Briefing Document: National decision-making framework for malaria vaccines

Moving from development to policy to implementation of new products in countries where malaria is endemic: historical context for a malaria vaccine

This is one of seven briefing papers produced for a country consultation to develop a decision-making framework for the use of future malaria vaccines. It was developed under the guidance of the consultation steering committee: Alan Brooks, PATH Malaria Vaccine Initiative (MVI); Dr. Carter Diggs, US Agency for International Development; Sarah Ewart, MVI; Dr. Dorothée Kinde-Gazard, Minister of Health, Benin; Annique Lennon, MVI; Dr. Rose Macauley, World Health Organization (WHO) Regional Office for Africa (AFRO); Dr. John Marshall, Consultant to PATH; Dr. Zarifah Reed, WHO; Dr. Magda Robalo, WHO AFRO; and Dr. Rick Steketee, PATH Malaria Control and Evaluation Partnership in Africa.

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1. Introduction

This briefing paper presents the experience, outcomes, and key issues from two public health interventions recently introduced in African countries where malaria is endemic: insecticide-treated mosquito nets (ITNs) and a pediatric *Haemophilus influenzae* type b (Hib) vaccine. Although only the first of these is used for malaria control, both offer insights relevant to the introduction of a malaria vaccine. It is the intention here to provide only summary information on each of the interventions; readers can obtain more detail from additional sources noted in the footnotes and appendix.

2. ITNs

2.1. History and development

Mosquito nets have been made and used by individuals for centuries. In the mid-1950s, widespread efforts to eradicate malaria were introduced. These malaria control efforts centered on two approaches:

- Reduction of mosquitoes by eliminating breeding sites and by killing mosquitoes in all their life cycle stages.
- Use of antimalarial drugs to treat infections and to provide prophylaxis against new infections.

These interventions were highly effective in reducing transmission and disease, but their implementation required substantial infrastructure to achieve high coverage rates in populations over long periods of time. As challenges to the wide-scale use of insecticides grew, investigators experimented with more focal uses of insecticides—on clothing and on mosquito nets.

The initial studies of ITNs were done in the late 1970s and 1980s. In the 1980s, the World Health Organization (WHO) reached consensus that large-scale trials of ITNs should be conducted in sub-Saharan African settings with different malaria transmission intensities and with sufficient sample size to assess child mortality as an outcome. Five randomized, controlled trials were conducted, and all found that ITN use substantially reduced infant and child mortality in African countries where malaria is endemic[1] (see Appendix).

Other studies of ITNs included social, behavioral, and economic assessments. Several demonstration projects revealed substantial reduction in child mortality and morbidity with the use of ITNs. Collectively, these studies demonstrated that, in sub-Saharan African settings where malaria is endemic, ITNs are a highly cost-effective, affordable intervention.

2.2. Policy and implementation

Roll Back Malaria (RBM) Partnership established a global policy on ITNs in a series of key events and publications. ITN use was included in the RBM Abuja Summit goals/targets of

[1]Lengler C. Insecticide-treated bed nets and curtains for preventing malaria. *The Cochrane Database of Systematic Reviews.* 2004;2. Art. No. CD000363. DOI: 10.1002/14651858.CD000363.pub2.

2000[2,3] and was further supported through the Insecticide Treated Netting Materials Working Group of the RBM Partnership in the publication *Scaling-Up Insecticide-Treated Netting Programmes in Africa—A Strategic Framework for Coordinated National Action*.[4] Most African countries have adopted the global policy; some have written their own country-specific policies (these are adaptations and generally conform to international recommendations).

Two recent joint statements from WHO and the United Nations Children's Fund (UNICEF) have highlighted opportunities for partnership between immunization programs and malaria control programs on ITN distribution[5] and emphasized the importance of achieving high coverage rates.[6] Two companies now produce ITNs that are WHO Pesticide Evaluation Scheme (WHOPES)–approved as "long-lasting ITNs." These ITNs have the ability to maintain effective concentrations of insecticide after many washings so that the durability of effective action against the mosquito may exceed three years. A 2004 meeting in Johannesburg and a 2005 meeting in Paris explored policy and procedural issues associated with scaling up production and use of long-lasting ITNs.[4]

2.3. Issues and challenges

- Despite general agreement that high coverage with ITNs is desirable, coverage is still limited five years after the Abuja Summit. Commodity production and procurement, management, and logistics continue to be problems, especially because many countries are now scaling up their malaria control programs.
- Much debate has occurred regarding appropriate methods for distribution of ITNs. Some experts call for ITNs to be sold to individuals and communities to support the development of local markets, while others call for a focus on achieving high coverage as quickly as possible, including through free distribution of ITNs.[4]
- Funding support for ITNs has been highly variable and continues to evolve. Between 2000 and 2004, while policy decisions were evolving, there was no substantial national and international donor commitment to achieving high rates of household coverage of ITNs. Recently, in part because significant numbers of Global Fund grants have gone to African

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[2]World Health Organization (WHO). *The African Summit on Roll Back Malaria, Abuja, Nigeria, 25 April 2000*. WHO/CDS/RBM/2000.17. Geneva: WHO; 2000. Available at: http://www.rbm.who.int/docs/abuja_declaration.pdf.

[3]United Nations Children's Fund (UNICEF), World Health Organization (WHO). *Africa Malaria Report 2003*. Geneva: WHO; 2003. Available at: http://www.rbm.who.int/amd2003/amr2003/about.htm.

[4]World Health Organization (WHO)/Roll Back Malaria. *Scaling-Up Insecticide-Treated Netting Programmes in Africa. A Strategic Framework for Coordinated National Action*. WHO/CDX/RBM/2002.43. Geneva: WHO; 2002. Also see http://www.rbm.who.int/cmc_upload/0/000/015/368/RBMInfosheet_5.htm. Report and updates are available at http://www.rbm.who.int/cgi-bin/rbm/rbmportal/custom/rbm/home.do; click on "Working Groups" and then on "Insecticide Treated Netting Materials."

[5]United Nations Children's Fund (UNICEF), World Health Organization (WHO). *Malaria Control and Immunization: A Sound Partnership With Great Potential*. WHO/HTM/RBM/2004.52. Geneva: World Health Organization.

[6]United Nations Children's Fund (UNICEF), World Health Organization (WHO). WHO/HTM/RBM/2005.57. *Protecting Vulnerable Groups in Malaria-Endemic Areas in Africa Through Accelerated Deployment of Insecticide-Treated Nets*. Geneva: World Health Organization.

countries, more money is available for ITN procurement. Several groups (Canadian International Development Agency, International Federation of the Red Cross/Red Crescent, and others) have committed substantial funding to ITN procurement—through a collaboration between those working on measles and malaria—which linked ITN distribution to measles campaigns, and more recently through initiatives exploring ITN distribution within the routine Expanded Programme on Immunization (EPI).

- The cost associated with procurement and distribution of individual ITNs is low—a summary cost of approximately US$3.50 to $6.00 per ITN delivered to a household (this includes the cost of the ITN, of distribution, and of annual re-treatment of the ITN with insecticide). With a lifetime for each ITN of three to five years, the approximate cost is $1.50 per year per ITN. However, the overall cost of achieving a high coverage rate—many millions of households—is substantial. Thus, gaining global commitment to ITN funding remains a challenge.

2.4. Summary

- ITNs are a long-standing tool adapted during an initial ten- to 15-year development period to improve efficacy and benefit in malaria control.
- A focused (eight-year) interval of randomized, controlled trials showed that ITNs are highly efficacious, reducing all-cause child mortality by one-fifth to one-quarter, and are highly cost-effective.
- A policy for ITN use was established and adopted relatively rapidly.
- Progress in achieving high rates of ITN coverage in the populations of countries where malaria is endemic has been slow, due in part to a mixture of inadequate funding, inadequate supply, strategy controversy, and distribution infrastructure challenges.

3. Hib vaccine

3.1. History and development

Hib is responsible for approximately 30 percent of bacterial meningitis among children under five years old in WHO's Africa region.[7] Data from the Gambia suggest it is also responsible for 20 percent of pneumonia in infants.[8] Hib vaccine first became available globally in the mid-1980s. Its efficacy against meningitis and pneumonia caused by Hib was high—at least 90 percent. No alternative treatments for Hib infection are used in the majority of areas where Hib is endemic or epidemic.

The current conjugate vaccine entered the market in the early 1990s and was quickly adopted in Latin America. However, it was not until two large vaccine trials (in the Gambia[8] and South Africa) demonstrated the Hib disease burden and vaccine efficacy in sub-Saharan Africa, noted earlier, and the launching of the Global Alliance for Vaccines and Immunization (GAVI) in 2000

[7] World Health Organization (WHO). Haemophilus influenzae *type b (Hib) Meningitis in the Pre-Vaccine Era: A Global Review of Incidence, Age Distributions and Case Fatalities*. Geneva: WHO; 2002. Available at: http://www.who.int/vaccines-documents/DocsPDF02/www696.pdf.

[8] Mulholland K, Hilton S, Adegbola R, et al. Randomised trial of *Haemophilus influenzae* type-b tetanus protein conjugate vaccine for prevention of pneumonia and meningitis in Gambian infants. *Lancet*. 1997;349(9060):1191–1197.

offering financial support, that Hib vaccine was introduced in sub-Saharan Africa at a significant level.

The inclusion of diphtheria, tetanus, and pertussis vaccine (DTP) in EPI programs paved the way for introduction of Hib vaccine. By 2004, WHO and UNICEF estimated that approximately 66 percent of infants in sub-Saharan Africa had received the recommended three doses of a DTP-containing vaccine (DTP3).[9] Hib vaccine is given on the same schedule as DTP, either as a separate injection or as a combination with DTP in single injection. Combination vaccines that include DTP with Hib (DTP-Hib), or DTP with hepatitis B (HepB) and Hib vaccines (DTP-HepB+Hib), and that are appropriate for developing countries, became available in the late 1990s. The price of DTP-HepB+Hib from UNICEF has remained at approximately $3.60 to $3.70 per dose, and therefore $10.80 to $11.10 per infant (not accounting for vaccine wastage), through 2004.

3.2. Policy and implementation

In 1998, WHO released a position paper suggesting that all countries with "appropriate burden of diseases and adequate resources" should use Hib vaccine.[10] This was followed in 2001 by management and introduction guidelines. In the same year, the Children's Vaccine Initiative at WHO created a model to estimate the burden of disease and cost-effectiveness of Hib vaccine in most countries of the world.

By 1999, Hib vaccine was routinely being used in infant immunization programs in all (or almost all) industrialized countries, with a consequent dramatic reduction in disease incidence. Use in Latin America increased rapidly, but almost no countries in sub-Saharan Africa included it as part of the routine EPI series until GAVI was launched.

In 2000, GAVI committed to supplying Hib vaccine, including as a DTP-HepB+Hib combination product for five years to countries with data on burden of disease (GAVI declared all countries in sub-Saharan Africa to be eligible) and DTP3 coverage above 50 percent. Because Hib surveillance is so difficult, countries that wished to adopt Hib vaccine were often forced to extrapolate data from trials in the Gambia and South Africa. Countries also looked closely at the amount of data available on the cost-effectiveness and duration of financing guaranteed by GAVI. Decisions to use or not use a Hib vaccine took countries anywhere from months to a number of years, with most taking years.

Despite GAVI's offer of financial support, the uptake in Africa has been limited. By the end of 2004, 11 of the 41 countries in sub-Saharan Africa eligible to receive Hib vaccine through GAVI had adopted and/or introduced it, and six more had decided to introduce only DTP-HepB combination vaccine. Hib can be given alone, but virtually all countries in Latin America and Africa have chosen a combination product that includes DTP, HepB vaccine, and Hib vaccine.

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[9] World Health Organization (WHO). Global and regional immunization profile: African region. In: *WHO Vaccine-Preventable Disease Monitoring System, 2005 Global Summary*. Geneva: WHO; 2005. Available at: http://www.who.int/immunization_monitoring/en/globalsummary/GS_AFRProfile.pdf.

[10] World Health Organization. Position paper on *Haemophilus influenzae* type b conjugate vaccines. *Weekly Epidemiological Record*. 1998;63:64–71. Available at: http://www.who.int/vaccines-documents/PP-WER/wer7310.pdf.

Countries that introduced Hib into their routine immunization programs (as combination vaccines) did so with very few programmatic problems. It took these countries one to two years to plan implementation and integrate Hib vaccine after a decision was made to adopt the vaccine, and there was a significant need for health care worker training.

3.3. Issues and challenges

- By 2004, it was clear that few, if any, of the sub-Saharan African countries that introduced Hib vaccine would be able to sustain its use when the Vaccine Fund's provision of vaccine came to an end, primarily because of the cost of the vaccine. Despite the introduction by GAVI of a financial sustainability planning process,[11] very few countries, even factoring in donor support, had the resources and infrastructure necessary for financial sustainability when they decided to introduce Hib vaccine, and at that time it was expected that the price of the vaccine would decrease significantly by 2006.
- Because Hib meningitis is hard to distinguish from other forms of meningitis (particularly pneumococcal and meningococcal), and the cause of pneumonia can be extremely difficult to determine, the burden of Hib disease is hard to estimate before introducing a vaccine—which makes it difficult for countries to get the data they need to make decisions about vaccine introduction. During 2004 and early 2005, GAVI conducted a country consultation process to examine the situation with Hib vaccine in those countries that had decided to adopt it, and this demonstrated that there was insufficient convincing evidence of Hib disease burden and cost-effectiveness on a country-by-country or region-by-region basis to allow governments to make evidence-based decisions about introduction of Hib vaccine. In 2005, GAVI established a $30 million initiative that attempts to provide countries with tailored support in making such decisions.
- By 2004, it was clear that the cost of Hib-containing vaccines, and particularly DTP-HepB+Hib, was not decreasing as expected (in fact, the cost of the Hib vaccine increased a little in 2004) and that no additional producers were likely to be capable of supply before 2007 or 2008. The price of the DTP-HepB+Hib vaccine was almost $3.70 per dose, and three doses are required per child—resulting in a cost per child of more than $11 (not including vaccine wastage). By comparison, the cost of vaccine for immunization with DTP alone is less than $0.50 per child. In addition, whereas DTP is available from a number of industrialized and developing-country suppliers, the combination vaccine is in limited supply from a single producer (GlaxoSmithKline Biologicals).
- To help countries find ways to sustain Hib (and HepB) immunization (or revisit their decision to introduce these vaccines) in conjunction with the Hib Initiative, GAVI has developed a proposal for a bridge funding approach. This approach will, in effect, prolong support for some HepB- and Hib-containing vaccines for as long as ten years, provided that participating countries take on an escalating co-financing commitment for the vaccine up to

[11] The Global Alliance for Vaccines and Immunization (GAVI) policy has been that all countries that receive vaccines will produce and submit to GAVI a Financial Sustainability Plan during the third of the five years of initial support. Further details can be obtained from www.vaccinealliance.org.

an agreed price, intended to reflect the expected "mature" price for developing countries. It is not yet clear whether these countries will be able to meet the co-financing requirements.

- The approximate annual (recurrent) costs of vaccine procurement for all GAVI-eligible countries, based on current vaccine prices and aiming at a coverage rate of 80 percent, are $25 million for DTP only, $200 million if all countries adopted DTP-HepB, and $390 million if all eligible countries in sub-Saharan Africa adopted DTP-HepB+Hib and all other countries adopted DTP-HepB. These calculations (which are estimates, and for illustration purposes only) exclude China, India, and Indonesia, which are funded differently by GAVI, and assume that Asian countries are not eligible for Hib vaccine assistance.

3.4. Summary

- Hib vaccine is highly effective in preventing Hib meningitis in infants and is widely and routinely used in industrialized countries, but until the advent of GAVI, its public sector use in sub-Saharan Africa was almost solely limited to the Gambia and South Africa.
- Assuming that Hib vaccine performs as expected in developing countries and in a manner similar to its performance in industrialized countries, it is highly likely that vaccine use in countries where Hib disease is prevalent would be a cost-effective means to reduce morbidity and mortality.
- No alternative treatment for Hib disease is widely available in developing countries.
- Eleven of the 41 countries in sub-Saharan Africa that qualified for Vaccine Fund assistance in Hib vaccine introduction had introduced the vaccine by the end of 2004. In most countries, Hib vaccine was introduced as part of the combination DTP-HepB+Hib vaccine. Six more countries introduced only DTP-HepB.
- Few, if any, of the countries that have introduced Hib vaccine will be able to sustain its use independently once the provision of vaccine by the Vaccine Fund comes to an end.
- Few of the countries that chose to introduce Hib vaccine generated strong data on the financial implications of sustaining its use once Vaccine Fund support ends.
- GAVI has developed two interventions that are designed to support countries for a period to allow them to revisit their decisions to introduce Hib immunization: one provides support for evidence-based decision-making, and the other provides additional bridge financial support to continue vaccine purchase beyond the first five years.
- Although there are clear differences between Hib and malaria vaccine introduction, the experiences from Hib vaccine introduction should be valuable in preparing the decision-making framework for a malaria vaccine.

4. Key implications for malaria vaccine decision-making

- ITNs are a proven malaria control intervention with substantial efficacy in reducing child mortality and morbidity. The adoption of global and country policies and recommendations for widespread use occurred relatively rapidly following key randomized controlled trials. However, current coverage with this intervention remains low, due in part to a mixture of inadequate funding, inadequate supply, strategy controversy, and distribution infrastructure challenges.

- Recent, more rapid scale-up of ITN programs stimulated by available Global Fund resources has led to an increased demand for ITNs and a relative shortage of the preferred “long-lasting ITNs,” demonstrating the need for effective advanced planning.
- Global consensus on strategy and a commitment to long-term planning for ITN funding support remain challenges, and their absence is a significant impediment to increased uptake.
- Global recommendations (such as those of WHO) are critical, but national decisions on use of a new intervention require the support of strong data as well. In the case of Hib vaccine, many countries do not have robust country-specific estimates of the burden of disease, cost-effectiveness, and sustainability, which undermines national decision-making and sustained use of the vaccine.
- Experiences with Hib vaccine have demonstrated that ministries of financing and planning should be more fully involved early in the national decision-making process.
- It can take at least one to two years for a country to weigh data and decide to adopt a new intervention (once relevant data are available) and another one to two years to plan and implement the integration into routine immunization services.
- Although both ITNs and Hib vaccine are highly cost-effective, their wide deployment will require additional financial inputs above and beyond other existing malaria control interventions. This places significant strain on countries’ health care budgets and therefore has implications for the adoption of both interventions.
- Many countries currently lack the financial capacity to sustain the use of ITNs and Hib vaccine after introduction. The successful introduction of a malaria vaccine will depend on planning for both near-term support of implementation to achieve desired health gains and long-term support from financial systems to maintain those health gains.

Appendix

Insecticide-treated bed nets and curtains for preventing malaria

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Abstract

Background
Malaria is an important cause of illness and death in many parts of the world, especially in sub-Saharan Africa. There has been a renewed emphasis on preventive measures at community and individual levels. Insecticide-treated nets (ITNs) are the most prominent malaria preventive measure for large-scale deployment in highly endemic areas.

Objectives
To assess the impact of insecticide-treated bed nets or curtains on mortality, malarial illness (life-threatening and mild), malaria parasitaemia, anaemia, and spleen rates.

Search strategy
I searched the Cochrane Infectious Diseases Group trials register (January 2003), CENTRAL (*The Cochrane Library*, Issue 1, 2003), MEDLINE (1966 to October 2003), EMBASE (1974 to November 2002), LILACS (1982 to January 2003), and reference lists of reviews, books, and trials. I hand searched journals, contacted researchers, funding agencies, and net and insecticide manufacturers.

Selection criteria
Individual and cluster randomized controlled trials of insecticide-treated bed nets or curtains compared to nets without insecticide or no nets. Trials including only pregnant women were excluded.

Data collection and analysis
The reviewer and two independent assessors reviewed trials for inclusion. The reviewer assessed trial methodological quality and extracted and analysed data.

Main results
Fourteen cluster randomized and eight individually randomized controlled trials met the inclusion criteria. Five trials measured child mortality: ITNs provided 17% protective efficacy (PE) compared to no nets (relative rate 0.83, 95% confidence interval (CI) 0.76 to 0.90), and

23% PE compared to untreated nets (relative rate 0.77, 95% CI 0.63 to 0.95). About 5.5 lives (95% CI 3.39 to 7.67) can be saved each year for every 1000 children protected with ITNs. In areas with stable malaria, ITNs reduced the incidence of uncomplicated malarial episodes in areas of stable malaria by 50% compared to no nets, and 39% compared to untreated nets; and in areas of unstable malaria: by 62% for compared to no nets and 43% compared to untreated nets for *Plasmodium falciparum* episodes, and by 52% compared to no nets and 11% compared to untreated nets for *P. vivax* episodes. When compared to no nets and in areas of stable malaria, ITNs also had an impact on severe malaria (45% PE, 95% CI 20 to 63), parasite prevalence (13% PE), high parasitaemia (29% PE), splenomegaly (30% PE), and their use improved the average haemoglobin level in children by 1.7% packed cell volume.

Authors' conclusions
ITNs are highly effective in reducing childhood mortality and morbidity from malaria. Widespread access to ITNs is currently being advocated by Roll Back Malaria, but universal deployment will require major financial, technical, and operational inputs.

Synopsis
Insecticide-treated nets can reduce deaths in children by one fifth and episodes of malaria by half.

Sleeping under mosquito nets treated with insecticide aims to prevent malaria in areas where the infection is common. They are widely promoted by international agencies and governments to reduce the bad effects of malaria on health. This review showed that good quality studies of impregnated nets markedly reduce child deaths and illnesses from malaria.