Institution: University of Warwick and Liverpool School of Tropical Medicine

Unit of Assessment: A2 - Public Health, Health Services and Primary Care

Title of case study: Enduring Impact on WHO Guidelines for Malaria Treatment

1. Summary of the impact

The World Health Organization (WHO) estimate 3.3 billion people are at risk of malaria, with 219 million cases and over half a million deaths annually. The Liverpool School of Tropical Medicine (LSTM) has applied new methods of research synthesis to malaria, and the results of this work have directly influenced important global decisions on malaria policies, including the adoption of new antimalarial drugs. In this case study, we report on the influence of the LSTM on malaria control over the last 15 years by preparing rigorous, up-to-date, timely systematic reviews on malaria. This work has also contributed to substantive improvements in the methodological rigor and transparency of the WHO malaria policy group in evidence-based policy formulation and guideline development.

2. Underpinning research

Since 1994, the LSTM has been preparing systematic reviews on the benefits and harms of healthcare interventions for tropical diseases. Meta-analysis can generate new knowledge by combining data from a number of smaller studies; and can demonstrate consistency of findings leading to unequivocal global policy recommendations. Before this period, the World Health Organization and other guideline groups rarely used systematic reviews and concise summaries of findings for developing recommendations. Instead, processes usually relied heavily on experts in a particular specialty, rather than methodologists specialising in synthesis and interpreting evidence, or representatives of those who will have to live with the recommendations. The LSTM have forged a relationship with the World Health Organization (WHO) in tropical diseases to ensure that the right policy questions are being addressed by LSTM reviews. LSTM staff who conducted this body of research has included Professor Paul Garner the Co-ordinating Editor of the Cochrane Infectious Diseases Group CIDG and the LSTM Evidence Synthesis for Global Health Group since (1994 – present,) David Sinclair, Clinical Lecturer, Author and Editor with the Cochrane Infectious Diseases Group (2007-present) and Helen Smith, Lecturer in Research Methods (1998 – present.)

In 1994 Paul Garner engaged Dr Piero Olliaro at WHO in a meta-analysis of data from 40 malaria trials to compare the therapeutic efficacy of amodiaquine with that of chloroquine in patients with malaria. Chloroquine was failing as a treatment due to parasite drug resistance in Africa and amodiaquine was a cheap potential alternative. Garner and Olliaro wrote a protocol and identified all available malaria trials, including trials published in French, and unpublished studies obtained from pharmaceutical companies. These approaches were ground-breaking, and the analysis revealed new findings from combining many small studies-that amodiaquine was clearly much more effective than chloroquine, the results published in the Cochrane Library and the Lancet.[1] LSTM was also commissioned to evaluate amodiaquine safety as it had been suggested it had serious adverse effects. In 2003, the systematic review of over 370 studies (in all languages) showed that the risk of severe adverse effects in patients treated with amodiaquine is not higher than that in patients treated with chloroquine.[2]

Subsequently, the LSTM worked with Dr Olliaro and Abdel Babiker (MRC Trials Unit in London) to carry out a prospective meta-analysis of individual patient data from all trials that compared artemisinin-based combination therapies (ACTs) with existing antimalarial treatments given by themselves. The LSTM research team contributed to the WHO template used by investigators to plan each randomised controlled trial (RCTs). The LSTM organised the individual patient data analysis across all these studies, a much more substantive analysis were all the data are managed in a single data base and analysed together; they engaged the researchers in the analytical plan and co-ordinated the analysis and interpretation of the data. The LSTM organised the investigators meeting of the International Artemisinin Study Group in WHO Geneva in 2002 to discuss the

findings and their interpretation.[3] The analysis included results from a number of trials that had not previously been published. The overall analysis showed there was no doubt that adding artesunate substantially increased cure rate, whatever drug it was added to.

In 2008, the WHO asked the LSTM to summarise the relative effectiveness of various ACTs. The analysis showed that a new ACT, dihydroartemisinin piperaquine, which at that time was not pre-qualified, was at least as good as, and probably better than, the other ACTs that were currently in use. Cochrane methods combined with the grades of recommendation, assessment, development and evaluation (GRADE) approach were used to assess the quality of evidence.[4] Subsequently, new evidence on the efficacy of ACTs in children with severe malaria was published, and the WHO asked the LSTM to rapidly incorporate this with existing trials of ACT for severe malaria in children so that the WHO were able to change its global guidelines to strongly recommend ACTs rather than quinine for treating severe malaria in children.[5, 6]

In 2012, the LSTM's reputation with the malaria panel led the WHO Director Generals' office asking LSTM to evaluate how well the organization was meeting current methodological standards for guideline development.[7] This analysis showed that WHO guideline development methods in all topic areas had become more transparent since 2007, but that some departments were bypassing procedures, and that the quality assurance standards set were not fully embedded in the organization.

3. References to the research (LSTM authors are underlined)

1. Olliaro P, Nevill C, LeBras J, Ringwald P, Mussano P, Garner P, Brasseur P. Systematic review of amodiaquine treatment in uncomplicated malaria. *Lancet* [1996]; 348:1196–201. [DOI: 10.1016/S0140-6736(96)06217-4].

2. MacLehose H, Klaes D, Garner P. Amodiaquine: a systematic review of adverse events (unpublished document available on WHO website) [2003]

3. International Artemisinin Study Group Artesunate combinations for treatment of malaria: meta-analysis. *Lancet* [2004]; 363 (9402):9–17 [DOI: 10.1016/S0140-6736(03)15162-8] (corresponding author: P Garner).

4. Sinclair D, Zani B, Donegan S, Olliaro P, Garner P. Artemisinin-based combination therapy for treating uncomplicated malaria. *Cochrane Database of Systematic Reviews* [2009]; 3: Art. No. CD007483 [DOI: 10.1002/14651858.CD007483.pub2]. **(Submitted in UoA2 REF2).**

5. Sinclair D, Gyansa-Lutterodt M, Asare B, Koduah A, Andrews, E, Garner P. Integrating Global and National Knowledge to Select Medicines for Children: The Ghana National Drugs Programme. *PLoS Med* [2013]; 10(5): e1001449. [DOI:10.1371/journal.pmed.1001449].

6. Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. *Cochrane Database of Systematic Reviews* [2012]; 6: Art. No. CD005967. [DOI: 10.1002/14651858.CD005967.pub4].

7. Sinclair D, Isba R, Kredo T, Zani B, Smith H, Garner P. World Health Organization Guideline Development: An Evaluation. *PLoS One* [2013]; 8(5):e63715 [DOI: 10.1371/journal.pone.0063715].

Key Research Grants

- DFID (UK) Effective Health Care Research Consortium (HD26) £6 Million. **PI Garner P**. 2010-16.
- DFID (UK) Effective Health Care Alliance Programme (EHCAP) (HD7). Increase in decisions related to the health sector based on best available evidence in middle and low-income countries, £4,022,649, **PI Garner P**. 2005-10

4. Details of the impact

Several factors have made malaria control difficult in sub-Saharan Africa and led to substantial increases in malaria burden on the continent during the 1980s and 1990s. The first was the widespread emergence of resistance of *P. falciparum,* particularly to chloroquine (CQ), then the most commonly used anti-malarial drug. This has been managed by changing treatment policy to ACTs in most sub-Saharan African countries.

***Re-introduction of amodiaquine for treating uncomplicated malaria in Africa*.**
The results of the joint studies of the LSTM and the WHO on the efficacy and safety of amodiaquine led to it being reintroduced for uncomplicated malaria in 2003, and has had an enduring impact since. The WHO technical report (page10) refers to the reviews leading to the recommendation that amodiaquine be added to the Model List as a core list medicine.[a, b] In 2006, WHO guidelines recommended amodiaquine combined with artesunate as one of the three ACTs for malaria treatment in Africa.[c] As a result, it is currently estimated that amodiaquine-containing ACT accounts for 30% of ACTs taken by adults with malaria in Africa. The 2008 Global Malaria Action Plan states *"There has been a remarkable adoption of ACTs in sub-Saharan African countries: in 2003, only two sub-Saharan African countries had adopted ACTs; as of September 2007, all sub-Saharan African countries except Swaziland and Cape Verde have adopted ACT policy."*[d] This is having an on-going impact on the treatment of uncomplicated malaria across Africa.

***WHO recommendation for replacement of monotherapy with ACTs in* P. falciparum *malaria*.**
The analysis of ACT safety and efficacy in 2004 provided unequivocal evidence (70% more patients cured with artesunate combination treatments than with monotherapy; meta-analysis of 16 trials) that ACT was more effective in treating malaria than the single antimalarial drugs alone. This led the WHO Expert Panel to recommend strongly in its 2006 guidelines that countries should stop using monotherapy.[c] Garner was the methodologist on the WHO Guideline Panel and drafted the evidence box for these guidelines. Evidence provided by the LSTM team led to the Global Recommendation in 2010 to replace monotherapy with combination therapy and also supported other WHO recommendations for treating uncomplicated and complicated malaria.[e, f] Introduction of ACTs is the most important treatment advance in malaria this century. This decision led to a massive increase in the manufacture and testing of co-formulated products and has probably been critical in reducing mortality from malaria globally. There were an estimated 11 million ACT treatment courses purchased in 2005, an estimated 287 million ACT treatments were purchased in 2011 as documented in UNITAID's Malaria Response.[g] (UNITAID is a global health organisation hosted by the WHO that uses innovative financing to increase funding for greater access to treatments and diagnostics for HIV/AIDS, malaria and tuberculosis in low-income countries).

Dihydroartemisinin–piperaquine added as a treatment option for malaria. During the development of the WHO malaria guidelines, the LSTM team was commissioned to assess new ACT treatment options. In the Cochrane review prepared for the WHO Guidelines panel, the analysis showed clearly that the dihydroartemisinin–piperaquine combination drug had failure rates of less than 10% and consistently performed as well as and often better than other ACTs, which led the panel to recommend it as a new option for treating malaria. The Medical Officer from the WHO's Global Malaria Programme confirms the new recommendations in the 2010 addition of the Malaria Treatment Guidelines, are based on the findings of these systematic reviews.[h]

***Artesunate recommended for severe malaria*.** At the 2010 Guideline review panel, the Cochrane Review of artesunate versus quinine was considered; this review showed that artesunate produced a 38% reduction in mortality in adults with malaria, when compared with quinine. Thus, the WHO Malaria Guidelines Panel in 2010 recommended that artesunate be used instead of quinine for severe malaria in adults. In 2011 a trial of artesunate in children was published and quickly added to the meta-analysis, providing additional data on children; this summary was considered by the Panel, who then recommended its adoption in children.[f, i]

Direct impact on the decision-making process of the technical expert group on malaria chemotherapy and beyond.

Paul Garner introduced systematic reviews and meta-analysis to malaria, against all the advice of experts in the field (who said that malaria was so varied that the methods were not appropriate). The early reviews on the efficacy and safety of amodiaquine and ACT indicated that rigorous up-to-date scientific reviews could drive policy and led the WHO to move from consensus decision making to evidence-informed approaches. Whilst this is part of a global movement, the LSTM team was instrumental in the introduction of evidence-informed approaches to decision making on malaria guidelines. [h, j] This is reflected by the fact that WHO routinely turns to the LSTM for Cochrane reviews, summaries and GRADE analyses. Importantly, malaria guidelines that are based on an externally validated tool have been demonstrated to be among some of the best WHO guidelines in terms of quality, as indicated by high quality scores using an international assessment tool (AGREE).[j]

The reputation of the LSTM led the Director-General's office of the WHO to ask the team to evaluate progress in evidence-based guideline development across the whole organization. The findings of the WHO guideline development evaluation were presented in 2013. In addition, the paper was presented to the WHO Senior Management Team, which is the highest decision-making body in the organization, and includes the Director General. This was then used to help refine and reinforce policies within the organization in relation to guidelines, and to extend quality assurance processes to other aspects of WHO publications.[j]

5. Sources to corroborate the impact

a. WHO technical report that informed the decisions on the essential medicine list, 2003, page 10. http://tinyurl.com/kh9khf2

b. WHO essential medicines list reintroduced amodiaquine in 2003 http://tinyurl.com/m4mqknf

c. WHO Guideline 2006 stating the meta-analysis of 11 RCTs found clear benefit of adding ACTs it significantly reduces treatment failure, recrudescence and gametocyte carriage. Annex 1 of the first edition of the guidelines. http://whqlibdoc.who.int/publications/2006/9241546948_eng.pdf

d. Roll Back Malaria Global Malaria Action Plan http://www.rollbackmalaria.org/gmap/3-2.html) Part III: Regional Strategies 2. Africa.

e. LSTM are part of the WHO Malaria Treatment Guidelines Panel and contributed towards this new edition 2010. http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf

f. 2010 WHO Guidelines for the treatment of malaria: http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html

g. UNITAID's Malaria Response http://www.unitaid.eu/en/what/malaria?id=1151

h. Medical Officer from the WHO's Global Malaria Programme talking about the new edition of Malaria Treatment Guidelines: YouTube video: Http://Tinyurl.Com/Mb5zety

i. WHO Recommendation: Intravenous artesunate should be used in preference to quinine for the treatment of serve malaria. http://www.who.int/malaria/areas/high_risk_groups/children/en/index.html

j. **Person who can be contacted**: A statement can be provided from the **Director of Strategy**, Office of the Director General, confirming that processes in the WHO have changed due to the evaluation. (Identifier 1).