



*Maternal
and Neonatal
Immunization
Field Guide
for Latin America
and the Caribbean*



**Pan American
Health
Organization**



**World Health
Organization**

REGIONAL OFFICE FOR THE **Americas**

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Preface

Over the past several decades, important advances have been made in reducing infant and under-five mortality due to vaccine-preventable diseases. This downward trend has not, however, been observed for maternal and neonatal mortality. In the context of the post-Millennium Development Goals (MDGs) and the current Sustainable Development Goals (SDGs) framework, targets have been set to reduce the global neonatal mortality rate to 12 or less per 1,000 live births, and the maternal mortality rate to 70 deaths or less per 100,000 live births by 2030. In the Americas, the MDG goal of reducing maternal mortality by 75% by 2015 was not met. In 2015, the Region reported a maternal mortality rate of 67 deaths per 100,000 live births corresponding to a reduction of 49% between 1990 and 2015. In 2015, a mortality rate of 15 deaths per 1,000 live births was recorded among children aged less than five years.

Maternal and neonatal immunization can contribute significantly to the reduction of maternal and neonatal morbidity and mortality associated with vaccine-preventable diseases. However, challenges persist in providing universal and equitable access to high-quality maternal and neonatal care, making it difficult to meet the established goals.

The World Health Organization (WHO) and other institutions have given priority to maternal immunization as an innovative and effective way to address maternal and neonatal mortality. It has become a priority platform on the global health agenda given its potential to decrease serious morbidity and mortality not only in the mother, but also in the fetus, the neonate, and the young infant who are not able to immunologically respond to most vaccines. There is a growing body of research evidence regarding the potential benefits of maternal immunization, including safety and ethics. Additionally, new evidence is being generated to explore the potential benefits of new vaccines for the woman and her infant, such as Group B Streptococcus and Respiratory Syncytial Virus vaccines.

The Region of the Americas has been a leader in maternal immunization, as demonstrated by the significant progress made towards the elimination

of neonatal tetanus. Out of the current 35 countries and territories that vaccinate pregnant women against influenza worldwide, 31 of them are located in the Region of the Americas. Moreover, in April 2015, the Region was declared free of rubella endemic transmission and of congenital rubella syndrome, a result that has prevented the estimated 20,000 babies born annually from having congenital rubella syndrome. Years of programmatic experience in vaccinating pregnant women against tetanus, diphtheria, and influenza have generated important lessons and helped establish the practices. The progress made in the Americas has been possible through the political commitment and financial resources of Member States; the unstinting dedication of healthcare workers; and the integrated efforts of maternal and child health services with immunization programs. Extensive access to antenatal care and the high proportion of births occurring in health facilities in the Region have contributed to the past achievements and offer a real opportunity to increase coverage of maternal and neonatal interventions. In order to meet the SDG targets, further strengthening of collaboration between stakeholders and strategic partners involved in maternal and neonatal immunization will be critical.

With the objective of facilitating the implementation or strengthening of maternal immunization programs across the Americas, the Pan American Health Organization (PAHO) has developed the present field guide, targeting primarily maternal and child health personnel and immunization program staff. This field guide aims to provide key information on the current maternal and neonatal vaccines available or under development, as well as recommendations for their introduction or the expansion of their use. It also covers aspects of social communication and vaccine acceptance that are fundamental for promoting maternal immunization. The authors of this document have made every effort to ensure that the language and format are user-friendly and accessible to a wider audience beyond healthcare workers.

Carissa F. Etienne,
Director of the Pan American Health Organization

ABOUT THIS PUBLICATION

A soft, watercolor-style illustration of a woman with dark hair, wearing a light-colored top, holding a baby. The woman's eyes are closed, and she has a gentle expression. The baby is wrapped in a light-colored cloth. The background is a mix of warm, muted colors like yellow, pink, and orange, with a textured, painterly appearance.

OBJECTIVE

The Pan American Health Organization's *Maternal and Neonatal Immunization Field Guide* aims to provide a practical road map of maternal and neonatal immunization to healthcare workers at all levels of the health system, integrating immunization programs and maternal and child health services. The guide might also be of use for health education programs.



AUDIENCES

The intended audiences for the various sections of this Field Guide are:

- Section I** • Managers of maternal and child health services including immunization program managers and personnel.
- Section II** • Immunization program personnel.
- Personnel working with immunization, including maternal and neonatal immunizations (during pregnancy and post-partum for the mother and newborn).
- Healthcare providers: obstetricians, pediatricians, midwives, nurses, and any healthcare team members who provide care to women of childbearing age, including pregnant women or women in the post-partum period.
- Women of childbearing age.
- The media.



KEY DEFINITIONS

Preconceptional Counseling

According to the Latin American Center for Perinatology (CLAP), preconceptional counseling is defined as a set of interventions aimed at women of childbearing age that are designed to identify and, if possible, modify risk factors related directly or indirectly to the risk of malformations or other poor perinatal outcomes.

Maternal and Neonatal Immunization

In this field guide, maternal and neonatal immunization refers to immunization given prior to pregnancy, during pregnancy, and during the post-partum period (both for the mother and her newborn), in order to provide protection to both the mother and her newborn child.

Post-partum

The post-partum is understood as the 42-day period following the conclusion of an obstetric event, irrespective of the outcome of the pregnancy.

ACRONYMS

AASLD	American Association for the Study of Liver Diseases
ACOG	American Congress of Obstetricians and Gynecologists
AEFI	Adverse Event Following Immunization
aP	Acellular pertussis vaccine
BCG	Bacillus Calmette-Guérin (anti-tuberculosis vaccine)
CDC	Centers for Disease Control and Prevention
CLAP	Latin American Center for Perinatology
DT	Tetanus toxoid and diphtheria toxoid (pediatric)
DTaP	Combined vaccine against diphtheria, tetanus, and pertussis (acellular) (pediatric)
DTP	Combined vaccine against diphtheria, tetanus, and pertussis
DTwP	Combined vaccine against diphtheria, tetanus, and pertussis (whole cell) (pediatric)
EPI	Expanded Program on Immunization
FDA	Food and Drug Administration (USA)
GACVS	Global Advisory Committee on Vaccine Safety (WHO)
GBS	Group B streptococcus
GVAP	Global Vaccine Action Plan
HAV	Hepatitis A virus
HBcAg	Hepatitis B virus core antigen
HBeAg	Hepatitis B virus e-antigen
HBsAg	Hepatitis B virus surface antigen
HBIG	Anti-hepatitis B immunoglobulin
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HPV	Human papilloma virus
ICC	Interagency Coordinating Committee
IDU	Injection drug users
IEC	Information, education and communication
IU	International units

JRF	WHO/UNICEF Joint Reporting Form
MDG	Millennium Development Goals
mg	micrograms
ml	milliliters
NIH	National Institute of Health
NITAG	National Immunization Technical Advisory Group
NNT	Neonatal tetanus
PAHO	Pan American Health Organization
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PMNCH	Partnership for maternal, newborn and child health
RIAP	Regional Immunization Action Plan
RV	Rotavirus
RSV	Respiratory syncytial virus
SAGE	Strategic Advisory Group of Experts on Immunization (WHO)
SDG	Sustainable Development Goals
STD	Sexually transmitted disease
SWOT	Strengths, Weaknesses, Opportunities and Threats
TAG	Technical Advisory Group (on vaccine-preventable diseases)
Td	Tetanus toxoid and diphtheria toxoid (adults)
Tdap	Tetanus, diphtheria, and pertussis (acellular) combined vaccine (adults)
TT	Tetanus toxoid
TTCV	Tetanus toxoid-containing vaccines
UNICEF	United Nations International Children's Emergency Fund
VAERS	Vaccine Adverse Event Reporting System
WHA	World Health Assembly
WHO	World Health Organization
wP	Vaccine against pertussis (whole cell)

SECTION

I

**Context of
Maternal
and Neonatal
Immunization**



I.1. Introduction to Maternal and Neonatal Immunization

Maternal and neonatal immunization refers to immunization prior to pregnancy, during pregnancy, and during the post-partum period that is intended to provide protection to both the mother and her child. This is a critical concept, as neonates and premature infants are particularly vulnerable to infections with vaccine-preventable diseases. Additionally, their immature immune systems cannot mount protective immune responses to specific vaccine antigens until several weeks or months after birth. This creates a gap during which newborns are extremely vulnerable. Maternal and neonatal immunization has the potential to lessen early childhood morbidity and even mortality. Infections such as influenza, tetanus, and pertussis are associated with adverse outcomes in young infants—i.e., prior to initiation or completion of the primary infant immunization series. Approximately 40% of childhood deaths worldwide occur in the neonatal period, and many of these deaths are due to infections that can be prevented through existing or future maternal vaccines.

Immunization during pregnancy not only protects the mother but also protects the fetus by allowing high concentrations of protective antibodies to be transferred transplacentally. As such, it provides the neonate with a maternal source of protection against disease until active immunization of the infant can take place. Maternal immunization is particularly important when considering vaccine-preventable diseases, such as influenza, for which there are no other options for protecting infants too young to be vaccinated.

The success of maternal immunization in preventing neonatal tetanus and its potential

in preventing influenza and adverse fetal and neonatal outcomes as emphasized by WHO's SAGE, WHO's Strategic Group of Experts (SAGE) on Immunization (1) highlight the potential for a broader maternal and neonatal immunization platform to prevent other high-burden diseases in pregnancy or the neonatal period. However, challenges remain for carrying out maternal immunization strategies with currently available vaccines that have not been specifically approved for use in pregnant women or with vaccines that are still being developed. Pregnancy is generally seen as an exclusion criterion for clinical trials. As a result, there is a dearth of scientific evidence on the risks and benefits of drugs and/or vaccines for use during pregnancy. Similarly, in clinical practice, regulators and manufacturers adopt a precautionary approach with regard to the use of vaccinations during pregnancy. Finally, further implementation research is needed to support the value and assess the impact of maternal immunization.

Vaccine recommendations for pre-pregnancy, during pregnancy, and during the post-partum differ from country to country. Some vaccines are routinely recommended for use during pregnancy, while others are recommended for use during pregnancy given additional risk factors, and some are recommended specifically for the post-partum period.

Vaccination of neonates is an important part of the maternal/neonatal immunization platform and includes both hepatitis B and BCG vaccines to be administered as soon as possible during the first 24 hours of life.

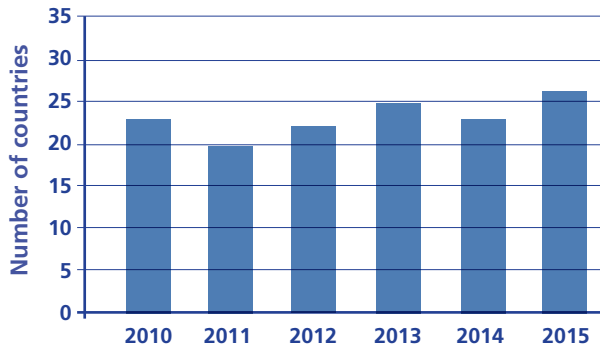
Evolution of Maternal and Neonatal Immunization

- Routine vaccination during pregnancy with vaccines against tetanus, diphtheria, influenza, and polio began during the 1950s and 1960s.
- In 1977, the United States Food and Drug Administration (FDA) prohibited pregnant women from participating in drug trials.
- The safety and benefits of vaccinating pregnant women were first demonstrated during polio outbreaks in Finland and Israel, and during a meningococcal outbreak in Brazil between 1970 and 1990.
- During the H1N1 influenza pandemic in 2009, the risk of influenza during pregnancy was confirmed, as were the benefits of immunization.
- The pertussis outbreaks that swept through many countries of the Americas during 2012-2014 highlighted the high risk of mortality among neonates.

As of 2016, in the Region of the Americas, 31 countries currently conduct routine vaccination of pregnant women against influenza, 15 routinely vaccinate pregnant women against pertussis using Tdap, and 23 vaccinate with Td. Regarding neonate immunization, 21 countries routinely vaccinate newborns against hepatitis B, and 31 routinely vaccinate newborns with BCG. **Figure I.1.1** shows the progress of maternal and neonatal immunization in the Region between 2010 and 2015. Even though vaccines such as hepatitis B and pertussis are not currently recommended by the Technical Advisory Group on Vaccine Preventable Diseases (TAG) for pregnant women, some countries routinely administer them to pregnant women as part of their national policies to control or eliminate these diseases. Lessons learned from these countries should be documented to inform future regional recommendations.

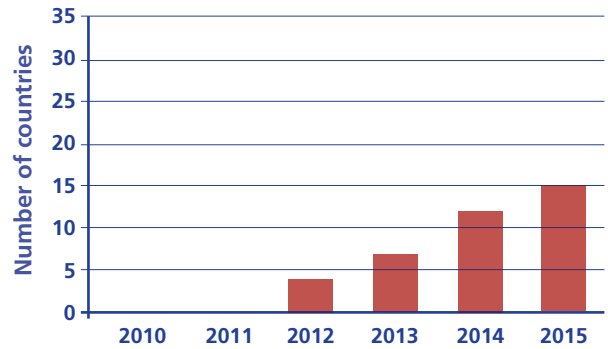
Figure I.1.1. Progress in maternal and neonatal immunization, Region of the Americas, 2010–2015

A. Countries that use the Td vaccine among pregnant women and/or women of childbearing age



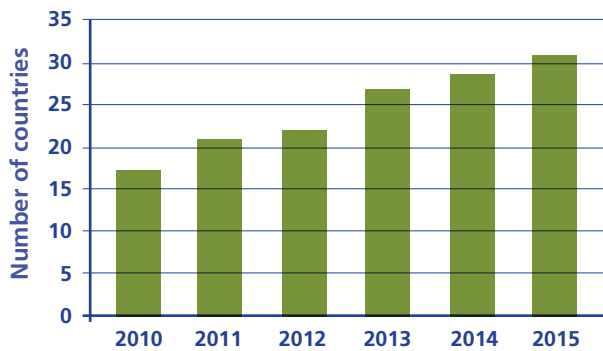
Source: Country reports from the JRF.

B. Countries that use the Tdap vaccine among pregnant women



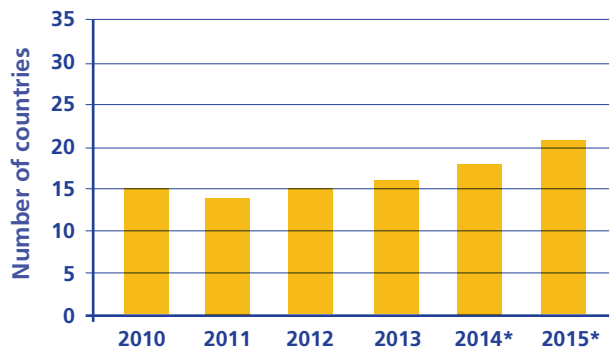
Source: Country reports from the JRF.

C. Countries that use the seasonal influenza vaccine among pregnant women



Source: Country reports from the JRF.

D. Countries that use the HepB vaccine among newborns



Source: Country reports from the JRF.

* Including Canada, where 3 of the 13 provinces/territories administer the HepB birth dose.

Analysis of the Strengths, Weaknesses, Opportunities, and Threats (SWOT) of Maternal and Neonatal Immunization

Given the momentum that maternal and neonatal immunization is gaining globally and regionally, it is paramount to identify the

main strengths, weaknesses and gaps, as well as opportunities to strengthen both maternal and neonatal immunization and other existing programs through synergies and inter-institutional collaboration. **Table I.1.1** shows a SWOT analysis of current maternal and neonatal immunization practices in the Region.

Table I.1.1. SWOT analysis of current maternal and neonatal immunization practices, Region of the Americas

STRENGTHS	WEAKNESSES
<ul style="list-style-type: none"> • Tradition of immunization and trust in the Expanded Program on Immunization (EPI) in Latin America and the Caribbean. • History of Td vaccination among pregnant women. • Important progress made with other maternal vaccines. • The experience of vaccination against influenza A H1N1 among pregnant women, which strengthened the development of a maternal immunization platform in several of the Region's countries. 	<ul style="list-style-type: none"> • Insufficient research on the safety and efficacy in pregnant women. • Difficulties in estimating of denominators for vaccination coverage in pregnant women. • Insufficient training of residents/OBGYNs on immunization, compared to pediatricians. • Inadequate communication of the risks: uninformed patients and healthcare workers, as well as maintenance of incorrect beliefs regarding maternal and neonatal immunization. • Lack of active promotion of the vaccination policy by health authorities. • Insufficient availability of some vaccines to cover all pregnant women.
OPPORTUNITIES	THREATS
<ul style="list-style-type: none"> • Develop a regional platform for maternal immunization. • Integrate maternal health and immunization services. • Bring in maternal and neonatal immunization champions, such as scientific societies. • Promote the importance and safety of maternal and neonatal immunization. • Build upon other existing maternal and neonatal initiatives such as HIV and syphilis elimination. 	<ul style="list-style-type: none"> • Potential hesitancy regarding vaccination during pregnancy by healthcare providers and vaccine recipients. • Low acceptability of some vaccines among health personnel and some anti-vaccine groups.

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I.2. Background and Rationale for Maternal and Neonatal Immunization

Maternal and Child Morbidity and Mortality

Global maternal and child morbidity and mortality

Each year, approximately 300,000 women die in childbirth or from complications during pregnancy. Between 1990 and 2015, the worldwide maternal mortality rate decreased by 44%, dropping from 385 deaths per 100,000 live births to 216 (1). However, this reduction falls far short of the Millennium Development Goal 5 (MDG 5) target to reduce the maternal mortality ratio (MMR)¹ by 75% by 2015. A systematic analysis for the Global Burden of Disease Study 2013 showed global rates of change in which only 16 countries would achieve the MDG 5 target by the end of 2015.

Building on the momentum generated by MDG 5, to reduce child mortality rate by 2/3 and maternal mortality ratio by 3/4 between 1990 and 2015, the United Nations Sustainable Development Summit, held on 25 September 2015, adopted the 2030 Agenda for Sustainable Development. The Agenda includes a set of 17 Sustainable Development Goals (SDGs) to end poverty, fight inequities, and tackle climate change by 2030. SDG 3 aims to ensure health and well-being for all, and includes a bold commitment to end the epidemics of AIDS, tuberculosis, malaria, and other communicable diseases by 2030. Its target 3.1 is to reduce the global MMR to under 70 maternal deaths per 100,000 live births by 2030, and its target 3.2 is to end preventable deaths of newborns and children under 5 years of age by 2030.

Currently, only half of the pregnant women in developing countries get the four antenatal checkups recommended by WHO (2). These antenatal visits are crucial to provide pregnant women with the required clinical monitoring during each trimester, as well as to

provide preventive health services, including immunizations, to protect both the mother and her unborn child, more recently, in 2016, the WHO highlighted the need for each pregnant woman to have at least 8 antenatal visits (3).

Preventable diseases are the leading causes of death in children under 5 years old, and are responsible for nearly half of deaths in children in this age group during the neonatal period. Neonatal mortality accounts for almost 40% of the estimated 6.6 million deaths in children under the age of 5 years and for nearly 60% of all infant deaths (children under the age of 1 year).

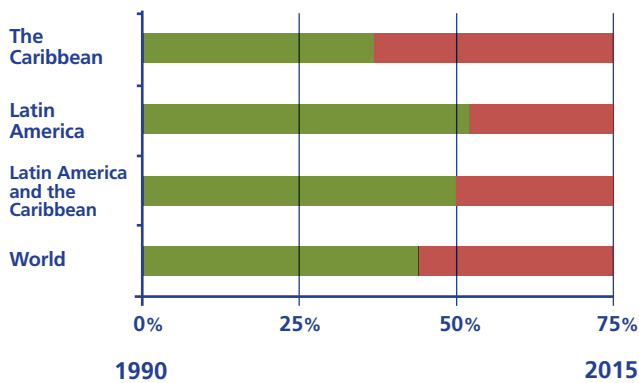
Regional maternal and child morbidity and mortality

The target set for reducing the maternal mortality ratio by 75% between 1990 and 2015, set under the MDG 5 (Improve Maternal Health), was not achieved in the Region. In 1990, according to PAHO's 2014 Basic Indicators (4), maternal mortality ratio in the Region was 110 deaths per 100,000 live births, falling to 68 deaths per 100,000 live births in 2014.

Regarding mortality among children under 5 years old in the Region, the rate was 15.0 deaths per 1,000 live births in Latin America and the Caribbean in 2014. Based on progress made to date (**Figures I.2.1 to I.2.4.**), the Region of the Americas was expected to achieve the target for Millennium Development Goal 4—to reduce child mortality by 2015 and, specifically, the infant mortality rate to 12.60 per 1,000 live births. Regarding neonatal deaths in Latin America and the Caribbean, 34% of deaths that occur during the neonatal period are related to prematurity and 4% to acute lower respiratory infections.

¹ Maternal mortality ratio (MMR): number of maternal deaths per 100,000 live births.

Figure I.2.1. Maternal mortality reduction and gap for fulfilling MDG 5, Region of the Americas, 1990–2015



Source: Maternal mortality estimates (MMIG), PAHO-CLAP/WR 2015.

Figure I.2.2. Achievements in the reduction of infant and neonatal mortality rates in children under 5 years old, Latin America and the Caribbean, 1990–2013

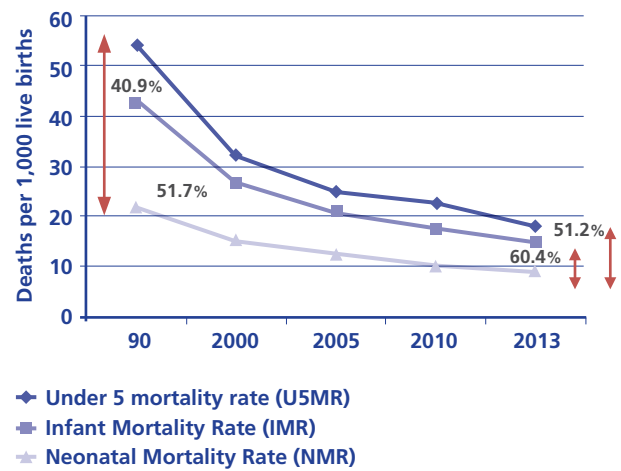
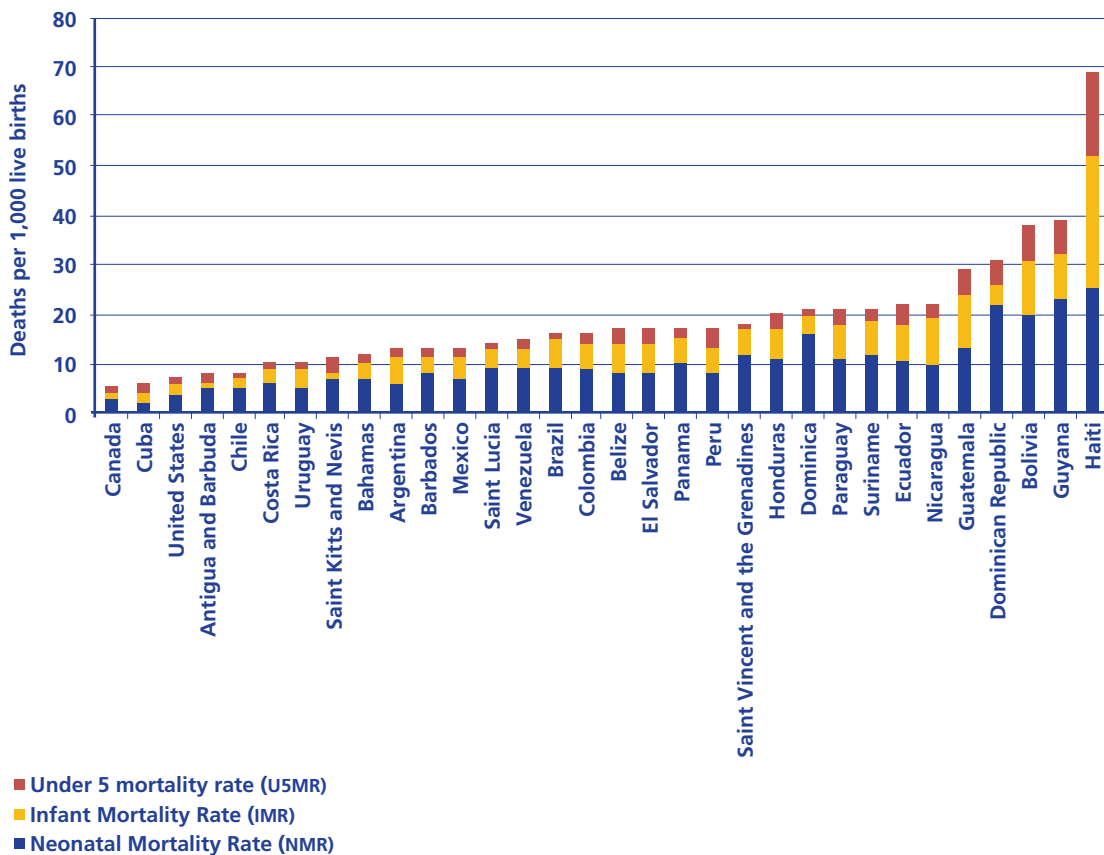
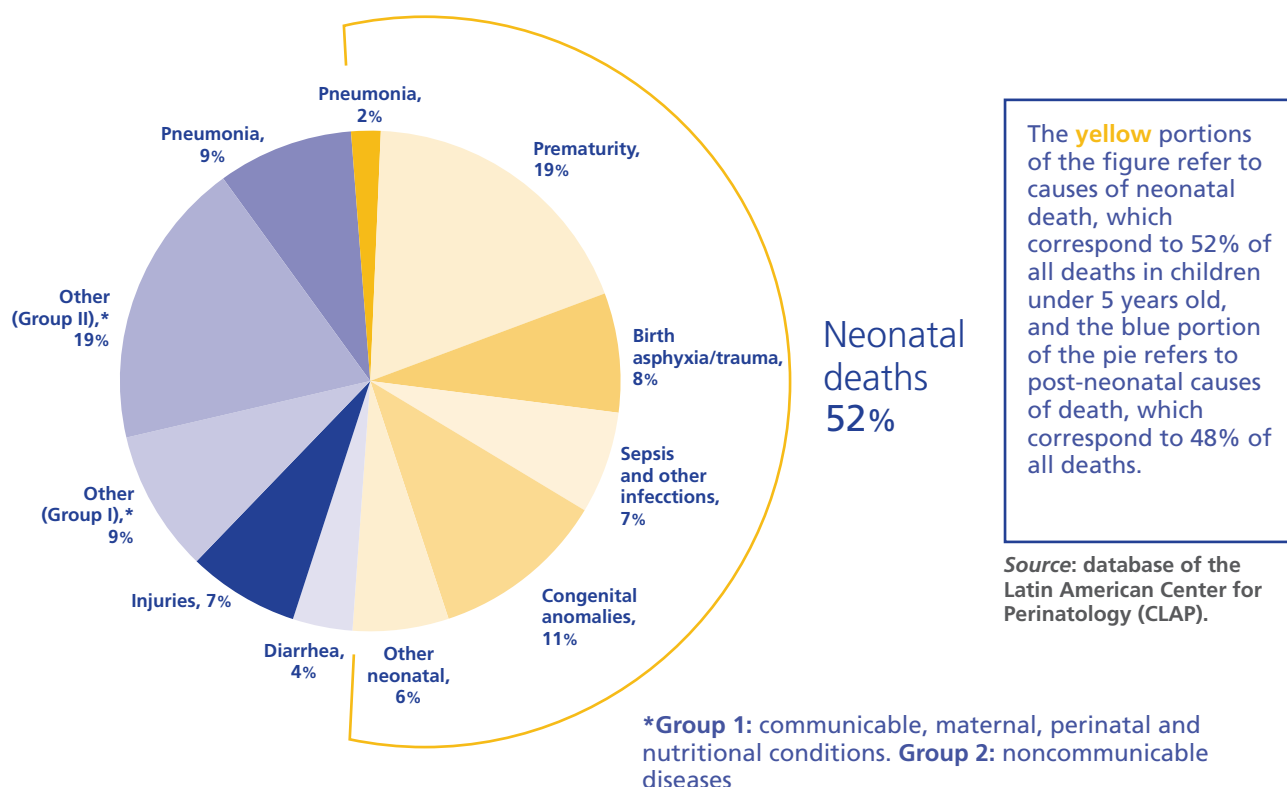


Figure I.2.3. Estimates of neonatal mortality, infant mortality, and mortality in children under 5 years old, Latin America and the Caribbean, 2015



Source: Estimates developed by the UN Inter-agency Group for Child Mortality Estimation.

Figure I.2.4. Mortality in children under 5 years old by cause, Latin America and the Caribbean, 2013



Initiatives for Maternal and Neonatal Mortality Reduction

Reproductive rights

According to the International Conference on Population and Development, held in Cairo in 1994, exercising the right to sexual and reproductive health involves both an individual's responsibility for self-care and the State's responsibility to create a social and political environment that guarantee access to reproductive and sexual health services. The latter include: family planning counseling, prenatal care, safe delivery and post-natal care, the prevention of abortion and the management of the consequences of abortion or other reproductive health procedures and conditions, and education and counseling, as appropriate, on human sexuality, reproductive health, and responsible parenting.

Continuum of maternal, newborn, and child care

In 2008, the PAHO Member States, during the 48th Directing Council meeting, adopted the Regional Strategy and Plan of Action for Neonatal Health within the Continuum of Maternal, Newborn, and Child Care (Resolution CD48.R4, Rev. 1) (5). This resolution called on Member States to "consider strengthening health systems based on primary health care to support the implementation of evidence-based strategies aimed at reducing maternal and neonatal mortality, and improving collaboration between programs and the different levels of care." The resolution set forth measures to improve neonatal health in the Region, including bolstering "newborn care within the framework of the continuum of care, involving stakeholders and linking measures to those proposed in the Plan of Action to accelerate the reduction of maternal mortality and severe maternal morbidity."

Additionally, the 2015 PAHO Plan of Action for the Prevention and Control of Viral Hepatitis, which includes the elimination of mother-to-child transmission of hepatitis B, supports the maintenance of broad hepatitis B vaccination coverage within the routine immunization schedule for children below the age of 1 year, as well as adherence to the 2009 WHO recommendation (6) to administer a birth dose of hepatitis B vaccine to newborns within first 24 hours of life to prevent the vertical transmission of HBV and its chronicity.

Reduction of maternal morbidity and mortality

Later, during the 51st Directing Council in 2011, PAHO Member States approved the Plan of Action to Accelerate the Reduction in Maternal Mortality and Severe Maternal Morbidity through Resolution CD51.R12 (7), urging Member States to “adopt national policies, strategies, plans, and programs that increase women’s access to culturally appropriate, quality health services adapted to their needs, including, in particular, promotion and prevention programs based on primary health care provided by skilled personnel” Vaccinating pregnant women against influenza was one of the recommended activities at the regional and national levels.

Framework for Maternal and Neonatal Immunization

Maternal and neonatal immunization is a core component of the new immunization model, which has evolved from a focus on childhood immunization to a broader immunization scope encompassing the whole family. Maternal and neonatal immunization deserves special attention, in that it serves to protect the health of both the mother and her infant. The establishment of a routine maternal and neonatal immunization platform represents a new paradigm that includes the universal use of influenza, tetanus, and diphtheria vaccines and consideration of the routine

use of other relevant vaccines that are or will become available.

The Global Vaccine Action Plan

The Global Vaccine Action Plan (GVAP), approved by the World Health Assembly in May 2012, is designed to achieve the Decade of Vaccines vision by delivering universal access to immunization. The plan envisions six guiding principles: country ownership, shared responsibility and partnership, equity, integration, sustainability, and innovation. Sound immunization systems are an integral part of a well-functioning health system. The success of national immunization programs in introducing new vaccines; attaining quality, equity, and coverage goals; and becoming financially sustainable relies on a well-functioning health system. In order to build a cohesive, non-fragmented and well-functioning program that coordinates and works in synergy with other primary healthcare programs, the many interconnected components of an immunization system require multi-disciplinary attention.

Recommendations on the Vaccination of Pregnant and Lactating Women from the SAGE

In 2015, the World Health Organization’s Strategic Advisory Group of Experts (SAGE) on Immunization emphasized the overall importance of the maternal immunization platform, and called upon WHO to affirm its commitment to build an evidence base to strengthen vaccine delivery during pregnancy, as this has great potential for preventing infection in high-risk groups worldwide (8). SAGE encouraged WHO to promote additional implementation research to generate generalizable data on the best ways to integrate maternal immunization into routine antenatal care in low resource settings. SAGE also encouraged the Pan American Health Organization (PAHO) to document the successful regional experience of delivering influenza vaccine to pregnant women.

A year earlier, at the request of SAGE, WHO's Global Advisory Committee on Vaccine Safety (GAVCS) conducted a comprehensive review of the evidence on the safety of vaccination during pregnancy (9). It reported no safety concerns regarding non-live vaccines and no significant adverse outcomes regarding live vaccines. GAVCS's review will be dealt with in greater detail in section I.4.1. of this publication, related to Vaccine Safety.

The Regional Immunization Action Plan (RIAP)

The Regional Immunization Action Plan (RIAP) is an adaptation of GVAP tailored for the Americas. The RIAP sets forth a roadmap that countries in the Region can follow from 2016 to 2020, and details the design and implementation of immunization policies and programs in four strategic areas:

1. protecting achievements;
2. completing the unfinished agenda;
3. facing new challenges;
4. strengthening health systems to deliver vaccinations.

The first three areas are a continuation of the Regional Immunization Vision and Strategy, 2007-2015, and the last one is aligned with the Strategic Plan of the Pan American Health Organization, 2014-2019. According to this document, achieving universal health coverage is an essential tenet, as envisioned in the Strategy for Universal Access to Health and Universal Health Coverage, which the 53rd Directing Council of PAHO adopted in 2014. This strategy underscores that strong immunization systems are an essential part of a well-functioning health system and are critical to the development of appropriate interventions to integrate them into routine health services so that synergistic effects are maximized.

Recommendations of PAHO's Technical Advisory Group on Vaccine-preventable diseases for Maternal and Neonatal Immunization

During its 23rd Regional Meeting in 2015,² PAHO's TAG encouraged the Organization to provide guidance to countries on maternal immunization, including supplying any necessary information on vaccine safety and on communicating risk, in order to successfully implement a maternal immunization program. PAHO was asked to foster a model whereby immunization is integrated into a platform of care for pregnant women and newborns. Additionally, PAHO's TAG reaffirmed its existing recommendations for the universal use of the influenza vaccine among pregnant women and the use of Tdap among pregnant women where indicated by pertussis outbreak among young infants. Regarding hepatitis B, PAHO's TAG emphasized the importance of vaccinating newborns as soon as possible during the first 24 hours of life.

² TAG Recommendations, Meeting XXIII in Cuba, July 2015.

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I.3. Integration of Programs and Services

Achieving the health-related Millennium Development Goals and the next wave of targets beyond 2015 will depend largely on how countries succeed in moving towards universal health coverage, which is defined as ensuring that all people are able to use the promotive, preventive, curative, rehabilitative, and palliative health services they need, that these services be of sufficient quality to be effective, and that the use of these services does not expose users to financial hardship. Universal coverage brings the hope of better health and protection from poverty for hundreds of millions of people, especially those in the most vulnerable situations.

The integration of the delivery of immunization services with other health services is potentially beneficial for all services involved, in that it improves coverage, reduces costs, and creates synergies, hence furthering the universal health coverage agenda. However, for integrated efforts to be successful, health system planning and careful forethought is critical. Integrated approaches also need to be supported by the availability of sufficient human resources and delivery systems. Integrated service delivery may increase the daily burden of work for health workers and may necessitate additional training. Supply chain issues, logistics, and the realities of service delivery must also be considered. When designing integrated approaches, attention is also required to ensure that the tools and documents used across different programs and services are consistent.

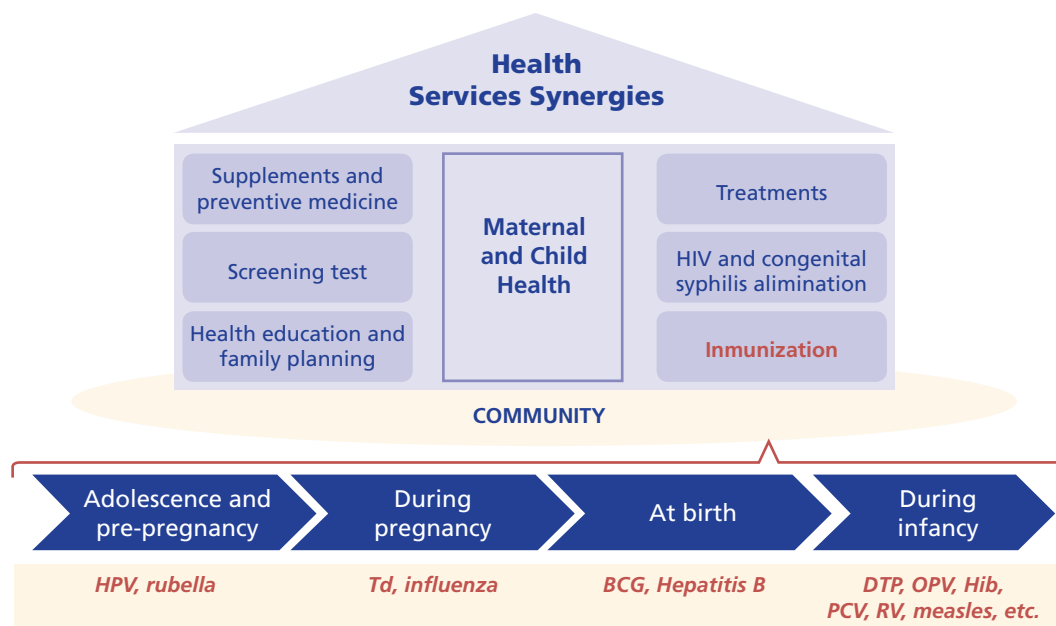
In order not to strain a weak or fragile health system, integrated interventions should be carefully selected and then monitored to

identify and correct unforeseen challenges in a timely way. In a climate of scarce human and financial resources, the integration of services has the potential to increase efficiency. It also streamlines the time that families must invest in traveling to health facilities, in that they would be provided multiple services at the same encounter with the health system.

The Partnership for Maternal, Newborn & Child Health (PMNCH) recently undertook a comprehensive review to identify essential interventions and key activities that improve maternal and child health during pre-pregnancy and through infancy. PMNCH reported on eight childhood health interventions that have the potential to be directly integrated with immunization services, including: exclusive breastfeeding for six months; ongoing breastfeeding; malaria prevention and disease management, supplementation with vitamin A, management of malnutrition, pneumonia, and diarrhea; and care for children who have been exposed to HIV. The review also showed other interventions in the realm of reproductive and maternal health services that could be integrated with immunization visits, including nutrition counseling, family planning services and education, distribution of iron tablets to prevent anemia, and care during the postnatal period.

Maternal and neonatal immunization is a key component of the maternal, neonatal, child, and adolescent care continuum. **Figure I.3.1** describes those health interventions that can be integrated with WHO's Expanded Program on Immunization (EPI) delivery.

Figure I.3.1. Integration of maternal immunization with other health services



HPV: Human papiloma virus; Td: Tetanus toxoid and diphtheria toxoid; BCG: Bacillus Calmette-Guérin vaccine; DTP: Combined vaccine against diphtheria, tetanus and pertussis; OPV: Oral polio vaccine; Hib: Vaccine against *Haemophilus influenzae* type b; PCV: Pneumococcal conjugate vaccine; RV: Rotavirus vaccine.

Comprehensive efforts are also needed to maximize the obstetric provider’s recommendation for and administration of all maternal and neonatal immunizations indicated for his or her patients. Technical guidelines of antenatal health services should include the recommended vaccines for pregnant women, and obstetricians/gynecologists and other antenatal health workers should be appropriately educated and trained on the technical and communication aspects of maternal and neonatal immunization.

To that end, the Latin American Center for Perinatology (CLAP) was established in 1970 to strengthen healthcare services with a focus on primary health care, particularly the health care of mothers and their newborns. One of the Center’s activities is to conduct passive surveillance. CLAP is expanding its perinatal information system as well as its perinatal health record to begin recording variables relevant to maternal and neonatal immunization. **Table I.3.1** shows a few of those variables.

Table I.3.1. Vaccines and tests recommended by the Latin American Center for Perinatology (CLAP) for evaluating maternal and neonatal immunization

	Vaccines	Tests
Mother	Status of immunization of mother with tetanus/diphtheria, Tdap, influenza, rubella, hepatitis A and B, and other vaccines	Hepatitis B screening
Newborn	Hepatitis B and BCG vaccination	Respiratory Syncytial Virus (RSV), Group B Streptococcus, and Chorioamnionitis testing

With this perinatal information system, countries will be able to evaluate outcomes relevant to maternal and neonatal immunization, such as disease burden, birth weight, pre-term birth, undersize for gestational age, congenital anomalies, spontaneous abortion, still birth, chorioamnionitis, in association with immunization.

As part of the Regional Action Plan, maternal and neonatal immunization is considered as a key element to be integrated into maternal and child health services and immunization.

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I.4. Vaccine Safety and Regulatory Considerations

Vaccine Safety

Several vaccines can be administered safely during pregnancy (see maternal and neonatal immunization schedule). In general, live and live-attenuated vaccines are contraindicated during pregnancy. That said, it is important to mention that, to date, there is no evidence to demonstrate a teratogenic risk from any currently available vaccines (including mumps, rubella, and varicella).

In 2014, WHO's Global Advisory Committee on Vaccine Safety (GACVS) conducted a comprehensive review of the evidence on safety of vaccination during pregnancy. Reviewing data on various non-live vaccines, including inactivated virus, inactivated bacteria, and the acellular vaccines and toxoids, revealed no safety issues, and GACVS concluded that pregnancy should not preclude women from vaccination when it is otherwise indicated. In terms of live vaccines, such as measles, mumps, and rubella (MMR), GACVS concluded that while there was a theoretical risk to the fetus, no significant adverse outcomes following vaccination had been reported. GACVS's report noted that the contraindication for the MMR vaccine during pregnancy is purely precautionary (1). **Table I.4.1** summarizes the vaccines reviewed by GACVS and the corresponding WHO recommendations.

Pregnancy is an exclusion criterion for enrollment into many vaccine trials worldwide, which limits the availability of data regarding the safety of routine vaccines in pregnancy. Policies regarding the use of vaccines in pregnancy are often guided by post-marketing vaccine surveillance systems and by data from the small numbers of pregnant women inadvertently vaccinated in clinical trials and in vaccination campaigns. The safety of many vaccines used in the course of maternal and neonatal immunization has been assessed using data generated from post-marketing surveillance and other small studies. In the United States, vaccination of pregnant women against influenza

and poliomyelitis was recommended after longitudinal surveillance studies following mothers vaccinated during pregnancy and their children (birth through age 7 years) showed no increased risk for development of learning disabilities, malignancy, or congenital malformations. Maternal tetanus toxoid (TT) has been administered to millions of women during pregnancy worldwide with no known risks to mother or fetus.

Receipt of live attenuated vaccines during pregnancy is contraindicated due to the theoretical risk of perinatal infection. Even though it is theoretically possible for clinical infection to occur after inadvertent receipt of a live attenuated vaccine, it has rarely been a reported event. Illness that has occurred after receipt of a live attenuated vaccine has been reported to be milder than natural infection and is classified as an adverse reaction.

Co-administration of vaccines

Sometimes, multiple vaccines (Tdap and influenza vaccines, for example) must be administered simultaneously during pregnancy. Studies conducted among non-pregnant individuals to evaluate the safety of simultaneously administering Tdap and influenza, compared to administering these vaccines separately, found no increased risk of adverse events (2, 3). Similarly, a large study conducted in the United States that compared rates of medically attended acute events (fever, any acute reaction) and adverse birth outcomes (preterm delivery, low birthweight, small size for gestational age) among two groups of pregnant women, one who received Tdap and influenza vaccines in the same visit and another that received them separately, showed no greater risk of adverse events associated with the co-administration of the two vaccines (4).

Table I.4.1. Vaccines reviewed by WHO's GACVS for use during pregnancy and relevant recommendations

Inactivated vaccines	WHO recommendation on vaccination during pregnancy
<p>Influenza vaccines:</p> <ul style="list-style-type: none"> Pregnant women and children suffer disproportionately from severe outcomes of influenza. Vaccine effectiveness has been demonstrated, with transfer of maternally-derived antibodies to the infant providing additional protection. Excellent and robust safety profile of vaccines over many decades. 	<p>YES</p> <p>Source: <i>World Health Organization. Influenza Vaccines: WHO Position paper. Wkly Epidemiol Record, 2012; 47(87): 461-476.</i></p>
<p>Tetanus toxoid vaccines:</p> <ul style="list-style-type: none"> Widespread use of TT-containing vaccines showed no harm signal for pregnant women and their fetus. 	<p>YES</p> <p>Source: <i>World Health Organization. Tetanus Vaccines: WHO position paper, Wkly Epidemiol Record, 2006; 81,197-208.</i></p>
<p>Tdap:</p> <ul style="list-style-type: none"> Vaccinating pregnant women with Tdap did not show any safety concerns regarding maternal, fetal and infant outcomes. There is growing evidence of the safety of vaccinating pregnant women in the third trimester as a useful strategy to prevent pertussis in infants too young to be vaccinated. 	<p>YES</p> <p>Source: <i>World Health Organization. Pertussis Vaccines: WHO position paper. Wkly Epidemiol Record, 2010; 385-400.</i></p>
<p>Meningococcal vaccine:</p> <ul style="list-style-type: none"> Mostly passive surveillance data for conjugate vaccine and small studies on bi- and tetravalent polysaccharide meningococcal vaccine. Data suggest vaccination of pregnant women is safe and not associated with increased risk of adverse pregnancy outcome. Given data limitations, further active surveillance is warranted. 	<p>Polysaccharide vaccine: NO.</p> <p>Conjugate vaccine: only as part of mass campaigns.</p> <p>Source: <i>WHO Position paper on influenza vaccines. Wkly Epidemiol Record, 2012; 47(87): 461-476.</i></p>
Live attenuated vaccines	WHO recommendation on vaccination during pregnancy
<p>Yellow fever vaccines:</p> <ul style="list-style-type: none"> Documented in several hundred women, risk of adverse outcome of pregnancy and childbirth appear similar to those in the general population. 	<p>Only during epidemics and when traveling to endemic areas</p>
<p>Rubella mono and combined live attenuated vaccines:</p> <ul style="list-style-type: none"> Usually contraindicated, as they are live attenuated (purely precautionary measure). Inadvertent administration is not considered an indication to terminate pregnancy. 	<p>NO</p>
<p>Oral polio vaccines:</p> <ul style="list-style-type: none"> Small theoretical risk of adverse events during pregnancy. Immunization of pregnant women at high risk of exposure is recommended by SAGE and several NITAGs. 	<p>Only prior to travel to endemic areas with ongoing outbreaks</p>
<p>Measles vaccines:</p> <ul style="list-style-type: none"> Possible higher abortion rate. Infrequently, congenital measles. If premature, possible high case/fatality rate. 	<p>NO</p>
<p>Mumps vaccines:</p> <ul style="list-style-type: none"> Possible increased rate of abortion in the first trimester. 	<p>NO</p>

GACVS: Global Advisory Committee on Vaccine Safety. NITAG: National Immunization Technical Advisory Group. SAGE: Strategic Advisory Group of Experts on Immunization (WHO). WHO: World Health Organization.

Source: *WHO position paper on vaccines and vaccination against yellow fever. Wkly Epidemiol Record, 2013; No. 27, 269–284.*

PAHO's CLAP Network

As a way to actively search for and investigate suspected cases of neonatal and/or maternal adverse health outcomes potentially related to immunization, the Latin American Center for Perinatology (CLAP) is establishing a network of surveillance centers using sentinel hospital sites in the Region.

Regulatory Considerations

Immunization is increasingly recognized as an important strategy to protect pregnant and lactating women. Inactivated influenza vaccines include product insert pregnancy and lactation (PI P&L) information, based on:

- Regulations of national regulatory authorities in the vaccine's country of manufacture.
- Product-specific clinical trial evidence which is generally presented as cautionary phrasing, e.g. "vaccine should be used only following advice of a healthcare professional, based on consideration of benefits and risks to the mother and fetus."

The language in influenza vaccines package inserts may differ according to vaccine manufacturer. Because they are mainly drafted based on the precautionary principle, these inserts may be interpreted by immunization program managers and medical staff as cautions against use in pregnancy. Even in countries where the National Immunization Technical Advisory Groups (NITAGs) advise strongly in favor of such vaccination. Thus, it is important to accompany these vaccination efforts with complementary communication messages.

In December 2015, WHO conducted a review of the wording of several package inserts. Current package inserts examined did not mention a contraindication for use in pregnancy in most countries. However, the language could have been misinterpreted by the national vaccine program administrators, healthcare providers, and patients. A document outlining the important information to be included in the pregnancy subsection of package inserts is under consideration for further development. Meanwhile, countries importing vaccines should, based on information provided in regional and global guidelines:

- Review language in the PI P&L subsection given global recommendations on safety of vaccine.
- Ensure communication among relevant stakeholders to avoid misinterpretation of PI P&L.

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I.5. Introducing or Expanding the Use of Maternal and Neonatal Vaccines

Criteria for the Introduction or Expanded Use of Maternal Vaccines

Decision-making

After examining all relevant factors—such as political, technical, programmatic, and feasibility considerations—EPI managers should be able to make a preliminary, evidence-based decision regarding the introduction of new vaccines or the expanded use of existing ones. Any decision must be supported by the National Immunization Technical Advisory Group (NITAG). Once a technical consensus has been reached, a proposal can be presented to political decision-makers.

In deciding whether or not to introduce or expand maternal and neonatal immunization, national authorities should take the following factors into consideration.

Political and Technical Issues

- A. **Political and Public Health Priorities.** This consideration includes how countries will make the political and technical decision to introduce a vaccine for pregnant women. For example, is there a National Immunization Technical Advisory Group (NITAG) and other multidisciplinary working groups in place, are there available national financial resources, what role do scientific societies and national champions play? In this regard, the extent of the disease's visibility in society and how it compares to other public health concerns also should be taken into account.
- B. **Burden of Disease.** This category entails understanding the magnitude of a given disease in terms of its incidence and prevalence, and its related morbidity and mortality in a population.

- C. **Vaccine Safety, Efficacy, and Quality.** Safety and efficacy are measured during a vaccine's clinical trial (both pre-licensure and post-marketing). Even though a vaccine may be considered safe, adverse events may occur once it is administered on a massive scale. To ensure vaccine quality, WHO employs a pre-qualification process, which is used to purchase all vaccines purchased through PAHO's Revolving Fund for Vaccine Procurement. If data are unavailable, countries should weigh the benefits against the risks for each target population.

- D. **Comparison with other Interventions (Including other Vaccines).** To this end, it is necessary to assess the pros and cons of the various interventions that can be implemented to prevent and/or control the disease that the vaccine is targeting. Specific aspects to consider include the estimated impact of interventions on disease burden, and the effectiveness and cost of each intervention.

- E. **Economic and Financial Criteria.** Decision-makers should address three issues in this regard:

1. disease's economic burden,
2. vaccine's cost-effectiveness, and
3. roll-out costs of maternal and neonatal immunization.

Feasibility and Scheduling

- A. **Characteristics of Vaccine Presentation.** This issue considers the product options available on the market and how each would fit into the national schedule. For example, it is important to assess whether

a vaccine is monovalent or combined, whether it is available as a single dose or multi-dose presentation, whether the product is in liquid form or lyophilized, and whether there are different schedule options.

- B. **Vaccine Supply.** This establishes whether there is sufficient vaccine available through the selected purchase mechanism to ensure a regular and timely supply of the product and avoid stock-outs.
- C. **Vaccination Program Performance.** Prior to introducing a vaccine, the overall performance of a national immunization program should be analyzed, in order to identify areas that need to be strengthened to sustain the impact of introducing a new vaccine without weakening the program as a whole.

Implementation

Vaccines clearly offer the most cost-effective approach for controlling infectious diseases, but access to vaccines remains unequal and suboptimal, particularly in some poorer developing countries. The introduction of new vaccines and the long-term sustainability of immunization programs requires proactive planning from conception to implementation. International and national coordination efforts, as well as local and cultural factors, must be understood and taken into account during the implementation process. Moreover, adequate infrastructure should be in place to monitor the disease burden, vaccine effectiveness, and vaccine safety.

Plan of Action for the Introduction of New Maternal Vaccines

A plan of action for the introduction of any new maternal vaccine should contemplate the following areas of work.

Planning and programming

Planning and programming includes defining the target populations for the new vaccine at all levels of the health system (national, regional, and local), as well as an estimate of resources needed and resources available to support the introduction. It is recommended that procurement mechanisms to ensure an adequate vaccine supply be established at least six months prior to the vaccine's introduction.

Standardization

This aspect includes all steps needed to modify the official vaccination schedule and establish the operational norms for the application of the new vaccine. Once completed, operational norms should be validated in coordination with the NITAG.

Coordination

Coordination encompasses all those activities related to vaccine introduction that should be done in consultation or collaboration with other institutional departments and programs or external partners, such as the NITAG, social security, universities that train health workers, and the inter-institutional coordinating committee (ICC), among others.

Vaccination strategies

These include the selection of mechanisms that will ensure a new vaccine's high population coverage among target populations. In the case of maternal and neonatal immunization, in addition to institutional vaccination activities, strategies and tactics may include collaborative efforts with other healthcare providers, such as obstetricians and gynecologists, and vaccination outreach efforts in the community.

Procurement of vaccines, cold chain, and logistics

These considerations specify how a new vaccine will be purchased, stored, and transported throughout the health system, starting at the central level and reaching all the way to local

health centers. Procurement and distribution of a new vaccine should be integrated into the national immunization program's existing mechanisms, and may provide an opportunity to strengthen such mechanisms.

Vaccine safety

This consideration includes all checks and balances that ensure vaccine quality, from the moment that the national level receives a new vaccine to when it is administered to the population.

Safe injection

Safe injection considerations include all the norms that ensure the safe administration of injectable vaccines, including the promotion of the use of auto-disable (AD) syringes and the procurement of safety boxes.

Waste management

Waste management includes those protocols that ensure the safe disposal of all vaccine waste; they work hand in hand with safe injection norms.

Monitoring of adverse events following immunization (AEFI)

This consideration includes the creation of a plan for AEFI surveillance, preferentially incorporated within existing surveillance platforms. It also envisions putting in place protocols for responding to inadvertent situations, such as when a pregnant woman is mistakenly vaccinated with a non-recommended vaccine.

Crisis plan

A crisis plan involves the development of protocols for responding to adverse events and other unforeseen occurrences. Such a plan should include the implementation of thorough and timely investigations in response to reported AEFIs, as well as strategies for delivering clear and transparent messages to the public and policies for working with the media.

Regulatory aspects

Regulatory aspects encompass all those actions needed to obtain approval from national regulatory authorities for vaccine use.

Training

The introduction of a new vaccine requires a period of training. Such training should include initial activities for national and departmental coordinators of all areas related to vaccine introduction, including information systems, communications, and cold chain and AEFI surveillance. This personnel can subsequently facilitate additional training, until the information reaches the local level. Some training activities should also include additional stakeholders, such as the scientific community and other institutions within the health sector, in order to develop a common knowledge base.

Social mobilization and communication

This effort includes the design and implementation of an information, education, and communication plan, targeted both at the general public and at scientific societies and health workers in the private sector, among other actors. Given the media's often strong influence over the public's perceptions, forging strategic alliances with media outlets is essential for getting support for the dissemination of clear and accurate information.

Adapting the information system

The information system's forms and paperwork used to register immunization-related information, as well as the information technology platform itself, should be adapted in order to incorporate the new vaccine. Early coordination with national departments of statistics and information is critical to ensure that these adaptations occur prior to the vaccine's introduction.

Epidemiological surveillance

Incorporating surveillance for the specific disease prevented by the new vaccine into the national surveillance system, with the corresponding modifications to protocols, should be done prior to the new vaccine introduction. For high incidence diseases, a sentinel surveillance system may suffice; less apparent diseases may require nationwide surveillance efforts in order to detect cases.

Calculating the plan's costs

Costing out the vaccination plan includes calculating the total cost of vaccine introduction, in order to be able to mobilize sufficient resources to ensure its sustainability. These costs should be incorporated into the annual budget for the national immunization program, so that they can be approved in future fiscal years.

Monitoring, supervision, and evaluation

Activities should be monitored throughout the new vaccine's introduction, starting during the planning period. Specific indicators (such as coverage and surveillance) should be established for the new vaccine and should then be included in the guide for supervision of the routine program. Specific studies to evaluate vaccine effectiveness should also be contemplated. **Table I.5.1** details the characteristics of monitoring, supervision and evaluation.

Table I.5.1. Characteristics, monitoring, supervision, and evaluation of immunization programs

Characteristics	Monitoring	Supervision	Evaluation
Definition	The ongoing process of measuring and systematically analyzing data in order to follow up on the progress of programs and plans	Providing technical advice <i>in situ</i> in order to improve program performance	Conducting a global analysis of the program or service that is carried out through the application of diverse tools in specific moments
Objectives	Identifying achievements and problems, analyzing their causes, and applying effective measures to attain desired results	Strengthening the technical capacity of personnel and improving their performance	Determining whether the program is achieving the desired objectives in terms of access, quality, effectiveness, efficiency, and impact of interventions
Methodology	Collecting data and establishing indicators that are systematically analyzed to assess progress toward achieving objectives and targets	Application in the field, in accordance with programmed field visits during which trained personnel apply standardized tools	Utilizing a set of methods and procedures applied at specific stages to analyze access, service quality, user satisfaction, resource utilization, and the objectives and effect of interventions, among others
Periodicity	Ongoing data analysis and decision-making	Periodic visits at short intervals	Conducting periodic assessments at specific stages of the program or service
Uses and applications	Making decisions based on progress toward achieving objectives and targets	Adopting corrective measures, enhancing them, and encouraging best practices for achieving objectives and targets	Ascertaining whether the results, objectives, and targets have been achieved, in order to learn from experience and make decisions to improve the effectiveness and efficiency of the program or service

Source: Toolbox for Coverage Monitoring of Integrated Public Health Interventions. Available at: <http://www.paho.org/immunization/toolkit/monitoring-reporting.html>.

Other Resources

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I.6. Regional Maternal and Neonatal Immunization Schedule and Vaccination Strategies

Regional Maternal and Neonatal Immunization Schedule

Countries pursue various approaches to vaccinate pregnant women, depending on the type of vaccine and its availability, the seasonality of a given disease and the immunization strategies in place for different target populations. **Table I.6.1**

shows the regional maternal and neonatal immunization schedule based on PAHO's TAG latest recommendation or update of existing recommendation for the Region of the Americas or latest SAGE recommendation if no TAG recommendation is available.

Table I.6.1. Regional maternal and neonatal immunization schedule

VACCINES RECOMMENDED DURING PREGNANCY				
Vaccine	Pre-pregnancy	Pregnancy	Post-partum	Year of PAHO/TAG recommendation
Tetanus/diphtheria	Yes, ideal time	Yes, two doses if she was not previously vaccinated	Yes, to complete schedule	2017 ^a
Inactivated influenza		Yes, ideal time	Yes, if she was not vaccinated during pregnancy, to protect the newborn	2012 ^b
VACCINES RECOMMENDED DURING PREGNANCY IN SPECIAL SITUATIONS ONLY				
Vaccine	Pre-pregnancy	Pregnancy	Post-partum	Year of PAHO/TAG recommendation
Tdap		Yes, during outbreaks (ideal moment between 27–36 weeks of gestation)	Yes	2014 ^c
Hepatitis B		Yes, if she did not complete schedule and if under high risk situation (e.g., more than one sexual partner during the previous six months, STD, IDU, partner + for HBsAg)	Yes, to complete schedule (three doses)	
Hepatitis A		Yes, during outbreaks		2013 ^d
Yellow fever	Yes, ideal moment (in endemic areas)	Yes, prior to travel to endemic areas under current outbreak, with prior risk/benefit analysis		2013 ^e

Continues on the next page

Table I.6.1. Regional maternal and neonatal immunization schedule (continued)

VACCINES RECOMMENDED DURING PREGNANCY IN SPECIAL SITUATIONS ONLY				
Vaccine	Pre-pregnancy	Pregnancy	Post-partum	Year of PAHO/TAG recommendation
IPV		Yes, prior to travel to endemic areas under current outbreak		2013 ^f
OPV		Yes, prior to travel to endemic areas under current outbreak		2015 ^f
Rabies		After high-risk exposure		2013 ^g
Meningococcus conjugate		Yes, during outbreaks		2013 ^h
Meningococcus polysaccharide (MPSV4)		Yes, during outbreaks		2013 ^h
VACCINES NOT RECOMMENDED DURING PREGNANCY				
Vaccine	Pre-pregnancy	Pregnancy	Post-partum	Year of PAHO/TAG recommendation
Rubella	Yes, ideal moment	No	Yes, if not vaccinated during pre-pregnancy	2013
Measles				2013
Mumps				2013
HPV	Yes, ideal moment	No		2013
VACCINES RECOMMENDED FOR THE NEWBORN				
Newborn vaccines		Birth dose	Year of PAHO/TAG recommendation	
BCG		As soon as possible after birth	2004 ⁱ	
Hepatitis B		In the first 24 hours after birth	2011 ^{j,k}	

STD: sexually-transmitted diseases. TAG: Technical Advisory Group. PAHO: Pan American Health Organization.

^a WHO position paper on tetanus vaccination, *Wkly Epidemiol Rec.*, No 6, 2017; 92: 53–76

^b World Health Organization. Vaccines against influenza. WHO position paper, November 2012. *Wkly Epidemiol Rec.* 2012; 87: 461-76.

^c Final report of the XXII Technical Advisory Group (TAG) Meeting on Vaccine-preventable Diseases of the Pan American Health Organization, held in Washington, DC, USA, 1-2 July 2014.

^d WHO position paper on Hepatitis A vaccination, *Wkly Epidemiol Rec.*, No. 28-29, 2012; 87: 261–276.

^e WHO position paper on yellow fever vaccines and vaccination, No. 27, 2013; 88: 269–284.

^f WHO position paper on Polio vaccines, *Wkly Epidemiol Rec.*, No. 12, 2016; 91: 145–168.

^g World Health Organization. WHO Expert Consultation on Rabies. Geneva: WHO; 2013.

^h WHO position paper on meningococcal vaccines 2011, *Wkly Epidemiol Rec.*, No. 47, 2011; 86: 521–540.

ⁱ Final report of the XVI Technical Advisory Group (TAG) Meeting on Vaccine-preventable Diseases of the Pan American Health Organization, held in Mexico City, Mexico, November 3-5, 2004. Available at: http://www1.paho.org/hq/dmdocuments/2009/tag16_2004_FinalReport_Eng.pdf.

^j World Health Organization. Position paper on Hepatitis B, No. 40, 2009; 84: 405-420.

^k Final report of the XIX Technical Advisory Group (TAG) Meeting on Vaccine-preventable Diseases of the Pan American Health Organization, held in Buenos Aires, Argentina, July 2011.

Strategies for Maternal Vaccine Delivery

Maternal and neonatal immunization should be delivered consistently and sustainably. Depending on the vaccine in question, different strategies and modalities will work best. Tables I.6.2 and I.6.3 summarize the strategies

for vaccine delivery and the vaccination modalities that should be considered in planning to introduce or expand a maternal and neonatal immunization program.

Table I.6.2. Strategies and corresponding objectives for vaccine delivery

Strategy	Objective	Description
Routine	Reach and vaccinate 100% of the population according to the schedule of the national immunization program.	This strategy consists of administering the vaccines in the national schedule on all working days throughout the year, taking advantage of all opportunities for vaccination within the health services. Although the strategy emphasizes vaccination within the health services, it also involves extramural vaccination tactics, such as the mobilization of brigades to vaccinate house to house and in institutions, such as schools or workplaces, to capture unvaccinated population and achieve a uniform coverage of $\geq 95\%$.
Intensive	Achieve high vaccination coverage in a short time.	These special campaigns involve extramural vaccination modalities, including the mobilization of brigades to vaccinate people in their homes. They also include capturing target populations in institutions and at vaccination posts located in strategic places where people tend to gather. Within the health services, communication efforts are stepped up and regular working hours are extended to improve access to vaccination.

Source: Toolbox for Coverage Monitoring of Integrated Public Health Interventions. Available at: <http://www.paho.org/immunization/toolkit/monitoring-reporting.html>.

Strategy	Objective	Description
Emergency and rapid response	Interrupt or avoid transmission of an infectious agent in areas at risk because of the presence of a suspected or confirmed case.	Vaccination brigades are mobilized in the community to go house to house, fixed vaccination posts are established using tactics of population micro-concentrations, and vaccinations are given in institutions where the population at risk is located. Vaccination is promoted in health units, where working hours are extended and communication efforts are intensified. Vaccination is combined with active surveillance of suspected cases in areas at risk.

Source: Toolbox for Coverage Monitoring of Integrated Public Health Interventions. Available at: <http://www.paho.org/immunization/toolkit/monitoring-reporting.html>.

Table I.6.3. Vaccination modes and tactics

Type of vaccination	Strategies
Vaccination in the health services	<p>Spontaneous demand: administering vaccines during all working days of the year.</p> <p>Taking advantage of opportunities: using prenatal health services to capture pregnant women if they have not been already vaccinated. In terms of newborn immunization, the administration of hepatitis B vaccine and BCG vaccine is an essential component of good quality childbirth care and should be integrated with newborn care practices.</p> <p>Taking advantage of opportunities: identifying target populations that come to the health services for consultation (for various reasons) to capture them if they have not already been vaccinated.</p>
Extramural vaccination	<p>House to house: going to neighborhoods and towns to visit houses and vaccinate people at home.</p> <p>Facility: Identifying places where target populations may concentrate, such as schools and businesses, in order to vaccinate people at those locations.</p> <p>High concentration: placing fixed posts in strategic locations where target populations concentrate, such as markets and bus stops.</p> <p>Penetration to difficult-to-reach areas: forming mobile teams or vaccination brigades who can visit communities facing geographic, cultural, or social barriers in accessing the health services.</p>

Source: Toolbox for Coverage Monitoring of Integrated Public Health Interventions. Available at: <http://www.paho.org/immunization/toolkit/monitoring-reporting.html>.

Routine Immunization

During the preconceptional counseling period

Ideally, every woman should have an updated immunization schedule before becoming pregnant. Rubella immunization is especially important. It should be noted that women are advised to wait one month after receiving any live vaccine and three months after receiving a rubella-containing vaccine before trying to become pregnant. Immunization records should be reviewed and immunization schedules should be updated as needed according to national schedules.

During pregnancy

Vaccines recommended during pregnancy in the national schedule could be offered to pregnant women through the healthcare services (seizing opportunities for vaccination) including:

- antenatal care (ANC),
- spontaneous demand of vaccination services,
- outpatient care (general practice, gynecology, family planning, high-risk clinics), and
- any other health services that pregnant women might seek for their care or for the care of their children.

Also through **outreach strategies** like the following:

- house-to-house vaccination,
- vaccination posts (micro-concentrations),
- vaccination brigades and/or mobile vaccination teams, and
- vaccinating pregnant women in educational and work facilities (such as schools, churches, work places).

During the post-partum period

The mother's hospitalization should be used as an opportunity for vaccination; review the immunization records and update them

according to national immunization schedules. The immunization records of a pregnant woman should include rubella, hepatitis, influenza and pertussis vaccination.

Regarding the use of vaccines among lactating women, the Strategic Advisory Group of Experts (SAGE) on immunization considered that there is little concern regarding the currently available vaccines, and that their benefits substantially outweigh any potential risks.

The following strategies are crucial for maximizing opportunities for vaccination during the post-partum period:

- Train all health personnel involved in post-partum and lactation services on the immunization schedule for both the mother and her newborn.
- Provide educational talks for women on the importance of vaccination for their health and for that of their infants.
- Provide women with information on the immunization schedule in an accessible language.
- Ensure that the immunization schedule of a mother and her newborn are checked prior to hospital or health center discharge.
- Identify women in the recent post-partum period who gave birth in non-institutional settings during intensification and outreach strategies.

Maternal immunization campaigns

Maternal and neonatal immunization and other maternal and child health interventions can be provided collectively through vaccination campaigns, annual vaccination weeks, or child health days. Many countries use such opportunities to deliver other health interventions, such as vitamin A, folic acid supplementation, and health education,

among others. Such efforts involve the massive mobilization of the target population in a short time and the participation of intra- and extra-sectorial health personnel. These efforts may have a local, sub-national, or national focus, and rely on various strategies to reach the target population.

The campaign's objective is to increase vaccination coverage in a short time, facilitate access to populations with limited access to health services for a variety of reasons, and/or improve the protection of a specific population at risk for a vaccine-preventable disease.

In order to ensure the success and acceptance of maternal and neonatal immunization during campaigns, it is important to involve scientific societies and national champions, and to count on well-designed social communication campaigns.

All vaccination strategies are complementary to each other, and can be combined as needed to achieve the desired goals.

Vaccination of pregnant women in special situations

During outbreaks

Yellow fever. Pregnant women may be vaccinated during yellow fever outbreaks at the discretion of local health authorities. The benefits of vaccination during outbreaks are likely to far outweigh the risk of potential transmission of vaccine virus to the fetus or newborn. Pregnant women and nursing mothers should be counseled on the potential benefits and risks of vaccination, so that they may make an informed decision about whether or not to vaccinate.

Hepatitis A. PAHO's TAG³ recommends vaccinating those persons at increased risk for Hepatitis A virus (HAV) infection, and vaccination may be especially warranted

during outbreaks. Because the HepA vaccine is produced from inactivated HAV, the risk to the developing fetus is expected to be low. No significant adverse events have been identified in pregnant women or their infants in the United States following hepatitis A or hepatitis A and B immunization during pregnancy, based on reports to the Vaccine Adverse Event Reporting System (VAERS). The risk associated with vaccination should be weighed against the risk for acquiring hepatitis A among pregnant women who may be at high risk for exposure to HAV.

Travelers

With care, most pregnant women can travel safely. A review of the patient's travel itinerary, including destinations, types of accommodation, and planned activities, should inform pre-travel health advice.

Most live-virus vaccines, including **measles-mumps-rubella (MMR)** vaccine, **varicella vaccine**, and **live attenuated influenza vaccine (LAIV)**, are contraindicated during pregnancy. The administration of yellow fever vaccine is an exception, for which a risk-benefit assessment should be undertaken for all pregnant and lactating women. The proportion of vaccinated pregnant women who seroconvert is variable and may be related to the trimester during which they are vaccinated (with more seroconversion in the earlier months of pregnancy). PAHO's TAG recommends yellow fever vaccination, if indicated, for pregnant or breastfeeding women who will travel to endemic areas, if such travel cannot be avoided or postponed.⁴

Both pregnant women and nursing mothers at high risk of contracting yellow fever should be counseled regarding the benefits and potential risk of vaccination so they can make informed decisions about vaccination. There are limited data on the use of **yellow fever** vaccine in pregnant and lactating women. Current data do not suggest a risk of viscerotropic or neurologic disease in mothers or their fetuses/newborns after immunization and there is

³ TAG recommendations, Meeting XIX, Argentina, July 2011.

⁴ TAG recommendations, Meeting XXI, Ecuador, July 2013.

no evidence of congenital abnormalities due to yellow fever vaccine. Globally, there have been three documented cases of virus transmission to infants through their mother's breast milk. For lactating women, the benefits of breastfeeding infants far outweigh those of other nutritional alternatives.

Regarding **polio**, until the disease has been certified as eradicated globally, risks remain of acquiring polio for those travelling to infected areas and of reinfection of polio-free areas by travelers from infected areas. All travelers to and from countries and areas infected by wild or circulating vaccine-derived poliovirus should be adequately vaccinated. Both orally administered, live attenuated polio vaccines (OPV), and inactivated polio vaccines (IPV) for intramuscular (or subcutaneous) injection are widely used internationally. There is not any contraindication for using these vaccines in pregnant women. The IPV vaccine should be the first choice, if available.

Certain vaccines, including **meningococcal polysaccharide (MPSV4)**, **inactivated polio vaccine (IPV)**, and **hepatitis A and B vaccines**, that are considered safe to be administered during pregnancy may be indicated based on risk. **Rabies** post-exposure prophylaxis with rabies immunoglobulin and vaccine should be administered after any moderate- or high-risk exposure to rabies; pre-exposure vaccine may be considered for travelers when the risk of exposure is substantial.

Strategies for Neonatal Vaccine Delivery

As part of a comprehensive maternal and neonatal immunization approach, it is critical to enforce the administration of hepatitis B and BCG vaccines to the newborn as early as possible during the first 24 hours of life.

In all facilities where deliveries occur, the infrastructure and procedures should be in place to allow for the administration of these vaccines in conjunction with vitamin K administration, to take advantage of the current practice of early administration of vitamin K during the first hours after birth. BCG and hepatitis B vaccines may be administered to newborns simultaneously in different anatomical locations.

Rationale for BCG vaccination in the newborn

Mycobacterium tuberculosis, the etiological agent of tuberculosis (TB), is a leading cause of human disease and death, particularly in developing countries. Worldwide, TB is intimately linked to poverty, making the control of TB a matter of justice and human rights. In some areas with a high burden of TB, existing strategies for TB control cannot keep pace with the rising number of cases of TB occurring in parallel with the HIV/AIDS pandemic. Emerging mycobacterial drug resistance further complicates the situation. After decades of steady decline, the incidence of TB is also increasing in industrialized countries, mainly as the result of outbreaks in particularly vulnerable groups.

The bacillus Calmette–Guérin (BCG) vaccine has a documented protective effect against meningitis and disseminated *Mycobacterium tuberculosis* (TB) in children. Countries with a low burden of TB may choose to limit BCG vaccination to neonates and infants of known high-risk groups for the disease or to skin-test negative older children. In countries with a high burden of TB, a single dose of BCG vaccine should be given to all infants as soon as possible after birth (1). If the mother is HIV positive, the newborn should first be tested for HIV: if the child tests negative for HIV at 5 weeks of birth, he/she can get vaccinated with BCG.

Rationale for hepatitis B vaccination in the newborn

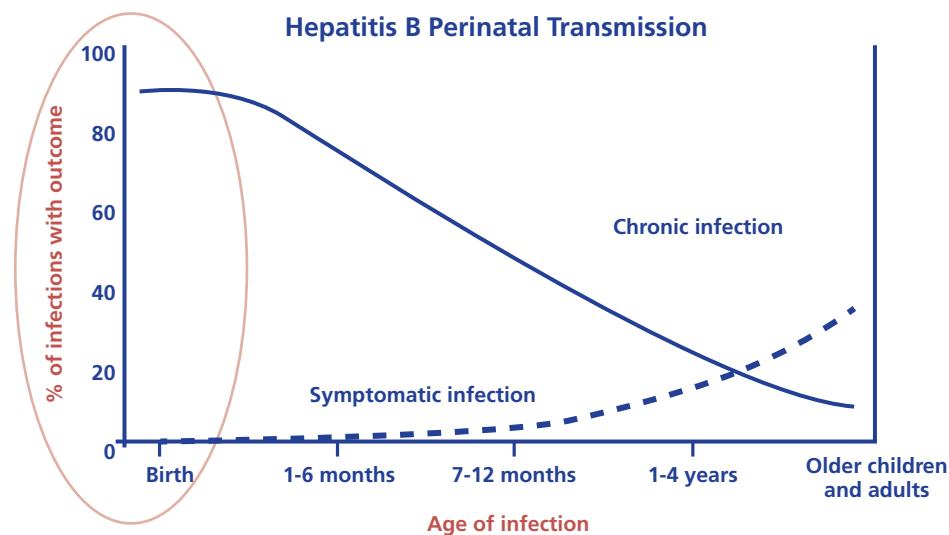
The best way to prevent mother-to-child transmission of hepatitis B is through the hepatitis B vaccination of their infants, with the first dose administered during the first 24 hours of life.

The risk of chronic infection is inversely related to the age at acquisition of acute infection (see **Figure I.6.1**). The vast majority (up to 90%) of infants infected with HBV from their mothers (HBsAg positive and especially HBeAg positive) through exposure to blood and cervical fluid during birth, will go on to develop chronic infection. Neonatal vaccination can prevent 80-95%

of these cases. Hepatitis B immunoglobulin, in addition to vaccination, may offer added protection to newborns with mothers who are HBsAg positive, especially if they are HBeAg positive, although this might not be feasible due to supply. When feasible, the PAHO CLAP recommends administering both hepatitis B vaccine and anti hepatitis B immune globulin in the first 24 hours of life (2, 3).

Globally, two-thirds of HBV-related deaths result from infection acquired in the perinatal and early childhood period, underscoring the need for routine infant hepatitis B immunization, with the first dose administered at birth, as the cornerstone of a hepatitis B prevention strategy.

Figure I.6.1. Outcome of hepatitis B virus infection by age at infection



If the mother is positive for HBsAg and HBeAg:	<ul style="list-style-type: none"> • 70%-90% of infants infected • 90% of infected infants become chronically infected
If positive for HBsAg only:	<ul style="list-style-type: none"> • 5%-20% of infants infected • 90% of infected infants become chronically infected

Source: Morse SA, Holmes KK, Ballard RC. Atlas of sexually transmitted diseases and AIDS. 4.^a ed. United Kingdom: Saunders; 2010.

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I.7. Maternal and Neonatal Immunization Information System

WHO/UNICEF Joint Reporting Form Data

Countries systematically report maternal and neonatal vaccination data to PAHO using the official WHO/UNICEF Joint Reporting Form.⁵ The report allows for the identification of immunization with vaccines including Td (for the mother), pertussis (for the mother and infant), influenza (for the mother and the infant), hepatitis B (for the mother and newborn), and BCG (for the newborn).

Information from the Latin American Center for Perinatology (CLAP)

The Latin American Center for Perinatology (CLAP) has developed a perinatology clinical record and information system that has been put in place in 29 Latin American countries (see **Figure I.7.1**). This information system has been recently modified to improve surveillance of vaccination during pregnancy, including screening for hepatitis B and group B *Streptococcus*.

Figure I.7.1. Sample of the maternal immunization record developed by the CLAP

VACCINES		Yes, before pregnancy	Yes, during pregnancy	Yes, post-partum/abortion	Day	Month	Year	# Total doses
Tetanus/diphtheria	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>				<input type="text"/>
Tdap	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>				Gest. age (weeks) <input type="text"/>
Influenza	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>				<input type="text"/>
Rubella	<input checked="" type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>				<input type="text"/>
Hepatitis B	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>				<input type="text"/>
Hepatitis A	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>				<input type="text"/>

Screening hepatitis B No Yes

Group B *Streptococcus* screening 35-37 weeks

- + Not performed

⁵ World Health Organization. WHO/UNICEF joint reporting process. Geneva: WHO; 2009. Available at: http://www.who.int/immunization_monitoring/routine/joint_reporting/en/index.html.

Establishing the Target Population

Accurately estimating the number of pregnant women in a given population remains a challenge. The number of live births gives a good approximation of the number of pregnant women, and has been traditionally used to that end. Abortions and miscarriages, as well as multiple births, may under or overestimate the number of pregnant women in a population. In calculating vaccination coverage for pregnant women, the following parameters should be taken into consideration in establishing the denominator of pregnant women—i.e. the target population of routine immunization services:

- Live births should be used as a proxy to estimate the expected number of pregnant women identified. Since pregnancy lasts nine months, during a short campaign (say, of one month), the entire yearly cohort of pregnant women expected for the year would not be covered, some women would become pregnant later in the year, after the campaign has ended. Therefore, a one-month campaign would cover only approximately 75% (9/12 months) of the cohort of pregnant women for the year.
- Because women are often unaware of their pregnancy during the first month of gestation, they will not seek vaccination services. Countries may include this first month of pregnancy in their denominator estimation (9/12, which represents 75% of the live birth cohort) or may exclude the first month (8/12, which represents 67% of the live birth cohort).
- Since live births will be used as a baseline to estimate the denominator, countries should note that the vaccination coverage of pregnant women will be overestimated, because it does not account for pregnancies that did not result in a live birth.

Based on these considerations, the following estimation method is proposed for calculating the denominator of pregnant women, (the calculations use the hypothetical scenario shown in **Figure I.7.2**):

Estimation of the denominator for one-month campaigns

- 1) Live birth cohort for a given year: ($Z = 156,688$).
- 2) Expected deliveries in a given month is assumed to be the live birth cohort for the year, divided by 12 months: $156,688/12 = 13,057$.
- 3) The number of pregnancies that begin in a given month are assumed to be equal to the number of expected deliveries in that month.
- 4) As established previously, during any given month there are pregnant women in their 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, 8th, and 9th month of gestation. Therefore, in a given month there will be the number of pregnancies that begin in any given month multiplied by nine months (which is the duration of the pregnancy)—($13,057*9 = 117,513$, or 75% of the annual live birth cohort).

This would be the denominator for a campaign that lasts one month.

- 5) If the campaign lasts two months—we need to add the number of pregnant women corresponding to one additional month ($13,057* 9 + 13,057 = 13,057* 10= 130,570$, or 83% of the annual live birth cohort).

This would be the denominator for a campaign that lasts two months.

- 6) If the campaign lasts three months, the equivalent of 2 additional months of pregnant women should be added—($13,057* 11 = 143,627$, or 91% of the annual live birth cohort).

This would be the denominator for a campaign that lasts three months.

- 7) If the campaign lasts four months, the equivalent of three additional months of pregnant women should be added—($13,057* 12 = 156,684 \approx 100\%$ of the annual live birth cohort.)

Therefore, if the campaign lasts four or more months, the denominator for the campaign is the total live birth cohort for the year.

Figure I.7.2. Sample scenario for calculating the denominator of pregnant women

Expected deliveries in 12 months = 156,688

Expected deliveries in 1 month = 13,057

Month of pregnancy	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr
1								13,057								
2								13,057	13,057							
3								13,057		13,057						
4								13,057			13,057					
5								13,057				13,057				
6								13,057					13,057			
7								13,057						13,057		
8								13,057							13,057	
9								13,057								13,057

One-month campaign x nine cohorts =	11,7513			
Percentage of the cohort	75%			
Two-month campaign = one-month campaign + one month of new pregnant women		130,570		
Percentage of the cohort		83%		
Three-month campaign = two-month campaign + 1 month of new pregnant women			143,628	
Percentage of the cohort			92%	
Four-month campaign = three-month campaign + 1 M of new pregnant women				156,685
Percentage of the cohort				100%

Maternal Immunization Indicators

Specific indicators (such as indicators of vaccination coverage and surveillance performance) should be established for the new vaccine (Table I.7.2). Subsequently, they should be

included in the supervision guide for the routine immunization program. Such indicators can be part of a monitoring and evaluation plan, as described in the preceding section. Special studies to evaluate vaccine effectiveness should also be contemplated.

Table I.7.1. National and regional indicators relevant to maternal and neonatal immunization

National indicators relevant to maternal and neonatal immunization
Percentage of pregnant women with at least four antenatal care (ANC) visits
Percentage of pregnant women with an ANC visit in the first trimester
Vaccination coverage in pregnant women (Td, influenza, pertussis, hepatitis B)
Vaccination coverage with the birth dose of hepatitis B within the first 24 hours of life
BCG vaccination coverage
Percentage of AEFI reported with final classification
Comparability of newborn BCG and hepatitis B vaccination
Influenza and hepatitis B vaccination coverage among healthcare workers, as a proxy for vaccine acceptance among healthcare workers and hence their recommendation of vaccination to the target population

Regional indicators relevant to maternal and neonatal immunization
Number of countries and territories whose immunization schedules include vaccination of pregnant women using influenza and/or tetanus-diphtheria vaccines, as tracers of maternal vaccination
Number of countries and territories that administer hepatitis B vaccine to newborns during the first 24 hours of life
Number of countries and territories that offer other preventive interventions integrated with vaccination (e.g., antenatal care visits, routine childhood medical visits, iron supplementation, health education, and others)

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World Health Organization. Practical guide for the design, use and promotion of home-based records in immunization programs. WHO/IVB/15.05. Geneva: WHO; 2015.

I.8. Social Communication and Vaccine Acceptance

Definitions

Vaccination confidence is the population's trust in the effectiveness and safety of vaccines and in the system that delivers them. That includes the reliability and competence of the health services and health professionals, and in the motivations of policy-makers who decide which vaccines are needed and when. Vaccination confidence is only one of several factors that affect an individual's decision to accept a vaccine.

Vaccine hesitancy is a behavior that leads to mistrust of vaccines. Such a behavior is influenced by a number of factors, including issues of confidence (mistrust of a vaccine or a provider), complacency (do not perceive a need for a vaccine, do not value the vaccine), and convenience (access). Individuals who are hesitant about vaccination are a heterogeneous group whose decision about specific vaccines or vaccination in general varies. While vaccine-hesitant individuals may accept all vaccines, they may still harbor concerns about them; some may refuse or delay some vaccines but accept others; some may reject all vaccines.

Vaccine complacency occurs when perceived risks of vaccine-preventable diseases are low and vaccination is not viewed as necessary. Besides low perceptions of the threat of a disease's severity or transmission, complacency about a particular vaccine or about vaccination in general can be influenced by under-appreciation of the value of vaccine (effectiveness and/or safety profile) or lack of knowledge. Immunization program success also may lead to complacency and ultimately in hesitancy, as individuals weigh the risks of vaccines against the risks of diseases that are no longer common as a result of immunization.

Vaccination convenience also is a factor in vaccine acceptance. The quality of the service

(real and/or perceived) and the degree to which vaccination services are delivered at a time and place and in a way that is considered appealing, affordable, convenient and comfortable, also affects the decision to vaccinate. Vaccination convenience and complacency are also determined by the priority that any given person places on vaccination.

As a way to increase vaccination confidence and minimize hesitancy in the Region of the Americas, PAHO, based on experience and lessons learned in the past 35 years, gives high priority to communication, advocacy, and social mobilization. PAHO's *Introduction and Implementation of New Vaccines Field Guide* recommends (1):

“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 healthcare workers from the public and private sectors, 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.”

PAHO's proposed general guidelines suggest that communication and advocacy strategies should aim at achieving the following objectives:

- Raising awareness among all parties about the importance of maternal and neonatal immunization.
- Promoting confidence in the vaccination schedule, and in the safety and effectiveness of the vaccines.
- Avoiding rumors and misinformation.
- Improving vaccination coverage.
- Enhancing detection and reporting of possible AEFIs.

Barriers and Missed Opportunities for Maternal and Neonatal Immunization

National and international studies have demonstrated that vaccination is less likely among pregnant women of lower socio-

economic status, lower educational level, and who belong to racial or ethnic minorities. Non-vaccination among some sub-populations is likely mediated, at least in part, by sociocultural and psychological factors influencing maternal vaccine acceptance, as has been demonstrated in non-pregnant populations. Other factors such as accessibility to the health system might also exert an influence.

According to the health belief model (HBM) (Table I.8.1), in order for a person to adopt a behavioral change, their perceived threat of a disease and its severity and the benefits of action must outweigh their perceived barriers. In developing an intervention to increase maternal and neonatal immunization, the six key concepts of HBM should be considered: perceived susceptibility, perceived severity, perceived benefits of action, perceived barriers to action, cues to action, and self-efficacy.

Table I.8.1. The health belief model (HBM), concepts and their application

Concept	Definition	Application
Perceived susceptibility	One's opinion of chances of getting a condition	Define population(s) at risk, risk levels; personalize risk based on a person's features or behavior; heighten perceived susceptibility if too low
Perceived severity	One's opinion of how serious a condition and its consequences are	Specify consequences of the risk and the condition
Perceived benefits	One's belief in the efficacy of the advised action to reduce risk or seriousness of impact	Define action to take; how, where, when; clarify the positive effects to be expected
Perceived barriers	One's opinion of the tangible and psychological costs of the advised action	Identify and reduce barriers through reassurance, incentives, assistance
Cues to action	Strategies to activate "readiness"	Provide how-to information, promote awareness, reminders
Self-efficacy	Confidence in one's ability to take action	Provide training, guidance in performing action

Source: Glanz K, Rimer BK. *Theory at a glance: A guide for health promotion practice*. Bethesda: HHS; 1997.

Evidence-based Approaches to Promote Acceptance of Maternal and Neonatal Immunization

The following key tasks are evidence-based approaches⁶ to promote maternal and neonatal immunization acceptance:

A. Educate. Insufficient knowledge about the susceptibility to and the morbidity of vaccine-preventable diseases and about the risks and benefits of vaccination are barriers to vaccine uptake that can be modified. Health providers should explicitly address the importance of vaccination with all obstetric patients; counseling should focus on the effectiveness and safety of vaccination for both mother and infant.

For example, it is known that those who are aware of their susceptibility to influenza and believe in the vaccine's effectiveness are more likely to get vaccinated. To that end, delivering a positive message that stresses the benefits of vaccination (such as, "influenza vaccination protects you and your baby from influenza") may be more effective than communicating a negative message that stresses the risk of foregoing influenza or pertussis vaccination (such as, "if you don't get the influenza vaccine, you could get really sick and need to receive intensive care"). This may be particularly true if the message emphasizes the validated benefits to the infant.

B. Recommend. Face-to-face communication from a physician appears to function as a powerful motivator of vaccine acceptance during pregnancy. Similarly, the absence of a recommendation from an obstetric provider appears to be a strong predictor of not receiving indicated maternal vaccines. Obstetric practitioners should talk directly and openly to patients about recommended vaccinations, clearly

stating their support for recommended vaccines during pregnancy and specifically recommending indicated vaccines for the particular patient.

C. Normalize. Obstetric practitioners should frame infectious disease prevention for women and infants as a routine part of obstetric care, presenting vaccines as a standard part of anticipatory guidance during first obstetric visits. In terms of the influenza vaccine, all providers who care for pregnant women should themselves accept the vaccine: this sends a powerful message in support of immunizations and demonstrates that the providers care for the well-being of their patients. It also can help to contribute to a culture of immunization normalization in the office setting. On a health systems level, organizations can implement strategies to ensure consistent provider recommendation of vaccination, including standing orders, ongoing provider education about vaccination, and use of vaccination as a quality indicator.

D. Maximize convenience. Obstetric providers see pregnant women frequently and are viewed as a trusted, reliable source of medical information. As such, obstetric providers should offer on-site administration of recommended vaccines in pregnancy, to reduce the investment in time and cost for patients. Obstetric caregivers can consider using prompts (such as pop-up reminders or best-practice tabs in the electronic record) to consistently and clearly identify vaccine-eligible obstetric patients. Electronic records also afford opportunities to remind staff to order recommended vaccines and to streamline documentation of vaccination counseling. It is also important to implement reimbursement structures that can incentivize maintaining a vaccine supply and cover the cost of vaccine administration.

⁶ These concepts have been adapted from the American Congress of Obstetricians and Gynecologists (ACOG) Committee Opinion on Integrating Immunizations into Practice.

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SECTION

III

Maternal and Neonatal Vaccines Currently in Use and a View toward the Future



II.1. Influenza Vaccination during Pregnancy

KEY FACTS

- Pregnant women are at increased risk of influenza illness and its complications; so are their infants.
- Influenza vaccines are effective in preventing infection and reducing illness severity in the mother and the newborn.
- Influenza vaccines have been used for decades and their safety has been well documented.
- Pregnant women, regardless of their stage of pregnancy, should only receive inactivated influenza virus vaccines, administered intramuscularly.
- Monitoring the influenza disease burden, vaccine effectiveness and vaccination coverage allows health authorities to evaluate the impact of the program on the health of pregnant women and their children.
- Communication strategies that encourage influenza vaccination among pregnant women should emphasize the safety of the vaccines and the benefits for infants.

Background

Seasonal influenza is an acute viral infection caused by an influenza virus. Influenza viruses circulate worldwide and are classified into three seasonal types—A, B, and C. Type A influenza viruses are further classified into subtypes, according to the combinations of various virus surface proteins. Among the many subtypes of influenza A viruses, influenza A(H1N1) and A(H3N2) subtypes are currently circulating among humans. Only influenza A and B viruses are included among seasonal influenza vaccines, because type C virus infections are much less common and only result in mild illness.

Influenza activity is seasonal, peaking from December to March in the temperate climates of the Northern Hemisphere in the Americas and from May to October in the temperate climates of the Region's Southern Hemisphere. While influenza can occur throughout the year in tropical areas, most countries such as Central America experience the highest disease burden at mid-year, much as Southern Hemisphere countries do.

Influenza surveillance in the Region's countries monitors the prevalence of circulating influenza viral strains and detects new strains necessary for vaccine formulation. It also makes it possible:

- to estimate influenza's impact in terms of morbidity, mortality, and economic losses;
- to rapidly detect outbreaks; and
- to assist disease control through rapid preventive action (e.g., chemoprophylaxis of unvaccinated, high risk patients).

Influenza is a seasonal viral respiratory illness, which affects mostly children, the elderly, pregnant women, and individuals with underlying medical conditions

The participation of sentinel sites (hospitals or health-care centers) that collect clinical information and respiratory specimens is the pillar of surveillance. Most PAHO Member States currently participate in the

Global Influenza Surveillance and Response System by sharing data through FluNet.⁷

In 2012, WHO and its Strategic Advisory Group of Experts (SAGE) on immunization recommended that countries considering the initiation or expansion of programs for seasonal influenza vaccination include pregnant women as the highest priority group (1). The following high risk groups, in no particular order of priority, were also recommended for vaccination: children aged 6–59 months (especially 6–23-month-olds), the elderly, individuals with chronic medical conditions, and health-care workers. The Pan American Health Organization’s Technical Advisory Group (TAG) on Immunization for Latin America subsequently endorsed these recommendations.⁸

A pregnant woman should be vaccinated with the trivalent inactivated influenza vaccine (TIV) at any stage of her pregnancy. This recommendation is based on evidence of a substantial risk of severe disease in this sub-population and of vaccine safety throughout pregnancy, as well as effectiveness in preventing influenza in women and their young infants, among whom the disease burden is also high.

Disease Burden

Pregnant women are more vulnerable to respiratory illnesses than are their non-pregnant counterparts, because pregnancy involves physiological changes in the cardiopulmonary and immunological systems. The increased oxygen consumption, dyspnea, and decreased functional residual capacity cause an increased susceptibility to respiratory pathogens such as virus and

bacteria. Moreover, evidence suggests that in order to tolerate fetal antigens during pregnancy, the maternal immune system suppresses cell-mediated immunity, which increases susceptibility to infections. Therefore, as gestational age advances, the risk of serious morbidity and hospitalization due to influenza infection increases substantially. Pregnant women who are hospitalized with influenza virus infections have significantly longer hospital stays, irrespective of gestational age, and pregnant women with comorbidities are more likely to be admitted to intensive care.

Pregnant women are the highest priority group for influenza vaccination

Influenza illness in pregnant women can result in fetal death, premature onset of labor, decreased birth weight, and intrauterine growth restriction (infants born small for gestational age). Studies have shown a risk of infant death almost two-fold greater among children born to mothers who had influenza during pregnancy compared to children of mothers who did not have influenza-associated illness during pregnancy. Teratogenic effects, including cleft lip and palate, neural tube defect, and cardiovascular malformations were two to three times more common among infants born to mothers infected with influenza during the first trimester of pregnancy compared to children of mothers who did not have influenza-associated illness during pregnancy. Scientific evidence also suggests that there is an increased risk of schizophrenia in the child associated with influenza illness during pregnancy, with studies showing a 3.7-fold increase in schizophrenia later in life among children born to mothers who contracted influenza during pregnancy.

⁷ According to WHO’s website, “FluNet is a global tool for influenza virological surveillance. The virological data entered into FluNet, e.g. number of influenza viruses detected by subtype, are critical for tracking the movement of viruses globally and interpreting the epidemiological data. The data is publically available and it is real-time. The results are presented in various formats including tables, maps and graphs. The data are provided remotely by National Influenza Centres (NICs) of the Global Influenza Surveillance and Response System (GISRS) and other national influenza reference laboratories collaborating actively with GISRS, or are uploaded from WHO regional databases.” For additional information, please visit: http://www.who.int/influenza/gisrs_laboratory/flunet/en/

⁸ TAG recommendations, Meeting XX, United States, October 2012.

The negative impact of influenza infection in pregnant women and newborns is well documented

During the A(H1N1)2009 influenza pandemic, high morbidity and mortality were observed among pregnant women, including in Latin America.

Types of Vaccines

Only inactivated influenza vaccines are recommended for use among pregnant women (1). Such vaccines are made from highly purified viruses grown in eggs. There are three types of inactivated vaccines - whole virus vaccines, split virus and subunit vaccines. Inactivated seasonal vaccines are conventionally subunit or split virion vaccines. Split virus preparation contains viruses that have been treated with an organic solvent to remove surface glycoproteins and thus reduce vaccine reactogenicity. The influenza vaccine contains 15 µg of each antigen per 0.5 ml dose of the three virus strains (usually two type A and one type B) that are likely to circulate during the upcoming influenza season. Inactivated vaccines used in Latin America and the Caribbean currently correspond to four manufacturing products. Vaccines are normally given intramuscularly in the upper arm. Quadrivalent vaccines containing two lineages of influenza B viruses are also available for use.

Immunogenicity and Effectiveness

Seasonal influenza epidemics—driven by population’s level of immunity and antigenic changes (drift) of influenza viruses—can be very heterogeneous, differing in their timing, incidence, and severity, as well as in the match between circulating influenza virus strains and strains included in the vaccine. In addition to age, health status, and prior immunity to influenza viruses among other factors, this match between influenza vaccine strains and circulating strains will partly dictate the influenza vaccine effectiveness for every season.

Several studies have demonstrated the adequate immunological responses to inactivated influenza vaccines during pregnancy and the efficient transplacental transfer of antibodies. Studies to date have shown that the effectiveness of seasonal inactivated influenza vaccination in preventing influenza infection in pregnant women was moderate, while the potential for maternal vaccination to protect infants ranged from 41% to 91%. A study in the United States found that infants of vaccinated mothers were 45%–48% less likely to be hospitalized due to influenza than those of unvaccinated mothers.

Seasonal influenza vaccines are not recommended in infants younger than 6 months old, but transmission of protective antibodies from the vaccinated pregnant woman is thought to occur and to provide some protection to the newborn. In this regard, passive transfer of antibodies from the mother to the newborn has been shown to be 29% effective in preventing influenza in infants aged <6 months (2).

Monitoring the influenza disease burden, vaccine effectiveness and vaccination coverage allows health authorities to evaluate the impact of the program on the health of pregnant women and their children.

Vaccine Safety

The WHO Global Advisory Committee on Vaccine Safety (GACVS), in its review of available safety data for all the vaccines recommended for pregnant women, concluded that inactivated influenza vaccines were safe for use at any stage of pregnancy (3).

While an estimated 11.8 million pregnant women received the non-adjuvanted, inactivated influenza vaccine in the United States between 1990 and 2009, that country's Vaccine Adverse Event Reporting System (VAERS) database received only 20 notifications of serious adverse events and 128 reports of non-serious adverse events following administration of trivalent influenza vaccine during that period. Multiple studies have not found new, unusual, or unexpected patterns of serious acute events, adverse pregnancy outcomes, or congenital anomalies.

The inactivated influenza vaccine does not cause fetal harm when administered to pregnant women. The vaccines used among pregnant women have been associated with less local reactions than other influenza vaccines. **Mild adverse events** have been reported, the most frequent being soreness at the vaccination site which lasts up to two days and does not require further medical attention. Although systemic reactions cannot be ruled out, studies have found no association between vaccination with inactivated influenza vaccines and higher rates for systemic symptoms (e.g., fever, malaise, myalgia, and headache) among young adults, compared with placebo injections. Immediate, presumably allergic reactions (e.g. hives, angioedema, wheeze and anaphylaxis) occur rarely after influenza vaccination (See **Table II.1.1** for adverse events typically reported among vaccinees of all ages).

Vaccine Contraindications

Influenza vaccines should not be administered to pregnant women if (3):

- there has been a confirmed anaphylactic reaction to a previous dose of the vaccine,
- there has been a confirmed anaphylactic reaction to any component of the vaccine,
- there is a confirmed anaphylactic hypersensitivity to egg products (vaccines preparation is egg-based),
- a careful history does not rule out previous non-life-threatening reactions (e.g., rash or other, not fully anaphylactic reactions),
- the woman is severely asthmatic (level 4 or above) or actively wheezing at the time of vaccination.

There is sufficient evidence globally that shows vaccines are safe for pregnant women

Timing and Schedule

Influenza vaccination is recommended at any stage of pregnancy to protect both mother and infant (1). It should be kept in mind that it takes at least two weeks after receiving the influenza vaccine for the mother to be protected against influenza. Until she is protected, she remains at risk for contracting the disease and spreading it to her vulnerable newborn.

Because the influenza vaccine can be given at any stage of pregnancy there are many opportunities to vaccinate pregnant women throughout prenatal care. That said, it is important to take into consideration the disease's seasonality in order to vaccinate pregnant women prior to the main epidemic peak in tropical countries or prior to the winter seasons in temperate countries. In areas of limited access to health services, it may be preferable to vaccinate at the first (and possibly only) antenatal care visit or any other medical consultation during pregnancy with the influenza-vaccine formulation available at the time.

Implementation Strategies in Latin America and the Caribbean

As of 2015, 40 out of the Region's 45 countries and territories had policies in place for influenza vaccination, of which 31 currently target pregnant women. This number has significantly increased after the 2009 A(H1N1) pandemic (from 7 to 31) due to the high disease burden that was observed for this group at that time. Information reported by 19 countries of the Americas that target pregnant women for vaccination suggests that the median vaccination coverage for this group was 59% in 2014, with significant variations from country to country.

Adverse events reported following influenza vaccination are usually infrequent and mild

The main vaccination strategy throughout Latin America and the Caribbean is to vaccinate intensively prior to the peak of highest burden of influenza illness, reaching high vaccination coverage through a single campaign. Influenza vaccine then continues to be offered through the routine health services throughout the influenza season until vaccine stocks exhaust or expire. See **Figure II.1.1** for information on the use and formulation of seasonal influenza vaccines in the Americas in 2015.

For tropical and subtropical countries, PAHO stresses the importance of following PAHO's TAG recommendation to vaccinate prior to the primary influenza epidemic peak and reaching high vaccination coverage (recommendation that was reiterated during PAHO's TAG 2015). These countries usually experience a second influenza peak, which makes it important to continue vaccinating throughout the season to reach any pregnant women who may not have been vaccinated.

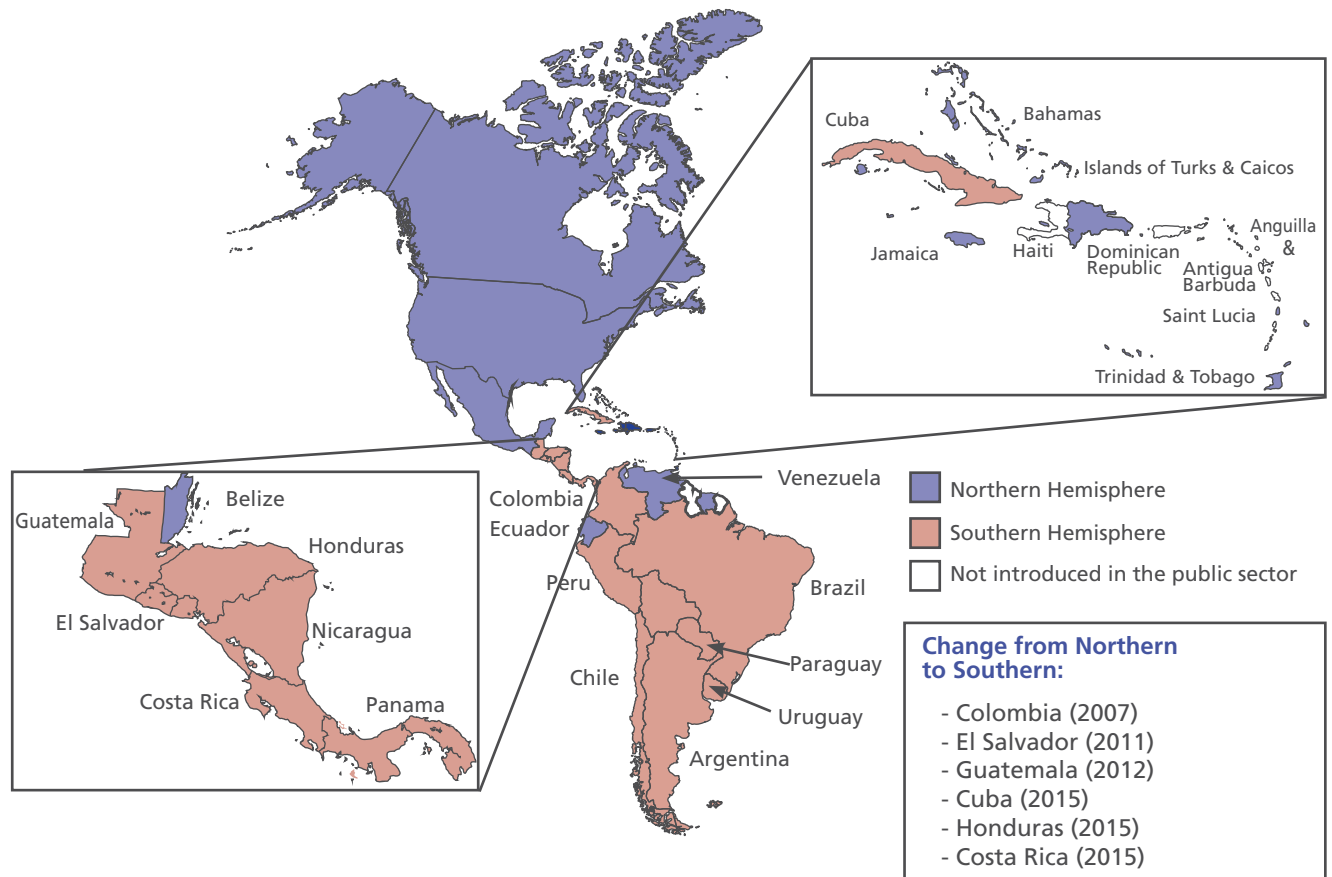
Table II.1.1. Summary of mild and severe adverse events after administration of the inactivated influenza vaccine, 2012

Nature of adverse event	Description	Rate/doses
Mild	Local reactions: Injection site reactions	10-64 per 100
Severe	Anaphylaxis Guillain-Barré Oculo-respiratory syndrome (events of moderate severity)	0.7 per 10 ⁶ 1-2 per 10 ⁶ 76 per 10 ⁶

Source: World Health Organization. World vaccine reaction rates information sheets. Available at: http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/

Pregnant women should receive standard inactivated influenza vaccines

Figure II.1.1. Use and formulation of seasonal influenza vaccines in the Americas by country, 2015



Source: Country reports to PAHO, MOHs Webpage, PAHO/WHO Surveys

An efficient vaccination campaign takes place before the biggest epidemic peak of the year

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II.2. Tetanus-containing Vaccines during Pregnancy

KEY FACTS

- Tetanus is a life-threatening noncommunicable disease caused by a potent neurotoxin produced by the bacterium *Clostridium tetani*; it is vaccine-preventable.
- Neonatal tetanus can be prevented through vaccination of women before or during pregnancy.
- WHO's goal is to eliminate neonatal tetanus worldwide.

Tetanus is particularly common in newborn infants and their mothers when they have been inadequately vaccinated or are unvaccinated

Neonatal tetanus can be prevented by immunizing women of reproductive age with TTCV, either prior to or during pregnancy

Background

While people of all ages can get tetanus, the disease is particularly common in newborn infants and their mothers, if women have been inadequately vaccinated or are unvaccinated against tetanus. Most infants who become infected with *Clostridium tetani* die. Tetanus occurring during pregnancy or within six weeks of the conclusion of pregnancy is called “maternal tetanus”; tetanus occurring within the first 28 days of life is called “neonatal tetanus” (NNT).

Neonatal tetanus more commonly occurs in difficult to reach, rural areas where deliveries typically take place at home, in unclean environments without adequate hygienic childbirth practices. Tetanus can be easily prevented through immunization with tetanus-toxoid-containing vaccines (TTCV). Neonatal tetanus can be prevented by immunizing women of reproductive age with TTCV, either prior to or during pregnancy. TTCV protects the mother and—through a transfer of tetanus antibodies to the fetus—her infant. Hygienic childbirth practices are also important to prevent neonatal and maternal tetanus.

Tetanus-toxoid-containing vaccines are included in childhood immunization schedules worldwide. Nonetheless, to achieve lasting protection, booster doses need to be administered. To be protected throughout life, WHO recommends that a person receive three doses of DTP in infancy, followed by TTCV boosters at school-entry age (4–7 years), in adolescence (12–15 years), and in early adulthood or during a first pregnancy (1). People who recover from tetanus do not develop natural immunity and can be re-infected; therefore they should be immunized with a TTCV.

In 1989, the World Health Assembly, WHO's governing body, adopted a resolution for the worldwide elimination of NNT by 1995. The Directing Council of PAHO endorsed that

resolution, thereby launching the effort to eliminate NNT in the Americas. To that end, ministries of health in Member States began to implement specific programmatic activities, with the support of PAHO and other international organizations.

Hygienic childbirth practices are also important to prevent neonatal and maternal tetanus

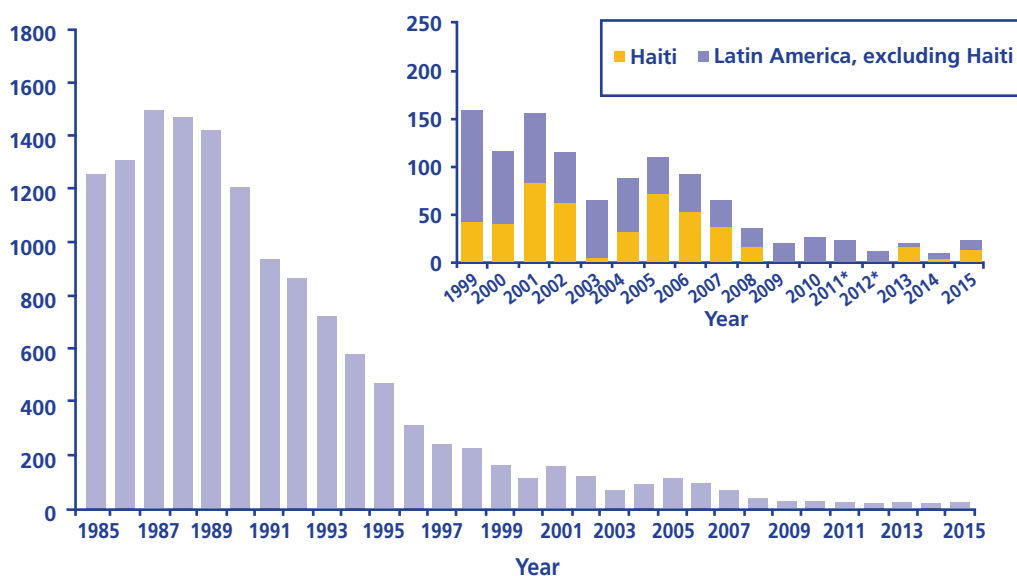
The goal of eliminating NNT as a public health problem differs from other eradication goals, such as those targeting smallpox and polio. Because *C. tetani* is prevalent in the environment, particularly in the soil of warm and moist areas, and because humans and animals may carry the bacterium in their intestinal tracts, it is impossible to completely eliminate it. For operational purposes, neonatal tetanus is considered to be eliminated as a public health problem when all the municipalities in a country have annual rates of NNT below 1 per 1,000 live births.

Despite the remarkable progress made, the original objective of eliminating neonatal tetanus before 1995 was not achieved. **Figure II.2.1** shows the progress in the elimination of neonatal tetanus in the Region up to 2015.

In May 2012, the World Health Assembly, during its 65th session, supported the Global Vaccine Action Plan (GVAP) through Resolution 65.17, which aimed at strengthening the achievements in immunization and stimulating Member States to uphold their commitment to protect their populations against vaccine-preventable diseases. The GVAP included achieving global and regional elimination goals and, in the case of NNT, proposed its elimination in all WHO regions before 2015.

Neonatal tetanus is considered to be eliminated as a public health problem when all the municipalities in a country have annual rates of NNT below 1 per 1,000 live births

Figure II.2.1. Progress in the elimination of neonatal tetanus, Region of the Americas, 1985–2015



Source: PAHO-WHO/UNICEF Joint Reporting Form (JRF) and country reports; *2011-2012 Haitian data not available.

All countries/territories of the Americas have reached the NNT elimination goal, except Haiti. Haiti has advanced substantially towards NNT elimination. Nevertheless, Haiti is putting in place vaccination activities to achieve this goal. In addition to vaccinating pregnant women during routine immunization activities, three rounds of Td vaccination campaigns were conducted in Haiti's 140 communes to immunize all women of reproductive age, regardless of their previous vaccination status, in 2013, 2014, and 2015. Haiti also integrated NNT surveillance into acute flaccid paralysis, measles/rubella, diphtheria and pertussis case-based surveillance in 2013.

Disease Burden

In the early 1990s, WHO estimated that maternal tetanus was responsible for 5% of maternal deaths, particularly in the developing world. Although the World Health Assembly had called for the elimination of NNT in 1989, the disease continued to be a significant public health problem in some countries. Moreover, neonatal tetanus is one of the most underreported notifiable diseases. Because NNT tends to occur in areas with scant or no access to health care, NNT often remains silent in the community. Many of the non-reported cases and deaths occur at home before the baby reaches 2 weeks of age. When cases do reach a health facility, staff often do not report due to lack of training, high staff turnover, work overload. These reasons have led to neonatal tetanus often being called the "invisible killer."

WHO estimated that 49,000 newborns died from NNT in 2013, a 94% drop from the estimates recorded in the late 1980s.

*WHO estimated that
49,000 newborns
died from NNT in 2013*

In the 1970s, more than 10,000 newborns were estimated to have died annually from NNT in the Americas. By 2013, only 20 cases of NNT were reported in the Region and 15 of them (43%) were from Haiti. By 2014, the number had dropped down to 10 cases and 3 (30%) of these were from Haiti. Between 1987 and 2014 there has been a 99% reduction of NNT cases. In 2013 five deaths due to NNT were reported in the Americas; in 2014 three such deaths were reported.

Types of Vaccines

Tetanus vaccines contain tetanus toxoid, a modified neurotoxin that induces the development of a protective antitoxin. The immunized mother transfers the antitoxin to the fetus through the placenta, preventing neonatal tetanus.

There are three tetanus toxoid-containing vaccines available for vaccinating pregnant women:

- tetanus toxoid vaccine (TT),
- tetanus and diphtheria toxoids vaccine, either in low dose for adults (Td), and
- tetanus and diphtheria toxoids, and acellular pertussis (whooping cough) vaccine (Tdap).

Td is administered to all those older than 7 years. When tetanus vaccination is indicated, Td is preferred to TT vaccine, because Td also maintains protection against diphtheria.

Tdap is a relatively new vaccine, recommended for use among adolescents and adults. It has been used primarily in countries that are using the diphtheria, tetanus and acellular pertussis combined vaccine (DTaP) in children to boost protection against pertussis in adolescents and adults. Tdap is also recommended for pregnant women to prevent pertussis in very young infants (5). The use of Tdap is discussed in the next section.

Both the efficacy and the effectiveness of TTCV are well documented

Immunogenicity and Effectiveness

To increase immunogenicity, the tetanus toxoid in tetanus vaccines is adsorbed to aluminum or calcium salts. Although both diphtheria- and tetanus-toxoid-containing vaccines induce satisfactory immune responses in infants aged up to 6 weeks, the diphtheria, tetanus and whole-cell pertussis (DTwP) or DTaP vaccines are recommended for infants aged 6 weeks or older, in order to improve the immune response to the pertussis component.⁹

Both the efficacy and the effectiveness of TTCV are well documented, and most of the clinical studies have reported efficacy estimates between 80% and 100%.

The first vaccination with the conventional adsorbed tetanus toxoid induces a low and non-protective level of antibodies but leaves

a lifelong imprint on the individual's immune system. Accordingly, a second vaccination administered any time after four weeks will rapidly produce a protective antibody antitoxin level. A third dose induces immunity in nearly 100% of vaccinated individuals.

The interval between each of the first three doses should be at least four weeks. Longer intervals can increase the magnitude and duration of the immunological response, but this should not be a reason for delaying immunization.

As with other vaccines, the antibody response to tetanus toxoid is impaired in children with AIDS. However, in HIV-infected children during the perinatal period, satisfactory antibody responses to TTCV were obtained during their first two years of life. In HIV-infected adults, the antibody response to TTCV is lower than that in non-infected individuals, but the concentration of antibody is substantial and represents a positive response to immunization.

Duration of Protection

Two doses of TTCV provide an efficacy of 80% to 90% over at least three years. In 95% of people who receive three doses of TTCV administered at adequate intervals, a high concentration of anti-tetanus antibodies is

Table II.2.1. Efficacy of the tetanus toxoid vaccine per dose administered

Dose	Minimum interval between doses	Percentage of protection	Duration of protection
TT1	---	---	---
TT2	4 weeks	80%	3 years
TT3	6 months	85%	5 years
TT4	1 year	99%	10 years
TT5	1 year	99%	Probably lifelong

⁹ TAG Recommendations, XXIII Meeting in Cuba, July 2015.

produced, well over the minimum required to provide protection (0.01 UI/ml) over at least five years. It is believed that 5 doses provide practically 100% protection (Table II.2.1).

Vaccine Safety

Tetanus toxoid (TT), administered either alone or in combined vaccines, is considered very safe. Large historical studies on the use of TT during pregnancy have not reported clinically significant severe adverse events in the woman or newborn. TT and Td vaccines can be administered safely during any trimester of pregnancy. Immunodeficiency, including HIV, is not a contraindication for its use.

Tetanus toxoid vaccines can cause minor local reactions such as pain and erythema in about 25% to 85% of cases, occasional nodules, and, very rarely, sterile abscess (1 to 10 per 1,000,000 doses administered). After the booster doses, 0.5% to 1% of vaccinated individuals show mild systemic reactions, such as fever, pain, and discomfort. In general, local and systemic reactions increase with the number of doses administered. Severe systemic outcomes such as anaphylactic reactions and brachial plexus neuritis are extremely rare, ranging from 1 to

Tetanus toxoid, administered either alone or in combined vaccines, is considered very safe

6 and 5 to 10 per 1,000,000 vaccinated people, respectively. Despite the occasional rumors, tetanus toxoid-containing vaccines do not contain substances that cause contraceptive or abortive effects.

Timing and Schedule

Table II.2.2 shows the recommended immunization schedule with Td for previously unvaccinated pregnant women, as well as the minimum acceptable interval between doses. There is no maximum interval. The same schedule can be applied to unvaccinated women of childbearing age who can receive other live and inactivated bacterial and viral vaccines simultaneously.

Table II.2.2. Recommended tetanus and diphtheria toxoid (Td) immunization schedule for previously unvaccinated pregnant women and women of childbearing age

Dose	Tetanus-containing vaccine schedule for pregnant women
Td1	At first contact or as early as possible during pregnancy
Td2	At least 4 weeks after the first dose
Td3	6 to 12 months after second dose or during a subsequent pregnancy
Td4	1 to 5 years after third dose or during a subsequent pregnancy
Td5	1 to 10 years after fourth dose or during a subsequent pregnancy

Pregnant women who cannot show that they have received adequate TTCV doses should be given the first dose (Td1) as soon as possible during pregnancy; the second dose should be given no later than three weeks before the expected date of childbirth. Women who have received two doses of tetanus and diphtheria toxoid during a previous pregnancy should be given a third dose in a new pregnancy. The third dose provides protection for up to five years.

Pregnant women who received four doses of TTCV during childhood only need one TTCV dose during pregnancy, which should be given at the first possible opportunity.

Implementation Strategies in Latin America and the Caribbean

A childhood tetanus immunization schedule of five doses is recommended.¹⁰ The primary three-dose series of DTP (DTP3), either in whole-cell or acellular form (DTwP or DTaP), should be given in infancy (age <1 year), with a booster dose of a tetanus toxoid-containing vaccine ideally given at age 4–7 years, and a second booster in adolescence (e.g., at age 12–15 years). The exact timing of the booster doses should be flexible, able to take into account the most appropriate health service contacts in different countries. Where a high percentage of children, including girls, attend school, school-based immunization programs should be used where feasible to deliver the booster doses. Special efforts to reach school non-attendees should be considered.

In addition to the childhood vaccination program, an adult TTCV booster dose will provide additional assurance of long-lasting, possibly lifelong, protection. Therefore, a sixth dose of TTCV should be recommended for adults (e.g., at the time of the first pregnancy or during military service). Those who receive their first TTCV doses as adolescents or adults require a total of only five appropriately spaced doses to obtain the same long-term protection.

To achieve the goal of neonatal tetanus elimination, countries should implement the following measures:

- Establish or strengthen a tetanus surveillance system that can identify neonatal tetanus cases versus non-neonatal tetanus cases.
- Investigate all neonatal tetanus cases and initiate a detection campaign in “silent” areas, that is, in those areas where there likely were or are unreported cases of neonatal tetanus.
- Focus vaccination activities on women of childbearing age who live in high risk areas, guaranteeing that every interaction with these women becomes an opportunity for TTCV vaccination and for them to keep a vaccination card or document.
- Ensure that traditional midwives participate in vaccination activities with Td and in neonatal tetanus surveillance.
- Improve hygienic childbirth delivery and post-partum practices and procedures.

In districts with limited access to routine vaccination services and where the NNT elimination target (<1 case per 1,000 live births) has not been met, the “high-risk approach” to control maternal and neonatal tetanus should be adopted. This approach targets all women of childbearing age and consists of campaign-like immunization (supplementary immunization activities) with three doses of Td administered at the appropriate intervals. Promotion of clean childbirth practices is part of this approach. In addition to the three TTCV doses provided in the SIAs, two additional booster doses, given through the routine program, are needed to provide long-term protection to women who cannot document having been vaccinated with TTCV in childhood.

¹⁰ TAG Recommendations, XXIII Meeting in Cuba, July 2015.

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II.3. Pertussis-containing Vaccines during Pregnancy

KEY FACTS

- Pertussis is a globally endemic disease caused by *Bordetella pertussis*, an extremely contagious bacterium.
- *B. pertussis* bacteria attach themselves to the upper respiratory system and release toxins, which damage the tract and cause the airways to swell.
- Pertussis continues to be a public health concern, even in countries with high childhood immunization rates.
- Maternal immunization is likely to be the most effective strategy to prevent pertussis in infants too young to be vaccinated.

Pertussis affects all age groups worldwide, but is particularly severe in infants. The highest morbidity and mortality occurs among young infants before they are old enough to receive pertussis vaccines. Thus, maternal immunization is the most promising strategy to prevent pertussis disease in infants.

Background

Pertussis (whooping cough) disease affects all age groups worldwide, and continues to be a public health concern, even in countries with high childhood immunization rates. Its clinical presentation is particularly severe in infants. The highest morbidity and mortality occurs among young infants before they are old enough to receive pertussis vaccines. The majority of hospitalizations following pertussis occur in children under 6 months of age. In the United States, studies have identified household members, most commonly a parent or sibling, as the source of pertussis infection in infant cases.

In addition to infant vaccination, some countries, particularly those using acellular pertussis vaccine (aP vaccine) for primary vaccination series, recommend that an acellular pertussis booster vaccine (Tdap) be administered to adolescents and adults as a protection from pertussis. The vaccine is effective at preventing disease in this population, but does not provide long-lasting protection. To prevent pertussis in infants too young to be vaccinated, two strategies have been implemented using the Tdap vaccine: maternal immunization during pregnancy and immunization of close contacts of infants (i.e., “cocooning”).

Cocooning is a strategy to protect infants through vaccination of their close contacts. This strategy may have an impact on disease prevention in some settings, provided that high vaccination coverage can be achieved in a timely manner. Nevertheless, the evidence is uncertain as to whether Tdap vaccination prevents pertussis transmission, since acellular pertussis vaccines may not prevent colonization (bacteria carriage) or spread of the bacteria. The overall impact and cost-effectiveness of cocooning is likely to be substantially lower than that of vaccinating the mother during pregnancy, which requires only one dose. Cocooning indeed requires doses of Tdap for multiple family members (e.g., parents, siblings, grandparents) to protect each

infant. Implementing an effective cocooning strategy with high coverage has proven to be challenging in several countries, and the impact of this strategy in preventing pertussis in infants is unclear.

Some countries have introduced a maternal immunization strategy that recommends Tdap vaccination during pregnancy. Such vaccination prevents pertussis morbidity and mortality in infants too young to be vaccinated by providing them with maternal anti-pertussis antibodies. This strategy has also been shown to be more effective at preventing infant pertussis than post-partum Tdap. This is because young infants benefit from receiving passive immunity through the placenta before they begin the primary pertussis vaccination series. It is important to note that only the acellular pertussis vaccine is approved for use in adults and therefore pregnant women.

Given the recent resurgence of pertussis in some countries, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) formed a working group to review the latest evidence and update its 2010 recommendations on pertussis immunization. In 2012, the SAGE concluded the following:

- Maternal immunization with aP-containing vaccines during the third semester of pregnancy is safe and may have a high impact on morbidity and mortality in infants too young to be vaccinated.
- Vaccination of pregnant women is probably the most cost-effective complementary strategy to prevent pertussis-associated infant mortality.
- Countries may consider the immunization of pregnant women with one dose of Tdap (during the second or third trimester and preferably at least 15 days before the end of pregnancy) in addition to routine primary infant pertussis vaccination in countries or settings with high infant morbidity/mortality due to pertussis.

Since 2011, the TAG has recommended to vaccinate pregnant women with Tdap only in areas affected by a pertussis outbreak.¹¹ In 2013, the TAG reiterated that there was no evidence for recommending routine Tdap vaccination of pregnant women.¹² In order to address the gap in evidence regarding the interference of maternal antibodies and infants immune response to following vaccination with wP-containing vaccines, the Region would benefit from experiences and data from countries that have opted for routine maternal immunization.

Disease Burden

Pertussis, a globally endemic disease, is responsible for 20 to 40 million cases and 200,000 to 400,000 deaths in children every year. There is a scarcity of published information on pertussis in Latin America, which makes it difficult to adequately assess its burden in the Region. WHO estimated that in 2005, the Region of the Americas accounted for about 7% of the global pertussis disease burden.

Since 2000, 422,968 cases of pertussis have been notified in the Region, with two incidence peaks—in 2004-2005 and 2010-2014. More than 70,000 cases were notified in 2012. It should be noted, however, that it is extremely difficult to compare information between countries and analyze data region-wide, because of differences in case definition and laboratory diagnosis, as well as the under-recognition of the disease and under-reporting of cases. Furthermore, in the last few years, PAHO Member States have introduced new laboratory diagnosis techniques (PCR) and intensified pertussis surveillance.

¹¹ TAG Recommendations, Meeting XIX in Argentina, July 2011.

¹² TAG Recommendations, Meeting XXI in Ecuador, July 2013.

Pertussis is a cyclic disease that peaks every three to five years and has no distinct seasonal pattern, although in some countries pertussis cases may increase in the summer and fall. Case fatality rates remain highest in infants.

*Pertussis, a globally endemic disease, is responsible for **20 to 40 million cases and 200,000 to 400,000 deaths in children every year***

Current surveillance data probably underestimate the burden of pertussis among all age groups. Young infants under 2 months of age often present with atypical pertussis symptoms that do not meet the clinical criteria for a suspected case in many countries, and therefore surveillance systems do not capture them. Moreover, previously immunized adolescents and adults may present with mild symptoms (e.g., persistent cough without the characteristic whoop) and do not seek medical care or pertussis is not considered as a diagnosis. Despite this, in several countries there has been an increase in reported cases, partially attributed to better diagnosis, but a significant proportion appears to be related to an actual increase in cases, particularly in countries that use acellular vaccine (DTaP) in children.

Types of Vaccines

There are two Tdap vaccines licensed for use in adolescents and adults. One is approved for use among 10-64-year-olds, and the other for individuals aged ≥ 10 years and older.

*Pertussis is a **cyclic disease** that peaks every three to five years and has no distinct seasonal pattern*

Both are available in single-dose vial and pre-filled syringes, and neither product contains thimerosal.

The vaccine approved for use among 10-64-year olds, is a sterile isotonic suspension of tetanus and diphtheria toxoids and pertussis antigens [(2.5 μg detoxified pertussis toxin (PT), 5 μg filamentous hemagglutinin 290 (FHA), 3 μg pertactin (PRN), 5 μg fimbriae types 2 and 3 (FIM)] adsorbed on aluminum phosphate, as adjuvant, combined with residual formaldehyde, residual glutaraldehyde and 2-phenoxyethanol (not as a preservative), for intramuscular injection. This vaccine does not contain a preservative.

The vaccine licensed for use in individuals aged ≥ 10 years contains tetanus toxoid, diphtheria toxoid, and pertussis antigens (8 μg of inactivated pertussis toxin [PT] and formaldehyde-treated filamentous hemagglutinin [FHA] and pertactin [PRN]). Each 0.5-mL dose contains aluminum hydroxide as adjuvant (no more than 0.39 mg aluminum by assay), 4.5 mg of sodium chloride, a maximum of 100 μg of residual formaldehyde, and a maximum of 100 μg of polysorbate 80 (Tween 80).

Immunogenicity and Effectiveness

So far, only one study has compared the effectiveness of both vaccines in non-pregnant adolescents. This study was conducted in the state of Wisconsin (USA) and showed better effectiveness of the vaccine with the higher pertussis toxin content.

Two studies carried out in the United Kingdom have calculated the vaccine effectiveness (VE) of maternal pertussis vaccination in preventing pertussis infection in infants. A case-control study found an unadjusted VE of 91% (95% confidence interval [CI], 77%–97%) in preventing pertussis in infants younger than 8 weeks. When VE was adjusted for sex, geographical region, and birth period, the VE was 93% (95% CI, 81%–97%). An observational study estimated that VE in infants younger than 3 months was 91% (95% CI 84 to 95);

when the analysis was restricted to cases in children younger than 2 months, VE was 90% (95% CI 82 to 95).

Data from Canada, the United Kingdom, and the United States indicate some reduction in DTaP antibody responses in infants born to mothers vaccinated against pertussis. The clinical significance of these findings is uncertain. The United Kingdom's experience to date has shown no evidence of an increased risk of pertussis in infants aged 3–11 months. The immunogenicity data are limited to infants vaccinated with aP-containing vaccines. Thus, the observed effects cannot be extrapolated to infants receiving wP-containing vaccines in the absence of additional immunogenicity data. This is important to note, because many countries in the Americas are using wP-containing vaccines to vaccinate infants and children.

The potential for transplacental maternal antibodies to inhibit an infant's antibody production in response to vaccines has been a subject of concern. Recent studies have shown that maternal immunization with Tdap does not alter significantly the infant's immunologic response to acellular vaccine (DTaP). With regards to whole-cell vaccines, one early study evaluated the impact of transplacental antibodies originating from mothers who had been immunized with a DTP vaccine in the past, but not during pregnancy. Maternal antibodies did not substantially alter the infants' immune response to aP-containing vaccines, but a suppressive immune response was observed in infants who received whole cell pertussis vaccines. This study highlights the concern that pertussis antibodies derived from maternal Tdap immunization may interfere with the infant immune response to whole-cell pertussis vaccines. Studies are needed to characterize the immunoresponse of infants who receive wP-containing vaccine in the first year of life and verify whether there is maternal antibody interference. For TAG and countries that are administering whole-cell DPT for routine infant immunization, this is critical information for determining whether to recommend the routine immunization of pregnant women with Tdap.

Vaccine Safety

Growing evidence supports the safety of administering Tdap during the third trimester of pregnancy, and SAGE has fully endorsed this recommendation. Several studies from the United States and the United Kingdom have not shown an increase in adverse events after receipt of Tdap at any time during pregnancy. A comprehensive review of the Vaccine Adverse Events Reporting System (VAERS) reports over a five-year period from women who received Tdap during pregnancy did not identify any concerning patterns in maternal, infant, or fetal outcomes. In particular, there is no evidence of an increased risk of stillbirth. Even in studies that evaluated women who had been vaccinated during their first half of pregnancy, there were no differences found between vaccinated and unvaccinated women in rates of spontaneous abortion, therapeutic abortion, preterm delivery, low birth weight, or congenital anomalies.

In 2014, a large retrospective cohort study conducted in the United States showed that receiving Tdap during pregnancy was not associated with increased risk of hypertensive disorders of pregnancy, or preterm, or small-for-gestational-age birth, although a small but statistically significant increased risk of Chorioamnionitis diagnosis was observed. Despite the fact that an increased risk of preterm birth is a major sequela associated with Chorioamnionitis, this association was not observed in this study. A separate review of the U.S. VAERS database for reports following receipt of any vaccines in pregnant women found Chorioamnionitis to be uncommon (1% of pregnancy reports).

In terms of the safety of concomitant administration of Tdap and influenza vaccines during pregnancy, a retrospective cohort study

*A comprehensive review
did not identify any concerning
patterns in maternal, infant, or
fetal outcomes associated with
the vaccine*

did not find an association with a higher risk of medically attended adverse acute outcomes or birth outcomes compared with sequential vaccination.

Timing and Schedule

Timing of Tdap vaccination is critical to ensure the protection of both mother and infant. Post-partum Tdap administration provides protection only to the mother, not to the infant. Additionally, it takes at least two weeks after receiving Tdap for the mother to have protection against pertussis, thereby putting her at risk for contracting and transmitting the disease to her vulnerable newborn during this time. Once the mother has developed vaccine immunity, she may be less likely to become infected with pertussis, thereby not exposing her infant to the disease. That said, the newborn remains at risk of being exposed to pertussis from others, including siblings, grandparents, and other caregivers.

Thus, women vaccinated with Tdap during pregnancy provide the infant with maternal pertussis antibodies. Because antibody transport via the placenta happens in a linear fashion as the pregnancy progresses, and antibody titers against pertussis antigens begin to wane over time, the timing of vaccination during pregnancy is extremely important. Although, Tdap can be given at any time during pregnancy, the optimal timing to vaccinate pregnant women with Tdap is between 27 and 36 weeks of gestation, to coincide with the peak of antibody response and transfer via the placenta.

*Timing of Tdap vaccination is critical to **ensure protection** of both mother and infant*

Several studies have found that immunizing pregnant women with Tdap during weeks 27-30 of gestation was associated with higher concentrations of antibodies in the umbilical cord, compared to women vaccinated after week 31 of pregnancy. In the case of populations with limited access to health care, pregnant women should be vaccinated during the first opportunity, rather than waiting until the optimal vaccination period of 27–36 weeks of gestation.

Implementation Strategies in Latin America and the Caribbean

In line with PAHO's TAG recommendations for Tdap administration to pregnant women in areas affected by an outbreak, some of the Region's countries are administering Tdap to pregnant women as part of campaigns in response to outbreaks. However, other countries recommended giving Tdap routinely to women during every pregnancy (Argentina, Bahamas, Bermuda, Brazil, Cayman Islands, Colombia, Costa Rica, El Salvador, Mexico, Panama, Paraguay and Uruguay). The last TAG recommendation to the publication date of this guide indicates that the response to outbreaks of whooping cough should include initiating the vaccination schedule at 6 weeks of age and immunizing pregnant women only in the areas affected by the outbreak. The TAG has indicated that, to date, there is not enough evidence to recommend the routine vaccination of pregnant women. Based on the available information, the TAG recommendation of vaccinating pregnant women only in situations of outbreaks still stand. In the case of emergence of new evidence, this topic may be reassessed by the TAG.

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II.4. Hepatitis B Vaccines during Pregnancy and for the Newborn

KEY FACTS

- Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease.
- The hepatitis B virus is highly infectious and remains viable on surfaces for seven days or longer, and can be transmitted in the absence of visible blood.
- Perinatal transmission can occur from mother to infant, especially during delivery.
- The risk of transmission among infants born to hepatitis B-infected mothers is as high as 90%, with a 25% risk of premature death among the chronically infected (from liver failure or cirrhosis).
- Vaccination of the newborn starting with the first dose during the first 24 hours of life is the cornerstone for preventing perinatal transmission, followed by completion of the entire vaccination series.

Background

Hepatitis B is a liver infection caused by the hepatitis B virus (HBV). Hepatitis B is transmitted when blood, semen, or other body fluids from a person infected with the hepatitis B virus enter the body of someone who is not infected. The hepatitis B virus is highly infectious and remains viable on surfaces for seven days or longer, and can be transmitted in the absence of visible blood.

Transmission can happen through sexual contact; sharing needles, syringes, or other drug-injection equipment; household exposure; or from mother to infant at birth (perinatal transmission). The best way to prevent hepatitis B is through vaccination, and the best way to prevent mother-to-child transmission is through the vaccination of the newborn during his/her first 24 hours of life.

Symptoms of acute hepatitis B include anorexia, malaise, nausea, vomiting, abdominal pain, and jaundice. Extrahepatic manifestations (e.g., skin rashes, arthralgias) may also occur. Acute infection is typically asymptomatic among infants and children.

*The **best way to prevent hepatitis B is by getting vaccinated**, and the best way to prevent mother-to-child transmission is through the vaccination of the newborn during his/her first 24 hours of life*

Hepatitis B virus (HBV) infection is a leading cause of infectious disease mortality worldwide, with an estimated four million new HBV infections and 780,000 deaths annually. Globally, the World Health Organization estimates that more than two billion people are infected with HBV and an estimated 240 million individuals live with chronic infection. It is thought that around half of individuals with chronic infection were initially infected with the virus during the perinatal period or in early childhood, particularly in countries endemic for the disease. A vaccine against HBV has been available since 1982.

Across the Region of the Americas, the seroprevalence of the hepatitis B surface antigen (HBsAg) among children aged 5–9 years old varies substantially among countries, ranging from <2% in Brazil, Canada, and the United States, to 2%–4% in Argentina, Chile, Colombia, and Mexico, and to 5%–7% in Bolivia, Ecuador, and Peru.

*Hepatitis B virus (HBV) infection is a leading **cause of infectious disease mortality worldwide**, with an estimated four million new HBV infections and **780,000 deaths annually***

Most Latin American and Caribbean countries introduced hepatitis B vaccine as part of their routine immunization schedules in the late 1990s, following PAHO's TAG recommendations on introducing the vaccine in routine schedules and in vaccination of high-risk groups.¹³ In 2004, WHO issued a position paper recommending vaccination of newborns in countries with high endemicity

(HBsAg prevalence higher than 8%) to prevent mother-to-child transmission and child to child transmission during early infancy. In 2009, WHO recommended universal vaccination of newborns to reduce the mother-to-child transmission of hepatitis B (1).

At the regional level, all countries in the Americas have introduced hepatitis B in their routine immunization schedules. The vaccination coverage for the third dose in children under 1 year of age was 89% in 2015. Only 20 countries in the Region have also introduced a hepatitis B vaccine dose for the newborn. It is very important that the remaining countries in the Americas introduce this hepatitis B dose at birth to prevent vertical transmission of hepatitis B.

Disease Burden

Hepatitis B infection in pregnant women may not be different from that in the general population. The infection does not seem to increase mortality or be teratogenic. However, lower birthweight and prematurity have been reported. The risk of perinatal transmission of the virus increases the later in pregnancy the acute HBV infection occurs. Chronic HBV infection is generally mild during pregnancy and women tend to recover easily, but the disease may worsen after delivery and should be monitored.

*The infection does not seem to increase mortality or be teratogenic; however, **lower birth weight and prematurity have been reported**. The risk of perinatal transmission of the virus increases the later in pregnancy the acute HBV infection occurs*

¹³ TAG recommendations, Meeting XIX in Argentina, July 2011.

The management of HBV in pregnant women involves taking into account a woman's disease status and minimizing the risk of perinatal transmission of infection. Antiviral therapy administered to the mother during pregnancy may be useful in preventing perinatal transmission for women with high viral load or who are HBeAg positive. In the Guidelines for the Prevention, Care and Treatment of Persons with Chronic hepatitis B infection, published in 2015, WHO recommends treatment of HBV-positive pregnant women with Tenofovir, but no recommendation is made on the routine use of antiviral therapy to prevent mother-to-child transmission of the virus (2). The American Association for the Study of Liver Diseases (AASLD) suggests that antiviral therapy be administered to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level greater than 200,000 IU/mL (3). There are currently no standards in place for the best medical management of a woman who becomes pregnant while receiving antiviral therapy. Both passive and active vaccination and the subsequent monitoring of infection status in newborns are essential parts of disease prevention and management.

Feasibility of HBV Elimination

WHO is promoting the elimination of HBV infection by the year 2030, with a target of 90% reduction in new cases of chronic infection. The feasibility of eliminating HBV was established through modeling studies. The results of these studies were used to set the targets that include elimination by 2030 through a combination of high routine three–four dose infant vaccination coverage, starting at <24 hours after birth, and the scale up of treatment services for persons with chronic HBV infection. Elimination of mother-to-child transmission of HBV is considered a milestone on the road to HBV elimination.

*WHO is promoting the elimination of HBV infection by the year 2030, with a target of **90% reduction in new cases of chronic infection***

Elimination of mother-to-child transmission of HBV infection is considered a milestone on the road to HBV elimination

The 2015 PAHO Plan of Action for the Prevention and Control of Viral Hepatitis recommends adherence to the 2009 WHO recommendation to administer a birth dose of Hep B vaccine to newborns during the first 24 hours of life to prevent vertical transmission of HBV and chronicity (4).

Encouraging results in HBV childhood immunization coverage suggest that public health elimination of perinatal transmission is a feasible target for the Region. To that end, PAHO's Plan of Action on Immunization (Resolution CD54/7, 2015) includes the elimination of perinatal transmission of hepatitis B within its strategic lines of action, with the indicator being the number of countries and territories administering HB birth dose, with a baseline of 18 countries in 2013 and a target of 25 in 2020.

Types of Vaccines

A vaccine against hepatitis B has been available since 1982. WHO has reported that more than one billion doses of the vaccine have been administered worldwide. As a result, the rate of chronic infection has fallen below 1% among immunized children.

Recombinant hepatitis B vaccine was introduced in 1986 and has gradually replaced the plasma-derived hepatitis B vaccine. The active substance in recombinant hepatitis B vaccine is HBsAg that has been produced in yeast or mammalian cells into which the HBsAg gene (or HBsAg/pre-HBsAg genes) has been inserted using plasmids. Some vaccines have adsorbed on aluminum hydroxide as adjuvant and thimerosal as preservative.

The Hepatitis B vaccine is available as:

- monovalent (used in the birth dose) formulations, or

- in combination with other vaccines such as pentavalent including diphtheria–tetanus–pertussis (DTP), *Haemophilus influenzae* type b, and hexavalent vaccine including inactivated polio. The immune responses and safety of these combinations of vaccines are comparable to those observed when the vaccines are administered separately.

Immunogenicity and Effectiveness

The hepatitis B vaccine is highly effective

The hepatitis B vaccine is highly effective. After three intramuscular doses of hepatitis B vaccine, more than 90% of healthy adults and more than 95% of infants, children, and adolescents develop adequate antibody responses. Immunogenicity is reduced among certain populations, including premature infants, persons with diabetes, immunocompromised persons, and older adults. Protection lasts at least 20 to 30 years. Thus, WHO does not routinely recommend booster vaccination for persons who have completed the three-dose vaccination schedule (6).

A recent meta-analysis of randomized controlled trials of the hepatitis B vaccine administered at birth found that immunized infants born to mothers infected with hepatitis B were 3.5 times less likely to become infected with HBV (relative risk, 0.28; 95% confidence interval, 0.20–0.40).

Passive immunization: temporary immunity may be obtained by administering HBIG. HBIG prophylaxis in conjunction with HBV vaccination (that is, active immunization) may be of additional benefit for newborn infants whose mothers are HBsAg-positive, particularly if they are also HBeAg positive.

Protection lasts at least 20 to 30 years

A recent meta-analysis found that infants immunized at birth, born to mothers infected with hepatitis B were 3.5 times less likely to become infected with HBV

Vaccine Safety

Vaccine-associated adverse events following immunization against hepatitis B are infrequent and generally mild. The most common reactions are the following:

- mild soreness,
- erythema,
- induration,
- fatigue,
- fever,
- malaise, and
- influenza-like symptoms.

Vaccine-associated adverse events following immunization against hepatitis B are infrequent and generally mild

Less common systemic reactions include nausea, vomiting, diarrhea, abdominal pain, abnormal liver function tests, arthralgia, myalgia, rash, pruritus, and urticaria.

Despite numerous studies, there is no evidence of serious long-term adverse events that have been causally linked to hepatitis B vaccination. Reports of severe anaphylactic reactions are extremely rare. Data do not indicate a causal association between hepatitis B vaccine and Guillain–Barré syndrome or demyelinating disorders, including multiple sclerosis, nor are there any epidemiological data to support a causal association between hepatitis B vaccination and chronic fatigue syndrome, arthritis, autoimmune disorders, asthma, sudden infant death syndrome or diabetes. WHO’s Global Advisory Committee on Vaccine Safety (GACVS) has confirmed the excellent safety profile of the hepatitis B vaccine.

Contraindications

The Hepatitis B vaccine is contraindicated only for persons with a history of allergic reaction to any of the vaccine's components or who are allergic to yeast. The vaccine is not contraindicated during pregnancy or lactation.

There are no serious adverse events definitively attributed to vaccinating pregnant women. Data are limited, but have not shown that developing fetuses are at risk for adverse events when the vaccine is given to pregnant women. Premature infants, infants with low birthweight and small for gestational age, infants with jaundice as well as HIV-positive individuals can receive this vaccine safely.

Timing and Schedule

In October 2016, WHO's SAGE in immunization recommended that all infants receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours. When not feasible, the birth dose can still be effective in preventing perinatal transmission if given within 7 days, particularly within 3 days, although somewhat less than if given within 24 hours, but with declining effectiveness with each passing day. Even after 7 days, a late birth dose can be effective in preventing horizontal transmission and therefore remains beneficial. Thus, SAGE recommended that all infants receive the birth dose during the first contact with health facilities at any time up to the time of the first primary dose. Any birth dose given after 24 hours should be reported as a late birth dose vaccination.

In 2016, PAHO's Technical Advisory Group (TAG) on Vaccine-preventable Diseases emphasized previous recommendations on hepatitis B vaccination.¹⁴ PAHO's TAG recommended that countries that have not yet introduced a birth dose of hepatitis B vaccine (within the first 24 hours of birth), should introduce it, aiming for at least 95% vaccination coverage, with the goal of reaching at least 95% coverage. The hepatitis B birth dose should be followed by an additional two or three doses (often as part of combined vaccines, such as pentavalent vaccines) in order to complete the primary series (Table II.4.1).

Pre-term infants should be vaccinated at birth and subsequently follow the national hepatitis B vaccination schedule. For preterm infants weighing under 2,000 g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of the hepatitis B vaccine in these infants; three additional doses of vaccine (for a total of four doses) should be administered beginning when the infant reaches one month of age.

Vaccination of Pregnant Women

Pregnant women who are identified as being at risk for HBV infection during pregnancy should be vaccinated, such as in the following circumstances:

- having had more than one sex partner during the previous six months,
- having been evaluated or treated for an STD,
- recent or current injection drug use, or
- having had an HBsAg-positive sex partner.

Table II.4.1. Hepatitis B routine vaccination schedule^a

Dose	Age	Minimum interval with previous dose
Newborn dose	Birth < 24 hours	Not applicable
1st dose	2 months	4 weeks
2nd dose	4 months	4 weeks
3rd dose	6 months	4 weeks

^a According to national immunization schedules.

¹⁴ TAG recommendations, Meeting XXIII in Cuba, July 2015.

Dosage and Administration:

Pediatric dose vaccine: 5 µg dose (in 0.5 ml suspension) is recommended for neonates, infants, children, and adolescents up to 19 years of age (5).

Adult dose vaccine: 10 µg dose (1.0 ml suspension) is recommended for adults aged 20 years and older (5).

Implementation Strategies in Latin America and the Caribbean

In the Region, 20 countries currently target newborns with the hepatitis B vaccine. The PAHO's TAG has recommended that the remaining countries introduce the vaccine into their routine schedules.¹⁵ Furthermore, PAHO's TAG recommended that PAHO develop a comprehensive plan to achieve the elimination goal, including strengthened surveillance and targeted surveys for all countries, and provide

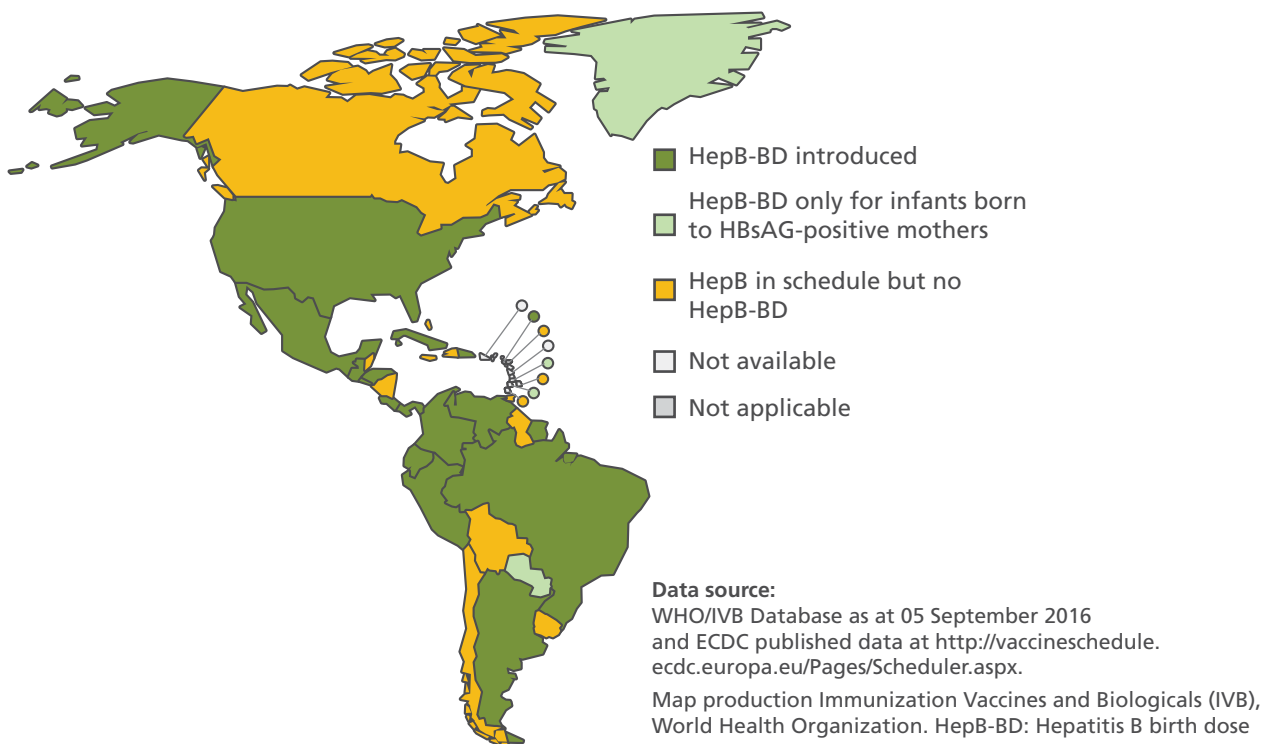
special technical support to those countries with the highest prevalence of HBsAg and those that have not yet introduced the birth dose in their routine schedule, such as some Caribbean and Central American countries. **Table II.4.2** outlines the implementation of the policy to immunize newborns against hepatitis B.

Ensuring that all infants receive a dose of hepatitis B vaccine within 24 hours of birth requires implementation of specific programmatic measures, such as the following:

1. Increasing the number of infants born in facilities or attended by trained health staff to improve birth-dose coverage;

Ensuring that all infants receive a dose of hepatitis B vaccine within 24 hours of birth requires implementation of specific programmatic measures

Figure II.4.1. Use of the hepatitis B vaccine in the Americas, April 2016



¹⁵ TAG recommendations, Ad-hoc Virtual TAG Meeting, May 2016

2. Ensuring that there is coordination between immunization services and maternal health services so that the vaccine is available at the place of delivery or immediately after birth;
3. Expanding vaccine management systems and innovative outreach to provide vaccine for home births so that the hepatitis vaccine is available in settings where births take place;
4. Engaging in health promotion efforts targeting at parents and training for providers to increase awareness about the importance of administering hepatitis B vaccine within 24 hours of birth;
5. Having hepatitis B vaccine not combined with other childhood immunizations available so that HBV vaccines can be administered alone as a birth dose;
6. The delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for all immunization programs. Reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose.

...coordination between immunization services and maternal health services so that the vaccine is available at the place of delivery

Table II.4.2. Implementing the policy of vaccinating newborns against hepatitis B

Policy	Monitoring	Integration of health services and immunization	Health personnel
Introduction of one dose of the hepatitis B vaccine to newborns in countries that have not done so previously	<p>Include or adapt the EPI information system in order to register the hepatitis B birth dose during the first 24 hours of life</p> <p>Monitor administration of the newborn dose during the first 24 hours of life and reach 95% coverage</p> <p>Monitor the implementation of this recommendation in the private sector, where appropriate</p>	<p>Integrate birth dose vaccination with newborn care policies and practice</p> <p>Policy and procedure documentation for health facilities should clearly specify administration of HepB-BD within the first 24 hours after birth as an essential component of good quality childbirth care</p> <p>Assign responsibility for administering vaccine in health facilities including vaccine availability, handling, administration, reporting, and recording, and the necessary cold chain capacity)</p>	<p>Train and supervise health personnel in the implementation of vaccination policies (where, when, how, to whom, and why)</p> <p>Implement a strategy to reach newborn delivered at home. There are two options: the newborn must be brought to a health facility to receive HepB-BD, or the vaccine must be taken to the newborn through a home or community visit</p>

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II.5. Future of Maternal and Neonatal Immunization

Vaccines under Development

There have been important vaccine advances relevant to maternal immunization, including:

- safety and efficacy trials in pregnant women for influenza
- clinical trials in pregnancy to support indication of Group B Streptococcus (GBS) and Respiratory Syncytial Virus (RSV)
- capacity-building for clinical pregnancy trials in developing countries for GBS and influenza
- consensus-building on clinical trials studies in pregnancy (NIH, Brighton Collaboration, WHO)

Figure II.5.1 shows the vaccines currently under development that are relevant to maternal and neonatal immunization. Two of the vaccines under development that could be used in pregnant women in the near future are described below:

Group B Streptococcus (GBS)

Approximately 10% to 25% of pregnant women are colonized (temporarily, intermittently, or chronically) with group B streptococcus in the

vagina or rectum. In the absence of preventive measures, approximately 50% of newborns will be colonized with GBS during labor, and approximately 2% of these will develop invasive group B strep disease. Chemoprophylaxis with intrapartum penicillin G or ampicillin reduces colonization and early sepsis of the newborn, as long as it is administered four hours or more before delivery.

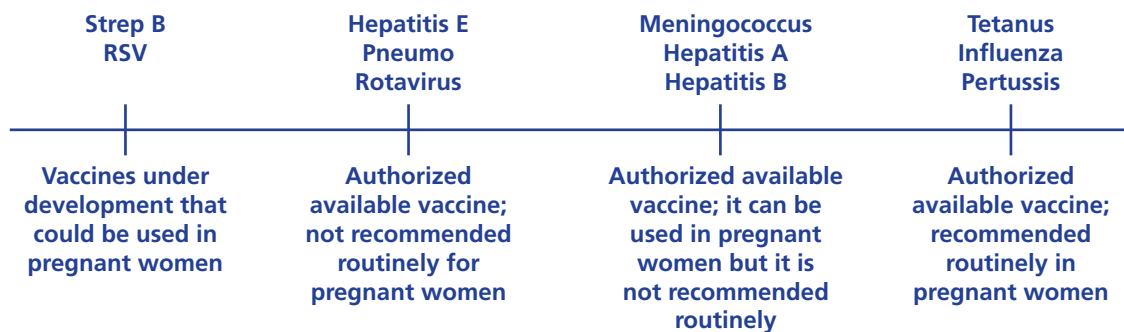
Invasive disease among newborns can be divided into early onset (within 7 days after birth) and late onset (7 to 89 days after birth). Vertical transmission explains the early onset disease, but not the late onset disease. Maternal transmission explains 50% of the late onset cases of newborn disease.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a very common virus that leads to mild, cold-like symptoms in adults and older healthy children. It can be more serious in young babies, especially those in certain high-risk groups. It is so common that most children have been infected with the virus by age 2.

Respiratory syncytial virus can lead to a lower respiratory tract illness such as pneumonia or bronchiolitis. Most children and adults recover

Figure II.5.1. Upcoming vaccines currently in the development pipeline that are relevant to maternal and neonatal immunization



Sources: ClinicalTrials.gov. Safety and immunogenicity of a trivalent group B streptococcus vaccine in healthy pregnant women. Washington DC: NLM/NIH/ClinicalTrials.gov; 2016. Available at: <https://clinicaltrials.gov/ct2/show/NCT02046148>.
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from the illness in one to two weeks. But in young babies, infants born prematurely, or infants or adults who have chronic heart or lung problems, the virus may cause a more severe —occasionally life-threatening— infection that requires hospitalization.

Recommended Fields of Research

Studies on such issues as the safety and antibody interference of vaccines, and Knowledge, Attitudes and Practices (KAP) surveys should be conducted in countries that routinely vaccinate pregnant women with Tdap and hepatitis B vaccines.

Tdap

While there is a growing body of evidence to support the safety and effectiveness of Tdap maternal immunization, exploring the following research questions would boost the evidence base regarding this issue:

- Impact of maternal Tdap on
 - the severity of pertussis disease in infants
- Safety and immunogenicity for
 - Tdap with subsequent pregnancies (short interval between pregnancies)
 - concomitant vaccination of Tdap and the influenza vaccine during pregnancy
- The possible interference of Tdap vaccination of pregnant women on the child's immunological response to whole cell pertussis vaccine

Because the overall burden of pertussis in the Americas is not well understood, countries should strengthen pertussis surveillance, which would help measure the impact of maternal Tdap immunization on infant pertussis.

Influenza

More evidence needs to be gathered on the effectiveness and impact of maternal immunization against influenza in Latin America and the Caribbean.

A View towards the Future

Maternal and neonatal immunization is becoming a priority platform in the global health agenda. As a result, maternal and neonatal morbidity and mortality will decrease, and the quality, access, and equity of maternal and neonatal health services will improve in Latin America and the Caribbean.

To achieve this vision, it will be critical to:

- Strengthen collaboration with space agencies, universities, and institutions working in the field of maternal and child health, including associations of obstetricians and gynecologists.
- Create alliances with the media and scientific societies to better reach various audiences in order to increase vaccine acceptance and uptake among pregnant women.
- Promote the integration of immunization with other maternal health services.
- Promote the use of electronic immunization registries (EIRs) with high-quality information.
- Strengthen surveillance of events supposedly attributable to vaccination or immunization (ESAVI) surveillance, including the active surveillance of events related to maternal vaccination (e.g., through sentinel hospitals).
- Strengthen the evidence base to support decision-making around maternal and neonatal immunization.
- Disseminate recommendations on maternal immunization in coordination with scientific societies and National Immunization Technical Advisory Groups (NITAGs).
- Monitor and evaluate the progress and impact of maternal and neonatal immunization.

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