On its September 2004 teleconference the GAVI Board requested the GAVI Working Group to solicit ideas for investment cases which would be shared with the Board at its December meeting. Thereafter the Board would formally request investment cases to be developed to inform the process to make policy decisions on GAVI phase 2.

Initial exploration by the Working Group has highlighted the need for more time for thorough consultation. While it was initially envisioned that countries would apply for phase 2 support in 2005 and begin receiving it in early 2006 it has become evident that the country application process should start in 2006, with the first phase 2 support reaching countries in 2007.

This document, which outlines a revised process and timeline is provided to the Board for information only. Early concept papers on potential areas for GAVI support in phase 2 are provided in Annex 1.

Process to prepare for decisions on strategic priorities for Vaccine Fund resources in phase 2

A critical lesson from the first phase of GAVI is the importance of alerting national decision makers to the full range of options available for GAVI/Vaccine Fund support over the coming years. Furthermore, an explicit process for the development of future allocation policies will be essential to increase the transparency and rationality of the discussions. The process should be open and promote innovative thinking.

To determine the strategic priorities during GAVI Phase 2, the GAVI Board has decided to request the immunization community propose options for support. The evaluation and comparison of these options by the Board will be facilitated by proposals outlining the case for investment in each.

To begin the process, in September the GAVI Board requested the Working Group to identify potential areas for investment cases to be developed, as well as institutions, groups or individuals who would be best suited to develop the cases, for presentation to and decision by the Board at its December 2004 meeting.

However, initial work highlighted the need for a longer timeline; while it was initially envisioned that countries would apply for phase 2 support in 2005 and begin receiving it in early 2006 it has become evident that the country application process should start in 2006, with the first phase 2 support reaching countries in 2007.

<u>Proposed process and timeline:</u>

1. The Working Group and Secretariat has already initiated an informal solicitation of ideas via email (see Annex 1: Investment case concept papers).
2. To ensure maximum developing country input, the Working Group will dialog with national counterparts and technical experts. The objective of these dialogs will be to discuss potential options for GAVI/Vaccine Fund support in phase 2 and to provide developing country decision makers with a forum in which they can directly feed into the priorities.

3. The Working Group with additional technical experts, will meet in early February to prepare a shortlist of options for Board consideration. The shortlist will ensure several options available to address each of the priority windows outlined by the GAVI Board: (a) strengthening immunization services; (b) expanding use of existing vaccines; (c) accelerating use of under-used vaccines; and (d) introducing new vaccines and technologies.
4. In preparation for the March 2005 Board meeting, Working Group members will individually brief each Board member to elicit Board feedback.
5. At the March 2005 meeting, the Working Group will present a prioritized list of options. The GAVI Board will be asked to review the overall "portfolio" and the list of options and formally request suggested entities to prepare proposals outlining the investment case for each option.

Preparing proposals for November/December 2005 Board meeting

1. Requested entities will be charged with preparing investment cases for comparison and review by the Board. Other proposals that have not been explicitly requested may still be submitted for review.
2. The proposals will follow the investment case framework to ensure completeness and comparability of data , however, any sections considered not to be relevant or requiring data that is not available to a particular case can be highlighted as such and left blank. In this way, the Board will be aware of gaps when comparing proposals.
3. The proposals will be reviewed by a small impartial independent evaluation committee comprised of four to five technical experts able to provide an objective evaluation of the proposals' data and assertions.
4. The evaluation committee will provide comments to the proposal preparers and to the GAVI Board for its decision making.

Board decisions November/December 2005:

The Board will review make its first policy decisions on the investment priorities for phase 2 regarding strengthening immunization services, expanding the use of existing vaccines, accelerating the use of under-used vaccines, and introducing new vaccines and technologies. Subsequently, the Board may wish to evaluate new investment proposals in 2007 or 2008.

GAVI Board Concept Paper

Introduction of Rotavirus Vaccine in GAVI/VF-eligible Countries in Latin America Prepared by the Rotavirus ADIP

Background

Objective and strategy: The objective of the investment case is to request a policy decision by GAVI to offer financial support for the purchase of rotavirus vaccines for GAVI/VF-eligible countries in Latin America (LA). Data in this document only reflect the six current GAVI/VF-eligible countries: Bolivia, Cuba, Guyana, Haiti, Honduras and Nicaragua. It is foreseen that live, oral rotavirus vaccines would be delivered through the routine immunization systems according to the regional EPI schedule. This concept paper addresses only LA, as efficacy and safety data addressing the appropriateness of the current late-stage rotavirus vaccines in other regions (e.g., Asia, Africa) will not be available until 2008 at the earliest. The GAVI Board will be asked to consider a policy to support rotavirus vaccines in other countries as data become available.

Burden of disease: Nearly every child born in the six LA countries currently eligible for GAVI/VF support will have at least one case of rotavirus diarrhea during their first five years of life. Based on current estimates prepared by the US CDC, 960,000 cases of rotavirus diarrhea will occur each year in these six countries, leading to 193,000 clinic visits for rehydration, 15,000 hospitalizations, and an estimated 3,125 deaths. Therefore, by the age of five years, one child in every five will visit a clinic, one in every 64 will be hospitalized, and one in every 315 will die from rotavirus disease.

Impact of vaccination: If rotavirus vaccines are introduced in all the GAVI/VF-eligible countries of LA and assuming current levels of vaccine coverage, vaccination can prevent 60 percent of the most severe outcomes, including 1,875 deaths and more than 9,000 hospitalizations annually.

Cost-effectiveness of rotavirus vaccination: In the six countries, the total cost of medical care for moderate and severe disease is estimated to range from US$9 million to US$19 million. Depending on the price of the vaccine, rotavirus vaccination is very likely to be as cost-effective or more cost-effective when compared to other interventions to prevent diarrheal morbidity and mortality.

Estimated time frame: Currently, there are two, live, oral rotavirus vaccine candidates in late-stage development by GlaxoSmithKline Biologicals (GSK) and Merck, respectively. Key milestones in the development and licensure of these rotavirus vaccines include:

- Q3 2004 GSK vaccine licensed in Mexico and Dominican Republic
- Q4 2004 Safety trials for intussusception completed by GSK and Merck
- Q3 2005 Phase III efficacy study in LA completed by GSK
- Q4 2005 GSK vaccine licensed by WHO-qualified National Regulatory Authorities (NRA) in LA and/or Europe

- Q1 2006 Merck vaccine licensed by FDA (projected). Standardization guidelines for production of rotavirus vaccines issued by WHO
- Q3 2006 Prequalification of GSK vaccine by WHO completed

The time frame associated with the need for GAVI funding will be developed as part of the investment case.

Risks along the time frame

Vaccine development, licensing, and prequalification by WHO: As the two vaccine candidates are currently in late-stage development, a number of prerequisites for eventual use and purchase of the vaccines must be met, including the availability of the efficacy and safety data for the products, licensure by NRA, and prequalification of the products by WHO. Plans are in place to meet these prerequisites; however, at this point in time, unanticipated problems in any of the steps could arise.

Price negotiation: In order for the PAHO Revolving Fund to agree to purchase rotavirus vaccines on behalf of its member countries, an affordable price consistent with sustained use of the vaccine must be negotiated with the manufacturer.

Support for rotavirus vaccine in LA is consistent with GAVI/VF funding principles

Respond to the needs and priorities that governments have themselves defined, be funded directly through them, and be cost-effective and within a country's ability to maintain and sustain: Countries in LA have initiated activities preparing the way for the introduction and use of rotavirus vaccines in the region. For example, on the occasion of the recent 6th International Rotavirus Symposium, representatives from most LA countries signed a declaration that included the following statement: "Urge PAHO and the Revolving Fund to acquire rotavirus vaccines by working with other organizations like GAVI and the manufacturers and to assist their introduction when available at prices accessible to countries in the region."

During their recent meeting, the PAHO Technical Advisory Group and Inter-country Coordination Committee made a series of recommendations relating to rotavirus vaccines for LA, including accelerating rotavirus epidemiology studies in the region, standardizing cost-benefit and cost-effectiveness methodologies, and convening a meeting of the Ministers of Health and Finance to discuss the economics of rotavirus vaccine introduction. Similar recommendations were put forth at the recent meeting of the Caribbean EPI Managers.

Once certain criteria are met for the current late-stage vaccines (e.g., availability of appropriate efficacy and safety data, WHO prequalification, negotiation of an affordable price), it is anticipated that the purchase of these vaccines for use in the public-sector EPI program in LA will be implemented through the PAHO Revolving Fund. It is imperative that any support from GAVI for the purchase of rotavirus vaccines be consistent with the operating principles and legal requirements governing the PAHO Revolving Fund, as is currently the case in GAVI/VF support to Guyana and other countries.

LA has been at the forefront of developing countries taking strong, sustainable immunization decisions. History in LA reflects that countries will not introduce a vaccine or strategy unless they can sustain it. Rotavirus will be no different.

Be time limited, flexible, and performance based: GAVI's support in LA will be time-limited and consistent with policies and procedures established by the GAVI Board. Countries will be challenged to prepare rigorous implementation and financial sustainability plans that take into consideration the time-limited nature of GAVI support. Lastly, countries in LA in the first phase of GAVI received very little support largely because of their excellent performance implementing new vaccines. Providing financial support for rotavirus vaccines is a means to recognize and encourage their continuing strong performance.

Contribute to the development of innovative models or approaches that can be applied more broadly: The Accelerated Development and Introduction Plan (ADIP) for Rotavirus Vaccines is working with countries and partners to support the development of an evidence base in LA relevant to national and regional decision-making. Examples include investments in examining rotavirus disease burden estimates, cost-effectiveness, and mortality rates in the region. In addition, the GAVI Rotavirus ADIP is participating in a partnership in Honduras including the government of Honduras, PAHO, CDC, USAID, and the Sabin Institute. If the decision is made to introduce rotavirus vaccines in Honduras, then this project will yield important information regarding the impact of a rotavirus vaccine in the context of a national EPI program. Taken together, the investments made by the GAVI's rotavirus ADIP should accelerate rotavirus vaccine use in the GAVI/VF-eligible LA countries.

Have an impact that goes beyond that of the immediate investment and be expected to substantially contribute to the achievement of global goals related to immunization including the MDGs: At present, there is considerably more efficacy and safety data available or planned for LA than for other regions of the world, including Asia and Africa. While efforts are underway to collect regionally appropriate efficacy and safety data for late-stage rotavirus vaccine candidates, it is anticipated that post-marketing vaccine impact (e.g., as part of the Honduras parternship project) and safety data the from GAVI/VF-eligible countries in LA will contribute to the global evidence base, thus improving the global understanding of vaccine as a means of controlling diarrheal disease.

GAVI's financial support for rotavirus vaccines in Latin America will provide an important signal regarding GAVI's commitment to these vaccines. This signal will be important for encouraging both GAVI/VF-eligible countries to begin planning for the introduction of rotavirus vaccines, as well as to other manufacturers engaged in or contemplating the development of rotavirus vaccines.

If GAVI can reduce global deaths attributable to rotavirus diarrhea through support of rotavirus vaccine use, first in LA and eventually worldwide, it will make a sizeable contribution to achieving the MDGs. As with other childhood immunization programs, rotavirus vaccination will also improve educational development and other related MDGs.

Help to further universal access to immunization and reduce inequities between and within countries: The experience with rotavirus vaccine use in LA countries will contribute to the eventual development of a GAVI investment case for the global use of rotavirus vaccines. In light of current projections for the availability of important data from Asia and Africa, significant investments of GAVI funding for non-LA countries are not anticipated until at

least 2008. Advancing the use of a rotavirus vaccine will significantly contribute to the global effort to effectively control diarrheal disease.

Be coherent with GAVI partners' individual institutional obligations and mandates: WHO and international partners have prioritized the use of rotavirus vaccines. The prioritization of rotavirus vaccines by GAVI is evidenced by the commitment of US$30 million to the GAVI Rotavirus ADIP.

GAVI Board Concept Paper

Introduction of a Meningococcal A Conjugate Vaccine in Sub-Saharan Africa
Prepared by the Meningoccocal Vaccine Program

Objective and Strategy: Based on experience in Africa and the stunning success of the meningococcal serogroup C conjugate vaccine in the United Kingdom, the meningococcal serogroup A conjugate vaccine should target two groups to achieve the greatest public health impact:

- Single dose mass immunization of all 1 to 29 year olds in meningitis belt countries (about 250 million persons) over a 10-year period.
- A two-dose EPI-based strategy in under ones with first dose at 13 weeks (same time as DTP3) and a second dose at 9 months (same time as measles) in all meningitis belt countries.

Burden of disease: Over the last ten years 700,000 cases of acute meningitis have been reported to WHO from African countries and 90 percent of cases have originated from the so-called "meningitis belt," a massive swath of sub-Saharan Africa from Senegal in the West to Ethiopia and Somalia in the East.

Likely impact of investment: Comprehensive use of a meningococcal A conjugate vaccine in 1 to 29 year olds will dramatically decrease carriage of serogroup A *N. meningitidis* and result in elimination of large epidemics due to this strain, preventing a conservatively estimated average of 70,000 cases per year and 5,700 deaths in epidemic years. The vaccine could also prevent thousands of cases of epilepsy, hearing loss, hemiplegia, mental retardation, or other permanent sequelae in meningitis survivors, thereby alleviating the sufferings of the victims and the social and economic burden imposed on their families and communities. Ongoing use in EPI programs will ensure that mortality and morbidity remain low relative to era of epidemics.

Cost effectiveness: Informal estimates relative to other existing vaccines suggest Men A conjugate will be cost-effective. However additional cost-effectiveness data would be developed to inform an investment case.

Estimated timeframe:

- Q1 2005 Start of phase I clinical trial of the Men A conjugate vaccine.
- Q4 2005 Start of phase II clinical trials in Africa.
- 2008-2009 Submission of the file for Indian licensure with a 1-29-year-old indication.

Risks along the timeframe: The major risks are the usual ones associated with developing a new vaccine, with the exception that a price and supply agreement has been negotiated with Serum Institute of India, Ltd., the vaccine manufacturer, in advance. Conjugate and meningococcal vaccines have been commercially available for decades and much is known about preparing such a product, suggesting this has a high likelihood of success within the estimated timeframe.

GAVI's mission is saving children's lives and protecting people's health through the widespread use of vaccines. Introduction of the Men A conjugate vaccine adheres closely with GAVI/Vaccine Fund principles to achieve this mission as summarized below:

1. Respond to the needs and priorities that governments have themselves defined, be funded directly through them, and be cost-effective and within a country's ability to maintain and sustain:

Epidemic meningitis is one of the most feared plagues in sub-Saharan Africa. Affected countries are very interested in implementing more effective preventive vaccines like a Men A conjugate vaccine. African ministries of health have given a clear message to the Meningitis Vaccine Project: "… develop a meningococcal conjugate vaccine at an affordable price and we will use it …"
African countries are already heavily invested in an epidemic response strategy that uses a polysaccharide vaccine for mass immunizations when epidemics occur. However, use of polysaccharide vaccines for preventive immunizations requires multiple doses and has not been successful. Because conjugate vaccines offer the opportunity for long-term protection after a single dose, African public health officials have been very interested in the development of the product. The Men A conjugate vaccine will be priced at about US$0.40 per dose, costing about the same as the currently available, but less effective, meningococcal A/C polysaccharide vaccine. Since most countries in the meningitis belt already purchase polysaccharide vaccine a significant portion of the vaccine purchase will be substitutive. It has been estimated that cost for mass campaigns is about US$1.00 per vaccinee to which the vaccine cost of US$0.40 is added.

2. Be time limited, flexible, and performance-based:
It is anticipated that GAVI support for a Men A vaccine would occur according to guidelines and standards established by the GAVI Board, as has been done with other vaccines in the past. Time-limited GAVI funding would be needed in two areas:

- Vaccine purchase in those countries that have not routinely purchased polysaccharide meningococcal vaccines.
- Funding of mass immunization campaigns of 1 to 29 year olds according to country plans and ability to implement such campaigns successfully. This “catch-up” campaign needs to be done once, and not at the same time in each country, to reap the important public health goal of decreasing carriage and increasing herd immunity.

3. Contribute to the development of innovative models or approaches that can be applied more broadly:
The development strategy for Men A is an innovative model that began with intensive consultations with African countries and WHO/AFRO. The model both began and has resulted in establishing a final price to countries of approximately US$0.40, and in addition has established product availability guarantees but no preestablished purchase guarantees. Collaborators working on Men A development have established an effective consortium that has successfully transferred fermentation, purification, and conjugation methods to a developing country vaccine manufacturer. The model could serve as a template for the development of other needed conjugate vaccines for poor countries.

4. Have an impact that goes beyond that of the immediate investment and be expected to substantially contribute to the achievement of global goals related to immunization including the MDGs:
The MDG goal is a two-thirds reduction in child mortality from baseline by 2015. A successful Men A conjugate vaccine will help achieve this goal in two ways:

- It will eliminate the most important cause of epidemic meningitis in sub-Saharan Africa. The considerable funds (national and donor) that are used to combat these epidemics will be available for other health interventions
- When meningitis epidemics occur virtually all preventive services cease in order to combat the meningitis epidemic. In short, routine immunization services cease and at risk populations from measles and other diseases increase.

5. Help to further universal access to immunization and reduce inequities between and within countries:
The proposed 2-prong strategy of catch-up campaigns with routine use in EPI promotes equitable access across populations within countries. Catalytic support from GAVI helps to ensure equity

across countries in the meningitis belt. Large Western vaccine manufacturers are currently developing expensive polyvalent (A/C/W/Y) meningococcal vaccines that are targeted for developed countries. The development model for a Men A conjugate vaccine will furnish a needed and desired product at a price that developing countries can afford to pay.

6. Be coherent with GAVI partners' individual institutional obligations and mandates:
There is broad support for the development of a Men A conjugate vaccine for sub-Saharan Africa. WHO, as a Meningitis Vaccine Project partner with PATH, has been involved at every step of the project and is committed to the initiative. An MVP Project Advisory Group that reports to the AFRO Division of Communicable Disease Prevention and Control meets regularly and is involved in advancing the project and providing key Africa-specific advice to MVP as the project moves from a product development to an introduction phase. The project enjoys broad support in African ministries of health and local WHO offices. Support from Médecins sans Frontières, USAID, the Pasteur Institute, and Association pour l'Aide à la Médecine Préventive has been assured, and the project is developing a plan to collaborate more closely with other key introduction partners such as UNICEF and the World Bank.

Global Alliance for Vaccines and Immunization (GAVI) Board Concept Paper
Introduction of a Japanese Encephalitis Vaccine in Asia
Prepared by PATH

Background

Objective and strategy: The objective of JE vaccination is to control clinical disease, thus avoiding death and disability caused by JE infection. The strategy is through a one-time preventative campaign in the at-risk age group (1 to 15 years old) in high-risk areas followed by routine immunization in EPI. This strategy is the same as the World Health Organization (WHO) strategy used to control yellow fever, which is also a mosquito-transmitted Flavivirus. One JE vaccine used by some countries in Asia is believed to provide essentially life-long protection with a single dose, at a price on the order of US$.50 to US$1.50 per child.

Burden of disease: Japanese encephalitis has been reported in 15 of the 74 GAVI Vaccine Fund (GAVI/VF) eligible countries. JE affected countries account for 68 percent of the total birth cohort of GAVI/VF-eligible countries. However, as JE is a disease of the rural poor with distribution primarily in rice growing areas where pig rearing also occurs this likely over represents the true number of infants and children to be vaccinated. We can estimate the population at-risk by looking at the rice growing areas in JE affected areas (Table 1).

JE is a WHO reportable disease, but it is believed to be severely under-reported. Annually, 30,000 to 50,000 cases are reported to WHO; however, if we extrapolate from the incidence rate calculated during vaccine trials in Thailand and China, the number would be much higher. Assuming the lowest incidence rate for the 1 to 15 year age group in at-risk areas of GAVI/VF-eligible countries, approximately 100,000 cases would be expected annually without intervention. Case fatality rates and long-term disability rates also vary significantly in the literature, but an average would be approximately 70 percent of children either dying or with a serious long-term disability.

Table 1. JE at-risk population in GAVI/VF-eligible countries

	Estimated number of countries	Birth cohort (1,000)	< 15 years of age (1,000)
Countries with partial vaccination**	4	6,000	98,860
Countries considering vaccination	2	13,954	185,290
Countries needing further data or assistance	9	12,246	171,845

** Assuming a pre-existing 50 percent vaccine coverage

Likely impact of investment: Impact of investment would allow the JE affected countries that have not had access to vaccine to integrate it into their immunization programs. Using the above estimates, vaccination could avert approximately 76,000 cases annually (assuming 80 percent coverage and 95 percent efficacy) with 53,200 cases that would lead to death or disability.

Cost effectiveness: Two studies (in Thailand and China) have documented that JE vaccination is not only cost-effective, but cost-saving due to the severity of the disease with long hospitalizations and high rates of morbidity and mortality. Additional preliminary work in India using reported figures for disease incidence produce similar results.

Estimated timeframe: The live attenuated vaccine from China has been used since 1988 and administered to more than 200 million children in China. It is produced by three main Chinese manufacturers and licensed in three countries (China, South Korea, and Nepal) with a preliminary

license in a fourth (Sri Lanka). An independent team of experts has evaluated a Chinese producer in 2004 and recommended, consistent with manufacturer plans, submission of a complete file for WHO pre-qualification in 2005. WHO has reported a two-year waiting list for new pre-qualification submissions; however, there are no currently pre-qualified JE products suggesting this might shorten the review timeline.

A second JE vaccine is under development by Acambis Ltd (United Kingdom). It is in Phase II trials now and will be entering Phase III trials in 2005. The manufacturer has affirmed its commitment to provide vaccine to both developed and developing countries.

There is a JE vaccine produced in Japan used widely in the developed world and some developing countries (e.g., Thailand), but it requires multiple doses and boosters, has had issues with side effects, and has cost an estimated US$15 per child. It is not a viable product for GAVI/VF consideration.

Risks along the timeframe: China has not yet exported a WHO pre-qualified vaccine. However, the Chinese and South Korean national regulatory authorities are both considered functional by WHO.

Risks associated with the Acambis product are typical of those for a product at Phase II and Phase III stage of development.

Introduction of a Japanese encephalitis vaccine in Asia adheres closely to GAVI/VF principles:

Responding to the needs and priorities of governments. JE disease has had very little support from the international community. All countries that have recognized JE have worked to control it using their own national budgets; this is evidenced by the four GAVI/VF-eligible countries currently using a JE vaccine and two countries that were using vaccine but have had to discontinue use due to cost of the inactivated vaccine. JE is widely feared in communities and outbreaks routinely garner political and media attention due to the public outcries. Often this leads governments to implement costly but relatively ineffective control measures such as spraying houses or killing pigs.

Since the onset of GAVI many countries have asked why there is no support for JE vaccine, as there is for yellow fever and Hib in Africa. GAVI consideration of JE vaccine support would be in direct response to countries' requests. In search for support, the GAVI Regional Working Groups in Asia formally submitted on behalf of the countries a request to the former GAVI R&D Task Force for support for JE vaccine development. This need has been partially addressed through partner activities and the new JE Project at PATH. A highly efficacious, single-dose vaccine given at the same time as measles vaccine for approximately US$1 responds to the call from countries and creates a very strong scenario for sustainability.

Be time limited, flexible, and performance-based: Support from GAVI for JE would be fully compatible with GAVI's performance-based and catalytic approach, and consistent with GAVI's application and criteria based application mechanism. Supporting countries to plan and implement in a manner best integrated with their national priorities would maximize public health impact. Phased-out support, with clear sustainability planning in advance of an application would ensure that GAVI's support for routine immunization activities would also be time-limited. Current country commitments to vaccination and other less-effective control strategies reflect the ground swell of commitment from countries for JE control.

Contribute to the development of innovative models or approaches that can be applied more broadly: A key innovation that JE brings is a strong integration of different parts of the government towards shared objectives, including those working on health/immunization, vector borne diseases, environmental issues, and even farming (due to rice and pig relationship to JE). The use of targeted campaigns with the integration of JE vaccine into EPI could have impact on other future projects and programs that will likely need to use similar techniques such as meningitis, malaria, and dengue.

Having an impact that goes beyond the immediate investment and substantially contribute to the achievement of global goals related to immunization including the Millennium Development Goals (MDGs): Successful JE immunization will have impact, help meet global immunization goals, and help meet the MDGs in two ways:

- Global objectives and MDG goals of reducing extreme poverty by half will be impacted by JE vaccination. JE is the leading viral cause of disability in Asia, which makes a large contribution to the ongoing poverty cycle. Sixty-eight percent of the world's poorest children are born at risk for JE infection.
- The absolute number of cases of JE is not high, relative to some other diseases, but JE will contribute to achieving the two-thirds reduction in under-five mortality called for in the MDGs. Lastly, JE is an emerging infection with an increasing population at-risk.

Help to further universal access to immunization and reduce inequities between and within countries: JE is a feared disease in countries where it is recognized. As such, the demand for vaccine has been high where it has been introduced. JE will be integrated into EPI with measles, which is not perceived to be as severe a disease. Therefore it is possible the fear of JE and demand for vaccine could increase measles coverage. JE vaccine support could also decrease the inequities between countries as vaccine is currently distributed along economic lines. For example, the vaccine is available to Japan, Taiwan, South Korea, and Thailand, yet Myanmar, Bangladesh, North Korea, and Nepal do not have access.

Consistency with GAVI partners' individual institutional obligations and mandates: Control of JE through immunization is consistent with GAVI and GAVI partner goals of providing lifesaving vaccine to children in the developing world. Already there is a JE Core Working Group that has been functioning for two years as a group of interested parties at regional and global levels to help support JE control. The group includes the United Nations Children's Fund, WHO headquarters and regional offices, the International Vaccine Institute, the U.S. Centers for Disease Control and Prevention, and PATH. The demand for JE vaccine is being communicated directly from countries. Responding to this call is part of each of the GAVI partner's mandates.

GAVI Board Concept Paper
Rubella Vaccine Introduction and Control of Rubella in Eligible Countries
Prepared by CDC

Rubella, usually a mild rash illness, may result in devastating consequences when a pregnant woman is infected, particularly in the first trimester of pregnancy. These may include miscarriages, stillbirths and infants born with a constellation of birth defects known as congenital rubella syndrome (CRS) including cataracts, hearing impairment and heart defects. Globally, it is estimated that more than 100,000 infants are born each year with CRS. Cost analyses conducted in Guyana and Barbados estimate that the lifetime cost of treating an infant with CRS ranges from US$50,000-63,000. Cost-benefit studies in developing countries (Guyana, Barbados, and English-speaking Caribbean Countries) with routine vaccination coverage of $\geq$80% have demonstrated that rubella vaccination is cost saving, particularly when combined with measles vaccination. Rubella vaccine may be administered as a single antigen, but is preferably given in combination with measles – (MR) or measles and mumps vaccine (MMR).

In 2002, 124 (58%) of WHO reporting countries/territories were using rubella vaccine in their routine immunization services. When countries are compared by economic status, only 76 (48%) of the 159 developing countries have incorporated rubella into their national program, compared to 100% of developed countries, and 71% (21 of 28) countries in economic transition. The poorest countries, including most that are eligible for GAVI support, are the least likely to have incorporated rubella vaccine into their immunization programs.

To achieve rapid and sustained rubella control, several strategies are used: 1) introduction of rubella vaccine into routine infant schedule, preferably as combined MR or MMR vaccine; 2) catch-up campaigns in children aged 1-15 years to achieve rapid population immunity and/or 3) vaccination of older adolescent and young adults either through routine services or a campaign to reduce susceptibility in child-bearing age women. The use of catch-up vaccination campaigns to achieve rapid population immunity is similar to the strategy to achieve measles control currently supported by GAVI. If vaccination coverage is low in a childhood program, this may result in increasing the susceptibility in the adult population, thus increasing the risk of rubella in women of childbearing age and of CRS in their infants. Therefore, countries that introduce rubella-containing vaccine into their childhood program should have already achieved and be able to sustain high coverage in this population.

It is proposed that GAVI provide support to eligible countries to introduce rubella vaccine and achieve rapid decrease in rubella virus circulation and incidence of CRS, using the strategies described above. Countries that have not introduced rubella vaccine and have sustained high measles vaccine coverage will be targeted. Use of combined MR vaccine will be supported both for routine infant vaccination and catch-up campaigns where appropriate, to greatly reduce the circulation of both measles and rubella at relatively low incremental cost.

The proposal is consistent with the GAVI principles of front-loading, utilizing national introduction of rubella vaccine (as MR or MMR) and campaigns to achieve rapid population immunity that would lead to rubella control and decrease in CRS. Support of rubella immunization as MR vaccine would generate a larger market for combined MR vaccines, potentially increasing the number of manufacturers and decreasing the cost of the vaccine. GAVI support would also increase equity in global immunization, bringing rubella vaccine to the poorest countries, and potentially catalyze increased support for global rubella control, further diminishing disease burden. Support for rubella control is likely to be less costly than support for other new or underutilized vaccines, as rubella vaccine is inexpensive, even combined as MR ($0.44/dose as MR UNICEF). If given as MR vaccine either through routine or campaign, there is no additional cost for administration, injection materials and no additional injection safety risk.

The GAVI investment would achieve global immunization goals of reducing the burden of a devastating lifetime birth defect that still occurs mainly in the poorest countries. The impact would be measured by monitoring the vaccination coverage (routine and by campaigns), through surveillance for measles/rubella (febrile rash illness surveillance) and CRS surveillance. Measles/rubella surveillance,

currently being enhanced in measles control projects, would further promote strong field and laboratory surveillance capabilities in countries.

Key challenges would include defining the thresholds for immunization programs to introduce rubella vaccines (i.e. sustained measles vaccine coverage above 70 or 80%), and the key strategies to incorporate into each country's rubella control program. It is expected that about 1/3-1/2 of GAVI eligible countries would be eligible for rubella vaccination support using the first criterion.

Concept Paper to GAVI Board
HPV Vaccine
Submitted by PATH

Objective and Strategy

Human Papillomavirus (HPV) vaccines will be commercially available in developed countries within two years. Accelerating access to these vaccines in the developing world through systematic introduction in four to six early adopter countries will be an important contribution to reducing the burden of HPV disease and its sequelae—most importantly cervical cancer—in developing countries. Further, HPV vaccine will be delivered to adolescents—with a focus on adolescent girls—and therefore will extend vaccination programs to this important, often underserved population.

Burden of Disease

HPV is the primary cause of cervical cancer. Six types of HPV account for about 85 percent of cervical cancer cases worldwide; two of these types—16 and 18—account for 70 percent of cases.[1] HPV results in almost 500,000 cervical cancer cases each year and over 270,000 deaths.[2] The developing world—where cervical cancer commonly is the leading cause of cancer death among women—accounts for about 85 percent of the burden of disease. The high prevalence of HPV infection, combined with lack of effective cervical cancer prevention programs in poorer countries, is the cause of this burden of disease inequity between developed and developing countries.[3]

Likely Impact of Investment

Research to date suggests that vaccines against HPV—when administered to young adolescent girls in a three-dose regimen—are likely to be highly effective in preventing type-specific HPV infection and its most serious long-term sequelae: high-grade cervical dysplasia and cancer. Preliminary data suggest that an HPV 16 vaccine is at least 95 percent effective in preventing persistent HPV 16 infection and 100 percent effective in preventing type-specific cervical intraepithelial lesions (based on 40 month follow-up).[4] Decision-science modeling suggests that an HPV 16/18 vaccine—if 98 percent effective at preventing persistent HPV infection and administered to adolescent females before the onset of sexual activity—would reduce the total burden of cervical cancer by 51 percent over several decades.[5] At a recent meeting on HPV infection and cervical cancer prevention (EUROGIN, Nice, October 21, 2004), Dr. Peter Boyle, Director of the International Agency for Research in Cancer, reported that, if current trends continue, there will be over one million new cervical cancer cases occurring each year by the year 2050, with the vast majority occurring in developing countries. Therefore, broad-scale access to an HPV vaccine could reduce cervical cancer cases by 500,000 each year within that time frame. Access to vaccines, combined with continued strengthening of simple, evidence-based screening and treatment approaches, has the potential to bring developing-country cervical cancer rates down to the levels currently observed in many developed countries.

Cost-Effectiveness

Cost-effectiveness estimates for HPV vaccine primarily have focused on hypothetical developed-country populations, where screening and treatment programs are well established and effective.

---

[1] Muñoz N, Bosch FX, Castellsague X, et al. Against which human papillomavirus types shall we vaccinate and screen for? The international perspective. *International Journal of Cancer*. 2004;111(2):278–285.

[2] Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5, Version 2.0. Lyon, France: IARC*Press*; 2004.

[3] Herdman C, Sherris J. Planning Appropriate Cervical Cancer Control Programs. 2nd ed. Seattle: PATH; 2000.

[4] Mao C. Presentation on HPV vaccine findings at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, November 1, 2004, Washington, DC. Article available at: www.nlm.nih.gov/medlineplus/news/fullstory_20996.html.

[5] Goldie SJ, Kohli M, Grima D, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *Journal of the National Cancer Institute*. 2004;96(8):604–614.

Even in these settings, studies suggest that HPV vaccine could be a cost-effective health intervention.[5,6] In developing-country settings, where broad-reaching screening and treatment programs are largely non-existent, the cost-effectiveness equation will be different; work is ongoing at Harvard University and elsewhere to develop natural history models that can estimate the impact and cost-effectiveness of developing-country HPV vaccine programs.

Estimated Timeframe

Currently, two L1 VLP vaccines against HPV are in late stages of development: one vaccine against types 16 and 18 (GlaxoSmithKline) and the other against types 16 and 18 plus two HPV types associated with genital warts—types 6 and 11 (Merck and Co., Inc.). The status of these vaccines is described below. It is anticipated that the first product could be submitted for WHO prequalification in 2006.

Company	Vaccine type	HPV types	Status	Study characteristics
Merck & Co., Inc.	L1 VLP based on recombinant yeast technology	16, 18, 6, 11	Phase III underway; regulatory submissions expected late 2005; expected launch 2006	Enrolled 23,000 women and children to date in North America, Latin America, Europe, Southeast and East Asia, Australia, and New Zealand
GlaxoSmithKline (GSK)	L1 VLP (Cervarix™) based on recombinant baculovirus technology	16, 18	Phase III underway; expected launch recently moved up to 2006	15,000 women aged 18–25 in Costa Rica (run by NCI); 13,000 women aged 15–25; multicenter representing four continents

Risks

Risks faced in achieving the potential for HPV vaccine to reduce cervical cancer include the following:

- **Timing**. Providing global demand estimates to industry in a timeframe that they can adjust manufacturing capacity and marketing plans to meet developing-country demand.
- **Pricing strategy**. Price-volume negotiations have not begun with industry. Any future GAVI/VF commitment would likely outline parameters and criteria in advance of committing to actual purchase on behalf of a country.
- **Reaching adolescents**. Identifying service delivery approaches that reach adolescent girls (and perhaps boys) in countries where this population has little access to health services.
- **Policy barriers**. An HPV vaccine program will not produce measurable reductions in cervical cancer mortality for several decades. Further, some questions about the vaccine—e.g., duration of protection—remain unanswered. Therefore, securing "buy-in" from country policy makers could be challenging.

Alignment with GAVI/Vaccine Fund Principles

HPV vaccine aligns with GAVI's overall objective of saving children's lives and protecting people's health through the widespread use of vaccines, at the same time reflecting a new direction for immunization programs.

1. Respond to the needs and priorities that governments have themselves defined, be funded directly through them and be cost effective and within a country's ability to maintain and sustain.

[6] Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA.* 2003;290(6):781–789.

For the past five years, the Alliance for Cervical Cancer Prevention (ACCP) has explored strategies for screening and treating women in developing countries for precancerous cervical lesions. This work has reached some developing 50 counties and has raised awareness of—and demand for—cervical cancer prevention services around the world. The ACCP also has provided a unique platform to address the policy, logistic, clinical, financial, and sociocutural issues that will influence introduction of an HPV vaccine. Countries are searching for means to prevent cervical cancer deaths, and there is evidence to suggest that both traditional immunization systems and systems focused on adolescent and maternal health will seek strategies to launch and sustain an HPV vaccine program.

2. Be time limited, flexible and performance-based.

The support from GAVI/VF would be implemented according to GAVI Board policy and procedures. While research is ongoing, it is anticipated that vaccination (through a three-dose protocol) will likely be sufficient to provide long-term protection. Therefore, GAVI/VF support could include time-limited catch-up activities, after which vaccine could be provided through routine systems with GAVI/VF resources phasing out. It will be important for GAVI's support to allow countries some flexibility in delivering HPV vaccine, so that innovative delivery strategies to best target adolescent can be verified.

3. Contribute to the development of innovative models or approaches that can be applied more broadly.

The HPV vaccine delivery strategy, with its focus on adolescents, will provide an important platform for delivering vaccines and other health services to adolescents in developing countries. In many regions, adolescent girls face a range of reproductive health risks, including HIV and other sexually transmitted infections, gender-based violence, as well as HPV infection. Developing effective, sustainable delivery systems to reach this population will have positive health implications far beyond reducing risk of cervical cancer.

4. Have an impact that goes beyond that of the immediate investment and be expected to substantially contribute to the achievement of global goals related to immunization including the MDGs.

Women are the foundation of families in many societies, and drivers of economic growth that is essential to development. Loss of women in their late 30s, 40s, and 50s impacts the health and development of societies, from education to child health to poverty and economic growth. The growing HIV epidemic increases the responsibilities of these women in many countries, where they often are caring for ill family members and their orphaned grandchildren. The MDGs directly impacted by a decrease in deaths due to cervical cancer include MDGs 2, 3, and 4.

5. Help to further universal access to immunization and reduce inequities between and within countries.

HPV vaccine will be introduced in developing countries within two years. There is a substantial market in the developed world, and it appears likely that Western women will have broad access to the vaccine before the end of this decade. Yet the burden of disease from HPV infection falls heavily on women in the developing world, and particularly the poorest women in this region. Accelerating access to HPV vaccine throughout the developing world will be an essential step towards bringing cervical cancer death rates to levels comparable to those found in much of the Western World. GAVI's support for immunization to all age groups, as reflected in its mission, would be highlighted by opening a new and much needed scope for support to adolescents.

6. Be coherent with GAVI partners' individual institutional obligations and mandates.

A number of GAVI partners (e.g., WHO, UNICEF, and the Bill & Melinda Gates Foundation) have addressed the importance of reducing cervical cancer deaths and planning for HPV vaccine introduction in strategic and/or planning documents. Further, other key agencies—including the World Bank—are working to support cervical cancer prevention programs at the country level. One of the unique elements of an HPV vaccine is the potential for new partners to be brought in to support GAVI, including UNFPA, major international medical organizations that focus on the health of women (e.g., FIGO), and international and national cancer prevention institutions. Engaging this broader array of stakeholders could contribute to strong immunization programs aimed at young adults and women, and ultimately lead to improved health systems and health outcomes.

Submitted by the Pneumo ADIP

Dr. Tore Godal
Executive Secretary
Global Alliance for Vaccines & Immunization
Geneva, Switzerland
November 16, 2004

Dear Dr. Godal,

S. pneumoniae (ie, pneumococcal) infections are the leading cause of vaccine-preventable deaths worldwide – WHO currently estimates that ~1,600,000 persons die each year from pneumococcal pneumonia and meningitis, about ½ of whom are children <5 years old. A safe, effective pneumococcal conjugate vaccines containing 7 serotypes is currently available and routinely used for infant immunization in industrialized countries. In the United States, where this pneumococcal conjugate vaccine has been routinely used since 2000, childhood immunization has nearly eliminated pneumococcal disease due to vaccine serotypes among children and through 'herd immunity' it has significantly reduced the incidence of pneumococcal disease and mortality among adults.

One efficacy study from South Africa has shown a high degree of efficacy in preventing severe pneumococcal infections in both HIV-infected and –uninfected infections. Results of a second randomized trial from a high mortality rural area of The Gambia are expected by March 2005. Thus, by mid 2005, we expect to have a situation where the value of pneumococcal conjugate vaccination is well-established in Africa and where the vaccines are routinely used in industrialized countries. As they become aware of this information we anticipate that there will be substantial interest from Vaccine Fund-eligible countries regarding what GAVI is doing to make these new, life-saving vaccines available to them.

Currently, there is one licensed pneumococcal conjugate vaccine (Prevnar, Wyeth). Limited supplies of this vaccine as early as 2005 or 2006 are possible. This 7-valent vaccine is an interim solution at best for developing countries. The 7 serotypes included in this vaccine cover ~50-60% of strains causing disease in many developing countries but this formulation does not include serotypes 1 and 5, which are important causes of severe disease in developing countries. By as early as 2008, we expect one other major manufacturer to license a global formulation of pneumococcal conjugate vaccine (an 11-valent vaccine including serotypes 1 and 5). By 2010, we expect to have at least 2 and possibly 3 manufacturers of 11-13 valent vaccines. And by 2016, we believe that emerging market manufacturers can be important suppliers and help to bring about price maturation and with it an affordable, sustainable supply of quality vaccines.

I understand that the GAVI Board intends to request an investment case for rotavirus vaccines by July 2005. In light of the important disease burden, established efficacy of the vaccines, and the possibility to procure vaccine as early as 2008, we wish to convey the intention of GAVI's PneumoADIP to submit an investment case on behalf of pneumococcal conjugate vaccines at the same time as rotavirus.

I hope that you will share this letter with the GAVI Board and that we will be invited to submit an investment case along with rotavirus and any other new vaccines that GAVI may consider supporting.

If you have any questions or comments regarding this letter, please do not hesitate to contact me.

Sincerely yours,

Orin S. Levine, PhD
Executive Director, GAVI's PneumoADIP
Associate Professor, International Health
Johns Hopkins Bloomberg School of Public Health

GAVI Board Concept Paper
Investment Case Initiative for Technologies that Support Immunization
Submitted by PATH

Strategy: Vaccine-related technologies have the potential to significantly extend and improve the impact of immunizations by making them safer, more economical, more efficient, and more effective. For example, the fragility of vaccines, inadequate or damaging refrigeration, unsafe injections, and unsafe disposal practices are all problems that threaten the efficiency and effectiveness of immunization and other health programs. As new and more expensive vaccines become available, the cost and impact of these problems will only be exacerbated. Investments in vaccine-related technologies should be considered necessary and complementary to vaccines themselves in order to achieve GAVI's intended public health impact.

Vaccine-related technologies will be available at different times. Some of these solutions, such as vaccine stabilization, are only in the discovery phase, with timelines of 10-15 years. At the same time, some technologies related to immunization systems, such as the cold chain or injection delivery, are currently (or nearly) available, and can swiftly and effectively enhance the benefit of vaccines today.

Extent of problem: The problems facing immunization programs today are measurable and significant. We have estimated that approximately 374 million vaccine doses were compromised due to heat or freeze damage in 2004. In the same year, the Safe Injection Global Network (SIGN) estimates that approximately 5 billion injections, or almost 30% of the total 17 billion curative and immunization injections administered in developing countries, risked cross-infection with HIV, Hepatitis B, and/or Hepatitis C.

Process to select technologies for investment cases: Criteria have already been developed to help GAVI evaluate and select vaccine investments. However, these criteria need to be adapted for vaccine-related technologies. In comparison to vaccines, the benefits for vaccine-related technologies are more indirect, can be more difficult to calculate, and therefore are harder for countries to value. For example, the current investment case framework measures impact in disability-adjusted life years (DALYs). This is a more straightforward estimate for vaccines, but not for evaluating systems or technologies, since technologies tend to work in conjunction with vaccines to reduce DALYs. Therefore, we suggest that technology investments may have some different criteria for evaluation, and that vaccine-related technologies should not be directly evaluated against vaccines for investment decisions.

PATH has been asked by the Bill and Melinda Gates Foundation (BMGF) to assist in developing criteria for the selection of vaccine-related technologies through consensus from key stakeholders. Suggested criteria include the seriousness of the problem that the technology is designed to address; the value the technology brings in terms of reduced cost to the immunization system; increased efficiency; increased safety and/or improved effectiveness; the potential for sustainability; and the likelihood of success in the GAVI investment context. Stakeholders will be contacted to obtain agreement on a short-list of technologies that meet the criteria. Also, with input from key stakeholders, the current GAVI investment case framework will be evaluated and adapted for technologies. Investment cases will then
be submitted to GAVI for selected technologies.

Timeline:

By December 31, 2004:	***Criteria finalized to select technologies***
	Landscape of technologies compared to criteria
	Selected technologies invited to develop investment case
By January 31, 2005:	***Investment case guidelines adapted for technologies***
By July 1, 2005:	***Investment cases submitted for GAVI review***