevalence of malaria parasitaemia in 2 to 12-month-old infants at the end of the dry season was 8.6% (95% CI 6.6, 11.0); this increased to 52.8% (95% CI 10.1, 15.4) at the end of the rainy season (Figure 1). At the end of the rainy season, the prevalence of malaria parasites was high even in two-month-old infants (40%), and it reached up to 60% by 6 months of age. The incidence of malaria in 2–23-month-old infants was low during the dry season as compared with the rainy season (Figure 2). During the rainy season, the incidence of malaria peaked at 6 to 14 months of age and remained relatively high up to 23 months of age.

The mean ages for receiving DPT2, DPT3 and measles vaccines were 3.0 (range 1.8–13.4), 4.1 (3.0–14.5), and 9.5 (6.2–19.2) months, respectively (Figure 3). In the placebo group, the annual incidence of malaria peaked between 4 months (1 episode/child) and 21 months (1.4 episode/child) of age (Figure 3). The incidence of malaria was significantly reduced by each IPT course; the greatest protective effect was after course 2 (at 4 months). Infants who received IPTi courses 1 and 2 during the wet season had the maximum protective effect (52%, 95% CI 37, 63) while those who received courses 1 and 2 during the dry season had a much lower protective effect (15%, 95% CI –1, 28) (Chandramohan *et al.* 2005).

Potential effectiveness of intermittent preventive treatment for malaria to infants in West Africa

Expected protective effectiveness (PE) of delivering IPTi through the EPI programme was calculated for 11 coun-

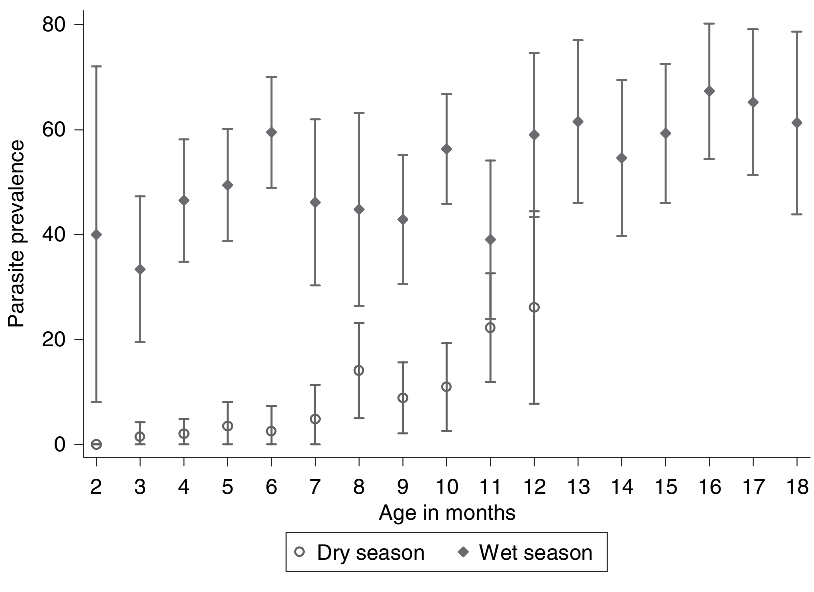

Figure 1 Prevalence of malaria parasitaemia by age and season in Navrongo, Ghana. The dry season (June 2000) survey included 618 children. The wet season (November 2000) survey included 876 children.

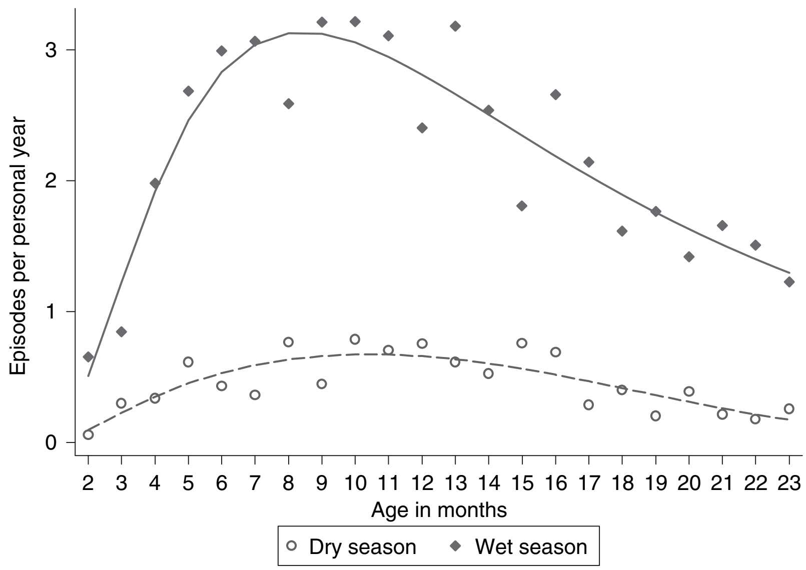

Figure 2 Incidence of malaria fever episodes by age and season in Navrongo, Ghana. The age-specific incidence of malaria in the placebo group was estimated separately for episodes occurring in the dry season (December to June) and the wet season (July to November), and this was aggregated over the whole study period (September 2000 to May 2004). A fractional polynomial Poisson regression analysis (Royston *et al.* 1999) was used to describe the fit of the age-specific incidence data during the different malaria transmission seasons.

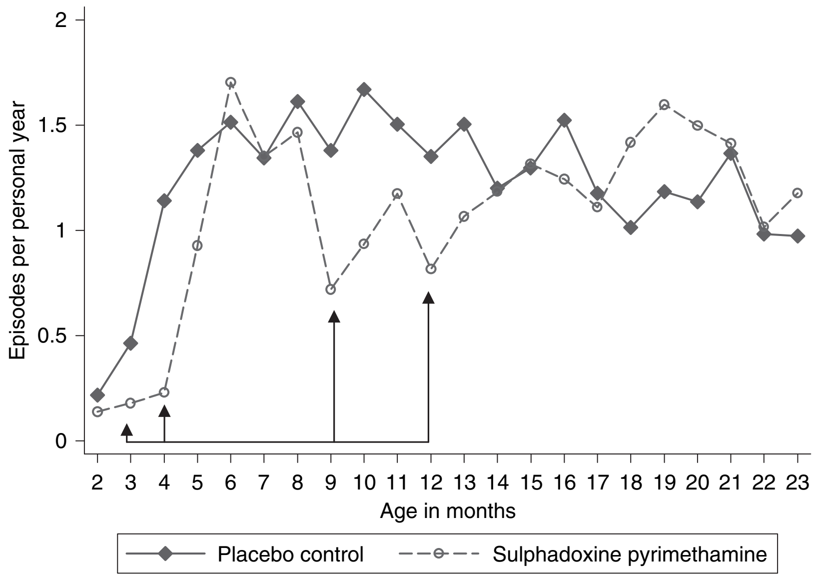

Figure 3 Annual Incidence of malaria in IPTi and Placebo group, Navrongo, Ghana. The age-specific incidence of malaria was estimated from one-calendar-year of recruitment to avoid any seasonality bias.

tries of West Africa by multiplying the coverage of DPT3 by the protective efficacy (24.8%) observed in the Navrongo trial (Chandramohan *et al.* 2005). Data on national level coverage of DPT3, disaggregated by rural/urban residence and by socio-economic quintile, were obtained from demographic and health surveys (DHS) and multiple indicator cluster surveys (MICS) (ORC Macro; UNICEF).

The expected PE of IPTi based on efficacy from the Navrongo trial and DPT3 coverage ranged from 5% in Nigeria to 20% in Ghana (Table 1). The potential PE of IPTi was higher in urban areas (median 17.2%, range 10–21%) than rural areas (median 12.7%, range 3–19%), with the exception of The Gambia. Similarly, with the exception of The Gambia, the potential PE was higher in the least poor quintile (median 17.0, range 13–22%) than in the poorest quintile (median 10.8, range 2–18%). The Gambia is the only country in which there is a greater PE of IPTi in rural areas and amongst the poorest socio-economic groups than amongst those in urban areas (18.2% *vs.* 17.4%) and the least poor (17.6% vs 16.0%). Excluding

Table 1 Episodes of malaria averted per year by EPI linked IPTi and IPT delivered through other systems in West Africa

Country	Impact of EPI-linked IPTi in infants: <1 year population	DPT3 coverage (%)	Expected protective effectiveness (%)†	Number of malaria cases‡	Malaria cases averted§	Impact IPTc through other delivery systems: 0–4 year population	Number of malaria cases¶	Cases averted at 75% IPTc coverage††	Cases averted at 50% IPTc coverage††	Cases averted at 25% IPTc coverage††
Benin	310 276	72.5[a]	18.1	698 121	126 534	1,406,291	3,164,155	2 040 880	1 360 587	680 293
Burkina Faso	539 029	57.0[b]	14.1	1 212 815	171 444	2,392,816	5,383,836	3 472 574	2 315 049	1 157 525
Cote d'Ivoire	605 489	61.9[c]	15.4	1 362 350	209 137	2,750,887	6,189,496	3 992 225	2 661 483	1 330 742
Gambia	48 370	72.2[c]	17.9	108 833	19 487	227,908	512,793	330 751	220 501	110 250
Ghana	642 437	79.5[b]	19.7	1 445 483	284 991	3,068,789	6,904,775	4 453 580	2 969 053	1 484 527
Guinea	352 474	46.2[d]	11.5	793 067	90 866	1,562,478	3,515,576	2 267 546	1 511 697	755 849
Guinea-Bissau	68 754	37.7[c]	9.3	154 697	14 464	300,471	676,060	436 059	290 706	145 353
Nigeria	4 868 478	21.4[b]	5.3	10 954 076	581 355	21,943,290	49,372,403	31 845 200	21 230 133	10 615 067
Senegal	389 846	78.0[e]	12.4	877 154	169 677	1,819,534	4,093,952	2 640 599	1 760 399	880 200
Sierra Leone	211 867	45.5[c]	11.3	476 701	53 791	925,141	2,081,567	1 342 611	895 074	447 537
Togo	214 710	56.6[c]	14.0	483 098	67 811	995,961	2,240,912	1 445 388	963 592	481 796
Total	8 251 730	–	–	18 566 393	1 789 557	37,393,566	84,135,524	54 267 413	36 178 275	18 089 138

Source of DPT 3 coverage data: [a]DHS 2001; [b]DHS 2003; [c]MICS 2000; [d]DHS 1999; [e]DHS 2004.
†protective effectiveness = DPT3 coverage × 0.25 (protective efficacy in Ghana IPTi trial).
‡<1 population × 2.25 episodes of malaria per child per year (episodes of malaria observed in the placebo group in the Senegal IPTc trial).
§Number of malaria episodes in <1 year population × 0.25 (protective efficacy of IPTi in Ghana) × respective national coverage of DPT3.
¶0–4 population × 2.25 episodes of malaria per child per year (episodes of malaria observed in the placebo group in the Senegal IPTc trial).
††Number of malaria episodes in 0–4 population × 0.86 (protective efficacy of IPTc in Senegal) × hypothetical coverage of IPTi.

The Gambia, the potential PE was approximately 30% lower in rural areas as compared with urban areas and 43% lower in the poorest quintile as compared with the least poor quintile.

Potential impact of intermittent preventive treatment for malaria to infants and children in West Africa

Episodes of malaria averted per year by IPTi delivered through EPI or by IPTc delivered through other systems were estimated by the following model: number of cases of malaria averted = target population × annual incidence × observed protective efficacy × expected coverage of IPT. In total, 18.6 million episodes of malaria are expected annually in infants across the 11 countries of West Africa. At the current level of EPI linked IPTi coverage, only 10% of these episodes (1.8 million) would be averted (Table 1). The expected number of episodes annually in population under 5 years old is 84.1 million, and 43% of these episodes (36.2 million) can be averted by achieving 50% coverage of IPTc.

There are issues to address in generalising the protective efficacy of IPTi observed in northern Ghana across countries of West Africa, and in approximating coverage ofDPT3 to the coverage of IPTi. However, we would expect that the efficacy observed in the trial setting is the best that can be achieved in most parts of West Africa with the exception of the forest and costal regions where malaria transmission is perennial. Similarly, the coverage of DPT3 is likely to be higher than the coverage of all three courses of IPTi because the proportion of children receiving all three vaccines (DPT2, DPT3 and measles) are likely to be lower than those receiving DPT3 alone. Thus, in this analysis, the effectiveness and impact of IPTi may be overestimated. Generalising the incidence of malaria observed in children under 5 years old- in the control group in one study in Senegal to the whole of West Africa is debatable. However, two more studies using weekly active surveillance showed comparable estimates of annual incidence of malaria in children under 5 years old when adjusted for the study duration, age and parasite density: 1.7 episodes per child per year in Ghana, and 1.8 per child per year in Mali (Carneiro *et al.* 2005).

Our analyses suggest that the probable effectiveness of EPI-linked SP-IPTi will be very low and inequitable in most countries in West Africa. This is due to two major factors, which are the low efficacy of IPTi unless seasonally targeted and the low and inequitable coverage of EPI. This contrasts with the situation in East Africa where higher efficacy of IPTi has been observed in the trials, and there is relatively high and equitable coverage of EPI in comparison with West Africa (Webster *et al.* 2005). We suggest the need for different regional IPT strategies in the timing of administration of IPT and in the delivery system.

Optimum age for administration of intermittent preventive treatment

The Navrongo trial data support the administration of IPT to children at 4, 9 and 12 months of age as the incidence of malaria is high from 4 months of age onwards. The value of the first course of IPTi administered with DPT2 when the average age of the child is 3 months is debatable. It can be argued that reducing the malaria parasite load during early infancy and/or delaying the first exposure to malaria until 5 months of age would lead to a better immune response to malaria infection and thereby give prolonged protection against malaria. For instance, the extended protection against malaria in the second year of life after discontinuing IPTi at 9 months of age observed in Tanzania may be attributed partially to the improved immune status achieved by three courses of IPTi including the one at DPT2 (Schellenberg *et al.* 2005). However, such an extended protection against malaria was not seen in Ghana – instead, there was an increase in high-parasite-density malaria after IPTi was stopped at 12 months of age (Chandramohan *et al.* 2005). The incidence of malaria in the second year of life was relatively high, and this supports the argument for administering IPT for an extended period, particularly in the second year of life. There is currently insufficient data to support the need for IPT course 1 linked with DPT2 vaccination.

Interaction between intermittent preventive treatment for malaria to infants and expanded programme on immunisation vaccines

There is no evidence suggestive of an interaction between SP and EPI vaccines (Macete *et al.* 2006). Further studies of interaction between candidate IPTi drugs (SP, amodiaquine, artesunate and mefloquine) and EPI vaccines are currently ongoing (Egan *et al.* 2005).

Mothers' perception of intermittent preventive treatment for malaria to infants

The perception of mothers of infants who received IPTi in Ghana was positive, and there was no negative effect on the uptake of EPI services (Chandramohan *et al.* 2005). However this cannot be generalised to the routine IPTi programmes linked to EPI because the level of information about the potential beneficial and adverse effects of IPTi and health care support given to study participants is much higher than would be routinely available in a programme setting. Perceptions of caretakers regarding IPT and the impact of IPT on EPI coverage should be studied rigorously in routine programme conditions before rolling out IPTi.

Expanded programme on immunisation linked intermittent preventive treatment or seasonal intermittent preventive treatment?

There are clear logistical advantages to delivering IPTi through the EPI where this is as effective as alternative options. In many areas of Africa, this is likely to be the best model for delivery. Under the highly seasonal malaria transmission settings of Sahelian and sub-Sahelian West Africa, a high proportion of malaria deaths are in children over one year of age (Jaffar *et al.* 1997), and much of the IPT given through EPI will potentially be taken in the low transmission season. In these circumstances, IPT administered seasonally has the potential to have a greater impact than does IPTi tied to an EPI schedule given the same level of effectiveness.

The Navrongo data confirm the extreme seasonality of the burden of malaria and suggest that seasonal targeting of IPTi is more appropriate. IPTi had a much greater protective efficacy when children received the first two courses during the rainy season (i.e., the high malaria transmission season) than when they received the same courses during the dry season (52% *vs.* 15%). Targeting of IPTi during the malaria transmission season is, therefore, more appropriate than offering IPTi throughout the year. Targeting administration of IPTi during the high malaria transmission season, however, has implications for the mode of delivery.

Delivery systems of intermittent preventive treatment

The below optimal success of public health systems in reaching children with efficacious interventions, and the need for efficient and equitable delivery systems, has recently been emphasised (Bryce *et al.* 2003; Victora *et al.* 2003). Our analysis suggests that delivering IPTi through EPI is unlikely to reach a large proportion of the target group and will miss the most vulnerable infants in some countries in West Africa, particularly in Nigeria where half of children of West Africa live, because the coverage and equity of coverage of EPI is extremely low.

The publication of a joint statement by WHO and UNICEF on the integrated delivery of ITNs and childhood immunisation (WHO/UNICEF 2004) has contributed to a recent focus on co-delivery through EPI. However, although increases in cost effectiveness are likely to be achieved, co-delivery of interventions may contribute to clustering of coverage of a range of interventions amongst certain groups (Victora *et al.* 2005), whilst others receive nothing, thereby increasing inequities (Victora *et al.* 2004). These inequities will decrease with increasing coverage. With delivery of both ITNs and IPT linked to EPI, IPTi would reach infants sleeping under ITNs and not those infants without access to ITNs. Thus, delivering IPTi through EPI would not only increase the existing inequity in health care but also lead to inefficiency in the use of antimalarials as the risk of malaria is lower in children sleeping under an ITN, living in urban areas, and away from the least poor communities.

The major challenge is to establish a system to deliver the correct doses of drug to the right age group of children at the right points in time. One option for West Africa is to offer IPT to 4 to 24-month-old children or all children under 5 years old only during the rainy season through village heath workers or 'village mothers'. High coverage of malaria chemoprophylaxis was achieved through such a delivery system over a four-year study period in The Gambia, and a relatively high coverage was sustained for five more years after the study with a low level of supervision (Allen *et al.* 1990). Establishing a vertical programme to deliver IPTc has its disadvantages. However, it would be feasible to utilise the existing maternal and child health programme and/or disease control programme managers to organise and supervise a community based delivery system. Such delivery systems have been shown to be feasible and sustainable for control of onchocerciasis (Katabarwa *et al.* 2005), filariasis (Ramaiah *et al.* 2001), and guinea worm disease (Cairncross *et al.* 1996).

Another practical option is to deliver IPT with measles supplementary immunisation campaigns (SIAs) or other mass treatments such as polio vaccine during National Immunisation Days (NIDs). Measles SIAs have taken place in several countries of West Africa since 2003, achieving high coverage and a substantial impact upon the disease burden (Otten *et al.* 2005). Integrated delivery of interventions has recently included combinations of measles and polio vaccinations, vitamin A, mebendazole, and ITNs in Ghana (Grabowsky *et al.* 2005), Zambia (Grabowsky *et al.* 2005), and Togo (*Morbidity and Mortality Weekly Report* 2005). Measles SIAs aim to interrupt transmission; they are, therefore, conducted during the dry season when measles transmission is at its lowest. Maximum efficacy of IPT in West Africa is ensured by delivery during the rainy season. In countries where measles transmission is relatively low, it may be possible to conduct the campaign during the rainy season and still manage to interrupt transmission. This would enable delivery alongside IPT. In Nigeria, where delivery together with measles SIAs would not be feasible as measles is still hyperendemic (Schimmer & Ihekweazu 2006), delivery with polio NIDs may be a promising option.

Way forward

There are many challenges to establishing a delivery system to implement an IPTc programme, and such systems are less likely to have the advantages of the longer-term sustainability of EPI; they should, therefore, only be considered where there are clear advantages. However, whether administration of IPT is a long-term solution to control malaria in children is debatable. If IPT is viewed as a short- to medium-term programme while waiting for an effective vaccine, then the focus should be on the coverage and equity of coverage than on the long-term sustainability of the programme. We suggest that reducing the disparities in delivery of IPT to the most vulnerable is a more appropriate focus than the long-term sustainability of the delivery system and that it is worthwhile to look beyond EPI-linked IPTi for control of burden of malaria in West Africa.

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Le Programme Etendu d'Immunisation est-il le système de la délivrance le plus approprié pour le traitement préventif intermittent de la malaria en Afrique de l'ouest?

objectif Etudier la couverture et l'équité du Programme Etendu d'Immunisation (PEI) et son effet sur les couches d'âge, le caractère saisonnier pour le risque de malaria et le traitement préventif intermittent (TPI) associé en Afrique de l'ouest.
méthode Analyses secondaires de données provenant d'une étude du TPI au Ghana. L'efficacité et l'impact potentiels du TPI associé au PEI en Afrique de l'ouest ont été calculés en utilisant la couverture de la vaccination diphtérie-coqueluche-tétanos (DPT3) obtenue à partir des surveillances nationales et des efficacités rapportées sur le TPI.
resultats En Afrique de l'ouest où la transmission de la malaria est fortement saisonnière, seuls 10% des épisodes de malaria chez les enfants en bas âge seraient évités avec la couverture actuelle du PEI.
conclusion Dans la région étudiée, le TPI associé au PEI n'est pas nécessairement l'approche la plus appropriée. Des programmes de TPI et des systèmes de délivrance alternatifs sont nécessaires.

mots clés Programme Etendu d'immunisation, traitement préventif intermittent, malaria, caractère saisonnier, couverture, Ghana

Es el Programa Ampliado de Inmunización el sistema más apropiado para entregar el Tratamiento Preventivo Intermitente para malaria en África Occidental?

objetivo Investigar la cobertura y equidad del Programa Ampliado de Inmunizaciones (PAI) y su efecto en el calendario por edad, la estacionalidad del riesgo de malaria y el Tratamiento Preventivo Intermitente (TPI) en África del Oeste.
método Análisis secundarios de datos de un ensayo de TPI en Ghana. Se calculó la efectividad potencial y el impacto del TPI relacionado con el PAI en África del Oeste utilizando la cobertura de la vacunación con Difteria Pertusis Tétano (DPT3), obtenida de encuestas nacionales, y eficacias reportadas del TPI.
résultados En África del Oeste, en donde la transmisión de malaria es altamente estacional, solo un 10% de los episodios de malaria en lactantes serían prevenidos con la cobertura actual del PAI.
conclusión En este enclave, el TPI relacionado con el PAI no es necesariamente el enfoque más apropiado, siendo necesarios calendarios de TPI y sistemas de entrega alternativos.

palabras clave Programa Ampliado de inmunizaciones, tratamiento preventivo intermitente, malaria, estacionalidad, cobertura, Ghana