

Impact case study (REF3b)

<p>Institution: London School of Hygiene & Tropical Medicine (LSHTM)</p>
<p>Unit of Assessment: UoA2 – Public Health, Health Services & Primary Care</p>
<p>Title of case study: Developing a new approach to malaria prevention in children: seasonal malaria chemoprevention in West Africa</p>
<p>1. Summary of the impact Research in West Africa by LSHTM and partners has shown that monthly treatment with effective antimalarial drugs during the rainy season provides children with a very high degree of personal protection against malaria, can be delivered on a large scale by community health workers at moderate cost, and with no serious side-effects. Based on this research, WHO now recommends that children living in Sahel areas where malaria is a major problem should receive such ‘seasonal malaria chemoprevention’ (SMC) with sulfadoxine-pyrimethamine plus amodiaquine. Ten countries have incorporated SMC into their strategic plans for malaria control.</p>
<p>2. Underpinning research Studies pre-1993 undertaken in the Gambia by Greenwood and colleagues showed that administration of Maloprim[®] (pyrimethamine plus dapsone) fortnightly to children under 5 during the malaria transmission season was highly effective in preventing malaria and reduced overall child mortality by about 35%. However, this approach to malaria control was not pursued due to increasing use of insecticide treated bednets (ITNs) and concerns over safety and costs.</p> <p>Interest in chemoprevention of malaria in children revived when, in 2002, a LSHTM study with partners in Senegal, planned by Greenwood (Professor of Clinical Tropical Medicine at LSHTM since 1996) and coordinated by Cissé (then LSHTM PhD student), showed that administration of sulphadoxine-pyrimethamine (SP) plus one dose of artesunate monthly for three months to children under 5 reduced the incidence of malaria over three months by 86%.^{3.1} The proportion of parasites with genotypes associated with resistance to SP at the end of the malaria transmission season was higher in children who had received the intervention than in the controls, but the number of children carrying resistant parasites was less in the intervention group.^{3.2} Several drug regimens for SMC were then considered.^{3.3} Two long-acting drug combinations (SP combined with amodiaquine (AQ) or piperaquine) were more effective than artemisinin-containing combinations, giving a high degree of protection for about four weeks. Because both SP and AQ retain efficacy in areas of the Sahel where SMC has a role, the SP+AQ combination was chosen for further studies. Initial trials of SMC had been conducted in communities with low use of ITNs. To determine whether SMC would give any added benefit in populations with high ITN coverage, trials planned by Greenwood and coordinated by Diallo (then Research Fellow at LSHTM) were conducted simultaneously with partners in Burkina Faso and Mali in 2009, in children who were all provided with an ITN. A 77% reduction in the incidence of uncomplicated malaria was observed in children who received SMC with the SP+AQ combination, with similar protection being seen against severe malaria. There was no evidence of substantial increase in risk of malaria in the first year after the intervention in children who received SMC with SP+AQ.^{3.2,3.3}</p> <p>Important policy questions that remained following these trials concerned the safety of SMC and the practicality and cost of administering SMC to children in rural areas. These issues have been investigated with partners in Senegal by Milligan (Reader in Epidemiology and Medical Statistics, LSHTM staff since 2004 as Reader), Cissé (LSHTM staff since 2008 as Clinical Lecturer) and colleagues. Their studies have shown that SMC with SP+AQ delivered by community health workers coordinated by the district health team is safe, acceptable to the community, can achieve high coverage and is highly cost effective (papers in preparation). To determine the geographical regions where SMC might be an appropriate malaria intervention, research conducted by Cairns (Research Fellow, now Lecturer, LSHTM staff since 2010) and colleagues defined the areas of Africa where malaria is highly seasonal and where incidence is high enough to warrant implementation of SMC.^{3.4}</p>

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3. References to the research

3.1 Cissé, B, Sokhna, C, Boulanger, D, Millet, J, Bâ, eIH, Richardson, K, Hallett, R, Sutherland, C, Simondon, K, Simondon, F, Alexander, N, Gaye, O, Targett, G, Lines, J, Greenwood, B and Trape, JF (2006) Seasonal intermittent preventive treatment with artesunate and sulfadoxine-pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo-controlled, double-blind trial, *Lancet*, 367(9511): 659–667, doi:10.1016/S0140-6736(06)68264-0. Citation count: 107

3.2 Dicko, A, Diallo, AI, Tembine, I, Dicko, Y, Dara, N, Sidibe, Y, Santara, G, Diawara, H, Conaré, T, Djimde, A, Chandramohan, D, Cousens, S, Milligan, PJ, Diallo, DA, Doumbo, OK and Greenwood, B (2011) Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Mali: a randomised, double-blind, placebo-controlled trial, *PLoS Medicine*, 8(2): e1000407, doi:10.1371/journal.pmed.1000407. Citation count: 21

3.3 Konaté, AT, Yaro, JB, Ouédraogo, AZ, Diarra, A, Gansané, A, Soulama, I, Kangoyé, DT, Kaboré, Y, Ouédraogo, E, Ouédraogo, A, Tiono, AB, Ouédraogo, IN, Chandramohan, D, Cousens, S, Milligan, PJ, Sirima, SB, Greenwood, B and Diallo, DA (2011) Intermittent preventive treatment of malaria provides substantial protection against malaria in children already protected by an insecticide-treated bednet in Burkina Faso: a randomised, double-blind, placebo-controlled trial, *PLoS Medicine*, 8(2): e1000408, doi:10.1371/journal.pmed.1000408. Citation count: 18

3.4 Cairns, M, Roca-Feltrer, A, Garske, T, Wilson, AL, Diallo, D, Milligan, PJ, Ghani, AC and Greenwood, BM (2012) Estimating the potential public health impact of seasonal malaria chemoprevention in African children, *Nature Communications*, 3(881), doi: 10.1038/ncomms1879. Citation count: 6

Key grants

- Greenwood, Gates Malaria Partnership (GMP), Bill & Melinda Gates Foundation, 2001–2010, \$40M.
- Cissé, GMP Studentship (LSHTM), October 2001–2005, \$176,961.
- Greenwood, A Trial of the Combined Impact of Intermittent Preventive Treatment and Insecticide Treated Bednets on Morbidity from Malaria in African Children, Bill & Melinda Gates Foundation, 2007–2010, \$2,991,720.
- Gaye, Large Scale Implementation of Intermittent Preventive Treatment through the Health Service in Senegal, Bill & Melinda Gates Foundation, 2007–2011, \$4,464,546, including LSHTM award (Milligan) \$986,000 for coordination.
- Greenwood, Defining the Role of Seasonal Intermittent Preventive Treatment in Children in Malaria Control, Bill & Melinda Gates Foundation, 2007–2010, \$309,487.

4. Details of the impact

Following encouraging results of early trials of SMC, a meeting was held in Dakar, Senegal, in October 2008 to discuss what further research questions needed to be addressed before SMC could be considered as a potential control tool. An important feature of this meeting was the attendance of malaria control managers and policy-makers as well as researchers. Areas identified for further research included drug safety, delivery of SMC to older children and the added benefit of SMC to children using an ITN. These were addressed subsequently in studies described above.

In July 2010, WHO's Global Malaria Programme convened an informal consultation to determine if there was sufficient evidence for a formal review of SMC. The committee agreed but requested more information on cost effectiveness, and on the geographical areas where SMC would be most appropriate. Following provision of this information, the SMC dossier compiled by LSHTM staff,^{5.1,5.2} was reviewed by WHO's Technical Expert Group (TEG) on malaria treatment and prophylaxis.^{5.3} Professor D Schellenberg (LSHTM since 2003) was a co-opted member of the TEG. On the basis of the dossier, the TEG recommended implementation of SMC with SP+AQ in areas of the Sahel with seasonal transmission of malaria but requested further information on the duration of protection provided by each cycle, on the optimal dosing by age and on the level of

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malaria transmission at which SMC would no longer be cost effective. This information was generated by an SMC working group (including LSHTM staff Cairns, Greenwood, Milligan) and provided to WHO. A GRADES assessment was prepared.^{5.4} In March 2012, the report of the TEG was presented to the recently established WHO Malaria Policy Advisory Committee (MPAC); Greenwood is a member. The committee endorsed the TEG recommendations and made a formal recommendation, endorsed by the Director General, that children living in areas of the Sahel and sub-Saharan with highly seasonal malaria transmission should receive SMC with SP+AQ for up to four months of the year.^{5.5}

The areas currently targeted for SMC have about 22m children under 5 among whom there are approximately 20m cases and 90,000 deaths annually from malaria. Thus, there is a potential for SMC to prevent millions of cases of malaria and tens of thousands of unnecessary deaths each year. The speed at which SMC is implemented in the target areas, and hence its impact, will depend upon local political commitment and the availability of funds to purchase and distribute antimalarials, but the process has already commenced. SMC implementation started in two countries in July 2012, and by December an implementation guide on SMC had been published by WHO, and a total of 10 countries had plans for SMC.^{5.6} In 2012, SMC was implemented by MSF in Koutiala district in southern Mali and in two areas of Moïssala district, in Chad. In Mali, malaria cases fell by 65% in the week following the first monthly cycle of SMC treatment and malaria-associated hospitalisations by 70%.^{5.7} The Senegalese Ministry of Health has secured finance to implement SMC in five regions starting in 2013 and SMC will be implemented in Northern Togo starting in 2013. With support from the Medicines from Malaria Venture (MMV), steps are being taken to obtain SP+AQ packages for SMC as cheaply as possible from a manufacturer in China.

Several factors have contributed to the rapid adoption of SMC. Firstly, LSHTM research has been conducted in close partnership with scientists in the endemic countries where SMC might be implemented. Secondly, LSHTM researchers and their partners kept in close contact with policy-makers in WHO and with national Ministries of Health from early in the development process. Thirdly, the implementation guide, based on experience in Senegal (co-authors included LSHTM staff Milligan, Cissé, Diallo), was published by WHO quickly,^{5.8} and meetings coordinated jointly by LSHTM (Milligan) and the Université Cheikh Anta Diop (Senegal), and subsequently by WHO, were held^{5.6} with national malaria control programme managers to help develop implementation plans.

The way in which SMC has progressed rapidly from pilot research studies to early implementation is widely regarded as a model of how this process should be conducted. Staff from LSHTM, working together with their partners in Africa, have played a key role in all stages of this process.^{5.9,5.10}

5. Sources to corroborate the impact

5.1 Seasonal Malaria Chemoprevention Bibliography: Publications on IPTc in children in the community under five years of age, http://www.who.int/malaria/mpac/feb2012/smc_bibliography.pdf (accessed 13 September 2013).

5.2 NDiaye, JL, Cissé, B, Ba, EH, Gomis, JF, Molez, JF, Fall, FB, Sokhna, C, Faye B, Kouevijdin, E, Niane, FK, Cairns, M, Trape, JF, Gaye, O, Greenwood, BM and Milligan, PJM (2011, unpublished) *Safety of seasonal Intermittent Preventive Treatment against malaria with Sulfadoxine Pyrimethamine +Amodiaquine when delivered to children under 10 years of age by district health staff in Senegal*. Unpublished report submitted to WHO TEG in April 2011.

5.3 WHO (2011) *Report of the Technical Consultation on Seasonal Malaria Chemoprevention (SMC)*, 4–6 May. Geneva: WHO, http://www.who.int/malaria/publications/atoz/smc_report_teg_meetingmay2011/en/index.html (accessed 11 September 2013).

5.4 Sinclair, D, Meremikwu, MM and Garner, P (2012) *Seasonal Malaria Chemoprevention for Preventing Malaria Morbidity in Children Aged Less than 5 years Living in Areas of Marked*

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Seasonal Transmission: GRADE tables to assist guideline development and recommendations, MPAC Inaugural Meeting, 31 January–2 February, http://www.who.int/malaria/mpac/feb2012/smc_grade_tables.pdf (accessed 11 September 2013).

5.5 WHO (2012) *WHO Policy Recommendation: Seasonal Malaria Chemoprevention (SMC) for Plasmodium falciparum Malaria Control in Highly Seasonal Transmission Areas of the Sahel Sub-region in Africa*. Geneva: WHO, http://www.who.int/malaria/publications/atoz/who_smc_policy_recommendation/en/index.html (accessed 11 September 2013).

5.6 Milligan, P, et al. (2013, unpublished) *Implementation of Seasonal Malaria Chemoprevention. Report of Two Meetings*.

5.7 <http://www.msf-me.org/en/news/news-media/news-press-releases/novel-program-shows-strong-promise-in-malaria-prevention-1.html>.

5.8 WHO (2013) *Seasonal Malaria Chemoprevention with Sulfadoxine-pyrimethamine Plus Amodiaquine in Children: A Field Guide*. (July 2013) Geneva: WHO, <http://www.who.int/malaria/publications/atoz/9789241504737/en/index.html> (accessed 11 September 2013).

5.9 Director, Global Malaria Programme, WHO.

5.10 Director of National Malaria Control Programme, Ministry of Health, Senegal [French].