



Title	A comprehensive review of influenza and influenza vaccination during pregnancy
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INTRODUCTION

Influenza is a highly infectious respiratory disease that can impose significant health risks leading to increased morbidity and mortality. Annual influenza epidemics are estimated to contribute to approximately 3,000,000 to 5,000,000 cases of severe illness and approximately 250,000 to 500,000 deaths worldwide.¹ In addition, annual influenza epidemics cause an average of 31.4 million outpatient clinic visits, 3.1 million hospital admission days and more than 610,000 life-years lost in the United States (US).² When consumer and societal costs are included, the annual economic burden in the US from influenza infections is estimated to be approximately \$87.1 billion.² Receiving influenza vaccination is the most important and effective means of preventing the infection and its related complications. Pregnant women are now the highest priority group for vaccination as the physiological changes in pregnancy increase susceptibility to infection.³ However, the vaccination uptake rate among pregnant women has been unacceptably low. Many studies have shown that pregnant women are often not aware that they are at increased risk for influenza infection and should be vaccinated.^{4,5} Many health providers do not recommend that pregnant women receive the vaccine.^{6,7} This article reviews the complications of influenza infection for pregnant women, the fetus and the newborn infant. It also provides current recommendations for influenza vaccination for pregnant women, delineates

the factors influencing vaccine uptake and makes recommendations to increase vaccine uptake.

INFLUENZA INFECTION DURING PREGNANCY

Historical perspective

The increased morbidity and mortality from influenza among pregnant women was first recognized in the influenza pandemics of 1916 to 1918⁸ and 1957 to 1958.⁹ In one of the earliest studies, Harris⁸ observed a higher risk of complications from pneumonia due to influenza in pregnant women and increased mortality in the third trimester. During the 1957 global influenza pandemic, pregnant women had higher mortality rates from influenza-related pneumonia than non-pregnant women.⁹ A case-control study of over 25,000 US women from 1974 to 1993 showed that healthy pregnant women, irrespective of gestational age, had increased risk of hospitalization from cardiorespiratory illnesses.¹⁰ In a review of data from the 1975 to 1979 influenza seasons, researchers found that pregnant women had 2.3 times higher rates of outpatient consultations for acute respiratory diseases than non-pregnant women.¹¹

In 2009, when a novel strain of influenza A/H1N1 virus was first identified in North America, there was a substantial impact on the general population. There were

xan estimated 70,000 hospital admissions, 9,700 Intensive Care Unit (ICU) admissions and 2,500 deaths attributable to A/H1N1 influenza infection within an eight-month period across 19 countries and administrative regions.¹² The risk was higher in the young, the obese, and pregnant women. In a 2009 US study,¹³ the hospitalization rate among pregnant women from mid-April to mid-May, 2009 was estimated to be 0.32 per 100,000 which was 3.2 times higher than non-pregnant peers. In another study conducted from May to June 2009, a significantly higher morbidity rate was observed among pregnant women compared with non-pregnant peers.¹⁴ In the US, pregnant women were 7.1 times more likely to be hospitalized due to A/H1N1 virus infection than non-pregnant women.¹⁴ Correspondingly, from June to August 2009, there were a total of 722 ICU admissions in Australia and New Zealand due to A/H1N1 infection, among which 9.1% were pregnant women.¹⁵

Physiologic changes of pregnancy

Pregnant women are more vulnerable to respiratory illnesses than their non-pregnant peers because the pregnancy leads to physiological changes in the cardiopulmonary system as well as the immunological system.¹⁶ During pregnancy, women experience an increase in progesterone and beta-human chorionic gonadotropins.¹⁷ As pregnancy advances, there are alterations in the chest shape and dimensions and elevation of the

diaphragm. These changes contribute to increased dyspnea, increased oxygen consumption and tidal volume, and decreased functional residual capacity, all of which increase susceptibility to respiratory pathogens.^{17,18} Furthermore, to tolerate fetal antigens during pregnancy, evidence suggests that the maternal immune system suppresses cell-mediated immunity, which increases susceptibility to intracellular pathogens such as viruses and bacteria.¹⁹ Thus, as gestational age advances, the risk of serious morbidity and hospital admission from influenza infection increases substantially.^{10,20} Pregnant women who are hospitalized with influenza infection have significantly longer hospital stays, irrespective of gestational age^{21,22} and pregnant women with co-morbidities are more likely to be admitted to the ICU.²³

Adverse neonatal outcomes

Women contracting infectious diseases during pregnancy are more likely to have adverse neonatal outcomes. In a 13-year Canadian population-based cohort study from 1990-2002, infants born to mothers who were hospitalized for respiratory illness were more likely to be small for gestational age. In addition, these infants were more likely to have a lower mean birth weight than infants whose mothers were hospitalized for reasons other than respiratory illness.²⁴ A small study of pregnant women (n=41) infected with influenza during the 2009 A/H1N1 pandemic found a

significantly lower birth weight in infants of H1N1 infected mothers.²⁵ Data from 113,331 women in Norway showed that infants born to pregnant women infected with influenza had an almost two-fold greater risk of infant death than infants born to non-infected women.²⁶ Teratogenic effects such as cleft lip and palate, neural-tube defects and cardiovascular malformations were 1.7 times to 3.2 times more common in infants born to mothers infected with influenza during the first trimester of pregnancy.²⁷ Results from a national sample in Denmark found that there is an increased risk of schizophrenia associated with influenza infection during pregnancy.²⁸ Results from a case-control study in California showed a 3- to 7-fold increase in schizophrenia in later life among the offspring of mothers who had influenza during pregnancy.²⁹

INFLUENZA VACCINATION DURING PREGNANCY

Healthy lifestyle practices, such as adequate hydration and nutrition and influenza vaccination, are the primary strategies to prevent influenza infection.³⁰ In addition, adoption of personal protective measures, for example, proper use of face masks and frequent hand hygiene,³¹ are recommended to prevent the spread of respiratory infections. Influenza vaccination is widely considered to be the most effective preventive strategy, as it has a documented efficacy of about 90% in young,

healthy population groups.³ Two types of influenza vaccines are currently available, trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV). TIV contains dead viruses and is administered by the intradermal or intramuscular route while LAIV contains weakened live viruses and is administered via the nasal route. TIV is recommended for pregnant women of any gestation age while LAIV should not be given during pregnancy because it contains live viruses.³² Contraindications to influenza vaccination include a history of allergy to eggs or other vaccine components or a serious reaction to a previous dose of influenza vaccine.³² Both TIV and LAIV are equally effective with minimal side effects and both vaccines are generally well tolerated. When the vaccine composition is well-matched with the circulating virus, it can offer up to 90% protection.³³

Vaccination recommendations

To lower the number of medical consultations and the risk of hospitalization due to respiratory illnesses in pregnant women, as shown in table 1, most public health agencies and advisory groups recommend that women who are, or who will be pregnant during influenza season, receive influenza vaccination regardless of gestational age. In 2012, the World Health Organization (WHO) recommended that

pregnant women, regardless of gestational age, have the highest priority for seasonal influenza vaccination in national vaccination programs.³

Benefits of vaccination

Influenza vaccination is essential in public health programs aimed at decreasing seasonal influenza transmission and during pandemics.³⁴ The vaccine is both cost-effective and safe. Influenza vaccine has a well established safety record and prevents excess doctors visits, hospitalizations and deaths resulting from influenza infection.³² Influenza vaccination during pregnancy is beneficial to both mothers and infants. A randomized controlled trial (RCT) conducted in Bangladesh demonstrated that influenza vaccination during pregnancy reduced respiratory illnesses among pregnant women by 36% and laboratory-confirmed influenza illnesses in infants up to six months old by 63%.³⁵ In addition, during the peak influenza season, infants born to vaccinated mothers had a higher mean birth weight (200 grams) and were less likely to be born small for gestational age (25.9% versus 44.8%).³⁶ Further evidence from a recent cohort of over 18,000 infants born to vaccinated mothers and a similar number of infants born to unvaccinated mothers, supported a 15-20% reduction in low birth weight, preterm birth and stillbirth in vaccinated mothers.³⁷

When compared with older children, infants under six months old have higher hospital admission rates for influenza³⁸ and higher influenza-associated mortality.³⁹ Data from a population-based, laboratory surveillance system in the United States (US) showed that from 2002 to 2009, infants <6 months of age born to vaccinated mothers were 45-48% less likely than infants of unvaccinated mothers to have influenza hospitalizations.⁴⁰ Currently, no influenza vaccine is approved for infants less than six months of age. Thus immunization of pregnant women is important, not only to protect pregnant women but also to protect infants during the first six months of life.⁴¹

Antiviral treatments

At present, antiviral medications are recommended for use in critically ill patients infected with influenza. Neuraminidase inhibitors such as Oseltamivir (Tamiflu®) and Zanamivir (Relenza®) are recommended as first-line treatment.³ For highest effectiveness, it is generally recommended that antivirals be administered within the first 48 hours of the onset of illness.⁴² Amantadine and Rimantadine should not be used to treat influenza A infection because of a high level of drug resistance.⁴³ Although a low level of drug resistance (0.05%) has been observed for Oseltamivir and Zanamivir, both medications are still recommended as useful antiviral treatments

for influenza. Nevertheless, the potential for drug resistance will likely increase with broader use.⁴³ The early detection and treatment of influenza in pregnant women is recommended to improve maternal outcomes.⁴⁴ One study of 356 hospitalized pregnant women with influenza-like illness found that women requiring ICU admission were less likely to have been treated with antiviral medications within 48 hours after illness onset.²³ A recent Cochrane review (2012),⁴⁵ however, found that there was no substantial evidence that either Oseltamivir or Zanamivir lowered the risk of complications from influenza infection such as pneumonia, influenza-related hospitalization or mortality. Given the clearly demonstrated efficacy and safety of the influenza vaccine in protecting both mothers and newborns against influenza infection, influenza vaccine should always be the first line of defense.³

Vaccine safety

In 1976, a total of 1,098 patients contracted Guillain-Barré Syndrome after vaccination against swine flu. Guillain-Barré syndrome is an uncommon inflammatory disorder of the peripheral nervous system causing muscle paralysis and respiratory failure and in severe cases, death may result.⁴⁶ Thereafter, the US started a national surveillance program to monitor vaccine safety. From October 1976 to January 1977, the baseline attributable risk of Guillain-Barré syndrome resulting from

influenza vaccination was estimated at 1 per 100,000 vaccinations.⁴⁷ In 2010, several federal surveillance systems began actively monitoring the safety of and adverse reactions to the influenza 2009 A/H1N1 monovalent vaccine in the US. From October 2009 to March 2010, the incidence of Guillain-Barré syndrome was 1.92 per 100,000 person-years among vaccinated persons which corresponds to 0.8 excess cases per 1,000,000 seasonal influenza vaccinations.⁴⁶ Therefore, although there is a potential risk of adverse reactions like Guillain-Barré syndrome, cases are very rare.

According to the Vaccine Adverse Event Reporting System (VAERS) in the US, there is no evidence of unusual pregnancy complications or adverse fetal outcomes from influenza vaccination during pregnancy.⁴⁸ A recent retrospective cohort study reported that maternal influenza vaccination in the first trimester was not associated with any increase in congenital malformations.⁴⁹ Approximately 15-20% of influenza vaccine recipients have mild, transient local reactions, such as redness and pain over the injection site, which generally resolves within one to two days.³³ No vaccine is 100% safe or effective.⁵⁰ The risk from influenza infection is significantly greater than the risk of mild adverse reactions and the previously identified benefits of vaccination significantly outweigh the short-term, self-limiting side effects.³ Overall, there is

substantial evidence that the influenza vaccine is effective against influenza infection and is safe for pregnant women at any stage of pregnancy.⁵¹

Prevalence of vaccination

Despite the accumulated evidence of the safety and effectiveness of influenza vaccination during pregnancy, seasonal influenza vaccination uptake among pregnant women remains suboptimal.⁵² Recent studies have reported vaccination uptake rates ranging from 1.7%^{7,53} to 88.4%,⁵⁴ but are often less than 20%.^{5,55} In the US, it was estimated that between 38-50% of pregnant women were vaccinated during the 2010-2011 influenza season.⁵⁶ Numerous studies have shown that pregnant women who refuse influenza vaccination generally underestimate the seriousness of influenza and are unaware of the increased susceptibility to influenza infection.^{5-7,55} In a cross-sectional study, nearly 90% of pregnant women perceived no difference in the risk of complications from influenza between pregnant women and non-pregnant women.⁵⁷ A perception that the vaccine is not effective in preventing influenza is another barrier to vaccination⁵ and a history of uncomfortable side effects after vaccination discourage pregnant women from receiving the vaccine.^{58,59}

Lack of trust in the medical community and the health care system is an issue.⁶⁰⁻⁶² One Canadian study reported that pregnant women who refused to be vaccinated believed that the vaccine had not been sufficiently tested.⁶⁰ Studies in the US and Europe have reported that pregnant women explicitly refused vaccination because of distrust of the health care system.^{61,62} This perception could result from contradictory and confusing opinions in the medical community.⁶³ On the other hand, vaccinated mothers were more likely to have confidence in the benefits of the vaccines and were more trustful of the health providers or the health care system.^{62,64}

Concerns about the vaccine's safety and the possibility of birth defects were the predominant barrier to vaccination.^{4,5,57} In a Canadian study conducted during the 2006-07 influenza season, 45% of participants perceived that the influenza vaccination was unsafe during pregnancy and nearly 80% believed that it could cause birth defects in newborns.⁵⁷ Similarly, in a US study conducted during the A/H1N1 pandemic, almost 60% of unvaccinated pregnant women were concerned about the vaccine safety.^{5,57} Furthermore, as noted in Table 2, pregnant women had common misconceptions towards influenza infection and influenza vaccine. Many pregnant women perceive that they are not at risk of influenza^{4,6,59} and that the vaccine can cause influenza infection,^{65,66} is potentially harmful to the fetus^{67,68} and that effective

treatments for influenza infection are available.^{6,68} Studies have shown that primiparous pregnant women are more reluctant than multiparous women to receive the influenza vaccine.^{7,69} The first pregnancy can be stressful and anxiety provoking, and primiparous women may be especially concerned with the health and viability of fetus throughout pregnancy. Thus, primiparous pregnant women may be more reluctant to receive influenza vaccine fearing harm to the fetus.⁷⁰ Overall, some pregnant women lack information concerning the risks of influenza infection versus the benefits of influenza vaccination to make them feel confident enough to be vaccinated.⁵

The high morbidity and mortality rates among pregnant women due to A/H1N1 infection brought global attention to an issue that had previously largely been ignored. Although awareness about the consequences of a novel influenza strain were increased during the pandemic, there were concerns about the safety of the A/H1N1 vaccine as it was generally perceived by the public as a 'new' vaccine that had not been thoroughly tested.⁷¹ Hence, vaccination uptake among pregnant women against A/H1N1 infection was suboptimal. Reported vaccination rates were 6.2% in Hong Kong,⁵ 6.9% in Australia,⁷² 8.9% in Turkey,⁶¹ 46.6% in the US,⁷³ and 63% in the Netherlands.⁶³ Subsequently, because the influenza A/H1N1 virus continues to be

the predominant circulating virus strain, it has been included in the trivalent seasonal influenza vaccine since 2010-2011 and it has been shown to be safe and highly effective.³⁷

Health provider recommendations

Previous studies demonstrated that health provider recommendations were significantly associated with vaccination acceptance.^{4,63,74,75} However, researchers in the US, Australia and Hong Kong have reported that about 42-92% of pregnant women did not receive any vaccination recommendations from health providers and vaccination was not discussed.^{7,59,66,76} US studies have reported that some health providers may perceive that pregnant women are unwilling to be vaccinated.⁷⁷⁻⁷⁹ Reluctance to recommend the vaccine could be due to liability concerns⁷⁷ and to avoid perceived association between vaccination and spontaneous abortion or birth deficits.⁷⁸ One US study found that health providers underestimated pregnant women's susceptibility to influenza infection and had doubts about the benefit and effectiveness of the vaccine.⁸⁰ Suboptimal influenza vaccination uptake in health providers has been observed in many studies⁸¹⁻⁸³ and uptake varies substantially across health provider groups.^{84,85} Lack of knowledge about influenza infection and misconceptions about influenza vaccination were identified as the foremost reasons.

In contrast, vaccinated health providers are more likely to believe in the vaccine's safety and effectiveness, thus they are more willing to recommend it.⁸⁶

While the 48-85% of US obstetricians surveyed provided influenza vaccine in their practice^{87,88} some obstetricians view vaccinating pregnant women as primarily the responsibility of family physicians.^{55,89} Health providers who demonstrate indifferent attitudes toward vaccination discourage pregnant women from seeking additional advice.⁹⁰ Most studies examining health provider practices in vaccinating pregnant women have primarily focused on either obstetricians or family physicians.^{87,88,91,92} In one of the few studies involving nurses, midwives in Ontario, Canada in 2002⁸⁶ reported that health providers who had been vaccinated were more likely to recommend the vaccination to pregnant women. Furthermore, they believed that recommending vaccination was outside their scope of practice and that it was the doctor's primary responsibility to conduct such discussions. As pregnant women rely on health providers as information providers, who in many countries are primarily midwives, the inability to obtain the necessary information further decreases the chance that pregnant women will get vaccinated.⁹⁰ Thus, a trustful relationship between all health providers and pregnant women is important to enhance vaccination uptake.

Increasing vaccination uptake

Targeted interventions have been effective in enhancing influenza vaccination uptake among pregnant women.^{75,93} As noted in Table 3, reluctance to be vaccinated could be addressed by offering accurate information to counteract the misperceptions about the risk of influenza infection during pregnancy as well as to educate mothers about the safety and benefits of maternal influenza vaccination.⁷⁶ Pregnant women can be informed that although local side effects are not uncommon and more serious adverse reactions following vaccine administration are rare.³² Vaccination rates could be increased to near 80% if vaccination was included as a component of antenatal care.⁹³ As pregnant women require regular antenatal care, health providers can use antenatal sessions as valuable therapeutic encounters to reinforce vaccination recommendations.⁹⁴ Provision of a simple printed information leaflet during antenatal consultations has been effective in enhancing knowledge and improving vaccination uptake.⁹⁵

IMPLICATIONS FOR HEALTH PROVIDERS

The role of health providers, especially perinatal nurses, midwives and obstetricians, is critical in promoting vaccine uptake, as they have extended contact

with pregnant women during antenatal visits. These visits provide an excellent opportunity to enhance pregnant women's knowledge of and accessibility to influenza vaccination.⁹⁴ Studies have shown that midwives were more likely to recommend that pregnant women be vaccinated if they had been vaccinated.^{52,86} Thus, the vaccination rates of nurses and other health providers have implications for promoting the vaccine to pregnant women.⁵² At the administrative level, it may be necessary to reinforce that providing vaccination recommendations to pregnant women is within the scope of practice of most providers in high resource countries and one of the primary responsibilities.⁸⁶ Recommending influenza vaccination to pregnant women is the responsibility of all health providers to protect mothers and infants.^{53,96}

Many cross-sectional studies have examined predictors of influenza vaccination uptake among pregnant women.⁹⁷ Recently, three RCTs have been conducted to improve prenatal vaccination rates, all in the US.⁹⁸⁻¹⁰⁰ Text message reminders were effective in increasing vaccine uptake in one study¹⁰⁰ but failed to have any impact in another.⁹⁹ A patient-centered education pamphlet was shown to be effective in improving both vaccination uptake and perceptions of the safety and benefit of influenza vaccination.⁹⁸ Meanwhile, no published trials have been undertaken to evaluate the effectiveness of health providers' vaccination recommendation in

improving vaccination uptake in pregnant women. Thus, further high quality studies are recommended to evaluate the effectiveness of individual or multifaceted approaches to increase vaccine uptake. Research during the A/H1N1 pandemic has shown that public health education targeting of pregnant women can improve the uptake of both seasonal and pandemic influenza vaccines in this group.^{4,74}

CONCLUSION

Influenza infection is a serious global public health problem and vulnerable populations have been prioritized to receive the vaccination in order to lower the risk of influenza-related illness, hospitalization and mortality. Vaccination can prevent influenza infection during pregnancy, protect the fetus from the unintended consequences of infection, and protect newborns from respiratory infection during the first six months of life, a three-for-one benefit. Vaccination refusal is due to an underestimation of susceptibility to and the seriousness of influenza infection and the failure of health providers to recommend the vaccine. Vaccine promotion strategies that address the known barriers to vaccination have been effective in boosting the vaccination rate. Success in preventing morbidity and mortality from influenza infection in pregnant women cannot be accomplished without the combined efforts of public health officials, health care providers, and patients.

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Table 1: Overview of vaccination recommendations for pregnant women

Organization	Country	Recommendations	Year Implemented
American College of Obstetricians and Gynecologists ¹⁰¹	US	<ul style="list-style-type: none"> ● Influenza vaccination is recommended for all women who will be pregnant during the influenza season 	2010
Centers for Disease Control & Prevention ¹⁰²	US	<ul style="list-style-type: none"> ● Influenza vaccination is recommended for all women who are or will be pregnant (in any trimester) during the influenza season 	2013
American College of Nurse-Midwives ¹⁰³	US	<ul style="list-style-type: none"> ● Influenza vaccination is recommended for all pregnant women in any trimester 	2014
National Advisory Committee on Immunization under Public Health Agency of Canada ¹⁰⁴	Canada	<ul style="list-style-type: none"> ● Influenza vaccination is recommended for all pregnant women regardless of gestational age 	2013
National Health Service ¹⁰⁵	England	<ul style="list-style-type: none"> ● Influenza vaccination is recommended for all pregnant women at any stage of pregnancy 	2014
Australian Government Department of Health and Ageing ¹⁰⁶	Australia	<ul style="list-style-type: none"> ● Influenza vaccination is recommended for all pregnant women at any stage of pregnancy, particularly those who will be in the 2nd or 3rd trimester during the influenza season 	2013
Centre for Health Protection ¹⁰⁷	Hong Kong	<ul style="list-style-type: none"> ● Influenza vaccination is recommended for all pregnant women ● Pregnant women have the highest priority for vaccination 	2012
World Health Organization ³	Europe	<ul style="list-style-type: none"> ● Pregnant women should have the highest priority for vaccination ● Pregnant women should be vaccinated with TIV at any stage of pregnancy 	2012
European Commission ¹⁰⁸	Europe	<ul style="list-style-type: none"> ● A high number of Member States recommend vaccination for pregnant women ● For 2011/12, 22 countries recommended the vaccination for all pregnant women; one country recommended the vaccination for pregnant women with an additional clinical indication ● Thirteen countries recommended the vaccination at any stage of pregnancy; ten countries recommended vaccination in either the 2nd or 3rd trimester. Five countries reported that vaccination was not recommended for this population 	2014

TIV: Trivalent Inactivated Vaccine

Table 2. Common myths and misconceptions about influenza and influenza vaccination during pregnancy

Myth 1	Influenza is a mild disease ^{6,59}
Myth 2	If necessary, influenza can be treated effectively with medication ^{6,68}
Myth 3	The risk of influenza infection in pregnant women is the same as non-pregnant women ^{4,57}
Myth 4	Healthy pregnant women do not need influenza vaccine ^{4,6,71}
Myth 5	Influenza vaccine can cause influenza infection ^{65,66}
Myth 6	Influenza vaccine during pregnancy can cause birth defects, miscarriage or preterm birth ^{57,67,68}
Myth 7	The risks associated with influenza vaccination during pregnancy are greater than the risks associated with influenza infection ⁶
Myth 8	If you do not usually receive influenza vaccine, it is better not to receive the vaccination during pregnancy ^{4,71}

Table 3: Recommendations to improve influenza vaccination rates among pregnant women

Recommendation 1	Assess vaccination status ¹⁰⁹
Recommendation 2	Inform about the benefits and safety of the vaccine ¹¹⁰
Recommendation 3	Inform about the risks of influenza infection for pregnant women and infants ⁶⁵
Recommendation 4	Involve the husband and/or family in the discussion of vaccination recommendations ¹¹¹
Recommendation 5	Provide on-site influenza vaccination ^{7,110}
Recommendation 6	If on-site vaccination is not available, provide a list of clinics or providers where the vaccine can be obtained ¹¹¹
Recommendation 7	Provide printed materials to enhance the take-home message about the importance of vaccination ⁹⁵
Recommendation 8	Send email or text message reminders to inform about the benefits, safety and availability of the vaccine ¹⁰⁰
Recommendation 9	Place an alert reminder in the maternal record to remind HCPs to document vaccination status and reasons for vaccination refusal ¹⁰⁹
Recommendation 10	Reassess vaccination status at each antenatal visit and postpartum ¹⁰⁹

HCP: Health Care Provider