Institution: London School of Hygiene & Tropical Medicine (LSHTM)

Unit of Assessment: 2

Title of case study: Developing a new seasonal approach to malaria prevention in children

Period when the underpinning research was undertaken: 2002-2012

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed:
Brian Greenwood	Professor	1/1/1996-present
Diadier Diallo	Assistant Professor	1/2/08-31/8/11
Paul Milligan	Reader; Professor	1/8/04-present
Matthew Cairns	Assistant Professor; Associate Professor	31/5/10-present
Catherine Pitt	Research Fellow; Assistant Professor	8/9/08-present
& associated research teams		

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? Yes

1. Summary of the impact (indicative maximum 100 words)

Millions of children in Africa benefited from a life-saving approach to malaria prevention, following research by LSHTM and partners showing its benefits. The studies demonstrated that taking antimalarial treatments every month during the rainy season, when the risk of malaria is highest, provided very high personal protection with no serious side-effects. It could also be delivered at scale by community health workers at moderate cost. As a result, the World Health Organization (WHO) recommended 'seasonal malaria chemoprevention' (SMC) for children in malaria-affected Sahel areas. Evaluations revealed high coverage: 13 countries had national SMC programmes treating about 21.5 million children in 2020. During the LSHTM-led ACCESS-SMC project supporting scale-up in 2015-16, an estimated 60,000 deaths were prevented.

2. Underpinning research (indicative maximum 500 words)

Malaria remains one of the world's biggest health problems. In 2019, nearly half of the world's population was at risk of malaria with an estimated 229 million cases worldwide. Most malaria cases and deaths occur in sub-Saharan Africa, and children under 5 are the most vulnerable group, accounting for 67% of all malaria deaths worldwide in 2019. Malaria control and elimination is therefore a global health priority, guided by global targets of reducing malaria incidence and mortality by 90%, aligned with the 2030 Agenda for Sustainable Development. Antimalarial drugs are one method of malaria prevention for high-risk populations. Studies before 2000 carried out in The Gambia by LSHTM staff demonstrated that giving 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, policy at that time focused on insecticide-treated nets (ITNs) as the dominant form of malaria control.

Interest in chemoprevention of malaria in children was revived in 2006 following an LSHTM study led by Greenwood and colleagues, with partners at the Institut de Recherche pour le Développement and the Université Cheikh Anta Diop in Dakar, Senegal. The study was a randomised, placebo-controlled, double-blind trial in 1,203 Senegalese children under 5 from 2002 to 2005. It showed that monthly administration of sulphadoxine-pyrimathine (SP), plus one dose of artesunate to children under 5 during the rainy season, reduced the incidence of malaria over three months by 86% (3.1). A further trial carried out in 2004 evaluated the most effective drug combinations; SP combined with amodiaquine (AQ) was found to be more effective than artemisinin, giving a high degree of protection and retaining efficacy in key areas of the Sahel (3.2).

These trials of SMC were carried out in communities where ITNs were not much used. Further LSHTM trials, led by Greenwood and Diallo, were simultaneously conducted in 2009, with partners at the University of Bamako and Centre de Santé de Référence de Kati, Mali, and Centre National de Recherche et de Formation sur le Paludisme, Burkina Faso, to determine whether SMC would give additional protection and benefit in populations where there was high ITN coverage (3.3, 3.4). They observed a 77% reduction in severe and uncomplicated malaria incidence in children who received SMC with the SP+AQ combination. These children did not appear to be at a substantially increased malaria risk in the first year after trial completion.

Important policy questions about the safety, practicality and cost-effectiveness of administering SMC at scale were investigated in 2012 by Milligan, Pitt and colleagues with partners at the Université Cheikh Anta Diop, Institut de Recherche pour le Développement, Dakar, Senegal, and the Senegal Ministry of Health. Their studies showed that SMC with SP+AQ delivered by district health teams using community health workers was safe, acceptable, achieved high coverage at moderate cost, and was highly effective in preventing malaria (3.5). Research by Cairns and colleagues in 2012 defined the areas of Africa where malaria is highly seasonal, to show where SMC might be an appropriate malaria intervention (3.6).

3. References to the research (indicative maximum of six references)

3.1 Cissé, B, Sokhna, C, Boulanger, D, Milet, J, Bâ, elH, 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.

3.2 Sokhna C, **Cisse B**, Ba EH, **Milligan P,** Hallett R, **Sutherland C,** Gaye O, Boulanger D, Simondon K, Simondon F, Tagett G, **Lines J, Greenwood B**, Trape J. 2008. A trial of the efficacy, safety and impact on drug resistance of four drug regimens for seasonal intermittent preventive treatment for malaria in Senegalese Children. *PLoS ONE.* 3(1):e1471. doi: 10.1371/journal.pone.0001471

3.3 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.

3.4 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.

3.5 Cisse B, Ba EH, Sokhna C, Ndiaye J, Gomis JF, Dial Y, **Pitt C**, Ndiaye M, Cairns M, Faye E, M ND, Lo A, Tine R, Faye S, Faye B, Sy O, Konate L, Kouevijdin E, Flach C, Faye O, Trape JF, **Sutherland C,** Fall FB, Thior PM, Faye OK, **Greenwood B,** Gaye O, **Milligan P**. 2016. Effectiveness of Seasonal Malaria Chemoprevention in Children under Ten Years of Age in Senegal: A Stepped-Wedge Cluster-Randomised Trial. *PLoS Medicine.* 2016;13(11):e1002175. doi: 10.1371/journal.pmed.1002175.t003

3.6 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.

We believe this body of research meets the 'at least 2*' definition given its reach, significance and rigour.

4. Details of the impact (indicative maximum 750 words)

LSHTM's researchers, in partnership with scientists in Senegal, Mali, The Gambia, Burkina Faso and Ghana, were at the forefront of research to find new ways to combat malaria in sub-Saharan Africa. Their findings led to SMC being introduced and rolled out on a wide scale as a new malaria prevention strategy. This dramatically reduced the disease in under 5s, the age group associated with the highest malaria death rate.

Having demonstrated that SMC was safe and effective, LSHTM staff facilitated a project to support national malaria control programmes and in-country health policy officials with high-quality evidence on delivery mechanisms, outcomes, and treatment efficacy and effectiveness. Before the Achieving Catalytic Expansion of SMC in the Sahel (ACCESS-SMC) project, there were several critical barriers to expanding the rainy season antimalarial treatment approach. These included lack of infrastructure and human resources, insufficient production of drugs, lack of evidence on cost-effectiveness at scale, limited evidence of safety outside a trial setting, and insufficient funding. ACCESS-SMC supported national malaria control programmes to scale up their SMC coverage, providing technical, logistical, and financial support and operational evaluation.

Evidence that seasonal malaria chemoprevention works

In 2012, the WHO Technical Expert Group reviewed the research findings as part of the WHO Global Malaria Programme consultation on SMC (5.1). As a result, the WHO recommended in the same year that children aged 3 to 59 months living in areas of the Sahel and sub-Sahel with highly seasonal malaria transmission should receive SMC for up to four months of the year (5.2). The major impact of this recommendation, underpinned by LSHTM-led research, has been realised during this REF period. In August 2013, the WHO published a guide to help countries adopt and implement the new intervention (5.3).

Regional meetings were then held with malaria control programme managers to explain the new strategy and develop implementation plans; these were initially led by the scientists, and subsequently organised by the West Africa regional Roll-Back Malaria network. SMC was rapidly implemented. In 2014, 8 countries began SMC programmes: Mali, Niger, Chad, Senegal, Nigeria, Togo, The Gambia and Burkina Faso, reaching about 2.5 million children. Also in 2014, UNITAID approved funding for SMC via the ACCESS-SMC project, which further supported SMC programmes in Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger and Nigeria. ACCESS-SMC was led by the Malaria Consortium and LSHTM, and other in-country implementation partners (Centre de Support en Santé Internationale, Management Sciences for Health, Medicines for Malaria Venture, the Malaria Modelling Consortium, and Speak Up Africa.) The project rolled out SMC in a phased manner in 2015 and 2016 to a total of around 7 million children.

In Burkina Faso and The Gambia, implementation of SMC was associated with a 42.4% and 56.6% reduction respectively in the number of malaria deaths in hospital during the high transmission period following the introduction of seasonal antimalarial treatment (5.4). The number of confirmed malaria cases at outpatient clinics in the ACCESS-SMC-supported countries reduced by between 25.5 and 55.2% (5.4). Treatment with SMC was associated with 88.2% protective effectiveness in reducing incidence of clinical malaria over 28 days in case-control studies, with low frequency of drug resistance (5.4). Through modelling, it was estimated that over the course of ACCESS-SMC, the project averted over 10 million malaria cases and 60,000 deaths in children in the seven study countries (5.5). Potential overall cost savings of USD66 million were estimated through averting costs of malaria treatment, care and death across Africa, and the net economic cost savings (after deducting the cost of administering SMC) were USD43.2 million across the 7 ACCESS-SMC countries (5.4).

Assisting expansion of SMC

Roll-out beyond ACCESS-SMC was financed by the Global Fund, UNICEF and the President's Malaria Initiative (PMI), and implemented by the Malaria Consortium and other NGOs. The 2020 World Malaria Report stated that in 2019, the mean total of children treated each month was 21.5 million in 13 countries, in increase from approximately 1.4 million children in 6 countries treated in 2013 (5.6).

LSHTM, as ACCESS-SMC's academic partner, and collaborators generated evidence on a large scale to demonstrate the long-term safety and effectiveness of SMC. Continued evaluation carried out alongside implementation demonstrated the value of SMC and so allowed implementation to continue during and beyond the ACCESS-SMC project. LSHTM also co-hosted a workshop with WHO providing pharmacovigilance training in 2015 in Morocco, to build and strengthen pharmacovigilance systems in SMC countries. Participants included representatives from national malaria control programmes and national pharmacovigilance centres (5.7).

LSHTM led evaluations which enabled and underpinned implementation by showing SMC to be highly effective even though it was complex to deliver. An independent safety review of the data by the WHO Advisory Committee on Safety of Medicinal Products corroborated SMC's effectiveness in 2017, endorsing the activities which supported the safe implementation of SMC and concluding that the benefit-risk profile of SMC was positive (5.8).

ACCESS-SMC created demand which led to increased manufacturing capacity for seasonal antimalarial drugs and the development of dispersible formulations. ACCESS-SMC guaranteed funded demand of up to 30 million treatments, which provided an incentive for medical suppliers to increase production. Dispersible tablets produced by Guilin were available for use from 2016 and those from a second supplier, S Kant Healthcare Ltd, developed in partnership with ACCESS-SMC, was submitted for review by the WHO prequalification programme in late 2020.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 World Health Organization. 2011. Report of the Technical Consultation on Seasonal Malaria Chemoprevention (SMC), 4-6 May. Geneva: WHO

- WHO/ GMP technical expert group on preventative chemotherapy reviewed LSHTM evidence (references 2, 6, 7, 8)
- Recommends SMC as malaria control strategy

5.2 World Health Organization. 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

- WHO adopts WHO/ GMP technical expert group recommendation

5.3 World Health Organization (2013) Seasonal Malaria Chemoprevention with Sulfadoxine-pyrimethamine plus Amodiaquine in Children: A Field Guide. Geneva: WHO

5.4 ACCESS-SMC partnership. 2020. Effectiveness of Seasonal Malaria Chemoprevention at scale in West and Central Africa. *Lancet.* 396; 10265, P1829-1840. doi: 10.1016/S0140-6736(20)32227-3

Unitaid project evaluation: Achieving Catalytic Expansion of Seasonal Malaria Chemoprevention in the Sahel (ACCESS-SMC). November 2016-April 2018. Final report

5.5 Seasonal malaria chemoprevention at scale: saving lives. ACCESS-SMC Technical Brief. 13 November 2017, accessed at: https://www.access-smc.org/pages/resources/45

5.6 World Health Organization (2020) World Malaria Report 2020. WHO: Geneva, pp 62-63

5.7 World Health Organization. Feature: Seasonal Malaria Chemoprevention and Pharmacovigilance, Morocco, May 2015. WHO Pharmaceuticals Newsletter. 2015(3):37-8.

5.8 World Health Organization. Integrating pharmacovigilance in seasonal malaria chemoprevention: the story so far/ Fourteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) in: WHO Pharmaceuticals Newsletter no. 4. World Health Organization, Geneva. 2017: 33-36

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