Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

EXPOSING A MURDEROUS TRADE

Summary of the impact:

With over half a million malaria-related deaths every year, the existence of counterfeit antimalarial medication continues to have a devastating effect on malaria-related mortality and morbidity on a global scale. Primary investigations into this murderous trade, led by Dr Paul Newton at the University of Oxford's Centre for Tropical Medicine, have prompted criminal investigations, drug trafficking arrests, intervention from the World Health Organization, and have also led to the establishment of new screening facilities and mobile screening technology in affected areas. This research, and the interventions it has fuelled will save thousands of lives.

Underpinning research:

The introduction of highly effective artemisinin combination drug therapies over the past decade has significantly reduced malaria transmission across Africa, with a 25% global reduction in malaria mortality since 2000. In spite of this, the 2011 "World Malaria Report" estimated there were 655,000 malaria-related deaths in 2010, with the majority of these occurring among children in Africa. One such reason for this continued death toll is the existence of fake antimalarial drugs.

Concerned about the public health impact of counterfeit antimalarial drugs, a team of researchers at the University of Oxford's Centre for Tropical Medicine, based in Bangkok, Thailand, set out to investigate this damaging trade as far back as 1999.

In a primary study led by Dr Paul Newton at the University of Oxford's Centre for Tropical Medicine, researchers were the first to identify the characteristics and to describe the epidemiology of fake antimalarial drugs in Southeast Asia. After analysing 104 samples of artesunate-based medication from stores and pharmacies in Cambodia, Laos, Myanmar (Burma), Thailand, and Vietnam, they found that 38% of the drugs did not contain any detectable artesunate. They also noted that the cost and physical appearance of the fake packaging made the counterfeits difficult to distinguish from genuine drugs. This discovery shed light on the illicit trade of counterfeit antimalarials, prompting further investigation into the problem[1,2]. In a collaborative study led by Dr Newton and an international multidisciplinary group, supported by the International Criminal Police Organization (INTERPOL) and the Western Pacific World Health Organization Regional Office, Oxford researchers aimed to determine the source of counterfeit drugs in Southeast Asia. The research team confirmed that the 49.9% of drugs thought to be counterfeit (on the basis of packaging), contained no, or very small quantities of artesunate; they also found 16 different types of counterfeit packaging of escalating sophistication. In a chemical analysis, Oxford researchers also demonstrated that many of the fake drugs identified contained a variety of banned pharmaceuticals, such as safrole (a carcinogen), a raw material used in the street drug methylenedioxymethamphetamine, also known as "ecstasy". This suggested that manufacturers of narcotics were involved in making counterfeit antimalarials. In a novel analysis of pollen within the tablets, to obtain evidence pertaining to the flora around the manufacturing site, as well as detailed chemical analysis of a rare type of chalk in the counterfeits, research data strongly suggested that some of the counterfeit artesunate was manufactured in southern China. This prompted a criminal investigation through INTERPOL, by the Chinese government[3] and the (then) Burmese Government, resulting in the interruption of the counterfeit artesunate trade route.

Following increasing reports of poor quality antimalarials in Africa, the University of Oxford scientists led a team of researchers in collecting seven artemisinin derivative monotherapies, ACT, and halofantrine malarial medications of suspicious quality in eleven African countries, between

2002 and 2010. This research confirmed that the production of harmful antimalarial counterfeit drugs had spread to Africa[4].

The University of Oxford's most recent collaboration with the National Institute of Health (United States) indicated that one-third of antimalarial drugs tested from the private sector in Southeast Asia and sub-Saharan Africa are now fake, this particular paper has gained worldwide media attention[5].

References to the research:

1. Newton, P. *et al.* Fake artesunate in southeast Asia. *Lancet* **357**, 1948–1950 (2001). ***Primary Paper from Dr Newton investigating counterfeit drugs in Southeast Asia.***

2. Dondorp, A. M. *et al.* Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop. Med. Int. Health* **9**, 1241–1246 (2004). ***Subsequent Paper from Oxford's Professor Dondorp and Dr Newton investigating prevalence of counterfeit drugs in Southeast Asia.***

3. Newton, P. N. *et al.* A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS Med.* **5**, e32 (2008). doi: 10.1371/journal.pmed.0050032. ***Collaborative investigation into counterfeit drug trafficking in Southeast Asia.***

4. Newton, P. N. *et al.* Poor quality vital antimalarials in Africa - an urgent neglected public health priority. *Malar. J.* **10**, 352 (2011). doi: 10.1186/1475-2875-10-352. ***Paper investigating counterfeit antimalarial drug trade in Africa.***

5. Nayyar, G. M. L., Breman, J. G., Newton, P. N. & Herrington, J. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis.* **12**, 488–496 (2012). doi: 10.1016/S1473-3099(12)70064-6. ***Collaborative paper reviewing poor-quality antimalarial medication in Southeast Asia and sub-Saharan Africa.***

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Details of the impact:

The existence of fake antimalarial medication has had a devastating effect on malaria-related deaths in highly affected areas. The continued use of counterfeit drugs could lead to advancing drug resistance and loss of efficacy for artemisinin combination therapies, resulting in devastating global outcomes[6]. Dr Newton's research into the counterfeit drug trade initiated public awareness into this damaging activity and has led to several criminal investigations, arrests of drug traffickers, and further investigation from the World Health Organization (WHO).

Response from the World Health Organization

In 2005 the WHO launched a rapid alert system, enabling information about counterfeit drugs to be rapidly reported to relevant authorities in participating countries. At the time the alert was rolled out the WHO estimated 10% of all drugs sold globally were counterfeits and that the figure was as high as 25% in developing countries[7]. The WHO is now investigating the global expansion of this system. In January 2011, the WHO released a report[8] surveying the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa, referencing Dr Newton's 2001[1] paper on *Fake artesunate in southeast Asia* as a primary source, as well as the 2004 paper by Dondorp and Newton[2]. The information obtained in this report outlined the overall quality of antimalarial medications being distributed in sub-Saharan Africa; this has contributed to the development of regulatory systems and enforcement, improvement in surveillance technology, the introduction of Minilabs, and increased cooperation between national drug regulatory authorities[8].

Advanced Screening Technology

In February 2011 the Global Pharma Health Fund announced they would be establishing 20 Minilabs in Nigeria, which will enable efficient and effective identification of counterfeit drugs and low quality medication. They also reported that health organisations and local governments will roll out a total of 420 Minilabs throughout the 70 African, Asian and Latin American regions[9].

The University of Oxford's underpinning research has provided academic justification for the mPedigree Network (www.mpedigree.net), a Ghana-based organisation empowering African patients and consumers to protect themselves from pharmaceutical counterfeiting. The Network, which connects a number of African countries to a central registry where pedigree information of product brands are stored, allows all patients and consumers to verify the safety and quality of their medicines instantly by using their own (or a shared) mobile phone at no cost, where a mobile signal is available. This technology has since been rolled out for use in Nigeria and Kenya and is now being tested in Uganda, Tanzania, South Africa, India and Bangladesh. Since the establishment of mPedigree in 2007, 6.5 million packs of medication have been tested in various pilots[10]. *"The problem of counterfeit drugs in Africa came to our attention in 2004. With the help of the Ghana government, local activists, and academics we established a network of people who were committed to creating change. The underpinning research from Dr Newton and his collaborators, not only gave our cause academic credibility; it also gave us a better understanding of the reach and proximity of the problem."* – mPedigree Network, founder Bright Simons[10].

Criminal Investigations

The University of Oxford's research and its collaboration with other investigators, the WHO, and INTERPOL, has led to the arrest of alleged traders of fake antimalarial drugs in southern China and Burma, and the seizure of a large quantity of drugs in 2006. The suspects from China's Yunnan Province were alleged to have traded 240,000 blister packs of counterfeit artesunate in 2006, enough to treat almost a quarter of a million adults over the coming years. Chinese authorities were able to seize 24,000 of these packs before they were distributed, potentially saving the lives of thousands[11]. In February 2011 a similar operation supported by INTERPOL took place in Ghana, leading to the seizure of thousands of illegal and fake antimalarial drugs and other medications. Initiated by the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) and supported by INTERPOL, Operation Harmattan led to the arrest and prosecution of over 30 counterfeit drug traffickers[12].

Public Outreach and Media Engagement

This research has led to the Worldwide Antimalarial Resistance Network (WWARN) Antimalarial Quality Surveyor, an antimalarial mapping module enabling researchers, government, and the public to access studies on the type of medications on the market, the source of these medications and the quality of antimalarial medicines[13]. The work of Dr Paul Newton and his collaborators has been widely publicised around the world. As an expert in the field of counterfeit medications, Dr Newton has been quoted and referenced in a number of articles by several world news providers, including The Guardian, BBC News and the New York Times[14,15]. As a result of this public outreach, Oxford's research into counterfeit medications continues to garner worldwide attention, inspiring ongoing action from global leaders, criminal investigators and international health organisations.

Sources to corroborate the impact:

6. Newton, P. N., Green, M. D. & Fernández, F. M. Impact of poor-quality medicines in the 'developing' world. *Trends Pharmacol. Sci.* **31**, 99–101 (2010). doi: 10.1016/j.tips.2009.11.005. ***Review from Dr Paul Newton and colleagues outlining the global impact of fake antimalarial medication.***

7. Parry, J. WHO combats counterfeit malaria drugs in Asia. *BMJ* **330**, 1044 (2005). ***An independent paper reviewing the World Health Organization's interventions on fake***

drug trafficking.

8. Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa. January 2011. *World Health Organization* at http://www.who.int/medicines/publications/WHO_QAMSA_report.pdf (Accessed 2013). ***Report on the World Health Organization's survey into the quality of antimalarial medication in sub-Saharan Africa. This report refers to two of Dr Newton's papers as primary sources.***

9. Latest news. *GPHF Global Pharma Health Fund E.V.* at http://www.gphf.org/web/en/news/meldungen.htm (Accessed 2013). ***News items from the Global Pharma Health Fund website, listing information about the establishment of Minilabs in Ghana.***

10. *mPedigree Network* Website http://mpedigree.net/mpedigree/index.php?option=com_content&view=article&id=46&Itemid=53 (Accessed 2013). mPedigree Founder Statement (available on request). ***mPedigree Network information and statement from Mr Bright Simons.***

11. Fake antimalarial drugs analysis highlights threat to global health. *Wellcome Trust* at http://www.wellcome.ac.uk/News/Media-office/Press-releases/2008/WTX043187.htm (Accessed 2013). ***Press Release from the Wellcome Trust, information about criminal investigation into counterfeit drug trafficking.***

12. Ghana INTERPOL-supported operation leads to counterfeit medical products seizures. *INTERPOL* at http://www.interpol.int/News-and-media/News-media-releases/2011/N20110214 (Accessed 2013). ***Press Release from INTERPOL including information about Operation Harmattan.***

13. WWARN Antimalarial Quality Surveyor. *Worldwide Antimalarial Resistance Network (WWARN)* at http://www.wwarn.org/resistance/surveyors/antimalarial-quality (Accessed 2013). ***Worldwide Antimalarial Resistance Network (WWARN) Antimalarial Quality Surveyor and interactive map.***

14. Fake and poor quality malaria drugs risk crisis in Africa, warn scientists. *The Guardian* at http://www.guardian.co.uk/society/2012/jan/16/fake-poor-quality-malaria-drugs-africa (Accessed 2013). ***Article from The Guardian featuring commentary from Dr Paul Newton.***

15. Malaria: Fake and Substandard Drugs Grow as Threat to Fight Disease. *The New York Times* at http://www.nytimes.com/2012/05/22/health/policy/fake-and-substandard-drugs-grow-as-threat-to-fight-malaria.html?_r=2 (Accessed 2013). ***Article from The New York Times based on Dr Newton's collaboration with the National Institute of Health into the poor quality of drugs in Asia and Africa. Article published May 21st 2012.***