Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

ALERTING THE WORLD TO ARTEMISININ RESISTANCE

Summary of the impact:

Researchers at the Mahidol-Oxford Research Unit (MORU) in Thailand performed the first comparative trials to unambiguously show artemisinin resistance in *Plasmodium falciparum* parasites in western Cambodia, as well as its emergence on the Thailand-Myanmar border. These studies emphasised the importance of urgent containment, leading to rapid responses from the World Health Organization (WHO) and international governments for the tracking and containment of drug-resistant malaria.

Underpinning research:

The *Plasmodium falciparum* parasite is transmitted by the female Anopheles mosquito and causes the most dangerous form of malaria in humans. Due to vital research from the University of Oxford's Mahidol-Oxford Research Unit (MORU) in Thailand, ACT was recommended by the WHO as the first-line treatment for malaria in 2006, and has since been used to treat both mild and severe *Plasmodium falciparum* malaria worldwide. As a result, ACT, along with scaled up preventative measures in malaria endemic areas, has been responsible for significant reductions in malaria-related mortality of more than 25% globally over the past decade. The continued success of artemisinin as the gold-standard antimalarial has been a major public health priority for local governments, the WHO, and MORU for the past two decades. But while MORU researchers were collating data for a longitudinal study on the resistance profile of artemisinin on the northwestern border of Thailand, concerns regarding tolerance to artemisinin in western Cambodia began to emerge[1]. These concerns were confirmed in a 2008 study[2], which reported artemisinin resistance in approximately 3% of patients in the Battambang Province[2].

Responding quickly, University of Oxford researchers at MORU performed two randomised trials comparing the effectiveness of artemisinin-based treatments for uncomplicated falciparum malaria in western Cambodia and northwestern Thailand[3]. Published in June 2009, this study showed reduced *in vivo* susceptibility to artesunate in *Plasmodium falciparum* parasites in western Cambodia, resulting in a resistance rate of approximately 30% – ten times higher than previous reports[3]. One month later, in July 2009 the MORU published a study showing that standard dosing of artemisinin can cause resistance in patients with low drug levels and high parasite burdens, particularly among children and pregnant women. This study also showed that patients with hyperparasitaemia (a parasite blood count greater than 250,000 per µL), who had received several treatments, were at a greater risk of reoccurrence and resistance to artemisinin therapy. This research emphasised the importance of ensuring that only artemisinin combinations are used, rather than monotherapies. It also highlighted the importance of tailoring treatment regimens to suit the pharmacokinetic needs of patients, particularly children, pregnant women, and those suffering from hyperparasitaemia[4].

A 2010 review from MORU summarised the extent of artemisinin resistance and outlined key strategies to delay and contain its spread, including[5]: increased coverage with prompt and effective antimalarial treatment; reduction of drug pressure, e.g. exploring alternative treatments; mass ACT administration to targeted populations; increased surveillance, investigation, and targeted control measures; further research into identifying multiple first-line therapies; and further research into alternative control methods, e.g. malaria vaccines[5].

In 2012 MORU published its ten-year longitudinal study on the resistance profile of artemisinin

therapy on the northwestern border of Thailand, between 2001 and 2010. This pivotal study not only showed that artemisinin-resistant *Plasmodium falciparum* parasites had emerged along the Thailand-Myanmar border, eight years prior to publication, it also reported that rates of resistance were rapidly increasing[6], further emphasising the need for rapid containment.

References to the research:

1. Jambou, R. *et al.* Resistance of Plasmodium falciparum field isolates to in-vitro artemether and point mutations of the SERCA-type PfATPase6. *Lancet* **366,** 1960–1963 (2005). http://dx.doi.org/10.1016/S0140-6736(05)67787-2. ***First study to raise concerns about tolerance to artemisinin in western Cambodia.***

2. Noedl, H. *et al.* Evidence of artemisinin-resistant malaria in western Cambodia. *N. Engl. J. Med.* **359,** 2619–2620 (2008). doi: 10.1056/NEJMc0805011. ***Study reporting artemisinin resistance in 3% of patients in the Battambang Province, western Cambodia.***

3. Dondorp, A. M. *et al.* Artemisinin resistance in Plasmodium falciparum malaria. *N. Engl. J. Med.* **361,** 455–467 (2009). doi: 10.1056/NEJMoa0808859. ***Mahidol-Oxford's pivotal study showing a 30% resistance rate to artesunate in Plasmodium falciparum parasites in western Cambodia.***

4. White, N. J. *et al.* Hyperparasitaemia and low dosing are an important source of anti-malarial drug resistance. *Malar. J.* **8,** 253 (2009). doi: 10.1186/1475-2875-8-253. ***Mahidol-Oxford's study showing that standard dosing of artemisinin can cause resistance in patients with low drug levels and high parasite burdens, as well as patients with hyperparasitaemia.***

5. Dondorp, A. M. *et al.* Artemisinin resistance: current status and scenarios for containment. *Nat. Rev. Microbiol.* **8,** 272–280 (2010). doi: 10.1038/nrmicro2331. ***A review from Mahidol-Oxford summarising the extent of artemisinin resistance and outlining key strategies to delay and contain its spread.***

6. Phyo, A. P. *et al.* Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study. *Lancet* **379,** 1960–1966 (2012). doi: 10.1111/j.1365-2125.2011.04103.x. ***Mahidol-Oxford's ten-year longitudinal study showing that artemisinin-resistant Plasmodium falciparum parasites had emerged along the Thailand-Myanmar border eight years prior to publication, and that rates of resistance were rapidly increasing.***

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Details of the impact:

Researchers from the University of Oxford's Mahidol-Oxford Research Unit, Thailand (MORU), were the first to expose the full extent of artemisinin resistance in western Cambodia, prompting urgent action from local governments and the WHO[7]. The Unit's longitudinal study showing the spread of resistance to the Thailand-Myanmar border confirmed the ferociousness of the problem, prompting further action and funding from health authorities and governments around the world for rapid research and containment programmes. Following the publication of MORU's June 2009[3] paper on artemisinin resistance in western Cambodia the WHO released a *Global report on antimalarial drug efficacy and drug resistance: 2000–2010*[8], which cites MORU's 2009 study as key evidence to artemisinin resistance. This research also provided evidence for the WHO's definition of resistance, characterised by slow rates of parasite clearance[8].

MORU's July 2009[4] paper also provided evidence to the WHO that measures can be taken in the clinic to prevent the spread of resistance[8]. The study was cited in the WHO's *Global report on*

antimalarial drug efficacy and drug resistance: 2000–2010[8], which emphasised the need for correct prescribing, adherence to prescribed drug regimens, and provision of effective treatment regimens, particularly among hyperparasitaemic patients. In 2011 the WHO released its *Global plan for artemisinin resistance containment (GPARC)*[9] – a worldwide "call to action" for the prevention of further resistance. The GPARC report cites evidence from MORU[4] studies and recommends several courses of action, reflecting MORU's key strategies[5] for the containment of malaria resistance, including[9]:

- Stopping the spread of resistant parasites, e.g. mass screening and drug administration in target areas;
- Increasing monitoring and surveillance to evaluate the threat of artemisinin resistance;
- Improving access to diagnostics and rational treatment with ACTs;
- Investing in artemisinin resistance-related research; and
- Motivating action and mobilising resources (from stakeholders at global, regional, and national levels)[9].

As a result of the University of Oxford's research and the subsequent call to action from the WHO, a number of government organisations have pledged assistance for further research into artemisinin resistance in Southeast Asia. The UK Department for International Development has set up the *Artemisinin Resistant Malaria Program* appointing MORU as the lead research institute on the project. The aim of this collaborative program is to rapidly identify and geographically contain artemisinin resistance, in order to prevent its spread to other parts of Southeast Asia and Africa[10]. As part of this program the *Tracking Resistance to Artemisinin Collaboration* was launched in January 2011, to investigate the spread of parasite resistance to artemisinin-based therapies in western Cambodia, and on the Thailand Myanmar border[11]. MORU's 2012 study, which emphasised the global threat of artemisinin resistance, has received worldwide media attention from Reuters[12] and TIME magazine[13], to The Times of India[14], and the Deccan Herald (India)[15]. Such widespread media attention has highlighted the problem of resistance, encouraging charities and investors to support global containment programs. This media attention has also improved social understanding of the problem in high-risk areas, such as India.

Increased funding for research into artemisinin resistance has led to ground-breaking outcomes in the genetic understanding of malaria parasites. A recent discovery from Oxford University researchers, published in April 2013, shows that malaria parasites in western Cambodia are genetically different from the strains of parasites found in other parts of the world, such as Africa. These findings will make it possible for health care workers to track the resistant strains of malaria parasites as they emerge, and to develop an appropriate response[16].

Sources to corroborate the impact:

7. Samarasekera, U. Countries race to contain resistance to key antimalarial. *Lancet* **374,** 277–280 (2009). http://dx.doi.org/10.1016/S0140-6736(09)61349-0. ***Review by Udani Samarasekera, senior editor of The Lancet, regarding the emergence of artemisinin resistance. This review outlines the timeline of the discovery of resistance, showing the pivotal role of Mahidol-Oxford's research in identifying resistance, and prompting action from local governments and the WHO.***

8. World Health Organization. *Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000-2010*. Geneva:WHO (2010). [Accessed June 2013] http://whqlibdoc.who.int/publications/2010/9789241500470_eng.pdf ***WHO report released in 2010 following Mahidol-Oxford's identification of artemisinin resistance. This report directly cites Mahidol-Oxford's June 2009 study as key evidence for artemisinin resistance, and its July 2009 study as evidence for the use of combination therapy over monotherapy, for the prevention of resistance.***

9. World Health Oganisation. *Global Plan For Artemisinin Resistance Containment (GPARC).* Geneva: WHO, (2011). [Accessed July 2013] http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf ***WHO's Global plan for artemisinin resistance containment, a worldwide "call to action" for the prevention of further resistance, citing evidence from Mahidol-Oxford, and recommending several courses of action, reflecting Mahidol-Oxford's key strategies for the containment of malaria resistance.***

10. Department for International Development - Research for Development Project Record. *Artemisinin Resistant Malaria Programme,* 2010-2014. [Accessed July 2013] http://r4d.dfid.gov.uk/Project/60881/Default.aspx. ***Mahidol-Oxford is the lead research institute working on the UK Department for International Development's, Artemisinin Resistant Malaria Program.***

11. WorldWide Antimalarial Resistance Network (**WWARN**).Tracking Resistance to Artemisinin Collaboration (TRAC) [Accessed July 2013] http://www.wwarn.org/partnerships/projects/trac. ***Mahidol-Oxford is the leading partner institute for the Worldwide Antimalarial Resistance Network's, Tracking Resistance to Artemisinin Collaboration.***

12. Lyn, T.E. Drug-resistant malaria spreads along Thai-Myanmar border-study *Reuters (U.S. Edition)* [online] (6 April 2012) [Accessed July 2013] http://www.reuters.com/article/2012/04/05/us-malaria-myanmar-drugresistance-idUSBRE8340ZI20120405. ***News article about artemisinin resistance on Thai-Myanmar border.***

13. Walshe, B. Drug-Resistant Malaria Is Spreading, and It Could Be a Public Health Disaster. *TIME* [Online] (6 April 2012) [Accessed July 2013] http://healthland.time.com/2012/04/06/drug-resistant-malaria-is-spreading-and-it-could-be-a-public-health-disaster/. ***News article about artemisinin resistance on Thai-Myanmar border.***

14. Sinha, K. Drug-resistant malaria spreading faster and wider. *Times of India* [online] (6 April 2012) [Accessed July 2013] http://articles.timesofindia.indiatimes.com/2012-04-06/science/31299610_1_drug-resistant-parasite-artemisinin-resistance-drug-resistant-malaria ***News article about artemisinin resistance on Thai-Myanmar border.***

15. Drug-resistant malaria may spread, India warned. *Deccan Herald* [Online] (6 April 2012) [Accessed July 2013] http://www.deccanherald.com/content/240094/drug-resistant-malaria-may-spread.html***News article about artemisinin resistance on Thai-Myanmar border.***

16. Miotto, O. *et al.* Multiple populations of artemisinin-resistant Plasmodium falciparum in Cambodia. *Nat Genet*. 45(6):648-55 (2013). doi: 10.1038/ng.2624. ***The most recent discovery from Mahidol-Oxford shows that malaria parasites in western Cambodia are genetically different from the strains of parasites found in other parts of the world, such as Africa. This will enable researchers to track resistant strains of malaria parasites, allowing rapid detection of resistance as it emerges.***