Institution: St George's, University of London

Unit of Assessment: 1 Clinical Medicine

Title of case study: Optimising malaria treatment with artemisinins

Period when the underpinning research was undertaken: 2001 – 2017

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:
Sanjeev Krishna	Professor of Molecular Parasitology and Medicine	1994 – 2020 (present)
Tim Planche	Senior Lecturer in Medical Microbiology	2010 – 2020 (present)
	Clinical Senior Lecturer	2010 – 2010

Period when the claimed impact occurred: 2013 to 2020 (present)

Is this case study continued from a case study submitted in 2014? No

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

The St George's research group has significantly improved global health by developing new ways to treat malaria including the first artemisinin-based combination therapy (artesunate with amodiaquine) that is effective, affordable, safe and now standard of care in much of sub-Saharan Africa. Defining the rectal route for giving artesunate as being efficacious and optimising its dose has subsequently reduced the mortality rates in children with malaria. A molecular marker devised to detect risk of treatment failures with mefloquine-artesunate combination treatment has been widely adopted. A less expensive, simplified once daily artesunate regimen to treat severe childhood malaria has been shown to be equivalent to more complex treatments.

2. Underpinning research (indicative maximum 500 words)

Defining the efficacy of a new combination therapy for malaria

Malaria remains one of the most important causes of death in children. The treatment of malaria was revolutionised by the development of the artemisinins in the 1990s. However, artemisinin-based combination therapy was not available for African children with uncomplicated malaria until the group demonstrated its effectiveness. In randomised trials of 941 children across 3 African countries, the group demonstrated that a 3-day course of artesunate with amodiaquine was safe and efficacious compared with amodiaquine monotherapy [1].

This collaboration with WHO-TDR (the Special Programme for Research and Training in Tropical Diseases) stimulated subsequent studies examining efficacy of the same combination treatment, involving the administration of over 9,000 treatment courses in areas of emerging multidrug resistant malaria. The quality of the original study merited inclusion in a meta-analysis [2], while scientifically robust findings of overall superiority of the combination and its safety were used to develop co-formulated tablets.

Establishing the optimal route for artesunate administration

Giving antimalarial treatments to the millions of children who cannot access healthcare for hours or days can be life-saving. A new formulation of rectal artesunate was being developed through WHO-TDR when the group initiated an urgent collaborative study into its efficacy, toxicity, pharmacokinetics and dose optimisation in hospitalised children who required injectable antimalarial treatment [3]. Results demonstrated that the rectal route for artesunate administration was reliable, as well as being simpler and safer.

The same choice of dose was used in studies that demonstrated an increase of 50% in survival rates for children who were delayed more than 6 hours in reaching clinics, after more than 16,000 African children with presumptive malaria were treated with rectal artesunate or placebo whilst awaiting transfer from remote regions to hospitals [4]. This publication won the BMJ's paper of the year award.

Developing an assay to predict treatment failure

Drug resistance is a common cause of treatment failure and therefore a key consideration when choosing an antimalarial for national malaria programmes. The group developed new assays for molecular markers that predict treatment failures with the artemisinin-based combination therapy of mefloquine and artesunate in malaria. Developing a quantitative assay to assess copy number of *pfmdr1* – a parasite multidrug resistance gene, took several years. The group used the assay to relate gene amplifications in *pfmdr1* to treatment outcomes with mefloquine monotherapy and in combination with artesunate [5].

It is now used globally to assess drug resistance to mefloquine and related antimalarials, and is an important variable when recommending antimalarial combinations. It was the first example of a molecular marker predicting treatment failures in artemisinin combinations and demonstrated that the partner drug and not the artemisinin component was failing. SNPs in *pfmdr1* were also studied and have proved to be informative.

Demonstrating equivalence of a simpler, less expensive dosing regimen

Until recently, no parenteral regimen of artemisinin had been optimised to treat severely ill children. The group compared an empirically used, WHO-recommended, 5-dose regimen with simplified once daily dosing regimens (over 3 days) in prospective pharmacokinetic and pharmacodynamic studies, and showed that the simpler regimen is comparable to the more cumbersome one [6] and that the intramuscular route of administration is reliable and well tolerated.

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

1. Amodiaquine-artesunate versus amodiaquine for uncomplicated Plasmodium falciparum malaria in African children: a randomised, multicentre trial.
Adjuik M, Agnamey P, Babiker A, Borrmann S, Brasseur P, Cisse M, Cobelens F, Diallo S, Faucher JF, Garner P, Gikunda S, Kremsner PG, Krishna S, Lell B, Loolpapit M, Matsiegui PB, Missinou MA, Mwanza J, Ntoumi F, Olliaro P, Osimbo P, Rezbach P, Some E, Taylor WR.
Lancet. 2002 Apr 20;359(9315):1365-72. PMID:11978332. DOI: 10.1016/S0140-6736(02)08348-4. Journal article cited 233 times (WOS 23.02.2021).

2. The effect of dosing strategies on the therapeutic efficacy of artesunate-amodiaquine for uncomplicated malaria: a meta-analysis of individual patient data. WorldWide Antimalarial Resistance Network (WWARN) AS-AQ Study Group, Adjuik MA, Allan R, Anvikar AR, Ashley EA, Ba MS, Barennes H, Barnes KI, Bassat Q, Baudin E, Björkman A, Bompart F, Bonnet M, Borrmann S, Brasseur P, Bukirwa H, Checchi F, Cot M, Dahal P, D'Alessandro U, Deloron P, Desai M, Diap G, Djimde AA, Dorsey G, Doumbo OK, Espié E, Etard JF, Fanello CI, Faucher JF, Faye B, Flegg JA, Gaye O, Gething PW, González R, Grandesso F, Guerin PJ, Guthmann JP, Hamour S, Hasugian AR, Hay SI, Humphreys GS, Jullien V, Juma E, Kamya MR, Karema C, Kiechel JR, Kremsner PG, Krishna S, Lameyre V, Ibrahim LM, Lee SJ, Lell B, Mårtensson A, Massougbodji A, Menan H, Ménard D, Menéndez C, Meremikwu M, Moreira C, Nabasumba C, Nambozi M, Ndiaye JL, Nikiema F, Nsanzabana C, Ntoumi F, Ogutu BR, Olliaro P, Osorio L, Ouédraogo JB, Penali LK, Pene M, Pinoges L, Piola P, Price RN, Roper C, Rosenthal PJ, Rwagacondo CE, Same-Ekobo A, Schramm B, Seck A, Sharma B, Sibley CH, Sinou V, Sirima SB, Smith JJ, Smithuis F, Somé FA, Sow D, Staedke SG, Stepniewska K, Swarthout TD, Sylla K, Talisuna AO, Tarning J, Taylor WR, Temu EA, Thwing JI, Tjitra E, Tine RC, Tinto H, Vaillant MT, Valecha N, Van den Broek I, White NJ, Yeka A, Zongo I.
BMC Med. 2015 Mar 31;13:66. doi: 10.1186/s12916-015-0301-z. PMID: 26343145. Journal article cited 29 times (WOS 23.03.2021).

3. Bioavailability and preliminary clinical efficacy of intrarectal artesunate in Ghanaian children with moderate malaria. Krishna S, Planche T, Agbenyega T, Woodrow C, Agranoff D, Bedu-Addo G, Owusu-Ofori AK, Appiah JA, Ramanathan S, Mansor SM, Navaratnam V. Antimicrob Agents Chemother. 2001 Feb;45(2):509-16. PMID: 11158748. DOI: 10.1128/AAC.45.2.509-516.2001. Journal article cited 69 times (WOS 23.02.2021).

4. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Gomes MF, Faiz MA, Gyapong JO, Warsame M, Agbenyega T, Babiker A, Baiden F, Yunus EB, Binka F, Clerk C, Folb P, Hassan R, Hossain MA, Kimbute O, Kitua A, Krishna S, Makasi C, Mensah N, Mrango Z, Olliaro P, Peto R, Peto TJ, Rahman MR, Ribeiro I, Samad R, White NJ; Study 13 Research Group. Lancet. 2009 Feb 14;373(9663):557-66. doi: 10.1016/S0140-6736(08)61734-1. Epub 2008 Dec 6. PMID: 19059639 [*S. Krishna was a member of the WHO Task force on severe malaria that designed this study and contributed to the writing of this paper as well as attending meetings with regulators on behalf of WHO-TDR. The smaller study (ref 3) established the correct dose to use for this larger study, as well as defining which patient populations would be most appropriate to study*] Journal article cited 121 times (WOS 23.02.2021).

5. Mefloquine resistance in Plasmodium falciparum and increased pfmdr1 gene copy number. Price RN, Uhlemann AC, Brockman A, McGready R, Ashley E, Phaipun L, Patel R, Laing K, Looareesuwan S, White NJ, Nosten F, Krishna S. Lancet. 2004 Jul 31-Aug 6;364(9432):438-447. doi: 10.1016/S0140-6736(04)16767-6. PMID: 15288742 Journal article cited 551 times (WOS 23.02.2021).

6. Intramuscular Artesunate for Severe Malaria in African Children: A Multicenter Randomized Controlled Trial. Kremsner PG, Adegnika AA, Hounkpatin AB, Zinsou JF, Taylor TE, Chimalizeni Y, Liomba A, Kombila M, Bouyou-Akotet MK, Mawili Mboumba DP, Agbenyega T, Ansong D, Sylverken J, Ogutu BR, Otieno GA, Wangwe A, Bojang KA, Okomo U, Sanya-Isijola F, Newton CR, Njuguna P, Kazungu M, Kerb R, Geditz M, Schwab M, Velavan TP, Nguetse C, Köhler C, Issifou S, Bolte S, Engleitner T, Mordmüller B, Krishna S. PLoS Med. 2016 Jan 12;13(1):e1001938. doi: 10.1371/journal.pmed.1001938. eCollection 2016 Jan. PMID: 26757276. Journal article cited 27 times (WOS 23.02.2021).

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

Improvements in oral antimalarial treatments for children

Before 2000, national malaria programmes typically relied on antimalarial monotherapy, in spite of decreasing efficacy due to drug resistance. The WHO called for antimalarial monotherapies for uncomplicated malaria to cease in 2006. Following the group's study, demonstrating the efficacy of amodiaquine artesunate (ref [1] above), the not-for-profit NGO Drugs for Neglected Diseases initiative had taken over the fixed dose amodiaquine artesunate project in 2003, and accelerated the production of this combination. This combination treatment for malaria is now registered in 35 countries and more than 516,000,000 doses have been distributed [A]. It remains on the current WHO's Model List of Essential Medicines that identifies medicines that "satisfy the priority health care needs of the population" [B].

There are currently 5 different products of amodiaquine artesunate that are pre-qualified by WHO and treatment access optimisation was handed over to Medicines for Malaria Ventures (MMV) for further management in 2015. The treatment regimen for a child costs approximately USD0.50 and for an adult is USD1.00. The combination remains safe and effective, and one of the first line treatments for uncomplicated malaria in African countries [Ca, b]. It is also safe and efficacious and used to treat malaria in the second and third trimesters of pregnancy [Cc].

Providing a new and lifesaving route to treat childhood malaria

Following the group's work on rectal delivery, WHO had recommended the use of rectal artesunate, but a suitable formulation has only been made available recently through MMV's

efforts to encourage 2 manufacturers to supply this formulation. In June 2017, 100mg presentation of rectal artesunate suppositories was added to the WHO's Model List of Essential Medicines for Children (EMLc) [D] and is registered in 16 countries.

In 2018, Strides Pharma and Cipla Limited were prequalified by WHO and 1,500,000 orders for suppositories placed by international donors. MMV works closely with the Clinton Healthcare Access Initiative to deliver rectal artesunate as part of a spectrum of care to patients with severe malaria [E]. The continuing impact on mortality rates of this treatment in children was demonstrated by a study in Zambia, which has shown that deaths in children with severe malaria experienced a decrease of 96% after introduction of rectal artesunate [F].

Rapid and reliable prediction of antimalarial efficacy with *pfmdr1* copy number and polymorphisms

Molecular surveillance of markers is one of the most cost-effective ways to inform antimalarial drug policy because treatment efficacy studies are expensive and difficult to implement. The group's method has been confirmed in multiple geographic settings, and the efficacies of drugs related to mefloquine such as lumefantrine are also influenced by *pfmdr1* copy number and SNPs. *Pfmdr1* copy number assay is adopted in guidelines by the Worldwide Antimalarial Resistance Network in their handbook of procedures [G]. The WHO routinely tracks *pfmdr1* copy number as a molecular marker of drug resistance [H]. In addition to copy number assay, single nucleotide polymorphisms in *pfmdr1* have proved useful in informing policy on how antimalarial drug use should be optimised [I].

Simplifying the management of severe childhood malaria

Artesunate superseded quinine as the first line treatment for severe malaria more than a decade ago but the best way to administer either treatment had never been studied. The group's comparative trials provided the scientific underpinning for a much simpler, cheaper, and more convenient way of administering artesunate, greatly simplifying management of children in busy paediatric wards in endemic countries. Children are also much more likely to receive lifesaving treatments in a timely way with once daily, intramuscular injections [J].

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

A. https://www.mmv.org/access/products-projects/asaq-winthrop-artesunate-amodiaquine (updated November 2020)
B. WHO Essential medicines list, 21st List, July 2019. Available for download at : https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06 Please see page 23
C. a. Assi SB et al. Safety of a fixed-dose combination of artesunate and amodiaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in real-life conditions of use in Côte d'Ivoire. *Malaria Journal*. 16:8 (2017). DOI: 10.1186/s12936-016-1655-1.
b. Assi SB et al. Sustained Effectiveness of a Fixed-Dose Combination of Artesunate and Amodiaquine in 480 Patients with Uncomplicated *Plasmodium falciparum* Malaria in Côte d'Ivoire. *Malar Res Treat*. 2017:3958765. DOI: 10.1155/2017/3958765
c. PREGACT Study Group, Pekyi D, Ampromfi AA, Tinto H, et al. (2016). Four Artemisinin-Based Treatments in African Pregnant Women with Malaria**.** New England Journal of Medicine Mar 10;374(10):913-27. doi: 10.1056/NEJMoa1508606.
D. https://www.mmv.org/access/products-projects/rectal-artesunate-ras and https://www.who.int/publications/i/item/WHOMVPEMPIAU201907 (see page 17-18)
E. https://www.clintonhealthaccess.org/community-access-rectal-artesunate-malaria-caramal-project/
F. https://www.mmv.org/newsroom/press-releases/severe-malaria-case-fatality-reduced-96-pilot-project-zambia-led-transaid
G. 5th Dec 2014, Available at https://www.wwarn.org/tools-resources/procedures/copy-number-estimation-plasmodium-falciparum-pfmdr1-gene
H. https://www.who.int/malaria/areas/drug_resistance/drug_efficacy_database/en/ please see under: molecular markers of antimalarial drug resistance data

I. Emerging implications of policies on malaria treatment: genetic changes in the *Pfmdr-1* gene affecting susceptibility to artemether-lumefantrine and artesunate-amodiaquine in Africa Okell LC, Reiter LM, Ebbe LS, Baraka V, Bisanzio D, Watson OJ, Bennett A, Verity R, Gething P, Roper C, Alifrangis M. BMJ Glob Health. 2018 Oct 19;3(5):e000999. doi: 10.1136/bmjgh-2018-000999. eCollection 2018.
J. Testimonials from A. WHO Global Malaria Programme, B. Medicines for Malaria Venture