

Global Plan of Action for New and Under-Utilized Vaccines Implementation: 2010-2011

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Executive Summary

Building on the successes of routine immunization programmes in countries, the wide-spread use of new and under-utilized vaccines has the potential to contribute significantly to Millennium Development Goal 4 of reducing global childhood mortality by two thirds by 2015. To enable countries to make rational, evidence-based decisions when they are choosing whether to implement new vaccines and technologies, it will be valuable for them to have information on disease burden, vaccine product characteristics, planning, financing and delivery methods, the cost-effectiveness and affordability of various strategies and the potential of integrating vaccines into broader approaches to disease control.

The original objective of the Global Plan of Action for the Introduction of New and Under-Utilized Vaccines was to provide a dynamic framework for global partners to prioritize the most immediate requirements for introducing new and under-utilized vaccines. As these included many areas not necessarily within the purview of WHO, it was hoped that, based on their comparative strengths, partners would support and complement WHO's work to ensure the efficient introduction of new vaccines. This document has evolved as a programmatic overview of all activities required for the successful introduction of new vaccines and is therefore a "living" document that is to be updated annually.

The following narrative part of the Plan of Action provides descriptions of the six Work Areas under which the activities to be undertaken fall as well as current status and issues to be addressed for the seven new vaccines currently viewed as those most needed in developing countries:

- I. Norms and Standards
- II. Country Decision Making
- III. Planning, Financing & Procurement
- IV. Vaccine Delivery
- V. Integrated Approaches
- VI. Monitoring and Surveillance

Background

Launched in 1974, the Expanded Programme on Immunization (EPI) was first designed to deliver vaccines against diphtheria, tetanus, pertussis, polio, measles and tuberculosis (BCG). Together, these vaccines prevent close to 2.5 million deaths every year.

Recent years have seen a dramatic increase in the implementation of new and under-utilized vaccines providing additional prevention of untimely deaths and disabilities. These include vaccines against hepatitis B, Haemophilus influenzae type b (Hib), Streptococcus pneumoniae (pneumococcus), rotavirus, and rubella.

Other vaccines against a number of important public health problems have now been developed or have been improved. Vaccines against human papillomavirus (HPV) provide an opportunity to reduce global cervical cancer morbidity and mortality through immunization activities in older age groups. Widespread use of vaccines of regional importance, such as those against Japanese Encephalitis, epidemic meningococcal meningitis, yellow fever, and typhoid could further decrease disease burden in some of the poorest countries of the world.

Addition of new vaccines to routine immunization schedules requires several critical issues to be addressed at the country level. These include: decision-making and prioritization of these vaccines for use; addressing the weaknesses in the immunization system to absorb these new vaccines and ensuring equitable distribution; creating long term plans to ensure sustainable use of the vaccines; and placing these vaccines within the broader context of disease prevention and control, by simultaneously scaling up the use of complementary disease controls strategies.

Building on the successes of routine immunization programmes of countries, wide-spread use of new and under-utilized vaccines has the potential to contribute significantly to the Millennium Development Goal 4 of reducing global childhood mortality by two-thirds by 2015. To enable countries to make rational, evidence-based decisions when they are choosing whether to implement new vaccines and technologies, it will be valuable for them to have information disease burden, vaccine product characteristics, planning, financing and delivery methods, the cost-effectiveness and affordability of various strategies and the potential for integrated approaches to disease control.

The Role of Partners

WHO's mandate in immunization is to provide independent, technical guidance on all aspects of immunization to its Member States. As an increasing number of new vaccines and more complex vaccine presentations and delivery strategies become available, capacity to provide technical guidance on a broad array of issues is required. Examples of needed support include normative guidance related to vaccine product development, production and regulation; policy advice for the use of vaccines of public health importance; technical support for decision-making at national level and for the actual introduction of the vaccines into immunization programmes; and technical support for disease surveillance as well as in the monitoring and evaluation of immunization activities.

UNICEF's collaboration has been key in all aspects of new vaccine introduction, but especially so in the supply and procurement of vaccine, technical assistance in the areas of vaccine management and cold chain and logistics, and with the advocacy and communication required to ensure the acceptability of these vaccines in the community.

In addition to the work of WHO and UNICEF, substantial and critical contributions come from partner agencies and organizations such as PATH, the International Vaccine Institute (IVI), the World Bank, the U.S. Centers for Disease Control (CDC), Johns Hopkins University, the London School of Hygiene and Tropical Medicine, Aga Khan University, and the University of the Witwatersrand, to name but a few.

The Global Alliance for Vaccines and Immunization (GAVI Alliance) has, since 2000, greatly facilitated the introduction of new vaccines in the 72 poorest countries in the world.

The U.S. Centers for Disease Control (CDC) as a technical partner of WHO, contributes not only its technical and scientific expertise in a number of areas including surveillance, impact evaluation, and capacity building, but also through human and financial support to WHO for it to carry out its work.

The continued involvement of all the partners will be crucial for the success of new vaccine introduction.

Work Area I Norms and Standards

Over time, an increasing number of vaccine formulations and presentations have become available: different combinations of antigens; different formulations of vaccines (lyophilized, liquid or a combination of both); different methods of vaccine administration; and different vaccine presentations (single or multi-dose vials, pre-filled syringes, mono-dose injection devices), with different packaging. As new vaccines are developed, choices will need to be made on the optimal formulations and presentations for use in the respective national programmes. To assist this process, a "Vaccine Product Menu" is being developed to address all programmatic issues and product characteristics for all WHO pre-qualified vaccines.

Through the development of guidelines and manuals on vaccine characteristics and implementation issues, WHO, UNICEF and their partners assist countries with decisions related to vaccine availability and supply.

WHO headquarters, regional and country counterparts are involved in activities to ensure the quality and safety of new vaccines. These activities include developing new regulatory pathways, strengthening of National Regulatory Agencies and their collaboration with National Immunization Technical Advisory Committees and streamlining the vaccine prequalification process to ensure programmatic suitability of vaccines.

Work Area II Country Decision Making

Past country experiences with introducing new vaccines have made it apparent that deliberations about incorporating a new vaccine into a national immunization schedule are influenced by multiple factors.

EPI vaccines are considered to be among the most efficient uses of scarce health care resources. Decision-makers will need information, among other things, on their affordability and relative cost-effectiveness to determine the value for money of new vaccines. The availability and awareness of disease burden is important and global burden of Hib and *Streptococcus pneumoniae* disease and mortality estimates for the year 2000 were published in 2009. Other important considerations for introducing new vaccines are availability and price of vaccines, and safety and suitability of available vaccine products for national programmes.

To assist countries with preparing for and evaluating such decisions, the global immunization partners provide a range of tools and information to national policy makers and programme managers. WHO is in the process of revising the generic framework that discusses the multiple dimensions to consider for making informed decisions for introducing a new vaccine. Several vaccine and product specific guidelines have also been or are being developed to facilitate introduction. Position papers are available for several new vaccines (Hib, Pneumococcal, Rotavirus, HPV, Typhoid, Cholera) and are being updated as new findings are made apparent. A tool to conduct post-introduction evaluations as well as one to support cold chain assessments to prepare countries for the increased space that will be required by the addition of new vaccines are also being finalized this year.

To date, WHO and partners' activities for new vaccine introduction have focused on strengthening national decision making processes through providing technical information packages, promoting the establishment and strengthening the capacity of national immunization advisory bodies, and providing models and estimates of cost-effectiveness to allow prioritization of vaccine introduction. Further activities encompass the functions of policy advice, process guidance, other quantitative assessment, experience sharing and planning. WHO is currently revising and integrating the Vaccine Introduction Guidelines and the Vaccine Product Menu into one resource covering updated policy and programmatic aspects to introducing new vaccines. The need to make important decisions about the use of new vaccines vis-à-vis other health interventions provides an excellent opportunity for countries to consider the use of broader advisory committees to deliberate and address strategic issues and health priorities. These activities are important for a middle-income country strategy as well, though they should be carefully tailored to meet the different needs of the individual members of this group of countries.

Following the publication of the GIVS, WHO, UNICEF and their partners recommended that national programme managers attempt to consolidate existing plans for their multiple immunization objectives into a single document that includes an evaluation of the costs and financing of that plan. Comprehensive multi-year plans (cMYP) are also proposed as a mechanism to involve all relevant national and international partners in the planning process and the determination of the future financing mechanisms for the programme.

Work Area III Planning, Financing and Procurement

As the global immunization community advocates implementation of new and more expensive vaccines, the constraints on national budgets to sustain the cost of these new vaccines are increasing. The goal of reaching more children with newer vaccines has resulted in increases in the cost of immunization programmes, not only to cover increased vaccine costs, but also for the additional investment required in the immunization delivery systems. Given constraints on national budgets, cost-effectiveness analyses will help in determining the value for money of immunization programmes compared to alternative investments in health.

Options for immunization financing increased substantially with the development of multi-year financing approaches to accelerate new vaccine introduction, such as GAVI, International Finance Facility for Immunization (IFFIm) and the Advance Market Commitment (AMC) for pneumococcal vaccines.

In the past, the global immunization community's efforts in vaccine introduction have prioritized assistance to the poorest countries, in particular the 72 countries eligible for financial and programme assistance from the GAVI Alliance. However, middle income countries also need access to the same new vaccines and are increasingly facing important financial constraints and barriers to procure products on the international market, and additional focus on introducing new vaccines in middle-income countries is required to rectify this disparity.

The financial challenge presented by the long-term use of new vaccines has been a strong incentive to strengthen national capacities in financial planning for immunization in a health systems context. Policies that promote co-financing will help countries to recognize and consequently begin to address the financial challenges of introducing these vaccines and to guarantee their affordability in the long-term. Since 2006, WHO, UNICEF and GAVI have promoted the use of comprehensive multi-year planning as a mechanism to systematically address the main strategic approaches for efficient immunization programme delivery and appropriate financial planning.

WHO and partners also provide technical expertise to countries to assure that adequate quantities of high quality and affordable vaccines are purchased by countries to meet national immunization needs and to increase capacity building within countries to improve vaccine provision through strategies directed towards sustainable financing and procurement.

Pooled procurement is potentially one of the strategies to make vaccines more affordable to a group of countries, jointly procuring vaccines and medical products and technologies. Immunization partners are supporting countries in the EMR and AFR region with options to develop pooled procurement mechanisms.

Work Area IV Vaccine Delivery

When introducing a new vaccine, countries are faced with many programmatic and vaccine management issues, including: the capacity of the cold chain to accommodate additional volumes; ability of managers to assess vaccine needs accurately, plan for timely replenishment of vaccine stocks, and carefully monitor vaccine wastage; and the revision of records and reporting tools to accommodate the new antigens.

To ensure equitable access to vaccines in all populations, WHO and partners provide technical expertise to countries to strengthen existing and develop new delivery systems by providing assistance on vaccine management, perform effective vaccine management assessments in preparation of new vaccine applications, support cold chain and logistics upgrades related to new vaccines, as well as improved vaccine data usage and wastage data flow. In addition, partners support operational research for new immunization implementation and delivery strategies.

The introduction of new vaccines may require an expansion of the health workforce and, should the presentation and administration of the vaccine be novel, provision of appropriate training. Therefore, immunization partners aim to provide technical support to countries to facilitate human resource development and incentives for staff retention and to develop guidelines and training materials related to immunization service delivery and supervision for new vaccines.

Communication strategies contribute to a variety of important goals in the context of new vaccine introduction. One of the most important strategies is to mobilize and engage communities not only to accept, but to demand, the new vaccines for their well-being. With any new intervention, there are risks around actual or perceived harm that may arise. Communication to deal with rumours, allegations and coincidental adverse events following immunization are an essential part of a programme's efforts.

Work Area V Integrated Approaches to Disease Control

Rotavirus, pneumococcal and HPV vaccines represent significant new interventions for reducing the burden of diarrhoeal disease, acute respiratory infections and cervical cancer. However, they are not the only new or established interventions for prevention and control of these diseases.

Zinc treatment for diarrhoea (and potentially for pneumonia), improved oral rehydration solution (ORS), antibiotics, exclusive breastfeeding, improved nutrition, safe water, adequate sanitation and hygiene, are just a few of the other interventions that when applied effectively, can complement the impact of vaccines and together have a huge impact in reducing the burden of diarrhoea and pneumonia, the two largest killers of young children.

The WHO-UNICEF Global Action Plan for the Prevention and Control of Pneumonia was launched on 2 November 2009. Around the same time, WHO and UNICEF also published a document titled "Diarrhoea: why are children still dying and what can be done." Both these documents articulate the burden of pneumonia and diarrhoea, the fact that effective interventions to reduce mortality from these two conditions are available and that the introduction of new vaccines against Hib, pneumococcus and rotavirus in developing countries offer the opportunity to simultaneously scale up the use of other complementary intervention and create synergies between different health programmes to maximize benefits. The strategies aim to scale up the use of interventions to prevent pneumonia and diarrhoea, protect children by addressing risk factors for disease morbidity and mortality, and provide timely treatment at the community level to treat children with pneumonia and diarrhoea.

Significant momentum has been created through the advocacy efforts around World Pneumonia Day and the May 2010 World Health Assembly resolution on pneumonia. WHO and UNICEF are currently negotiating a grant to conduct regional workshops in preparation for the launch of integrated pneumonia and diarrhoea control strategies in countries.

In the area of cervical cancer prevention and control, HPV vaccines offer an important new prevention tool. Until recently, cervical cancer prevention has consisted of screening and treatment of precancerous lesions of the cervix. Although the cervical screening approach has been very successful for a number of populations, lack of access or delayed access to screening has hampered prevention efforts. An integrated approach to cervical cancer prevention and control which combines HPV vaccination and cervical screening and which comprehensively reaches girls and women, regardless of income, will reduce cervical cancer deaths, improve equity in cervical cancer prevention, and improve the health of women. The possibility of introducing HPV vaccines has spurred many countries to begin developing national comprehensive strategies for cervical cancer prevention and control which incorporate HPV vaccine introduction and strengthening of cervical cancer screening activities.

Work Area VI Monitoring and Surveillance

High quality information is critical to evaluate and improve programmes and thereby allow national governments to decide on how best to immunize more people against more diseases. Quality data which demonstrate vaccine impact are also necessary to justify and advocate for public health investments by organizations and governments that provide immunization funding.

One of the Global Framework for Immunization Monitoring and Surveillance's (GFIMS) goals is to provide programmatic data to monitor immunization coverage trends and other programme performance indicators. Key monitoring activities include the registration of vaccine doses administered and their reporting from the service delivery level to the national level. Periodic analysis, interpretation, and evaluation of those data, as well as monitoring programme process indicators, are critical to guide programme management and to identify rapidly problems that require corrective action. Monitoring data are thus used to sustain coverage achievements and to reach additional children, especially minority or disadvantaged populations, through both routine and outreach services. These data need to be linked to disease surveillance data to better understand vaccine performance.

Surveillance data provide decision makers with critical information both before vaccine introduction, as related to the existing disease burden and justification for vaccine introduction, and after vaccine introduction to monitor vaccine impact on disease and to assess vaccine safety. Surveillance for diseases caused by infectious agents targeted by newer vaccines are likely to require a syndromic approach as many of these infectious agents cause a variety of clinical syndromes such as diarrhoea, meningitis, sepsis, and pneumonia. Hence, a strong laboratory component of surveillance must complement the clinical syndromic surveillance to allow for diagnostic confirmation of the specific disease.

Over the past decade, considerable progress has been made in establishing global, regional and national systems for surveillance of vaccine preventable diseases. Since 2008, various existing networks for rotavirus and invasive bacterial disease (IBD) surveillance supported by the ADIPs and other partners have been transitioned into a WHO coordinated surveillance network. During 2009, 47 and 53 countries, respectively, reported data to the WHO coordinated IBD and rotavirus surveillance networks. These existing global surveillance networks and systems can be further enhanced by ensuring Ministry of Health ownership and supervision, and by further improving the availability and use of high quality data. The new surveillance systems require additional efforts to establish regional and global standardization and to become integrated with existing surveillance and health information systems.

Vaccine specific issues

WHO and UNICEF, in collaboration with countries and global immunization partners, are actively involved in devising and refining strategic approaches to maximize the public health return from new and under-utilized vaccines, providing mechanisms to assist national decision-makers with making the best informed decisions and documenting ongoing country experiences.

Many of the existing under-utilized vaccines represent diseases of regional importance, or for which the use of vaccine in population-based programmes has not yet been broadly experienced.

The Global New and Underutilized Vaccines Implementation Plan of Action focuses on one vaccine that is now rapidly progressing towards global utilization (Hib); three vaccines at early stages of implementation (pneumococcal, rotavirus and HPV); and five with regional and country importance (epidemic meningitis, Japanese encephalitis, yellow fever, typhoid, and cholera). Further diseases for which vaccines have important implications will be added as the vaccines reach the implementation stage.

I. *Haemophilus influenzae* type b (Hib) Disease

As of the end of 2009, 165 of 193 (85%) WHO member states had introduced Hib vaccines for infants in their routine national immunization schedule (of which three have introduced in part of the country only); 48% of the 2010 global birth cohort lives in a country with nationwide availability of Hib vaccine.

Hib is estimated to be responsible for 386,000 deaths per year, principally due to pneumonia or meningitis. Hib disease predominantly affects children under the age of 5, with a peak of morbidity between 4-18 months. Invasive Hib disease and pneumonia are associated with high mortality, especially in populations in developing countries with limited access to quality medical care. In addition, an estimated 15% to 35% of meningitis survivors are left with permanent sequelae such as loss of hearing or mental retardation. Hib meningitis is relatively straightforward to diagnose, particularly in areas that routinely perform lumbar punctures and have available competent microbiology laboratories or antigen detection kits. Hib pneumonia, though, is difficult to diagnose even in developed country settings and reliable disease burden estimates have come only from a few sites using lengthy and expensive vaccine probe studies. With any Hib disease syndrome, isolation of Hib bacteria can be complicated by the use of antibiotics before medical examination.

Currently available conjugate vaccines (PRP-T, PRP-OMP, and PRP-CRM₁₉₇) are highly effective. In November 2006, WHO published a position paper based on the recommendations from its Strategic Advisory Group of Experts (SAGE) on the global utilization of Hib vaccine. In view of the proven safety and efficacy of the vaccine, the paper urges all countries to include Hib vaccine in their national infant immunization programmes.

Following the closure of the GAVI-funded Hib Initiative in mid-2009, all technical assistance to countries to assist in making informed decisions on introduction of Hib vaccines and to address logistics for vaccine introduction is provided by WHO and UNICEF.

Introduction issues for Hib vaccine

Several Hib vaccine product presentations are currently available. These include monovalent vaccines as well as several combination products that can include diphtheria, tetanus, acellular or whole-cell pertussis and hepatitis B in particular. These products are available in fully liquid presentations, or in combination of lyophilized and liquid presentations that require reconstitution. They are also provided with varying number of doses per vial. Those differences in vaccine presentations have implications on storage capacities, vaccine wastage and injection safety in particular.

The combination form (DTP-HepB+Hib) is the preference of most countries, but in spite of it being a very cost-effective intervention, the relatively high price had been a deterrent to country introduction of the vaccine. Recently, the price was reduced by 20%. It is hoped that the emergence of multiple manufacturers of Hib-containing vaccines will help to further reduce vaccine price. For GAVI-supported countries, financial support has been guaranteed until 2015 with low co-financing levels required from the countries.

While there are only 26 countries which have not introduced Hib vaccine, several large countries are included in this number. In countries where Hib vaccine has been introduced, issues relating to concerns about vaccine safety and quality has occasionally affected ongoing Hib vaccine use. Adverse events following immunization with two pentavalent products resulted in suspension of use in two countries, while precautionary concern about a third pentavalent product resulted in a recent recall of that product from several countries.

Surveillance for Hib primarily relies on the establishment of sentinel sites with adequate laboratory support to investigate cases of clinical meningitis. The possibility of using syndromic surveillance for paediatric clinical meningitis in order to document an impact on disease occurrence without requiring laboratory confirmation is currently being explored. However, a major disease burden from Hib disease in developing countries is from pneumonia. Vaccine impact on pneumonia has not been shown outside of trial settings.

The vast majority of data on disease burden from Hib disease have been obtained from probe and impact studies. Due to difficulties with laboratory confirmation and widespread use of antibiotics, existing surveillance is less than optimal. To address this issue, additional impact studies are underway in Pakistan, Bangladesh, and Mozambique and Vietnam.

II. Pneumococcal Disease

As of the end of 2009, 42 (22%) of 193 WHO member states have introduced pneumococcal conjugate vaccine (PCV) for infants in their routine national immunization schedule (of which three have introduced in part of the country only); 11% of the 2010 global birth cohort lives in a country with nationwide availability of PCV.

Of the estimated 1.6 million annual deaths due to pneumococcal disease, approximately 826,000 occur in children under the age of 5. Deaths are primarily the result of pneumonia, sepsis or meningitis, and occur mainly in the developing world, where access to curative care is limited. Pneumococcal disease is a major cause of child death and illness but surveillance for clinical pneumococcal disease always underestimates the burden of disease locally because the diagnostic techniques are poorly sensitive. Surveillance for laboratory confirmed pneumococcal disease is a useful and important tool for monitoring vaccine impact and for managing pneumococcal vaccine programmes.

WHO published a position paper in 2007, providing guidance on the public health value and use of pneumococcal conjugate vaccines in childhood immunization. Based on the high burden of pneumococcal disease in children in developing countries and the proven immunogenicity, efficacy and safety of pneumococcal conjugate vaccines in randomized trials in developing countries and in routine programmes in industrialized countries, WHO recommends the use of pneumococcal conjugate vaccines for all countries and urges the highest priority be given to countries with high mortality rates.

Pneumococcus was chosen as the pilot vaccine for the Advance Market Commitment (AMC) financing instrument. To utilize this financing instrument, vaccines must adhere to a Target Product Profile (TPP) which was approved in November 2007. The TPP defines essential criteria that maximize the public health impact and facilitates its use in developing country immunization programmes.

In 2009, the 7-valent pneumococcal conjugate vaccine (PCV7) was prequalified. This vaccine contains 7 serotypes that account for 50% or more of invasive disease among children <5 years old in most countries, but does not contain certain serotypes that are also important in developing countries. Serotype 1, for example, is capable of causing large outbreaks of pneumococcal meningitis among persons of all ages, and may cause up to 25% of invasive disease in children <5 years old some countries in Africa and Asia. PCV7 is not available through the AMC since it does not meet the TPP.

The 10-valent pneumococcal vaccine (PCV10) includes the 7 serotypes in PCV7 as well as serotypes 1, 5, and 7F. PCV10 has been prequalified in 2010 for the one-dose and two-dose vial presentations, with the requirement that the two-dose preservative-free liquid presentation undergo a study to monitor potential adverse events following immunization in a GAVI-eligible country which received the vaccine through the AMC.

The 13-valent pneumococcal vaccine (PCV13) includes the 10 serotypes of PCV10 and serotypes 3, 6A, and 19A. Prequalification of PCV13 is anticipated to occur later in 2010. Availability of PCV10 and PCV13 will expand the global supply of vaccine substantially and also expand the coverage of serotypes causing severe

disease globally. Emerging market suppliers are developing pneumococcal conjugate vaccines containing 5 to 14 serotypes. In addition, several candidate vaccines based on pneumococcal common protein antigens are in pre-clinical or early clinical development. These may be used as "stand alone" vaccines or incorporated into combinations with pneumococcal conjugate vaccines.

Introduction issues for pneumococcal vaccine

The major challenges to introduction and sustained use of pneumococcal conjugate vaccines are to generate political will for vaccine introduction based on existing evidence and policy recommendations, and to address issues of vaccine price, supply and delivery. From 2012 onwards, the supply situation is expected to improve as the market will be supplied by 2 manufacturers and the pneumococcal AMC is expected to provide incentives for expansion of vaccine manufacturing capacity in emerging economies.

As with surveillance for Hib disease, surveillance for pneumococcal disease relies on establishment of sentinel sites to evaluate pediatric meningitis and other forms of invasive disease, such as sepsis. Also similar to Hib, a major burden from pneumococcal disease is due to pneumonia. Surveillance of pneumococcal disease will provide the data necessary to quantify the need and to select the appropriate formulation of vaccine at the country level. Continuing surveillance of the impact of large-scale immunization programmes on the population of pneumococci of non-vaccine serotype is essential to monitor for an effect known as "serotype replacement."

III. Rotavirus Disease

At the end of 2009, 23 (12%) of 193 WHO member states have introduced rotavirus vaccine for infants in their routine national immunization schedule; 11% of the 2010 global birth cohort lives in a country with nationwide availability of rotavirus vaccine.

Rotavirus infections are responsible for approximately 527,000 deaths each year. Children under five are most vulnerable. Virtually all children in developing countries are infected with rotavirus in their first two years of life, but many are asymptomatic and most cases are mild. However, rotavirus is responsible for hundreds of thousands of deaths annually in the developing world as a result of severe dehydration due to diarrhoea, vomiting and fever. Rotavirus is estimated to be responsible for over one-third of deaths caused by diarrhoeal diseases, especially in children aged between six months and two years. The high incidence and attack rates of rotavirus in both developing and developed countries indicates that other preventive measures, such as improved water and sanitation and hygienic conditions, have not reduced the transmission of the virus, and vaccination is the most promising method to control the disease.

In 2009, based on review of results from clinical studies of populations in Africa and Asia where there is high child mortality to intermediate child mortality, WHO's Strategic Advisory Group of Experts (SAGE) on Immunization recommended the inclusion of rotavirus vaccination of infants into all national immunization programmes. In countries where diarrheal deaths account for $\geq 10\%$ of mortality among children aged < 5 years, the introduction of the vaccine is strongly recommended. WHO recommends that the first dose of either RotaTeq or Rotarix be administered at age 6–15 weeks, while the maximum age for administering the last dose of either vaccine should be 32 weeks.

Clinical trial efficacy estimates for rotavirus vaccines correlate with mortality quartiles:

WHO mortality strata	Under-5 child mortality	Vaccine efficacy	Countries with rotavirus vaccine clinical trials
HIGH	Highest (top 25%)	50-64%	Ghana, Kenya, Malawi, Mali
INTER-MEDIATE	High mid (next 25%)	46-72%	Bangladesh, South Africa
LOW	Low mid (next 25%)	72 - 85%	Vietnam, Region of the Americas
	Least (lowest 25%)	85 - 100%	Region of the Americas, Europe, Western Pacific

Although vaccine efficacy is lower in countries with high under-5 child mortality, the vaccine prevents more episodes of severe gastroenteritis due to a higher burden of rotavirus disease. In Malawi, where vaccine efficacy was found to be

50% compared with 77% in South Africa, the number of episodes of severe gastroenteritis prevented by vaccination was 3.9 per 100 vaccinees compared with 2.5 per 200 vaccinees in South Africa.

Two pre-qualified rotavirus vaccines are currently available, one with a two-dose schedule and the other with a three dose schedule:

	Rotarix® (GSK Bio)	RotaTeq® (Merck)
Origin	Human monovalent	Bovine pentavalent
Strain	G1, P[8]	G1, G2, G3, G4, P[8] & G6P[7]
Vaccine course	2 doses - oral	3 doses - oral
Schedule	With DTP1 and DTP2	With DTP1, DTP2, and DTP3
Age restrictions	First dose at 6-15 weeks of age. Maximum age for last dose of either vaccine is 32 weeks of age.	
Presentation	Lyophilized, reconstituted or liquid	Liquid
Intussusception risk	No association observed	No association observed
WHO Pre-qualification	Yes, in 2007	Yes, in 2008

Introduction issues for rotavirus vaccine

The potential risk of intussusception associated with the two new rotavirus vaccines has been extensively studied through large safety studies under clinical trial conditions as well as through postmarketing surveillance. The WHO Global Advisory Committee on Vaccine Safety (GACVS) reviewed safety data with regards to intussusception in December 2008 and June 2009 and affirmed that intussusception risk of the order of which had been associated with Rotashield® can be ruled out with confidence. In June 2009, GACVS further stated that no data directly support a hypothesis that administration of rotavirus vaccine even outside of the age range 6–15 weeks for the first dose and 32 weeks for the second dose is associated with an increased risk of intussusception. Current age restrictions will require additional training of health workers, but may also be an opportunity to encourage parents to bring their infants for on-time immunization. Assessments of inadvertent vaccine use outside of the recommended age ranges are underway to identify whether it may be safe to loosen the age restrictions.

In early 2010, porcine circovirus was incidentally detected in both rotavirus vaccines during a study using a new technology for detecting viral genetic material. Circoviruses are small, circular, single-stranded DNA viruses which infect birds and pigs. Porcine circovirus (PCV) 1 and 2 infect pigs. PCV2 is not known to cause disease in any animals; PCV2 can cause disease in pigs. Fragments of PCV1 were identified in Rotarix and fragments of PCV1 and PCV2 were identified in RotaTeq. GACVS reviewed Rotarix safety data and issued a statement in March 2010 noting that the benefits of vaccination far outweighed any currently known risk associated with Rotarix. The WHO Strategic Advisory Group of Experts (SAGE) on Immunization reviewed Rotarix data during its April 2010 meeting and in the absence of any known risk, strongly recommended the continued use of Rotarix for immunization programmes.

The price of the two rotavirus vaccines offered by the manufacturers for low-income countries through UNICEF is not yet established.

IV. Human papillomavirus (HPV) disease

As of the end of 2009, 26 (13%) of 193 WHO member states have introduced HPV vaccine in their national immunization schedule; 7% of the 2010 global birth cohort lives in a country with nationwide availability of HPV vaccine.

Genital types of HPV are sexually transmitted. They are highly transmissible; peak infection incidence occurs soon after sexual debut. Most people acquire the infection during their lifetime. Infection is generally asymptomatic and frequently clears spontaneously, but some infections persist. Persistent infection with HPV of common "high-risk" types (e.g., 16 and 18) causes about 70% of cervical cancer cases. Cervical cancer resulted in 274 000 deaths worldwide in 2008, of which about 85% or more occurred in developing countries. High-risk HPV types are also associated with other anogenital and head and neck cancers. HPV of common "low-risk" types (e.g., 6 and 11) cause anogenital warts in sexually active populations and respiratory papillomatosis in infants which result in substantial morbidity and health care costs for women, men, and infants.

A quadrivalent vaccine prevents the most common high- and low-risk types of HPV (16, 18, 6, and 11). A bivalent vaccine prevents infection with high-risk types 16 and 18. In women who have no evidence of past or current infection with the HPV genotypes in the vaccines, both vaccines provide >90% protection against persistent HPV infection with vaccine types. The very high clinical efficacy in women without evidence of infection with vaccine HPV types, and the lower efficacy among those already exposed to HPV, show that vaccinating girls before they are exposed to HPV would have the greatest impact. Although the duration of protection is not yet known, there is evidence of protection for five to eight years after vaccination. Studies are continuing to evaluate longer-term protection. Studies of vaccine immunogenicity and/or efficacy are underway in men, HIV-infected persons and African populations.

Both the quadrivalent and bivalent vaccines are now licensed in >100 countries and both were WHO-prequalified in 2009.

WHO published a position paper in April 2009, providing guidance on the public health value and use of HPV vaccines. WHO recommends that HPV vaccination should be introduced into national immunization programmes where prevention of cervical cancer and other HPV-related diseases is a public health priority; vaccine introduction is programmatically feasible, and financially sustainable; and the cost-effectiveness aspects have been duly considered. The primary target population for HPV vaccine is likely to be girls 9-10 through 13 years old.

Introduction issues for HPV vaccine

Delivering HPV vaccine to 9-13 year old girls is consistent with the Global Immunization Vision and Strategy (GIVS) to expand vaccination beyond the traditional target age group. For many developing countries, this will require new routine immunization infrastructure for vaccine delivery to reach this age group. Promising delivery approaches for HPV vaccine include established primary care systems serving young adolescents in industrialized countries and school-based delivery and child health days in middle and low-income countries with limited primary care systems. Countries should use approaches that are compatible with their delivery infrastructure and cold chain capacity; that are affordable, cost-effective and sustainable; and that achieve the highest possible coverage.

Vaccine use may raise sensitive issues related to sexual behaviour, sexually transmitted infection, and genital cancer. Vaccines that protect against HPV types 16 and 18 have the potential to substantially reduce, but not eliminate, the risk of cervical cancer. Women will still be at risk of cancer from other high-risk genotypes, and cervical screening and treatment of precancerous lesions and cancer will still be required, if available. However, cervical cancer screening procedures may need to be adapted after introduction of vaccine to maximize cost-effectiveness.

Currently, private and public sector costs of the vaccines are very high. The prices of HPV vaccines are among the most critical determinants of the affordability and cost-effectiveness of vaccination. Financing delivery costs are also important, since in many settings new systems will be needed to reach young adolescents. If a two-dose schedule could be used, or if vaccination could be given at an earlier age with other vaccines (e.g., at school entry), delivery costs could possibly be reduced. The first approach is being tested, but not the second one, as further information on the duration of protection is needed before this type of study is undertaken. Steps are needed to accelerate public sector affordability and create sustainable financing of vaccine and screening programmes.

It will be useful for countries to assess their existing cervical cancer screening activities and their capacity to deliver vaccines to 9-13 year old girls in order to develop national comprehensive cervical cancer prevention and control plans and follow an evidence-based approach to decide whether HPV vaccine introduction is a priority.

V. Epidemic Meningitis

In the African “meningitis belt,” a region of Savannah that extends from Ethiopia in the east to Senegal in the west, group A meningococcal disease has posed a recurrent threat to public health for at least 100 years. Major group A epidemics occur at intervals of 7-14 years and particularly affect children and young adults. When epidemic meningococcal disease occurs, annual incidence rates can reach 1,000 cases per 100,000 population (1%) and it commands public health attention and calls for a large-scale public health response. The case-fatality rate of meningococcal disease is 5–25% and, among survivors, there is also considerable morbidity, including persistent neurologic sequelae. The current approach to epidemic response and control (reactive vaccination with polysaccharide meningococcal A vaccine) is inefficient, expensive and highly labour-intensive. Furthermore, the polysaccharide vaccine does not protect very young children, induce immune memory or provide long lasting protection at the individual level, or enhance herd immunity at the community level.

As with Hib conjugate vaccines and pneumococcal conjugate vaccines, group A, C, Y and W-135 meningococcal polysaccharides have been chemically conjugated to carrier proteins. Conjugate vaccines induce a T-cell-dependent response, resulting in an improved immune response in infants and young children and a priming of immunologic memory leading to a booster response to subsequent doses. These vaccines are expected to provide long-lasting immunity even when given as a series in infancy, and to enhance herd immunity by decreasing nasopharyngeal carriage and thus transmission of the causing bacteria.

In collaboration with African public health officials, a new meningococcal A conjugate vaccine was developed through the Meningitis Vaccine Project (MVP, a product development partnership between the World Health Organization and PATH) in association with partners. The project, set up in 2001 with core funding from the Bill & Melinda Gates Foundation, included transfer of technology for manufacture of the vaccine to the Serum Institute of India Ltd. Clinical trials, beginning in 2005, have been carried out in the Gambia, Ghana, India, Mali and Senegal. The vaccine was safe and highly immunogenic, inducing immune memory and a persistent antibody response in the target population 1 to 29 years of age. Immune responses at all time points were found to be superior to those induced by the licensed polysaccharide vaccine. In addition, the vaccine had a boosting effect in antibody concentrations against tetanus. Vaccine licensure for export was issued by the Indian national regulatory authority, the country of manufacture, in December 2009; and WHO vaccine prequalification is expected by the end of June 2010, with an indication for use in 1 to 29 years of age. Vaccine trials in the infant population are still underway in Africa.

Introduction issues for epidemic meningitis vaccine

At less than US\$0.50 per dose, the new conjugate vaccine will be affordable to Meningitis Belt countries. Most importantly, a well-planned introduction of the conjugate vaccine should achieve herd immunity and virtually eliminate meningococcal A epidemics. As such, this vaccine represents meningitis belt countries’ first opportunity to implement a preventive strategy that will protect an estimated 450 million persons from group A *Neisseria meningitidis*. The implementation plan involves 2 phases – first, single dose mass vaccination campaigns targeting 1-29 year olds with sufficiently high coverage to achieve herd immunity and eliminate epidemics and second, a maintenance phase where

future birth cohorts will be protected through vaccination within the Expanded Programme on Immunization (EPI) schedule or through follow-up mass campaigns targeting 1-4 year olds every 5 years.

An initial introduction is planned for September 2010 in selected districts of 3 hyper-endemic countries in West Africa (Burkina Faso, Mali, Niger), followed by phased introduction in the remaining districts of these 3 countries. Operational research in Burkina Faso will evaluate the impact of large-scale vaccine introduction in all 1- to 29-year-olds on carriage of the disease, closely monitor meningococcal disease in the population, evaluate vaccine safety when implemented on a large scale and document operational lessons.

Lessons learned in Burkina Faso, as well as in Mali and Niger, will be applied to inform "best practice" recommendations, tools, and approaches for subsequent introduction in all Belt countries, particularly in the remaining hyperendemic countries of Ethiopia, Northern Nigeria, and Sudan, which present special challenges due to their large populations. Introduction must be phased over three or more years to ensure adequate vaccine supply.

Because of its epidemic potential and high disease burden, controlling group A meningococcal disease is an important public health priority in Africa. Countries in the Meningitis Belt have been very eager to host the clinical trials of the vaccine and have demonstrated great enthusiasm and commitment to ensuring their successful conduct. The same enthusiasm is now present for vaccine introduction. At the political level, at the 58th session of the WHO Regional Committee for Africa, in September 2008, health ministers from countries in the African Meningitis Belt committed themselves to introducing the meningococcal A conjugate vaccine when it became available.

At this time, no funds have been identified for further introductions after 2010 and continued funding of the MenA investment case is very uncertain. Key next steps are to mobilise champions and resources (soft loans, grants, etc.) for introduction of MenAfriVac in rest of the Meningitis Belt.

VI. Japanese Encephalitis

It has been estimated that Japanese Encephalitis (JE) virus causes at least 50,000 cases of clinical disease each year, mostly among children aged <10 years, resulting in about 10,000 deaths and 15,000 cases of long-term, neuro-psychiatric sequelae. A new estimation based on a recent review of quality studies in peer-reviewed journals and careful extrapolation to other regions suggests that the actual figures could be twice as high. There is no specific antiviral treatment for JE. Although the use of pesticides and improvements in agricultural practices may have contributed to the reduction of disease incidence in some countries, vaccination is the single most important control measure.

JE affected countries can be grouped into three categories: endemic countries which recognized the burden of disease early and put in place comprehensive immunization programmes; countries that are most likely endemic but lack a full documentation of the burden, and in consequence have no or only limited immunization activities; and countries with limited or sporadic cases of JE, which typically have not put in place immunization programmes. The most likely endemic countries with incomplete epidemiologic information should be the target of public efforts, and progress has been made recently in Cambodia with the introduction decision for JE immunization, based on quality sentinel surveillance.

The live, attenuated cell-culture-derived vaccine SA 14-14-2 is now the most widely used vaccine in endemic countries. It is normally used in a one or two dose schedule without booster. Inactivated mouse-brain derived vaccine is still in use, requiring three doses for primary immunization, followed by repeat boosters. Another live vaccine is under review for marketing authorization, and the travellers market has seen the introduction of new cell-culture based inactivated JE vaccines. No JE vaccine is currently WHO-prequalified, but applications by manufacturers are expected during 2011.

Introduction issues for JE vaccine

Surveillance is necessary to determine impact of vaccination and to document disease burden for decision-making on vaccine introduction. Larger countries may need to understand local patterns of disease in order to develop the most appropriate immunization strategy. A layered surveillance strategy is recommended which includes syndromic surveillance for acute encephalitis or meningitis/encephalitis syndromes and sentinel surveillance with laboratory back-up. WHO has issued surveillance standards that are being regionally adapted. More recently, sentinel surveillance sites have been established in several countries using multiple funding sources. Funding is needed to implement and maintain an adequate standard surveillance system.

The fact that current JE vaccines are not WHO prequalified limits procurement through UNICEF and makes it essential for countries to assure proper NRA oversight for vaccine licensure and use in accordance with WHO recommendations. For countries wanting to license JE vaccine but lacking sufficient NRA competency, the strengthening of NRA competency should be a priority.

The live attenuated JE vaccine is now the most widely used JE vaccine. There is a need for more data and better documentation on certain product characteristics,

including: (1) the potential requirement of a booster dose; (2) the confirmation that single dose primary immunization confers durable protection, and (3) clarification on co-administration with measles. As a co-administration study of JE with measles vaccine in one country found a possible moderate decrease in measles immunogenicity, an additional study has been recommended to provide clarification on the potential level and clinical impact of a possible interference between the two vaccines. Finally, AEFI monitoring should help to further document the long-term safety of the product.

Resources available to date have resulted in a significant increase in the understanding of JE disease burden in different countries and in improving vaccination strategies. However, significant funding gaps have emerged. Securing further funding is critical to maintaining the progress already made, as well as to effectively expand JE control into JE-prone areas. Inclusion of JE in the GAVI Accelerated Vaccine Introduction process and creation of a collaborative partnership are steps which could provide the necessary technical support and assist in resource mobilization for vaccination.

Other Vaccine specific issues

Other vaccine-preventable diseases that are key public health issues with their own sets of constraints for control are listed below. It is suggested that these be on the agenda for ongoing discussion.

Yellow Fever Vaccine: A highly efficacious, live attenuated vaccine (17D) has been available for more than 70 years, and 36 of the 45 affected countries in Africa and the Americas have now introduced routine yellow fever vaccination, up from 12 just over a decade ago. Most countries offer this vaccine at 9 months of age, and seventeen countries in Africa benefit from GAVI support for routine yellow fever vaccine introduction. In 2010, official WHO/UNICEF estimates of routine yellow fever vaccination coverage were developed for the first time. This is being done for all countries with routine yellow fever vaccination for the period during which yellow fever vaccine has been used.

Intensive effort to secure the yellow fever vaccine supply has given good results. There are now four manufacturers producing WHO pre-qualified yellow fever vaccine and vaccine production has tripled in the last decade with seven different prequalified presentations now available. Generally, smaller vial sizes are recommended for routine immunization to reduce vaccine wastage. All the currently available vaccine formulations are presented freeze-dried with accompanying diluent and must be used within 6 hours of reconstitution.

Prevention strategies also include mass preventive vaccination campaigns to protect susceptible older age groups. These campaigns have been carried out in ten countries since 2007 under the Yellow Fever Initiative. To sustain population protection following mass campaigns, maintaining high routine coverage is critical.

Case-based yellow fever surveillance is now functional in 19 countries to detect outbreaks early in Africa. Outbreak response vaccination campaigns must be carried out with minimum delay to limit the spread of the disease and the potential for devastating urban epidemics. Countries can apply for vaccine and support for operational costs through the International Coordinating Group (ICG) for Yellow Fever Vaccine Provision.

Further information on the Yellow Fever Initiative is available at www.who.int/yellowfever.

Typhoid Vaccines: Following SAGE recommendations in November 2007, WHO revised its typhoid vaccines position paper in March 2008. With several manufacturers worldwide, the access to affordable Vi polysaccharide vaccine has increased greatly. In addition, the live attenuated oral Ty21a vaccine is available, possibly at greatly reduced prices. Countries are encouraged to use typhoid vaccines as a complementary tool to an integrated approach to typhoid prevention and control in typhoid endemic countries.

WHO, in collaboration with partners, is providing technical assistance to countries to strengthen typhoid surveillance and develop appropriate typhoid vaccination strategies as well as improving the dissemination of information about the pathogen and the disease. Not having a simple and accurate tool to diagnose typhoid makes it difficult to have accurate surveillance and burden of disease data. Several countries have shown interest in using typhoid vaccines but availability of resources continue to be a major challenge. Although listed as a

priority for GAVI, there is no financial allocation to support its use. In the meantime, better typhoid vaccines such as the conjugate typhoid vaccines are being developed for the future.

Cholera Vaccines: WHO revised its 2001 position paper on cholera and published the new position paper in March 2010. There are three cholera vaccines, Dukoral [WC-rBS], Shanchol and mORCVAX, the latter two are bivalent oral vaccines based on serogroups O1 and O139; these vaccines are closely related, but formulated differently by different manufacturers.

WHO recommends, in conjunction with other prevention and control strategies, the use of vaccines in risk areas or groups. Vaccination provides an immediate short-term response while the longer term interventions such as improving water and sanitation are put into place. Although all age groups are vulnerable to cholera, where resources are limited immunization should be targeted at high-risk children aged ≥ 1 year (Shanchol or mORCVAX) or ≥ 2 years (Dukoral). WHO is currently assessing the programmatic feasibility, acceptability and effectiveness of pre-emptive mass vaccination with cholera vaccine in Zanzibar which will help shape future guidelines on optimal strategies for use of vaccines to control and prevent cholera, and also help understand the feasibility of developing a strategic stockpile for cholera vaccines. Following the development of an investment case for cholera, country-by-country financing and vaccination strategies may be needed.

Dengue: This disease is a major public health concern in affected countries in South East Asia and Latin America. While dengue immunology and pathophysiology remain a major research area, the vaccine pipeline is progressing well. A phase 2b study involving more than 4000 children aged 4-11 years is ongoing in Thailand, and preparations for a multicentric phase 3 study have commenced.

Major efforts are needed to create an enabling environment for immunization, which include a better estimation of the burden of disease, standardized surveillance, and disease reporting. More work is needed to model the potential impact of dengue vaccines on disease epidemiology and to develop immunization strategies. Vaccination will most likely be outside established EPI system, which will present challenges to the delivery of the vaccine.

Malaria: This is by far the world's most important tropical parasitic disease, killing more people than any other communicable disease except AIDS and tuberculosis and with the vast majority of deaths occurring among children under five years of age. Evidence suggests that a prophylactic malaria vaccine for humans is feasible. An increasing number of malaria vaccine candidates have entered Phase 1 trials and some have progressed to field efficacy trials in populations where malaria is endemic. A pivotal phase 3 trial of the most advanced candidate, RTS,S/AS01, started in 2009 with 12-16,000 infants to be enrolled in 7 sub-Saharan African countries. Data from the Phase 3 trial will be available to consider policy recommendation in 2015 or so, if all goes well. Other promising candidate vaccines are progressing through to phase 2 field efficacy evaluations.