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Jannat Saini Date

Evaluating the Impact of Package Inserts on Vaccine Prescribing Habits of Obstetricians/Gynecologists for Pregnant Women in the United States

By

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Master of Public Health

Department of Global Health

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Evaluating the Impact of Package Inserts on Vaccine Prescribing Habits of Obstetricians/Gynecologists for Pregnant Women in the United States

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Jannat Saini

PharmD, University of Rhode Island, 2017

Faculty Thesis Advisor: Dr. Saad B. Omer, MBBS MPH PhD

An abstract of

A thesis submitted to the Faculty of the

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Abstract

Background:

In the United States, gaps exist between the overlap of national guidelines' maternal vaccination recommendations and the indications listed in Food and Drug Association (FDA) package inserts for those vaccinations. Certain vaccines, while strongly recommended by national and international bodies, were classified as Category B drugs ('*animal studies failed to find fetal risk, inadequate studies in pregnant women*'). Recently, the FDA amended the Pregnancy Category rule of package inserts with the Pregnancy and Lactation Labeling Rule (PLLR). Effectively communicated recommendations from obstetricians/gynecologists are important in improving the awareness and uptake of maternal vaccination, however, there is insufficient general understanding of vaccine recommendations and labeling among providers.

Objectives:

To examine the extent to which providers utilize package inserts to make maternal vaccine recommendations, and compare how different vaccine package insert statements and labeling affect their perceptions regarding safety and effectiveness of vaccines during pregnancy.

Methods:

A cross-sectional survey was mailed to a random sample of 800 American College of Obstetricians and Gynecologists (ACOG) Fellows in the United States in March 2019. The survey evaluated providers' attitudes about vaccine inserts and asked whether they'd recommend a vaccine following sample package insert statements with both Pregnancy Categories and the Pregnancy Lactation and Labeling Rule.

Results:

Currently, 303 of 762 surveys mailed have been received (Response Rate = 39.8%). The majority (90.7%) of providers recommended and/or administered maternal vaccination, with very few respondents (7.0%) reading package inserts for information regarding it. After reading sample insert statements, Pregnancy Lactation and Labeling Rule (47%) complying inserts were not as highly recommended as Pregnancy Category inserts (88%). Thematic analyses of open-ended responses showed provider doubt in vaccine manufacturers and inserts.

Conclusions:

Our study suggests providers do not actively consider package inserts in maternal vaccination decision-making. Providers were more likely to prefer using the old Pregnancy Categories rule instead of PLLR. Although there is value in providing more data, improved communication style may be needed in inserts. Collaborative efforts are necessary to update inserts with recent clinical practices for pregnancy and reduce the apprehensiveness around package inserts to generate safer and more cognizant recommendations for pregnant women.

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Chapter I. Background and Literature Review

A. Burden of Influenza and Pertussis Disease among Pregnant Women and Their Infants

a. Pregnant Women

Pregnant women and their infants have an increased vulnerability to certain infections, which causes higher morbidity and mortality. Physiological and immunological changes during pregnancy not only increase susceptibility to certain diseases, but may also increase the risk of exacerbating other diseases.[1] Alterations in cell-mediated immunity as a result of pregnancy have lead mothers to have inadequate responses to viral infections such as influenza.[2] Steroid hormones, for example estrogens and progesterone, gradually increase in concentration during pregnancy, leading to a change in the occurrence of pro-inflammatory and anti-inflammatory responses; the pro-inflammatory phase in the first trimester contributes to changes such as morning sickness, and the anti-inflammatory changes in the second and third trimester, which are important to get the mother ready for delivery, can cause more severe outcomes from diseases such as influenza, malaria, and lupus (diseases caused by inflammatory responses).[1]

i. Pregnancy and Influenza

According to the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), an estimated 11% of pregnant women are exposed to influenza each season.[3,4] Rising heart rates, stroke volume, and oxygen consumption levels, as well as diminished pulmonary capacity, are some examples of cardiopulmonary changes during pregnancy. These factors play a part in furthering the severity of influenza in this population. During the 2009 – 2010 H1N1 pandemic,

pregnant women were only ~1% of the population at risk, but represented 5% of all influenza-related deaths.[5]

b. Infants

During the first few months of life, infants are susceptible to some vaccine-preventable diseases. This is in part due to the immunity gap that occurs since their immunization schedules can only begin once they reach 2 months of age in high- and middle-income nations (including the United States (US)), and 6 weeks of age in the majority of low-income nations. The initial vaccination schedule is incomplete before 6 months of age for infants in nearly all high- and middle-income countries, or 14 weeks in most low-income countries. As a result, infants do not receive optimal coverage until they are several months old.[6,7] This susceptibility gap can be solved by maternal vaccination owing to the transmission of antibodies from the mother to the developing fetus and the newborn – both transplacentally and subsequently, through breastmilk – resulting in the infants acquiring antibodies against vaccine-preventable diseases such as influenza, tetanus and pertussis.[7,8] The concentrations of antibodies in infants at birth are associated with those of the mother. At the same time, levels of maternal antibodies are often insufficient to confer complete immunity to the infant, and start declining and diminish over approximately six months from the time of birth. Maternal vaccination thus increases the concentrations of antibodies that are passively transferred to the fetus, and provides protective coverage until infants can be immunized, or until they are not substantially immunosuppressed.[1,9]

i. Infancy and Influenza

Newborns born to mothers with influenza have a higher risk of detrimental neonatal outcomes such as low birth weight, preterm delivery, or being stillborn.[5] The "Barker Hypothesis" states that influenza infections or other distresses *in utero* have the potential to cause persistent pathological consequences through adulthood.[10] In addition, the risk of hospitalization due to influenza is higher in infants <6 months of age versus older children, or the elderly.[11,12] This risk is considerably higher since no influenza vaccine is licensed to be used in children in this age group.[13]

ii. Infancy and Tetanus, diphtheria, & pertussis

Infections due to tetanus and diphtheria are uncommon in industrialized countries such as the US, and scheduled immunization for tetanus, pertussis and diphtheria is routinely administered. Tetanus occurs in developing countries in newborns or mothers following childbirth under unsanitary circumstances.[14] When compared with the late 1980s, vaccination has helped reduce neonatal tetanus by 96%. However, according to reports published by the WHO, an estimated 34,000 newborns nevertheless died due to the disease in 2015.[15]As of June 2017, 16 countries were yet to reach the goal of <1 case of neonatal tetanus per 1,000 live births.[15] Pertussis, on the other hand, is a highly infectious bacterial disease, causing acute respiratory infection.[16] Adults can develop symptoms, however, newborns ≤ 3 months are overwhelmingly affected by this disease.[17] They are the most susceptible to the infection and have the highest morbidity and mortality rates.[18] Infants are not vaccinated against pertussis until they are two months old, and are critically dependent on their family members and caregivers for protective immunity against pertussis (a "cocoon" of protection).[16] Starting in 2006, the ACIP endorsed

"cocooning", or the vaccination of postpartum women, all other family members, and caregivers.[19] However, this has proven difficult to implement on a larger scale, and inadequate as a sole strategy to prevent pertussis in newborns.[20]

B. Benefits of Maternal Immunization

a. Safety and Efficacy of the Influenza Vaccine

The possibility of severe infection due to influenza is greater in pregnant women compared with women of reproductive age who are not pregnant. This is due to changes occurring in organs such as their heart, lungs and immune system, which make them more prone to severe illness and hospitalization. Such risks are reduced by 50% due to vaccination against influenza during pregnancy.[20]A retrospective trial which enrolled 245,386 women and 249,387 infants revealed that within the first 6 months of life, infants born to mothers who were vaccinated had a 64% reduced risk for influenza-like illness, a 70% reduced risk for influenza confirmed in the laboratory, and an 81% reduced risk for hospitalizations related to influenza.[21] Studies have also shown an associated reduced incidence of acute respiratory illness related-hospitalization in infants who are aged <6 months and maternal vaccination against influenza.[22] Maternal influenza immunization can also reduce the risk of infection being spread from the mother to the infant, and in turn cause antibodies to transfer to the infant through breastfeeding.[23] In the US, among infants aged <6 months, the vaccine was observed to be 45 – 92% effective in the prevention of hospitalizations associated with seasonal influenza.[24,25] In South Africa, Mali, Nepal and Bangladesh, four randomized, controlled trials evaluated the efficacy of inactivated influenza vaccine during pregnancy in preventing laboratory-confirmed maternal and infant infection.[26,27] Efficacy ranged from 30% in Nepal, to 63% in

Bangladesh.[27,28,29,30,31] Maternal influenza immunization was associated with protective effects against low birth weight in the Nepalese (43g higher mean birth weight in newborns of vaccinated mothers versus controls) and Bangladeshi trials (193g higher mean birth weight in maternal vaccination group versus controls).[30,31] No association was seen in the South African and Malian trials.[28,32] The Nepalese trial had the least opportunity for a type II error, and administered the vaccination between 17 – 34 weeks of gestation, increasing the likelihood of influencing fetal growth and weight gain.[2,7] Increased risk of fetal death, unplanned abortion, or congenital malformations was not observed with the vaccination.[1] In addition, influenza infection has a potential synergistic effect with other bacterial infections, especially pneumococcal infections. [7,33] Studies have seen higher efficacy of pneumococcal conjugate vaccination in early infancy if their mothers had received inactivated influenza vaccine during pregnancy.[34,35] There have been no links found between vaccination with both adjuvanted or unadjuvanted pandemic influenza vaccines, and increased risk of spontaneous abortion, genetic abnormalities, stillbirth, early neonatal disease, or later mortality.[36,37] An exception to this was a modest association, seen in a US database analysis, between spontaneous abortion and receiving inactivated influenza vaccine (IIV) containing pH1N1 within 28 days in women who were injected with the vaccine in the prior influenza season.[38]

b. Safety and Efficacy of the Tdap Vaccine

The administration of maternal Tdap vaccination has proven to be safe as well as immunogenic, since there have been no accounts of acute safety incidents in the mother, or increased maternal or infant risks.[39,40] In the United Kingdom (UK), the likelihood of having confirmed pertussis infections was lower in infants born to mothers receiving

Tdap vaccination during the course of their pregnancy, along with a higher likelihood of decreased hospitalizations due to pertussis compared with those born to mothers who were not vaccinated with Tdap during pregnancy.[41] Higher quantities of pertussis antibodies in the infant (remaining at 2 months of age)[42,43] and the cord blood were also seen with maternal immunization, and were linked with protection against pertussis.[44] In these infants, effectiveness of Tdap against pertussis was 90-93%.[45,46] A 51% relative reduction in cases of pertussis was seen in Argentina in states with Tdap coverage of ≥ 50% versus ≤50% in the same age group.[47] It was not associated with fetal or maternal hazards, with the only exception being a slightly higher risk of chorioamnionitis seen in a retrospective database analysis.[48] In the US, however, many fevers during the third trimester are labeled as chorioamnionitis due to litigation concerns.[7] For preventing pertussis infection with Tdap vaccination in infants <8 weeks of age, vaccinating at 27-36 weeks of gestation has shown to be 85% more effective than administering the vaccine postpartum.[49] In addition, enacting a program supporting maternal tetanus immunization in countries with a high prevalence of neonatal tetanus showed a 94% decrease in neonatal mortality.[50,51,52] In a study using administrative and surveillance data, the vaccine was 91% effective in preventing pertussis in young infants, and in a case-control study, it was 93% effective. [41,53] Besides the theoretical concern of vaccine-induced maternal antibodies reducing the immunogenicity of infant diphtheria-tetanus-pertussis (DPT) vaccine, studies have shown no increase in acute events (local reactions, fever, or allergy), or in adverse birth outcomes (preterm delivery, small size corresponding to gestational age, or low birth weight) connected to the time since earlier receipt of the vaccine containing tetanus.[7,54]

C. Vaccine Recommendations and Uptake

a. Influenza

The administration of maternal influenza vaccination has proven to be an effective approach in guarding infants <6 months from influenza-like illness, influenza-related hospitalizations, and additional secondary advantages, such as a reduction in number of infants with low birth weight, a lower rate of preterm birth, and other improved outcomes.[6] In the 1960s, the ACIP first recommended that the inactivated influenza vaccine should be administered during pregnancy in women with high-risk conditions. In 2004, this advice was updated to include women who might become pregnant during the influenza season, and extended to pregnant women during any trimester.[6,55] The American College of Obstetricians and Gynecologists (ACOG) recommends that the inactivated influenza vaccination be given with each influenza season as soon as the vaccine is available, in any trimester.[56] In 2012, after witnessing the increased complication risk throughout the H1N1 pandemic, the World Health Organization (WHO) recommended that all pregnant women should receive the influenza vaccine irrespective of pregnancy trimester, identifying pregnant women as the main target population for countries trying to introduce or grow programs for seasonal influenza immunization.[57] In 2014, 59% of all member states of the WHO confirmed having a policy for nationwide influenza vaccination, with 42% having a policy directed towards pregnant women.[58] During the 2017 – 2018 influenza season, 36.8% of pregnant women in the US were immunized against influenza during pregnancy.[55] This suggests moderate uptake compared with the Healthy People 2020 goal of 80%.[16] Levels of vaccination in this priority group are persistently at much lower rates than countrywide goals globally as

well (the UK being at 40 – 65%, with other European countries at <25%, and Hong Kong at <2%) barring countries like Brazil and Argentina (~95%).[1]

b. Tetanus, diphtheria, pertussis

Since 2012, pertussis vaccination has been recommended in the US and the UK for every pregnancy, to try to decrease the number of infants who cannot yet be vaccinated, being infected with pertussis.[1,7] According to the ACOG and American Academy of Pediatrics (AAP) guidelines, maternal vaccination is most optimal at 27 to 36 weeks of gestation, to maximize antibody transfer and immunity for the newborn.[56] The WHO advises national programs to additionally consider vaccinating pregnant women with one dose of Tdap in the second or third trimester, ≥ 15 days before the end of pregnancy, when infant infection or death due to pertussis disease is elevated or rising.[1] An observational study conducted in the US from 2007 – 2013, which looked at 438,487 live births, discovered that out of all enrolled mothers, only 14% were administered the Tdap vaccine while pregnant.[6] In the US, an online survey conducted by the CDC during 2017 – 2018 showed that 54.4% of women with a live birth received Tdap during pregnancy. Only 32.8% of women received both influenza and Tdap.[55]

D. Roadblocks to Maternal Vaccination in the United States

a. Barriers to Vaccine Uptake in Pregnancy

Both healthcare providers (HCPs) and patients are often reluctant to consider vaccinations in pregnancy due to a variety of reasons. One barrier is the perception of lack of clinical safety data due to underrepresentation of pregnant women in clinical trials, and contradictions between national guidelines, centered on postmarketing reports, and FDA vaccine package inserts, based on pre-licensure clinical studies.[59,1] Besides

barriers to the inclusion and retention of pregnant women in clinical trials (structural and policy issues, lack of investigator or research study-team outreach to providers in the community, transportation and access barriers, lack of social approval and support from family and friends, and personal issues), there are several obstacles to vaccine uptake in pregnancy.[60] According to the WHO, barriers also include generalizability of safety research, and assimilation of large safety datasets.[61] The WHO Strategic Advisory Group of Experts (SAGE) on Immunization also raised concerns regarding overly precautionary language in vaccine safety in pregnancy, which has the potential to contribute to hesitancy.[62] Legal barriers such as the "one – petition rule" and the Vaccine Injury Compensation Program (VCIP) being silent on claims concerning adverse effects *in utero*, as well as those possibly related to newer vaccinations, also play a part.[6] Other difficulties include poor awareness of disease risk, belief that vaccines are not necessary, prior vaccination behavior and issues related to delivery of vaccinations.[1] In the US, during the 2017-2018 influenza season, the most frequently stated reason for not receiving the influenza vaccination before or during pregnancy was the opinion that the 'vaccine is ineffective'. The most common reason for not receiving Tdap was a 'lack of knowledge about needing the vaccine during each pregnancy', and the second most common reason for not receiving both vaccinations was 'concern of safety risks to the baby'.[55]

i. The Role of Obstetricians/Gynecologists (OB/GYNs)

In the US, during the 2017-2018 influenza season, influenza vaccination coverage in pregnant women improved with an increasing number of provider visits since July 1, 2017 – from 18.1% (0 visits) to 56.8% (>10 visits).[55] Vaccination coverage in pregnant

women who received a provider offer of Tdap was 73.5%, while in women who received no recommendation it was 1.6%. Referring patients to a vaccination provider facilitated improved coverage, particularly for Tdap.[55] Results from a survey conducted by ACOG showed that often times although providers believe they are providing a vaccine recommendation, it might not be strong enough to be remembered by patients. It is important for OB/GYNs to communicate the importance of vaccination effectively.[55] Over 98% of women in the US have at least one prenatal visit, which provides an opportunity for vaccination or at least vaccine counseling.[63] Additionally, providers are gatekeepers to clinical research, and when that research involves pregnant women, OB/GYNs are those gatekeepers. Studies have shown that active engagement of medical providers is important in improving the recruitment and retention of pregnant women in clinical trials.[6, 60] Among clinicians who provide obstetric care, there is insufficient general understanding of new labeling, and to have increased confidence in pregnancy-related vaccines, collaborative efforts need to be put in place.[61] Effectively communicated recommendations from OB/GYNs are important in improving awareness and the uptake of maternal vaccination.[1]

b. Considerations for Pregnant Women in Clinical Trials

From a regulatory perspective, most studies describing the use, safety, and efficacy of a number of vaccines during pregnancy are observational, and provide limited ability to study safety and efficacy.[64] Most information on vaccine safety is acquired from passive surveillance systems such as Vaccine Adverse Event Reporting System (VAERS), while active surveillance systems are utilized infrequently to gather information directly from women who were recently vaccinated.[1] Inadequate or nonclinical postmarketing data is

available from the first and early second semester, or from randomized clinical trials.[59,61] Women of childbearing age have historically been excluded from participation in clinical trials, leading to a dearth of data on best practices to recruit and retain pregnant women in studies.[60] Certain vaccines licensed in the US are recommended by organizations such as ACOG and ACIP for use during pregnancy. However, based on regulations from the US Federal Drug Administration (FDA), pre-licensure maternal immunization trials conducted in the US are needed in order to study efficacy and safety in pregnancy. This would allow prescribing information to include an indication and usage statement specifically for pregnancy. It is important to note, however, that the lack of a specific statement as such does not impede use of licensed vaccinations in pregnancy (i.e., this is not "off-label use"). Exclusionary criteria set by Institutional Review Boards (IRB) and federal guidelines have added to barriers to pregnant women in clinical studies. The Code of Federal Regulations, Title 45 (45 CFR 46, Subpart B), established in 2009, instructs trials to include pregnant women.[60] Prior to the inclusion of pregnant women in Phase 2 clinical studies, both animal studies, and Phase 1 clinical testing in non-pregnant adults is required. Phase 3 clinical trials are double-blind, randomized control (inert placebo) trials with pregnant women. In assessing safety for a product to be permitted specifically for use in pregnant women, two exclusive challenges are presented – 1) the vaccine exhibiting risks for the mother as well as the child, requiring a reasonable guarantee of the vaccine's safety before advancing into further clinical development stages, and 2) pregnancy complications not being infrequent, even in "low-risk" pregnancies. Both less serious events (musculoskeletal pain and gastrointestinal symptoms), and more serious events (deep vein thrombosis and severe hypotensive states) are more likely to occur in

pregnant women. Therefore, in some cases, the onset of such symptoms could occur in sequential association with immunization.[64] Therefore, there needs to be a widely accepted ethical framework and gold standard definitions included in guidelines for clinical trials enrolling pregnant women. Terms such as *minimal risk*, informing ethical frameworks for research, are not properly defined for studies involving pregnancy. IRBs often end up classifying most research with pregnant subjects as "high-risk", without said framework present.[1,6,61] Since normal ranges of pharmacokinetic and pharmacodynamic parameters differ in pregnant women compared to non-pregnant women, these need to be established first.[1] Data from safety and efficacy studies with clinical endpoints that are conducted abroad, pooled with information from connecting immunologic studies in the US, can help understand and prove vaccine safety and effectiveness for a US population. Repeated timely communication between the FDA and vaccine manufacturers is important to outline a suitable clinical development route.[64] Sponsors should consider including an ethicist in planning this.[59]

E. Vaccine Package Inserts

Prior to December 4, 2014: Labeling (package insert or prescribing information) is the main approach that FDA and drug manufacturers take in communicating drug (including vaccine) information required by HCPs in order to make decisions regarding prescribing. Regulations that explain the content and layout requirements for this are present in Title 21 of the CFR (CFR 201.56 and 201.57), and necessitate that prescribing information cannot be false or misleading and can list claims or uses only when there is adequate evidence of safety and effectiveness. FDA published a final rule, called the *Physician Labeling Rule* (PLR), which added requirements for 3 sections – Highlights, Full

Prescribing Information (FPI), and Contents. For vaccine labeling following this rule, evidence for use in pregnancy was instructed be present under the "Use in Specific Populations" section (including subsections in pregnancy, labor and delivery, and nursing mothers).[65]

a. Pregnancy Categories

The regulations on pregnancy, labor and delivery, and nursing mothers in labeling were established by the FDA in 1979 following the thalidomide tragedy. These required each product to be classified under one of five pregnancy categories, namely, A, B, C, D or X, based on risk of teratogenicity, or for certain letter codes, based on risk versus benefit. Prescribing information for US vaccines, excluding certain vaccines (e.g. anthrax), classified them as either Category B or C, permitting providers to vaccinate pregnant women.[65] There was a lack of harmonization of recommendations by organizations such as ACOG with FDA labeled indications for vaccines, and the system was cumbersome in practice, tough to interpret and hard to explain to the patient while elucidating the balance between risks and benefits of administering the medication (or in this case, vaccination) during pregnancy.[6,63]

b. Pregnancy Lactation and Labeling Rule

To improve the content and format of labeling and reduce the aforementioned challenges, FDA amended the category rule on December 3, 2014, with the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, or the *Pregnancy and Lactation Labeling Rule* (PLLR). It eliminates the old classification by letter categories, and instead provides a new framework, which includes a narrative summary of all the risks of a pregnant woman

using the medication. Drug information for pregnant and lactating populations is provided in two subsections of the "Use in Special Populations" section; *Pregnancy* (now includes the *Labor and Delivery* subsection) and *Lactation* (taking place of the *Nursing Mothers* subsection).[6, 65] However, while the PLLR does not modify any considerations for vaccinating pregnant women, it does include narrative summaries of risks, clinical considerations, and the discussion of supportive facts, which could be included from diverse sources of information, such as randomized control studies, pregnancy exposure and surveillance registries, observational post-licensure trials, and animal data. The PLLR does not standardize language for vaccines with similar safety profiles, aim to impact use of currently licensed vaccines in pregnant women, or link the package insert to current ACOG or ACIP recommendations.[63,65] It went into effect on June 30, 2015, and necessitates an assessment of existing information regarding the use of the product in pregnancy and provides sponsors with a chance to revise package inserts as and when new data is made available.[63,65] Logistical challenges to implementation include the need for a mock/sample label providing guidance on how to include and format information in the sections relevant to pregnancy and lactation.[61]

F. Future Maternal Vaccinations Under Consideration

Several new maternal vaccinations to prevent neonatal infectious diseases are currently under development. These diseases include respiratory syncytial virus (RSV), group B streptococcus (GBS), herpes simplex virus (HSV), and cytomegalovirus (CMV). RSV is the leading viral cause of lower respiratory tract infections in infants and young children, and no vaccines are currently available to prevent this. One of the candidate vaccines is currently being evaluated in Phase 3 trials, while several others are under

development.[1,66] GBS is a main causal pathogen of pneumonia, meningitis, and sepsis in newborns, and since the disease has such an early onset, administering a vaccine at birth does not guarantee that they would be able to develop an immune response in time to fight off the disease. Several contenders have been clinically evaluated in Phase 1 and 2 trials.[67] In women with primary infection during pregnancy, there is an increased possibility of neonatal herpes and congenital CMV infection. Currently, in clinical trials, several candidates are being assessed to offer elevated protection if given to seronegative women before pregnancy.[1,68,69]

Chapter II. Manuscript

Introduction

The Advisory Committee on Immunization Practices (ACIP) within the Centers for Disease Control and Prevention (CDC), recommends the inactivated influenza vaccine, and the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination for all pregnant women.[3,13,55,70] The safety and efficacy of both vaccines during pregnancy has been researched and demonstrated in many studies.[7,20-23,26-31,39,40,42,46] During the 2017 – 2018 influenza season, during pregnancy, 36.8% of pregnant women in the US received the influenza vaccination, 54.4% received Tdap vaccination, and 32.8% of women received both influenza and Tdap. Higher coverage was reported in women who received a vaccination recommendation from their provider (influenza: 63.8%, Tdap: 73.5%), than in women who did not (influenza: 9%, Tdap: 1.6%). Influenza vaccination coverage in pregnant women improved with an increasing number of provider visits – from 18.1% at 0 visits to 56.8% at >10 visits, highlighting the importance of providers in increasing the uptake of vaccines during pregnancy.[55]

The dearth of pre-licensure maternal immunization studies prohibits US Food and Drug Administration (FDA) vaccine package inserts from including an indication and usage statement specific to pregnancy.[1,59] The lack of a specific statement does not necessarily indicate that the product cannot be used in that population. However, the absence of clear prescribing guidelines from the FDA, and lack of human safety data included in package inserts may lead to both healthcare providers and patients being reluctant to consider vaccinations in pregnancy.[60] Several vaccines remained Category B drugs (“animal reproduction studies failed to demonstrate a risk to the fetus, no adequate

and well-controlled studies in pregnant women"), while national and international bodies strongly recommend those vaccines.[71] This dissimilarity between FDA-approved labels and the advisory committee recommendations has led to the misperception that use of these vaccines in pregnant women is "off-label".[59] A recent study conducted by Top et al. among obstetricians found that the majority of providers from both low- and middle-income countries and high-income countries claimed package insert information affects how they counsel pregnant women. The findings indicated that, much like in the US, providers felt that Canadian package insert wording differed from WHO and national immunization recommendations.[62]

In part to try and address this barrier, the FDA amended the Pregnancy Category rule of package inserts, on December 3, 2014, with the *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, or the *Pregnancy and Lactation Labeling Rule (PLLR)*. It eliminated the old classification by letter categories (A, B, C, D, and X) and provided a new framework which includes a narrative review of all the risks of using the medication during pregnancy.[61,65] However, in 2016, the National Vaccine Advisory Committee (NVAC) recognized that barriers to implementing and understanding the new labeling rules exist. Among clinicians who provide obstetrical care, there is insufficient data about the level of knowledge and trust in vaccine package inserts.[6,61]

We administered a cross-sectional, nationally representative survey among US obstetricians through the American College of Obstetricians and Gynecologists (ACOG) to evaluate the extent to which they review FDA vaccine package inserts in making prescribing decisions, their opinions on the updated labeling, and their confidence in their

ability to interpret the information.[62] This data could be used to inform future efforts to educate providers, patients, and national organizations, and overcome this barrier to maternal immunization.

Materials and Methods

Sample Population

A 24-item self-administered survey was sent to a sample of 800 US practicing OB/GYNs (excluding residents) from a sampling frame of 31,000 ACOG members. Given the novel nature of this particular study, the predicted proportions of providers' preferences for administering maternal vaccines due to FDA package insert language and wording were unknown, and we were unable to make a priori sample size calculations. ACOG provided the study team with a random sample, weighted to represent the distribution of population characteristics such as gender, geographic distribution, and subspecialty.

Data Collection Methods (Enrollment, Screening, Consent)

Since the surveys did not request any identifiable information from the physicians who consented to participate, Emory University Institutional Review Board (IRB00104565) determined the study to be exempt from further review prior to data collection and analysis. Survey packets containing a signed cover letter, printed survey, informed consent, along with a postage-marked return envelope, a pen and gift card as an incentive, were mailed on March 1st, 2019. Providers could utilize the postage-marked envelope to return the hard-copy of the survey or complete the survey online (a link and QR code were provided in the cover letter). By completing the survey and returning it to the study staff, respondents provided consent to participate.

Survey Design

This survey was divided into three different sections. Items were informed by the Top et al. study[62] as well as the literature available on vaccine labels in the United States. The first section included questions about participants' medical practice and sub-specialty, and their role in vaccine prescribing and administration. The second section inquired about their most trusted sources of vaccine information, and how often, if at all, they read package inserts, using Likert-scales. Again, using Likert-scales, we assessed providers' trust in, and perceptions of, vaccine package inserts in several ways. First, we asked about their level of trust in vaccine package inserts and an evaluation of the ease of interpreting package insert statements. Lastly, we provided some mockups of vaccine package insert statements (vaccine names hidden) with Pregnancy Categories labeling, and updated package inserts with the PLLR.[72-76] Participants were asked to rate their recommendation of use and perception of safety of the vaccination from the excerpt, depending on disease prevented, trimester of pregnancy, and whether they would recommend and/or administer vaccines that are also recommended by the CDC. For vaccines also recommended by the CDC, we decided to pose statements from inserts using the same labeling rule with either neutral or negatively framed sentences, to assess the difference of using overly precautionary language. For the first Pregnancy Category passage, we utilized a more neutral statement – *'Safety and effectiveness for use in pregnancy is not yet established. Use only if clearly needed'.* For the second category passage, we used a more negative passage – *'Animal reproduction studies have not been conducted with B vaccine. It is also not known whether B vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. B vaccine*

should be given to a woman only if clearly needed. Xcompany Inc. maintains a surveillance registry to collect data...women who receive B vaccine during pregnancy are encouraged to contact directly or have their healthcare professional contact Xcompany Inc.'. For the PLLR passage, we selected a more neutral statement – *'All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. In a 10 – year CDC survey involving over 700 pregnant women who received C vaccine within 3 months before or after conception (of whom 189 received the X strain), none of the newborns had abnormalities compatible with Z syndrome'*. Statements were extracted from or modeled after package inserts of FDA-approved vaccines, complying with either the PLLR or the category rule. In the last section, Pregnancy Categories and the PLLR were explained, after which providers were inquired about their thoughts on the helpfulness of each rule. The survey ended with an open-ended question, asking respondents for further comments on package inserts and maternal vaccination.

Data Entry

Data was entered in MS Excel by hand for hard copies of surveys that were mailed to the study team. Data entered via the online link was exported as a .xlxs file using Survey Monkey software. Both datasets were then merged and kept in a password-protected and encrypted shared drive.

Data Analysis

All quantitative analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and Tableau Desktop 2018.2. Frequency distributions of responses to each

question in the survey were calculated, after excluding nonresponses from the denominators of each variable. Variables for each question (excluding open-ended responses) were set up as categorical for ease of interpretation. Since vaccines were deidentified in the survey, with language quoted from inserts with either Pregnancy Categories or PLLR, we were also able to analyze the difference in perception of safety and likelihood of recommendation depending on which labeling rule was followed in each specific insert. Responses were stratified by specialty, years since residency, and whether or not the individual administered vaccines in their practice. Differences in proportions were assessed using Fisher exact tests. However, owing to the pilot nature of the study, analyses were largely limited to descriptive exploration. Using hand coding, free text responses were analyzed qualitatively through inductive content analysis in order to detect themes for the questions, *'What are your thoughts and comments about package inserts' safety statements under "pregnancy and lactation" for vaccines that are recommended for use in pregnancy?'* and *'Do you have any other comments on vaccine package inserts and maternal immunization to add?'*.[77]

Results

Out of the 800 surveys to be mailed, 25 could either not be mailed out due to missing labels (not provided by the courier), or were returned as undeliverable. Seven returned surveys were removed due to being only ~25% complete, and 6 respondents refused to participate, resulting in a survey response rate of 39.8% (303 out of 762).

Professional Characteristics and Practices

Out of the providers who returned the survey, 87.8% currently provided care for pregnant women at their practice site. The most common medical sub-specialty of

respondents was general obstetrics and gynecology (n = 211, 69.6%), and a majority had completed their residency 11 – 20 years ago (93, or 30.7%). Most providers either recommended and/or prescribed maternal vaccination (274, or 90.7%). Over fifty percent of providers (57.1%) recommended both influenza and Tdap, and 72.9% prescribed both influenza and Tdap (Table 1).

Vaccine Information Accessibility and Impression of Package Inserts

Most frequently used resources for information regarding maternal vaccination were professional organizations such as ACOG (90.4%) and ACIP/CDC (84.5%). Some providers indicated using "articles published in high impact factor OB/GYN journals" (23.1%) as resources. Only 6.9% of providers stated they review vaccine package inserts for information regarding maternal vaccination. Seventy-one percent (215) of respondents stated they did not read package inserts, while 17.9% read them in case of an updated insert or new product (Table 2). The majority of respondents maintained they were unfamiliar with the wording of package inserts (107, or 36%). Twenty-six percent (78) stated that package inserts were hard to read, whereas 9.1% (62) acknowledged they were easy to read (Table 2).

After reading deidentified mock excerpts from both categories of vaccine package inserts (either pregnancy category labeling or the PLLR), 46.9% (142) of all respondents said they would recommend the vaccine with the PLLR insert, and 88.1% (267) stated they would recommend the vaccine having the insert complying with the Pregnancy Categories rule. Seventy-three percent (222) of respondents perceived the vaccine with the PLLR insert as being safe for use in pregnancy, or were neutral to it, while 93.4% (283) identified the vaccine with the Pregnancy Category insert as being safe in

pregnancy, or were neutral to it. These responses were not based on disease state or trimester. The remaining responses are summarized in Figures 1 and 2.

Providers were asked if they would change their initial recommendation of the vaccine depending upon whether the disease prevented was either Meningococcal disease, Influenza, Pertussis, Group B Strep (GBS), or Respiratory Syncytial Virus (RSV). Most providers did not change their answers based on the disease for either category of vaccine insert. Providers were also asked if they would change their initial recommendation based upon the trimester of pregnancy. While a majority of the answers remained the same for the second and third trimester, 56.4% (171) of participants were less likely to recommend the vaccine with PLLR labeling during the first trimester. These responses are explained in further detail in Tables 3A and 3B, and responses stratified by initial recommendation are shown in Figures 3A, 3B, and 3C.

Sixty-four percent (191) of providers stated they would recommend and/or administer the vaccine with neutral Pregnancy Category labeling if also recommended by the CDC. Thirty-two percent (95) of providers said they would recommend the insert with the more negatively worded Pregnancy Category statement, and 62.1% (185) indicated that they would recommend the insert with the neutral PLLR statement. (Figure 4)

Stratified analyses conducted to evaluate associates between perceived difficulty of package insert wording and recommendations for maternal vaccination, or change in perception depending upon package insert labeling, found no significant association. ACOG Fellows who completed their residency less than 20 years ago were approximately 28% less likely to not recommend maternal vaccination than ACOG

Fellows who completed their residency over 20 years ago (p = 0.006, 95% CI [0.115, 0.695]). No significant association was observed between years since residency completion and difference in recommendation of vaccine depending upon package insert labeling category.

Pregnancy Categories and Pregnancy Lactation and Labeling Rule – an Overview

Eighteen percent (55) of providers stated they did not know of the PLLR, and 3% (9) stated they did not know of the Pregnancy Category rule. A majority of providers preferred a combination of both PLLR and the categories included in inserts. Twenty-seven percent (81) of respondents stated they considered categories more helpful in making their decision to recommend or administer vaccines to their pregnant patients. (Figure 5)

Results from the qualitative analyses showed that 69% percent (210) of respondents provided comments when asked for thoughts on the safety statements under the pregnancy and lactation section of the package inserts for vaccines recommended for use in pregnancy. Forty-two percent of respondents who provided comments (126) answered the question asking for general comments regarding vaccine package inserts and maternal immunization.

For the first question (comments regarding PLLR), there were five central themes (Table 4A). Firstly, providers stated that they did not read vaccine package inserts and preferred ACOG or CDC recommendations over inserts (*'if there was new data to change prescribing habits, I'd still utilize ACOG and CDC as my references to determine the standard of care'*). Most providers deemed the PLLR to be vague or unclear, and *'sometimes contradictory'* or *'convoluted'*, with *'small print'*. Perceiving PLLR language

to be designed to avoid liability seemed to be a main theme. Lastly, providers felt that the information provided under the 'Pregnancy and Lactation' section was inadequate, and needed to be expanded upon more. Another common theme was that respondents considered package inserts as tools for patients or patient counseling, instead of decision-making. Eighteen respondents (8.6% of 210) provided positive comments for PLLR, saying that it was *'very much needed'*, *'adequate'* and that they *'appreciated being able to refer to them'*. One comment stated that although the pregnancy portion was very clear, the lactation portion was very vague. Several providers also stated that due to this survey they would pay more attention to package inserts, called for more studies to be conducted in pregnant women, and for package inserts to be consistent with current practices and guidelines.

For the second question (comments regarding vaccine package inserts for maternal immunization), we found four central themes (Table 4B). Firstly, a general theme of package inserts being legal documents was seen in responses to this question as well, with providers strongly believing that *'package inserts are written by lawyers for other lawyers and should not be taken as highly accurate information'*, and wording serving as *'protection for manufacturers against litigation'*. These responses often utilized colloquial language, with the abbreviation "CYA" mentioned several times, which, according to Random House Unabridged Dictionary (2019), is a slang term (*sometimes vulgar*), which stands for '*Cover Your A***'.The second principal theme was package insert wording being too complex, especially the PLLR, with a related theme being comfort in using the *'old rule'* or *'relying on the pregnancy categories as busy physicians'*. Another main theme was providers' belief that the package inserts were for

patients, and not for physicians, with some expressing that *'often FDA package inserts frighten patients and do not improve patient care'*. The last key theme was respondents conveying that they highly preferred ACOG and CDC recommendations over package inserts, and that they *'hardly'* or *'never read'* package inserts, owing to confusing language, small print, and being unclear. A vaccine surveillance registry for pregnant patients seemed to be appealing to several providers, with some asking ACOG or CDC to make it *'mandatory to register pregnant women in vaccine registries'* in order to provide *'more data for the future'*.

Discussion

The results of this study suggest that although most providers recommend or administer vaccines during pregnancy, complying with ACOG and/or CDC recommendations, they do not read package inserts or consider package insert statements in order to make an informed decision on maternal vaccination. Instead, most solely rely on guidelines from ACOG or the CDC. These findings also communicate the lack of confidence among obstetric care providers in the US regarding package inserts, and distrust of vaccine manufacturers.

We found that although a majority of healthcare providers (73.3%) either considered the sample vaccine with PLLR labeling (not based on disease or trimester) to be safe or were neutral towards it, almost half did not recommend it. This was in stark contrast to the majority of providers both considering the vaccine in the example vaccine with Pregnancy Categories labeling to be safe (or neutral) and recommending it. Alongside statements from physicians saying they had limited time to read through PLLR

inserts, this could suggest their preference for inserts with Pregnancy Categories labeling, or a combination of both for more cautious providers.

When provided with different diseases and asked if their perception would change, most respondents stayed with their initial decision to either recommend or not recommend the vaccine. For the most part, their answers did not change when provided with the situation of recommending novel vaccines such as GBS and RSV. Additionally, answers largely remained the same when asked if their perception would differ depending on the pregnancy trimester. The only exception to this was that most providers in our sample were less likely to recommend the vaccine in the first trimester of pregnancy when provided with inserts complying with PLLR.

The differing statements extracted from package inserts of similar vaccines following the same labeling rule (Pregnancy Categories) were perceived differently by the survey respondents. When accompanied by a CDC (ACIP) recommendation, while almost half of the respondents did not recommend the sample vaccine described using a negatively worded Pregnancy Category excerpt (with approximately the other half still recommending it), most providers recommended the neutral one. A majority (62.1%) recommended the sample vaccine described using a neutral PLLR statement. Respondents expressed the need for more clear and succinct wording, and emphasized the need for evidence-based vaccine package inserts that comply with ACOG and CDC recommendations. This explains why providers recommended vaccines based on inserts that were also recommended by the CDC, regardless of wording. Most respondents preferred having a combination of both PLLR and Pregnancy Category labeling, suggesting they favored inserts with subheadings expanding on studies and narrative

benefits and risks during pregnancy, but also with a category to, ultimately, make their decision easier.

Study Limitations

Our study had limitations. The survey was self-administered, due to which we were unable to reach a higher response. The non-responders could lead to non-response bias in our analysis – while this is less than optimal, survey respondents offer a representative picture of the ACOG membership. According to reports on ACOG membership, similar to our respondents, most OB/GYNs did not sub-specialize, and were in practice between 11 to 20 years.[78,79] In order to get a comprehensive opinion from all obstetrics and gynecology-related medical sub-specialties, we also included providers who are not currently taking care of pregnant women, contributing to non-responses for questions regarding professional practices. Most providers did not read package inserts, which may imply a predisposition to undervalue package insert statements or a lack of awareness of package insert statements.

As previously stated, PLLR is a labeling rule with several components. Thus, it is difficult to fully gauge provider opinions about the labeling rule by only providing a few statements extracted from the package insert. It is possible we might have picked sections that seemed less than useful to participants, or that the statements we selected were insufficient in aiding in the decision-making process.

Conclusions

Our study established that generally, providers do not consider vaccine package inserts in decision-making for maternal vaccination. When presented with sample package inserts, providers preferred the old Pregnancy Categories over the PLLR, or

some combination of both. Qualitative analysis indicated a lack of reliance in package inserts and vaccine manufacturers. We propose that the FDA, along with vaccine manufacturers, and other trusted professional organizations, work with communication experts to collaboratively 1) update the inserts to reflect most recent guidelines for use in pregnancy, and 2) help reduce the apprehensiveness around package inserts to generate safer and more cognizant recommendations for pregnant women.

Appendices

Table 1. Professional characteristics and practices among a sample of ACOG Fellows, N=303

	Frequency	Percent (%)
Providing care for pregnant women		
Yes	266	87.8
No	37	12.2
Medical sub-specialty		
General obstetrics and gynecology	211	69.6
Gynecology only	32	10.6
Maternal fetal medicine	24	7.9
Reproductive endocrinology/infertility	13	4.3
Urogynecology	8	2.6
Obstetrics only	8	2.6
Gynecologic oncology	4	1.3
Other	3	1
Years since residency completion		
<5 years	20	6.6
5-10 years	49	16.2
11-20 years	93	30.7
21-30 years	85	28.1
30+ years	56	18.5
Recommend and/or administer vaccines in pregnancy		
Yes	274	90.7
No	26	8.6
Refuse to answer	2	0.7
Vaccines administered		
Influenza		
Yes	190	62.7
No	113	37.3
Tdap		
Yes	183	60.4
No	120	39.6
Both influenza and Tdap	173	57.1
Vaccines prescribed		
Influenza		
Yes	245	80.9
No	58	19.1
Tdap		
Yes	223	73.6
No	80	26.4
Both influenza and Tdap	221	72.9
Refuse to answer overall (prescribed and/or administered)	7	2.31

Table 2. Vaccine Information Accessibility and Package Insert Impressions among a sample of ACOG Fellows, N=303

	Frequency	Percent (%)
Commonly used resources for information regarding maternal vaccination		
Professional organizations like ACOG	274	90.4
CDC's ACIP recommendations	256	84.5
Articles from high impact factor OB/GYN journals	70	23.1
Who recommendations	61	20.1
Colleagues	37	12.2
Vaccine package inserts	21	6.9
IDSA guidelines	10	3.3
Refuse to answer	9	3
Respondents ever reading package inserts		
No	215	71
Yes	79	26.1
Refuse to answer	9	3
Frequency of reading package inserts*		
Rarely	187	61.9
Only if there is a new product/updated insert	54	17.9
Occasionally	40	13.3
Often	10	3.3
Before each administration and/or recommendation	2	1
Refuse to answer	9	3
Difficulty of wording of package inserts		
Unfamiliar with package inserts	107	36
Hard to read	78	26.3
Neither easy nor hard to read	62	20.9
Easy to read	27	9.1
Very hard to read	18	6.7
Very easy to read	4	1.4

*Could be a discrepancy here since most of the participants who responded they do not read package inserts also stated they read them rarely, due to lack of a response option for those who wanted to select "never").

Table 3A. Change in perception of use of vaccine with PLLR labeling versus vaccine with pregnancy category labeling based on disease prevented

	PLLR - n (%)	Pregnancy categories - n (%)
Meningococcal disease		
Less likely to recommend	48 (15.8)	13 (4.3)
More likely to recommend	87 (28.7)	81 (26.7)
Remain the same	148 (48.8)	196 (64.7)
No answer	20 (6.6)	13 (4.3)
Influenza disease		

Less likely to recommend	25 (8.3)	10 (3.3)
More likely to recommend	117 (38.6)	100 (33)
Remain the same	147 (48.5)	186 (61.4)
No answer	14 (4.6)	7 (2.3)
Pertussis disease		
Less likely to recommend	27 (8.9)	6 (2)
More likely to recommend	98 (32.3)	98 (32.3)
Remain the same	165 (54.5)	191 (63)
No answer	13 (4.3)	8 (2.6)
GBS*		
Less likely to recommend	84 (27.7)	34 (11.3)
More likely to recommend	58 (19.1)	90 (29.9)
Remain the same	149 (49.2)	163 (54.2)
No answer	12 (4)	14 (4.7)
RSV*		
Less likely to recommend	63 (20.8)	28 (9.2)
More likely to recommend	70 (23.1)	79 (26.1)
Remain the same	157 (51.8)	186 (61.4)
No answer	13 (4.3)	10 (3.3)

***GBS: Group B Strep; RSV: Respiratory Syncytial Virus**

Table 3B. Change in perception of use of vaccine with PLLR labeling versus vaccine with pregnancy category labeling based on pregnancy trimester

	PLLR - n (%)	Pregnancy categories - n (%)
First trimester		
Less likely to recommend	171 (56.4)	91 (30)
More likely to recommend	4 (1.3)	31 (10.2)
Remain the same	112 (37)	170 (56.1)
No answer	16 (5.3)	11 (3.6)
Second trimester		
Less likely to recommend	17 (5.6)	10 (3.3)
More likely to recommend	68 (22.4)	74 (24.4)
Remain the same	201 (66.3)	209 (69)
No answer	17 (5.6)	10 (3.3)
Third trimester		

Less likely to recommend	9 (3)	7 (2.3)
More likely to recommend	94 (31)	86 (28.4)
Remain the same	182 (60.1)	200 (66)
No answer	18 (5.9)	10 (3.3)

Table 4A. Themes identified from open-ended question *'What are your thoughts and comments about package inserts' safety statements under "pregnancy and lactation" for vaccines that are recommended for use in pregnancy?'*

Themes	**Example Answers**
Does not read/refer package inserts	*'Would not rely on them for safety. Prefer third party recommendations'* *'Not familiar enough. as with many products, package inserts are often not consistent with current practices.'* *'Never look at them'* *'Does anyone actually read these?'*
Manufacturers only care about litigation/package inserts (especially PLLR) are just legal documents	*'Generally no manufacturer will admit that ANYTHING is safe for pregnant women'* *'These are legal phrases designed to avoid liability'* *'Too protective for the company and overly state unknown risks'* *'Written to minimize manufacturers legal exposure not for ease of communication of information or best practice"* *'Long. Ridiculous! CYA bologna!'* *'Assume that they are "CYA", and thus don't pay much attention to them'*
Vague/unclear/contradictory	*'Never considered before - just pulled one up for review on the flu vaccine and it states safety and effectiveness not established - this is confusing given the recommendations by CDC and ACOG to administer'* *'Purposefully vague'* *'I don't like that the Tdap insert says "should be given to a pregnant woman only if clearly needed". Haven't we established that it is a benefit in pregnancy? Is that the same as "needed"?'* *'Should be simplified and based on scientific data, not manufacturer guides and precautions'*

	'It is not any different from a category B statement. I have never enrolled my pregnant patients in XXXX's registry'
Package Inserts are for patients	*'Should be clear enough for patient to understand'* *'Not clear to the average provider and patient'* *'Would be helpful to have more detailed/easy to read inserts for patients re: vaccines'* *'Difficult for patients to understand'*
Positive comments about PLLR	*'The overall inserts are long and difficult but the pregnancy and lactation sections are not alarming'* *'Important - should always be thoroughly stated'* *'Very helpful + aids in discussion with patient'* *'Very much needed'*
Prefer ACOG/CDC recommendations	*'Often a clumped recommendation - I don't generally trust this over ACOG/CDC'* *'I usually don't look at them. Use ACOG+CDC guidelines'* *'I have never read them, would use guidelines to make recommendations. Similar to drug package inserts; I also don't read those'* *'I go with ACOG recommendations --> if they advise it, it doesn't matter what package insert says'*

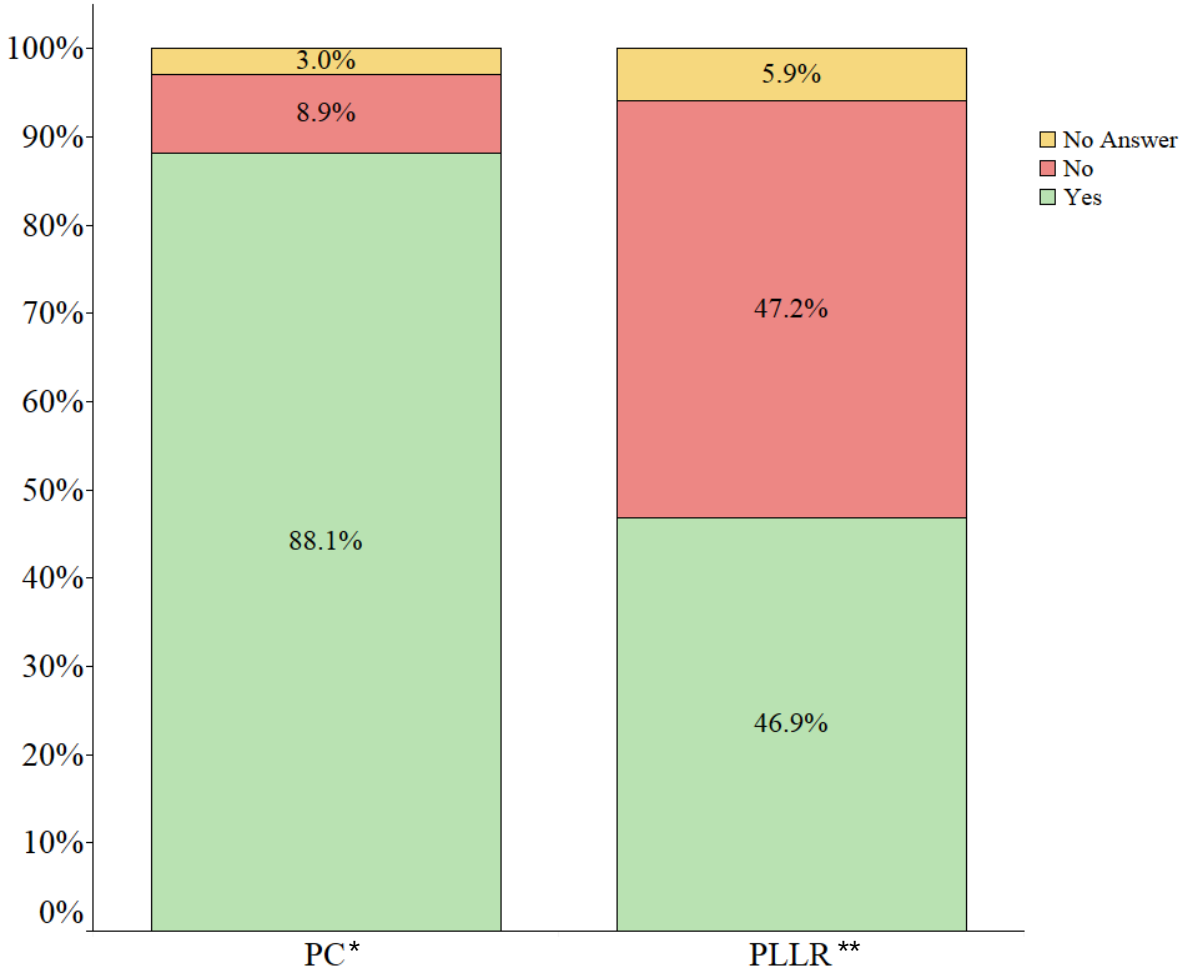
Table 4B. Themes identified from open – ended question *'Do you have any other comments on vaccine package inserts and maternal immunization to add?'*

Themes	**Example Answers**
Too complex/prefer CDC or ACOG guidelines	*'State recommendations by ACOG/CDC, include any trimester exclusion, include disease risk reduction by giving vaccine, # of adverse outcomes in registry'* *'Clinically the recommendations of societies, i.e. CDC, ACOG, IDSA, SMFM are incredibly helpful. Difficult to find all primary data and interpret as busy clinician. Reliance on "experts" to review and recommend is much more important than package insert. If no recommendation yet then more information rather than less better in package inserts'* *'As a practicing physician, we just want to know if the medication is safe for pregnancy or lactation. Most of the wording, in my opinion, is CYA for the manufacturer. It leaves us deciding whether or not it should be used. Fortunately, the CDC and ACOG do help.'*

	'Need to be more clear'
Surveillance registry	*'If ACOG (or) CDC makes it mandatory to register pregnant women in the vaccine registry, we might be able to collect the data for the future/for our pregnant patients'* *'I think a national vaccine database website cosponsored by the CDC/ACOG/WHO with an easy to use mobile app would be the most helpful, user friendly approach for busy provider'*
Comfortable with old rules	*'Hard to erase 20 years of using old ways :)'* *'I grew up with old rules. was comfortable with them - best would be combination for older MDs - the new MDs get trained in new rules - I find new rules unclear'*
Package Inserts are for patients	*'We need patient driven materials, materials that are written in basic language that describes exactly what the vaccine is and how it helps. We need CDC/ACOG and organizations to increase education of vaccines in schools and media'* *'For very health literate patients, the PLLR might be helpful'* *'Many of our patients are misinformed by non-medical sources against the safety of vaccines such as social media, google, friends etc. - hard to overcome'* *'Too extensive and confusing for patients'*
Advice for changes to labeling	*'Pregnancy categories are easier and faster but more data can be helpful to understand exactly what we know. That's why I'd like both!'* *'The risks of not vaccinated should be clearly stated'* *'"clearly needed" is just terrible language. This is way too open for interpretation for something that is designed to prevent a problem'* *'Have inserts list results and titles of studies'* *'Larger print outside boxed warnings would be helpful!'*
Do not read inserts	*'Doing this survey tells me I have relied too much on what the governing bodies say since I don't look at package inserts'* *'Amazing how much I do not know. I will make sure to go read those inserts!'* *'Perhaps I should read them more'* *'I don't know anyone who reads the package insert - other than for administration or maybe storage temp for a vaccine! refer to CDC/College guidelines!'*

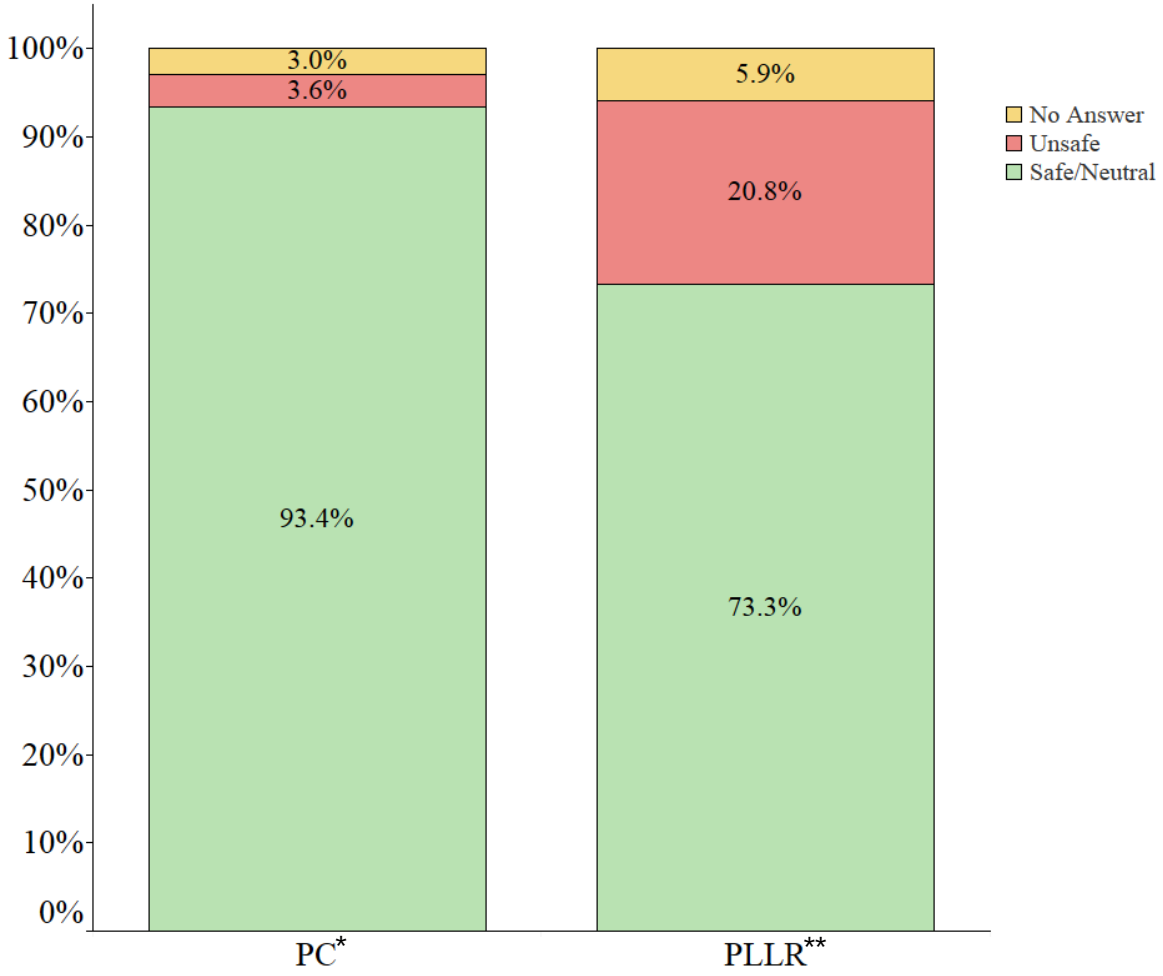
Manufacturers only care about litigation/package inserts are just legal documents	*'Lots of disclaimers, no commitment'* *'I follow ACOG + CDC guidelines and haven't been reading immunization package inserts b/c of those recommendations, but I can see how the inserts can be more 'CYA' than helpful...'* *'Often FDA package inserts frighten patients and do not improve patient care.'* *'Not truthful'* *'I do not rely on packing inserts. It is my assumption that this information is more about avoidance of litigation than best medical evidence. The CDC is my primary resource for evaluation of the best clinical evidence and review of risk/benefit for vaccines in pregnancy'*

Figure 1. Initial Perception of Recommending Use in Pregnant Women among OB/GYNs in the US: Vaccine with Pregnancy Categories Labeling vs. Vaccine with Pregnancy Lactation and Labeling Rule.



*PC: Pregnancy Categories, **PLLR: Pregnancy Lactation and Labeling Rule

Figure 2. Initial Perception of Safety of Use in Pregnant Women among OB/GYN in the US: Vaccine with Pregnancy Categories Labeling vs. Vaccine with Pregnancy Lactation and Labeling Rule.

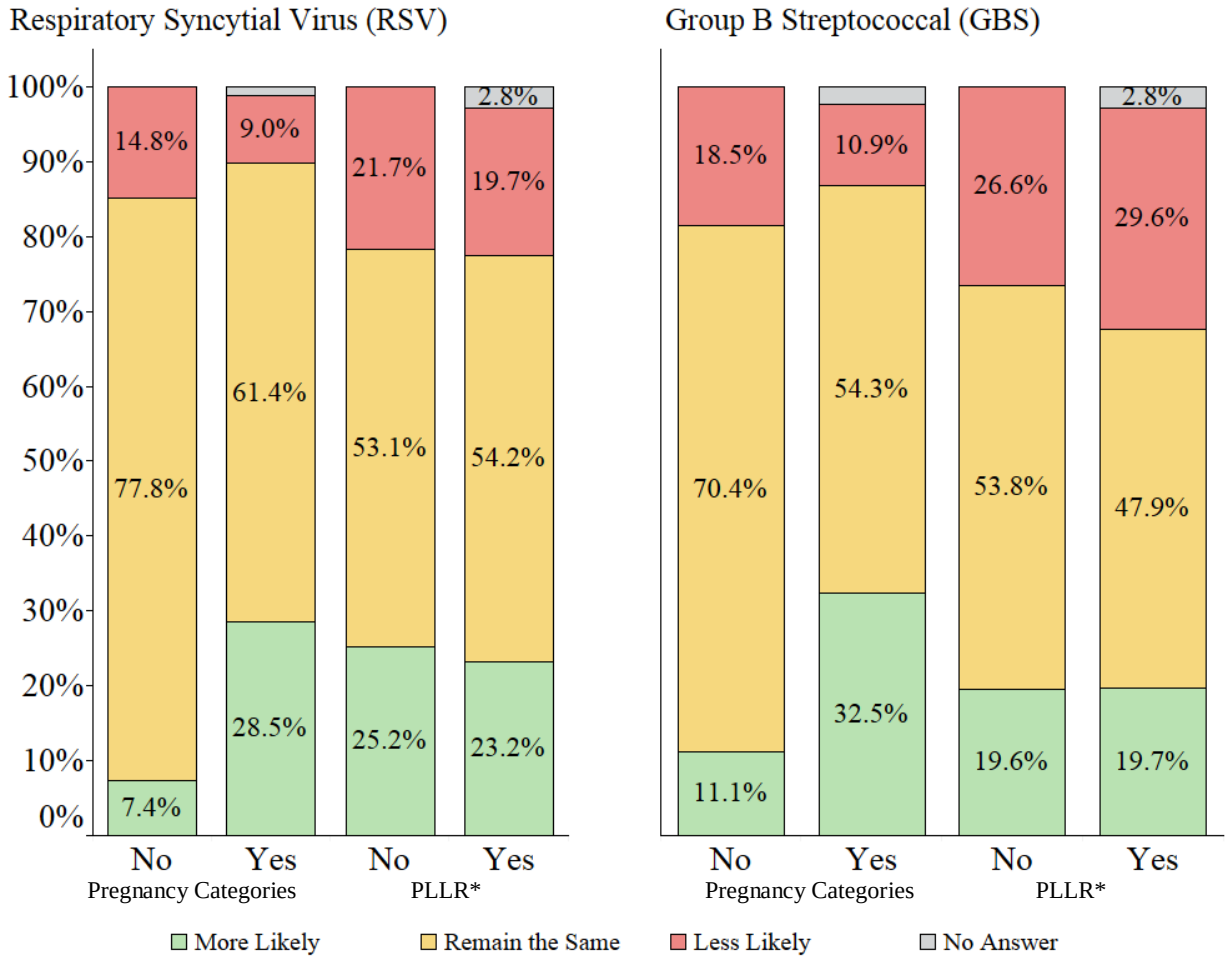


*PC: Pregnancy Categories, **PLLR: Pregnancy Lactation and Labeling Rule

Figure 3A. Likelihood of Provider Changing Recommendation of Vaccine with Pregnancy Categories Labeling or Pregnancy Lactation and Labeling Rule Depending on Disease Prevented (Labeled by Initial Recommendation)

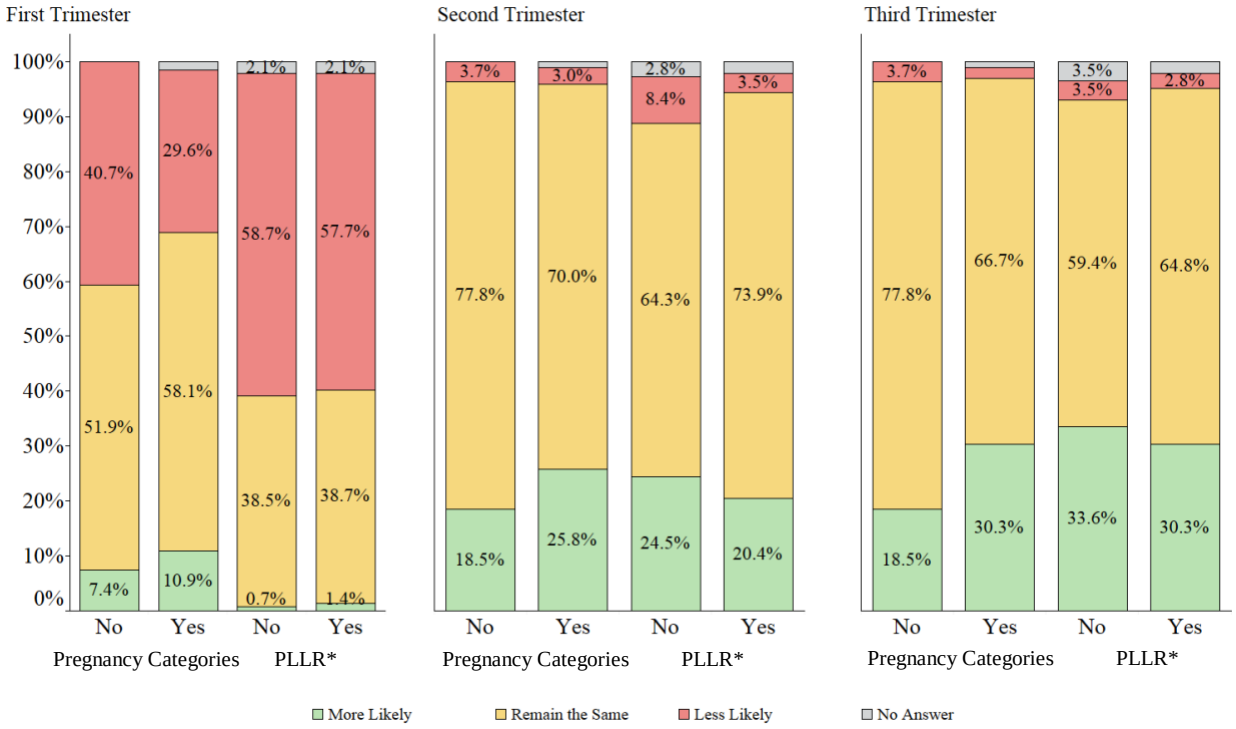
*PLLR: Pregnancy Lactation and Labeling Rule
Numbers might differ due to missing values and non-responses

Figure 3B. Likelihood of Provider Changing Recommendation of Vaccine with Pregnancy Categories Labeling or Pregnancy Lactation and Labeling Rule if Disease Prevented by Novel Vaccine is Group B Strep or Respiratory Synctial Virus (Labeled by Initial Recommendation)



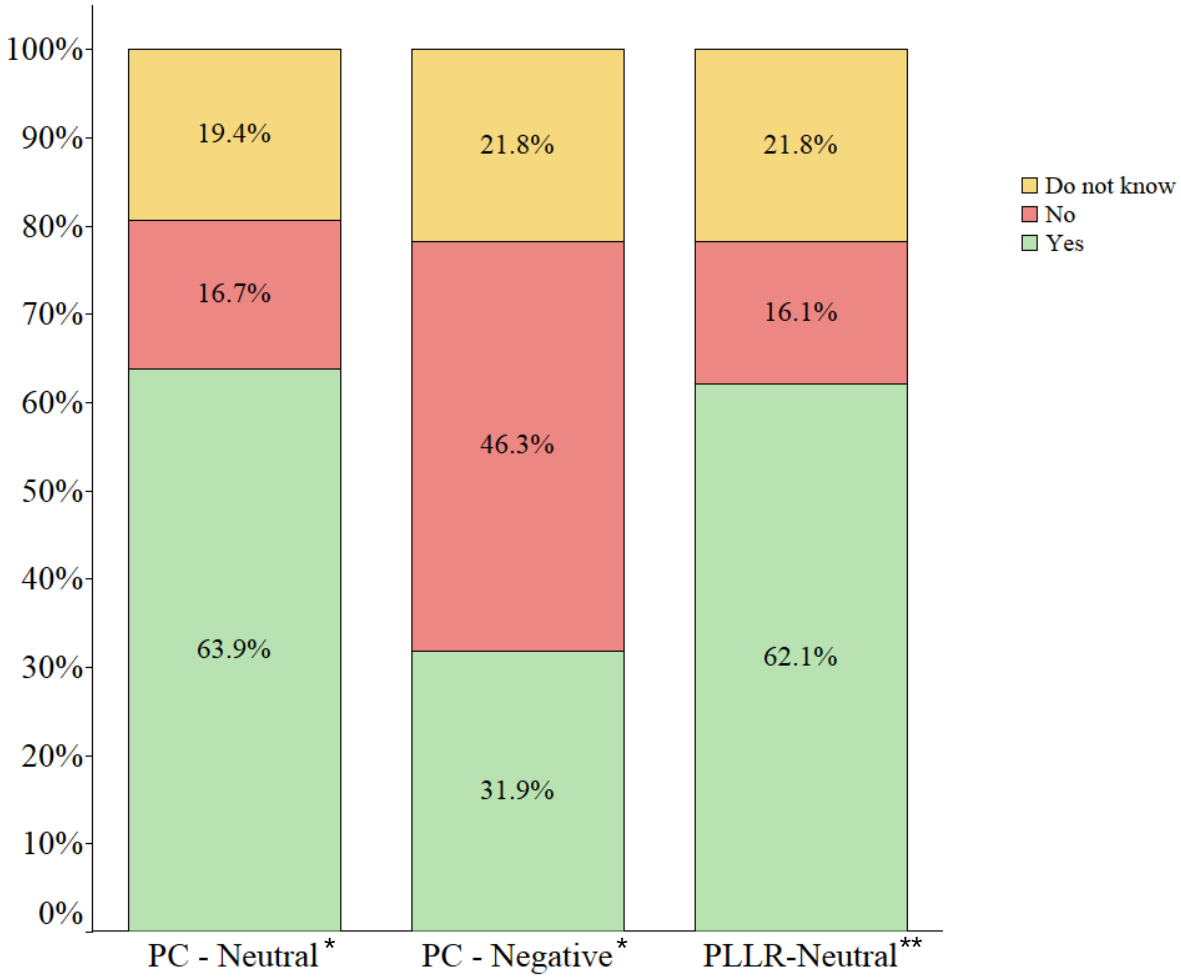
*PLLR: Pregnancy Lactation and Labeling Rule

Figure 3C. Likelihood of Provider Changing Recommendation of Vaccine with Pregnancy Category or Pregnancy Lactation and Labeling Rule by Trimester of Pregnancy (Labeled by Initial Recommendation)



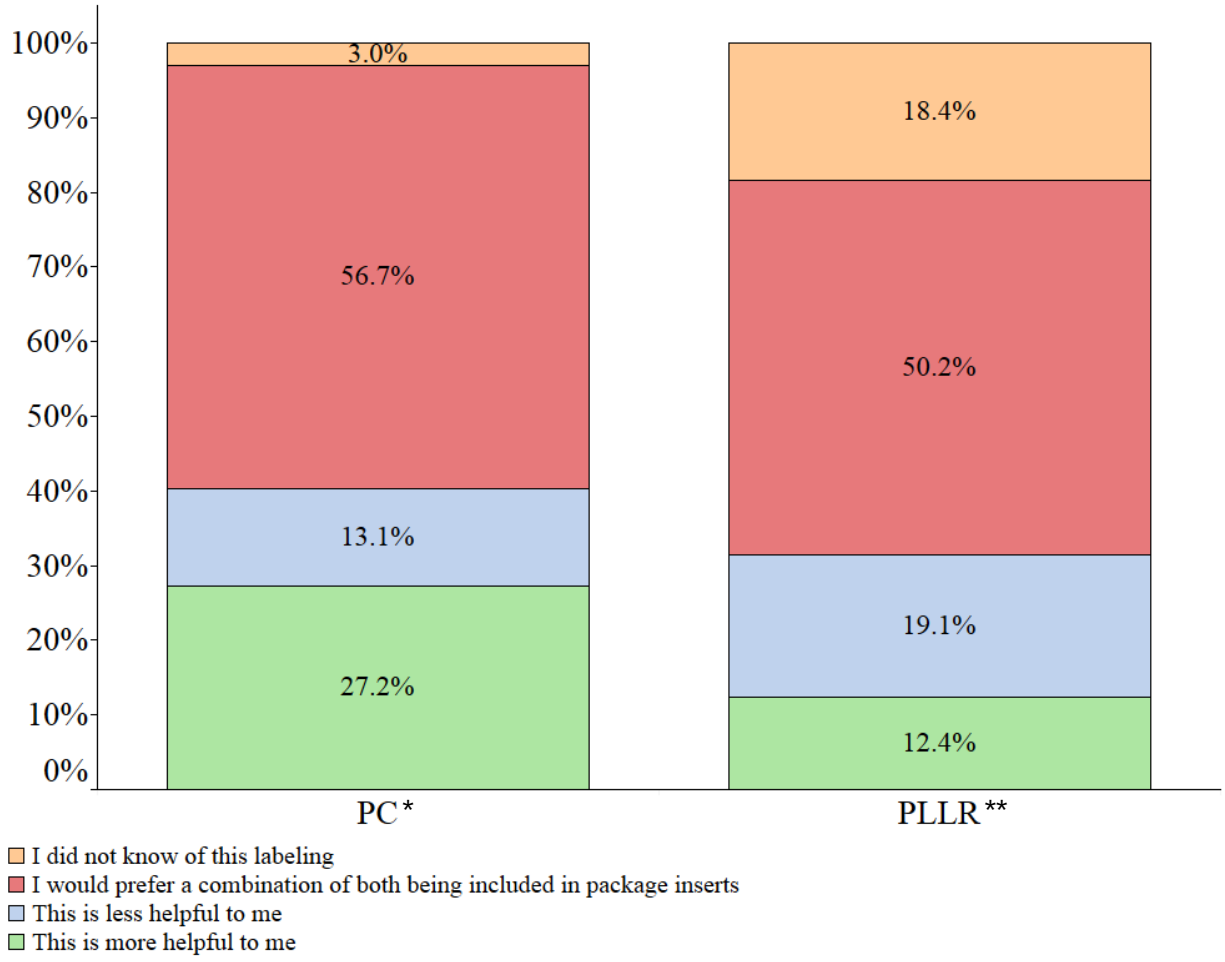
*PLLR: Pregnancy Lactation and Labeling Rule

Figure 4. Recommendation of Vaccines after Reading Package Insert Statements if Recommended by the CDC (ACIP)



*PC: Pregnancy Categories
**PLLR: Pregnancy Lactation and Labeling Rule
¶ The first two statements were pulled from package inserts complying with the Pregnancy Category rule – the first statement was neutral, and the second was more negative. The third statement was a neutral one from an insert complying with the Pregnancy Lactation and Labeling Rule (PLLR).

Figure 5. Overall Opinion on and Awareness of Utility of Pregnancy Categories and Pregnancy Lactation and Labeling Rule among OB/GYNs in the US



*PC: Pregnancy Categories

**PLLR: Pregnancy Lactation and Labeling Rule

Chapter III. Public Health Implications

Clinical Implications

We found that obstetric-care providers are skeptical of vaccine package inserts, and do not take them into account while making decisions regarding vaccines for pregnant women. Although the FDA is working with manufactures, ACOG and the CDC to update package inserts to comply with current guidelines, engaging with risk communication experts could be valuable – despite most providers in our sample recommending vaccines for their pregnant patients, vaccine uptake is still modest in this population. When searching for drug information or primary data regarding vaccines, package inserts are an often overlooked, but easy-to-use and freely available resource. Attempts should be made to increase the salience of package inserts in this community, so that a higher number of providers not only read the Pregnancy and Lactation section, but also encourage their patients to enroll in surveillance registries. This will provide pregnant women and their providers with higher quality data, and substantial evidence for vaccine safety and efficacy in the future.

Research Implications

Many of our respondents identified package inserts as a resource for patients and patient counseling, and although they can serve that purpose, efforts should be made to ensure package inserts are a useful resource for healthcare providers as well. Currently, differing recommendations in clinical practice and package inserts serve as a hurdle to increasing vaccine uptake in pregnancy, and inconclusive statements confuse providers. Moreover, while the FDA is trying to implement a phrasing standard, package inserts are still lacking. Our study hopes to inform policy and help vaccine manufacturers, the FDA

and CDC, as well as professional organizations to work with risk communication experts and combine efforts to create comprehensive package inserts in unambiguous language that is easy for OB/GYNs to interpret and act on. More studies are needed to examine whether or not reading package inserts can help improve decision-making regarding vaccines in pregnancy, and whether these decisions differ geographically, by practice-type, or by sub-specialty.

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