Introduction of Rotavirus Vaccine with Support from the GAVI Alliance

Information to Assist the National Decision-Making and Application Process

For countries of the European Region

ROTAVIRUS VACCINE PROGRAM

A partnership between PATH, WHO, and CDC with funding support from GAVI Alliance

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Introduction

This Information Pack was developed by the PATH Rotavirus Vaccine Program on behalf of the GAVI Alliance to summarize considerations for rotavirus vaccine introduction in countries eligible for support. This guide is meant to complement the broader Guidelines on Country Proposals available on GAVI's website: **http://www.gavialliance.org/resources/GAVI_Country_Guidelines_ISS_INS_NVS_15_July_07_en.doc**. The intended audience for this Information Pack is composed of policy- and decision-makers representing the ministries of health and finance in developing countries.

As new information is constantly being made available, updated versions of this Information Pack will be regularly posted on the GAVI Alliance website.

Rotavirus disease

Rotavirus is found throughout the world, in both developed and developing countries. Nearly every child is infected with rotavirus at least once before age five years, with the first infection usually occurring before age three.

Infants and young children with rotavirus infection suffer vomiting, fever, and diarrhea, and for children with severe disease, this combination of symptoms can progress rapidly to dehydration and death. At least 25 percent to 50 percent of all severe acute gastroenteritis in infants and children under five years of age is caused by rotavirus infection. Over 525,000 children die from rotavirus each year,[1] and over 2 million are hospitalized with pronounced dehydration. The highest mortality and morbidity associated with rotavirus infection occurs among children in developing countries. More than 90 percent of the deaths occur in developing countries, where adequate and timely medical care is often out of reach.

Prevention options that address other causes of diarrhea are significantly less effective for children with severe rotavirus disease. As a result, vaccines represent the best hope for preventing the most severe episodes of rotavirus infection, especially in impoverished regions where access to medical care is limited.

1 WHO. Estimated rotavirus deaths for children under 5 years of age: 2004, 527000. Available at: **http://www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/index.html**.

What is the burden of rotavirus disease in your country?

European Region

Six of the eight GAVI-eligible countries in the World Health Organization (WHO) European Region have initiated rotavirus surveillance, and of those six, Kyrgyzstan and Uzbekistan have collected data for two full years. The data in Table 1 show that, in general, one-quarter to one-half of hospitalized acute gastroenteritis cases in children under five years of age are laboratory-confirmed for rotavirus. This finding is sufficiently consistent to suggest that these data may be considered representative of countries in Eastern Europe, the Caucasus, and Central Asia.

TABLE 1. Rotavirus surveillance results among hospitalized children <five years of age with acute gastroenteritis, European Region, 2005–2007

COUNTRY	NUMBER OF SITES	REPORTING PERIOD	NUMBER STOOLS TESTED	ROTA POSITIVE	
				NUMBER	%
Azerbaijan	2 sites in Baku	12/06–9/07	883	208	24
Georgia	Tbilisi	12/06–9/07	411	160	39
Kyrgyzstan	Bishkek & Osh	1/05–6/07	3578	898	25
Tajikistan	Dushanbe	12/06–9/07	465	130	28
Ukraine	Kyiv & Odessa	12/06–9/07	1495	660	44
Uzbekistan	Tashkent & Bukhara	1/05–12/06	3550	1050	30
Total			**10382**	**3106**	**30**

Source: CISID home page. WHO Regional Office for Europe website. Available at: **http://data.euro.who.int/cisid**.

Other regions

Surveillance data from other regions reveal a similar burden of rotavirus gastroenteritis. The data in Table 2 show that, globally, one-third to one-half of hospitalized acute gastroenteritis cases in children under five years of age are laboratory-confirmed for rotavirus.

TABLE 2. Rotavirus surveillance results among hospitalized children <five years of age with acute gastroenteritis, by regions, 2005–2007

WHO REGION	REPORTING PERIOD	NUMBER STOOLS TESTED	ROTA POSITIVE	
			NUMBER	%
Africa	6/06–5/07	2114	975	46
Americas	2006	8926	3834	43
Middle East	Variable, 2005–07	12898	5172	40
Southeast Asia	Variable, 2005–07	15826	6180	39
Western Pacific	Variable, 2005–07	11185	4203	38

What are the characteristics of current rotavirus vaccines?

WHO strongly recommends the inclusion of rotavirus vaccination in the national immunization programs of regions and countries where vaccine efficacy data suggest a significant public health impact and where appropriate infrastructure and financing mechanisms are available to sustain vaccine utilization.[2]

Rotavirus vaccines are an important tool to complement existing and improved interventions to control diarrheal disease, such as exclusive breastfeeding, oral rehydration therapy, zinc treatment, and improved hygiene and sanitation through hand-washing. However, hygiene and sanitation measures do not impact rotavirus incidence. Therefore, prevention through vaccination is the best method for reducing rotavirus mortality.

Two orally-administered, live, attenuated rotavirus vaccines, one manufactured by GlaxoSmithKline (GSK) and one by Merck & Co., have been demonstrated to be efficacious and safe in large-scale clinical trials conducted in North America, Latin America, and the European Union. On the basis of the respective studies, these products were licensed by either the European Medicines Agency (EMEA) or both the EMEA and the US Food and Drug Administration, respectively, in 2006. Subsequently, both manufacturers applied for WHO prequalification, which is an essential prerequisite for vaccines provided through UN agencies, as well as for support from the GAVI Alliance. The GSK vaccine is now prequalified for use in regions where clinical trials have demonstrated safety and efficacy, and the Merck vaccine is expected to be prequalified in the very near future.

The GSK vaccine is called Rotarix® and has a two-dose schedule, given with any two of the three OPV doses. The Merck vaccine is called RotaTeq® and has a three-dose schedule, given with each of the OPV doses. The currently available efficacy and safety data support selection of either of the two vaccines for national use.

What are the efficacy and safety characteristics of these vaccines?

The current rotavirus vaccines are considered equally safe and efficacious, but differ in antigen composition and immunization schedule.[3,4] In general, they provide about 90 to 100 percent protection against severe rotavirus disease and about 74 to 85 percent protection against rotavirus diarrhea of any severity, depending on the schedule of administration and the population evaluated. The protection against severe rotavirus infection has been shown to extend into the second year of follow-up for both of these vaccines. For more detailed information, please consult the PATH website: **http://www.path.org/vaccineresources/rotavirus-efficacy-safety.php** (please note that, in addition to English, several key documents are available in Spanish and Russian).

In 2005, WHO's Strategic Advisory Group of Experts (SAGE) recognized that use of rotavirus vaccines is appropriate in the regions of the world where efficacy data have been generated, that is, in the Americas and Europe.[5]

Definitive studies evaluating the efficacy of these vaccines in impoverished populations in Asia and Africa are currently in progress, the results from which are expected by 2009. When those data become available, SAGE will be in a position to determine if the current regional recommendation should then be extended to the global level. In the meantime, the lessons of vaccine introduction and post-marketing surveillance in the WHO Americas and European Regions will be valuable to guide other regions and further establish the effectiveness and safety of these vaccines.

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2 WHO. *Weekly Epidemiological Record.* 82(32):285-296; 2007.
3 Ruiz-Palacios G, et al. *New England Journal of Medicine*. 354(1):11-22.
4 Vesikari T, et al. *New England Journal of Medicine*. 354(1):23-33.
5 WHO. *Weekly Epidemiological Record*. 81(1):8.

Is there a secure vaccine supply?

The manufacturers of the currently available rotavirus vaccines, GSK and Merck, have indicated their willingness to immediately make their respective rotavirus vaccines available at tiered prices. It is estimated that the current manufacturing capacity of these two companies will be sufficient to provide vaccine supply to meet the anticipated private- and public-sector demand.

Several manufacturers based in developing countries have initiated development of new rotavirus vaccines. Market availability for at least one of these products could begin as early as 2011 and market entry of additional products is projected through 2015, provided these companies have adequate development resources and demand for their products.

Are these vaccines cost-effective?

Rotavirus vaccines are either "cost-effective" or "very cost-effective" for all GAVI-eligible countries, according to criteria established in the 2002 World Health Report. The cumulative cost per disability-adjusted life year (DALY) for the period 2007 to 2025 is US$30 for all regions combined, and the average cost per death averted is US$600 or less for all regions combined, for the range of vaccine prices likely to be available to developing countries.[6]

For further information on vaccine cost-effectiveness, please consult the PATH and GAVI Alliance websites: **http://www.path.org/vaccineresources/rotavirus-cost-effectiveness.php** and **http://www.gavialliance.org/resources/Rotavirus_Investment_Case_Oct06.pdf**.

What are the operational and health systems requirements for introducing rotavirus vaccine?

Operational requirements for vaccine introduction are summarized in Annex 1 at the end of this document. Vaccine characteristics including per-dose volume for the two available vaccines are summarized, providing the technical basis for planning for vaccine introduction, cold chain capacity assessments, and health worker training.

Additional information on the technical specifications of each vaccine, as well as regulatory issues, are available on the PATH website: **http://www.path.org/vaccineresources/rotavirus-regulatory-issues.php**.

Countries should consider the systems and resources to be put in place to ensure effective, high-quality and sustainable vaccine introduction. Requirements and one-time costs for vaccine introduction should be quantified, as well as systems modifications needed. Areas to work through with various ministry of health and ministry of finance departments, and with the support of in-country partners, may include the following:

- **Goal-setting and dialogue:** Establish your goals and create the space for dialogue. Identify what you wish to achieve before, during, and following vaccine introduction.
- **Surveillance:** establish disease surveillance to help establish burden of disease and measure impact after vaccine introduction, and monitor adverse events to ensure vaccine safety.

6 Studies were conducted using a range of prices from US$2 to US$20. The actual price of the vaccine will be determined by the second quarter of 2008 following finalization of procurement and supply agreements between UNICEF and the vaccine manufacturers. Once price negotiations have been concluded, the weighted average price per dose for rotavirus vaccine will be published by the UNICEF Supply Division. The current GAVI product menu is available at **http://www.unicef.org/supply/index_gavi.html**.

- **Vaccine regulation and immunization program:** conduct a quick review of the immunization program to identify areas of planning required, such as support to national regulatory authorities and vaccine licensing, vaccine procurement, and logistics; cold chain and vaccine management; health records, immunization cards, and immunization coverage reporting; health personnel capacity assessment and training; and social mobilization.
- **Health planning, coordination, budgeting, and finance:** Secure sufficient and sustainable budget to co-finance the vaccine. Also, map all stakeholders and their roles and responsibilities to help identify sources of assistance and potential bottle-necks for decision-making. Involve all relevant health policy and decision-making bodies, government departments, and technical advisory groups, including those responsible for planning, budgeting, infrastructure, and human resources for health.
- **Advocacy and communication:** Create clear messages for your goals and activities. For example, these can be about the health consequences of vaccine-preventable disease such as rotavirus infection, vaccine introduction, and potential impact on health and socioeconomic development. Strive for evidence-based advocacy, coalition-building, and social mobilization at all levels. Civil society and non-government and professional organizations can play a prominent role.

Further suggestions are provided in Annex 2. It is up to the country to determine what and how much should be done locally, when regional data or resources are sufficient, and when to request technical assistance.

Which countries are eligible for GAVI Alliance support for rotavirus vaccine?

The GAVI Alliance main criterion of eligibility for support is that countries must have had a gross national income of less than US$1,000 per capita as of 2003 (World Bank data).[7]

Countries applying for new vaccine support (NVS) from GAVI must also demonstrate DTP coverage above 50 percent.

In the WHO European Region (one of two regions in which rotavirus vaccine introduction is currently recommended), the following eight countries are currently eligible to receive GAVI support for subsidized vaccine and health systems strengthening:

- Armenia
- Azerbaijan
- Georgia
- Kyrgyzstan
- Moldova
- Tajikistan
- Ukraine
- Uzbekistan

Studies to evaluate the safety and efficacy of these vaccines in Asia and Africa are currently ongoing. Results are expected by 2009 and will be used to determine whether WHO will issue a global recommendation on vaccine introduction. If a global recommendation is issued, GAVI support would begin for these regions shortly thereafter.

7 http://www.gavialliance.org/support/who/index.php

What is the procedure for applying for GAVI Alliance support for rotavirus vaccine?

All countries applying for NVS are required to follow the guidance provided by the GAVI Alliance (full details on NVS support are available from the GAVI Alliance website: **http://www.gavialliance.org/support/how/guidelines/index.php**).

Prior to introducing a new vaccine with GAVI support, it may need to be licensed by the responsible national regulatory authority, depending on the country. In some countries, WHO prequalification may be all that is needed. Other factors to be considered when applying for rotavirus vaccine introduction support include:

- Assessment of the estimated burden of disease.
- Assessment of potential impact (epidemiological and financial).
- Contribution toward national goals and milestones.
- Performance of the vaccine against alternative interventions.
- Intention to sustain use of the vaccine.

These considerations may already be a part of the national comprehensive multiyear plan (cMYP). If not, the cMYP will need to be updated to include the introduction plan. Regional data may be appropriate if rotavirus surveillance is not conducted in your country. Guidance is available in WHO guidelines for new vaccine introduction.[8] If needed, technical assistance is available for undertaking these analyses toward development of the application for NVS. Requests for such assistance should be directed to GAVI in-country partners, such as the World Health Organization or UNICEF country office, or the PATH Rotavirus Vaccine Program.

The deadlines in 2008 for GAVI applications for NVS are February 8, May 2, and September 25.

New and underused vaccine introduction grant

GAVI will also provide a one-time grant to support costs related to pre-introduction activities and requirements for new vaccine introduction. The grant consists of a lump-sum of US$100,000 or US$0.30 per child in the birth cohort of the year of introduction, whichever is higher. Countries applying for this grant must prepare a vaccine introduction plan, including a detailed budget of non-vaccine costs such as training, social mobilization, and system logistics. The grant is provided at the time of approval, which allows for investments ahead of the vaccine introduction.

What is the cost for subsidized vaccine provided by GAVI Alliance?

All countries applying for GAVI support are required to co-finance new vaccines—including rotavirus vaccines—from the time of introduction, in accordance with a sliding scale based on 2003 gross national income (see Table 3). It is expected that co-financing will encourage national governments and their partners to engage in more rigorous evidence-based decision-making, make greater investments in immunization services, integrate budgeting and planning, and ultimately transition from GAVI support to achieve financial sustainability of immunization programs.

All countries are encouraged to co-finance at levels higher than the minimum to accelerate their vaccine independence and sustainability.

8 WHO. Vaccine introduction guidelines. WHO publication WHO/IVB/05.18. See also **http://www.who.int/immunization_delivery/new_vaccines/10.WHO_V&B_02.11.pdf**.

TABLE 3: Minimum[9] co-financing levels per dose, US$: 2007–2010 (single or combination vaccines, including injection supplies, insurance, freight, etc.)

VACCINE	POOREST	INTERMEDIATE KYRGYZSTAN, MOLDOVA, TAJIKISTAN, UZBEKISTAN	LEAST POOR ARMENIA, AZERBAIJAN, GEORGIA, UKRAINE	FRAGILE STATES
1st vaccine	$0.20	$0.30	$0.30 (+15% annually)	$0.10
2nd additional vaccine	$0.15	$0.15	$0.15 (+15% annually)	$0.15
3rd additional vaccine	$0.15	$0.15	$0.15 (+15% annually)	$0.15

All the GAVI-eligible countries of Latin America and Europe fall into the "intermediate" or "least poor" categories, except Haiti which is classified as a "fragile state."

If rotavirus vaccine is the first vaccine selected by the government for introduction with GAVI support in "least poor" and "intermediate" countries, the co-finance contribution will be US$0.30 per dose, that is, US$0.60 per child vaccinated. If rotavirus vaccine is the second or third vaccine selected by the government for introduction, the co-finance contribution will be US$0.15 per dose, that is, US$0.30 per child vaccinated.

The country co-financing requirement for both rotavirus vaccines is equivalent, even though Rotarix® uses a two-dose series and RotaTeq® is administered in three-doses. If a government selects the three-dose vaccine, GAVI will apply an adjustment factor so that the vaccine co-financing per child vaccinated remains identical to that of the two-dose schedule.

Countries pay their contribution of the vaccine cost by purchasing the equivalent number of doses of the vaccine through regular vaccine procurement arrangements used for other EPI vaccines (e.g., through UNICEF).

9 Countries are required to co-finance at the minimum level, but higher contributions are encouraged.

ANNEX 1: Technical and operational details of two available rotavirus vaccines

A. GSK Rotarix®—human, live, attenuated, oral rotavirus vaccine

Lyophilized vaccine reconstituted with CaCO3 buffer:

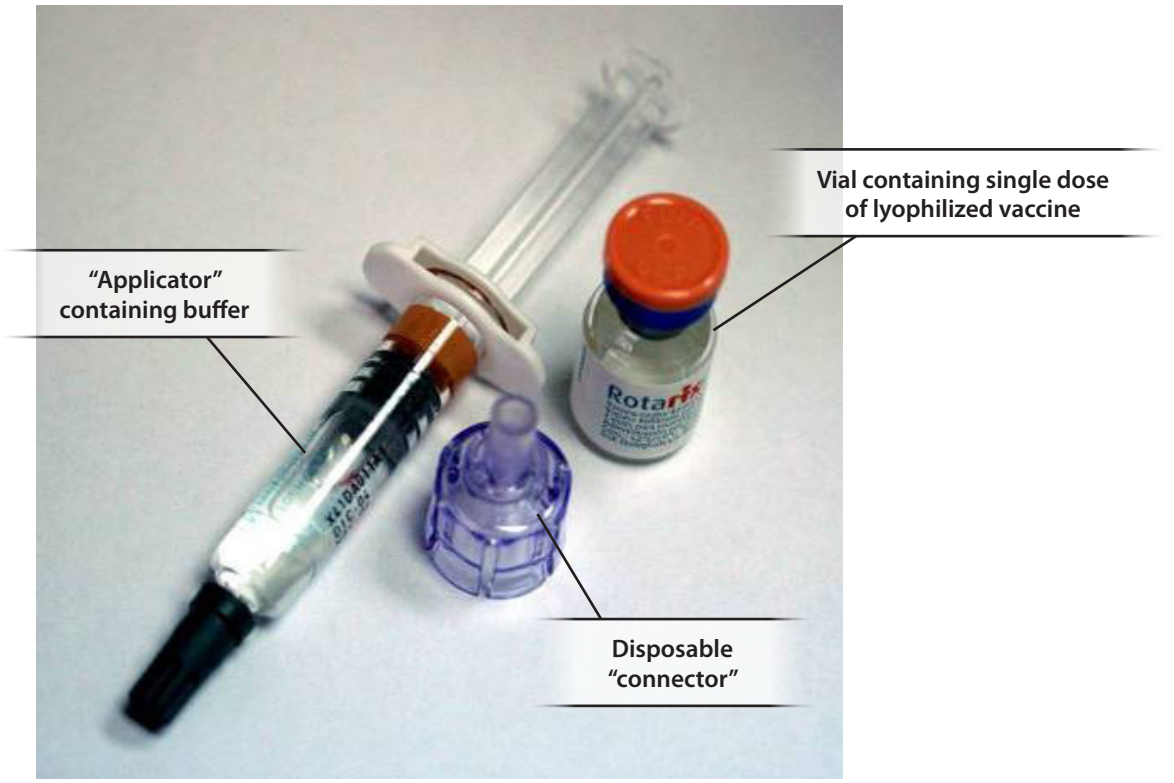
- Human G1P8 strain.
- Cross-protective of multiple strains (G1, G2, G3, G4 and G9).
- High efficacy and safety.
- Two-dose schedule, given with OPV1 and OPV2.

Current presentation:

- Single dose, 1 ml/dose.
- +2°C to +8°C, must not freeze.
- Non-standard handling.
- Administered orally using the applicator.
- Significant cold chain volume implications.
- Vaccine vial monitor (VVM) on UNICEF-supplied vaccine.

Future presentation (expected to be available by 2009):

- Rotarix® all-liquid formulation.



B. Merck RotaTeq®—pentavalent, human-bovine reassortant, live, attenuated, oral rotavirus vaccine

Liquid vaccine, five human-bovine reassortant strains:

- G serotypes—human G1, G2, G3, G4, and P1A[8]; bovine G6 and P7[5].
- Cross-protective of multiple strains.
- High efficacy and safety.
- Three-dose schedule, given with OPV1, OPV2 and OPV3.

Current presentation:

- Single dose, 2 ml/dose.
- +2°C to +8°C storage, must not freeze.
- Administered orally direct from the plastic tube.
- Significant cold chain volume implications.

Both vaccines require substantial additional space for transport and storage in the cold chain (see Table 4). However, both manufacturers are taking steps to reduce the packed per-dose volume of their vaccines. GSK's Rotarix® packed per-dose volume will be reduced when the all-liquid formulation becomes available, and Merck's RotaTeq® per-dose volume will be reduced by decreasing the size of the squeeze-dropper and external packaging.

TABLE 4: Comparison of storage volumes for two rotavirus vaccines*

GSK Rotarix®

PRESENTATION		25 SINGLE-DOSE PACK†
Physical dimensions (cm)	Length	10.0
	Breadth	7.7
	Height	3.7
Rotarix® total volume (cm^3)		284.9
Rotarix® volume per dose (cm^3)		11.4
Storage volume (cm^3) for standard vaccination schedule (1)	National/provincial level (2)	58
	Peripheral level	79
Storage volume (cm^3) for modified vaccination schedule (3)	National/provincial level	83
	Peripheral level	104

† Lyophilized vaccine in 25 single-dose pack—diluent carried outside cold chain.
(1) 1xBCG, 3xDPT, 3xHepB, 3xHib, 1xmeasles, 1xTT for women (ref: WHO, 2004).
(2) +4ºC to +8ºC storage only.
(3) same as (1), with addition of 2 doses of Rotarix® plus 10% wastage.

Merck RotaTeq®

PRESENTATION		10 SINGLE-DOSE PACK	25 SINGLE-DOSE PACK‡
Physical dimensions (cm)	Length	14.3	13
	Breadth	9.3	8.3
	Height	5.9	11
RotaTeq® total volume (cm^3)		810.8	1187
RotaTeq® volume per dose (cm^3)		81.1	47.5
Storage volume (cm^3) for standard vaccination schedule (1)	National/provincial level (2)	58	58
	Peripheral level	79	79
Storage volume (cm^3) for modified vaccination schedule (3)	National/provincial level	325	215
	Peripheral level	346	236

‡ Available soon.
(1) 1xBCG, 3xDPT, 3xHepB, 3xHib, 1xmeasles, 1xTT for women (ref: WHO, 2004).
(2) +4ºC to +8ºC storage only.
(3) same as (1), with addition of 3 doses of RotaTeq® plus 10% wastage.

*At the time of going to press, the GSK vaccine was WHO prequalified but in a different package—the procedure for requesting this small modification is brief. The Merck vaccine was not yet WHO prequalified but was held up by one technical issue which is being resolved. It is anticipated that prequalification for the modified GSK packaging and the Merck vaccine will be complete very early in 2008.

Annex 2: Health systems and immunization program components to consider for rotavirus vaccine introduction

TIMING	ACTIVITIES
Before introduction	Establish burden of disease and public health benefit: • Establish or strengthen surveillance, if desired. • Establish disease burden (or use regional data). • Undertake economic analyses (or use regional data). Health system and immunization program: • Policy analysis, dialogue, and decision-making. • Health system assessment. • Upgrade local infrastructure and logistics. • Assess and upgrade skills, capacity, and resources. • Communication and advocacy. Put financing in place: • Determine vaccine price and co-payment requirements. • Establish budget allocations and financing mechanisms. Vaccine regulatory activities and procurement: • In-country vaccine licensing, if appropriate. • Demand and supply planning. • Vaccine procurement arrangements.
Introduction	Support policy decisions made: • Establish or strengthen surveillance. • Ensure effective program coordination. • Advocacy to political and professional constituencies. Support the health system and immunization program: • Upgrade infrastructure, cold chain, and waste management. • Plan delivery strategies (strengthen routine) and logistics. • Train health workers. • Social mobilization (e.g., national launch, public information, media). • Establish monitoring and evaluation mechanisms. • Outbreak response and control. Ensure vaccine supply: • Supply negotiations and procurement. • Ensure country procurement of co-financed portion.
Routine after introduction	Monitoring and evaluation: • Sustain surveillance and monitor impact. • Ensure effective program coordination. • Sustain program effectiveness and coverage. • Communication and advocacy. • Outbreak response and control. • Evaluate post-introduction safety. Maintain vaccine supply and financing: • Sustain procurement capacity. • Maintain delivery systems/infrastructure. • Monitoring and evaluation. • Sustain commitment for co-financing and scale up.