S s e a c R e v e s

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

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Systematic review

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Key characteristics of a systematic review

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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

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 (. **2**), which has involved technical staff from the WHO from the outset. There is now a group of over 200 authors (. **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

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Cochrane Infectious Diseases Group

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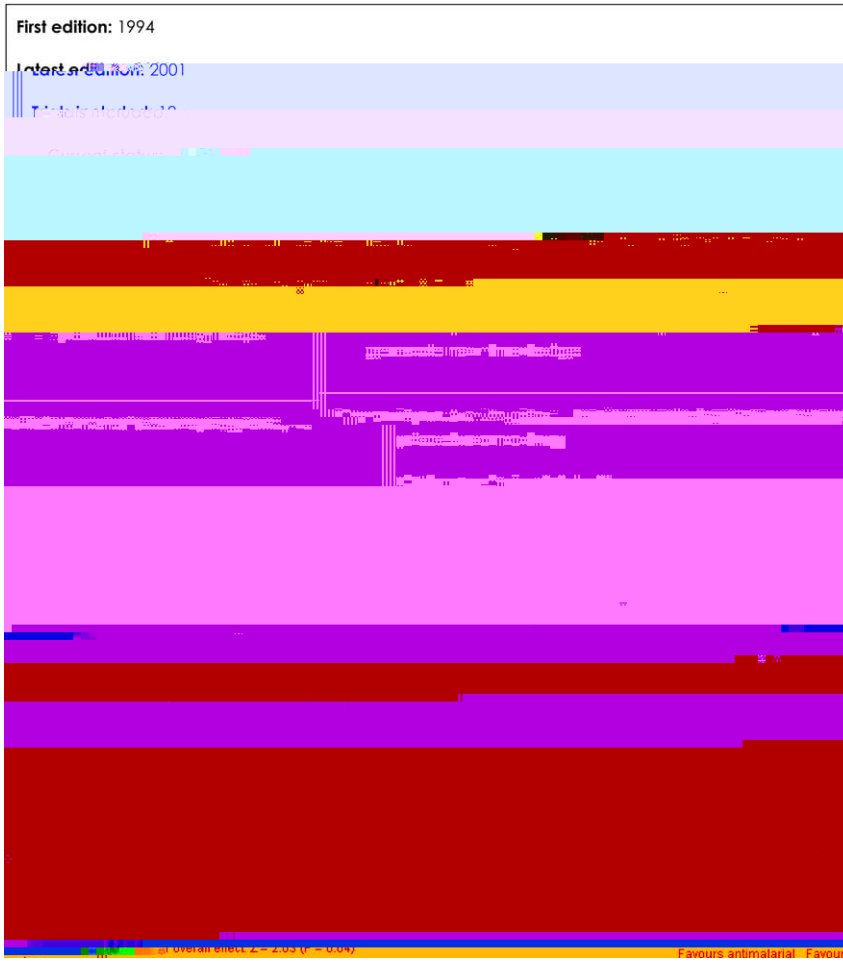
when pregnant. In the early 1990s, spreading resistance to 4-aminoquinolines (eg, chloroquine and amodiaquine) meant the options for prophylaxis were limited, and this reopened the debate: if prophylaxis or intermittent preventive treatment or malaria prevention is worth doing, then one really needs 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



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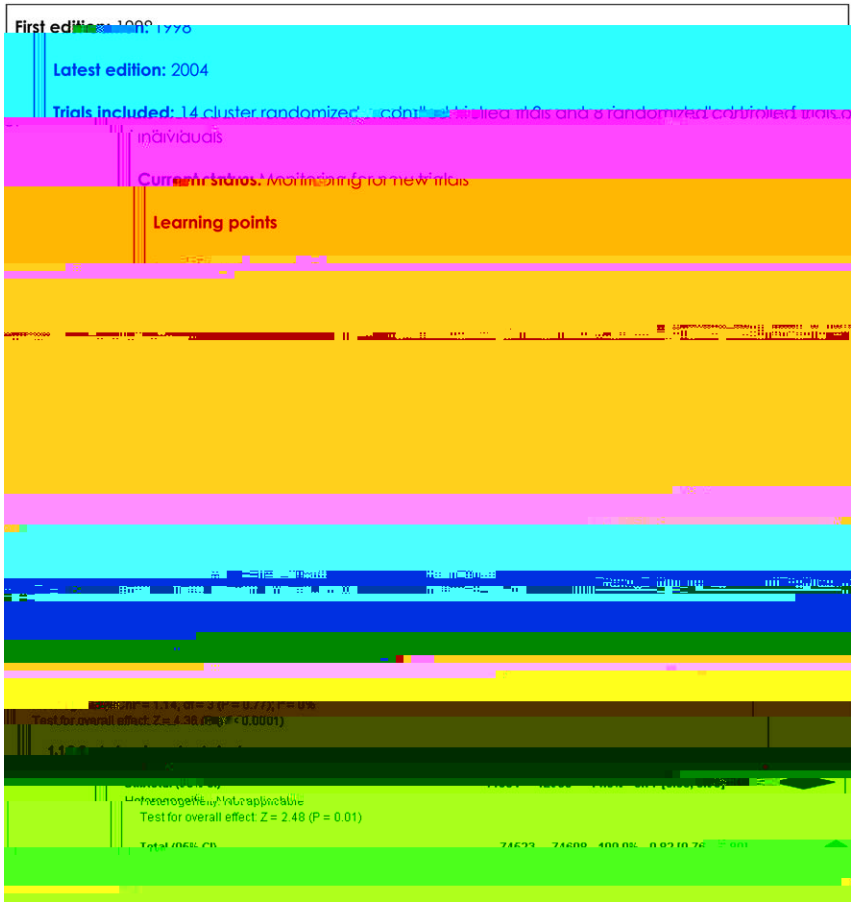
Insecticide-Treated Nets for Malaria: Public Health Interventions to the Test

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 (, **. 4**). This particular analysis provides graphic and



F g. 4. I c c - a a c a . (*From* L C. I c c - a b a c a a a a. C c a Da a-ba S R 2004;2; .)

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.

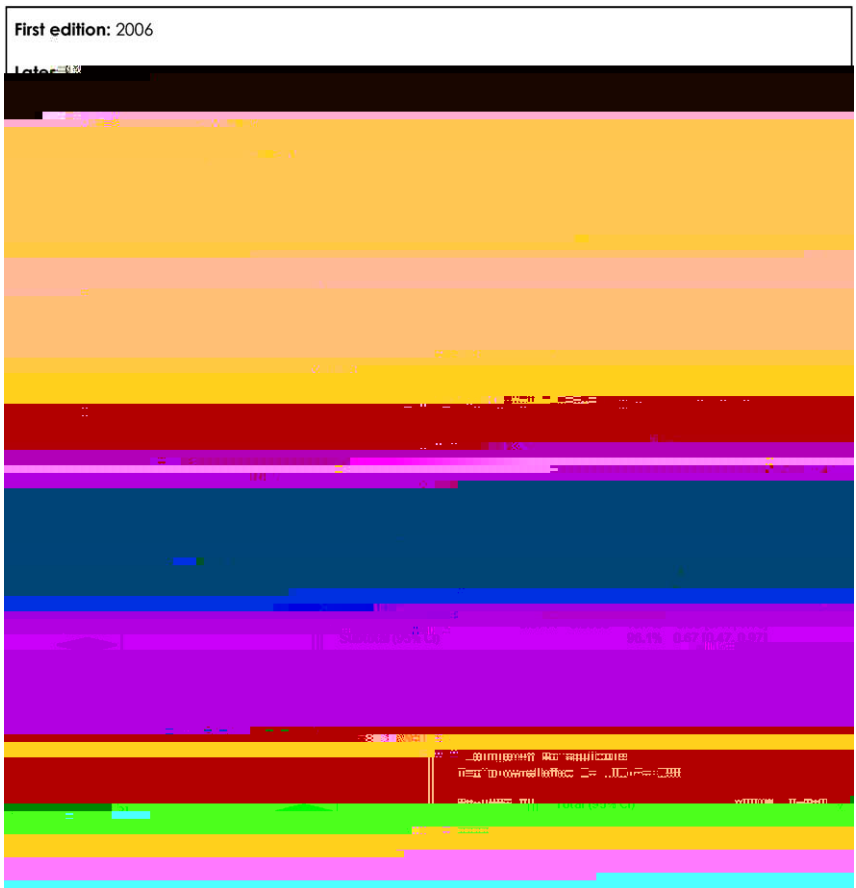
Insecticide-Treated Nets in Pregnancy: Meta-analysis Helps Consumers Understand

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 (, **. 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



F g. 5. l c c - a a c . (*From* Ga b C, E a JP, K FO. l c c - a a a a a c . C c a Da aba S R 2006;2; .)

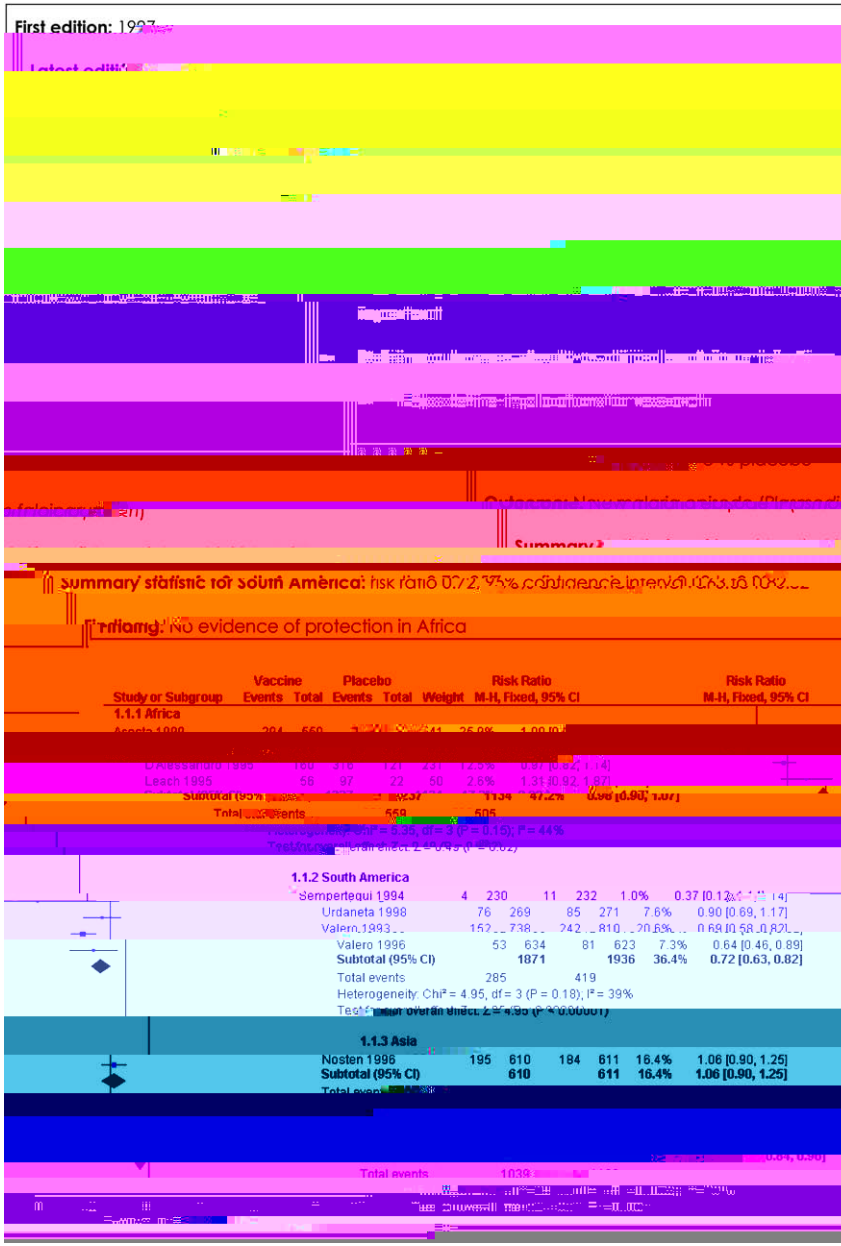
adverse effects were extracted from immunologic trials for those vaccines that also had challenge endpoints in other trials.

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 (, **. 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



Fg. 6. SP 66 a a a acc . (*From* G a P, G ba H. Vacc a a a (SP 66). C c a Da aba S R 2006;2; .)

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]

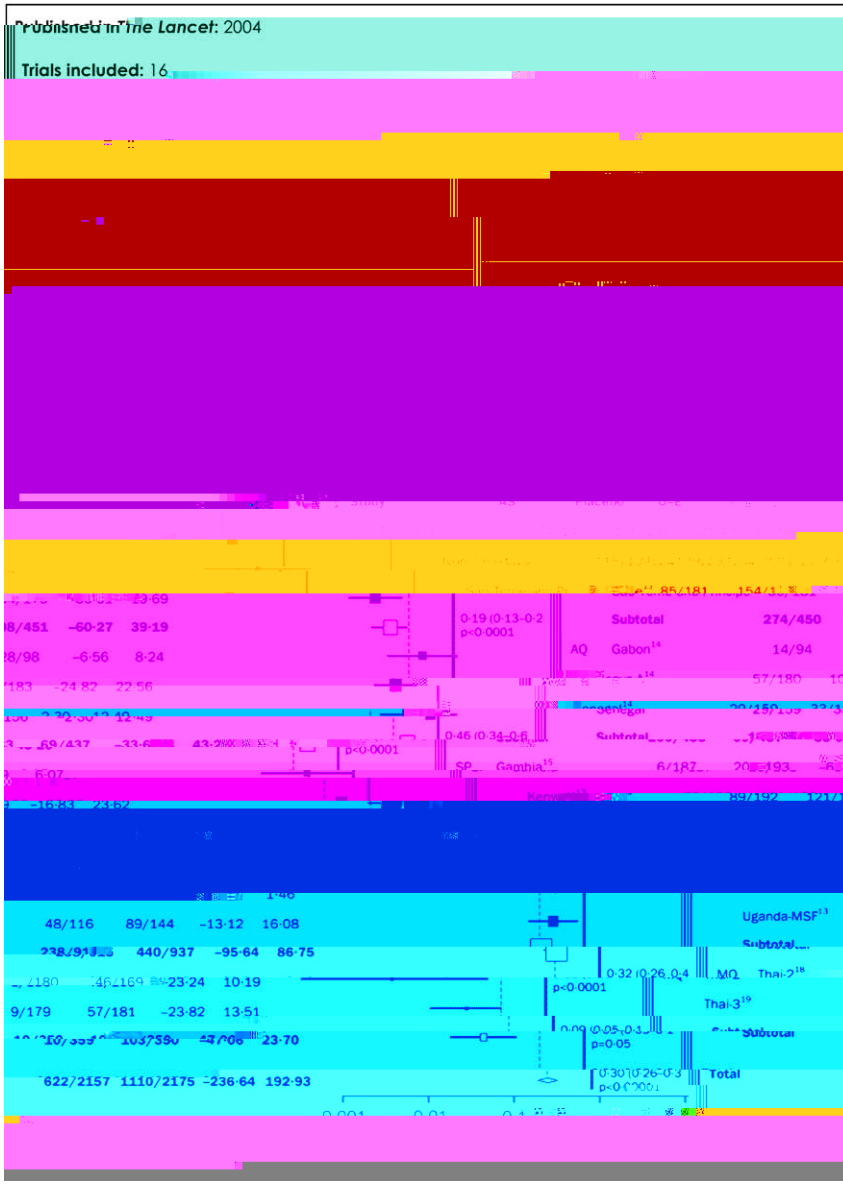
F g. 7. A a *Plasmodium falciparum* a a a. (*From* G a P, G ba H. Vacc a a a (SP 66). C c a Da aba S R 2006;2; .)

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 (, .). 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.



F g. 8. A a c b a a a a: a-a a . (*From* A M, Bab A, Ga P, a . A a c b a a a a: a-a a . La c 2004;363:9; .)

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 (.); it demonstrates that dihydroartemisinin–piperaquine,

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 **. 10**, the included trials demonstrated lower relapse rates for *P vivax* with the 14-day regimen and no effect

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 nesrom

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,

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