Institution: University of Oxford

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Elimination of malaria in remote regions of Myanmar

Period when the underpinning research was undertaken: Jan 2000- Jul 2020

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

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Nicholas White	Professor of Tropical Medicine, Chairman, Oxford Asian Tropical Research Units	1980 – present
François Nosten	Professor of Tropical Medicine, Director, Shoklo Malaria Research Unit (SMRU), Thailand & Myanmar	1998 – present
Frank Smithuis	Associate Professor, Director, Myanmar Oxford Clinical Research Unit (MOCRU)	2013 – present
Nicholas Day	Professor of Tropical Medicine, Director, Mahidol Oxford Tropical Medicine Research Unit (MORU), Thailand	1991 – present
Lorenz von Seidlein	Associate Professor, Senior Malariologist, MORU	2014 – present
Arjen Dondorp	Professor of Tropical Medicine. Deputy Director and Head of Malaria, MORU	2000 – present

Period when the claimed impact occurred: Aug 2013 – Dec 2020

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

1. Summary of the impact

Research by the University of Oxford's regional units in Southeast Asia developed and validated strategies to eliminate malaria in the Greater Mekong Sub-region, to prevent global spread of artemisinin-resistance. Implementation of malaria control programmes based on this research, including mass drug administration and providing health care in remote villages, has achieved near elimination of *Plasmodium falciparum* malaria in the Thailand-Myanmar border area, and dramatic reductions in *P. falciparum* and *P. vivax* in several Myanmar border regions. These interventions have transformed the health of poor and remote communities with a combined population of at least 1,000,000 people. The University of Oxford research directly influenced World Health Organisation (WHO) strategies on malaria elimination in Southeast Asia, including the goal of malaria elimination in the Greater Mekong Sub-region by 2030 and the use of mass drug administration, combating the spread of multi-drug resistant malaria.

2. Underpinning research

Identifying approaches for malarial elimination in the Greater Mekong Sub-region

The Greater Mekong Sub-region (GMS) is a trans-national region encompassing areas of 6 countries that share the Mekong River: Cambodia, Myanmar, Thailand, Vietnam, Lao People's Democratic Republic (Lao PDR), and parts of China. The GMS is particularly crucial in the global fight against malaria, as it is in this region that parasites with resistance to malarial drugs have emerged and spread around the world. International efforts are now focused on trying to prevent the global spread of resistance to artemisinin and partner drugs, which emerged in the GMS. The University of Oxford Nuffield Department of Medicine Centre for Tropical Medicine and Global

Health has several regional units working in the GMS engaged in research tackling malaria, including the Mahidol Oxford Tropical Medicine Research Unit (MORU), Shoklo Malaria Research Unit (SMRU) and Myanmar Oxford Clinical Research Unit (MOCRU). Ongoing research by these units, since 2000, has developed, tested, and implemented tools for malaria elimination.

University of Oxford researchers, including N. White, N. Day and A. Dondorp, have led the international Tracking Resistance to Artemisinin Collaboration, which carried out extensive mapping of artemisinin resistance across 10 countries between May 2011 and April 2013 [1]. They found that artemisinin-resistant *P. falciparum* was established in eastern Myanmar, western Cambodia and Thailand, and southern Vietnam, and was emerging in southern Laos and northeastern Cambodia, demonstrating an urgent need for radical measures in the GMS to prevent further spread [1]. To look in more detail at the prevalence and spread of malarial parasites in the GMS, the University of Oxford researchers developed an ultra-sensitive quantitative PCR method that was able to detect low levels of malarial parasites (limit of accurate detection, 22 parasites/mL), even in asymptomatic people in low endemic areas. Using this approach across the GMS, they discovered an unsuspected high prevalence of asymptomatic sub-microscopic parasitaemia, enabling them to work out the prevalence of parasitaemia and find "hot spots" of transmission [2]. Several University of Oxford studies showed that asymptomatic infections are an important source of malaria transmission in the GMS, and the need for interventions beyond treating symptomatic cases. For example, their modelling showed that to eliminate drug-resistant malaria in the GMS, it would be necessary to eliminate all malaria in the region [3], including mass drug administration (MDA) to eliminate foci of higher transmission.

Assessing risks of anti-malarial drugs

The University of Oxford researchers conducted large meta-analyses to assess the risks of several anti-malarial drug treatments, investigating whether they could be used on a large scale (e.g. in MDA) without substantial risks. Dihydroartemisinin-piperaquine is an effective artemisinin-based combination therapy, but there had been some evidence that piperaquine might be associated with cardiac arrhythmias. In a key example of assessing drug risk, the University of Oxford researchers performed a large systematic review and meta-analysis and found there was no increase in risk of cardiac sudden death following treatment with piperaquine [4]. This research showed that piperaquine could be used on a large scale without cardiotoxicity. The researchers also showed the safety of widespread primaquine use.

Field trials of mass drug administration

Based on these findings and their wider research in the GMS, the University of Oxford researchers undertook field trials to evaluate the acceptability, safety and effectiveness of targeted malaria elimination. Mass drug administration was tested initially on a small scale in four malaria-endemic villages in Karen (Kayin) State in Myanmar [5], and then in 16 remote villages (8 MDA-treated, 8 controls) with prevalent artemisinin resistance: in the 'epicentre' of resistance in western Cambodia, as well as Lao PDR, Vietnam and Myanmar [6]. The field trials achieved high coverage, were safe, and associated with at least short-term dramatic declines in *P. falciparum,* for example 92% decrease in *P. falciparum* prevalence in the villages treated with MDA, compared to a 29% decrease in control villages [6].

3. References to the research (University of Oxford employees in bold)

1. **Ashley EA** *et al.* for the Tracking Resistance to Artemisinin Collaboration (TRAC) (2014). Spread of Artemisinin Resistance in *Plasmodium falciparum* Malaria. *N Engl J Med* 371:411-423 DOI:10.1056/NEJMoa1314981. (**White NJ**, *corresponding author; 30 of 82 named authors at University of Oxford)*. Citations: 1637 (Google Scholar 02-2021)
2. **Imwong M, Stepniewska K, Tripura R, Peto TJ,**… **Day NPJ, Nosten F, Dondorp A, White NJ**.(2016) Numerical distributions of parasite densities during asymptomatic malaria. *J Infect Dis*. 213(8):1322-9. DOI:10.1093/infdis/jiv596. *(11 of 19 authors at the University of Oxford)*. Citations: 85 (Google Scholar 02-2021)
3. **Maude RJ,** Pontavornpinyo W, Saralamba S, Aguas R, Yeung S, **Dondorp A, Day N, White NJ, White L.** (2009). The last man standing is the most resistant: eliminating artemisinin-resistant malaria in Cambodia. *Malaria J.* 8:31 DOI:10.1186/1475-2875-8-31. Citations: 193 (Google Scholar 02-2021)

4. **Chan XHS,** Win YN, Mawer LJ, Tan JY, Brugada J, **White NJ**. (2018). Risk of sudden unexplained death after use of dihydroartemisinin-piperaquine for malaria: a systematic review and Bayesian meta-analysis. *Lancet Infect Dis*.;18(8):913-23. DOI:10.1016/S1473-3099(18)30297-4 Citations: 34 (Google Scholar 02-2021)
5. **Landier J**…**Dondorp A, White N, Nosten F**. (2017). Safety and effectiveness of mass drug administration to accelerate elimination of artemisinin-resistant falciparum malaria: A pilot trial in four villages of Eastern Myanmar. *Wellcome Open Research* DOI:10.12688/wellcomeopenres.12240.1 *(13/22 authors at University of Oxford)* Citations: 62 (Google Scholar 02-2021)
6. **von Seidlein L, Peto TJ, Landier J**,…**Nosten FH, Dondorp AM, White NJ**. (2019). The impact of targeted malaria elimination with mass drug administrations on falciparum malaria in Southeast Asia: A cluster randomised trial. *PLoS Med*. 16(2):e1002745. DOI:10.1371/journal.pmed.1002745 *(21 of 73 authors at University of Oxford)* Citations: 49 (Google Scholar 02-2021)

Examples of funding: Grants from Bill and Melinda Gates Foundation totalling USD42,200,000 for the period 2011-2018, to the University of Oxford for malaria elimination projects in the GMS.

4. Details of the impact

Influencing World Health Organisation strategies for malaria elimination

The University of Oxford-led research has influenced international strategy that is being implemented in the GMS. Specifically, in 2014, the WHO Drug Resistance and Containment Technical Expert Group for malaria (chaired by A. Dondorp, F Smithuis on committee) provided evidence to the Malaria Policy Advisory Committee of the WHO (MPAC; N. White on committee). This evidence included University of Oxford-led research on the prevalence of artemisinin resistance in the GMS [1], pilot MDA in the GMS [5, 6], and community health worker programmes in Myanmar (see below, led by F. Smithuis) [A]. On the basis of evaluation of this evidence, MPAC recommended the elimination of *P. falciparum* in the GMS by 2030 [B], to counter the threat of multidrug resistance – as advocated by the University of Oxford research (e.g. [3]) – and this goal was adopted as WHO strategy in 2015 [C].

Also, several tools for malaria elimination that were developed and assessed through University of Oxford research have been endorsed by the WHO. MDA has been controversial, and University of Oxford researchers and their findings (e.g. [3, 5, 6]) have had a major influence on the debate [D]. Since 2015, the WHO has endorsed MDA as a strategy for malaria elimination in low transmission areas [E], influenced by evidence from University of Oxford research projects (e.g. [5, 6]) [A, B]. Specifically for the GMS, the 2015 WHO recommendations state "*given the threat of multidrug resistance and the WHO call for malaria elimination in the Greater Mekong subregion (GMS), MDA may be considered as a component of accelerated malaria elimination efforts in areas of the GMS with good access to treatment, vector control and surveillance*" [E]. Also, the assessments of drug risk from University of Oxford research (e.g. [4]), contributed to the recommendations of drug choices for MDA, with the MPAC noting in 2017 that "*the cardiovascular risk associated with the antimalarial drugs piperaquine, amodiaquine, chloroquine is considered very low and these medicines can be used in mass drug administration for malaria"* [F], and the WHO 2017 Malaria MDA Field Manual recommending dihydroartemisinin-piperaquine as part of MDA [G].

Achieving elimination of malaria in remote regions of Myanmar

Myanmar has the greatest malarial burden in the GMS, with 79% of all malaria cases in the GMS in 2012. Reducing malaria transmission in high-transmission areas in Myanmar is one of the priorities of the WHO GMS strategy [C]. Much of the burden of malaria in Myanmar is in poor and extremely remote communities, particularly in the border regions; the villages may be accessible only on foot or by off-road vehicles, and inaccessible during monsoon rains. Before 2013, healthcare systems in these communities had been weakened by long-term under-investment and conflict, leaving poor infrastructure and most villagers with no access to healthcare professionals. The University of Oxford research units in the region applied the knowledge and tools they had developed (including [1-6]) to implement targeted malaria elimination strategies that have caused dramatic declines in cases of malaria, transforming the health of local communities with a

combined population of more than 1,000,000 people and contributing substantially to the WHO goal of malaria elimination by 2030.

MDA and early treatment in Karen (Kayin) State

Between May 2014 and April 2017, the Shoklo Malaria Research Unit (SMRU) established 1,222 malarial 'posts' providing free access to early malaria diagnosis and treatment to remote communities in Karen State, along the Myanmar-Thai border [H]. In this time, they diagnosed and treated approximately 365,000 people [H]. Using the ultrasensitive PCR methods (e.g. [2]), they identified villages that were malarial hotspots, and 50 hotspot villages were treated with MDA drug regimes - dihydroartemisinin–piperaquine plus single-dose primaquine once per month for 3 consecutive months - guided by University of Oxford research on using MDA as an elimination strategy and the choice of drugs (e.g. [3]). In the MDA-treated villages, there was a 5-fold decease in *P. falciparum* incidence. By April 2017, these interventions had resulted in 965 (79%) of 1,222 villages with malarial posts being free from *P falciparum* malaria for at least 6 months [H]. According to SMRU, in 2020, there were 1,222 malarial posts in operation and 1,060 of these (87%) had reported zero cases of *P. falciparum* malaria during 2020, showing sustained near-elimination of *P. falciparum* malaria. In the HpaPun district (the most remote and malarious area of Karen State) the yearly incidence of *P. falciparum* malaria has decreased by 96% since 2014, when the programme began, and by 83% since 2016, when the majority of the malarial post network was established. Importantly, the prevalence of artemisinin resistance molecular markers was stable over 3 years (2014-2017), indicating success in preventing spread of drug resistance [H].

This elimination of malaria has transformed health on both sides of the Myanmar-Thai border. Importantly, removing the burden of malaria from the health care systems in these remote areas enables their limited resources to be redirected to treating other diseases. The director of a hospital in Tak Province in Thailand, close to the border with Myanmar, credited the interventions by SMRU and MORU for a dramatic change numbers of patients with malaria, and stated: "*Malaria (P. falciparium) was one of the major causes of illness and hospital admission along the Thai-Myanmar border region until the last five years. Most of the malaria came from the Myanmar side of the border…Now it has almost gone*" [I]. The director of the Department of Medical Science in the Ministry of Public Health for Thailand confirmed that, due to the SMRU work in Karen State, "*by 2020, P. falciparum malaria had been almost completely eliminated, thus preventing the spread of artemisinin resistance…The impact on the health of the population has been remarkable"*, with cases in Tak Province (population approximately 600,000) being very rare in 2020 compared to being "*a major cause of morbidity and mortality in the past*" [J]. Refugees and migrant workers in the border region have particularly poor access to healthcare [D], and the director of a charity providing health services to these people confirmed that SMRU and MORU's malaria eradication campaigns have made *"significant changes"* in the region [K].

Community health workers in border regions

Since 2013, the Myanmar Oxford Clinical Research Unit (MOCRU) has worked together with the medical aid charity Medical Action Myanmar (MAM) to achieve malaria elimination through community health worker (CHW) programmes. These CHWs in remote border areas of Myanmar, adjoining Thailand, India, Bangladesh and China, use rapid diagnostic tests for malaria and provide high-quality treatment. The rationale for implementing these CHW programmes in these remote regions was based on University of Oxford research demonstrating the need for malaria elimination in these key areas with emerging drug resistance (including [1, 2, 3, 6]).

MAM initially started the programme in 2011 with 103 CHWs in Mon State, but working with MOCRU from 2013 the programme expanded to 1,326 CHWs across eight regions and covering approximately 728,057 people (1.3% of population of Myanmar) [L]. They diagnosed and treated more than 21,000 cases of malaria. For each year that the CHW programme operated, there was a 70% (95% CI 66–73%) decrease in *P. falciparum* incidence and a 64% (95% CI 59–68%) decrease in *P. vivax* incidence. Overall, this project led to a dramatic decrease in malaria: 97% decrease in falciparum malaria and 95% decrease of vivax malaria within 3 years (up to 2016) [L]. Crucially, from 2013, the CHWs began to provide a basic health care package in addition to malaria diagnosis and treatment. This included treatment for malnutrition, diarrhoea and respiratory tract infections, and it brought two strands of benefits. Firstly, local people with other

health conditions received diagnosis and treatment, including, in 2016, diagnosis of 14,509 cases of pneumonia and identification and referral to hospital of 6,278 patients with suspected tuberculosis [L]. Secondly, this provision of services beyond malaria by the CHWs ensured that people continued to seek their help even after there were large reductions in malaria, ensuring the few remaining cases of malaria continued to be detected and treated early, which is essential for elimination [L]. In all 167 communities in Mon state where MAM had introduced CHWs, falciparum malaria was eliminated, with only a single - imported - positive case detected from 55,000 rapid diagnostic tests during 2017-2018.

5. Sources to corroborate the impact

A. Minutes of WHO Drug Resistance and Containment Technical Expert Group for malaria, April 2014, discussing University of Oxford research.
B. MPAC recommendations to the WHO on malaria elimination in the GMS, Sept 2014.
C. WHO Strategy for elimination of malaria in the GMS (2015-2030), published 2015.
D. Science (AAAS) report "*Drug resistance triggers war to wipe out malaria in the Mekong region*", April 2016, DOI:10.1126/science.aaf9947, discussing strategies for malaria elimination, extensively quoting University of Oxford researchers.
E. WHO Global Malaria Programme recommendations for MDA, mass screening and treatment, and focal screening and treatment, Nov 2015.
F. MPAC presentation to WHO on MDA for malaria, Mar 2017.
G. WHO field manual on MDA for falciparum malaria, 2017 (including citation of WHO report "*Safety of 8-aminoquinoline antimalarial medicines"* by Recht, Ashley and White (May 2014)).
H. Landier J, Parker DM, Thu AM, Lwin KM, Delmas G, Nosten FH, Malaria Elimination Task Force G. Effect of generalised access to early diagnosis and treatment and targeted mass drug administration on *Plasmodium falciparum* malaria in Eastern Myanmar: an observational study of a regional elimination programme. *Lancet* 2018, 391(10133):1916-26. DOI: 10.1016/S0140-6736(18)30792-X
I. Letter from Director (1983-2019) and doctor at Mae Ra Mat Hospital, Tak Province, Thailand (Dec 2020), describing benefits of malaria elimination in border areas.
J. Letter from director general of the Department of Medical Science in the Ministry of Public Health, Thailand, describing effects of SMRU work in Myanmar.
K. Letter from director of non-governmental organisation, Mae Tao Clinic, which provides healthcare near the Myanmar-Thai border, particularly to refugees and migrant workers, describing contribution of SMRU/MORU in malaria eradication campaigns.
L. McLean ARD, Wai HP, Thu AM, Khant ZS, Indrasuta C, Ashley EA, Kyaw TT, Day NPJ, Dondorp A, White NJ, Smithuis FM. Malaria elimination in remote communities requires integration of malaria control activities into general health care: an observational study and interrupted time series analysis in Myanmar. *BMC Med*. 2018 Oct 22;16(1):183. DOI: 10.1186/s12916-018-1172-x.