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Introduction and Implementation of New Vaccines Field Guide

Pan American Health Organization
Regional Office of the World Health Organization

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ABOUT THE IMMUNIZATION FIELD GUIDES

The Expanded Program on Immunization is viewed as one of the most successful public health experiences in the Americas because it has played a pivotal role in reducing infant mortality from vaccine-preventable diseases in the Region. In fact, since the program was launched, our countries stopped the transmission of wild poliovirus in the Region in 1991 and interrupted indigenous measles transmission in November 2002; they also are making significant gains in the battle to eliminate rubella and congenital rubella syndrome. In addition, national immunization programs are undertaking extraordinary efforts to identify at-risk populations and overcome inequities in vaccination. To maintain these advances and to cope with new challenges, such as the introduction of new vaccines, partnerships will have to be strengthened among governments, donor agencies, the private sector, scientific associations, and society as a whole.

To this end, PAHO is promoting the best technical quality by issuing these practical field guides, which have been prepared by the Immunization Unit in the Family and Community Health Area. The most recent techniques presented in the field guides, coupled with useful illustrations, will aid health workers in their efforts to control, eliminate, or eradicate diseases such as poliomyelitis, neonatal tetanus, yellow fever, diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b infections, hepatitis B, measles, and rubella. The field guides also include standardized methods and procedures for conducting epidemiologic surveillance and maintaining an up-to-date information system that will make it possible to make timely and effective decisions.

These field guides are based on the latest scientific information, and they pool the experience of prominent health professionals in the field. As a result, they are particularly suitable for promoting strategies that have already proven to be effective. The strengthening of prevention activities, the reduction of health inequities, and the promotion of technical expertise in vaccination services were the principles that guided the preparation of the guides.

The Expanded Program on Immunization, a joint effort by all the countries of the Americas, effectively contributes to the attainment of the Millennium Development Goals.

Mirta Roses Periago
Director
Pan American Health Organization

ACRONYMS

AD	Auto-disable
CIN	Cervical intraepithelial neoplasia
CRS	Congenital rubella syndrome
DALY	Disability-adjusted life years
DTP	Diphtheria-tetanus-pertussis vaccine
EMEA	European Agency for the Evaluation of Medicinal Products
EPI	Expanded Program on Immunization
ESAVI	Event supposedly attributable to vaccination or immunization
FDA	United States Food and Drug Administration
HepB	Hepatitis B vaccine
Hib	*Haemophilus influenzae* type b vaccine
HPV	Human papillomavirus
ICC	Interagency Coordinating Committee
IEC	Information, education, and communication
MMR	Measles-mumps-rubella vaccine
NCIP	National Committee on Immunization Practices
NRA	National Regulatory Authority
UNICEF	United Nations Children's Fund

PREFACE

New, safe, and effective vaccines are licensed and introduced to the international market every year. Moreover, advances in biotechnology contribute to the improvement of current vaccines through new formulations of the vaccines in use. Although they are available, these vaccines have not yet become part of the official immunization schedule in many countries. Political authorities must often make decisions about public health interventions without the technical facts that would guarantee that their decisions are the most appropriate, in terms of cost-benefit, therefore ensuring the interventions' sustainability. Before a new vaccine is added to an immunization program, its feasibility and sustainability should be evaluated based on previously established technical criteria in order to determine whether it is actually a public health investment priority. This field guide has been adapted from the WHO report *Vaccine Introduction Guidelines: Adding a Vaccine to a National Immunization Programme: Decision and Implementation* (1). In this guide, PAHO offers a systematic tool with useful suggestions and information for political leaders and health authorities that will enable them to make informed decisions about new vaccines. The guide is also intended for managers of national immunization programs and other professionals working in this field, as a tool for resolving technical issues connected with the introduction of new vaccines to strengthen immunization programs in the Region of the Americas. The stages in the introduction of a new vaccine are analyzed: 1) Background, 2) Decision-making, 3) Implementation of the decision, and 4) Vaccine impact assessment.

1. INTRODUCTION

Immunization is one of the most cost-effective public health interventions. Since the creation of the Expanded Program on Immunization (EPI) in 1974, millions of deaths and disabilities from vaccine-preventable diseases have been prevented around the world.

Immunization programs in the Americas have been very successful. In 1970, the national immunization schedules included four vaccines to protect against six diseases (severe forms of tuberculosis, diphtheria, whooping cough, tetanus, poliomyelitis, and measles). During this period, coverage rates were under 10% (2). Later, systematic vaccination and polio eradication campaigns led to greater coverage. In the 1980s, average coverage of 70% to 80% was attained. In the 1990s, most countries introduced new vaccines: combination vaccines such as the trivalent measles-mumps-rubella (MMR) vaccine, *Haemophilus influenzae* type b (Hib) conjugate vaccine, and hepatitis B (HepB) vaccine. The Hib and HepB vaccines were soon replaced by a formulation that combined them with the diphtheria-tetanus-pertussis (DTP) vaccine.

The increase in the number of vaccines did not affect coverage levels, which continued to rise. In 2004-2005, the average coverage was 90% (3). The Region of the Americas has been considered a model for the rest of the world, since it was the first Region to eradicate smallpox and poliomyelitis. Indigenous transmission of measles has also been eliminated, and significant progress has been made in the elimination of rubella and congenital rubella syndrome (CRS). Diphtheria and whooping cough have been controlled, and neonatal tetanus is no longer a public health problem.

There are vaccines against diseases important for international public health that have not yet been introduced in the routine immunization schedule of most developing countries. Many countries have insufficient financial resources to introduce these vaccines in their immunization programs, and use is limited to the private sector. Consequently, the neediest children cannot access the new vaccines. This creates health inequalities and inequities between populations, as well as differences in national vaccination plans.

2. DECISION-MAKING CRITERIA FOR THE INTRODUCTION OF NEW VACCINES

2.1 Overview

Before deciding to introduce a new vaccine in the immunization program or change the route of administration or presentation of a vaccine, the factors contained in the *Decision-making Criteria for New Vaccine Introduction* flow chart (Figure 1) should be considered. The flow chart divides decision-making criteria into two groups. The first group, *Political and Technical Factors*, offers guidance for the senior authorities that must make decisions about the advisability of introducing the vaccine from the standpoint of an evidence-based immunization policy. The second group, *Feasibility and Scheduling*, considers the technical feasibility of introducing the vaccine. Although some criteria in the chart may be more important than others, they should always lead to a decision, which may be:

- To introduce the new vaccine and change the current vaccination schedule, or
- Postpone introduction of the vaccine until sufficient data has been obtained on the decision-making criteria proposed for each group.

In order to assist national immunization program managers in the analyses that will facilitate decision-making, the proposed criteria and their rationale are described below. Some key questions are also posed. The answers to these questions will help find sustainable responses for decision-making.

2.2 Political and Technical Factors

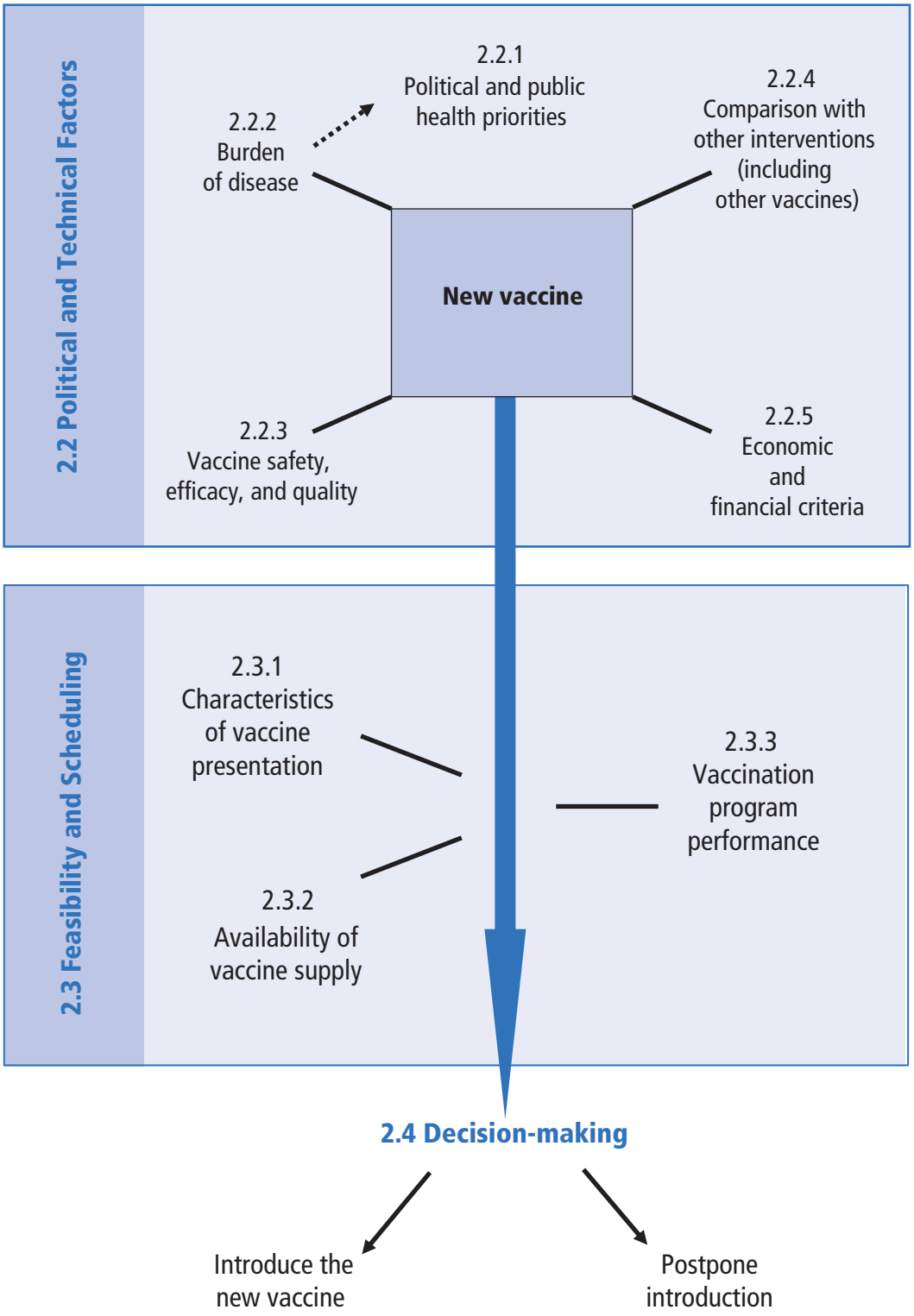
2.2.1 Political and Public Health Priorities

Rationale

A disease is a public health priority when:

- There is a high burden of disease and serious consequences for the health of the population;
- The scientific community, political authorities, and general population consider it a serious public health problem; and
- There is a consensus among opinion-makers, politicians, technical personnel, and the public that this problem should be solved.

Figure 1. Decision-making Criteria for New Vaccine Introduction



Is the disease to be prevented a political and public health priority?

The magnitude and importance of vaccine-preventable disease is one of the main arguments used to justify the setting of national health priorities. For example, it can be demonstrated that the pneumococcal and rotavirus vaccines currently available are a political priority in the field of health since these agents are responsible for a significant proportion of diseases of the respiratory and digestive tracts. Moreover, mortality is higher in children under 5 years in developing countries. It is important to present rational and convincing arguments for the vaccine to political authorities. These arguments should justify the need to allocate resources, which are usually limited, to the proposed intervention and make it a high priority.

The more important and visible a disease is, and the more the vaccine is perceived as a safe and effective measure, the greater the acceptance will be. The perception held by political authorities, the medical community, cooperating agencies, and the general public regarding the vaccine and its likely impact should be identified and documented by a qualitative evaluation, so that introducing the vaccine will be considered a priority.

2.2.2 Burden of Disease

Rationale

It measures the magnitude of the health problem in a given place and time in terms of incidence, prevalence, disability, hospitalizations, and mortality. Knowledge of the burden of disease can help target and rationalize health investments.

Is the burden of disease for the condition to be prevented known?

This is an essential question for decision-making. In order to answer it, data are required on the incidence, prevalence, disability, hospitalizations, and mortality associated with the causative agent in the population and the geographical region or area in which the vaccine is to be introduced. Ideally, these data can be obtained by public health surveillance systems, special studies, or both.

The current health surveillance systems should compile data about the network of public, private, and national health service facilities, as well as incidence, hospitalizations, disability, and mortality related to the disease to be prevented. Surveillance system capacity should be strengthened to include the control of other diseases for which safe and effective vaccines are already available, even if they have not been added to the national immunization schedule (e.g., pneumococcal, rotavirus, influenza conjugate, and human papillomavirus [HPV] vaccines). The data on these vaccines can be used to measure the impact of the intervention, as well as the bur-

den of disease. If surveillance of the disease to be prevented has not been conducted, it should be, taking the type of disease and its characteristics (e.g., hospital surveillance, sentinel surveillance, or other surveillance) into account.

When data from the national surveillance system cannot be used to measure the burden of disease, special studies may be required. Since studies can be expensive, it is important to insist on obtaining reliable national epidemiological data that can be used to analyze the burden of disease.

PAHO has prepared and published six field guides that are essential tools for combating vaccine-preventable diseases: *Neonatal Tetanus Elimination* (4), *Control of Yellow Fever* (5), *Control of Diphtheria, Whooping Cough, Tetanus,* Haemophilus influenzae *type b, and Hepatitis B* (6), *Measles Elimination* (7), *Poliomyelitis Eradication* (8), and *Rubella and Congenital Rubella Syndrome Elimination*, in addition to the epidemiological surveillance guide for rotavirus-related diarrheal diseases. These documents can be found at http://www.paho.org/english/ad/fch/im/vaccines.htm. The World Health Organization has prepared rapid evaluation instruments, generic surveillance protocols, and guidelines for assessing the burden of vaccine-preventable diseases, which can be very helpful. This material is available at http://www.who.int.

2.2.3 Vaccine Safety, Efficacy, and Quality

Rationale

Vaccine safety and efficacy is demonstrated during clinical trials conducted under ideal conditions prior to licensing and during the post-marketing surveillance stage.

Although the vaccines are safe, events may occur in some cases. When they occur on a large scale, adverse events are more likely to attract the attention of health care workers and the public.

Is the available vaccine safe, effective, and of good quality?

Certain characteristics of the vaccine must be demonstrated before it is introduced: immunogenicity and efficacy, duration of immunity, interaction with other antigens, expected adverse events and safety, dosage, route of administration, packaging, and thermostability. It is important to mention that the *efficacy* of the new vaccine is measured in clinical trials under ideal conditions, whereas its *effectiveness* is measured in the field under actual program conditions.

The new vaccine must have been registered by the National Regulatory Authority (NRA), which is the agency in charge of issuing the license that authorizes public distribution of drugs. The NRA is responsible for guaranteeing that the vaccines

registered are safe, have been properly evaluated, and meet other applicable WHO quality and safety standards.

All countries should have NRAs, which ideally are capable of carrying out the six essential control functions: 1) establishing and publishing licensing requirements, 2) presenting vaccine safety and efficacy results, 3) having a lot-clearance system, 4) conducting laboratory tests, if necessary, 5) verifying compliance with good manufacturing practices, and 6) evaluating clinical outcomes via authorized trials. Vaccine-producing countries should conduct these tasks competently and independently, with the backing of an executive authority. Non-producing countries that procure vaccines through United Nations agencies such as PAHO, through the Revolving Fund, or UNICEF, should at least perform the functions of vaccine registration, post-marketing surveillance, and lot clearance (9).

The NRA should establish post-marketing surveillance of the new vaccine in close collaboration with the immunization program's system for the observation of events supposedly attributable to vaccination or immunization (ESAVI).

2.2.4 Comparison with Other Interventions (Including Other Vaccines)

Rationale

There are other vaccines against the same diseases, as well as interventions other than vaccination for control of certain diseases.

The comparison of different control interventions requires an appropriate level of analysis for each intervention.

The key aspects to be considered in this analysis are burden of disease, effectiveness, and cost of each intervention.

Is the vaccine to be introduced the most appropriate intervention for disease control?

The new vaccine should be compared with other vaccines currently used against the same disease and with other interventions. Comparisons are based on effectiveness, safety, cost, usefulness, feasibility, potential microbiological and epidemiological changes that may occur over time, and adverse effects associated with each of the interventions.

It is also important to consider the vaccines that will be marketed in the near future. For example, the introduction of a vaccine may be postponed if it is known that it will soon be available as a combination vaccine. If another control intervention or a vaccine that is already available is more beneficial, there is no need to consider introducing the new vaccine.

2.2.5 Economic and Financial Criteria

Rationale

Vaccination programs represent one of the best health investments.
Evaluation of economic and financial factors related to the new vaccine provides the governments, manufacturers, and agencies cooperating in vaccine development and supply with valuable information for decision-making.
Several different types of financial analyses are used to evaluate health interventions.

How cost-effective is the vaccine?
What is the impact of vaccine introduction on the national budget?
Can the potential financial deficit caused by the vaccine introduction be covered with additional national or external financing?

The introduction of a new vaccine can significantly increase the cost of the immunization program. It is therefore essential to carefully evaluate the costs and benefits of new vaccines by analyzing financial factors, impact on the national budget, and financial sustainability. Each of these aspects is described briefly below.

Financial Analysis

There are different types of financial analyses that use different methodologies. Two types of widely used analyses are the cost-effectiveness analysis and the cost-benefit analysis (10). Both of these help determine whether investment in a new vaccine achieves better or worse health outcomes compared to other types of interventions or another vaccine.

Cost-effectiveness analysis is the methodology used most often in decision-making, since it can be used to compare the cost and effectiveness of two or more interventions. Therefore, variables such as the cost per fully immunized child, the cost per death prevented, the cost in terms of disability-adjusted life years (DALYs), and the cost per life years gained can be monitored. This analysis considers cases occurring regularly in the population and the health costs they entail (e.g., doctor's visits, hospitalization, drugs), the number of expected cases when the vaccine is introduced, considering vaccination coverage, vaccine efficacy, and costs related to the vaccine and its administration. In order to conduct cost-effectiveness studies, general information about direct and indirect costs associated with the disease is required.

Cost-benefit analysis can be used to directly compare costs and benefits, assigning a monetary value to benefits. It is most often used when there is a minimal difference between the expected results and the interventions.

Through the ProVac Initiative, which provides tools for financial analyses to facilitate evidence-based decision-making, PAHO promotes strengthening of Latin American and Caribbean capacity to evaluate the introduction of new vaccines in national immunization programs. WHO has published several methodologies and strategies for financial analysis.

Analysis of the Impact on the National Budget

National immunization program managers should analyze the impact that introducing the new vaccine will have on the national health budget and program expenditures, and calculate the medium- and long-term resources that the program will need. Program costs are divided into specific costs (e.g., vaccines, syringes, cold chain equipment, vehicles, and exclusive staff) and shared costs (e.g., infrastructure, equipment, vehicles, time of non-exclusive health care workers).

The new vaccine should be introduced only when its funding can be covered by the national budget in the middle or long term without affecting the available program resources.

An alternative methodology for establishing a financial arrangement that will guarantee the sustainable allocation of financial resources for the procurement of traditional and new vaccines is to enact a national vaccine law that includes program operating expenditures, as well as the cost of the vaccine.

Analysis of Financial Sustainability

Financial sustainability refers to timely mobilization of the resources required to defray the costs of a future intervention. It is related to maintaining funding for all components of the vaccination program after the introduction of a new vaccine.

The analysis of financial sustainability should begin by evaluating the current and future resources required and comparing them with the current and future funding of different program items, by source of funding, each year. Sources of funding include the general budget of the Ministry of Health and, when necessary, funds provided by donors. An indicator that should be used to establish the budget for the Ministry and convince donor agencies of the need for greater mobilization of resources is the financial deficit (total resources required minus available programmed funds) calculated each year. Other possible sources of funding are funds from local governments, Social Security, resources obtained from debt relief, development loans, and contributions by the private sector, foundations, and nongovernmental organizations (NGOs).

2.3 Feasibility and Scheduling

Rationale

Feasibility and scheduling are related to the characteristics of the product to be procured. They should be evaluated by technical personnel since they affect functionality, logistics, supplies, performance, and other aspects of the vaccination program that can influence decision-making on the introduction of new vaccines.

2.3.1 Characteristics of Vaccine Presentation

Is the available vaccine presentation functional for the program?

National immunization program managers should be familiar with the characteristics of the new vaccine to be introduced as they relate to the presentation already on the market. The vaccine can be a monovalent or combination vaccine, available in single or multiple doses, liquid or lyophilized, or in series with different numbers of doses. These characteristics have a direct impact on decision-making. For example, the introduction of a vaccine might be delayed if the current formulation or presentation creates functionality problems in the schedule or increases operating costs (Annex 1).

2.3.2 Vaccine Supply

Is the vaccine supply sufficient to guarantee a regular supply?

A vaccine procurement mechanism that ensures an adequate, timely, and regular supply must be established, because only a limited number of manufacturers can produce new vaccines, and this can create uncertainty about future supply. The PAHO Revolving Fund for Vaccine Procurement guarantees an uninterrupted flow of vaccines and vaccination supplies to the Member States in the Region. This has made it possible to expedite the introduction of affordable quality vaccines and offer safety and confidence to health authorities and national immunization program managers.

2.3.3 Vaccination Program Performance

Is the program prepared to introduce a new vaccine?

Before introducing any vaccine, the overall performance of the national vaccination program should be evaluated to identify any aspects that need to be improved. The introduction of a new vaccine can influence program performance in two ways: by increasing community demand and, consequently, coverage, or by weakening demand if performance is deficient. The priority of a poorly performing immuniza-

tion program should be to solve the current problems before introducing new vaccines.

PAHO has developed methodologies for evaluating immunization programs in the Region in order to measure their performance and capacity to introduce a new vaccine. They include a series of criteria that help gauge program capacity (Annex 2). This guide includes six technical elements with indicators and key questions that will help determine whether the program is prepared to introduce the new vaccine, based on its level of performance (Annex 2).

2.4 Decision-making

After analyzing political, technical, planning, and feasibility factors, and reviewing the results, national immunization program managers will have sufficient elements to support a preliminary technical decision. This decision should be reached by consensus with the National Committee on Immunization Practices (NCIP), in order to analyze all consequences of potential interventions and, consequently, recommend to political authorities and decision-makers the most effective control measure against the disease to be prevented. This analysis will conclude in two possible decisions: recommend introduction of a new vaccine or postpone introduction.

The NCIPs should be considered contributors to the evaluation process before vaccine introduction and to the decision to introduce it. Its members are experts from the scientific community, universities, and Social Security, representatives of international health organizations such as PAHO, and national immunization program managers.

3. IMPLEMENTATION: PLAN FOR THE INTRODUCTION OF VACCINES

In order to introduce a new vaccine in the national immunization program, a plan of action should be drafted that includes all aspects necessary for implementation at the national, departmental/state, and local/municipal level. The immunization program's plan of action is a valuable tool to guide national, departmental, or regional program managers in the design of the plan for vaccine introduction. It enables them to adapt each component of the plan to the special features of each level and the characteristics of the new vaccine. The elements of the plan, whose application requires a political and financial commitment, should be included in the annual and 5-year plans of action as well as the national health plan in order to ensure sustainability.

The essential elements that should be included in the plan for the new vaccine introduction are described below.

3.1 Background and Development of Immunization Program

The plan for new vaccine introduction should include the historical background—creation of the program and its evolution—in terms of vaccine introduction and modifications to the vaccination schedule.

3.2 Technical Justification for Introduction

This was already developed in the pre-introduction analysis, which considered political, technical, planning, and feasibility aspects that should be taken into account in order to decide on introduction of a new vaccine. Therefore, only this analysis should be included in the document.

3.3 Objectives and Goals

The objectives are based on the pre-introduction analysis, which includes the burden of disease and the proposed goal (control, elimination, or eradication of disease). The goals have consequences in terms of epidemiology and funding. Therefore, they are adopted after a consensus has been reached between program managers and policymakers, considering available resources.

3.4 Scope of Application and Target Population

Definition of the geographical area in which the vaccine will be administered and the target population will depend on the risk profile of the disease to be controlled or prevented, the introduction strategy selected, and the goals set.

3.5 Selection of Introduction Strategy

Selection of how the vaccine is introduced depends on the characteristics of the disease (whether it affects the entire population or only some risk groups), as well as national capacity to cover the costs of additional program activities and confront the challenges associated with introduction (e.g., number and capacity of human resources, public pressure).

3.6 Activities by Component

3.6.1 Planning and Scheduling

Planning and scheduling activities are key to the successful introduction of a vaccine. Therefore, a retrospective analysis from the programmed introduction date should be conducted. The main activities that must be carried out before vaccination begins will be defined. This will determine the time needed for the planning and scheduling process. These activities include defining the respective target populations at different levels (national, regional, and municipal or local), calculating the available resources, and assessing needs and costs for the entire program. Vaccine availability should be ensured at least six months in advance through the established procurement procedures.

3.6.2 Coordination

This includes all activities related to the immunization program's lines of coordination with other programs and departments for introduction of the new vaccine at the intrainstitutional level—for example, the NCIP, professional associations, Social Security, universities and health resources training institutes, the Interagency Coordinating Committee (ICC), nongovernmental organizations, and local governments.

3.6.3 Standardization

When a vaccine is introduced, the manager of the immunization program should:

- Establish the mechanisms required to make changes in the official vaccination schedule, including the technical description of the vaccine (i.e., name, disease it protects against, age of administration, dose, route of administration, number of doses and interval between doses, concurrent administration with other vaccines) and operational standards for implementation, such as technical content on the disease and the vaccine, cold chain, ESAVIs, and contraindications.
- Undertake technical validation of the standards for the vaccine with the NCIP and the health authorities. Later, the immunization program's manual of standards should be updated.

- If the new vaccine replaces a vaccine already available in the immunization program, put in place provisional measures for children who have already begun to receive vaccines under the previous official schedule (e.g., DTP as the previous vaccine and the combined DTP/HepB/Hib vaccine as the new vaccine).

3.6.4 Procurement and Distribution of Biologicals and Supplies

Procurement and distribution of the new vaccine and supplies should be included in the current procurement mechanism (e.g., the PAHO Revolving Fund) to guarantee a constant flow of safe vaccines and a strategic reserve to prevent crises connected with shortages or higher vaccine wastage rates. The introduction of a new vaccine offers the opportunity to improve the current procurement and distribution mechanism.

3.6.5 Storage and Cold Chain

The plan to introduce the vaccine should include the calculation of space requirements and cold chain equipment at the national, departmental/state, and local/municipal levels, and even in the vaccination rooms. The data on additional storage requirements are based on the dosage form and characteristics of the new vaccine and those currently in use. The calculation should include an evaluation of storage and transport capacity for biologicals at each level of the cold chain, determining the need for additional equipment. This evaluation offers an ideal opportunity to update the national cold chain inventory by type of equipment and operating condition. Annex 3 contains a sample calculation of storage needs for a new vaccine.

3.6.6 Safe Vaccination

Safe vaccination activities should include the following:

Vaccine quality. The activities begin when the vaccine is received. At this time, temperature conditions are checked, and verification is made that they were transported according to international packaging standards. Activities also include verification that individual lots received clearance certificates from the NRA in the country of manufacture. This documentation should be reviewed by the NRA in the country to authorize distribution.

Safe injections. If the new vaccine is administered by injection, it is important to ensure compliance with safe injection standards by promoting the use of autodisable syringes to prevent recycling. Biohazard boxes should be supplied to ensure proper disposal, as well as safe end use and destruction.

ESAVI surveillance. Surveillance of potential adverse events associated with the new vaccine should be included in the current ESAVI surveillance system in the country and intensified. The objective is to emphasize active, heightened surveillance of all adverse events associated with the new vaccine that are described by the manu-

facturer, as well as unanticipated events, in order to take the necessary steps at the appropriate time. It should be borne in mind that many events that occur around the same time as the vaccination are coincidental and erroneously attributed to vaccination. An appropriate and timely investigation, with the participation of experts, is critical for preventing rumors that could undermine credibility and acceptance of the vaccine and the program itself.

PAHO has published seven safe vaccination modules, which can be consulted on its website: http://www.paho.org/Spanish/AD/FCH/IM/Modulo_ImmSafety.htm (available in Spanish only).

3.6.7 Training

Introduction of a new vaccine requires training activities on components of the plan and compliance with vaccine administration standards. These activities should be geared to personnel at all levels, particularly staff in the field.

The training plan should initially target national and departmental coordinators of areas directly or indirectly related to vaccine introduction (e.g., information system, communication, cold chain, ESAVI surveillance, NRA), who will facilitate the training processes on the district/municipality and local levels.

Training in specific components of the plan should include participation by representatives of the scientific community, Social Security, and other health sector institutions in order to standardize criteria for the use of the new vaccine.

3.6.8 Social Mobilization and Communication

When a vaccine is introduced, it is necessary to guarantee that the population receives the necessary information about its characteristics and benefits. This is accomplished by designing and putting together an information, education, and communication (IEC) plan. Strategies for promoting the new vaccine should be developed, ensuring clear and effective information for the general public, as well as the scientific community and health care workers from the private sector, to boost community confidence and generate demand. It is important to ensure that opinion-makers and social communicators be given appropriate information so that they can provide extensive coverage on the vaccine's expected impact in terms of preventing or controlling the disease in question.

The media influence the public perception of vaccination. That influence may be either positive or negative. It is essential to forge partnerships with these actors from the outset in order to ensure their support in getting messages out.

Before preparing any informational material, the population's knowledge and perception of the disease should be evaluated so that information and education needs can be determined and appropriate content prepared. The preparation of IEC

materials is useful for vaccine promotion and the training of health workers. In addition to new material for the general public, materials for several different target populations, including physicians, vaccinators, and journalists, must be developed.

3.6.9 Implementation and Vaccination

Implementation should consider the vaccination strategies that will be implemented in line with the proposed objective (i.e., control, eliminate, or eradicate disease), the form of introduction (i.e., campaign, routine vaccination, or gradual introduction), characteristics of the target population, and how implementation is related to the regular schedule. Vaccination strategies should guarantee that the vaccine reaches the target population under ideal conditions. It is particularly important to ensure that it is administered at the proper time and at the right age in order to obtain the optimum benefit.

3.6.10 Amendment of Program Information Records

The introduction of a new vaccine requires the amendment of all immunization program information forms (e.g., daily registry, monthly registry, cards or records, tables indicating the movement of biologicals and supplies, and other vaccine-related forms designed and used by other health care programs).

In order to make changes in the immunization program records in the national health information system, early coordination must be established with the heads of statistics and informatics departments to ensure their commitment to the process. This in turn will ensure the necessary changes and adherence to the timetable of the plan.

All changes related to new vaccine introduction should be included in the immunization program's computerized information system in keeping with the variables defined in order to obtain program monitoring and evaluation indicators.

3.6.11 Epidemiological Surveillance

All vaccine-preventable diseases should be subject to epidemiological surveillance. This means that the disease to be prevented by the new vaccine must be covered by the national surveillance system if it was not during the pre-introduction period.

Disease surveillance should include a review of current protocols and prompt updating of the list of reportable diseases, according to the frequency established for each case. In high-frequency diseases, a sentinel surveillance model may be sufficient to characterize the problem. For low-frequency diseases, a national surveillance system must be created to detect the highest possible number of cases in order to characterize the disease. It may be necessary at times to modify the current system or design and develop new models.

Laboratory support in the diagnosis of disease will be essential to measure the impact of the vaccine. Therefore, operating capacity must be evaluated, and the requisite diagnostic methods should be established or strengthened throughout the national network. The supply of reagents and other materials required to meet surveillance needs should also be calculated.

3.6.12 Monitoring and Supervision

Monitoring and supervision should be conducted throughout the introduction of a new vaccine. They should begin in the planning and implementation stage in order to verify that the actions defined in the planning of goals for the population to be vaccinated have been conducted in each town and health unit. Process indicators should be defined, information registries adapted to the new vaccine should be available, staff training on plan components should be guaranteed, and progress in implementation of the IEC plan should be determined. The search for solutions will be based on the identification of problems that hinder implementation of the plan.

Indicators related to the new vaccine should be included in the regular program supervision guide, in accordance with the methodology established for implementation at all levels.

3.7 Cost of the Plan

In order to ensure implementation of the plan, the total budget must be calculated to mobilize and manage financial resources for its implementation. The cost of the plan, by activity and component, should be included in the annual Ministry of Health spending budget for approval in the respective fiscal year.

The plan to introduce the vaccine should also be included in the immunization program's annual plan of action, with a cost breakdown by activity and source of funding (national funds and external funds). The ICC is an important body for mobilizing additional plan resources.

3.8 Timetable

In order to ensure that the plan is implemented within the period stipulated, it is important to establish the time allotted to each activity in a timetable. Each activity should be monitored to ensure that it is completed within the established time frame. Provisions should be made to extend this period, if necessary, and the implementation of the entire plan in terms of the time allotted should be evaluated.

3.9 Evaluation

The plan to introduce the new vaccine should be evaluated at all levels of the immunization program evaluation process. Evaluations are usually performed twice a year. The primary method for evaluating the introduction of a new vaccine is to monitor vaccination coverage in the municipalities or districts. New vaccine introduction should lead to a reduction in disease over time. The indicators used for evaluating the new vaccine are the same as those used to evaluate immunization program management (e.g., vaccination coverage, dropout rates, vaccine wastage factor, and ESAVI rates). These indicators will be monitored regularly, and their analysis will be provided in the semiannual program evaluations.

Annex 4 contains a checklist that can be used to evaluate the plan for introducing the new vaccine. It should be applied six months to one year after the introduction of the vaccine, during the regular program supervisory activity.

4. IMPACT ASSESSMENT

Measuring the impact of a vaccine will depend on the nature of the disease to be controlled or prevented and the current surveillance system. There are different methods for assessing the impact of a vaccine. The most common are those that show the percentage reduction in the burden of disease attributed to vaccination, according to the level of coverage attained.

A key procedure in assessing the impact of a vaccine is the comparison of coverage data and incidence of disease. This is done to verify that the reduction of disease is consistent with expectations for the level of coverage attained. Another methodology employed involves the calculation of vaccine effectiveness. It consists of obtaining the vaccination history of all cases of the disease in question in order to establish the appropriate vaccination coverage. This will be compared to vaccination coverage for the general population in an area or country. However, this calculation should be interpreted carefully (11). This methodology is also useful for program surveillance.

In some situations, surveillance data must be supplemented with special studies to assess the impact of vaccination. Evaluation of hepatitis B vaccine (HepB) is an example in which the impact on chronic disease will not be evident until decades after vaccination. In this case, the impact of the vaccine can be evaluated by a serological survey to detect chronic infection.

The updated version of this guide will be available at www.paho.org/immunization.

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ANNEX 1. ASPECTS TO BE CONSIDERED WHEN INTRODUCING VACCINES: EXAMPLES OF APPLICATION

TYPE OF VACCINE	INFLUENZA	PNEUMOCOCCAL	ROTAVIRUS	HUMAN PAPILLOMAVIRUS (HPV)
Presentation	Trivalent vaccine from inactivated virus propagated in eggs. Available in 1- and 10-dose ampoules, liquid	1. 7-valent conjugate vaccine. Liquid in preloaded 1-dose syringe. In boxes of 10 doses 2. 23-valent polysaccharide vaccine. Contains 25 μg/ml of each serotype. Liquid in 1-dose vials	1. Pentavalent human-bovine vaccine. Liquid in 1-dose plastic tubes In boxes of 10 tubes 2. Monovalent human vaccine. Lyophilized in 1-dose vials	Contains the main L1 capsid proteins that bind to each other to form virus-like particles of HPV types 6, 11, 16, 18 (tetravalent vaccine) and types 16, 18 (bivalent vaccine). Both are liquid in 1-dose vials
Efficacy	70% to 90% in persons under 65 years; 30% to 40% in older adults; 50% to 60% in prevention of hospitalization; 80% in prevention of death	1. Conjugate: 97.4% for invasive disease in children under 2 years 2. Polysaccharide: many studies have shown variable efficacy against invasive disease	1. Pentavalent: 98% for rotavirus-related acute gastroenteritis 2. Monovalent: 85% for rotavirus-related severe diarrhea	100% against precancerous cervical lesions (NIC grade 2 and 3) produced by genotypes 16 and 18. Tetravalent vaccine offers 95%-99% protection against genital warts
Recommended age	Children over 6 months	1. Conjugate: 2, 4, and 6 months 2. Polysaccharide: over 2 years	1. Pentavalent: 2, 4, and 6 months 2. Monovalent: 2 and 4 months	Girls and women aged 9 to 26 years (some countries have granted a license for use of this vaccine in girls aged 9 to 15 years)
Dose and schedule	6 to 35 months: two 0.25-ml doses, 1-month intervals 3 to 8 years: one 0.5-ml dose (with vaccination history) each year Over 9 years of age: one 0.5-ml dose each year	1. Conjugate: three 0.5-ml doses at 2, 4, and 6 months. Booster dose at 12 to 15 months 2. Polysaccharide: one 0.5-ml dose for persons over 65 years and persons from 2 to 64 years with chronic diseases. Not recommended in children under 2 years	1. Pentavalent: three 2-ml doses at 2, 4, and 6 months. 2. Monovalent: two doses at 2 and 4 months. Reconstituted lyophilized for oral administration	Three 0.5-ml doses at 0, 2, and 6 month intervals
Route of administration	Intramuscular	1. Conjugate: intramuscular 2. Polysaccharide: intramuscular (preferable) or subcutaneous	Both: oral	Intramuscular
Concurrent administration with other vaccines	It can be administered concurrently with other vaccines at different anatomical sites	It can be administered concurrently with the influenza vaccine and other vaccines at different anatomical sites	It can be administered concurrently with other injectable vaccines	It can be administered concurrently with other injectable vaccines in adolescents
Storage temperature	2°C to 8°C	2°C to 8°C	2°C to 8°C	2°C to 8°C

TYPE OF VACCINE	INFLUENZA	PNEUMOCOCCAL	ROTAVIRUS	HUMAN PAPILLOMAVIRUS (HPV)
Volume per dose in cm^3	30 cm^3	1. Conjugate: 60.6 cm^3 2. Polysaccharide: 103.7 cm^3	1. Pentavalent: 46 cm^3 2. Monovalent: 110 cm^3	47.04 cm^3
License status and WHO prequalification	Registered by EMEA and FDA Prequalification: WHO evaluates a process for annual formulation	Conjugate 7-valent registered by EMEA and FDA Prequalification: process has started	1. Pentavalent: registered by FDA 2. Monovalent: registered by EMEA and prequalified by WHO	1. Tetravalent: registered by FDA and other countries 2. Bivalent: registered by European Union countries and others Prequalification: pending
Availability of supply+	Insufficient. Nine manufacturing laboratories. Annual formulation	1. Conjugate: one manufacturing laboratory 2. Polysaccharide: two manufacturing laboratories	1. Pentavalent: one manufacturing laboratory 2. Monovalent: one manufacturing laboratory	1. Tetravalent: one manufacturing laboratory 2. Bivalent: one manufacturing laboratory
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+ The increase in demand could affect vaccine supply.

ANNEX 2. ELEMENTS FOR EVALUATING MANAGERIAL AND OPERATIONAL CAPACITY OF THE PROGRAM TO INCLUDE NEW VACCINES

1. Program management and progress

- There is an annual plan and a 5-year plan of action, as well as a vaccine law.
- Vaccination coverage is greater than or equal to 95%, and dropout rates are less than 5%.
- Eradication, elimination, and control plans have been established, or implementation of these plans is progressing.

2. Program sustainability

- The program is prepared to mobilize and use current and future resources.
- The national health budget includes an allotment to ensure vaccine supply and other program costs established in the 5-year plan.
- The program is prepared to introduce the new vaccine without jeopardizing its financial sustainability.

3. Functional cold chain

- There is an inventory of equipment and updated plans for the maintenance and replacement of cold chain equipment.
- Cold chain storage capacity is sufficient for the vaccines used routinely in the program at all levels.
- Cold rooms are available in order to meet additional demand for storage of the new vaccine.

4. Proper vaccine management

- There are biannual or 5-year forecasts for all vaccines used routinely (including supplementary activities) and for new vaccines. These forecasts provide for the transitional period when the current vaccines are being replaced.
- Effective follow-up is conducted for wastage of all vaccines, and levels are considered to be acceptable based on the extent of coverage.
- Vaccine shortages at national level or at other levels are rare.

5. Safe vaccination

- All vaccines are administered with auto-disable syringes.
- Appropriate diluents and reconstitution methods are used for lyophilized vaccines.
- There is capacity to obtain, distribute, and eliminate additional injection supplies for the new vaccine.
- There is an ESAVI surveillance system and crisis response capacity.

6. Surveillance of vaccine-preventable diseases

- Timely, reliable, and comprehensive surveillance of vaccine-preventable diseases is conducted, and system indicators are met.
- There is a surveillance system for the disease associated with the vaccine to be introduced.

ANNEX 3. ESTIMATING VACCINE STORAGE CAPACITY

It is important to know the storage capacity available in high-volume cold storage equipment, as well as the space required for vaccine storage at the health centers. It should be borne in mind that vaccine storage space in cold storage equipment is 50% of its usable space. In order to estimate the volume required for vaccine storage, the criteria that should be considered include susceptible population, wastage rate per dose, additional doses or booster doses (if any), increased doses due to additional vaccination, new vaccine introduction, type and class of vaccine to be stored, and vaccine storage period.

The following exercise will help make rough calculations of cold storage space requirements for proper vaccine storage.

Calculation to estimate storage requirements for new vaccines

1. Calculation of capacity

Regardless of the type of vaccine, manufacturing laboratory, or dosage, the space required for a dose of vaccine should be calculated according to the differences in how it is supplied (size of packaging and vial containing the vaccine, and dosage per vial). It is important to bear in mind that there is a tendency to supply the vaccines in 1-dose vials. For doses used regularly, a volume of 30 cm^3 has been estimated. However, if a new vaccine dose occupies greater storage volume, the actual volume occupied must be recalculated based on size of the package and the number of doses of vaccine required. At present, for example, the size of the original package of a dose of the new vaccines on the market has shrunken from 260 cm^3 to the current volume of 110 cm^3.

2. Cold storage capacity

The proper way to store vaccines is in their own box. Therefore, the space that a vaccine dose occupies in its box (30 cm^3) will be used as an example for calculation.

Procedure:

- Multiply the total number of doses of vaccine required by 30 cm^3.
- Suppose 2,000,000 doses of all vaccines are required for implementation of the regular vaccination program.
- Multiply 2,000,000 x 30 cm^3.
- The result is 60,000,000 cm^3.

- The cubic space or volume of the cold storage equipment is usually calculated in liters of capacity. Each liter is equivalent to 1,000 cm^3.
- Divide 60,000,000 cm^3 by 1,000 cm^3: The result is 60,000 liters.
- Therefore, in order to store 2,000,000 doses of vaccine, 60,000 liters of cold storage space is required.
- 60,000 liters is equivalent to 60 m^3 (1 m^3 is equivalent to 1,000 liters).

3. Usable space and storage volume

Since the usable space for vaccine storage in cold storage equipment is 50% of its total capacity and 60 m^3 is needed for vaccine storage, a cold storage room or smaller cold storage equipment with a total internal volume of 120 m^3 is required.

4. Selection of cold storage equipment

Based on the previous calculation, the cold storage room or the amount of cold storage equipment that is most appropriate for the requirements will now be selected. Therefore, if a cold storage room with the following dimensions is used:

External: 4.65 x 3.65 x 2.75 m (with 15 cm insulation).

Internal: 44.50 x 3.50 x 2.60 m = 40.95 m^3 (internal dimensions are used for the calculation.) This is the result that will be used to calculate the amount of cold storage equipment required.

5. Equipment dimensions

Since the cold storage space required is a volume of 40.95 m^3, it is estimated that three rooms with the same dimensions and characteristics will be needed to store the vaccines in the example. Therefore, there will be a total area of 122.85 m^3 (i.e., 40.95 m^3 x 3) in the three rooms.

6. Smaller cold storage equipment

Internal dimensions of cold storage equipment:
0.65 x 0.60 x 0.45 = 0.1755 m^3 (equivalent to 175,500 cm^3 and 175.5 liters)

- The usable space is only half of this volume (i.e., 175.5 liters divided by 2 = 87.75 liters)
- 1 liter = 1,000 cm^3 = 1 dm^3
- 1,000 cm^3 divided by 30 cm^3 (the space occupied by each dose) = 33 doses x 1 dm^3 (i.e., per liter)
- Usable space: 87.75 liters (or dm^3)
- 87.75 liters x 33 doses per liter = 2,895.75 doses of vaccine, rounded off to complete doses: 2,895

6.1 Equivalents

- 1 meter = 3,281 linear feet (1 foot = 0.30478 m)
- 1 cubic foot = 0.028311 m^3 = 28,311 cm^3 = 28.31 liters
- At a rate of 33 doses per liter, 28.31 liters x 33 doses/liter = 934.23 doses will fit in 1 cubic foot. In other words,
- 934 vaccine doses can be placed in 1 cubic foot.

If the cold storage room in the previous example had a usable internal space of 87.75 liters, its usable capacity in cubic feet would be 87.75 liters divided by 28.31 liters/ft^3 = 3.0996 ft^3, which is rounded off to 3.1 cubic feet.

It is verified that, in fact, 3.1 cubic feet x 934 doses/ft^3 = 2,895.4 doses. This is rounded off to complete doses (2,895), which was the result already obtained in the calculation in paragraph 6.

Exercises

The following data are internal measurements (in linear meters) of the usable space of refrigerators.

Where:

Height		Width		Depth
0.70	x	0.60	x	0.50 m
0.80	x	0.55	x	0.50 m
0.80	x	0.60	x	0.50 m

Based on these data, calculate:

- Total capacity
- 50% of capacity or “usable capacity” in liters
- Usable capacity in cubic centimeters
- Usable capacity in cubic feet
- Number of doses of vaccine that could be stored in the cold storage equipment

ANNEX 4. CHECKLIST FOR EVALUATING THE VACCINE INTRODUCTION PLAN

1. Confirm the following indicators through direct supervision or review of program registries:	
Registries and forms	Are there updated registries and forms that include the new vaccine used?
Vaccination coverage	Is new vaccine coverage similar to coverage for regularly used vaccines that are administered concurrently?
	Are dropout rates for the new vaccine similar to rates for regularly used vaccines that are administered concurrently?
	Are there any differences in coverage for regularly used vaccines before and after introduction of the new vaccine?
Vaccine waste	Is the wastage rate for the new vaccine similar to the rate for regularly used vaccines with the same presentation (liquid or lyophilized) and vial size?
2. Analysis at the national level	
Pre-implementation phase	Were the following activities performed prior to introduction? • Calculation of burden of disease and cost-effectiveness • Planning for financial sustainability in future years • Promotional activities and social mobilization • Training and preparation of materials • Evaluation of cold chain capacity
Planning and operation	Is the implementation in progress consistent with the initial plan (nationwide or gradual introduction, important dates)?
	Have the new vaccine doses been planned in accordance with needs? Is the vaccine obtained and distributed appropriately?
	Are post-vaccination adverse events associated with the new vaccine recognized and reported?
	Is there a surveillance system for diseases related to the new vaccine?
Vaccine management	Have shortages of vaccine supplies been recorded since it was introduced?
Evaluation of impact	Has a plan been defined to evaluate the impact of the new vaccine? What methods are considered (program result indicators, regular surveillance system, special studies)?
	What is the general perception regarding introduction on the part of political decision-makers and the immunization program team?
3. Observation and verification in the health services	
Health care worker practices	Are correct practices observed during handling, reconstitution, and administration of vaccines?
Vaccination safety	Are auto-disable syringes and biohazard boxes used to dispose of injection material? Are syringes and biohazard boxes disposed of properly?
Vaccine management	Are vaccines frozen in the health care facilities that should NOT be frozen?
	Do health care facilities have problems with shortages of the new vaccine?

Vaccine wastage	Is vaccine wastage recorded and monitored in health care facilities? Is the vaccine wastage rate similar to the national rate?
Health care worker knowledge	Do health workers need additional training and supporting supervision for the new vaccine?
Community acceptance	Is the new vaccine well received by the community and health workers?
	Do family members know the name of the new vaccine and the disease it prevents? (Interview with service users)