Analysis of WHO Policy Development Processes for a New Intervention

Malaria Vaccines

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Acronyms

ACT	Artemisinin-based combination therapy
EPI	Expanded Program on Immunization
GACVS	Global Advisory Committee on Vaccine Safety (WHO)
GIVS	Global Immunization Vision and Strategy (WHO)
GMP	WHO Global Malaria Programme
GSK	GlaxoSmithKline Biologicals
HEAG	HPV Expert Advisory Group (WHO)
Hib	*Haemophilus influenzae* type b (vaccine)
HPV	Human Papilloma Virus (vaccine)
ITNs	Insecticide-treated nets
IPTi	Intermittent preventive treatment in infants
IPTp	Intermittent preventive treatment in pregnancy
IVB	WHO Immunization, Vaccines, and Biologicals
IVR	Initiative on Vaccine Research (IVR)
MALVAC	Malaria vaccine advisory committee (WHO)
MVI	PATH Malaria Vaccine Initiative
OPV	Oral polio vaccine
PnuemoADIP	Pneumococcal vaccines Accelerated Development and Introduction Plan
SAGE	Strategic Advisory Group of Experts (IVB)
SP	Sulfadoxine-pyramethamine
STAG	Strategic Technical Advisory Group (GMP)
TEG	Technical Expert Group (GMP)
WHO	World Health Organization

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Executive Summary

The PATH Malaria Vaccine Initiative (MVI) commissioned this analysis to begin elucidating the World Health Organization (WHO) process for developing policy guidelines for a malaria vaccine. The analysis considered past WHO recommendations on new interventions and assessed potential implications for a malaria vaccine. MVI and its partners may use guidance on these data requirements and timing to inform policy and research activities over the coming years, while WHO considers its specific requirements.

This analysis cut across at least two WHO departments: the Global Malaria Programme (GMP) and Immunization, Vaccines and Biologicals (IVB). It was conducted in consultation with staff and expert advisors to these two departments. It included review and analyses of the information available at the time key policy decisions were made. The workings of the two major policymaking bodies of the GMP and IVB were also analyzed, along with recommendations developed by their respective expert advisory groups in areas related to the prevention and treatment of malaria and the use of newer vaccines. Four malaria interventions and four vaccine interventions were analyzed in detail to understand the chronology of the data available at the time usage recommendations were considered by WHO policymaking bodies.

To facilitate comparison across WHO departments, findings were analyzed according to categories defined by a WHO publication outlining the guidelines-development process. The categories are:

- Safety and efficacy in relevant populations.
- Implications for costs and population health.
- Localization of data to specific epidemiological situations.

The results indicated that all three categories were important in the development of policy recommendations for the interventions analyzed. This was especially true for immunization interventions. These categories will likely be critical for data collection and recommendations concerning a malaria vaccine as well.

This analysis identifies data needs specific to a malaria vaccine. These data points relate to the demonstration of a range of efficacies; safety issues such as rebound; the duration of immunity and the need for boosting; the impact of the epidemiological setting (e.g., endemic or seasonal malaria); and unique regulatory issues related to approval if a vaccine is for use only in developing countries.

The findings lead to the following conclusions:

- Although efficacy and safety in the relevant target population—including displacement of disease to another susceptible age group—are the essential components of any policy- and guidelines-development process, additional factors may also be important. These include issues related to costs and population health, such as supply and demand, financing issues, cost-effectiveness, and the impact of use on other interventions; issues specific to the local situation, such as the proposed schedule in the context of national policies and disease incidence; distribution issues depending on the age range of the target population; and specific advocacy and communications issues.
- It will be critical to document the ability to use a malaria vaccine in the context of other malaria treatment and prevention interventions, and to rigorously document the impacts.
- Demonstration projects or pilot introduction studies in endemic countries will be important to better understand the impact of vaccine introduction on other interventions, on the overall health system, and on perceptions of other vaccines.
- The format of policy presentations will need to comply with the principles set by a WHO guideline review committee, with classification of data according to the three WHO publication categories described above.
- Because the policy development process typically takes several iterations, only limited progress can be expected during each individual meeting. The concerns of the advisory groups can be anticipated to some extent and addressed thoroughly in subsequent presentations.
- For a product such as a malaria vaccine with a complex policy development process, a working group convened specifically for this purpose may be useful to assist both GMP and IVB policy groups. Such an approach was found productive for both pneumococcal conjugate and human papillomavirus (HPV) vaccines, although the mechanisms of convening these two groups differed (see text).
- Specific issues unique to a malaria vaccine spelled out in the text will need additional consideration (see section titled Implications for Policymaking for a Malaria Vaccine).
- Considerable planning and capacity building will be required to address the unique regulatory issues related to use of a vaccine whose activity will depend on the endemicity of the setting.

Introduction

It is a priority for both the PATH Malaria Vaccine Initiative (MVI) and the World Health Organization (WHO) to determine the most appropriate role of a future malaria vaccine in the health systems of countries at highest risk for malaria mortality and morbidity. The most advanced first-generation malaria vaccine candidate could be available for regulatory marketing approval as early as 2011, with no other malaria vaccines anticipated until sometime after 2015. It is imperative to begin the process of defining how to most effectively develop malaria vaccine implementation policy at the national, regional, and global levels well in advance of the first vaccine.

MVI previously developed a policy pathway for malaria vaccines in consultation with WHO and other partners. One early step in MVI's policy pathway is to identify the data—and the timing—required for a WHO recommendation on malaria vaccines. MVI has engaged a consultant to analyze past WHO recommendations on new interventions and assess potential implications for a malaria vaccine. MVI and its partners may use guidance on these data requirements and timing to inform policy and research activities over the coming years, while WHO considers its specific requirements.

Ultimately, this analysis should assist in streamlining the process of establishing policy recommendations, leading to the most efficient and rapid availability of a feasible product. The information included in this analysis could also be useful in the future to guide other groups developing new treatment or prevention interventions in the developing world.

Methods

The analysis was conducted primarily by interviewing primary contacts (see Annex 1) and reviewing documents (see Annex 2). The information was analyzed according to general WHO policy guidelines for the development of policy recommendations.[a] Specific case studies of the policy development process for malaria interventions and for vaccines were used as guides.

Four malaria interventions and four vaccine interventions were analyzed in detail to understand the chronology of the data available at the time usage recommendations were considered by WHO policymaking bodies. The malaria interventions were insecticide-treated bed nets, artimisinin-based combination drug therapy, intermittent delivery of anti-malarial drugs during pregnancy, and delivery of anti-malarial drugs to children during immunization sessions. The vaccine interventions were *Haemophilus influenzae* type b conjugate vaccine, pneumococcal conjugate vaccine, rotavirus vaccine, and human papillomavirus vaccine. A list of the considerations informing decision-making was developed for each of the interventions already

[a] Global Programme on Evidence for Health Policy. *Guidelines for WHO Guidelines*. EIP/GPE/EQC/2003.1. Geneva: WHO; 2003. [Note that there is now a WHO Handbook for guideline development (WHO, March 2008, available on request to grcinfo@who.int)].

considered, and a summary table for potential needs was prepared as well. Eight conclusions were developed from the analysis.

Findings

WHO Policy Guidance

In 2003, WHO published *Guidelines for WHO Guidelines*.[1] This publication emphasized the use of systematic reviews for evidence of effects for a policy option (such as a treatment protocol or a preventive intervention), of processes that allow for explicit incorporation of other types of information, and of evidence-based dissemination and implementation strategies.[a] The *Guidelines* outlined a three-step process for development of guidelines:

- Reviewing and reporting of efficacy and safety.
- Considering the implications of adopting the recommendations in relation to costs and population health.
- "Localizing" the guidelines to their settings and determining where the tradeoff of additional cost vs. additional benefit will be set.

The *Guidelines* also provided for the selection and tasks of a technical guideline development group, with heavy emphasis on involvement of the end user as well as technical experts.

Although the *Guidelines* are not binding, recent publicity[2,b] suggests they will be given greater weight in the future. In fact, the *Guidelines* were used in formulating the *Guidelines for the Treatment of Malaria*.[c] In the discussion that follows, the three guideline categories have been used as a framework to define data available and future data needs.

WHO Policymaking Bodies

Global Malaria Programme

The Director of the Global Malaria Programme (GMP) has only recently established a Strategic Technical Advisory Group (STAG) charged with developing malaria policy recommendations, based on expert inputs. Therefore, the STAG's operating processes do not yet have the history seen in the corresponding group for vaccines (*vide infra*). The STAG is a high-level governance

[a] Oxman AD, Lewis JN, Fetheim A. Use of evidence in WHO recommendations. *The Lancet*. 2007;369:1883–1889.

[b] Comment. *The Lancet.* 2007;369:1842.

[c] WHO. *Guidelines for the Treatment of Malaria*. Annex 1. Geneva: WHO; 2006..

and advisory body to GMP and ultimately to the Director General of WHO.[a] All the technical expert groups (TEGs), of which there are currently three (on the chemotherapy of malaria, vector control, and economics and financing), report to the STAG. Previously, until the 2005 restructuring of the GMP, defining intervention and treatment guidelines was the responsibility of the WHO Expert Committee on Malaria, whose reports were published in the WHO technical report series. The roles, composition, and methods of working of WHO expert committees are formally defined by WHO.[b]

Vaccines

Vaccine policy recommendation development in the Department of Immunization, Vaccines and Biologicals (IVB) has evolved and has now come firmly to rest in the Strategic Advisory Group of Experts (SAGE), which was restructured in 2005 in the context of the Global Immunization Vision and Strategy (GIVS). Prior to that time, WHO policy on vaccine use was expressed in WHO position papers, which were published in the *Weekly Epidemiologic Record*. These papers were developed by a consultant with inputs from experts in the field, overseen by a group of IVB senior staff, reviewed by a large group of external experts, and then approved by the SAGE prior to publication. Since April 2006, the WHO position papers on immunization, which are designated as WHO policy on vaccine use, have been fully discussed and endorsed by the SAGE prior to publication, and every effort has been made to coordinate their publication as soon as possible after the relevant SAGE meeting.

Analogous to the role of the STAG in providing high-level advice on malaria treatment and prevention policies, the SAGE provides high-level advice with respect to immunization. However, in contrast to the situation with the GMP STAG, a wealth of information on the SAGE is available on the WHO website.[c] The SAGE has existed in its current configuration since November 2005 as the principal advisory group to WHO for development of policy related to vaccines and immunization. Its mandate is to provide strategic advice rather than technical inputs. This mandate extends to the control of all vaccine-preventable diseases, specifically on the "adequacy of progress towards the achievement of the goals of the Global Immunization Vision and Strategy." It has 15 members reflecting a range of technical specialties and includes national immunization managers. The composition is rotated on a regular basis. By the time the most advanced malaria vaccine will be considered for utilization recommendations by the SAGE, it is likely that the membership will have almost completely turned over.

An issue for a policy recommendation may go three or more times to the SAGE before the group issues a policy recommendation, if in fact one is issued. The first meeting is a horizon scanning

[a] K Mendis, GMP, personal communication, Sept, 2007. Information on the STAG is not available on the WHO website.

[b] Expert advisory panels page. WHO website. Available at: http://www.who.int/rpc/expert_panels/en/. Accessed May 12, 2008.

[c] WHO IVB website. Available at http://www.who.int/immunizations. Accessed May 12, 2008.

exercise. The second meeting, which occurs when the intervention is close to the finish, is extremely important, as it provides a clear indication of the kinds of information SAGE will need to make a global recommendation.[a] If all needed information is in place, the third meeting can be the decision-making session when a utilization recommendation is made.[b]

Previous Policies for Malaria Treatment and Prevention Interventions

A summary of the development of policy recommendations on recent treatment or prevention interventions for malaria provides insight into how this process works. The analyses that follow place these policy development activities into the three categories defined by the *Guidelines* (Table 1). The aim of the analyses was to define the framework for WHO policy decisions relative to malaria prevention, not to critique the decision-making process.

Some of these recommendations were developed under the previous WHO malaria structure. The policies to be analyzed include artemisinin-based combination therapy (ACT), insecticide-treated nets (ITNs), and intermittent preventive treatment in pregnancy (IPTp). Because of changes in the malaria decision-making structure, the process used and the completeness of the data review may not be completely relevant to this discussion. However, a summary can show the previous bases for malaria prevention and treatment policy decisions, and the associated issues.

Artemisinin-based combination therapy for malaria was first recommended as an effective substitute for single-component therapy during a WHO technical consultation in April 2001.[c] Although early efficacy data available at the time came largely from Asia, African data were also presented in the consultation. Implementation was delayed because of lack of immediate funding, because of the limitations of the African data, and also the limited availability of the products. There was a mismatch between supply and demand (some products were not projected to be available before 2005). Still, malaria-endemic countries in sub-Saharan Africa changed their national policies relatively rapidly. African efficacy data are now available, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria has addressed the financing issue.

[a] Global in this sense means a recommendation for use applicable to all target populations.

[b] Philippe Duclos, IVB, personal communication, August 2007.

[c] WHO. Antimalarial Drug Combination Therapy. Report of a WHO Technical Consultation. WHO/CDS/RBM/2001.35. Geneva: WHO; 2001.

Despite long-standing evidence of the efficacy of ITNs[a] in reducing malaria morbidity and mortality, attention to delivery strategies and local use promotion were apparently not fully considered when the policy was adopted by WHO.[b] As of the start of current efforts to increase ITN coverage (1998-2001), surveys suggested that less than 2 percent of African children under five years of age were sleeping under ITNs.[c] Delivery of ITNs to pregnant women and young children has been a challenge, complicated by a lack of consensus over whether ITNs should be delivered free of charge or through social marketing or cost-recovery schemes. However, a recent longitudinal study[d] carried out in a cohort of about 3,500 children in Kenya showed an increase in use of bed nets from about 7 percent to 67 percent during the study period and a 44 percent reduction in mortality over a two-year period, with about seven deaths averted for every 1,000 ITNs distributed. The authors concluded that a combination of social marketing followed by mass free distribution can have results comparable with those seen in controlled trials. A new policy on use of long lasting insecticide-treated nets has recently been elaborated by WHO.[e]

In 1998, the WHO Expert Committee on Malaria recommended that, in highly endemic areas of Africa, IPTp should be administered as part of antenatal care,[f] based on data[g] subsequently characterized as "limited."[h] However, the initial rate at which countries in sub-Saharan Africa adopted IPTp with sulfadoxine-pyramethamine (SP) as policy was characterized as slow in 2006.[i] Again, a factor in the delay was the lack of West-African data; another was concern over

[a] 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. *The Lancet* 1999;353(9153):632–636; Rogerson SJ, Chaluluka E, Kanjala M, Mkundika P, Mhango C, Molyneux ME. Intermittent sulfadoxine-pyrimethamine in pregnancy: effectiveness against malaria morbidity in Blantyre, Malawi, in 1997–99. *Trans R Soc Trop Med Hyg* 2000;94(5):549–53 ; Parise ME, Ayisi JG, Nahlen BL, et al. Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. *American Journal of Tropical Medicine and Hygiene* 1998;59(5):813–22.

[b] WHO. *WHO Expert Committee on Malaria*. Geneva: WHO; 2000.

[c] WHO. *The Africa Malaria Report*. Geneva: WHO; 2003.

[d] Fegan GW, Noor, AM, Akhwale WS et al. Effect of expanded insecticide-treated bednet coverage on child survival in rural Kenya: a longitudinal study. *The Lancet*. 2007;370:1035–1039.

[e] Global Malaria Programme. *Insecticide-Treated Mosquito Nets: a WHO Position Statement*, Geneva: WHO; 2007. Available at: http://www.who.int/malaria/docs/itn/ITNspospaperfinal.pdf. Accesed May 12, 2008.

[f] WHO. *WHO Expert Committee on Malaria, 20th Report.* Technical Report Series 892. Geneva: WHO; 2000.

[g] WHO. *Report of the Scientific Working Group Meeting on Malaria*. Geneva: WHO; 2003.

[h] WHO. *Report of the TEG meeting on IPTp*. Geneva: WHO; 2007.

[i] Hill J, Kazembe P. Reaching the Abuja target for intermittent preventive treatment of malaria in pregnancy in African women: a review of progress and operational challenges. *Tropical Medicine and Inernationalt Health*. 2006;11(4):409–18.

increasing resistance of malaria-causing organisms to SP. Studies on use of suitable drug alternatives in pregnancy were not available.[a] Experts at a recent WHO meeting acknowledged these issues but concluded that the policy was appropriate at the time it was developed.[18] However, because of increasing resistance to SP and its unknown impact on efficacy, this expert group called for urgent research to respond to these issues and to evaluate potential alternative antimalarial compounds. In addition, the group identified a need for information on cost-effectiveness of this intervention and on the interaction with and impact of other malaria treatment and prevention strategies.

Thus, earlier malaria prevention and treatment policies were adopted in the absence of data as defined by the *Guidelines* (Table 1). As noted above, this situation is likely to change in future.

Intermittent Preventive Treatment for Infants (IPTi)

Intermittent prevention therapy for infants is a recently described intervention which is reminiscent of IPTp, but it uses the delivery of vaccines by the national immunization program to distribute the antimalarial SP to children during routine immunization contacts. An analysis of the decision-making process associated with the development of an IPTi policy can be instructive in that it will go through the policy development processes both of the GMP STAG and of the IVB SAGE. This would also be the policy development pathway for the deployment of a malaria vaccine.

Promising research results from Tanzania,[b] Ghana,[c] and Mozambique[d] are available, and thus the GMP, along with the IPTi Consortium, outlined a plan for policy development for this intervention,[e] which included consideration by the relevant technical expert groups to GMP, the

[a] Crawley J, Hill J, Yartey J et al. From evidence to action? Challenges to policy change and programme delivery for malaria in pregnancy. *The Lancet Infectious Diseases*. 2007; 7(2):145–155.

[b] Schellenberg D, Menendez C, Kahigwa E, et al. Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a randomised, placebo-controlled trial. *The Lancet.* 2001;357(9267)**:**1471–7.; Massaga JJ, Kitua AY, Lemnge MM, et al. Effect of intermittent treatment with amodiaquine on anaemia and malarial fevers in infants in Tanzania: a randomised placebo-controlled trial. *The Lancet*. 2003;361(9372)**:**1853–60.; Schellenberg D, Menendez C, Aponte JJ, et al. Intermittent preventive antimalarial treatment for Tanzanian infants: follow-up to age 2 years of a randomised, placebo-controlled trial. *The Lancet.* 2005;365(9469)**:**1481–3.

[c] Chandramohan D, Owusu-Agyei S, Carneiro I, et al. Cluster randomised trial of intermittent preventive treatment for malaria in infants in area of high, seasonal transmission in Ghana. *British Medical Journal*. 2005;331(7519)**:**727–33.

[d] Macete E, Aide P, Aponte JJ, et al. Intermittent preventive treatment for malaria control administered at the time of routine vaccinations in Mozambican infants: a randomized, placebo-controlled trial. *Journal of Infectious Disease*. 2006;194(3)**:**276–85.

[e] Jane Crowley, IPTi Consortium, personal communication, 2007; IPTi Consortium website, http://www.ipti-malaria.org. Accessed May 12, 2008.

Technical Advisory Group on Chemotherapy of Malaria (TEG), by GMP's highest policy making body, the STAG, and by the SAGE. The analysis below summarizes the information that has been or will be presented to various advisory groups in the process, the issues they have identified, and their recommendations.

SAGE Response

Because of SAGE's policy of "horizon scanning"—that is, considering information on new interventions that may eventually be brought to them for a decision—and because an IVB expert review group has already been involved in potential interactions of IPTi with vaccine responses, the use of IPTi has already been considered by the SAGE, for information, in April 2006.[a] At that time they were presented with the following information:[b]

- Malaria disease burden in sub-Saharan Africa.
- Pooled data from five safety and efficacy studies in sub-Saharan Africa.
- Pooled data from three studies on impact of the intervention on serology *vs* Expanded Programme on Immunization (EPI) vaccines.
- Data from two cost-effectiveness studies.
- Information on drug resistance.
- One year of implementation experience.

The efficacy data in the first study, from Tanzania,[21] where SP or placebo was given at two, three, and nine months at routine EPI visits, showed a greater than 50 percent reduction in clinical malaria and a 30 percent reduction in hospital admissions. No evidence of rebound in clinical malaria was found in the six-month period following the last dose, but there was only a modest reduction in risk of anemia, contrary to the result found in the first study in Tanzania. The pooled data showed a summary primary endpoint of 29 percent protection against clinical malaria in the first year of life. Pooled safety data from five studies showed a small but significant reduction in relative risk for serious adverse events with SP compared to the placebo group; there was no significant difference in risk of death. No adverse impact on the serological responses to EPI vaccines was found. The cost-effectiveness data from Mozambique showed a cost per DALY avoided with IPTi of US $2.68.

It is instructive to review an extract from the SAGE report (italics added for emphasis), as it provides insight into the deliberation process:[c]

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[a] WHO. *Weekly epidemiological record.* 2006; 81(21):209–220. [note that safety issues were also considered by an IVB expert review group regarding potential vaccine interactions].

[b] SAGE presentations, agendas, and recommendations website. Conditionally available [password protected]: http://www.who.int/vaccines/meetings/sage/. Accessed May 19, 2008.

[c] WHO. *Weekly Epidemiological Record.* 2006;81(21):209–220.

Intermittent preventive treatment of infants for malaria, co-administered with immunization

SAGE was briefed on intermittent preventive treatment of infants (IPTi), a promising new approach to malaria control in which an antimalarial drug is administered to asymptomatic infants attending for routine vaccination at DTP2, DTP3 and measles contacts. The first IPTi randomized control trial, in Ifakara (United Republic of Tanzania), provided sulfadoxine–pyrimethamine (SP) at these immunization contacts and demonstrated **a >50 percent reduction in episodes of clinical malaria and anaemia and a 30 percent reduction in hospital admissions. . .** While acknowledging the positive attributes of using the EPI system to achieve broader child health benefits, SAGE highlighted *the limitations of designing an IPTi schedule solely around EPI contacts, as the interval between doses from a malaria control perspective may not be optimal or may be too restrictive.* It may be desirable to de-link IPTi from EPI outreach services where the ages of infants and children receiving immunization are more variable. It would also be valuable to have *information on the efficacy of IPTi when administered at ages other than those dictated by the EPI schedule*. Furthermore, *administration of antimalarial drugs through EPI is likely to be inappropriate in settings where malaria transmission is confined to a few months of the year*. Since there is considerable variation in EPI coverage among countries, SAGE suggested that *it would be informative to map EPI coverage and malaria risk in those countries where IPTi might be considered a possible malaria control strategy.* The *additional value of IPTi will also need to be assessed within the current context of increasing coverage with insecticide-treated nets*.

With regard to safety, *SAGE considered it important to have follow-up data for at least 12 months after the last dose of IPTi, in order to assess a possible rebound in episodes of clinical malaria and anemia*. The safety data arising from the southern Tanzania community effectiveness study will also be valuable. SAGE will wish to review operational data from the pilot implementation of IPTi with SP that UNICEF is planning in 6 African countries.

The impact of IPTi on other programmes needs to be explored. Amoxicillin or co-trimoxazole (an antifolate drug, similar to SP) is the antibiotic option recommended for the treatment of acute respiratory infections in the Integrated Management of Childhood Illness. Concurrent use of co-trimoxazole and SP may engender cross-resistance.

The highlighted portions indicate the kind of direction that SAGE is giving for information that would need to be presented for a policy recommendation. They include a strong insistence on safety, local effectiveness (generally through demonstration projects), and an appropriate delivery schedule.

It may be useful to analyze the various requests for additional data in terms of the *Guidelines* criteria. The SAGE asked for more safety and efficacy data in relevant populations, including longer term follow-up to rule out rebound and efficacy if the putative EPI schedule was not

rigorously followed. They requested more information on the impact of IPTi on alternative malaria control interventions already in force. Table 2 summarizes some of the information available for IPTi at the time of its first consideration by SAGE.

Technical Group Responses

The next step was the convening of GMP's TEG on Chemotherapy of Malaria, which met in Geneva in October 2006.[a] This group listened to presentations of working papers and then met in closed session. The group reviewed 11 studies on IPTi, 6 performed by the IPTi Consortium, and 5 done independently, all conducted in Africa in areas of high malaria endemicity. Nine studies were based on SP, and one each on amodiaquine and artesunate with SP. Although the mean efficacy results were consistent with the data reported to the SAGE, there was a consistent decline in protective efficacy from studies of IPTi with SP over time (1999-2005). Furthermore, a review of the safety data suggested a small, not statistically significant increase in severe dermatological reactions (Stevens-Johnson Syndrome) in the SP arms (these observations were in unpublished studies). Finally, the results suggesting protection from anemia were not supported in the further studies (the first study included administration of iron). No evidence was found for rebound in malaria mortality for 5 to 12 months after the intervention.

In summary, the TEG found IPTi with SP to be a promising intervention in settings where there is a malaria burden for infants; where there are rigorous systems to monitor adverse events and drug resistance; where IPTi intervention does not detract from current efforts to scale up other malaria control strategies; where the effectiveness of IPTi is monitored within the context of other existing control interventions; and where the medicines used do not compromise current and future medicines for curative malaria treatment. The TEG also called for more research on the question of SP resistance, optimal dosing, alternative drugs, and impact on other malaria control strategies, among other issues.[28]

GMP, after reviewing the available data, and some new studies that appeared in 2007,[b] reconvened the TEG in October 2007 to consider, *inter alia*, the following issues:[c]

- Better quantification of the risk of Stevens-Johnson Syndrome, if any.
- Scrutiny of reported instances of rebound effect, in anemia, malaria, or parasitemia.
- The declining trend in efficacy with time and its implications for the use of IPTi, especially in low transmission areas.

[a] Global Malaria Programme (GMP). *Report of Technical Consultation on Intermittent Preventive Treatment for Malaria in Infancy (IPTi)*. Geneva: WHO; 2006.

[b] Chandramohan, D, Webster J, et al. Is the Expanded Programme on Immunisation the most appropriate delivery system for intermittent preventive treatment of malaria in West Africa? *Tropical Medicine and International Health*. 2007;12(6):1–8.; Kobbe R, Kreuzberg C et al. A randomized control trial of extended intermittent preventive antimalarial treatment in infants. *Clinical Infectious Diseases.* 2007;45(1):16–25.

[c] Dr K Mendis, GMP, personal communication, September, 2007.

- The impact of IPTi in the face of scaled up alternative malaria control interventions.
- The implication of delivery of IPTi during routine EPI in areas where malaria is seasonal.

The TEG was asked to consider efficacy issues in the context of increasing SP resistance, as well as to review possible dermatological reactions. In terms of implications for costs and population health, the recent data suggest a need to further explore the impact of using a medicine to which resistance is increasing in a preventive mode on its effectiveness as a treatment. The SAGE had requested more information on the impact of IPTi on alternative malaria control interventions already in force, and this was a focus of the TEG as well. Finally, regarding localization of data, there is a question about the utility of a delivery strategy that is intended to be used year-round in areas where malaria incidence is seasonal.

The TEG concluded that, because of safety concerns related to a few cases of rebound of malaria susceptibility that might indicate issues if IPTi were to be administered to healthy children in a population with declining malaria disease and increasing resistance to SP, along with uncertainty related to the optimal dose and timing of administration, the committee could not recommend general deployment of SP in an IPTi strategy.[a] The TEG suggested additional research in these areas and agreed to reconsider the issue in 2008. Because of this, the issue has not yet gone back to SAGE as originally proposed.

Vaccine Policy Development

To similarly analyze the SAGE policy development process, we have focused on four new vaccines: *Haemophilus influenzae* type b (Hib), pneumococcal conjugate, rotavirus, and human papillomavirus (HPV) vaccines. A chronological history of SAGE decisions and recommendations is given, linked to the three types of data (safety and efficacy in the relevant population, implications for costs and population health, and localization of data) as *Guidelines* criteria available at the time these decisions were made. Table 2 summarizes the specific information available to SAGE at the time of its recommendations, and Table 3 analyzes this information in the context of WHO's *Guidelines* document.

Hib

In March 1998, WHO published the first position paper on Hib.[b] At that time safety and efficacy data were available in industrialized countries,[c] and results in the Gambia showing good efficacy

[a] Dr K Mendis, GMP, personal communication, December, 2007.

[b] Global Programme for Vaccines and Immunization. The WHO Position Paper on Haemophilus influenzae type b conjugate vaccines. *Weekly epidemiological record*. 1998;73(10):64–68.

[c] Eskola K, Peltola H, Takala AK et al. Efficacy of *Haemophilus influenzae* type b polysaccharide-diphtheria toxoid conjugate vaccine in infancy. *New England Journal of Medicine.* 317: 717–722 (1987); Black SB, Shinefield HR, Fireman B et al. Efficacy in infancy of oligosaccharide conjugate *Haemophilus influenzae* type b (HbOC) vaccine in a United States population of 61,080 children. The Northern California Kaiser Permanente Vaccine Study Center Pedatrics Group. *Pediatric Infectious Disease Jourbal.* 1991;10:97–104.

in Africa were available.[a] Efficacy was found to be at least 95 percent against invasive Hib disease after three doses, even in the Gambia, with no safety concerns. There was little quantification of disease burden outside of the industrialized world, and most countries did not have a surveillance system sufficiently tuned to measure vaccine impact. The WHO position paper made the following recommendation:

> In view of the demonstrated safety and efficacy of the Hib conjugate vaccines, Hib vaccine should be included, as appropriate to national capacities and priorities, in routine infant immunization programmes.
>
> In geographical regions where the burden of Hib disease is unclear, efforts should be made to evaluate the magnitude of this problem.

The position paper specifically mentioned the lack of good disease burden data in Asia and in the Newly Independent States. It also mentioned a need for attention to the appropriate presentation for national immunization programs. The uncertainty reflected in this position paper, which was not updated until 2006, may have been indirectly responsible for delaying introduction decisions at the country level.[b]

In July 2003, the SAGE considered disease burden data in Asia.[c] By that time the GAVI Alliance, which was launched in 2000, had made funds available to up to 75 of the world's poorest countries to introduce Hib vaccine where disease burden was sufficient, resulting in more experience with its use in developing countries. The SAGE noted that although Hib disease burden appeared to be lower in Asia, there was concern that it might be underestimated, and the SAGE strongly endorsed WHO's plans to develop a clearer picture of the potential impact of Hib vaccine use in Asia. SAGE revisited this issue in November 2005,[d] and reviewed the work of the GAVI Hib Initiative, which had recently been established. SAGE noted the need for studies on surveillance and disease burden to support evidence-based decision-making, identifying limitations in laboratory capacity. The issues of vaccine supply, cost, and financing options were raised, and SAGE noted that new financing opportunities would need to be encouraged.

At this meeting, SAGE recommended global implementation of Hib vaccination, unless there were robust epidemiological evidence of low disease burden, lack of benefit or overwhelming

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[a] 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. *The Lancet.* 1997;349:1191–1197 .

[b] Rana Hajjeh, Hib Initiative, personal communication, January 2008.

[c] WHO. Recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. *Weekly epidemiological record*. 2004;79(5):48–49.

[d] WHO. Conclusions and recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. *Weekly epidemiological record.* 2006;80(1):7.

impediments to implementation. A new position paper on Hib was then published in November 2006.[a] This paper gave a strong recommendation for Hib vaccine use, stating clearly that lack of local surveillance data should not delay vaccine introduction: "In view of their demonstrated safety and efficacy, conjugate Hib vaccines should be included in all routine infant immunization programmes."

Although most efficacy data had been collected by administering Hib vaccine on the three-dose EPI schedule for DTP, the SAGE at its May 2007 meeting recommended more work to determine optimal schedules and the utility of a booster dose.[b]

Thus, in summary, a global recommendation was made in 2006 for a vaccine that had been licensed in 1988 and had been covered by a WHO position paper since 1998. The recommendation was made soon after the presentation to SAGE of the requested data on disease burden and efficacy in relevant target populations and after supply issues were addressed.

Pneumococcal Conjugate Vaccine

The original pneumococcal vaccine position paper was published in April 2003.[c] The paper reviewed data on the safety and efficacy of the 7-valent conjugate vaccine in the United States and other industrialized countries. The paper found that efficacy was up to 97 percent against invasive disease caused by the serotypes in the vaccine, with no apparent safety concerns. It also noted that price would be an issue. The WHO position at that time was: "Where control of invasive pneumococcal disease in childhood is a public health priority and the vaccine serotypes are shown to match the most important local serotypes, the conjugate vaccine merits consideration for inclusion in national childhood immunization programmes."

In November 2005, the SAGE considered pneumococcal conjugate vaccines, recommending that WHO give a clear signal on the priority for its wider use in children. SAGE noted safety and efficacy data in a wide variety of settings. At that time, data from South Africa showed 83 percent efficacy against the first episode of invasive disease caused by vaccine serotypes, compared to 65 percent in HIV-infected children.[d] The Gambian data on safety and efficacy were available in March 2005 and also showed high efficacy and minimal safety concerns.[e]

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[a] WHO. WHO position paper on *Haemophilus influenzae* type b conjugate vaccines. *Weekly epidemiological record 81*. 2006;(47):445–452.

[b] WHO. Meeting of the immunization Strategic Advisory Group of Experts—conclusions and recommendations. *Weekly epidemiological record.* 2007;82(21):181–196.

[c] WHO. Pneumococcal vaccines – WHO position paper. *Weekly epidemiological record.* 2003;78(14):110–119.
[d] Klugman KP, Madhi SA, Huebner RE, et al. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *New England Journal of Medicine.* 349(14)1341–1348.

[e] Cutts FT, Zamor M, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomized, double-blind, placebo-controlled trial. *The Lancet*. 2005;365(9465)1139–1146.

SAGE noted the need for clarity of demand to allow scaling up of manufacturing capacity, thus allowing more affordable pricing, and pointed out the need for thorough studies on disease burden, pneumococcal serotype prevalence, and cost-effectiveness of vaccine introduction. However, SAGE recognized that "a global recommendation made before resolution of funding and supply issues would leave vulnerabilities that have been experienced with the implementation of Hib."[a]

At the November 2005 SAGE meeting, the Pneumococcal vaccines Accelerated Development and Introduction Plan Accelerated (PneumoADIP) requested that a SAGE subcommittee be established to lay out the groundwork for an evidence-based recommendation. The Terms of Reference for such a group included:[b]

- To summarize existing evidence on the burden of pneumococcal disease in developing countries, and the safety, immunogenicity, efficacy, and cost-effectiveness of pneumococcal conjugate vaccination in developing countries.
- To provide SAGE with summaries and analyses needed to support its discussion and recommendation process.
- To provide SAGE with a draft position statement for its review and approval based on the data and the discussions and inputs of the SAGE membership.

Between November 2005 and November 2006, the working group met many times, mostly by telephone conference,[c] to develop a draft position statement that considered the key issues of vaccine impact, schedule, replacement disease, and the HIV-infected population. In April 2006 the progress of this group, which included two SAGE members, was reported to the SAGE, which encouraged them to continue their efforts. Another key event in developing a position on pneumococcal vaccine described by the PneumoADIP[44] was the publication in May 2006 of a Call to Action by senior public health scientists in the field, in the Lancet.[d] This paper responded to issues on communication and advocacy.

The safety and efficacy of pneumococcal conjugate vaccines in numerous industrialized and developing country settings, including information on herd immunity of the seven-valent pneumococcal conjugate vaccine and evidence supporting a continued good safety profile,

[a] WHO. Conclusions and recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. *Weekly epidemiological record.* 2006;81(1):8

[b] OS Levine, PneumoADIP, personal communication, December 2007.

[c] Stephanie Schrag, Centers for Disease Control, personal communication, December, 2007.

[d] Levine OS, O'Brien KL, Knoll M, Cherian T, et al. Pneumococcal vaccination in developing countries. *The Lancet.* 2006;368(9536)644.

became available in 2006.[a] In addition, information on cost-effectiveness of immunization, subsequently published in the Lancet,[b] was available to the SAGE at that time. In November 2006, in response to this information, the SAGE, satisfied with the information provided on supply, cost, and cost-effectiveness, gave a strong recommendation for use of the seven-valent conjugate vaccine.[c] In addition, SAGE noted the vaccine's safety and efficacy in HIV-infected children and recommended including this target group as a priority in countries with significant HIV-related mortality. This recommendation was expanded to include populations with a high prevalence of other underlying conditions that increase the risk of pneumococcal disease, such as sickle cell disease. Finally, countries were encouraged to create surveillance systems to establish a baseline disease burden to monitor the impact of vaccination. These recommendations then formed part of the revised position paper on pneumococcal conjugate vaccine, published in March 2007:[d]

> Recognizing the heavy burden of pneumococcal disease occurring in young children and the safety and efficacy of PCV-7 in this age group, WHO considers that it should be a priority to include this vaccine in national immunization programmes, particularly in countries where mortality among children aged <5 years is >50/1000 live births or where >50 000 children die annually.

The recommendations of the April 2007 SAGE meeting related to exploring optimal schedules for Hib vaccine were also made for pneumococcal conjugate vaccines.[34] Thus, for this vaccine, licensed in 2000 and covered by a WHO position paper since 2003, a global recommendation was made in 2007. This occurred after receipt in late 2006 of stronger data on safety and efficacy in all target populations and with information on prospects for addressing supply and financing issues, assembled through a SAGE-convened working group.

Rotavirus Vaccines

WHO's original position paper on rotavirus vaccines appeared in 1999 and gave recommendations on the use of the rhesus tetravalent reassortant vaccine developed by Wyeth and licensed in the United States in 1998. Then, there was little information demonstrating efficacy at the provided dose in developing countries, and additional efficacy trials were begun

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[a] Centers for Disease Control. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States 1998–2003. *Morbidity and Mortality Weekly Report.* 2005;54(36):893–897.

[b] Sinha A, Levine O, Knoll M et al. Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: an international economic analysis. *The Lancet*. 2007;369(9559):389–396.

[c] WHO. Meeting of the immunization Strategic Advisory Group of Experts, November 2006 – conclusions and recommendations. *Weekly epidemiological record*. 2007;82(1/2):1–16.

[d] WHO. Pneumococcal conjugate vaccine / childhood immunization – WHO position paper. *Weekly epidemiological record*. 2007;82(12):93–84.

in Africa and Asia. When the reports of intussusception appeared, WHO convened a meeting to review the safety and efficacy data and to provide further directions.[a] At about the same time, the clinical trials in Africa and Asia having been stopped, the manufacturer withdrew the product. Subsequently, several additional manufacturers developed rotavirus vaccines. One of the conclusions of the meeting was that the case for continued use of this product in high-disease-burden settings would have been much stronger if data on efficacy in developing countries had been available at that time.

In July 2003, WHO published an update on the rotavirus vaccine situation,[b] providing the above information. The WHO recommended rapid development of new and safe vaccine candidates, and parallel evaluation of new candidates in both developed and developing countries. The paper also suggested that countries establish surveillance systems to develop disease burden information so that advocacy and risk-benefit analyses could be done when new candidates became available.

At its meeting in November 2004,[c] SAGE was presented information on surveillance networks established in Africa and Asia, which did not include intussusception surveillance. The group learned of the development of candidate vaccines, one of which, developed by GlaxoSmithKline (GSK), had been licensed in Mexico. This, and another candidate developed by Merck, had undergone large-scale clinical trials in Latin America, as well as in the industrialized world, with strong evidence for safety and efficacy. (Efficacy was 68.8–76.6 percent against any rotavirus gastroenteritis, regardless of severity, and 100 percent against severe rotavirus gastroenteritis for the first rotavirus infection season after vaccination for the Merck vaccine.[d] For the GSK vaccine, there was 60-90 percent development of IgA antibodies after two doses with 70-80 percent efficacy against rotavirus gastroenteritis).[e] Additional trials initiated in Asia and Africa would also investigate the question of potential interference with oral polio vaccine (OPV). The SAGE recommended that WHO keep SAGE updated on the progress of assessing rotavirus safety and efficacy, noting special interest in plans for monitoring incidence of intussusception in different settings. In addition, WHO was urged to continue to work with alternate vaccine candidates, including with developing country manufacturers.

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[a] WHO. *Report of the meeting on future directions for rotavirus vaccine research in developing countries*. WHO/V&B/00.23. Geneva: WHO; 2000.

[b] WHO. Rotavirus vaccines, an update. *Weekly epidemiological record.* 2003;78(1/2):1–8.

[c] WHO. Recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. *Weekly epidemiological record.* 80(2):15–16.

[d] Heaton PM, Goveia MG, Miller JM et al. Development of a pentavalnet rotavirus vaccine against prevalent serotypes of rotavirus gastroenteritis. Journal of Infectious Diseases 192: S17–21 (2005).

[e] DeVos B, Vesikari T, Lenhares AC et al. A rotavirus vaccine for prophylaxis of infants against rotavirus gastroenteritis. *Pediatric Infectious Disease Journal.* 2004;23:S179–S182.

SAGE again considered rotavirus vaccines at its November 2005 meeting.[a] At that meeting, the group received further updates on safety and efficacy studies of the Merck vaccine candidate and plans for rotavirus introduction in the Americas. SAGE noted that the vaccine seemed to reduce the severity of diarrhea rather than prevent infections but also noted that there was conclusive evidence of safety and one-year efficacy of the GSK vaccine in 11 Latin American countries and Finland. The work of PATH and the Rotavirus Vaccine Program (the GAVI Rotavirus ADIP) was helpful in bringing together some of this information, along with WHO. The SAGE recommendations were focused on the need for clear demonstration of safety and efficacy in developing country populations in field use (demonstration projects or pilot introduction studies) and on the continuing need for more information from Africa and Asia where the disease burden was very high. SAGE was also concerned with the importance of financing issues for this product, as well as the need to develop strong communication strategies because the vaccine was efficacious only to prevent severe rotavirus diarrhea and not prevent infection. This particular issue is receiving attention.[b] Moreover, other diarrhea control strategies, including oral rehydration, would continue to be very important.

SAGE then issued a limited recommendation for use of rotavirus vaccines which is echoed in the recently issued position paper:[c]

> WHO strongly recommends the inclusion of rotavirus vaccination into the national immunization programmes of regions where vaccine efficacy data suggest a significant public health impact and where appropriate infrastructure and financing mechanisms are available. However, until the full potential of the current rotavirus vaccines has been confirmed in all regions of the world, in particular in Asia and Africa, WHO is not prepared to recommend global inclusion of rotavirus vaccines into national immunization programmes.

This limited recommendation contrasts with the global recommendation for pneumococcal conjugate vaccine because of the lack of definitive efficacy data in some parts of the world. The vagueness of this recommendation regarding what type of efficacy data would be needed and what actually is meant by "all regions of the world" has been questioned;[d] presumably, the trials now in progress in several countries in Asia and Africa will provide the needed information.

The position paper also highlighted the need for surveillance systems to assess vaccine impact on disease and monitor for increased incidence of intussusception; expressed concern about the

[a] WHO. Conclusions and recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. *Weekly epidemiological record.* 2006;81(1):8.

[b] Enhanced Diarrheal Disease Control Resource Center website. Available at: http://www.eddcontrol.org. Accessed May 12, 2008.

[c] WHO. Rotavirus vaccines. *Weekly epidemiological record.* 2007;82(32):285–296.

[d] John Wecker, PATH Rotavirus Program, personal communication, January 2008.

timing of receipt of the first dose, which should be well before the age of 12 weeks, when intussusception is more likely to occur; and advocated consideration of cost-effectiveness and affordability of the vaccine and its financial and operational impact on the immunization delivery system and immunization practice. Although this concern is being addressed, the difficulty of detecting a rare event such as intussusception in developing countries has been noted by the PATH Rotavirus Program.[a]

The PATH Rotavirus Program has reported that despite requests to SAGE,[b] no working group for rotavirus vaccine has been established to develop an evidence-based document to help the SAGE in its deliberations. However, although WHO is looking more systematically at using working groups to prepare the information for a fruitful discussion at SAGE, the establishment of a working group on each topic is not a routine activity.[c] It is a decision of WHO and SAGE based on need and absence of an alternative means to review evidence.[62]

In summary, for the new rotavirus vaccines licensed in 2004, SAGE received data in 2004 on safety and efficacy in a limited number of countries and then requested more information, including a wider range of data, results of demonstration projects, and consideration of vaccine supply strategies, advocacy, and logistics issues. In 2005, having received the supply strategy information and information on advocacy initiatives, SAGE noted that a global recommendation would depend on safety and efficacy data and on results of demonstration projects in Asia and Africa. The position paper was thus issued in August 2007 with recommendation for use only in countries where this information was available.

Human Papillomavirus (HPV) Vaccine

The November 2005 meeting was the first time the HPV vaccine was presented to the SAGE.[d] This was part of SAGE's "horizon scanning" activities, to be updated on the status of this new vaccine. SAGE was informed of the status of two candidate vaccines, of a laboratory network being developed for isolating and typing HPV genotypes, and of work with other programs on reaching target groups outside of the normal EPI population. SAGE noted the potential communications challenges that might exist for a vaccine against a sexually transmitted disease and suggested the need to study the impact of population screening in conjunction with the vaccine, as well as the financial implications of such a course.

[a] John Wecker, PATH Rotavirus Program, personal communication, January 2008.

[b] John Wecker, PATH Rotavirus Program, personal communication, January 2008.

[c] Philippe Duclos, IVB, personal communication, January 2008

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[d] WHO. Conclusions and recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. *Weekly epidemiological record.* 2006;81(1):8.

At its April 2007 meeting,[a] SAGE was updated on the global burden of cervical cancer and the available data on safety, efficacy, and immunogenicity of one vaccine already licensed in more than 70 countries and one candidate vaccine that was under review by several national and regional regulatory authorities. In addition, work on cost-effectiveness and vaccine delivery options was described, as was ongoing research on alternative schedules, delivery costs, and acceptability. The SAGE concluded from the safety, efficacy (95–100 percent in previously uninfected adolescents and young women against infections caused by the serotypes in the vaccine[b]), and immunogenicity data presented that the use of the vaccine was likely to bring great benefits in settings with high cervical cancer burden, especially in countries where screening programs were limited or nonexistent. They highlighted that data on long-term duration of protection would be important in planning vaccine delivery strategies, especially the need for a booster dose. SAGE noted in particular the issue of delivery strategies and concomitant needs, as this would be an expansion into a new target group. Also discussed was the current high price of the vaccine licensed in industrialized countries. SAGE noted the willingness of manufacturers to work for affordability that may promote financing in lower-income countries. SAGE encouraged activities such as working to match demand and supply information and promoting technology transfer activities for vaccine manufacturing.

SAGE recommended heightened efforts to bring in partners at the regional level to be involved in these activities. IVB's HPV Expert Advisory Group (HEAG) was charged to develop the information for a background paper on HPV with involvement from regional technical consultative groups and to identify high-priority research questions. Some of these issues included vaccine safety and efficacy when delivered with prolonged or alternative dosing intervals, safety and efficacy among HIV-infected individuals, demonstration projects to assess various delivery options, and cost-effectiveness of immunizing older adolescents and young women, some of whom may have prior infection with vaccine-related HPV types. SAGE also advised WHO to explore resource mobilization for vaccine delivery. Finally, SAGE recommended that decision-makers at all levels collaborate to ensure that any proposed vaccine introduction activity be well integrated with other cervical cancer control strategies, such as screening programs.

The HEAG met in September 2007 to address these issues and proposed to submit proposed recommendations, a final background paper summarizing the available evidence, and a summary of regional opinions to SAGE by March 2008. At the SAGE meeting in November 2007, the chair of HEAG presented these conclusions, an updated summary of licensure status (as of October 2007, two vaccines are licensed in 88 and 35 countries), recommendations about vaccine use in several industrialized countries, and the summaries of the three regional consultations already held. The SAGE requested more efforts to address vaccine price and financing issues, commented on the barriers

[a] WHO. Meeting of the Immunization Strategic Advisory Group of Experts – conclusions and recommendations. *Weekly epidemiological record.* 2007;82(21):188–190.

[b] Centers for Disease Control, Quadrivalent Human Papilloma Vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Review*. 2007;56.

that vaccine delivery could pose, and indicated a need for regional consultations and a desire for regional WHO staff to outline plans for HPV introduction. IVB's Global Advisory Committee on Vaccine Safety (GACVS) at its June 2007 meeting had determined that there were no outstanding safety issues with use of the vaccine: "There was a strong consensus that evidence is now sufficient to draft recommendations on the use of HPV vaccine for consideration by SAGE…SAGE concluded that it should expeditiously discuss HPV vaccines after receiving a detailed background paper."[a]

Thus, once regional consultations are held in all regions, it is expected that SAGE will consider the total package at its November 2008 meeting, which would likely set the stage for recommendations that would be the basis for a WHO position paper.

In summary, the work on HPV is an important model for the evolution of recommendations for malaria vaccines, because of (1) the use of an expert advisory group to put together the requisite data into a background paper and to draft candidate use recommendations; and (2) the need for a specific focus on delivery strategies, possibly through demonstration projects. If, as appears likely, the SAGE is ready to make global recommendations in November 2008, this means only a two-year time lapse from licensing.

Implications for Policymaking for a Malaria Vaccine

Malaria vaccines will be unique from other malaria interventions and vaccines once available. As described above, the policy implications will fall within two areas of expertise, malaria and immunization. While the previous experience from these areas has provided the basis for this analysis, it is also worth recognizing a number of unique elements involved in setting policies around malaria vaccines:

- Malaria is the single largest killer of children in the world;
- Other interventions to prevent and treat malaria exist, although they have not as yet reached levels of utilization seen with vaccines;
- There has never been a human vaccine against a parasite, an organism far more complex than bacteria and viruses typically targeted by vaccines;
- There are no correlates of immunity for malaria, such that studies of efficacy must be done in very large, randomized double-blind control trials in malaria-endemic countries;
- There is limited market for a malaria vaccine outside of developed world, creating little incentive for pharmaceutical companies to invest in research and development; and
- It is possible that vaccines for malaria could be approved by regulatory bodies for use in the developing world years before a vaccine is approved for use in the developed world.

[a] Report of the Consultation of the HPV Expert Advisory Group (HEAG), September 3–5, 2007, Geneva, at the Consultation of the Strategic Advisory Group of Experts, November 7, 2007.

These elements highlight that the policy-making around malaria vaccines may build upon lessons from other interventions while also factoring in aspects which are unique.

GMP feels that its expert group, the TEG on the Chemotherapy of Malaria, is not best suited to look at the basic issues of launching a malaria control intervention such as a new malaria vaccine but that this is currently the most relevant constituted group. The issues of efficacy, safety, epidemiological background, impact on other existing interventions, and impact on malaria itself, especially in different settings, need to be considered. However, no member of the existing group has expertise in immunology or vaccinology, and the group is thus unable to effectively review data on immune response, impact on response to other vaccines, schedule information, logistics and delivery, or supply issues. A new TEG, or a new TEG subgroup, could be convened to represent the desired expertise.

Another possibility is a joint group representing the TEG and a working group of SAGE, which could then report back to SAGE and to the STAG. Such a Malaria Vaccine Expert Advisory Group would consist of technical experts who could consider the specific issues of safety and efficacy of a malaria vaccine in the context of current policy on malaria treatment and prevention interventions. They would be well versed in malaria epidemiology and the issues raised by specific schedules, target groups, and endemicity vs. seasonal malaria incidence. In addition, they would have experience in issues related to vaccine cost-benefit analysis, pricing, supply, production, regulation, and communications strategies. This could be the group charged with developing a malaria vaccine–specific background document, for consideration by both SAGE and STAG, which would jointly issue a global recommendation on malaria vaccine use. Finally, this group could access regional and national experts in malaria control and immunization to ensure that all relevant technical issues are adequately addressed and that all relevant partners are involved in the process.

A third potential line of action is to use the malaria vaccine advisory committee (MALVAC), which is IVB's group on research and development approaches to a malaria vaccine. MALVAC could be restructured because there are several vacant positions. The group's next meeting is on May 28, 2008.[a] The Terms of Reference of MALVAC are

- To assist the IVR secretariat in providing guidance to and coordination of the international malaria vaccine R&D effort, with specific emphasis and advocacy for public health needs in developing countries.
- To prepare the [Advisory Committee's] work plan and to identify opportunities for new lines of research.

[a] Zarifah Reed, IVB, personal communication, January 2008.

- To review the relevance, scientific quality, and budgets of all relevant research projects proposed to IVR and to monitor the technical and scientific progress of the research activities.[a]

In this approach, it would be important that MALVAC be staffed with experts in malaria such as members of the TEG. A useful activity at the next meeting could be the consideration of points for eventual deployment of a malaria vaccine that can be clarified by optimal design of clinical trials.

Whatever approach is used, it will be important to have strong communication channels between GMP and IVB from the outset. This will help to streamline the review process without neglecting any formal parts of the process, such as the role of IVB's Global Advisory Committee on Vaccine Safety to review the relevant safety issues.

An analysis of SAGE discussions, comments, and recommendations for the five (four vaccines and IPTi) interventions considered suggests the SAGE will likely:

- Increase the number of recommendations it issues with respect to other nonvaccine public health interventions.
- Continue to carefully scrutinize vaccine safety data under use conditions (relying on its GACVS).
- Consider implementation issues such as local disease burden data, surveillance abilities to measure impact, distribution strategies, and presentation.
- Look even more closely at the impact of an intervention on other prevention and treatment interventions in the future (it has already done so recently for HPV).
- Consider issues such as vaccine supply, price, availability, regulatory status (and/or prequalification as it impacts vaccine availability) and cost-effectiveness
- Look for documentation of successful introduction of the vaccine intervention in several representative developing countries prior to making firm recommendations for inclusion of interventions in country immunization programs.
- Specifically consider the impact of vaccines with different ranges of efficacy on other interventions.
- Look at the proposed schedule in the context of national policies.
- Ask for evidence that vaccine use would not result in displacing the disease burden to another susceptible age range.

The results of a phase 2B trial on the most advanced candidate malaria vaccine in Mozambique elucidate some of the specific issues that will be important for a malaria vaccine policy.[a] While

[a] WHO. Report *of the First Meeting of the Malaria Vaccine Advisory Committee (MALVAC).* WHO/V&B/04.01. Geneva: WHO; 2003.

this study was specifically designed to amass safety information, secondary endpoints included immunogenicity and analysis of new *Plasmodium falciparum* infections for three months after the third dose of vaccine. The vaccine was found to be safe, well tolerated, and immunogenic in young infants, 214 of whom were included in the study, 92–93 per arm. Adjusted vaccine efficacy in delaying time to the first infection was found to be 65.9 percent over the six-month period in this population receiving vaccine doses at 10, 14, and 18 weeks of age in a highly endemic area. This method of defining efficacy, which differs from the usual approach (in which efficacy was 11 percent for prevention of infection before the age of six months),[b] is needed for a malaria vaccine that delays but does not necessarily prevent infection or clinical malaria. Thus, some of the critical issues that need to be targeted for a malaria vaccine are included in Table 4.

Possible decisions on the use of a malaria vaccine through this process could be the following:

- Acceptable for global use (that is, in all countries where there is significant disease burden) with no reservations; it could be used universally unless there is overwhelming evidence that it should not be used in a particular setting.
- Acceptable for widespread use in a specific epidemiological situation, maybe defined as "regional" use.
- Acceptable in principle, but key data elements that would allow a recommendation for use are missing.
- Unacceptable for use.

The Table 4 list of considerations provides key data points that might feed into the decision-making process.

[a] Aponte JJ, Aide P, Renom M, et al. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomized controlled phase I/IIb trial. *The Lancet.* 2007;370:1543–1552.

[b] Epstein JE. What will a partly protective malaria vaccine mean to mothers in Africa? *The Lancet*. 2007;370: 1523–1524.

Conclusions

A number of conclusions can be drawn from these findings:

- Although efficacy and safety in the relevant target population, including displacement of disease to another susceptible age range, are the essential components of any policy and guideline development process, additional factors may also be important. These factors include issues related to costs and population health, such as supply and demand issues, financing issues, cost-effectiveness, and the impact of use on other interventions; issues specific to the local situation, such as the proposed schedule in the context of national policies and disease incidence; distribution issues depending on the age range of the target population; and specific advocacy and communications issues.
- It will be critical to document the ability to use a malaria vaccine in the context of other malaria treatment and prevention interventions and to rigorously document the impacts.
- In general, demonstration projects or pilot introduction studies in endemic countries will be important to better understand the impact of vaccine introduction on other interventions, on the overall health system, and on perceptions about other vaccines. Such demonstration projects will also facilitate the decision-making process.[a] In the analyses above, SAGE has specifically recommended that they be done in some cases (rotavirus and HPV vaccines).
- The format of policy presentations will need to follow that defined in WHO's *Guidelines for WHO Guidelines* document, with classification of data according to three categories: safety and efficacy in relevant populations; implications for costs and population health; and localization of data to the specific national situation (See Table 3).
- Because the policy development process will likely take several iterations, only limited progress can be expected from each individual meeting. Concerns of advisory groups can be anticipated to some extent and addressed thoroughly in subsequent presentations. From the previous analysis, it appears that the normal number of iterations might be three (see p. 3, footnote 10); and for the three interventions (Hib, pneumococcal conjugate, and rotavirus vaccines) for which usage recommendations have been made, the time period has been two to three years from first consideration by the SAGE. These products were already through the regulatory approval process when considered by SAGE, as is HPV, although an HPV recommendation could take less time. It is not yet clear what a probable time frame would be for a product such as a malaria vaccine, which might be considered by SAGE and the STAG concurrent with the regulatory approval process.
- For a product such as a malaria vaccine with a complex policy development process, a specifically convened working group may be useful to assist both GMP and IVB policy

[a] Note that while SAGE has not mandated these for all new vaccine recommendations, they appear to have been requested in cases where a new target population or delivery strategy is involved (such as HPV vaccine), or when there are specific product communication issues (such as rotavirus vaccine).

groups. Such an approach was found productive for both pneumococcal conjugate and HPV vaccines.

- Specific issues unique to a malaria vaccine spelled out in the text will require consideration (see section titled Implications for Policymaking for a Malaria Vaccine).
- The unique regulatory issues related to use of a vaccine whose activity will depend on endemicity of the setting will require considerable planning and capacity building.

It has been noted through the interview process that ongoing communication with the relevant secretariats and members of the advisory groups is a good way to understand changing concerns. In view of repeated requests of these advisory groups to involve local and regional staff in the decision-making process, suggestions of names of national program staff that could make constructive contributions to expert groups might be advisable.

Table 1. Consideration of *Guidelines* categories at the time of malaria treatment policy decisions.[a]

	Consideration of		
Intervention	**Safety and efficacy in relevant populations**	**Implications for costs and population health**	**Localization to setting**
ACT	Data available, but limited in primary target population	Limited product supply	Data relevant to use in Africa available
ITN	Efficacy well established	Disagreement over delivery strategies	Recommendation to promote coverage by locally appropriate communication strategies made
IPTp	Limited data from West Africa on efficacy and safety	Limited consideration of impact	Known probability of SP-resistance, (which is now prompting a review) potentially limits future use in some target populations

[a] In this table and the tables that follow, information available is placed in the relevant category as defined by the *Guidelines* according to the definitions in the Findings section.

Table 2: Data available prior to SAGE recommendations on intervention use.[a]

Intervention	Safety and efficacy in relevant populations		Implications for costs and population health		Localization of data		Recommendation Made
	Safety	***Efficacy***	***Supply, Financing, Cost-effectiveness***	***Impact on other Public Health Interventions***	***Delivery logistics / Schedule***	***Demonstration projects***	
IPTi	**+[b]**	**+/-**	**-**	**-**	**-**	**-**	More information needed
		29% but decreasing with increasing SP resistance	SP resistance lowers cost-effectiveness	Need for more studies, in collaboration with partners, to assess this	Impact of not following EPI schedule not completely elucidated	Results awaited	
Hib	**+**	**+**	**+**		**+**	**+**	Initial limited recommendation date; revised as more information became available
	Initially limited to information in some parts of the world. Safety OK	Efficacy > 95%, BoD initially limited, recommended more surveillance	Initially limited	NA	OK – EPI schedule Booster data to be developed Some discussion on presentation but resolved with emphasis on	Current data now show underestimation of disease burden by lab testing	

[a] +, data sufficient; +/- data weak; - data unacceptable for action

[b] Although SAGE noted acceptable safety data, subsequent deliberation by GMP groups suggested safety data were incomplete.

Intervention	**Safety and efficacy in relevant populations**		**Implications for costs and population health**		**Localization of data**		**Recommendation Made**
	Safety	***Efficacy***	***Supply, Financing, Cost-effectiveness***	***Impact on other Public Health Interventions***	***Delivery logistics / Schedule***	***Demonstration projects***	
					pentavalent		

Intervention	Safety and efficacy in relevant populations		Implications for costs and population health		Localization of data		Recommendation Made
	Safety	***Efficacy***	***Supply, Financing, Cost-effectiveness***	***Impact on other Public Health Interventions***	***Delivery logistics, Schedule***	***Demonstration projects***	
Pneumo-coccal conjugate	**+**	**+**	**+**	**+**	**+**		Global recommendation
	Safety data available	Wide range of data available, efficacy 95% in other populations, plus herd immunity effect	Appropriate groundwork done including cost benefit	Efficacy indicated in HIV infected and other immunocompro-mized hosts	Few issues as fits in EPI schedule. Booster data to be developed	Not felt to be necessary	
Rotavirus	**+/-**	**-**	**-**	**-**	**-**	**-**	Limited recommendation
	Need better AEFI monitoring	Limited to Latin America, US and Europe, (results 70-80%); need efficacy data in Asia and Africa	To date no emerging suppliers, but two industrialized country suppliers with significant amounts of	Does not protect but lowers severity	Size of packaging; Timing of first dose	Requested	

			product				

Intervention	Safety and efficacy in relevant populations		Implications for costs and population health		Localization of data		Recommendation Made
	Safety	***Efficacy***	***Supply, Financing, Cost-effectiveness***	***Impact on other Public Health Interventions***	***Delivery logistics, Schedule***	***Demonstration projects***	
	+	**-**	**-**	**+/-**	**-**	**-**	
HPV	Acceptable, GAVCS, June 2007	Efficacy close to 100% in industrialized countries, Duration of protection	Pricing will be an issue; cost-effectiveness data provided for high income countries only	Need for data on immunization of HIV infected. Data showing impact of screening, in conjunction with vaccine, in order to maximize impact	New target group	Requested for delivery methods; some work now in progress	More information requested

Table 3: Analysis of data available for SAGE vaccine decisions according to WHO Guidelines document criteria.[a]

Intervention; year of licensing	Safety and efficacy in relevant populations			Implications for costs and population health			Localization of data			Date of global recommendation in WHO position paper
	industrialized countries only	range of countries but still missing information	all data available	impact on disease addressed	demand, supply, financing addressed	all addressed, including other PH interventions	logistics issues addressed	all delivery strategies addressed	successful demonstration	
Hib; 1988	<1998	1998	2006	2005	2006	2006	NA	2003	2005	November 2006
Pneumo; 2000	1999	2003	2005	2005	2006	2006	NA	2003	NA	March 2007
Rotavirus; 2004	2004	2005	--	2004	2005	--	--	2005	--	August 2007 – limited recommendation
HPV; 2006	2006	2007	--	2007	--	--	2007	--	--	NA

[a] NA = not applicable; -- = not yet achieved

Table 4. Draft list of key data considerations with potential for informing malaria vaccine decision-making based on documentation and WHO interviews

Safety and efficacy in relevant populations	**Safety** • An acceptable safety profile • Freedom from "rebound" effect, that is, enhancing disease incidence in target groups following use. • Positive evaluation from WHO's Global Advisory Committee on Vaccine Safety • No significant adverse impact on other malaria prevention and treatment strategies (i.e. increasing adverse events from another product) or on response to concomitantly administered vaccines • Safety in immunologically compromised groups, e.g. HIV-infected
	Efficacy • Acceptable level of reduction of disease-related morbidity and/or mortality in target populations • Efficacy demonstrated in different malaria endemicity settings • Delivery schedules, dosing and administration route feasible and consistent with burden of disease in target countries
Implications for costs and population health	**Supply, financing, and cost-effectiveness issues** • Availability of product under the regulatory oversight of a fully functional regulatory authority and/or prequalification • Available supply related to anticipated demand • Affordability • Means of monitoring impact to feed into cost-effectiveness assessment • Prospects for competitive vaccine market
	Impact on other public health interventions • Vaccine delivery strategies to reach desired target groups (e.g., catch-up immunization where relevant) • Impact of vaccine use on compliance with other interventions, e.g. ITN • Community perception of malaria vaccine products given their likely characteristics • Impact of the vaccine demonstrated in the context of other malaria control strategies

"Localization" of data	**Local applications** • Evidence sufficient for local decision making available to the appropriate in-country groups (such as Immunization Advisory Committee, Interagency Coordinating Committee, etc), including, as relevant, national stakeholders and decision makers and key partners. • Ability to deliver vaccine through local cold chains • Specific evidence for unique epidemiological situations available, if applicable • Information from demonstration projects available particularly where new target groups or specific product acceptance issues are involved.

Annex 1. Individuals Consulted

PATH/MVI – Alan Brooks, James Cheyne, Vicky Cardenas, Laurent Bergeron
WHO GMP – Kamini Mendis
SAGE working group on pneumococcal conjugate vaccine - Stephanie Schrag,
CDC IPTi Coalition – Andrea Eagan, Jane Crawley
WHO IVB – Phillipe Duclos, Tracey Goodman, Zarifah Reed
GAVI's PneumoADIP – Orin Levine
PATH Rotavirus Vaccine Project – John Wecker
Hib Initiative – Rana Hajjeh
HPV Expert Advisory Group – Katy Irwin, Vivien Tsu

Annex 2. Documents Consulted

WHO Policies and Governance

Global Programme on Evidence for Health Policy. Guidelines for WHO Guidelines. Geneva: WHO, 2003 (EIP/GPE/EQC/2003.1)

Andrew D Oxman, John N Lewis, Atle Fetheim. Use of evidence in WHO recommendations. The Lancet 369: 1883-1889, June 2, 2007; Comment. The Lancet 369: 1842, June 2, 2007

WHO Websites

GMP website at http://www.who.int/malaria/

IVB website at WHO IVB website at http://www.who.int/immunization/en, on SAGE page or Vaccine position papers.

SAGE meeting site, at http://www.who.int/vaccines/meetings/sage/; User name: sage, Password: !sage! Limited access has to do with copyright issues and challenges of the current WHO web platform and not confidentiality issues.

Malaria Treatment Policies

WHO. Antimalarial Drug Combination Therapy. Report of a WHO Technical Consultation. Geneva: WHO, 2001, Document WHO/CDS/RBM/2001.35

WHO. Guidelines for the Treatment of Malaria. Geneva: WHO, 2006. Annex 1.

WHO. The Africa Malaria Report. Geneva: WHO, 2003.

Malaria Prevention Policies

Chandramohan D, Owusu-Agyei S, Carneiro I, et al. Cluster randomised trial of intermittent preventive treatment for malaria in infants in area of high, seasonal transmission in Ghana. BMJ 331(7519)**:**727-33, 2005.

Chandramohan, D., Webster J, et al. Is the Expanded Programme on Immunisation the most appropriate delivery system for intermittent preventive treatment of malaria in West Africa ? Tropical Medicine and International Health 12 (6): 1-8, 2007.

Crawley J, Hill J, Yartey J et al. From evidence to action? Challenges to policy change and programme delivery for malaria in pregnancy. Lancet Infectious Diseases 7 (2): 145-155 (February 2007).

Fegan GW, Noor, AM, Akhwale WS et al. Effect of expanded insecticide-treated bednet coverage on child survival in rural Kenya: a longitudinal study. Lancet 370: 1035 – 1039, 2007.

Global Malaria Programme. Insecticide-Treated Mosquito Nets: a WHO Position Statement, at http://www.who.int/malaria/docs/itn/ITNspospaperfinal.pdf

Hill J, Kazembe P. Reaching the Abuja target for intermittent preventive treatment of malaria in pregnancy in African women: a review of progress and operational challenges. Trop Med Int Health 11(4)**:**409-18, 2006.

Kobbe R, Kreuzberg C et al. A randomized control trial of extended intermittent preventive antimalarial treatment in infants. Clin Infect Dis 45 (1): 16-25, 2007.

Macete E, Aide P, Aponte JJ, et al. Intermittent preventive treatment for malaria control administered at the time of routine vaccinations in Mozambican infants: a randomized, placebo-controlled trial. J Infect Dis 194(3)**:**276-85, 2006.

Massaga JJ, Kitua AY, Lemnge MM, et al. Effect of intermittent treatment with amodiaquine on anaemia and malarial fevers in infants in Tanzania: a randomised placebo-controlled trial. Lancet 361(9372)**:**1853-60, 2003.

Schellenberg D, Menendez C, Aponte JJ, et al. Intermittent preventive antimalarial treatment for Tanzanian infants: follow-up to age 2 years of a randomised, placebo-controlled trial. Lancet 365(9469)**:**1481-3, 2005.

Schellenberg D, Menendez C, Kahigwa E, et al. Intermittent treatment for malaria and anaemia control at time of routine vaccinations in Tanzanian infants: a randomised, placebo-controlled trial. Lancet 357(9267)**:**1471-7, 2001.

WHO. WHO Expert Committee on Malaria, 20th Report. Technical Report Series 892. Geneva: WHO, 2000.

WHO. Report of the Scientific Working Group Meeting on Malaria. Geneva: WHO, 24-27 March, 2003.

WHO. Report of the TEG meeting on IPTp, Geneva, July 2007.

WHO. Report of Technical Consultation on Intermittent Preventive Treatment for Malaria in Infancy (IPTi). Global Malaria Programme, WHO, Geneva, 25-27 October 2006.

WHO. Weekly Epidemiological Record 81 (21): 209-220 (26 May 2006)

IPTi Consortium website at http://www.ipti-malaria.org/

Vaccine Policies

Hib

Global Programme for Vaccines and Immunization. The WHO Position Paper on Haemophilus influenzae type b conjugate vaccines. Weekly epidemiological record 73 (10): 64-68 (6 March 1998).

WHO. Recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. Weekly epidemiological record 79 (5): 48-49 (30 January 2004).

WHO. Conclusions and recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. Weekly epidemiological record 80 (1): 7 (6 January 2006).

WHO. WHO Position Paper on *Haemophilus influenzae* type b conjugate vaccines. Weekly epidemiological record 81 (47): 445-452 (24 November 2006).

WHO. Meeting of the immunization Strategic Advisory Group of Experts – conclusions and recommendations. Weekly epidemiological record 82 (21):181-196 (25 May, 2007)

Pneumococcal conjugate

WHO. Pneumococcal vaccines – WHO position paper. Weekly epidemiological record 78 (14): 110 – 119 (4 April 2003).
WHO, Meeting of the immunization Strategic Advisory Group of Experts, November 2006 – conclusions and recommendations. Weekly epidemiological record 82 (1/2): 1-16 (12 January 2007).
WHO. Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. Weekly epidemiological record 82 (12): 93-84 (23 March 2007)
WHO. Meeting of the immunization Strategic Advisory Group of Experts – conclusions and recommendations. Weekly epidemiological record 82 (21):181-196 (25 May, 2007)

Rotavirus

WHO. Report of the meeting on future directions for rotavirus vaccine research in developing countries. Geneva, 9-11 February 2000 (WHO/V&B/00.23).

WHO, Rotavirus vaccines, an update. Weekly epidemiological record 78 (1/2): 1-8 (10 January, 2003).

WHO. Recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. Weekly epidemiological record 80 (2): 15-16 (14 January 2005).

WHO. Conclusions and recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. Weekly epidemiological record 81 (1): 8 (6 January 2006).

WHO. Rotavirus vaccines. Weekly epidemiological record 82(32):285-296 (10 August 2007).

HPV

WHO. Conclusions and recommendations from the Strategic Advisory Group of Experts to the Department of Immunization, Vaccines and Biologicals. Weekly epidemiological record 80 (1): 7 (6 January 2006).

World Health Organization. Meeting of the immunization Strategic Advisory Group of Experts – conclusions and recommendations. Weekly epidemiological record 82 (21):188-190 (25 May, 2007).

WHO, Meeting of the immunization Strategic Advisory Group of Experts, November 2006 – conclusions and recommendations. Weekly epidemiological record 82 (1/2): 1-16 (12 January 2007).

HPV Expert Advisory Group. Working Documents for the September 2007 meeting.