Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

INTRODUCING ARTEMISININ TO THE WORLD

Summary of the impact:

The University of Oxford's Professor Nick White and his colleagues successfully demonstrated the effectiveness of artemisinin (an ancient Chinese remedy) in the treatment of malaria. They also pioneered artemisinin-combination therapy (ACT), the most effective and fast-acting malaria treatment in the world. Responsible for saving hundreds of thousands of lives every year, ACT was recommended by the World Health Organization (WHO) in 2006 as the primary method of malarial treatment globally. Malaria kills more than half a million and affects over 225 million people every year.

Underpinning research:

Malaria is a deadly mosquito-borne infectious disease that has been affecting humans for over 50,000 years. Until recently one of the most widely used treatments for malaria was quinine, isolated from the bark of cinchona trees. Quinine was first applied as an antimalarial in the 17th century, but after years of use malaria parasites have developed a resistance to quinine, as well as other antimalarial medications.

Artemisinin is a compound derived from the leaves of the annual wormwood *Artemisia annua*. Chinese herbalists have used derivatives of annual wormwood for thousands of years in the treatment of malaria and other diseases, however, the artemisinin compound capable of treating malaria was only officially discovered by Chinese researchers in 1972[1].

More than a decade after this initial discovery, the University of Oxford's Professor Nick White and his Bangkok-based research team began undertaking clinical trials to test the relative effectiveness of artemisinin as an antimalarial treatment. In their first trial, they found artemisinin compounds to be the most rapidly acting of all antimalarial drugs[2]. The team then undertook a series of prospective studies of 5,193 adults and children with acute malaria on the western border of Thailand, between 1990 and 1995. After finding that artemisinin derivatives reduce the transmission potential of malaria[3], they then trialed a combination treatment of mefloquine (a synthetic form of quinine) and artemisinin. Combining artemisinin-based derivatives to rapidly clear malaria parasites from the body, along with slower acting partner drugs to destroy any surviving parasites, proved to be the most effective way of treating malaria. Compared to monotherapy, artemisinin-combination therapy (ACT) reduced the risk of treatment failure, parasite resistance and side effects in patients[4].

In a landmark paper published in 2005, the University of Oxford team showed that in adults, intravenously administered artemisinin was a more potent and rapid antimalarial treatment than quinine[5]. They also found artemisinin to be safer, simpler to administer and more effective, with mortality rates reduced by 34.7% in artemisinin recipients compared to those treated with quinine[5].

Since the majority of malarial mortality occurs in children under the age of five, White and his team continued their research to prove the effectiveness of artemisinin in the treatment of infants and children. In a study of African children suffering from severe malaria, mortality occurred in 297 of the 2,713 children treated with quinine, in comparison to 230 deaths from the 2,712 children treated with artemisinin[6], a relative reduction in mortality of 22.5%. Post-treatment hypoglycaemia was also less frequent in the artemisinin treatment group than in the quinine group[6].

As a result of this research, the University of Oxford successfully showed artemisinin and ACT to be the superior treatment for malaria in both children and adults[6].

References to the research:

1. Antimalaria studies on Qinghaosu. *Chin. Med. J.* **92**, 811–816 (1979).

   Primary paper from Chinese researchers showing that artemisinin compounds are capable of treating malaria.

2. White, N. J. Artemisinin: current status. *Trans. R. Soc. Trop. Med. Hyg.* **88 Suppl 1**, S3–4 (1994).

   First trial from Oxford researchers showing artemisinin compounds to be the most rapidly acting of all antimalarial drugs.

3. Price, R. N. *et al.* Effects of artemisinin derivatives on malaria transmissibility. *Lancet* **347**, 1654–1658 (1996).

   Prospective study showing artemisinin derivatives reduce the transmission potential of malaria.

4. Nosten, F., Hien, T. T. & White, N. J. Use of artemisinin derivatives for the control of malaria. *Med Trop (Mars)* **58**, 45–49 (1998).

   Trial showing artemisinin-combination therapy (ACT) reduces the risk of treatment failure, parasite resistance and side effects in patients more effectively than monotherapy.

5. Dondorp, A. *et al.* Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet* **366**, 717–725 (2005).

   A landmark paper showing that intravenously administered artemisinin was a more potent, rapid, safer, simpler to administer and more effective antimalarial treatment than quinine in adults.

6. Dondorp, A. M. *et al.* Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet* **376**, 1647–1657 (2010). doi: 10.1016/S0140-6736(10)61924-1.

   Trial successfully showing artemisinin and ACT to be the superior treatment for malaria in children.

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Details of the impact:

The University of Oxford's research showing artemisinin and ACT to be the superior treatment for malaria in both children and adults, led the World Health Organization (WHO) to recommend ACT as the preferred antimalarial in 2006[7]. As a result, this research has led directly to the successful cure of millions of malaria sufferers worldwide.

Since 2000 an increasing number of countries in which malaria is endemic have adopted ACT in the treatment of malaria, with the number of ACT treatment courses surging from 500,000 in 2001 to 31.3 million in 2005[8] – more than 80% of these orders were placed through the WHO[8]. This number increased to 76 million in 2006 and reached 158 million people in 2009[9]. By the end of 2009, 11 African countries had provided sufficient courses of ACT to cover more than 100% of

malaria cases seen in the public sector, while a further 8 African countries delivered enough courses to treat between 50–100% of cases[9].

In 2008, 78 countries reported a policy of treatment with ACT for malaria[10]. In 2009, of the 108 countries in which malaria is endemic, 77 were using ACT for the treatment of malaria and 52 were offering ACT free of charge in the public sector for children under 5 years[10]. Due to the availability of ACT along with other malarial control measures, such as insecticide-treated nets and indoor-residual spraying, there has been a 50% reduction in confirmed malaria cases and malaria caused deaths in 13 African nations[11].

WHO guidelines recommending the use of ACT[7] along with other control measures, such as insecticide-treated nets and indoor-residual spraying, effectively saved the lives of 736,700 children in 34 African countries between 2001 and 2010[12]. A recent news release circulated by the WHO on World Malaria Day 2012, showed that the number of ACT courses distributed worldwide by government health departments had "increased exponentially", from 11 million in 2005 to 181 million in 2010. Along with long-lasting insecticidal nets, sprays, and better diagnostic tests, this increased coverage has led to more than 1 million lives saved over the past 10 years[13].

Sources to corroborate the impact:

7. Guidelines For The Treatment Of Malaria. *World Health Organization* at http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html (Accessed 2013).

WHO guidelines recommending the use of ACT as preferred antimalarial. These guidelines directly reference a number of Professor White's publications, including AQUAMAT, for recommendations for ACT use in children.

8. Bosman, A. & Mendis, K. N. A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies. *Am. J. Trop. Med. Hyg.* **77**, 193–197 (2007).

Paper reporting the increasing number of countries adopting ACTs as the preferred treatment for malaria.

9. Global Health Observatory (GHO). *World Health Organization* at http://www.who.int/gho/malaria/control/treatment_text/en/index.html

WHO report showing 100% coverage of sufficient courses of ACTs in 11 African countries.

10. World Malaria Report 2009. *World Health Organization* at http://whqlibdoc.who.int/publications/2009/9789241563901_eng.pdf (Accessed 2013).

WHO malaria report, showing uptake of ACT treatment policy in 78 countries between 2008 and 2009.

11. World Malaria Report Summary 2010. *World Health Organization* at http://www.who.int/malaria/world_malaria_report_2010/malaria2010_summary_keypoints_en.pdf (Accessed 2013).

WHO report showing a 50% reduction in confirmed malaria cases and malaria caused deaths in 13 African nations in 2010.

12. Roll Back Malaria Progress & Impact Series: Saving Lives with Malaria Control: Counting Down to the Millennium Development Goals. *Roll Back Malaria* at http://www.rbm.who.int/ProgressImpactSeries/report3.html (Accessed 2013).

Report showing that the introduction of ACTs between 2001 and 2010, (along with other interventions) have effectively saved the lives of 736,700 children in 34 African countries.

13. World Malaria Day 2012: Media Release and Report. *World Health Organization* at http://www.who.int/mediacentre/news/releases/2012/malaria_20120424/en/index.html (Accessed 2013).

WHO malaria day 2012 report showing the enormous increase in the number of ACTs distributed worldwide between 2005-2010. This has contributed to more than 1 million lives saved over the past 10 years.