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Aiden Kennedy Varan Date

Data analysis of investigation of *Bordetella pertussis* booster vaccine acceptance among pregnant women living in Mexico City

By

Aiden Kennedy Varan

Master of Public Health

Global Epidemiology

_____

Dr. Saad Bin Omer, PhD MPH MBBS

Committee Chair

_____

Dr. Alejandra Esteves, MD MPH

Committee Member

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Aiden Kennedy Varan

BSc, University of Melbourne, Melbourne, Australia, 2010

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Thesis Committee Chair: Dr. Saad Bin Omer, PhD MPH MBBS

An abstract of

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Abstract

Data analysis of investigation of *Bordetella pertussis* booster vaccine acceptance among pregnant women living in Mexico City

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OBJECTIVE: Adult booster vaccination against pertussis can help prevent severe infections in young infants. We examined influences on pertussis booster vaccine acceptance among pregnant women in Mexico City.

METHODS: We conducted a cross-sectional survey, recruiting convenience samples of pregnant women receiving prenatal care from three public clinics between March and May 2012. Our primary outcome was intention to accept pertussis vaccination during pregnancy. We examined socio-demographic factors, vaccination history, pertussis knowledge, perceptions of vaccine information sources and other potential influences on vaccine decision-making.

RESULTS: A total of 402 pregnant women agreed to participate, of which 387 (96%) provided their intention to accept or decline pertussis vaccination. Less than 1% received a recommendation for pertussis vaccination during pregnancy. Among respondents, 222 (57%) intended to accept a pertussis booster vaccine, but more than 80% would accept vaccination if recommended by an obstetrician-gynecologist. In multivariate analysis, rating doctors and nurses as good sources of vaccine information, and having ever heard of pertussis, were independently associated with vaccine acceptance ($P<0.05$). Interaction was detected between age and perceptions of religious leaders as vaccine information sources ($P=0.03$). Among health belief model dimensions, perceived disease susceptibility and vaccine safety for pregnant women, and disease severity for newborns, were independently associated with pertussis vaccine acceptance ($P<0.05$).

CONCLUSION: Promoting patient awareness about pertussis disease and vaccine safety, and encouraging obstetrical providers to recommend Tdap, may increase vaccine uptake among pregnant women.

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TABLE OF CONTENTS

CHAPTER I:

LITERATURE REVIEW

Introduction

Causes and transmission of pertussis

Pertussis (whooping cough) is a bacterial respiratory illness caused by Gram-negative bacillus *Bordetella pertussis* (1). Pertussis is transmitted through respiratory droplets and is extremely contagious, with secondary attack rates up to 90% among non-immune household contacts (1, 2). Pertussis displays epidemic peaks every 2-5 years (1). Humans are the only reservoir for pertussis (3).

Signs and symptoms of pertussis

The incubation period for pertussis is typically 9-10 days (range: 6-20 days), after which catarrhal symptoms including cough emerge (2). Untreated patients may be contagious for 3 or more weeks following the onset of cough. Symptoms during illness onset are indistinguishable from other upper respiratory infections (2). Over the subsequent 1-2 weeks, cough progresses to become paroxysmal which may end in a characteristic whoop, is especially severe at night, and is often followed by vomiting (1). In a small percentage of cases among infants and young children, pertussis can cause serious and potentially life-threatening complications (4). For others, recovery is gradual during the convalescence stage, with milder and less frequent paroxysms and the disappearance of whoop. However, cough may persist for many weeks (1). After natural infection, anti-PT antibodies are found in 80-85% of cases (2).

World Health Organization (WHO) defines a clinical pertussis case as either a case diagnosed as pertussis by a physician, or a person with a cough lasting two or more weeks and at least one of paroxysms, inspiratory whooping or post-tussive vomiting

without other apparent cause (5). Pertussis displays differential symptoms by age, with most clinically recognizable cases occurring in children aged 1-5 years (2). In young infants, pertussis may cause apnea and cyanosis without cough. In adolescents and adults, persistent cough without characteristic whoop may be the only visible symptom (2). Furthermore, adults who have previously received childhood vaccines against pertussis may not present with classical symptoms (3). The Global Pertussis Initiative has proposed a revised set of case definitions based on patient age (0-3 months, 4 months to 9 years, and ≥10 years old) (6).

Diagnosis of pertussis

B. pertussis is traditionally isolated by culture for laboratory confirmation (2). This method is 100% specific but 1-2 weeks are required before a culture can definitely be called negative. Sensitivity of culture method is 80-90% under optimal conditions but 30-60% in practice, dropping to 1-3% if the sample is taken 3 or more weeks after cough onset (7). Polymerase chain reaction (PCR) methods offer reduced processing time and 2-3 times greater sensitivity than culture, and are increasingly being used for laboratory confirmation (7). However, PCR methods have not been standardized or validated among laboratories (8). Serologic assays have also been developed, and may be useful for diagnosis in later disease phases when antibody titers peak (2-8 weeks following cough onset) (9). WHO defines criteria for pertussis laboratory confirmation using any of culture, PCR methods or positive paired serology (5).

Pertussis morbidity and mortality

Approximately 16 million annual cases of pertussis and 195,000 deaths occur worldwide (2). Although 95% of cases occur in developing countries (10), pertussis is poorly controlled relative to other vaccine-preventable diseases in the U.S., Canada, Australia and many other industrialized countries (11). In 2004-05, the Centers for Disease Control and Prevention (CDC) reported more than 50,000 pertussis cases in the U.S. (12). Pertussis incidence was highest in children under 6 months of age, who were too young to have completed their primary immunization series at 2, 4 and 6 months (12). Pertussis-associated infant mortality in the U.S. has been associated with low birth weight, female infant sex, less than 12 years maternal education, and Hispanic ethnicity (13). Disparities and localized deficiencies in pertussis vaccine coverage increase the risk of infant cases (14). Parental refusal of routine childhood pertussis immunization, personal belief exemptions for school immunizations, and the ease of granting these exemptions have also been associated with increased pertussis incidence (15-17).

Approximately 6% of child pertussis cases suffer from complications which can include bronchopneumonia, nutritional deficiencies resulting from repeated vomiting, and neurological complications (18). Rates of severe pertussis infections and associated complications and fatalities are highest among young infants (19-21). Compared with other ages, children under 6 months are four times more likely to experience complications from pertussis (22). Among infants under 2 months, severe complications may include seizures, encephalopathy and cardiac arrhythmias (18). Infantile malignant pertussis can occur in extreme cases, characterized by severe respiratory failure, pulmonary hypertension, leukocytosis and death (23).

Although pertussis incidence and severity are highest in young infants, adults and adolescents account for a sizable proportion of cases (24). In the U.S. in 2010, ~32% of reported pertussis cases were among individuals aged 15 years and older (25). Longitudinal data of serum antipertussis antibodies suggest that the infection is endemic, common and generally unrecognized in adults (26). Underreporting of pertussis among adolescents and adults is partly due to low physician awareness and index of suspicion (27). Pertussis-related deaths in adults are rare and typically occur in individuals with serious underlying medical conditions (3).

The economic burden of pertussis may be considerable. Direct medical costs are relatively high in infant cases, whereas indirect opportunity costs from lost productivity and diverted time are greater in adolescent and adult cases (28). In one U.S.-based study, societal costs of pertussis were estimated in excess of $390 per adolescent case and $770 per adult case (29).

Childhood vaccines against pertussis

Vaccination is the main disease control strategy against pertussis, and has been part of the WHO Expanded Program on Immunization since its inception in 1974 (1, 2). Global immunization programs in 2008 reached approximately 82% of all infants with 3 doses of pertussis vaccine, averting more than 680,000 deaths (10). Whole-cell vaccines against pertussis first became available in the 1920s, and multivalent vaccines against diphtheria, tetanus and pertussis (DTP) have been recommended for routine childhood immunization since the 1940s and 1950s (7). Beginning in the 1950s, large-scale DTP vaccination programs were introduced in the U.S., Japan and other industrialized countries, which

dramatically reduced pertussis incidence and mortality (2, 30). However, serious adverse effects were occasionally associated with whole-cell vaccines, prompting the development of acellular vaccine alternatives (31).

Acellular pertussis vaccines were first implemented in 1981 in Japan (1). In the U.S., diphtheria, tetanus and acellular pertussis (DTaP) multivalent vaccines were licensed in 1991 for the 4th and 5th dose of childhood immunization schedules, and later in 1996 for all pediatric doses (7). Acellular vaccines show comparable long-term effectiveness and fewer adverse events than whole-cell vaccines (32-34).

Although DTaP is typically administered from 2 months of age, pertussis immunization at birth has been investigated as a strategy to curb the incidence of neonatal infection (35). However, the efficacy of pertussis immunization in newborns is debatable. Studies of monovalent acellular pertussis vaccination in neonates have detected earlier antibody responses without increased risk of adverse events or interference with subsequent vaccination (36, 37). Conversely, in a randomized control trial of neonatal vaccination, a dose of DTaP at birth was associated with decreased serum pertussis antibody levels at 7 and 18 months of age relative to controls (38).

Contemporary resurgence of pertussis

Despite longstanding childhood vaccination programs and high vaccine coverage, pertussis has remained endemic and a resurgence has been observed in several countries (39), including the U.S. (3, 40), Europe (41), Canada (42), Australia (43), and the Netherlands (44). The proportion of recognized pertussis deaths has also shifted to younger infants, many of whom are too young to be protected by immunization (13). In

addition to improved diagnosis and reporting of pertussis (45), waning vaccine immunity is an important contributing factor in this resurgence. For both acellular and whole-cell pertussis vaccines, vaccine-induced immunity wanes after 4-12 years compared with 7-20 years following natural infection (46, 47). With fewer circulating pathogens and vaccines that do not confer lifelong immunity, diminished population immunity among adolescents and adults has been observed (39, 45).

Concomitantly, adolescents and adults (including mothers) are increasingly recognized as important sources of infant pertussis infections (20, 27). Household members may account for up to 83% of transmission to infants aged 6 months or younger (48). Mothers may be the source of infection in up to one-third of infant cases (49, 50). In one study from the Netherlands, 6% of pregnant women at delivery had serological evidence of pertussis infection (51). Maternal pertussis infection can be transmitted and cause neonatal infection and death (52).

Adolescent and adult pertussis booster vaccines

Pertussis booster vaccines are valuable tools to increase population immunity and interrupt transmission to infants. In 2005, two tetanus, diphtheria and acellular pertussis (Tdap) booster vaccines (Adacel®, sanofi-pasteur; and Boostrix®, GSK) were licensed by the U.S. Food and Drug Administration for use in adults and adolescents (20). In 2006, the U.S. Advisory Council on Immunization Practices (ACIP) recommended a dose of Tdap for adolescents 11-18 years who have completed the routine DTaP vaccination series (7). Tdap appears to be highly effective in boosting seropositivity rates for pertussis antigens (53).

Tdap contains reduced pertussis antigen concentrations compared with pediatric DTaP vaccine; tetanus and diphtheria toxoid concentrations are similar to adult Td booster vaccines (7). Td and Tdap vaccines have similar adverse reaction profiles (54). Contraindications to Tdap include a history of serious allergic reaction to vaccine components, or a history of encephalopathy associated with prior pertussis vaccination (1).

Strategies to implement Tdap booster vaccine in adolescents and adults

Universal Tdap vaccination

Universal vaccination of adolescents, adults or both with Tdap offers a comprehensive approach to reduce pertussis incidence through direct vaccine protection and increased herd immunity (39, 55). Universal adolescent Tdap immunization may be an effective disease control strategy in higher income countries. In Canada's Northwest Territories, offering free Tdap booster vaccines for 14-16 year olds was associated with reduced pertussis incidence among both adolescents and infants (56). In Australia during an epidemic period, national pertussis rates among adolescents targeted for Tdap were significantly lower than other age cohorts (57). In the U.S., targeted adolescent Tdap vaccination between 2005-2009 appears to have successfully reduced pertussis incidence in immunized age groups (58). Adolescent Tdap vaccination is likely to be cost-effective or cost-saving, especially in regions with higher pertussis incidence (59). However, cost and lack of healthcare infrastructure are major barriers to implementation in lower income countries (55, 60).

The evidence for universal Tdap immunization among adults is inconclusive (61, 62). ACIP estimated in 2006 that adult Tdap vaccination programs in the U.S. could be cost-effective where disease incidence exceeded 120 per 100,000 adult population (63). However, between 1980-2010, all-ages national pertussis incidence in the U.S. did not exceed 10 per 100,000 population (25). Provisional results for 2012 indicate a national adult population incidence below 4 per 100,000 (64). Hence, universal adult pertussis booster immunization may be cost-prohibitive.

Routine administration to women of childbearing age

One alternative to universal vaccination is targeted Tdap vaccination among adolescent and adult women of childbearing age. In 2008, ACIP highlighted Tdap administration during routine women's wellness visits as an effective vaccination strategy (20). In addition to reducing the risk of maternal-child transmission, immunization before conception might boost antibody transfer if the woman becomes pregnant. A 2011 study found significantly higher antibody titers in 1-month-old infants whose mothers were immunized prior to conception, compared with their older siblings (65). However, several studies have identified a rapid decay of antipertussis antibodies within 1 year of Tdap administration, approaching pre-vaccination levels after 3-10 years (66-69). Thus, booster vaccination during routine wellness visits alone may be insufficient to protect mothers and neonates against pertussis infection.

Cocooning

Cocooning refers to the booster immunization of postpartum mothers and other household contacts, in order to interrupt pertussis transmission to newborns and young infants (70). Cocooning has been implemented in several countries including the U.S., Australia, France, Germany, Costa Rica and Panama (2, 71). In 2008, ACIP recommended that pregnant women not previously vaccinated with Tdap should receive the vaccine immediately postpartum and before discharge, as short as 2 years since their most recent Td booster immunization (20).

There is some evidence of the feasibility of cocooning strategies for pertussis. In two U.S. hospital settings, standing orders for postpartum Tdap vaccination achieved 79-86% coverage (12, 72). Across several studies in which infant caregivers were routinely offered Tdap vaccination, 51-87% vaccine uptake among eligible caregivers was observed (73-75). U.S. National Immunization Survey data from 2007 suggested that 82% of unvaccinated respondents would be willing to receive Tdap if recommended by a provider (76).

On the other hand, there are several limitations associated with the cocooning strategy. Although an antibody response in postpartum women is detectable 5-7 days after Tdap vaccination, it does not approach peak levels until 2 weeks after administration (77). Given this delay, mothers could contract pertussis and transmit the infection to very young infants (77). Unlike Tdap administration before conception or during pregnancy, postpartum cocooning misses an opportunity to boost placental antibody transfer and enhance passive neonatal immunity.

The number of household contacts needed to vaccinate to interrupt transmission may also be prohibitively large. In provinces of Canada with relatively low pertussis

incidence, it was estimated that 100,000 parents would require Tdap vaccination to prevent one infant ICU admission, and at least 1 million parents to prevent one infant death (78). Other challenges include inaccessible or incomplete vaccination records for many adults, and billing and reimbursement issues with delivering vaccines to non-patient household contacts (79, 80). Few hospitals in the U.S. currently implement cocooning for Tdap vaccination (81), and no country with cocooning recommendations has requirements to enforce the policy (55).

Administering Tdap during pregnancy

Another strategy to prevent neonatal pertussis is Tdap administration during pregnancy. Unlike cocooning strategies, immunization during pregnancy supports maternal immunity from the time of delivery (69). Passive immunity via maternal antibodies may also confer infants with valuable protection against pertussis (82, 83). Elevated antipertussis antibodies have been observed in newborns of women vaccinated with Tdap during pregnancy; paired analysis of maternal serum and cord blood indicates active placental antibody transfer (84). Antipertussis antibodies are also transferred in breast milk (77). Furthermore, pregnant women are highly accessible to target for immunization given their frequent visits to health centers (39).

In conferring earlier maternal protection and maximizing antibody transfer, ACIP has estimated that a dose of Tdap during pregnancy would prevent more infant cases, hospitalizations and deaths than a postpartum dose (70). In one study from the Netherlands, Tdap administration during pregnancy was predicted to prevent ~30% more infant cases than parental cocooning (85). Given rapidly waning antibody titers (66-68),

Tdap administration during the third trimester is predicted to be most effective and repeated administration during subsequent pregnancies may be necessary (69).

WHO guidelines (last updated in 2010) stipulate that there is insufficient evidence to recommend vaccinating pregnant women against pertussis (2). WHO noted that pregnant women were excluded from prelicensure trials of Td and Tdap vaccines and that no animal reproduction studies were conducted for these vaccines (2). However, both Tdap vaccine manufacturers have established voluntary registries for clinicians to report Tdap administration during pregnancy (20). In the U.S., guidelines for Tdap administration during pregnancy have rapidly evolved over the last decade. In 2006, ACIP concluded that pregnancy is not a contraindication for Tdap vaccination but recommended Td in preference of Tdap (7). In 2008, ACIP stipulated that women can substitute Td vaccination during pregnancy for Tdap in the immediate postpartum period if they have sufficient tetanus immunity, but deemed the available evidence insufficient for further recommendations (20).

In 2011, based on ongoing infant pertussis rates and limited success with cocooning programs, ACIP recommended administration of Tdap during pregnancy (or immediately postpartum) in lieu of Td for women who have not previously received Tdap or are indicated for tetanus or diphtheria booster (70). The American College of Obstetricians and Gynecologists affirmed these updated recommendations (86), as did the American Academy of Pediatrics in the case of pregnant adolescents (87). In October 2012, citing low Tdap uptake and new safety and maternal antibody data, ACIP voted to recommend a dose of Tdap during each pregnancy regardless of the patient's prior Tdap vaccination history (88). Under current guidelines, Tdap may be administered at any time

during pregnancy, but the third trimester (27-36 weeks) is preferred to maximize maternal antibodies transfer (88). If not administered during pregnancy, Tdap should be provided to women immediately postpartum (88).

Challenges to implementing maternal Tdap vaccination

There are several important challenges to implementing Tdap vaccine recommendations among pregnant women. First, there is limited safety information on the use of Tdap during pregnancy, since pregnant women were not included in the original vaccine trials (20). However, analysis of surveillance data tracking more than 600,000 doses of Tdap in adolescents and adults of both sexes found no evidence of associations with predefined adverse events (89). Furthermore, a review by ACIP of Tdap manufacturer registry data did not identify any increased frequency or unusual pattern of adverse events among pregnant women receiving Tdap (70). Another concern is the risk of adverse events associated with repeated Tdap administration during every pregnancy. Studies examining short intervals (1 month to 2 years) between prior Td vaccination and Tdap administration in adults have observed some increase in minor localized or systemic adverse events, but no increase in serious adverse events (90-92).

Another potential challenge is immune blunting, whereby maternal immunization may interfere with an infant's immune response to pediatric vaccines. Blunting effects were characterized in studies of whole-cell pediatric vaccines (93), and may be caused by maternal-derived antibodies binding to vaccine antigens and masking them from recognition by an infant's B cells (20). However, available evidence suggests that acellular pertussis vaccines do not have the same blunting effect (39, 82, 94).

Additionally, given the rapid decline in maternal antipertussis antibodies, any blunting effects that do occur are likely to be short-lived (95). Hence, the benefits of passive immunity for neonates may outweigh this risk (70).

Yet another challenge to Tdap implementation during pregnancy is low vaccine uptake among pregnant women. For example, although ACIP has recommended seasonal influenza immunization for pregnant women during any trimester since 2004 (96), vaccine coverage rates were historically ~15% and have only recently approached 50% following the 2009 H1N1 pandemic (97-100).

Finally, routine maternal immunization alone will not address pertussis transmission by other household contacts. A successful program to prevent neonatal pertussis will likely incorporate multiple approaches including cocooning strategies (69, 101). However, given limited success to date with cocooning programs, Tdap vaccination during pregnancy may help overcome existing challenges in pertussis control.

Knowledge, attitudes and beliefs regarding maternal vaccination

The knowledge, attitudes and beliefs of pregnant women concerning vaccines are likely to influence the success of maternal vaccination programs. In the case of influenza vaccination during pregnancy, safety concerns for fetal and maternal health, fear of needles, lack of knowledge about infection, mistrust of the medical establishment and other barriers have been identified (100, 102). Conversely, greater levels of knowledge about maternal vaccination and positive attitudes towards influenza vaccination have been associated with vaccine acceptance (103).

Behavioral theories are useful in conceptualizing the determinants of vaccine decision-making. The health belief model (HBM) hypothesizes that health-related behaviors depend chiefly on the desire to avoid illness and the belief that a specific health action will prevent or ameliorate illness (104). In the context of vaccination, HBM can been framed in terms of the perceived susceptibility and severity of a vaccine-preventable disease, perceived benefits and barriers to vaccination, cues to action and self-efficacy (105, 106).

Several studies have examined the explanatory capacity of HBM for vaccination behavior in women of childbearing age. In one study of human papillomavirus (HPV) vaccination among college-aged women, perceived susceptibility to HPV, perceived vaccine benefits, and self-efficacy were significant predictors of intention to receive the vaccine (107). In a study of seasonal influenza vaccination among pregnant women, perceptions of susceptibility to influenza, vaccine effectiveness and barriers to vaccination, as well as cues to action (doctor reminders), were independently associated with vaccine uptake (108). Similarly, a study of H1N1 influenza vaccination among pregnant women found that perceived vaccination barriers and perceived disease severity were associated with vaccine acceptance controlling for age, race, prenatal care provider and education level (109).

Healthcare provider recommendations and maternal vaccination

As a cue to action, healthcare provider recommendations are an important determinant of patient attitudes and beliefs about vaccination (110). There is considerable evidence highlighting provider recommendations in relation to influenza vaccine acceptance

during pregnancy (100). In one study, 67% of postpartum women who accepted a vaccine against pandemic H1N1 influenza cited their obstetrician as playing a key role in their decision (111). In another study of seasonal influenza vaccination, pregnant women who received a doctor recommendation were three times more likely to be vaccinated (108). Conversely, in an earlier study, 57% of pregnant women who were not vaccinated against seasonal influenza cited that their doctor did not mention the vaccine (112).

Among U.S. healthcare workers, pertussis booster vaccine uptake may be relatively low (113, 114). However, a 2006 national survey of U.S. obstetricians found that the majority of respondents would recommend Tdap to patients either postpartum (78%) or during pregnancy (69%) (115). Those respondents who would recommend Tdap vaccination were significantly more likely to perceive themselves as having a role in promoting or administering the vaccine (115). Subsequently, in a national survey of U.S. family physicians and general internists, 81% of respondents indicated that they would recommend Tdap vaccine for adult patients according to ACIP guidelines (116). More recently, in a 2012 study of obstetrical-gynecological physicians in Taiwan, providers who intended to recommend postpartum Tdap vaccination were more likely to identify pertussis as highly contagious and severe for newborns (117).

Determinants of maternal Tdap vaccine acceptance

There are currently few studies examining the determinants of maternal Tdap vaccine acceptance. In one study of postpartum women attending a large teaching hospital in Taiwan, where healthcare workers were trained and a patient education campaign on Tdap was implemented, 53% of respondents were willing to receive Tdap (118). Among

respondents, 88% reported that they had received sufficient information to make an informed decision about postpartum Tdap vaccination (118). Using multivariate logistic regression modeling, the study authors found that rating maternal or infant risk of pertussis exposure as low, not trusting provided vaccine information, and vaccine safety concerns were independently associated with refusing postpartum Tdap vaccination (118).

Among other studies, one investigation found that black women were three times more likely to refuse postpartum Tdap vaccination for non-medical reasons than women of other races or ethnicities (12). In another study of women obtaining hospital-based obstetrical or gynecological care, 27% of respondents indicated willingness to accept Tdap vaccinations from their obstetrician-gynecologist (119). In that same study, several demographic variables were associated with willingness to accept provider recommendations for Tdap and other vaccines, including race, education level, insurance status, prior vaccine history and others (119). However, the determinants of maternal Tdap vaccine acceptance remain poorly understood at present.

Pertussis and maternal Tdap immunization in Mexico

Pertussis is a nationally notifiable disease in Mexico (120). DTP vaccine was introduced in routine childhood immunization schedules in Mexico beginning in 1973 (121). Since 2007, a pentavalent vaccine against polio, *Haemophilus influenza* type b, diphtheria, tetanus and pertussis (IPV-Hib-DTaP) has been used (121). The current childhood immunization schedule is a dose of IPV-Hib-DTaP at 2, 4, 6 and 18 months, followed by

one dose of DTP at 4 years old (121). In 2011, DTP3 vaccination coverage in Mexico was estimated at 97% among 1-year-olds (122).

Pertussis follows 3-4 year epidemic cycles in Mexico. In non-epidemic years, the average baseline incidence is 1 or 2 confirmed cases per million (120). At least four national seroepidemiologic surveys on pertussis have been conducted in Mexico (123). The most national recent survey, conducted in 1987 and sampling children and adolescents, observed an overall seroprevalence of 65% and elevated seroprevalence in northern and central regions and among children living in rural areas or classified as low socio-economic status (124). On a regional scale, in a 2008 study of over 12,000 adolescents in Mexico City, a PCR-confirmed pertussis rate of 5/1000 students was observed (125).

In recent years, high pertussis incidence has been observed in Mexico, with 3 cases per million in 2005 and 5 cases per million in 2009 (120). In 2009, 70% of reported pertussis cases were among children under 1 year and 100% of attributable deaths were among infants under 3 months (120, 121). Furthermore, with only ~20% confirmation of probable cases (compared with ~55% in the U.S.), these incidence rates severely underestimate the true pertussis burden in Mexico (120). The seroprevalence of pertussis among pregnant women in Mexico is currently unknown (121). However, a 2012 study found that 78% of PCR-tested mothers of infant cases were positive for pertussis (126).

Since adolescents and adults are believed to be important sources of pertussis transmission in Mexico, booster vaccines are critical in disease control strategies (120). The National Immunization Council of Mexico (CONAVA) voted in April 2012 to approve immunization of pregnant women with a booster dose of Tdap, but the strategy

has not been yet implemented nationally. Argentina and Uruguay have also initiated Tdap administration during pregnancy following severe outbreaks with high infant fatality rates (71).

Maternal Tdap immunization has great potential to reduce pertussis incidence among young infants in Mexico. Healthcare workers in Mexico appear willing to adapt to new vaccine recommendations, as observed during the H1N1 influenza pandemic (127). Anti-vaccination campaigns are also relatively weak in Latin America compared with other global regions (60). Efforts to improve pertussis diagnostic capabilities and surveillance methods in Latin America are currently being implemented in Argentina, Mexico and Panama, supported by the Sabin Vaccine Institute, CDC and the Pan American Health Organization (128). Epidemiologic data from this collaboration may help guide future recommendations for Tdap implementation during pregnancy (128). However, there remains an unaddressed need to better understand Tdap vaccine acceptance and its determinants among pregnant women in Mexico.

Summary

The global resurgence of pertussis and high rates of severe infant infections underscore the need for effective disease control strategies. Adolescents and adults (including new mothers) are important sources of infant infections, and Tdap booster vaccines provide a valuable tool to interrupt disease transmission. There are several possible strategies to implement Tdap booster vaccines. ACIP has previously endorsed cocooning and, more recently, recommended Tdap administration during every pregnancy to support maternal immunity and enhance antibody transfer to neonates.

However, there are numerous challenges to implementing Tdap vaccination, including low vaccine uptake among pregnant women. There are current knowledge gaps concerning the influence of maternal knowledge, attitudes and beliefs, as well as healthcare provider recommendations and socio-demographic factors, on perceptions about pertussis disease and decision-making about Tdap. In Mexico, where relatively high pertussis incidence and associated infant mortality is observed, CONAVA recently approved Tdap administration during pregnancy. To support forthcoming vaccination programs, future studies should examine the influences and determinants of pertussis vaccine acceptance among pregnant women in Mexico.

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CHAPTER II:

MANUSCRIPT

INTRODUCTION

Pertussis incidence and fatality rates are highest in children under 6 months of age (1). Adolescents and adults, including mothers, are key sources of infant pertussis infections (1-5). Tetanus, diphtheria and acellular pertussis (Tdap) booster vaccines for adolescents and adults have been licensed in the U.S. since 2005 (1). A strategy to prevent infant and maternal pertussis is Tdap administration during pregnancy (6). The U.S. Advisory Council on Immunization Practices (ACIP) recently recommended a dose of Tdap during each pregnancy (7).

Pertussis is a nationally notifiable disease in Mexico (8). In 2009, pertussis incidence reached 5 cases per million, with 70% of reported cases among children under 1 year (9). In a recent study, 78% of PCR-tested mothers of infant cases in Mexico were positive for pertussis (10). The National Immunization Council of Mexico (CONAVA) voted in 2012 to approve booster immunization of pregnant women with Tdap. However, this recommendation has not yet been implemented nationally.

Challenges to implementation include historically low vaccine uptake among pregnant women. There are currently few studies assessing maternal Tdap vaccine acceptance. In two U.S. hospital settings, standing orders for postpartum Tdap vaccination achieved 79-86% coverage (11, 12). In a 2010 study conducted in Taiwan, 53% of women accepted postpartum Tdap vaccination (13).

We sought to examine Tdap vaccine acceptance and decision-making among women receiving prenatal care at public hospitals and community centers in Mexico City. Our findings may help guide prenatal Tdap immunization programs in Mexico and among U.S. Hispanic/Latina populations.

MATERIALS AND METHODS

We invited 5 health centers affiliated with Mexico City's Ministry of Health (Secretaría de Salud de Distrito Federal) to participate in our study. Health centers were selected among institutions affiliated with Mexico City's Ministry of Health, based on highest reported attendance of pregnant women in 2010. All selected institutions provide medical care for uninsured individuals. Patients were enrolled from March 2012 to May 2012. Eligible study participants were pregnant women of any trimester receiving prenatal care at participating institutions who could read, write and speak in Spanish. Women deemed to have limited mental capacity to make an informed decision in the opinion of the treating physician were excluded from participation.

We obtained convenience samples of women waiting to receive prenatal care at participating health centers. Sample size calculations were performed using Open Epi 2.3.1 (http://www.OpenEpi.com), assuming 80% study power. A registered nurse (supervised by senior research staff) was trained to approach eligible potential participants, explain the purpose of the study, and obtain informed consent. For unmarried women less than 18 years old, assent to participate and informed consent from a parent was obtained. For married women of any age, informed consent to participate was obtained.

Participants were given a 64-item written questionnaire focused on their knowledge and attitudes of pertussis and vaccination. The outcome of interest was whether they would accept a vaccine against pertussis during pregnancy if offered. Demographic questions included age, education level, marital status, employment status, income, weeks of gestation, total number of pregnancies, self-reported health status

before becoming pregnant, and regularity of visiting a doctor when sick. We asked participants about any complications or hospitalization during pregnancy, their first attendance at prenatal care, and sites where they received prenatal care. We also asked about complications and hospitalizations during any prior pregnancies. In terms of vaccinations, we asked participants about the sources of any vaccine recommendations received during pregnancy (for tetanus, influenza, HPV or pertussis vaccination), the type and timing of vaccines administered, and any associated complications. We also asked about vaccinations during childhood and prior pregnancies, and their perceptions of the reliability of several information sources for vaccine recommendations.

Regarding pertussis, we asked participants whether they had ever heard of pertussis/whooping cough/100-day-cough, whether they knew someone who has contracted this disease, and what age group they thought was most likely to get this disease. Regardless of their stated intention to accept or decline vaccination, we asked participants to select from predetermined lists of reasons why they would accept, and reasons why they would decline, pertussis vaccination during pregnancy. Finally, participants were asked to rate the susceptibility and severity of pertussis infection, as well as the conferred protection and safety of pertussis vaccination (i.e. health belief model dimensions), for both a pregnant woman and a newborn.

The statistical software package SAS 9.3 (SAS Institute Inc., Cary, NC) was used for all data analysis. Unless otherwise specified, ‘don’t know’ responses for yes/no questions were categorized as no. We dichotomized the following study variables for analysis: age (based on median value), education level, employment status, income, marital status, tendency to visit a doctor when sick, perceptions of vaccine information

sources, and health belief model dimensions. Gestational age was categorized into trimesters. History of DTP vaccination during childhood was maintained as yes, no or don't know. Perceived age most likely to get pertussis was categorized into newborns and infants <1 year old, other specific ages or any person, or don't know.

Descriptive statistics were calculated in relation to intention to accept a pertussis booster vaccine during pregnancy. Simple logistic regression models were used to examine unadjusted associations between each study variable and vaccine acceptance, assessing for significance at $\alpha=0.05$ using exact Mantel-Haenszel Chi-square tests.

We constructed a directed acyclic graph including study variables with at least 95% response rate among participants (Appendix 1). We selected perceptions of vaccine information sources as our primary predictors, and used the directed acyclic graph to identify potential confounders for multivariate modeling.

Multivariate logistic regression modeling was based on a popular strategy (14). In addition to potential confounders, we specified first-order interaction terms between perceptions of vaccine information sources and each of age, education level, and any complications reported during pregnancy. We assessed multicollinearity using variance inflation factor (VIF) and condition index (CI) statistics, removing predictors as needed to address gross multicollinearity issues (threshold: VIF>10 and CI>0.5). Interaction terms were assessed using likelihood ratio tests at $\alpha=0.05$, and non-significant terms were successively eliminated. Hosmer-Lemeshow statistics were calculated to determine goodness of fit (assessed at $\alpha=0.05$). Sensitivity analysis comparing subjects included and excluded from multivariate modeling was performed using exact Mantel-Haenszel Chi-Square tests (assessed at $\alpha=0.05$).

All figures were produced using Microsoft Excel and Inkscape 0.48 (http://inkscape.org). This study was approved by Institutional Review Board of the Mexico City's Ministry of Health. Data analysis was deemed exempt for review by Institutional Review Board of Emory University, Atlanta, GA (Appendix 2). This study was supported by Sanofi Pasteur. No conflict of interest was related to this study. The participants did not receive any payment or incentives.

RESULTS

One general hospital, one maternal and child hospital and one community health center in Mexico City agreed to participate in our study. In total, 507 pregnant women receiving prenatal care at participating health centers were approached, of which 402 women agreed to participate (overall response rate=79%, range: 62%-86%). The median participant age was 24 years old (range: 15-43 years old). Twenty participants (5%) were less than 18 years old. Among participants, 387 (96%) provided their intention to accept or decline pertussis vaccination during pregnancy and were included in further analysis. Among these respondents, 222 (57%) indicated that they would accept pertussis vaccination during pregnancy.

Respondents were predominantly housewives (88%), married or cohabiting (76%), and with no monthly income (74%) (Table 1). Fifty-one percent had completed more than secondary school education. Most respondents began receiving prenatal care during their first trimester (76%) and were in their third trimester when surveyed (69%). Sixty-eight percent of respondents reported having at least one complication or illness during their current pregnancy, although only 10% were hospitalized. No significant

differences in demographic characteristics examined were observed between women accepting and women not accepting the pertussis vaccine (Table 1). Reported complications during pregnancy and sites of prenatal care are presented in Appendix 3.

Vaccine recommendations during pregnancy were predominantly for tetanus vaccination (78%) and influenza vaccination (50%) (Table 2). Only one woman was recommended for pertussis vaccination, and only three women for HPV vaccination; these women did not report receiving these vaccines. The most common sources of vaccine recommendations were general practitioners and nurses (Figure 1). Forty-five respondents (12%) received a vaccine recommendation from an obstetrician-gynecologist. No unadjusted associations were detected between any types or sources of vaccine recommendations and pertussis vaccine acceptance (Figure 1 & Table 2).

In terms of vaccines administered during their current pregnancy, 287 respondents (74%) received a tetanus vaccine while 174 (45%) received an influenza vaccine (Table 2). Ninety-one percent of women recommended for tetanus vaccination and 81% of women recommended for influenza vaccination received these vaccines, respectively. Among women with prior pregnancies, 183 (81%) received a tetanus vaccine during a prior pregnancy. In terms of childhood vaccination history, 103 women (27%) did not know whether they received the DTP vaccine as a child or adolescent (Table 2). Compared with women who knew that they received DTP during childhood or adolescence, women who did not know were significantly less likely to accept the pertussis vaccine (Table 2).

Among respondents, 328 (85%) rated doctors or nurses as a good source of vaccine information (Figure 2). In unadjusted analysis, compared with women giving

lower ratings, women rating doctors or nurses as good information sources were significantly more likely to accept pertussis vaccination (OR=1.92, 95% CI: 1.08-3.41). Rating each of mass media (OR=1.89, 95% CI: 1.22-2.93), pharmacy employees (OR=2.10, 95% CI: 1.09-4.05), the Secretary of Health of Mexico (OR=1.90, 95% CI: 1.12-3.22), and vaccine manufacturing companies (OR=1.74, 95% CI: 1.14-2.67) as good information sources was also associated with pertussis vaccine acceptance (Figure 2). No associations were detected between vaccine acceptance and perceptions of homeopathy or acupuncture providers, non-medical family and friends, or religious leaders.

Only 60 respondents (16%) had ever heard of pertussis/whooping cough/100-day-cough, and only 6 (2%) knew someone who has contracted this disease (Table 3). Women who had ever heard of the disease were more than twice as likely to accept pertussis vaccination (OR=2.11, 95% CI: 1.16-3.86). Conversely, women who didn't know what age was most likely to get the disease were less than half as likely to accept pertussis vaccination (OR=0.43, 95% CI: 0.27-0.68). No significant association was detected between vaccine acceptance and identifying newborns and infants <1 year old as most likely to get pertussis (Table 3).

More than 80% of both vaccine acceptors and non-acceptors would accept pertussis vaccination if recommended by an obstetrician-gynecologist (Figure 3). Seventy-one vaccine acceptors (32%) and 32 non-acceptors (19%) would accept pertussis vaccination if recommended by a general practitioner. Selecting a general practitioner recommendation as a reason to accept vaccination was significantly associated with pertussis vaccine acceptance (OR=1.95, 95% CI: 1.21-3.15).

The most frequently selected reasons to refuse pertussis vaccination were concerns that the vaccine might harm the unborn baby or might harm the pregnant woman (Figure 4). In unadjusted analysis, respondents who would refuse vaccination if they thought pertussis was not dangerous for a newborn were significantly less likely to accept pertussis vaccination during pregnancy (OR=0.45, 95% CI: 0.26-0.79). Unexpectedly, among reasons to refuse vaccination, we observed increased odds of vaccine acceptance associated with selecting concern of harming the unborn baby (OR=1.75, 95% CI: 1.16-2.63) or if their husband or spouse did not authorize it (OR=3.91, 95% CI: 1.11-13.75) (Figure 4). In an open-ended question about other reasons to refuse vaccination, 8 respondents (2%) stated that they would refuse if they did not have enough information.

We performed multivariate analysis examining perceptions of vaccine information sources in relation to vaccine acceptance. Variables pertaining to alternative healthcare providers (chiropractor, acupuncturist, etc.) were excluded; only 2 women received prenatal care from these providers and 26 participants (7%) did not rate their reliability for vaccine information. To resolve multicollinearity, we removed employment status from our model. We detected significant interaction between age and perceptions of religious leaders for vaccine information (P=0.03). All other interaction terms examined were non-significant.

We detected independent associations between vaccine acceptance and rating doctors or nurses as a good source of vaccine information (aOR=2.69, 95% CI: 1.29-5.61), as well as having ever heard of pertussis/whooping cough/100-day-cough (aOR=3.21, 95% CI: 1.47-7.01). No significant associations were detected between any

other model predictor and pertussis vaccine acceptance (Table 4). Fifty-five respondents (14%) were excluded from this multivariate model due to missing responses for one or more predictors. Among model predictors, excluded subjects were significantly less likely than included subjects to receive prenatal care at a pharmacy or medical office at work (2% vs. 11%, respectively; P=0.04), or to report any complications or illness during their current pregnancy (54% vs. 70%, respectively; P=0.02).

Response rates for health belief model questions were relatively low among respondents (84-92%). In unadjusted analysis, all dimensions were significantly associated with vaccine acceptance except for pertussis disease severity in a pregnant woman (Table 5). In multivariate analysis, three dimensions were independently associated with pertussis vaccine acceptance: rating the likelihood of a pregnant woman without vaccination contracting pertussis as probable, rating pertussis disease among newborns as severe, and rating pertussis vaccination for a pregnant woman as safe (Table 6). In our sensitivity analysis, excluded subjects were significantly less likely than included subjects to rate pertussis vaccination for a pregnant woman as safe (53% vs. 68%, respectively; P=0.02) or to rate the likelihood of a newborn acquiring pertussis as probable (58% vs. 70%, respectively; P=0.04).

DISCUSSION

In our study, only 57% of respondents were willing to accept booster vaccination against pertussis during pregnancy. Even among vaccine acceptors, more than half would refuse vaccination if they were concerned it would harm the fetus. Hence, implementation of Tdap vaccination during pregnancy may face resistance. On the other hand, among both

vaccine acceptors and non-acceptors, more than 80% would accept vaccination if recommended by an obstetrician-gynecologist. In multivariate analysis, we also found that positive perceptions of doctors or nurses for vaccine information and having ever heard of pertussis were independently associated with vaccine acceptance. Our findings may assist clinicians and public health officials in implementing Tdap vaccination programs during pregnancy.

Healthcare providers are important influences on vaccine decision-making. Prior studies have identified associations between provider recommendations and influenza vaccine uptake during pregnancy (15, 16). Our results suggest that obstetrician-gynecologist recommendations may strongly encourage vaccine acceptance among pregnant women, similar to another recent study (17). We also found that perceptions of information from healthcare providers influence vaccine decision-making, as observed elsewhere (18). Over 80% of respondents in our study rated doctors or nurses as a good vaccine information source, congruent with qualitative studies of healthcare provider perceptions among U.S. Hispanic/Latino populations (19-21).

Safety concerns are another determinant of vaccine acceptance (22). In an earlier study of postpartum Tdap acceptance in Taiwan, safety concerns about Tdap were associated with vaccine refusal (13). In our study, safety concerns were the most frequently selected reasons to refuse pertussis vaccination, and perceived vaccine safety for a pregnant woman was independently associated with vaccine acceptance. Patient education programs might increase Tdap uptake during pregnancy by emphasizing vaccine safety.

There are several limitations associated with this study. First, we obtained convenience samples of women receiving prenatal care from three public clinics. However, since these clinics are diverse in specialization, are located in three different boroughs of Mexico City, and handle different patient loads (between ~2,800 and ~8,300 annual births), they may capture diversity in patient experiences. Since our sampling was restricted to Mexico City, our findings could also have limited generalizability. On the other hand, U.S.-born and Mexico-born Hispanic populations may have similar awareness and uptake of vaccines, as one study found for seasonal influenza vaccination (23). Another potential limitation is that our sample was mostly low-income housewives, although immunization program planners may be interested in targeting low-income women for Tdap given existing socio-economic disparities in vaccination rates for influenza (24, 25) and HPV (26).

There are also important limitations of our statistical analysis. Unexpectedly, we observed positive bivariate associations between pertussis vaccine acceptance and two reasons to refuse vaccination (concern of harming the fetus and if their husband or spouse did not authorize it). While this directionality is implausible, we cannot necessarily infer confounding since we did not include these variables in our multivariate analysis. The precise relationship between study variables may also differ from our directed acyclic graph, which was used for variable specification. Nevertheless, our model controlled for a broad suite of potential confounders.

Additionally, we observed low response rates for some questionnaire items. Only 84-92% of respondents answered our health belief model questions, while 14% were excluded from our multivariate model examining perceptions of vaccine information

sources due to missing responses. Furthermore, in both multivariate models, we detected significant differences in select model predictors between subjects included and excluded from analysis. Hence, we interpret the results of our multivariate analyses with some caution.

As a final limitation, our study was conducted prior to widespread implementation of Tdap vaccination during pregnancy in the U.S. and Mexico. Knowledge and attitudes concerning Tdap may change as vaccination programs and education campaigns are initiated. Nonetheless, our results provide an important baseline assessment and may help in evaluating vaccine acceptance during future Tdap programs.

In conclusion, our study provides a timely assessment of prenatal Tdap vaccine acceptance and associated attitudes and beliefs prior to widespread introduction in the U.S. and Mexico. Encouraging healthcare providers (especially obstetrician-gynecologists) to discuss Tdap vaccination with patients, and strengthening public knowledge about pertussis and perceptions of healthcare providers for vaccine information, may increase vaccine acceptance among pregnant Hispanic/Latina women.

TABLES

Table 1: Demographic and clinical characteristics in relation to pertussis booster vaccine acceptance.

Variable	Sample *n = 387*	Accepted Vaccine (%) *n = 222*	Did Not Accept Vaccine (%) *n = 165*	*P*	OR[a]	95% CI
Age (n=381)						
< 24 years	194	112 (58%)	82 (42%)	0.92	1.04	0.70–1.57
≥ 24 years	187	106 (57%)	81 (43%)		(Ref)	
Education (n=383)						
Secondary school or below	184	102 (55%)	82 (45%)	0.47	0.85	0.57–1.28
Above secondary school	199	118 (59%)	81 (41%)		(Ref)	
Employment Status (n=386)						
Housewife	339	195 (58%)	144 (42%)	1.00	1.00	0.54–1.86
Other	47	27 (57%)	20 (43%)		(Ref)	
Income (n=331)						
No monthly income	288	171 (59%)	117 (41%)	0.32	1.40	0.73–2.65
Any monthly income	43	22 (51%)	21 (49%)		(Ref)	
Marital status (n=385)						
Married or cohabiting	294	171 (58%)	123 (42%)	0.63	1.14	0.71–1.83
Single or divorced	91	50 (55%)	41 (45%)		(Ref)	
Do you always visit the doctor when sick, regardless of being pregnant? (n=381)						
Yes	156	94 (60%)	62 (40%)	0.34	1.24	0.82–1.87
No	225	124 (55%)	101 (45%)		(Ref)	
Were you healthy before current pregnancy? (n=378)						
Yes	339	193 (57%)	146 (43%)	0.17	0.59	0.29–1.20
No	39	27 (69%)	12 (31%)		(Ref)	
Trimester of current pregnancy (n=385)						
1st trimester	25	12 (48%)	13 (52%)	0.55	0.70	0.31–1.59
2nd trimester	93	56 (60%)	37 (40%)		1.15	0.71–1.85
3rd trimester	267	152 (57%)	115 (43%)		(Ref)	
Is this your first pregnancy? (n=385)						
Yes	159	84 (53%)	75 (47%)	0.17	0.74	0.49–1.12
No	226	136 (60%)	90 (40%)		(Ref)	
When did you begin attending prenatal clinics during current pregnancy? (n=380)						
1st trimester	296	170 (57%)	126 (43%)	0.45	2.02	0.56–7.32
2nd trimester	74	45 (61%)	29 (39%)		2.33	0.60–8.97
3rd trimester	10	4 (40%)	6 (60%)		(Ref)	
Did you have any complications or illness during current pregnancy? (n=386)						
Yes	263	159 (60%)	104 (40%)	0.08	1.50	0.98–2.32
No	123	62 (50%)	61 (50%)		(Ref)	
Were you hospitalized during current pregnancy? (n=386)						
Yes	39	25 (64%)	14 (36%)	0.40	1.36	0.68–2.71
No	347	197 (57%)	150 (43%)		(Ref)	

[a] Unadjusted odds ratio comparing odds of accepting vs. not accepting pertussis booster vaccine during pregnancy if offered.

Table 2: Vaccine recommendations and administration in relation to pertussis booster vaccine acceptance.

Variable	Sample *n = 387*	Accepted Vaccine (%) *n = 222*	Did Not Accept Vaccine (%) *n = 165*	*P*	OR[a]	95% CI
During your medical visits, did any person (doctor, nurse or other) recommend vaccination? (n=384)						
Yes	316	180 (57%)	136 (43%)	0.79	0.93	0.55–1.58
No	68	40 (59%)	28 (41%)		(Ref)	
Did you receive a recommendation for tetanus vaccine? (n=387)						
Yes	302	175 (58%)	127 (42%)	0.71	1.11	0.69–1.81
No	85	47 (55%)	38 (45%)		(Ref)	
Did you receive a recommendation for influenza vaccine? (n=387)						
Yes	192	107 (56%)	85 (44%)	0.54	0.88	0.59–1.31
No	195	115 (59%)	80 (41%)		(Ref)	
Number of vaccinations received during current pregnancy (n=385)						
3+	54	37 (69%)	17 (31%)	0.30	1.55	0.77–3.14
2	144	81 (56%)	63 (44%)		0.92	0.55–1.55
1	91	48 (53%)	43 (47%)		0.80	0.45–1.42
0	96	56 (58%)	40 (42%)		(Ref)	
Did you receive tetanus vaccine during current pregnancy? (n=387)						
Yes	287	163 (57%)	124 (43%)	0.73	0.91	0.58–1.45
No	100	59 (59%)	41 (41%)		(Ref)	
If yes, in which trimester did you receive tetanus vaccine? (n=284)						
1st trimester	118	72 (61%)	46 (39%)	0.46	1.47	0.66–3.25
2nd trimester	135	73 (54%)	62 (46%)		1.10	0.51–2.41
3rd trimester	31	16 (52%)	15 (48%)		(Ref)	
If yes, did you have any adverse reaction to tetanus vaccine? (n=285)						
Yes	43	27 (63%)	16 (37%)	0.41	1.34	0.69–2.61
No	242	135 (56%)	107 (44%)		(Ref)	
Did you receive influenza vaccine during current pregnancy? (n=387)						
Yes	174	108 (62%)	66 (38%)	0.10	1.42	0.95–2.14
No	213	114 (54%)	99 (46%)		(Ref)	
If yes, in which trimester did you receive influenza vaccine? (n=173)						
1st trimester	58	38 (66%)	20 (34%)	0.63	1.90	0.49–7.35
2nd trimester	105	65 (62%)	40 (38%)		1.63	0.44–5.97
3rd trimester	10	5 (50%)	5 (50%)		(Ref)	
If yes, did you have any adverse reaction to influenza vaccine? (n=174)						
Yes	31	15 (48%)	16 (52%)	0.10	0.50	0.23–1.10
No	143	93 (65%)	50 (35%)		(Ref)	
Did you receive the DTP vaccine as a child or adolescent? (n=384)						
Don't know	103	50 (49%)	53 (51%)	0.06	0.59	0.37–0.93
Yes	270	166 (61%)	104 (39%)		(Ref)	
No	11	5 (45%)	6 (55%)		0.52	0.16–1.75
If yes, did you have any adverse reaction to DTP vaccine? (n=270)						
Yes	42	24 (57%)	18 (43%)	0.61	0.81	0.41–1.57
No	228	142 (62%)	86 (38%)		(Ref)	

Continued on next page…

Table 2: Vaccine recommendations and administration in relation to pertussis booster vaccine acceptance.

Variable	Sample *n = 387*	Accepted Vaccine (%) *n = 222*	Did Not Accept Vaccine (%) *n = 165*	*P*	OR[a]	95% CI
Did you receive tetanus vaccine during prior pregnancy? (n=385)						
Yes	183	116 (63%)	67 (37%)	0.06	1.99	1.02–3.89
No	43	20 (47%)	23 (53%)		(Ref)	
N/A (first pregnancy)	159					
If yes, did you have any adverse reaction to tetanus vaccine during prior pregnancy? (n=181)						
Yes	32	17 (53%)	15 (47%)	0.23	0.61	0.28–1.31
No	149	97 (65%)	52 (35%)		(Ref)	

[a] Unadjusted odds ratio comparing odds of accepting vs. not accepting pertussis booster vaccine during pregnancy if offered.

Table 3: Pertussis disease knowledge in relation to pertussis booster vaccine acceptance.

Variable	Sample *n = 387*	Accepted Vaccine (%) *n = 222*	Did Not Accept Vaccine (%) *n = 165*	*P*	OR[a]	95% CI
Have you ever heard of whooping cough/pertussis/100-day-cough? (n=381)						
Yes	60	43 (72%)	17 (28%)	0.02	2.11	1.16–3.86
No	321	175 (55%)	146 (45%)		(Ref)	
Do you know someone who has contracted this disease? (n=382)						
Yes	6	3 (50%)	3 (50%)	1.00	0.75	0.15-3.76
No	376	215 (57%)	161 (43%)		(Ref)	
Who do you think is most likely to get this disease? (n=380)						
Newborns and infants <1yo	62	45 (73%)	17 (27%)	<0.001	0.58	0.79–2.82
Don't know	143	62 (43%)	81 (57%)		0.43	0.27–0.68
Other ages or any person	175	112 (64%)	63 (36%)		(Ref)	

[a] Unadjusted odds ratio comparing odds of accepting vs. not accepting pertussis booster vaccine during pregnancy if offered.

Table 4: Results of multivariate logistic regression model for perceptions of vaccine information sources in relation to pertussis booster vaccine acceptance among n=332[a] respondents.

Model Parameter	aOR[b]	95% CI
Vaccine information sources rated as good		
Doctor or nurse	2.69	1.29–5.61
Mass media	1.63	0.90–2.95
Non-medical family or friends	0.43	0.18–1.03
Pharmacy employees	2.17	0.81–5.79
Religious leaders; <24 years old	3.54	0.36–35.11
Religious leaders; ≥24 years old	0.30	0.07–1.21
Secretary of Health of Mexico	1.73	0.84–3.55
Vaccine manufacturing companies	1.62	0.92–2.85
Vaccines recommendations received during current pregnancy		
Influenza vaccine	1.10	0.62–1.93
Tetanus vaccine	1.51	0.68–3.36
Sources of vaccine recommendations received during current pregnancy		
General practitioner	0.69	0.36–1.33
Mass media	1.10	0.15–8.27
Nurse	0.66	0.36–1.21
Obstetrician-gynecologist	0.79	0.32–1.91
Other pregnant women	0.23	0.04–1.20
Social worker	1.68	0.28–10.30
Sites of prenatal care during current pregnancy		
Community health center	0.73	0.36–1.49
Doctor's office	0.62	0.29–1.32
Hospital	1.66	0.78–3.55
Pharmacy or medical office at work	1.05	0.44–2.47
Trimester of current pregnancy (ref=3rd trimester)		
1st trimester	0.45	0.16–1.29
2nd trimester	1.34	0.73–2.47
Health Status		
Healthy before current pregnancy	0.58	0.24–1.39
Experienced at least one complication or illness during current pregnancy	1.72	0.98–3.01
I was hospitalized during current pregnancy	0.85	0.35–2.04
Knowledge of Pertussis		
Ever heard of pertussis/whooping cough/100-day cough	3.21	1.47–7.01
Demographic variables		
Age (<24 years old); religious leaders rated as good source of vaccine information	3.54	0.36–35.11
Age (<24 years old); religious leaders rated as bad or neither bad nor good source of vaccine information	1.05	0.63–1.74
Education level (secondary school or below)	0.90	0.53–1.51
Marital status (married or cohabiting)	1.02	0.58–1.82

[a] 55 subjects were excluded due to missing responses for one or more model predictors.

[b] Adjusted odds ratio comparing odds of accepting vs. not accepting pertussis booster vaccine during pregnancy if offered, controlling for other model predictors.

Table 5: Health belief model dimensions in relation to pertussis booster vaccine acceptance.

Variable	Sample *n = 387*	Accepted Vaccine (%) *n = 222*	Did Not Accept Vaccine (%) *n = 165*	*P*	OR[a]	95% CI
Likelihood of an unvaccinated pregnant woman acquiring pertussis (n=351)						
Probable	187	131 (70%)	56 (30%)	<0.001	2.92	1.88–4.52
Improbable or neither probable nor improbable	164	73 (45%)	91 (55%)		(Ref)	
Likelihood of a newborn acquiring whooping cough (n=353)						
Probable	238	157 (66%)	81 (34%)	<0.001	2.43	1.54–3.84
Improbable or neither probable nor improbable	115	51 (44%)	64 (56%)		(Ref)	
Severity of pertussis in an unvaccinated pregnant woman (n=326)						
Severe	177	108 (61%)	69 (39%)	0.50	1.18	0.76–1.84
Mild or moderate	149	85 (57%)	64 (43%)		(Ref)	
Severity of pertussis in a newborn (n=328)						
Severe	230	148 (64%)	82 (36%)	0.01	1.88	1.16–3.04
Mild or moderate	98	48 (49%)	50 (51%)		(Ref)	
Protection against pertussis conferred by vaccination for a pregnant woman (n=357)						
Protected	274	182 (66%)	92 (34%)	<0.001	3.15	1.90–5.24
Unprotected or neither protected nor unprotected	83	32 (39%)	51 (61%)		(Ref)	
Protection against pertussis for a newborn conferred by vaccination during pregnancy (n=349)						
Protected	268	175 (65%)	93 (35%)	<0.001	2.60	1.57–4.32
Unprotected or neither protected nor unprotected	81	34 (42%)	47 (58%)		(Ref)	
Safety of pertussis vaccination for a pregnant woman (n=352)						
Safe	229	159 (69%)	70 (31%)	<0.001	3.55	2.24–5.61
Unsafe or neither safe nor unsafe	123	48 (39%)	75 (61%)		(Ref)	
Safety of pertussis vaccination during pregnancy for an unborn baby (n=351)						
Safe	257	174 (68%)	83 (32%)	<0.001	3.23	1.98–5.27
Unsafe or neither safe nor unsafe	94	37 (39%)	57 (61%)		(Ref)	

[a] Unadjusted odds ratio comparing odds of accepting vs. not accepting pertussis vaccine during pregnancy if offered.

Table 6: Results of multivariate logistic regression model for health belief model dimensions in relation to pertussis booster vaccine acceptance among n=273[a] respondents.

Model Parameter	aOR[b]	95% CI
Perceived susceptibility		
Probable likelihood of a pregnant woman without vaccination acquiring pertussis	1.92	1.06–3.46
Probable likelihood of a newborn acquiring pertussis	1.49	0.76–2.92
Perceived severity		
Severe disease if a pregnant woman without vaccination acquired pertussis	0.53	0.28–1.01
Severe disease if a newborn acquired pertussis	2.21	1.15–4.23
Perceived benefits		
A pregnant woman would be protected if she was vaccinated against pertussis	1.92	0.92–4.03
A newborn would be protected if their mother was vaccinated against pertussis during pregnancy	1.01	0.42–2.45
Perceived barriers		
Vaccine against pertussis is safe for a pregnant woman	2.85	1.42–5.70
Vaccine against pertussis is safe for an unborn baby if their mother was vaccinated during pregnancy	1.15	0.46–2.86

[a] 114 subjects were excluded from due to missing responses for one or more model predictors.

[b] Adjusted odds ratio comparing odds of accepting vs. not accepting pertussis vaccine during pregnancy if offered, controlling for other model predictors.

FIGURES

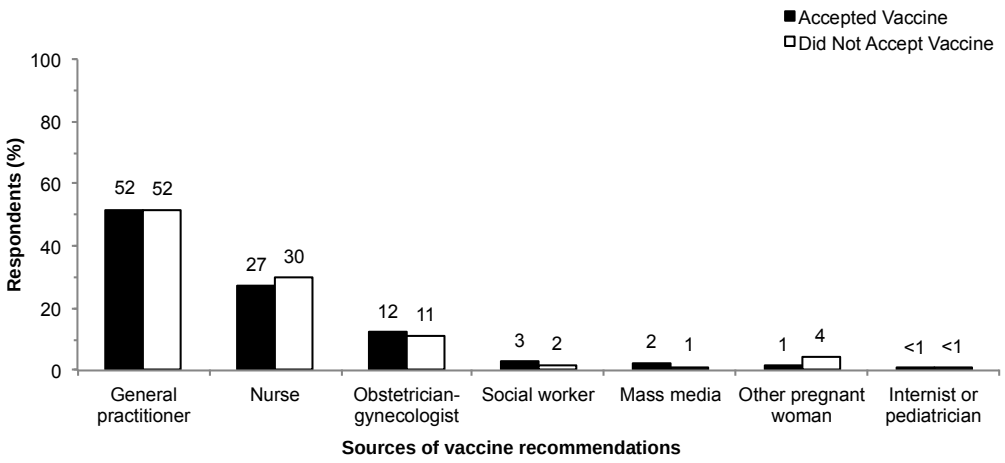

Figure 1: Sources of vaccine recommendations received during current pregnancy stratified by pertussis booster vaccine acceptance.

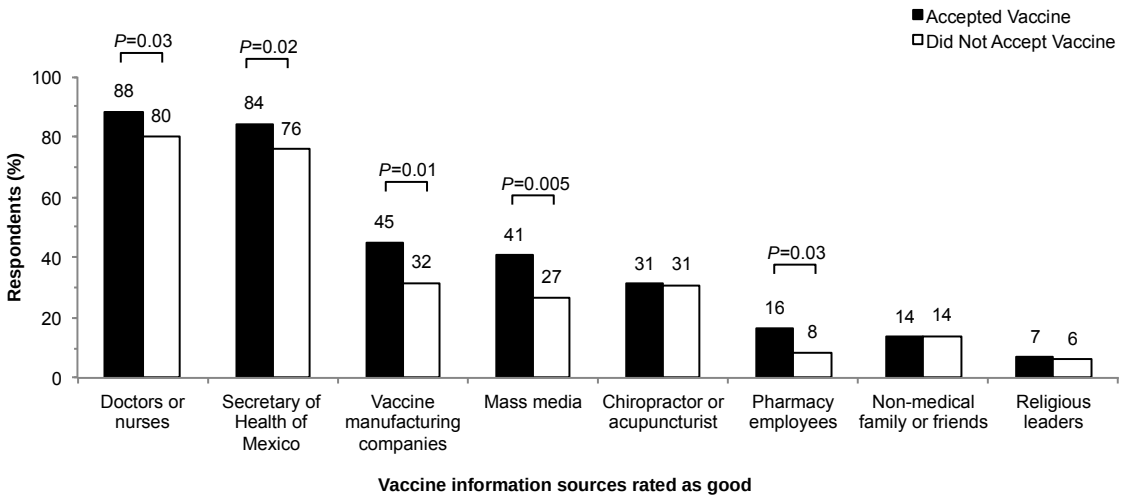

Figure 2: Vaccine information sources rated as good (vs. bad or neither bad nor good) stratified by pertussis booster vaccine acceptance. Significant associations were detected between pertussis vaccine acceptance and perceptions of doctors or nurses, mass media, pharmacy employees, Secretary of Health of Mexico and vaccine manufacturing companies for vaccine information.

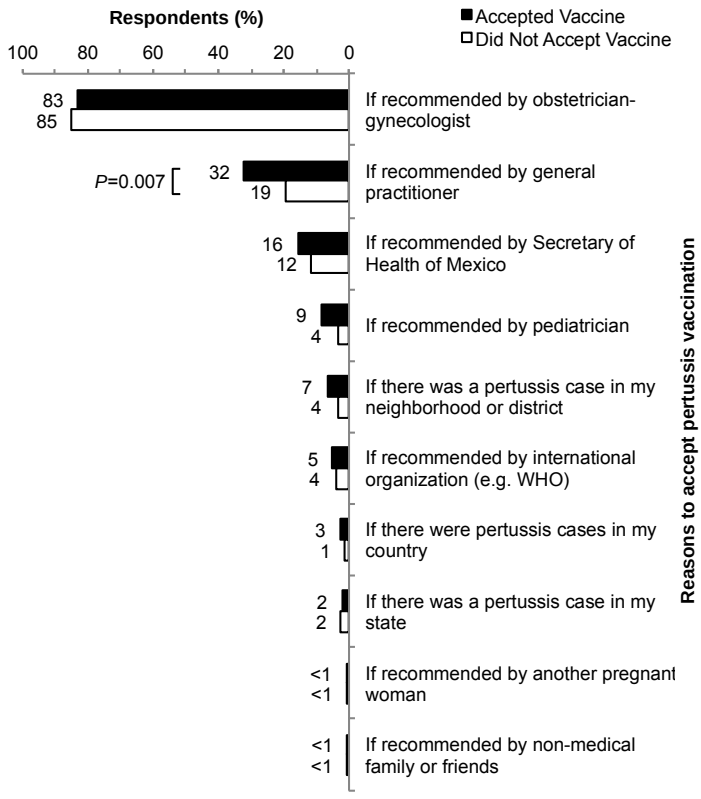

Figure 3: Reasons to accept pertussis booster vaccination stratified by vaccine acceptance. Significant associations were detected between vaccine acceptance and selecting recommendations from a general practitioner as a reason to accept vaccination.

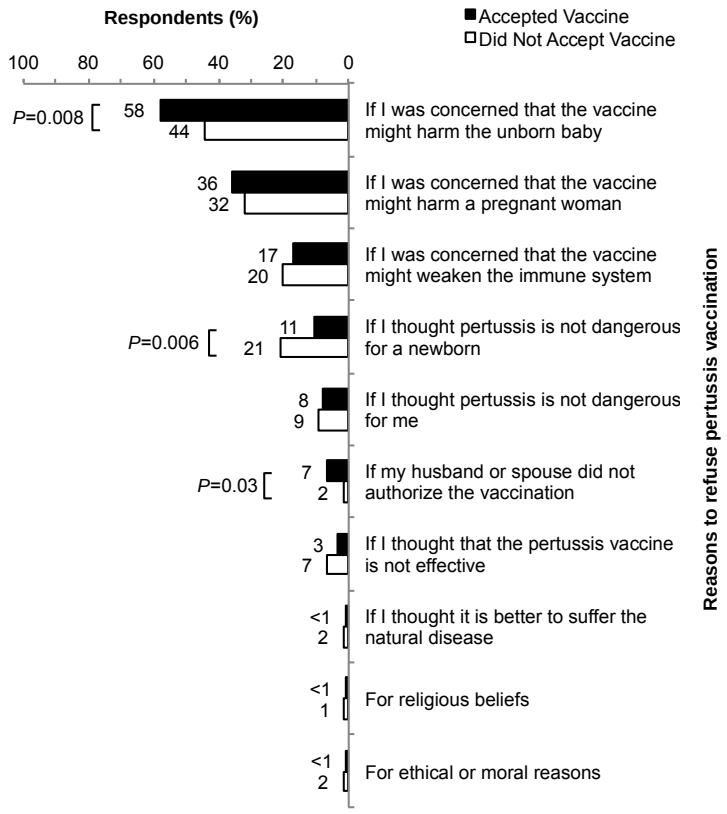

Figure 4: Reasons to refuse pertussis booster vaccination stratified by vaccine acceptance. Significant associations were detected between pertussis vaccine acceptance and selecting husband or spouse authorization, lack of danger of whooping cough for a newborn, or concern of vaccine safety for an unborn baby as reasons to refuse vaccination.

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CHAPTER III:

PUBLIC HEALTH IMPLICATIONS

New approaches are needed to prevent severe infant pertussis cases. The U.S. Advisory Council on Immunization Practices (ACIP) and National Immunization Council of Mexico (CONAVA) recently issued recommendations for Tdap booster vaccination during pregnancy. However, there remains an outstanding need for strategic, evidence-based approaches to implement these recommendations. Tdap vaccination programs should address patient barriers and vaccine hesitancy to achieve high vaccine coverage.

Our results suggest that vaccine program planners should focus on educating pregnant women about pertussis disease and emphasizing Tdap vaccine safety. Patients should understand the susceptibility of pregnant women to acquire pertussis infection (even if vaccinated during childhood), and the severity of infant pertussis cases. Program planners should also encourage women to consult with their doctor (particularly their obstetrician-gynecologist) about Tdap vaccination, even before pregnancy. Physician education initiatives to promote Tdap should also be implemented, given the apparently strong influence of obstetrician-gynecologists on pertussis vaccine decision-making.

If low acceptance rates persist once Tdap programs are fully implemented, our results may help guide research to understand Tdap vaccine hesitancy and patient barriers. Future research should examine the determinants of perceptions of doctors and nurses for vaccine information, given their apparently strong association with vaccine decision-making. Among other determinants, it may be valuable to examine how prior vaccine recommendations shape patient perceptions of healthcare providers. This research may inform clinician guidelines for delivering Tdap vaccine recommendations. Future research should also explore patient safety concerns over Tdap. In our study,

despite few women previously encountering Tdap vaccines, we identified safety concerns as a major factor in vaccine hesitancy.

Finally, it would be valuable to conduct binational studies of Tdap vaccine acceptance among Hispanic/Latina populations in both the U.S. and Mexico. The social and economic contexts for pregnant women, which may shape knowledge and attitudes concerning vaccination, differ between the two countries. A binational study would help clarify the applicability of our findings in understanding Tdap vaccine decision-making among Hispanic/Latina women in the U.S.

APPENDICES

APPENDIX 1: Directed acyclic graph (DAG) of study variables.

Figure A1: Directed acyclic graph of study variables for multivariate model examining perceptions of vaccine information sources. Using this figure, we identified potential confounders (*) of the association between perceptions of vaccine information sources (bold, center) and pertussis vaccine acceptance (bold, right) to include in our multivariate model.

APPENDIX 2: Letter of exemption from review – Emory IRB.

EMORY UNIVERSITY | Institutional Review Board

August 2, 2012

Aiden Varan
Rollins School of Public Health
Atlanta, GA 30322

RE: Determination: No IRB Review Required
Data analysis of investigation of Bordetella pertussis booster vaccine acceptance among pregnant women living in Mexico City
PI: Varan

Dear Aiden:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition of a study involving "human subjects" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will analyze data obtained from questionnaires previously administered in Mexico City among pregnant women regarding their pregnancy and vaccine histories. Your team will not have access to personal identifiers of any kind in performing this study.

HHS regulations define *human subject* at 45 CFR 46.102(f) as follows:

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) data through intervention or interaction with the individual, or
(2) identifiable private information.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Sam Roberts, CIP
Research Protocol Analyst
This letter has been digitally signed

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu

APPENDIX 3: Supplementary information on study population.

The most frequent complications reported during pregnancy among respondents were vaginal or urinary tract infection and threatened miscarriage (Figure A2). Few respondents (<10%) reported asthma, gestational diabetes, hypertension/preeclampsia, respiratory infection or threatened preterm labor during their current pregnancy. No subjects reported cardiovascular complications. No significant associations were detected between any complication during current pregnancy and pertussis vaccine acceptance (Figure A2).

Most women received prenatal care during their current pregnancy at a hospital or community health clinic (Figure A3). Only two respondents received prenatal care from a homeopath or acupuncturist. Receiving prenatal care at a hospital was significantly associated with pertussis vaccine acceptance (OR=1.86, 95% CI: 1.09-3.18). No other significant associations were detected between sites of prenatal care and pertussis vaccine acceptance (Figure A3).

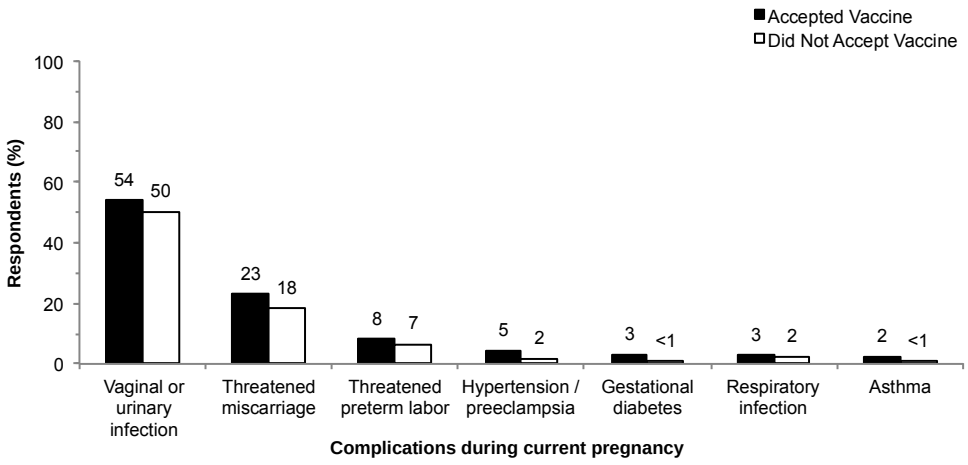

Figure A2: Complications or illnesses during current pregnancy stratified by pertussis vaccine acceptance.

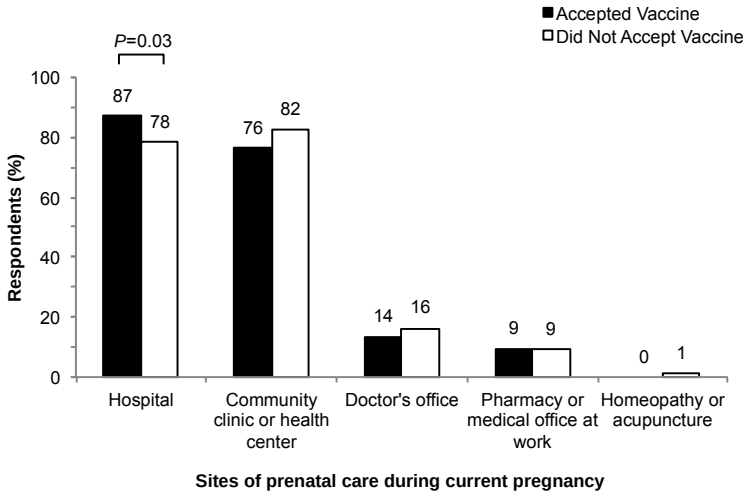

Figure A3: Sites of prenatal care received during current pregnancy stratified by pertussis vaccine acceptance. Receiving prenatal care at a hospital was significantly associated with pertussis vaccine acceptance.