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FINAL PROGRESS REPORT

Project Title		Primaquine radical cure of Plasmodium vivax malaria: a risk benefit analysis
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Award Received		2016 RACP NHMRC Awards for Excellence - Kincaid-Smith Scholarship
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Chief Investigator / Supervisor		Robert Commons / Professor Richard Price
Administering Institution		Menzies School of Health Research
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PROJECT SUMMARY

Recent intensification of malaria control efforts in Asia and South America has significantly reduced the worldwide burden of falciparum malaria, but Plasmodium vivax is more difficult to control. Vivax malaria causes significant morbidity with over 100 million clinical cases yearly. Without increased research into P. vivax the aim of malaria eradication is unlikely to be achieved.

Unlike P. falciparum, P. vivax can relapse due to dormant liver stage hypnozoites. Successful control and ultimate elimination of P. vivax requires prevention of recurrent infections by safe and effective radical cure, combining drugs active against both the blood and liver stages of the parasite. Primaquine is the only widely available hypnozoiticide (liver stage drug), but can cause severe drug-induced haemolysis in glucose-6- phosphate dehydrogenase (G6PD) deficient patients.

The risk of serious haemolysis associated with G6PD deficiency makes clinicians reluctant to prescribe primaquine without prior testing, which is often unavailable. When primaquine is prescribed, patient adherence to the standard 14 day regimen is poor, resulting in a high risk of treatment failure. Despite 60 years of clinical use, knowledge of primaquine safety, and efficacy is rudimentary. Effective radical cure is the key to vivax malaria elimination, but the clinical and public health consequences of primaquine demand a rigorous understanding of the risks and benefits to inform use.

This thesis aims to improve understanding of the risks and benefits of giving primaquine radical cure to cure vivax. Through a series of systematic reviews and pooling large numbers of patient data from existing malaria trials, the thesis investigates the risks for P. vivax recurrence including the effect of drug dose and primaquine use, quantifies the haematological risks of acute and recurrent vivax malaria including primaquine-induced haemolysis and investigates potential

benefits of primaquine radical cure in patients from co-endemic regions with P. falciparum infection.

PROJECT AIMS / OBJECTIVES

The aim of this project is to provide evidence to minimise Plasmodium vivax attributable anaemia, through safe and effective drug regimens, which target both the blood and liver stages of the malarial parasite. The ultimate objective is to reduce P. vivax attributable morbidity and mortality and accelerate malaria elimination.

The project addresses the following objectives through a series of two systematic reviews of antimalarial efficacy studies and three individual pooled meta-analyses:

i) What are the risk factors for P. vivax recurrence and relapse with or without primaquine?
ii) What are the haematological consequences of acute and recurrent vivax malaria in different endemic locations?
iii) How does the risk of primaquine-induced haemolysis vary between individuals?
iv) To what degree does drug induced haemolysis vary with the dose of primaquine?
v) What benefit does primaquine have in preventing P. vivax infection after P. falciparum infection?

SIGNIFICANCE AND OUTCOMES

Outcomes from this project will inform assessment of the risks and benefits of primaquine radical cure of P. vivax malaria for policymakers and clinicians. The finding that chloroquine dose effects risk of recurrence in children younger than five years will be discussed at the WHO's malaria expert advisory committee to consider changing the dose of chloroquine in response.

Evidence of the safety and benefits of primaquine will assist policy-makers as they review how to most rapidly eliminate malaria. These results will also be important for international and national policymakers and clinicians to inform the integration of new diagnostics tests for G6PD deficiency and the new hypnozoitocidal agent tafenoquine into management of P. vivax.

Demonstration of the high risk of vivax parasitaemia following falciparum infection highlights the potential for universal radical cure to be considered in all patients with uncomplicated malaria in some co-endemic regions. To fully inform policy-makers, additional investigation will be required, including a pooled analysis of individual patient data which is currently being undertaken to identify the patients and regions that would benefit most from this policy.

Future research is also planned to identify the benefit of primaquine dose over 6 to 12 months, to assess the effect of cumulative recurrences on haemoglobin and to better understand the risk of anaemia in G6PD deficiency.

PUBLICATIONS / PRESENTATIONS

Peer-Reviewed Papers

1. Commons RJ, Thriemer K, Humphreys G, Suay I, Sibley CH, Guerin PJ, Price RN, The Vivax Surveyor: Online mapping database for Plasmodium vivax clinical trials, Int J Parasitol Drugs Drug Resist, 2017; 7(2):181-190.

2. Thriemer K, Ley B, Bobogare A. Commons R, Baird KJ, Price RN, Challenges for achieving safe and effective radical cure of Plasmodium vivax: a round table discussion of the APMEN Vivax Working Group, Malar J, 2017; 16:141.

3. Commons RJ, Simpson JA, Thriemer K, et al., The effect of chloroquine dose and primaquine on Plasmodium vivax recurrence: a WorldWide Antimalarial Resistance Network systematic review and individual patient pooled meta-analysis, Lancet Infect Dis, 2018; 18: 1025-1034.

4. Commons RJ, Simpson JA, Thriemer K, et al., The risk of Plasmodium vivax parasitaemia after P. falciparum infection: a systematic review and meta-analysis, Lancet Infect Dis, 2019; 19:91-101

5. Commons RJ, Simpson JA, Thriemer K, et al., The haematological consequences of Plasmodium vivax malaria after chloroquine treatment with and without primaquine: a WorldWide Antimalarial Resistance Network systematic review and individual patient data meta-analysis, (submitted)

Book Chapters

1. Commons RJ, Simpson JA, Price RN, Artemether-Lumefantrine, in Grayson ML (Ed.), Kucers' the use of antibiotics 7th ed, 2017, London, UK: Hodder Education

2. Commons RJ, Simpson JA, McCarthy JS, Price RN, Artesunate, in Grayson ML (Ed.), Kucers' the use of antibiotics 7th ed, 2017, London, UK: Hodder Education

Conference Abstracts (oral)

1. Commons RJ, Simpson JA, Thriemer K, Hossain MS, Douglas NM, Humphreys GS, Sibley CH, Guerin PJ, Price RN, Universal radical cure of malaria, 1st Malaria World Congress, Melbourne, 2018

2. Commons RJ, on behalf of the WWARN Vivax Study Group, The effect of chloroquine dose and primaquine on Plasmodium vivax recurrence: an individual patient pooled analysis, ASID ASM, Gold Coast, 2018

3. Commons RJ, Thriemer K, Humphreys G, Suay I, Sibley CH, Guerin PJ, Price RN, The WWARN Vivax Surveyor: open access online mapping database for clinical trials of Plasmodium vivax, International Conference on Plasmodium vivax Research, Manaus, Brazil, 2017

Conference Abstracts (poster)

1. Commons RJ, on behalf of the WWARN Vivax Study Group, The effect of chloroquine dose and primaquine on P. vivax recurrence: an individual patient pooled analysis, American Society of Tropical Medicine and Hygiene, New Orleans, 2018

2. Commons RJ, on behalf of the WWARN Vivax Study Group, The haematological response following chloroquine treatment of Plasmodium vivax with or without primaquine: a pooled analysis of individual patient data, American Society of Tropical Medicine and Hygiene, New Orleans and 1st Malaria World Congress, Melbourne, 2018

3. Commons RJ, Simpson JA, Thriemer K, Hossain MS, Douglas NM, Humphreys GS, Sibley CH, Guerin PJ, Price RN, The risk of Plasmodium vivax parasitaemia after Plasmodium falciparum infection: a systematic review and meta-analysis, American Society of Tropical Medicine and Hygiene, New Orleans; 1st Malaria World Congress, Melbourne; and ASID ASM, Gold Coast, 2018

4. Commons RJ, on behalf of the WWARN Vivax Study Group, The haematological profile following treatment of Plasmodium vivax: a pooled analysis of individual patient data, International Conference on Plasmodium vivax Research, Manaus, Brazil, 2017

5. Commons RJ, on behalf of the WWARN Vivax Study Group, The effect of dose on the antimalarial efficacy of chloroquine for Plasmodium vivax: a pooled analysis of individual patient data, International Conference on Plasmodium vivax Research, Manaus, Brazil, 2017

6. Commons RJ, Thriemer K, Humphreys G, Suay I, Sibley CH, Guerin PJ, Price RN, The Vivax Surveyor: Online mapping database for Plasmodium vivax clinical trials, International Congress for Tropical Medicine and Malaria, Brisbane, 2016

Invited Presentations

1. The effect of chloroquine dose and primaquine Plasmodium vivax recurrence: an individual patient pooled analysis, 1st Malaria World Congress, Melbourne, 2018

2. Workshop on Conducting Clinical Trials, International Conference on Plasmodium vivax Research, Manaus, Brazil, 2017

3. WWARN Vivax Surveyor, APMEN Vivax Working Group, Bali, Indonesia, 2016