Summary of Previous SAGE Discussions on Hib vaccine

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SAGE November 2010

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" Global coverage with 3 doses of Haemophilus influenzae type b vaccine (Hib) is only 38% because many countries, including large countries such as India and Nigeria, have not yet introduced the vaccine. The need to develop specific strategies for working with large countries to implement recommended vaccine policies was highlighted."

Page 6 "Evidence suggests that focusing on targeted diseases has not hindered the introduction of new vaccines, since 30 countries and areas have include Hib vaccine in their routine schedules, and this is the only region in which all low-income countries have introduced Hib vaccine."

Page 13 "SAGE encouraged WHO to complete the project promptly, noting that a small investment could lead to major public-health gains by achieving the most efficient use of vaccines in different epidemiological contexts. SAGE requested a critical appraisal of alternative schedules for pneumococcal conjugate vaccine, rotavirus vaccine and Hib vaccine in 2011."

SAGE November 2007

Page 2: "There has been definite improvement in the uptake of Haemophilus influenzae type b (Hib) vaccine, with introduction in a further 28 countries planned for 2008. However, substantial portions of Asia and Eastern Europe have not planned to introduce the vaccine. Introduction of conjugate pneumococcal and rotavirus vaccines is also proceeding in developing countries."

Page 3 (Region of the Americas):"The region has made tremendous gains in eradicating polio, eliminating measles and controlling diphtheria, pertussis, hepatitis B and Hib disease. Protecting these achievements is critical, along with introducing new vaccines and technologies. The 2 main unfinished issues are the elimination of rubella and congenital rubella syndrome (CRS) and making the transition from a childhood immunization programme to a family immunization programme. The Directing Council of the Region of the Americas and the Pan American Health Organization recently endorsed the goal of eliminating rubella by 2010. The region has seen a 98% reduction inrubella cases as a result of high coverage with a routine dose of measles–mumps–rubella vaccine and campaigns with measles–rubella vaccine extended to adults and adolescents. Several campaigns were conducted in 2007. In 2007, only 5 cases of CRS were reported in all of the Americas. It was recognized, however, that CRS surveillance was hospital based and may lack sensitivity; other more sensitive options are being explored in some countries. The region has also successfully implemented an "immunization week" in the Americas, which targeted older age groups, including the elderly. The vaccines used vary between countries based on national priorities. Future immunization weeks will be synchronized with immunization weeks in the European Region."

Page 4 (European Region) "The introduction of Hib-containing vaccines shows a marked difference between countries in Western Europe and some of those in Eastern Europe and the Newly Independent States, with low uptake in countries in the Newly Independent States. Lack of recognition of the burden of Hib disease and relatively high vaccine prices are largely responsible. The approaches being taken to address these issues include finalizing a regional plan of action for the introduction of new vaccines, developing a regional strategic direction, and providing support for evidence-based decision-making for introduction.
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Page 5 (Report from the GAVI Alliance) " The GAVI Alliance's Executive Secretary noted that there has been strong growth in the introduction of new vaccines, with most eligible countries having been approved to introduce hepatitis B and Hib vaccines. The first country applications for support for pneumococcal and rotavirus vaccines have been approved. A recent analysis of applications by the Alliance's Independent Review Committee demonstrated that an increased number of countries have greater capacity to pay, there have been improvements in the completeness of information (including new vaccine introduction plans) and there has been an overall improvement in the quality of applications. WHO's technical assistance to these countries was commended. Countries were increasingly availing themselves of the new opportunities for health system support funds."

SAGE November 2005

Page 7 "**Haemophilus influenzae type b (Hib)** SAGE reviewed the morbidity and mortality of Hib pneumonia and meningitis in Africa and Asia and current national immunization recommendations against Hib disease. It also reviewed the GAVI Hib initiative whose purpose is to reduce the risk of childhood death and disability through sustained use of the vaccine. In countries that use Hib vaccine, the results of analyses indicate a significant reduction in pneumonia and meningitis, resulting in decreased use of health services for the treatment of these diseases. These potential gains need to be quantified in countries that are not using the vaccine. SAGE recognized that studies on surveillance and disease burden were needed to support evidence-based decision-making in countries that have not introduced routine Hib vaccination, bearing in mind issues such as vaccine supply and cost, and carefully exploring financing options. Cost-benefit studies would also be needed. Whether all countries need to undertake all of these activities has not been resolved. Limitations in laboratory capacity were identified as major impediments that needed to be properly addressed. New financing opportunities for the poorest countries, particularly through the Global Alliance for Vaccines and Immunization and the IFFIm, will need to be encouraged. SAGE strongly recommended that this new framework for Hib introduction should be expanded to the fullest extent possible to increase demand for the vaccine and accelerate the lowering of its price. SAGE also recommended global implementation of Hib vaccination – unless robust epidemiological evidence exists of low disease burden, lack of benefit or overwhelming impediments to implementation. This recommendation will enhance fulfillment of the Millennium Development Goal of reduced childhood mortality (Goal 4)."

Page 10 (Conjugate pneumococcal vaccines) " SAGE recognized the similarities in the work required for introduction of Hib and pneumococcal vaccine and commended the cooperation between the PneumoADIP and the Hib Initiative. In particular, evidence was required through studies on disease burden of the cost benefit of using pneumococcal conjugate vaccines and the feasibility of vaccine delivery to all vulnerable groups. Pneumococcal serotype prevalence studies, undertaken in different settings, are required to judge the appropriateness of the conjugate vaccine to be used. A firm position from SAGE will be required once serotype prevalence studies are completed to judge the appropriateness of the conjugate vaccine available. SAGE endorsed the proposal for the formation of a subcommittee to develop a position statement on pneumococcal conjugate vaccination. SAGE acknowledged the urgency of this work but recognized that a global recommendation, made before resolution of funding and supply issues, could leave vulnerabilities that have been experienced with the implementation of Hib vaccine. Since acute respiratory infection is a major cause of childhood morbidity and mortality, SAGE considers it likely that the use of a pneumococcal conjugate vaccine will, as in the case of Hib and rotavirus vaccines, contribute towards the Millennium Development Goal of reducing under-5-year mortality rates."

SAGE 2004

Page 16 "**Strategic challenges for Haemophilus influenzae type b** Currently 88 countries have introduced Hib vaccine, including 8 African countries. There are several barriers to its introduction, including its high price, limited supply of Hib-containing pentavalent vaccine and uncertainties about the true burden of disease in Asia. However, new data from a controlled trial in Indonesia show a substantial impact of Hib vaccine in preventing meningitis. Discussion highlighted the importance of effective

communication of what is already known about vaccine impact and increasing competition among manufacturers to decrease vaccine price. WHO has an important role to play with countries in strengthening evidence-based decision-making; mplementing recommended approaches and working to raise awareness and communicate the value of the Hib vaccine. SAGE reviewed the status of GAVI funding of Hib vaccine introduction in 15 countries. The transition to self-financing in these countries has not yet been made. Supply chain issues and financing structures are important areas for resolution. SAGE recommended that WHO should consult with countries in all regions, with particular emphasis in the WHO African Region, on their use of Hib vaccine. These consultations should aim at providing comprehensive information on existing evidence about Hib disease burden and the impact of Hib immunization in preventing meningitis and pneumonia. By the end of 2005, WHO should provide clarification on its recommendations for vaccine use in several geographical areas.“

SAGE 2003

Page 48-9 “ **Accelerated vaccine introduction (AVI) priority project** SAGE noted the scope of activities proposed by the Secretariat; the relative lack of coverage of hepatitis B vaccine and the need for strengthening that coverage; the lack of adequate data in some regions; and the limited uptake of Haemophilus influenzae type b (Hib) vaccines in Africa. SAGE further noted the priority of efforts; the need for funding support for this priority plan; and the need to sustain the momentum of the AVI priority project and to ensure that the lessons and experiences of introducing new vaccines are disseminated and incorporated into national immunization programmes. SAGE strongly endorses the proposals and plan of action.

Next steps in the introduction of Haemophilus influenzae type b (Hib) in Asia SAGE noted that available data suggest that the burden of Hib may be lower in Asia than in other regions, for reasons that are unclear, and that there is concern that the methods of assessment used might underestimate the true burden. WHO presented to the meeting plans for collecting the necessary information and developing clearer recommendations for introduction of Hib vaccine to Asia. SAGE strongly endorses WHO plans for proceeding with this approach, subject to the condition that the assessment protocols4 are first validated.“

SAGE 2002

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“ **New vaccine introduction** SAGE reviewed progress since 1997 on the introduction of Haemophilus influenzae type b (Hib) vaccine and new information on Hib levels in Asia. New data confirm that Hib rates in Asia are 2.5 to 10 times lower than rates elsewhere. Although the previous SAGE recommendations regarding Hib were still considered to be appropriate, the subgroup felt that a future statement of the WHO position, based on more studies, would be welcomed by ministries of health, since many might prefer to prioritize other vaccines, e.g. Japanese encephalitis (JE) vaccine. In relation to vaccination against hepatitis B, SAGE considered information on a new study showing substantial transmission of hepatitis B in childhood. The finding, that one-sixth of infections resulting in severe liver disease in the United States of America occur in this time period, provided the United States with retrospective endorsement of its infant immunization policy and has raised the possibility that countries which currently use adolescent immunization might wish to re-examine the situation in the light of these new data. “

Page ix “**Meningitis** Surveillance: Real progress has been made in the African Region in the area of hospital-based meningitis surveillance. For the first time countries are obtaining bacteriological confirmation of meningitis, verifying that Hib is a substantial cause of meningitis in the region and supporting the increased introduction of Hib vaccine in these countries. Surveillance is also obtaining pneumococcal isolates that will add to the information available on pneumococcus serotypes causing meningitis.
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Page xv “ **Hib in Asia** SAGE reaffirms the WHO position recommending introduction of Hib vaccine as appropriate to national capacities and priorities. Most studies from mainland Asia indicate a relatively low

incidence of Hib meningitis, data that are important for country-level prioritization. Additional studies on the impact of Hib vaccine on the burden of pneumonia in Asia are needed to clarify the utility of the vaccine. “

Page 3 (1.2 The Strategic Plan) “Target 3. One of the priority projects, acceleration of the introduction of new vaccines in developing countries, will shift to implementation with introduction of hepatitis B and Hib vaccines as well as underused vaccines like yellow fever. Among the challenges are shortages of combination vaccines. V&B will also look at the impact the introduction of these new antigens makes on routine immunization services. “

Page 10 (1.6 GAVI: Status and WHO role) “Kenya was awarded support in the form of pentavalent DTP–HepB–Hib and yellow fever (YF) vaccine and funding of US$ 11 million to increase coverage over the next five years. A data quality audit is being conducted to review how well their routine reporting system operates and how it can be improved. Development of financial sustainability plans is also under way. “

Page 16 (2.2 Prioritization of vaccines) “Proposed categories for the process included: Basic vaccines recommended for universal use (including Hib, excluded from the current essential vaccines list).“

Page 19 (2.3 Update on thiomersal and vaccines) “ Dr Dellepiane provided an update on the status of the debate over the use of thiomersal in vaccines. The issue of thiomersal had first been raised in 1999 on the basis that ingested maternal methyl mercury had caused neurological abnormalities – development delay in infants exposed in utero. There had been no guidelines to safe levels of ethyl mercury and so the existing guidelines for ingested methyl mercury had been used. The toxicity levels for methyl set by different bodies varied from 0.1 to 0.5 µg Hg/kg/day. A child receiving three doses of diphtheria–tetanus–pertussis (DTP), Hib and HepB within the first 14 weeks of age would receive a total dose of 187.5 µg Hg (ethyl mercury). “

Page 21-3 (2.4 Policy issues in new vaccine introductions: Hib and Hepatitis B) “ Dr Wenger described the work of the Accelerated Vaccine Introduction (AVI) project. Activities directed at facilitating introduction of new vaccines drew on skills across the whole Department. An important objective was to establish the extent of the disease burden in different countries and to support governments in their decision to introduce new vaccines.

Hib in Asia Dr Wenger informed SAGE that the decision to introduce Hib vaccine was made on the basis of information about the burden of vaccine-preventable disease (meningitis and pneumonia, as well as other Hib diseases) and the cost of implementing the vaccine programme.
SAGE heard that Hib vaccines were safe and easily administered; they had high efficacy and were remarkable for creating herd immunity. Price had held back the introduction of Hib vaccine: the cost of three doses of vaccine against hepatitis B was US$ 0.75 to US$ 1.50, whereas three doses of Hib vaccine cost from US$ 8 (lowest UNICEF tender). Uncertainty about the accuracy of low disease-burden estimates in Asia had troubled the immunization community. Preliminary results of studies in the north of Viet Nam, Thailand, and the Republic of Korea had shown relatively low rates of Hib meningitis, less than 10 cases per 100 000 children under five years of age, in line with previous studies, and several times lower than that seen in the Americas and Africa (see figure 2.1). The low Hib meningitis burden in Asia has been variously attributed to inadequate methodology, antibiotic use, genetic characteristics, socioeconomic factors, lifestyle, childcare patterns, etc. <Graph: Literature Review on Hib meningitis, 2002>

Dr Wenger asked SAGE to consider whether the current WHO position, based on a 1997 SAGE recommendation on Hib disease and vaccine use in Asia, was still appropriate. “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”.

These recommendations allowed flexibility and country-level decision-making. There had not been many inappropriate requests for Hib vaccine. Hib was offered to the poorest 74 countries, but the requirement to present disease burden data had apparently deterred Asian countries from applying for Hib. While five Eastern European countries had applied, most had some form of disease-burden data, and further studies were ongoing. Meanwhile, since 1997 there had been an increase in use of Hib vaccine elsewhere, from some 26 countries in early 1997 to around 90 by mid-2002. In the Region of the Americas almost all countries were using Hib vaccine. In the African Region, with the support of the Vaccine Fund, a number of countries had introduced Hib and more would do so over the next year or two.

An issue relevant to the WHO position was raised: was the rate of Hib pneumonia in Asia lower than elsewhere? Studies in Latin America and Africa had shown a larger number of pneumonia cases than meningitis cases in population studies. There were no similar data available from Asia, and a key study on Hib pneumonia burden in Lombok, Indonesia would be completed in 2002, showing the impact of the Hib vaccine on pneumonia in an Asian setting. Even if it were accepted that the Hib meningitis burden was lower, if Hib caused even 20% of pneumonia deaths in Asian countries, the useful effects of the vaccine in reducing mortality should be borne in mind. Steps being taken included: continued technical support to countries to check the reasonableness of the requests being made, use of the Hib surveillance protocol, Hib rapid-assessment tool and cost-effectiveness tools; enhanced demand estimate procedures for fund-allocation; and re-evaluation in the light of the Lombok Hib pneumonia study.“

Page 24-5 (SAGE Commentary on Points Raised)
Hib SAGE agreed that the present policy was flexible, with the decision-making process at country level. The WHO recommendations on vaccination still seemed appropriate. Concern was expressed about waiting too long before giving a more definite answer on Hib in Asia, but SAGE agreed that WHO should wait for the Lombok study before taking that step. The reasons for urgency were: Hib in combination cannot be supplied at short notice and it would take the vaccine industry years to change course. Vaccine Fund support might go to other diseases, e.g. JE. It was felt that SAGE should eventually give guidance on prioritization, and that it was important that SAGE should not give non-critical support to all vaccines. Countries should use Hib vaccine if it fitted with their priorities. SAGE suggested that WHO should support additional studies on pneumonia (radiological diagnoses), seeking funding for what would probably prove to be a very costly exercise. Hib was a devastating disease. Dr Bloom suggested reviewing relative data such as what even a low burden of a very crippling disease would cost. There were appropriate investments to be made for each disability. A number of SAGE members emphasized the global, regional and even national or subnational heterogeneity of Hib. SAGE questioned the impact of the private-sector Hib-vaccine market in Asia, on the basis that the privately-paid vaccinees might be confounding Hib studies. Dr Wenger confirmed that the herd immunity effect was very strong with Hib. However, as the private market in Asia was less than 10%, usually less than 5%, a relatively small impact could be expected.“

Page 25 (Recommendations): “ **Hib in Asia** SAGE reaffirms the WHO position recommending introduction of Hib vaccine as appropriate to national capacities and priorities. Most studies from mainland Asia indicate a relatively low incidence of Hib meningitis, data that are important for country-level prioritization. Additional studies on the impact of Hib vaccine on the burden of pneumonia in Asia are needed to clarify the utility of the vaccine.
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Page 29 (Progress in bacterial meningitis surveillance) “ Dr Nelson presented an overview of the surveillance network and its progress to date. Hib had been identified as a major cause of bacterial meningitis in children under five years of age, especially infants. The WHO Paediatric Bacterial Meningitis Surveillance network had been launched in 2001 in 27 countries in the African Region, with one sentinel site per country. Half of the countries in the network were already reporting and the proportion was expected to rise soon to 75%. The purpose of the network was to develop local surveillance capacity for evidence for disease burden and assessing the impact of vaccine; and to provide a base for national

meningitis surveillance and for sentinel S. pneumoniae and N. meningitidis surveillance. In reply to a question raised by SAGE it was confirmed that HIV status was not currently included in the data collection but that information could be obtained if necessary. There was a need to improve reporting and data quality, and for additional sites in countries introducing Hib vaccine. Isolates were not yet being typed but Hib data would be available in some countries soon. A network was also to be launched in the Eastern Mediterranean Region in 2002. The average results of the network were good and there had been very good results against indicators at Mulago National Referral Hospital, Kampala: 92% of patients with suspected meningitis had been given a lumbar puncture, 52% of purulent CSF specimens showed bacterial growth, and 10 out of 10 monthly reports had reached the Ministry of Health and the Regional Office for Africa on time. The plan of action for 2002 included developing the existing network; improving the quality of reported data; expanding to additional sites within countries introducing Hib vaccine, e.g. Uganda; and establishing a regional reference laboratory. In reply to a question raised by SAGE it was confirmed that the results of a pneumococcal vaccine study in South Africa had showed it to have been 80% or 90% effective in normal children.

Page 39 (3.2 New vaccine introduction in Vaccine Fund-eligible countries) " Dr Namgyal outlined to SAGE how the introduction of new vaccines was supported by AVI, a priority project within the Department of Vaccines and Biologicals. Six new vaccine medical officers had been placed in the WHO regional offices for Africa, the Eastern Mediterranean, Europe, South-East Asia, and the Western Pacific. One of their main activities, particularly in Africa, was to support the preparation of countries' applications to the Vaccine Fund for assistance with the introduction of new and underutilized vaccines. By the end of the sixth round of review of country applications to GAVI, 40 countries had received approval for the introduction of new and underutilized vaccines, namely hepatitis B, Haemophilus influenzae type b (Hib) and yellow fever vaccines. The substantial progress made in introduction of these vaccines was reported."

Page 62 (4.4 Vaccine supply for disease control initiatives) " Dr Costa reported to SAGE on the development of accelerated vaccine introduction or disease elimination strategies, describing the thorough analysis of demand, supply sources, manufacturing capacity, bottlenecks, pricing, funding etc required. Examples of fluctuation in demand and supply for measles, OPV, YF, hepatitis B and Hib vaccines were presented. Increased demand for OPV in 2001 had not been reflected in purchases (owing to supply problems). Measles campaigns since 1987 had had a strong effect on vaccine demand, and the new global recommendations on the "second opportunity" were expected to bring administration demand up to 350 million doses by 2004 and 2005. "

Page 66 (SAGE Commentary on points raised) " It was also important to know the interaction between various vaccines. If use of Hib and HepB was expanded, what would be the effect on measles and MMR, for example? Another concern expressed was that, as developing countries demanded more expensive vaccines, they appeared to be moving away from their own supply sources. In response, it was pointed out that developing country manufacturers were moving slowly towards combination vaccines (see section 2.5 for discussion of this issue). "

SAGE 1997 Accelerating the control of Hib vaccines *Electronic text not available online*