Systematic Reviews in Malaria: Global Policies Need Global Reviews

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KEYWORDS

• Malaria • Systematic review • Policy • Meta-analysis
• Research synthesis

An estimated 247 million cases of malaria occur every year, resulting in about 1 million deaths, mostly of children aged less than 5 years.[1] Families, endemic country governments, and donors spend considerable amounts in treating and preventing the disease. Indeed, in the last 5 years, a large amount of money has gone into malaria control from governments, aid agencies, and international organizations, so it is critical that it is spent wisely. Basing policies on the best available evidence will help ensure maximum impact in terms of reducing death and illness globally, and, with such a high disease burden globally, this has to be a priority in international health.

Randomized controlled trials evaluating comparative benefits and harms of new drugs to treat malaria, or the effect of public health policies such as using mosquito nets treated with insecticide, help delineate best policies within regions. But over the last 15 years, the number of published trials in malaria has increased, from 56 in 1980 to 1984 to 540 in 2000 to 2004 (**Fig. 1**). For policy makers, interpreting and keeping up to date with this emerging literature are difficult, if not impossible. In parasitic diseases, as in other areas of health care, expert opinion is not enough. There is a clear need to summarize knowledge using formal, accepted methods of research synthesis in the form of systematic reviews (**Box 1**). Yet early on, infectious and parasitic diseases largely had escaped the net of research synthesis; the techniques were

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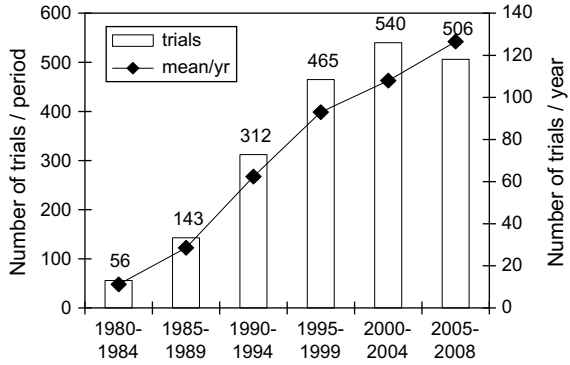

Fig. 1. Malaria trials indexed in PubMed. Search terms: malaria and clinical trial and randomized controlled trial.

honed and applied by researchers in wealthy countries, and the health conditions they addressed were important there. If they also affected the poor in developing countries, that was serendipity.

Applying the methods of research synthesis to an infectious disease like malaria is not straightforward. Countries vary substantially in the epidemiology of malaria, available resources, capacity of their health systems, and in their ability to mount effective prevention programs. Indeed, the outcomes of research in appropriate interventions often have been seen to be locally relevant but difficult to generalize and apply globally, as factors around host immunity, patterns of transmission, and types of parasite tend to be country- or region-specific. For these reasons, the application of research synthesis to malaria initially was regarded with skepticism. Up to the 1990s it had been

Box 1
Clarification of terms

Systematic review

A review that "attempts to collate all empiric evidence that fits prespecified eligibility criteria to answer a specific research question"[28]

Key characteristics of a systematic review

A clearly stated set of objectives with predefined eligibility criteria for studies

An explicit, reproducible methodology

A systematic search that attempts to identify all studies that would meet the eligibility criteria

An assessment of the validity of the findings of the included studies (eg, through the assessment of risk of bias)

A systematic presentation and synthesis of the characteristics and findings of the included studies[28]

Meta-analysis

A systematic review may include a meta-analysis, which is a statistical approach to combining data from two or more studies

Cochrane review

A systematic review prepared with the support of a Cochrane Review Group (which is part of The Cochrane Collaboration) and is published in the *Cochrane Database of Systematic Reviews* (part of *The Cochrane Library*)

consensus groups, drawing on expert opinion alone, which decided on the best global policies. Over the last 15 years, however, the World Health Organization (WHO) has shown considerable leadership in malaria research, in particular ensuring the application of research synthesis to this field. It has developed partnerships between key researchers and specialists in research synthesis, particularly with The Cochrane Collaboration, to prepare and regularly update systematic reviews about the benefits and harms of new and emerging interventions to prevent and treat malaria. The WHO now formally endorses systematic reviews as integral parts of its guideline development process.[2]

This article highlights some of these systematic reviews and what has been learned about applying methods of research synthesis in this particular infectious disease over the last 15 years. The authors' objectives in writing this article are to (1) illustrate how systematic reviews have been used to guide policy, (2) show what has been learned about synthesizing research in this area, and (3) reflect on how best to maximize their uptake in policy and practice.

COCHRANE INFECTIOUS DISEASES GROUP

The Cochrane Infectious Diseases Group was formed in 1994, one of the original review groups of The Cochrane Collaboration, an international nonprofit organization dedicated to preparing and keeping up-to-date reliable reviews about the effects of health care interventions.

In the early 1990s, systematic review and meta-analytic methods rarely were applied to parasitic diseases; early systematic reviews were of interventions for pregnancy and childbirth.[3] Iain Chalmers (now Sir Iain), founder of The Cochrane Collaboration, persuaded the authors to summarize all randomized controlled trials evaluating malaria chemoprophylaxis during pregnancy on substantive outcomes, including perinatal mortality. The authors were staggered how thin the evidence was for prophylaxis, yet it was WHO policy at the time.[4] This systematic review was performed at the epicenter of a tidal force emanating from the United Kingdom that was intent on summarizing research in a way that minimized bias.[5] This led the authors to explore how to establish a process to prepare and update systematic reviews in parasitic and other infections relevant to the tropics. In the process, the authors would carry out meta-analysis—the statistical combination of the results—where appropriate. What was to become the Cochrane Infectious Diseases Group started as a meeting of malaria specialists hosted by Professor Chitr Sitthiamorn at Chulalongkorn University in Thailand. The concept, developed as part of the wider Cochrane Collaboration, was to establish a network of authors who would offer their time to carry out and update systematic reviews of interventions and policies in malaria, to help make decisions more evidence-informed, and to guide priorities in research. The group was registered with The Cochrane Collaboration in 1994 under Professor Paul Garner's leadership and, following the guidelines of The Cochrane Collaboration as a whole, it is committed to conducting reviews that minimize bias, ensuring quality, and keeping reviews up to date. This is done in various ways:

- Protocols for Cochrane Reviews are mandatory and are published. These outline the materials and methods of the systematic review, including inclusion criteria, search strategy, and the analytical plan. No data are contained in them. Protocols are refereed by specialists in statistics, research synthesis, malaria, and health policy, and then published.
- Experienced information retrieval specialists carry out searches across multiple databases. In some cases, before literature indexing had improved, the

Cochrane Infectious Diseases Group employed people to search specialist journals by hand to identify relevant trials.
Protocols and Reviews are prepared using standard methods and software developed by The Cochrane Collaboration.
Extensive development by The Cochrane Collaboration and its associates to improve general methods and special methods in meta-analysis (eg, for cluster randomized trials that often are used in the trials of interest to Cochrane Infectious Diseases Group authors).
Central coordination of topics for reviews to avoid duplication, and to encourage academic groups to work together rather than compete.
Inclusiveness, enabling participation of authors whatever their background or experience, with more experienced volunteers providing training and mentorship in research synthesis.

The Cochrane Infectious Diseases Group always has focused on diseases of importance in low-income tropical countries and not all infectious diseases. Part of its mission has been to help develop expertise in systematic reviews in these countries. The group's editorial team is a mixture of grant- and university-supported staff and a volunteer editorial board (**Box 2**), which has involved technical staff from the WHO from the outset. There is now a group of over 200 authors (**Fig. 2**) who are committed to preparing and updating systematic reviews in relevant areas of parasitic and infectious diseases in the tropics. To date, the authors have prepared 35 reviews in malaria, 16 in tuberculosis, 13 in diarrhea, and 25 in other neglected tropical diseases and health problems relevant to middle- and low-income countries. The only reason this endeavor is possible is through the substantial amount of time that editors and authors donate as volunteers. On top of this, some support staff and funds for larger reviews come through the Department for International Development, which is part of the UK government, for the benefit of people living in developing countries, and commissioned projects through the WHO, in particular the WHO's Special Programme for Research & Training in Tropical Diseases (TDR).

Overall, there has been a shift toward using these systematic reviews in policy. The Technical Expert Group for the World Health Organization Malaria Treatment Guidelines drew on research evidence in systematic reviews in the first edition in 2006,[6] categorizing decisions and recommendations using the standard approach (highest based on systematic reviews, and lowest based on expert opinion). In 2008, the WHO had decided that all guideline development needed to follow an explicit, transparent process where systematic reviews were used,[2] and then the evidence formally assessed using one particular system called GRADE, which stands for Grading of Recommendations Assessment, Development, and Evaluation.[7] These GRADE profiles then are considered by the consensus panel in forming recommendations and provide a measure of the strength of evidence behind a recommendation, and will appear in the next edition of the Global Malaria Treatment Guidelines.[6,8]

The article now turn to topics in malaria prevention and treatment, and the systematic reviews conducted through the Cochrane Infectious Diseases Group to discuss how they came about, and what has been learned from them.

PREVENTING MALARIA

Drugs to Prevent Malaria in Pregnancy: A Place to Start

The most vulnerable members of the population in malarial areas are infants, children, and pregnant women. For reasons that are partially understood, women—especially low-parity women—lose some of their acquired immunity to malaria

Box 2
The Cochrane Collaboration: a global organization[29]

The Cochrane Collaboration is dedicated to improving health care decision making globally, through systematic reviews of the effects of health care interventions, published in the *Cochrane Database of Systematic Reviews*, part of *The Cochrane Library.*

The Cochrane Collaboration is a global network of dedicated volunteers and researchers. It relies on grants and donations, and does not accept conflicted funding. There are about 11,500 volunteers in more than 90 countries. The Cochrane Collaboration has 10 principles:

1. Collaboration
2. Building on the enthusiasm of individuals
3. Avoiding duplication
4. Minimizing bias
5. Keeping up to date
6. Striving for relevance
7. Promoting access
8. Ensuring quality
9. Continuity
10. Enabling wide participation

Production is coordinated through 52 Cochrane Review Groups. Methods groups help develop and advise on best methods, and Cochrane Centers coordinate activities within region.

Cochrane Infectious Diseases Group

Scope

The scope covers health care interventions for communicable diseases. The focus is mainly, but not exclusively, on diseases that affect people in low-income and middle-income countries. These diseases include malaria, acute diarrhea, tuberculosis, helminth infections, scabies and head lice, and other protozoan, bacterial, and viral infections that are found predominantly but not exclusively in tropical and subtropical regions of the world.

Editorial team

The editorial base is located in the Liverpool School of Tropical Medicine, United Kingdom. Thirteen editors, based around the world, provide support for individual reviews and editorial policies and decisions. The Group Web site is http://www.cidg.cochrane.org.

when pregnant. In the early 1990s, spreading resistance to 4-aminoquinolines (eg, chloroquine and amodiaquine) meant the options for prophylaxis were limited, and this reopened the debate: if prophylaxis or intermittent preventive treatment or malaria prevention is worth doing, then one really needs to know if it is of benefit to women and their infants. Although some authors had noted a positive influence of prophylaxis on birth weight, there was a debate as to whether this might do more harm than good.[9]

The first systematic review on the topic was published in the *Bulletin of the WHO*.[4] At this time, the authors pointed out that, although policies encouraging prophylaxis and intermittent preventive treatment looked promising, the impact of various approaches was not evident for pregnant women of all parity groups together, and impacts on substantive outcomes, including anemia in the mother and perinatal mortality in the fetus, were not sufficient to be sure the intervention was effective. In

Fig. 2. Global spread of Cochrane Infectious Diseases Group authors.

particular, none of the trials reported on the effect of the intervention in preventing anemia.

This first systematic review provided insight to preparing systematic reviews in malaria, and the first lesson was the degree to which researchers are willing to help with additional data analysis. One of the concerns raised by referees and literature at the time was whether malaria prophylaxis shifted the whole birth weight curve and caused an increase in high birth weight infants.[9] Authors of the original trials were cooperative in providing unpublished data that helped answer this question, and there did not appear to be an increased number of high birth weight infants in the intervention group. Professor Brian Greenwood and colleagues in The Gambia provided unpublished data (1991) on perinatal mortality, and Dr. François Nosten and colleagues in Thailand reanalyzed their birth weight data to examine for differences between prophylaxis and control groups in relation to the number of high birth weight infants. More than just reviewing the published literature, then, this systematic review helped reframe the questions relevant to the policy being tested, and then allowed the authors of the systematic review to obtain these data from the researchers who conducted the original studies.

In addition to summarizing existing evidence, systematic reviews aim to help identify research priorities. The first systematic review pointed out that none of the trials looked at point prevalence of anemia in the mothers, and it was recommended this be included in future studies. The first subsequent study, by Shulman and colleagues,[10] identified severe anemia in the mother as the primary outcome, and actually showed a significant effect of intermittent preventive treatment with sulfadoxine–pyrimethamine on this outcome. This finding was an important impetus in this intervention being recommended by the WHO, and it was adopted and promoted as national policy in countries.

Over time, the effects on perinatal mortality have accumulated, and the current reading is suggestive of a protective effect of drugs taken to prevent the effects of malaria in pregnancy (relative risk [RR] 0.73, 95% CI, 0.53 to 0.99; 1986 participants, three trials, **Fig. 3**).[11] This demonstrates how a systematic review can highlight the gaps in the knowledge and provide pointers for research, and how the accumulation of global knowledge can be captured by updating the systematic review over time.

First edition: 1994

Latest edition: 2001

Trials included: 19

Current status: Update in progress

Learning points

- Trialists can be very helpful in providing outcomes not published in the trials
- The review highlighted important outcomes to be measured in future trials
- Meta-analysis of uncommon but important outcomes (in this case perinatal mortality) helps generate new knowledge

Comparison: Any drug for preventing malaria given to women in first or second pregnancy vs placebo or no drug

Outcome: Perinatal death

Summary statistic: Risk ratio 0.73, 95% confidence interval 0.53 to 0.99

Finding: Antimalarial drugs in pregnancy reduce the number of perinatal deaths

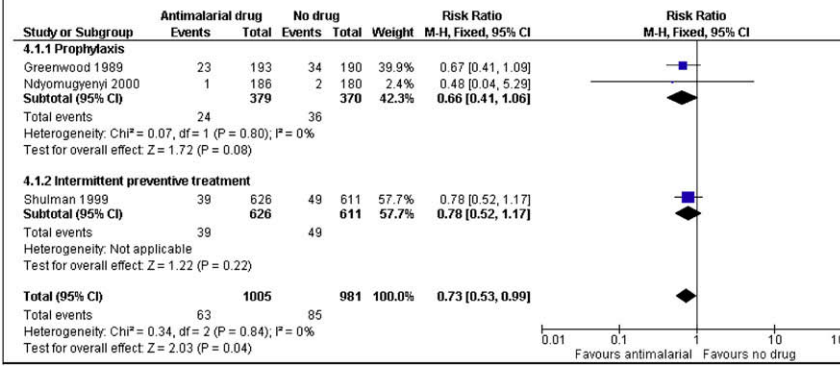

Fig. 3. Malaria prophylaxis in pregnancy. (*From* Garner P, Gülmezoglu AM. Drugs for preventing malaria in pregnant women. Cochrane Database Syst Rev 2006;2; with permission.)

Insecticide-Treated Nets for Malaria: Public Health Interventions to the Test

Preventing malaria by sleeping under mosquito nets treated with insecticide was a new technology in the 1970s. It was clear that the intervention was potentially powerful, a substantive technology that could have impacts similar in magnitude to insecticide spraying, but bringing it to scale would require considerable global investment. But before making the investment, further research was needed to evaluate this intervention. Major funders began embarking on cluster randomized trials comparing insecticide-treated nets to untreated nets or no nets with mortality in children as an outcome, and the WHO along with academic groups sought to ensure a systematic review was performed.

The trend in the trials in terms of lower mortality was encouraging, but when taken together in a meta-analysis,[12] with careful adjustment for design effects related to clustering, the effect was consistent, clear, and statistically significant in favor of the insecticide-treated nets (**Fig. 4**). This particular analysis provides graphic and

First edition: 1998

Latest edition: 2004

Trials included: 14 cluster randomized controlled trials and 8 randomized controlled trials of individuals

Current status: Monitoring for new trials

Learning points

- Trials and meta-analysis of potentially powerful, community-based interventions in poor areas is possible
- Statistical adjustment for clustering is required for all cluster randomized designs

Comparison: Insecticide-treated nets *vs* untreated nets or no nets

Outcome: All-cause child mortality

Summary statistic: Relative rate 0.82, 95% confidence interval 0.76 to 0.89

Finding: Insecticide-treated nets reduce mortality in children living in endemic areas

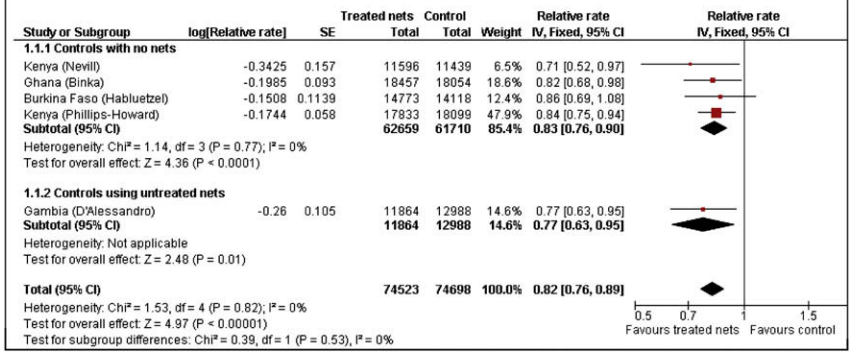

Fig. 4. Insecticide-treated mosquito nets and curtains to prevent malaria in children. (*From* Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev 2004;2; with permission.)

statistically robust evidence that this intervention reduces child deaths. This evidence has been tremendously important in establishing the effectiveness of insecticide-treated nets, and ensuring further development of the technology. When the concept first was tested, it relied on cloth nets that had to be treated by hand and renewed every few months. Several generations later, the insecticide is integrated into the fabric itself and lasts as long as the net, providing long-lasting protection.

Insecticide-Treated Nets in Pregnancy: Meta-analysis Helps Consumers Understand

Once it was clear that malaria prophylaxis or intermittent preventive treatment using drugs was effective during pregnancy in preventing severe anemia, increasing mean birth weight, and possibly lowering the risk of perinatal mortality,[11] the question remained as to whether insecticide-treated nets also would be beneficial for pregnant women. Several large trials were set up to address this question. It became particularly important as emerging drug resistance meant the options for malaria prophylaxis or intermittent preventive treatment were becoming more limited; expensive drugs with toxic effects (eg, mefloquine) were being tested.[13]

Policy makers in the WHO wanted a systematic review to help guide their policies in relation to insecticide-treated nets in pregnancy. The Cochrane Review[14] showed a clear effect in women of low parity on parasitemia and anemia. When data were extracted carefully on fetal loss, an interesting trend emerged, which in meta-analysis demonstrated statistical significance (**Fig. 5**). This was a powerful message—that insecticide-treated nets reduced fetal loss—useful in communicating to pregnant women the true value of nets in terms of outcomes that have meaning to them.

Malaria Vaccines: Focusing on Disease Outcomes and Improving Trial Design

The world has been waiting a long time for a malaria vaccine; the cycle of promise and disappointment has been constant since the 1960s. By the mid-1990s, a good deal of early phase malaria vaccine research had been performed, much of it leading to dead ends for particular antigens. When starting to synthesize the evidence on this topic, trials with only immunologic (mainly antibody titers) endpoints were eliminated from consideration, and reviews were focused on trials that tested the efficacy of vaccines in preventing or mitigating disease (either in laboratory or natural challenge). Data on

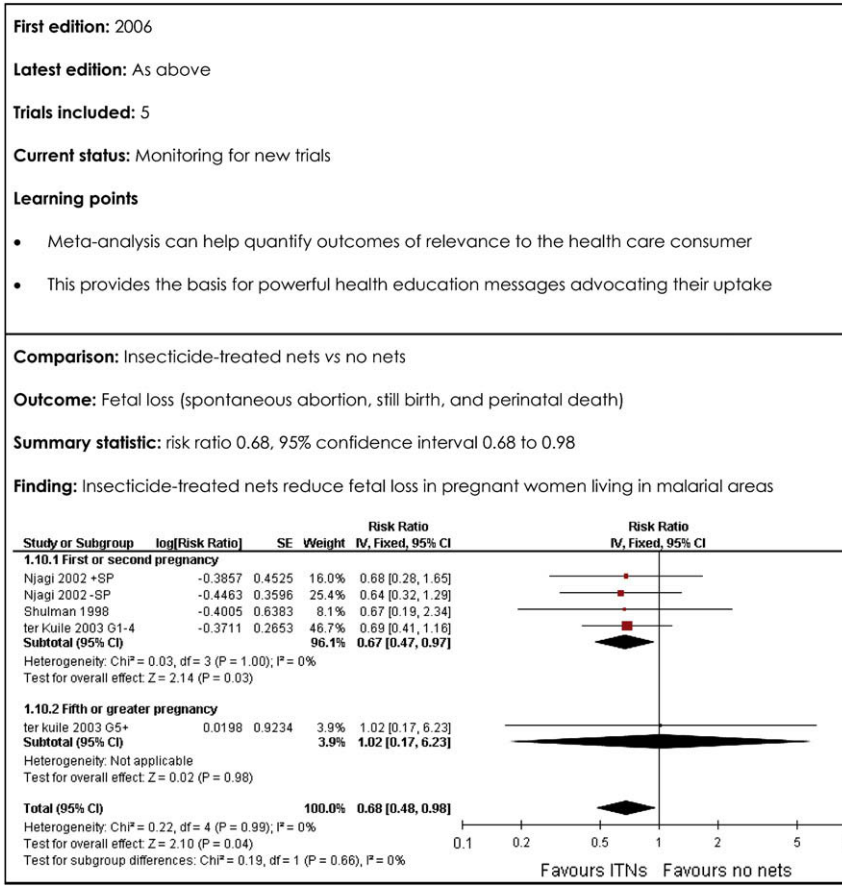

Fig. 5. Insecticide-treated mosquito nets in pregnancy. (*From* Gamble C, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. Cochrane Database Syst Rev 2006;2; with permission.)

adverse effects were extracted from immunologic trials for those vaccines that also had challenge endpoints in other trials.

Careful attention was paid to the stage of parasites used in a vaccine, the length of follow-up, the intensity of local transmission, and the effect of booster doses. A particular issue was how malaria cases were detected (active or passive), which can bias results, but were reported poorly in early trials. The authors believe that highlighting this in Cochrane Reviews has, resulted in standardized and improved collection methodology and reporting of outcomes in vaccine trials.

As trials of malaria vaccines have accumulated, what was originally a single Cochrane Review has been reorganized into three:

1. A systematic review that captures the history of SPf66 (**Fig. 6**)
2. One for pre-erythrocytic vaccines (intended to protect against or delay malaria infection)
3. One for blood-stage vaccines (intended to prevent invasion of red blood cells or diminish the severity of malaria)[15–17]

Together, they have helped to confirm a lack of effectiveness in Africa of SPf66, one early and controversial vaccine, and its limited effect outside Africa.[17] Another review raised awareness of the reduction in parasite load by potentially overlooked asexual-stage vaccines but also highlighted confusing effects that could be introduced in trials by predosing vaccine participants with antimalarial drugs.[15] The third review has summarized the effectiveness of the pre-erythrocytic RTS,S vaccine, which underlined the need for further multicountry trials of this vaccine.[16] As with other topics, the updating process allows authors to reorganize the information and present research questions and assembled data to reflect current questions with malaria vaccines—and here highlight the most promising vaccines at particular points in time.

TREATING MALARIA

Amodiaquine: Broad Literature Searches are Important

In the mid-1980s, reports of fatal adverse drug reactions to amodiaquine used for malaria prophylaxis led the WHO to stop recommending the drug in its programs.[18] There were some suggestions, however, that it might be more effective than chloroquine for treatment. In some countries, amodiaquine was being used as first-line treatment, and in others it was banned entirely. Working with the WHO, the authors supported a Cochrane Review of amodiaquine treatment trials (**Fig. 7**), which were conducted mainly in Africa.

In the first edition of the Cochrane Review, 40 trials met the inclusion criteria. Seventeen were published; five were unpublished, and 18 were in the form of raw data. Twenty were written in French or performed in Francophone countries.[19] The authors' literature searches include strategies for locating studies regardless of publication status and language; without these broad searches, over half of the trials included in this review would not have been located.

The results for countries in Africa were remarkably consistent. Using the 14-day follow-up period recommended by the WHO at that time (now changed to 28 days or longer), amodiaquine cured a greater proportion of malaria cases than did chloroquine. The difference in cure rates was dramatic, despite the heterogeneity, which probably reflected different populations and variation in parasite sensitivity. Each trial was individually insufficient to shift policy in a country—many were quite small—but overall the picture was clear. As a consequence of this systematic review, the WHO listed amodiaquine again as an option for treating malaria,[20] and the drug was made more widely available again in Africa.

First edition: 1997

Latest edition: 2006

Trials included: 10

Current status: Monitoring for new trials

Learning points

- It is helpful sometimes to stratify results of trials by region
- In deciding on the balance between benefits and harms, summaries of adverse events are important
- Defining outcomes clearly as clinical malaria or infection
- Helps define implications for research

Comparison: SPf66 vaccine vs placebo

Outcome: New malaria episode (*Plasmodium falciparum*)

Summary statistic for Africa: risk ratio 098, 95% confidence interval 0.90 to 1.07

Summary statistic for South America: risk ratio 0.72, 95% confidence interval 0.63 to 0.82

Finding: No evidence of protection in Africa

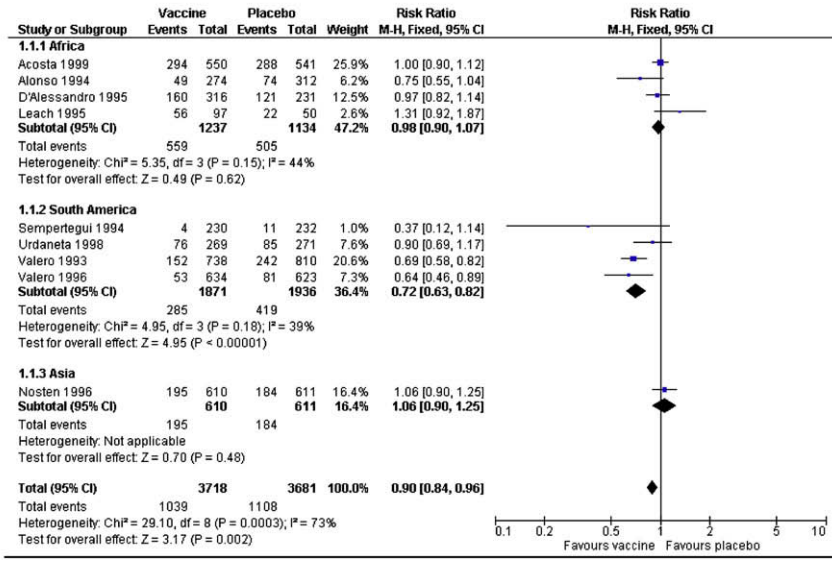

Fig. 6. SPf66 malaria vaccine. (*From* Graves P, Gelband H. Vaccines for preventing malaria (SPf66). Cochrane Database Syst Rev 2006;2; with permission.)

Artemisinin Combinations: Individual Patient Data Meta-analysis

Reviews of artemisinin derivatives[21,22] have evaluated 41 trials of various different artemisinin monotherapy and combination treatments, in various regimens and doses. In 1998, the systematic review then current was used by the WHO in considering next priorities in research in a meeting convened by the WHO in Annecy, France.[23]

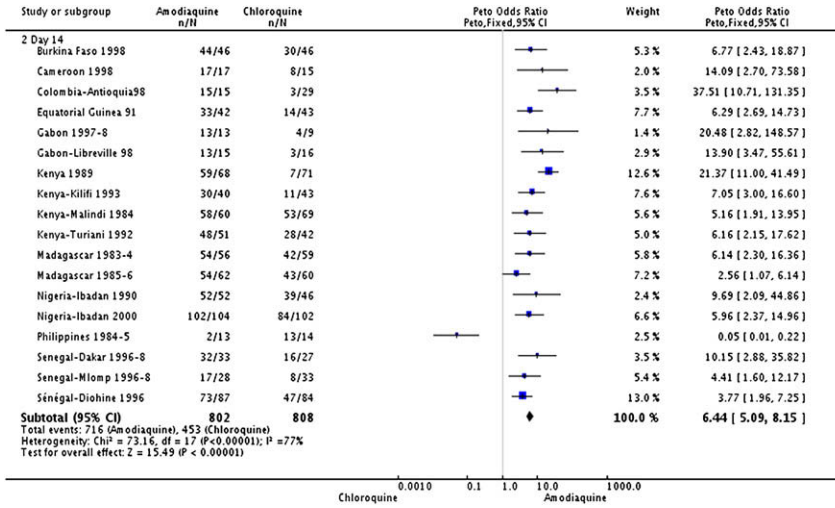

Fig. 7. Amodiaquine for *Plasmodium falciparum* malaria. (*From* Graves P, Gelband H. Vaccines for preventing malaria (SPf66). Cochrane Database Syst Rev 2006;2; with permission.)

Researchers recommended a more strategic approach to evaluating these compounds, giving them in combination with current first-line treatments within countries, to evaluate the effect on cure rate and other parameters.

A taskforce convened by the WHO's TDR encouraged a standard approach to trial design and facilitated formation of the International Artemisinin Study Group.[24] This group of researchers agreed to a standard protocol for meta-analysis using individual patient data across continents. This approach improves the quality of the meta-analysis. All trials were compiled in a single database; exclusions were dealt with in similar fashion, and the results synthesis was conducted as one analysis, stratified by drug and site. The trials and analysis took some 7 years to complete, and the meta-analysis was a substantive undertaking (**Fig. 8**). Representatives from each trial participated in a meeting to discuss the analysis and the results, and all agreed on the final manuscript, which gave the findings considerable weight. The effects showed that adding artemisinin derivatives for 3 days combined with the existing base drug used in the country resulted in substantially better cure rates than did monotherapy.[24] This systematic review, along with observational data on absolute cure rates and known pharmacologic effects of the drugs, helped the WHO make the recommendation that monotherapy no longer should be used, and wherever possible artemisinin-based combination therapy (ACT) be adopted for uncomplicated malaria.[6,25] That point now is considered settled science.

Head-to-Head Comparisons of Artemisinin-Based Combination Therapies: Adopting Grading of Recommendations Assessment, Development, and Evaluation Summaries

Once ACTs were established as the recommended first-line treatment for uncomplicated malaria, consideration of the best option needed evaluation, particularly as new combinations emerged, and resistance patterns varied around the world. A veritable explosion of trials obscured the overall picture. It is important, however, for the WHO to make timely decisions in this area.

Published in *The Lancet*: 2004

Trials included: 16

Learning points

- Individual patient data meta-analysis is a powerful methodological and political approach.
- Global questions can be answered despite varying drug resistance.
- Once the question is answered, updating is not required.

Comparison: Artesunate for 3 days plus base drug *vs* base drug. Base drugs either chloroquine (CQ), amodiaquine (AQ), sulfadoxine-pyrimethamine (SP), or mefloquine (MQ)

Outcome: Parasite failure at day 28 (not adjusted to exclude new infections)

Summary statistic: Risk ratio 0.30, 95% confidence interval 0.26 to 0.35

Finding: Adding artesunate substantially reduces parasitological failure by day 28 of follow up

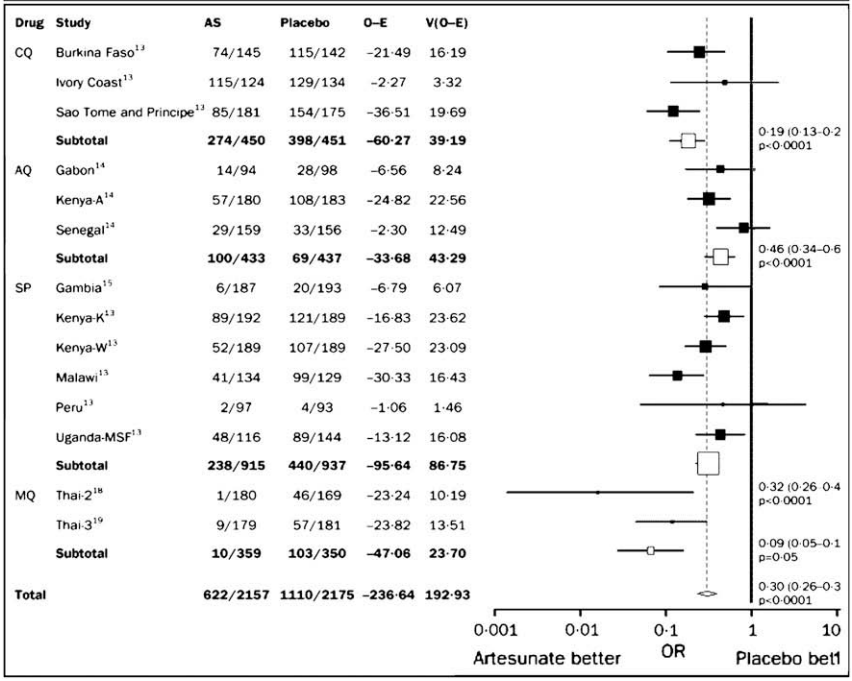

Fig. 8. Artesunate combinations for treatment of malaria: meta-analysis. (*From* Adjuik M, Babiker A, Garner P, et al. Artesunate combinations for treatment of malaria: meta-analysis. Lancet 2004;363:9; with permission.)

Over the last 2 years, an increasing number of head-to-head comparison trials have been performed. These trials, when put into meta-analysis, are beginning to show there are probably clinically significant differences in cure rate between different ACTs. Some are local, but others are applicable globally. This means that keeping systematic reviews up to date is important to inform decision making. A Cochrane Review of ACTs is in progress (**Fig. 9**); it demonstrates that dihydroartemisinin–piperaquine,

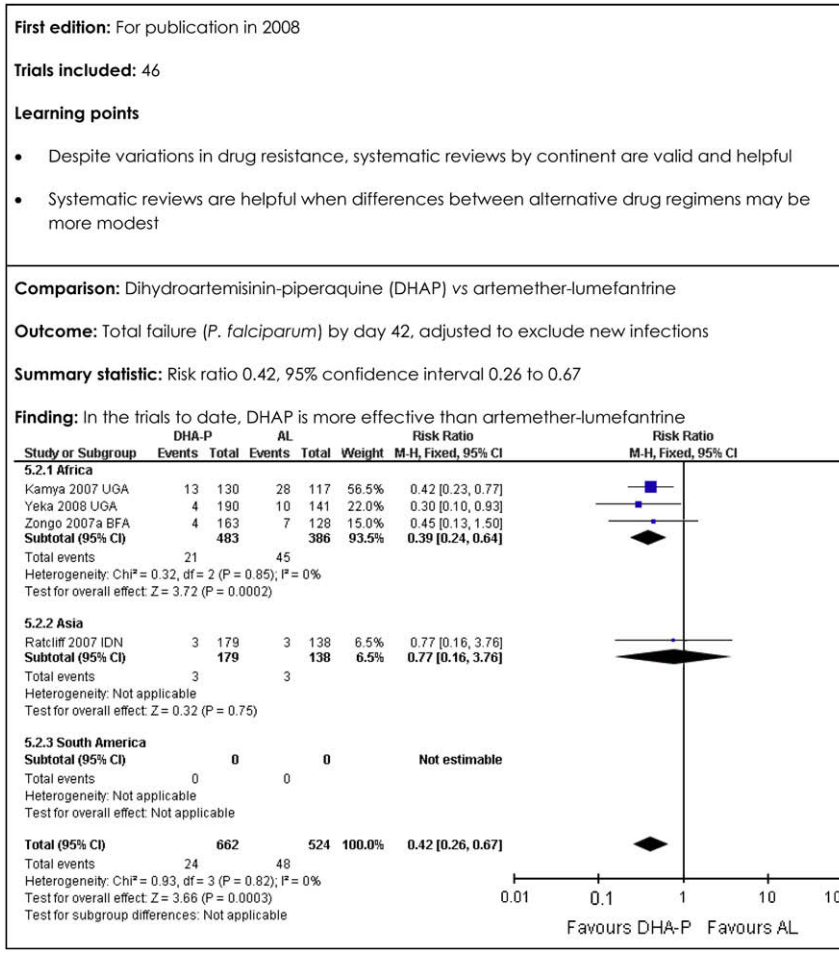

Fig. 9. Artemisinin combination therapy for treating uncomplicated malaria. (*From* Sinclair D, Zani B, Bukirwa H, et al. Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database Syst Rev 2008;4; with permission.)

an ACT that long has been used in Asia but has not been subject to extensive trials, is performing better than artemether–lumefantrine, the most tested ACT.[26]

Primaquine for Plasmodium Vivax: Policy Influence in India and Sri Lanka

For some years, the WHO has recommended a 14-day regimen of primaquine to prevent relapses of *Plasmodium vivax*, but in Sri Lanka and India, policy was for a 5-day regimen. A senior policy maker from Sri Lanka on study leave in Liverpool, United Kingdom, performed a Cochrane Review[27] of primaquine for preventing relapses of *P vivax* malaria with support from colleagues in India. As shown in **Fig. 10**, the included trials demonstrated lower relapse rates for *P vivax* with the 14-day regimen and no effect of the 5-day regimen. This evidence opened discussion about standard treatment both in Sri Lanka and India; Ministries of Health in both countries approved of a shift from the 5-day to 14-day regimen in the national guidelines.

First edition: 2006

Latest edition: 2006

Trials included: 9

Current status: Monitoring for new trials

Learning points

- National policies may be different to the WHO guidelines
- Cochrane Review done by a national policymaker led to new country guidelines

Comparison: Primaquine for 5 days vs primaquine for 14 days (both get chloroquine)

Outcome: *P. vivax* detected > 30 days after starting primaquine

Summary statistic: Odds ratio 13.33, 95% confidence interval 3.45 to 51.44

Finding: Primaquine for 14 days substantially reduces relapse, but 5 days does not

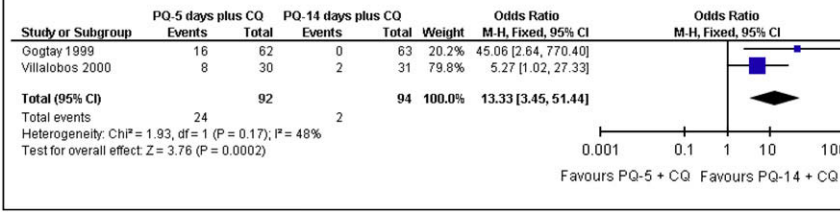

Fig. 10. Primaquine for *Plasmodium vivax*: changing regional policies. (*From* Galappaththy GN, Omari AA, Tharyan P. Primaquine for preventing relapses in people with *Plasmodium vivax* malaria. Cochrane Database Syst Rev 2007;1:CD004389; with permission.)

This illustrates that there is often a gap between global policies set by the WHO and national guidelines. In this instance, a systematic review that involved policy staff from the relevant countries facilitated a rapid change in national guidelines in line with the available evidence, and consistent with the WHO guidelines.

REFLECTIONS ON THE PROCESS

Malaria is a parasitic disease of massive global importance, with varying sensitivity to drugs related to time, place, host immunity, and the resistance profile of local parasites. Despite this variation, carefully conducted systematic reviews (some with meta-analysis) can provide substantive guidance to global policy. The collaboration between the WHO and the Cochrane Infectious Diseases Group has been constructive in providing solid evidence for policy change.

Although much of the developed world moved fast with systematic reviews and meta-analysis underpinning the treatment of chronic diseases, tropical diseases have not moved quite as quickly. Malaria, however, has been an important flagship to show it can be done for problems in low- and middle-income countries, involving researchers from endemic areas in gathering and evaluating the evidence. In malaria, the first author on over half of the Cochrane Reviews is from endemic regions. In such a rapidly growing organization, this is remarkable and has been possible for several reasons.

The first is the structure of The Cochrane Collaboration itself. It is international, and from the outset determined to have a global community contributing to it and

collaborating on individual reviews. Within the collaboration, it is easy to avoid duplication and enable wide participation. This inclusiveness has encouraged groups in low- and middle-income countries to engage in the process. Cochrane Centers in Brazil, South Africa, India, China, and other locations help train and assist review authors working with the Cochrane Infectious Diseases Group and other Cochrane Review Groups reviewing trials in particular areas of medicine and health. A second reason it has been relatively easy to involve people from endemic regions is that the methods are clear, explicit, and made widely available through materials (including software developed by The Cochrane Collaboration) and training. The third reason has been extensive political and financial support from countries themselves (in supporting the centers listed previously) and other donors, including core support to the Cochrane Infectious Diseases Group from the UK Department for International Development. Finally, preparing a systematic review does not require vast amounts of resources, and for people in countries with constraints on research infrastructure, systematic reviews are a good way to do a valuable piece of research, assuming randomized controlled trials have been conducted on the question of interest. Although this is the case today for malaria, in some of the neglected diseases covered by the Cochrane Infectious Diseases Group, it is not. Systematic reviews can point to research needs, but a systematic review is only as good as the trials underpinning it.

Malaria is the best example from the Cochrane Infectious Diseases Group of systematic reviews contributing consistently to policy. Indeed, there are more trials in malaria than any other tropical infection; the global spotlight is on the condition, and spending on it has gone from a few hundreds of thousands of dollars per year before 2000 to tens of millions today. The WHO has been a major consumer and supporter of the Cochrane Infectious Diseases Group's systematic reviews in malaria, particularly in understanding new preventive interventions (such as insecticide-treated mosquito nets) and treatment with ACTs—both of which have large, beneficial effects. The reviews have helped reinforce the optimism around these developments by quantifying the beneficial effect more precisely than is possible in individual trials. Also, in summary, three main factors appear to have helped make this an effective process:

- The structure and principles of The Cochrane Collaboration, avoiding duplication, encouraging a collective effort, and enabling wide participation.
- Commitment of technical scientists working at policy level and involvement of key malaria researchers, inside and outside endemic countries, in the systematic review preparation process.
- The editorial process is independent, although the WHO and the key researchers have been involved in critiquing and refereeing reviews during the development process.

Cochrane Reviews aim to be timely, good quality, accurate, and independent. In malaria, there is a true partnership between those synthesizing the research, those producing it, and those responsible for global policy. This helps ensure that reviews are timed to inform current policy decisions.

REFERENCES

1. World Health Organization. World malaria report 2008. Geneva (Switzerland): World Health Organization; 2008.
2. World Health Organization In: World Health Organization manual, September 2008, Part VIII, Section 1, Annex B. Geneva (Switzerland): World Health Organization; 2008.

3. Starr M, Chalmers I. The evolution of he Cochrane Library, 1988–2003. Available at: www.update-software.com/history/clibhist.htm. Accessed November 20, 2008.
4. Garner P, Brabin B. A review of randomized controlled trials of routine antimalarial drug prophylaxis during pregnancy in endemic malarious areas. Bull World Health Organ 1994;72:89–99.
5. Chalmers I, Dickersin K, Chalmers TC. Getting to grips with Archie Cochrane's agenda. BMJ 1992;305:786–8.
6. World Health Organization. Roll Back Malaria Department: guidelines for the treatment of malaria. Geneva (Switzerland): World Health Organization; 2006.
7. GRADE working group. Available at: http://www.gradeworkinggroup.org/. Accessed November 20, 2008.
8. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
9. Garner P, Kramer MS, Chalmers I. Might efforts to increase birthweight in undernourished women do more harm than good? Lancet 1992;340:1021–3.
10. Shulman CE, Dorman EK, Cutts F, et al. Intermittent sulphadoxine–pyrimethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomised placebo-controlled trial. Lancet 1999;353:632–6.
11. Garner P, Gülmezoglu AM. Drugs for preventing malaria in pregnant women. Cochrane Database Syst Rev 2006;4:CD000169.
12. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev 2004;2:CD000363.
13. Steketee RW, Wirima JJ, Slutsker L, et al. Malaria treatment and prevention in pregnancy: indications for use and adverse events associated with use of chloroquine or mefloquine. Am J Trop Med Hyg 1996;55:50–6.
14. Gamble C, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. Cochrane Database Syst Rev 2006;2:CD003755.
15. Graves P, Gelband H. Vaccines for preventing malaria (blood-stage). Cochrane Database Syst Rev 2006;4:CD006199.
16. Graves P, Gelband H. Vaccines for preventing malaria (pre-erythrocytic). Cochrane Database Syst Rev 2006;4:CD006198.
17. Graves P, Gelband H. Vaccines for preventing malaria (SPf66). Cochrane Database Syst Rev 2006;2:CD005966.
18. World Health Organization In: Practical chemotherapy of malaria. WHO Technical Report Series; 1990. p. 805.
19. Olliaro P, Mussano P. Amodiaquine for treating malaria. Cochrane Database Syst Rev 2000;2:CD000016.
20. World Health Organization. Management of uncomplicated malaria and the use of antimalarial drugs for the protection of travellers: report of an informal consultation, Geneva, 18–21 September 1995. Geneva (Switzerland): World Health Organization; 1997.
21. McIntosh HM, Olliaro P. Artemisinin derivatives for treating severe malaria. Cochrane Database Syst Rev 2000;2:CD000527.
22. McIntosh HM, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. Cochrane Database Syst Rev 2000;2:CD000256.
23. McIntosh HM, Olliaro P. Cochrane systematic reviews of published and unpublished randomized controlled trials in uncomplicated and complicated malaria. In Annex to the working papers of the Rational Use of Quinghaosu and its Derivatives conference: 1998 April 19–22; Annecy, France. Rhone-Polulenc (France): International Laveran Assocation, Marcel Merieux Foundation; 1998.

24. Adjuik M, Babiker A, Garner P, et al. Artesunate combinations for treatment of malaria: meta-analysis. Lancet 2004;363:9–17.
25. Arrow KJ, Panosian CB, Gelband H, editors. Saving lives, buying time. Economics of malaria drugs in an age of resistance. Washington, DC: The National Academies Press; 2004.
26. Sinclair D, Zani B, Bukirwa H, et al. Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database Syst Rev, in press.
27. Galappaththy GN, Omari AA, Tharyan P. Primaquine for preventing relapses in people with Plasmodium vivax malaria. Cochrane Database Syst Rev 2007;1: CD004389.
28. Higgins PT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Chichester (UK): Wiley-Blackwell; 2008.
29. The Cochrane Collaboration. Available at: www.cochrane.org. Accessed November 5, 2008.