

Protecting Two: Maternal Immunization Opportunities & Challenges



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Objectives



- Describe the burden of vaccine preventable diseases among pregnant women and their newborns
- Describe current vaccine recommendations for pregnant women
- Understand how to implement best practices for increasing immunization uptake in obstetric practices
- Explain how vaccine safety is monitored among pregnant women



Disclosures



I have no financial relationships or other conflicts of interest to disclose.

I will be discussing off-label use of the Tdap vaccine. Tdap is FDA approved for single use. The ACIP recommends use with each pregnancy.



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How many of you:



- Provide routine prenatal care?
- Routinely recommend Tdap and Influenza vaccination to pregnant women?
- Offer Tdap and Influenza vaccines in your clinic?

Routine ACIP Recommendations: Tdap and Influenza



Vaccine	Recommendation	Goal
Tdap	<p>2005- Dose of Tdap before or after pregnancy</p> <p>2011- Dose of Tdap during pregnancy if previously unvaccinated</p> <p>2013- Dose of Tdap during every pregnancy between 27 and 36 weeks</p>	Protection of newborn infants
Influenza	<p>1960- Pregnant women with high-risk medical conditions</p> <p>2004- All women who are pregnant or will become pregnant during flu season</p> <p>2010- Universal flu recommendation</p>	Protection of mothers and newborn infants



Not a new
concept...



OBSERVATIONS MADE DURING THE
EPIDEMIC OF MEASLES ON THE
FAROE ISLANDS IN THE YEAR 1846

PETER LUDWIG PANUM

History of Maternal Immunization

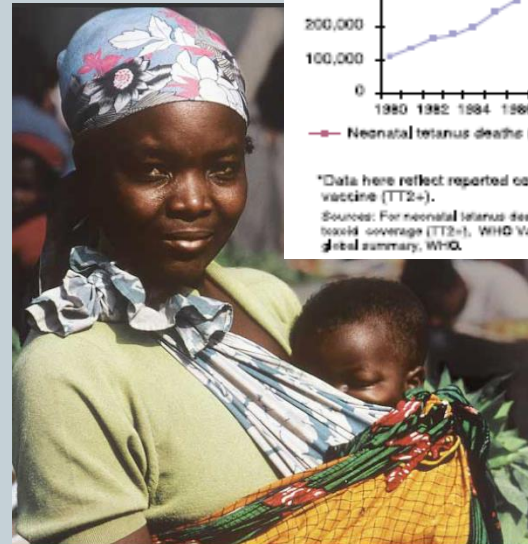
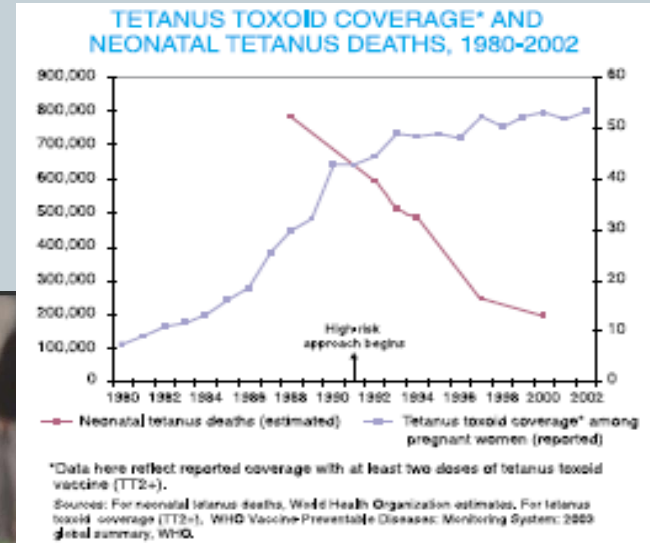


- 1846- Role of maternally derived immunity in infants first observed during a measles outbreak on the Faroe Islands
 - Noted that if pregnant mothers survived disease, their babies did not become infected
- 1879- Maternal immunization with vaccinia was found to protect infants against smallpox
- 1938- Whole cell pertussis vaccine was used in pregnancy
- 1959- Papua New Guinea- 61 women received 3 injections of fluid formalinized tetanus toxoid during pregnancy
 - Incidence of neonatal tetanus was 10% in those where the mother received either no or only 1 injection, 3.42% in those that received 2 injections and 0.57% in those that received 3 injections

Global Success- Maternal and Neonatal Tetanus Prevention Through Maternal Immunization

- >90% global reduction in neonatal tetanus since 1988*
- TT vaccination of high-risk

*From over 780,000 in 1988 to 49,000 in 2013.



ELIMINATING MATERNAL AND NEONATAL TETANUS

For every child
Health, Education, Equality, Protection
ADVANCING HUMANITY



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But still working
to gain
acceptance...

Vaccinations & PREGNANCY

Always	Sometimes
<p>Flu shot</p> <p>Once a year At anytime during your pregnancy.</p>	<p>Travel</p> <p>If you are traveling outside the U.S. check with your doctor if you need other vaccines.</p>
<p>Tdap</p> <p>Tetanus, diptheria and pertussis. During each pregnancy, ideally between 27 and 36 weeks.</p>	<p>Haemophilus influenzae type b Hepatitis A Hepatitis B Meningococcal Pneumococcal</p> <p>Recommended for women at high risk of getting these infections. Check with your doctor.</p>

HPV, MMR, Varicella are not recommended , but if received are not cause for concern.

Barriers



- Myths
- Misperceptions
 - Susceptibility
 - Disease burden
 - Safety
- Risk vs. Benefit
- Societal norms
- Obstetrical practice norms
- Litigation concerns
- No established immunization “platform” in pregnancy



Tremendous Rationale



- More severe illness in pregnancy, especially influenza
- Young infants are most vulnerable to vaccine preventable diseases
- Maternal-fetal physiology



Vulnerability

Lack of
Immunization

Window of
vulnerability



Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16-18 yrs
Hepatitis B ¹ (HepB)	1 st dose	2 nd dose			3 rd dose											
Rotavirus ² (RV) RV1 (2-dose series); RV5 (3-dose series)			1 st dose	2 nd dose	See footnote 2											
Diphtheria, tetanus, & acellular pertussis ³ (DTaP: <7 yrs)			1 st dose	2 nd dose	3 rd dose			4 th dose				5 th dose				
Tetanus, diphtheria, & acellular pertussis ⁴ (Tdap: ≥7 yrs)														(Tdap)		
<i>Haemophilus influenzae</i> type b ⁵ (Hib)			1 st dose	2 nd dose	See footnote 5		3 rd or 4 th dose See footnote 5									
Pneumococcal conjugate ⁶ (PCV13)			1 st dose	2 nd dose	3 rd dose		4 th dose									
Pneumococcal polysaccharide ⁶ (PPSV23)																
Inactivated poliovirus ⁷ (IPV: <18 yrs)			1 st dose	2 nd dose	3 rd dose						4 th dose					
Influenza ⁸ (IIV; LAIV) 2 doses for some: See footnote 8					Annual vaccination (IIV only) 1 or 2 doses						Annual vaccination (LAIV or IIV) 1 or 2 doses		Annual vaccination (LAIV or IIV) 1 dose only			
Measles, mumps, rubella ⁹ (MMR)					See footnote 9		1 st dose					2 nd dose				
Varicella ¹⁰ (VAR)							1 st dose					2 nd dose				
Hepatitis A ¹¹ (HepA)							2-dose series, See footnote 11									
Human papillomavirus ¹² (HPV2: females only; HPV4: males and females)														(3-dose series)		
Meningococcal ¹³ (Hib-MenCY ≥ 6 weeks; MenACWY-D ≥ 9 mos; MenACWY-CRM ≥ 2 mos)			See footnote 13											1 st dose		Booster

Placental Transfer of Maternal Ag-specific IgG



- Passive transport begins at 17 weeks gestation and increase with gestational age
- By 33 weeks' gestation, maternal and fetal levels are equal, then active transport begins
- By 40 weeks, total cord blood IgG levels exceed maternal levels unless placental abnormalities
- Optimal timing for administration differs by VPD

INFLUENZA OCCURRING IN PREGNANT WOMEN

A STATISTICAL STUDY OF THIRTEEN HUNDRED AND FIFTY CASES*

JOHN W. HARRIS, M.D.
BALTIMORE

In the latter part of October, 1918, when the epidemic of influenza was at its peak in this locality, the seriousness of the disease as seen in pregnant women caused considerable alarm among those in charge of obstetric cases. It soon became apparent that there was a great diversity of experience as regards the mortality, some of the practitioners losing most of their cases, others very few. In addition to its importance in contributing toward a more definite knowledge concerning the prognosis of influenza in pregnant women, it has seemed to me that a statistical study based on a large number of cases would also be of value in showing the effect of the influenza on the course of pregnancy. Owing to its severity and wide occurrence, and to the fact that it was especially prevalent among young women of the child-bearing age, the epidemic offered the best opportunity we have perhaps ever had to study the extent to which the progress of pregnancy is interfered with by an acute, severe, infectious disease.

With these purposes in view, a questionnaire was prepared which included data as to race and age of the individual patient, the month of pregnancy, character of the attack (whether mild or severe, and whether complicated by pneumonia), recovery or death of the mother, and whether or not pregnancy was interrupted. Copies of this blank were sent to all of the physicians of the state of Maryland, and also to the members of the American Gynecological Society, the American Association of Gynecologists and Obstetricians, and the local obstetric societies in four of the larger cities. I wish here to express my appreciation of the ready response on the part of the physicians who replied, and of the careful manner in which they supplied the information desired.

Of the total number of cases returned, 1,350 were reported in full detail, and it is on these that our statistics have been based. Other cases were reported but were not used, owing to incompleteness of the data in some particular respect. Of the 1,350 cases, 971 were from the state of Maryland, and hence the great majority occurred under the same general conditions. In race the patients were predominantly white, the proportion being 1,266 white, eighty-two negro, and two Japanese. Since in most instances the duration of pregnancy was expressed in calendar months, the same method has been followed in this paper.

The results of this study are given herewith in the form of a series of tables in which the statistics are presented so as to show their relation to the various aspects of our problem. By a comparative study of these tables important data are revealed, both as regards the course of influenza in pregnant women and the effect of the influenza on the course of pregnancy. No conclusions can be drawn, however, as to whether the incidence of influenza is greater among

pregnant women than among nonpregnant women or men of the same age. This question cannot be determined until we have reliable statistical data concerning influenza in general. Our own figures show only what happened in this group of 1,350 patients.

TABLE 1.—INCIDENCE OF PNEUMONIA AND PERCENTAGE OF MORTALITY IN CASES OF INFLUENZA REPORTED FOR THE DIFFERENT MONTHS OF PREGNANCY

Month of Pregnancy	Uncomplicated by Pneumonia			Complicated by Pneumonia			Total Cases	Gross Mortality
	No. of Cases	Recovery	Percentage of Mortality	No. of Cases	Recovery	Percentage of Mortality		
1	12	12	0	2	1	50	14	7
2	53	53	0	31	17	45	84	17
3	58	58	0	48	32	35	106	28
4	79	79	0	79	41	48	158	34
5	58	58	0	94	51	43	152	28
6	94	94	0	88	45	45	182	25
7	121	121	0	114	67	59	235	29
8	151	151	0	109	45	64	260	25
9	46	46	0	93	36	57	139	41
Total	672	672	0	678	313	365	1,350	27

As regards the course and prognosis of influenza in pregnant women, we may draw certain general conclusions from Table 1. Our first observation is that about one half of all the patients developed pneumonia, and of these about 50 per cent. died, giving a gross mortality of 27 per cent. In those developing

TABLE 2.—FREQUENCY OF INTERRUPTION OF PREGNANCY IN CASES IN WHICH INFLUENZA WAS UNCOMPLICATED BY PNEUMONIA

Month of Pregnancy	Total Cases	Pregnancy Uninterrupted	Pregnancy Interrupted	Percentage Interruption
1	12	8	4	33
2	53	27	26	49
3	58	40	18	31
4	79	55	24	30
5	58	46	12	21
6	94	81	13	14
7	121	65	56	46
8	151	108	43	28
Total	672	490	182	26

pneumonia, the mortality was somewhat higher in the last three months of pregnancy. From Table 1 it will be seen that the largest number of cases were reported for the sixth, seventh and eighth months, and fewer from the third to the fifth months. As to the first two months, we must assume that in many instances

TABLE 3.—FREQUENCY OF INTERRUPTION OF PREGNANCY IN CASES IN WHICH INFLUENZA WAS COMPLICATED BY PNEUMONIA

Month of Pregnancy	Total Cases	Pregnancy Uninterrupted	Pregnancy Interrupted	Percentage Interruption
1	2	0	2	100
2	31	7	24	77
3	68	29	39	57
4	79	43	36	46
5	94	59	35	37
6	88	47	41	46
7	114	57	57	50
8	109	41	68	62
Total	585	283	302	52

the existence of pregnancy was not suspected by the attending physician, and thus such cases would not be included in the reports. On the other hand, we may well reason that cases from the later months were likely to be reported, pregnancy being then more obvious. This would explain the larger number of

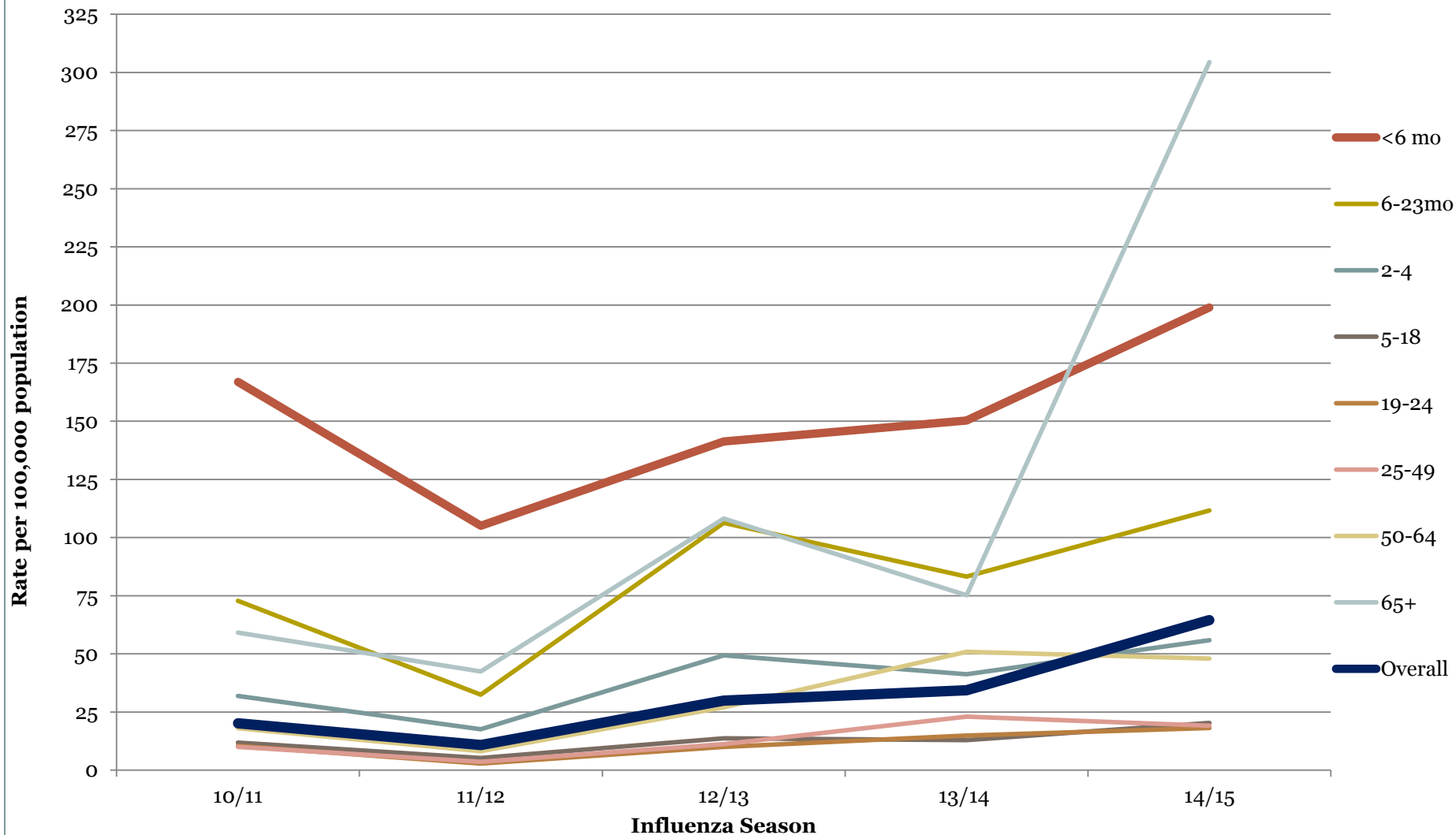
Influenza

Harris, J. JAMA, 1919

50% Mortality, increased later in pregnancy.

*From the Johns Hopkins Hospital and Carnegie Laboratory of Embryology.

Rates of Influenza-associated Hospitalizations by Age Group and Season, Colorado, 2010/2011 - 2014/2015



Rates of Influenza Hospitalizations Among Pregnant Women



Influenza Season	Flu Hospitalization Rate Among Pregnant Women Age 15-44*	Flu Hospitalization Rate Among All Women Age 15-44*	Rate Ratio
2009-2010	1.57	0.44	3.532577
2010-2011	0.51	0.14	3.590257
2011-2012	0.18	0.03	6.032586
2012-2013	0.65	0.13	5.035132
2013-2014	0.51	0.18	2.805494

*Rate per 1,000 based on general fertility rate; Colorado EIP Catchment Area (Adams, Arapahoe, Denver, Douglas, Jefferson).

Data Sources: Colorado EIP Influenza Data; CoHID Birth Data; CO Demographers' Population Forecasts 2010-2014



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Pregnancy is a Risk Factor for Severe Illness Due to Influenza

- **Pandemics**

- Increased mortality- 1918, 1957, 2009 H1N1*
 - ✦ Severity > Susceptibility

- **Non-pandemic years**

- ICEID 2105- Kline *et al.*
 - ✦ Emerging Infections Program- 14 sites, 2010-2012
 - ✦ Pregnant 18-49 year olds were more likely to have influenza-related hospitalizations than their non-pregnant counterparts (RR 5.23, 95% CI 4.57-5.99)
- Dodds *et al.* CMAJ. 2007
 - ✦ During influenza seasons, rate ratio of hospital admissions in the third trimester compared with admissions in the year before pregnancy was 7.9 (95% CI 5.0-12.5) among women with comorbidities and 5.1 (95% CI 3.6-7.3) among those without comorbidities.
- Neuzil *et al.*, Am J Epidemiol. 1998
 - ✦ OR associated with severe influenza illness increased from 1.44 (95% confidence interval (CI) 0.97-2.15) for women at 14-20 weeks' gestation to 4.67 (95% CI 3.42-6.39) for those at 37-42 weeks in comparison with postpartum women

- **Meta-analyses- mixed**

- **Confounders**



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*FREEMAN DW, BARNO A. Deaths from Asian influenza associated with pregnancy. Am J Obstet Gynecol 1959; 78:1172.
Hardy JM, Azarowicz EN, Mannini A, et al. The effect of Asian influenza on the outcome of pregnancy, Baltimore, 1957-1958. Am J Public Health Nations Health 1961; 51:1182.
Harris JW. Influenza occurring in pregnant women. JAMA 1919; 72:978.
Nuzum JW, Pilot I, Stangl FH, Bonar BE. 1918 pandemic influenza and pneumonia in a large civil hospital. IMJ Ill Med J 1976; 150:612.
Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010; 303:1517.
Callaghan WM, Creanga AA, Jamieson DJ. Pregnancy-Related Mortality Resulting From Influenza in the United States During the 2009-2010 Pandemic. Obstet Gynecol 2015; 126:486.
Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009; 374:451.

Why is Illness More Severe?



- Physiologic Changes in Pregnancy
 - ↑ Cardiac output
 - ↑ Oxygen consumption
 - ↓ Lung capacity
 - ↓ Tidal volume
 - ↓ Cell-mediated immunity
 - To protect the fetus from cytotoxic T lymphocyte activity
 - Impaired/modified response to infection
- Increased risk of severe disease appears to be at least partially due to the immunological and physiological changes that occur during pregnancy

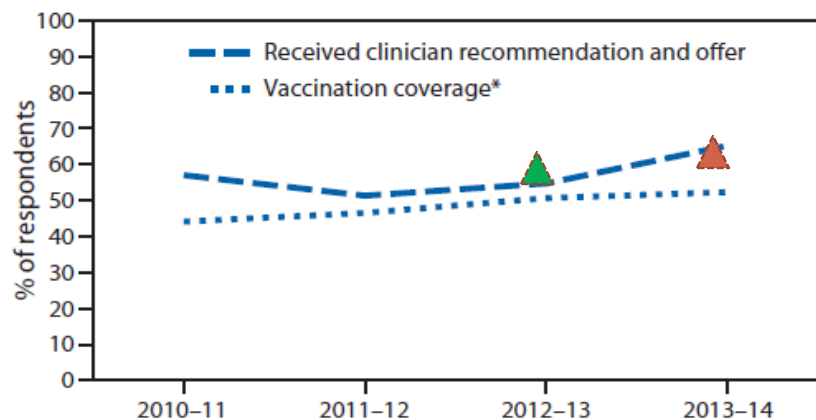
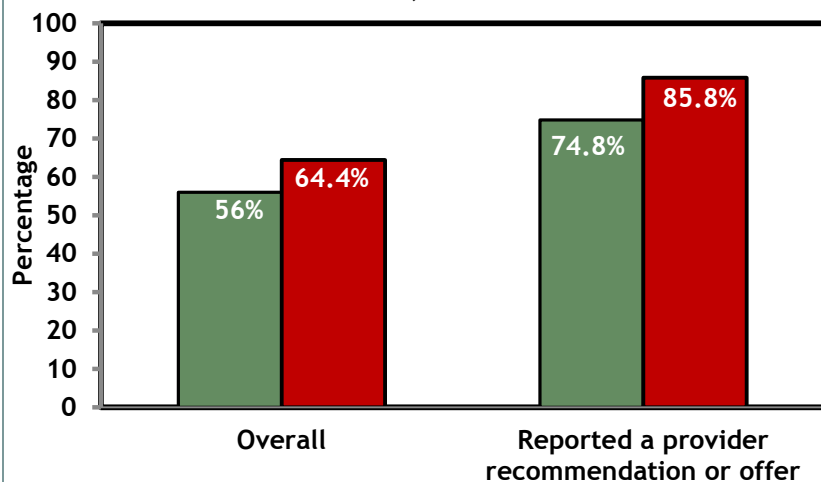




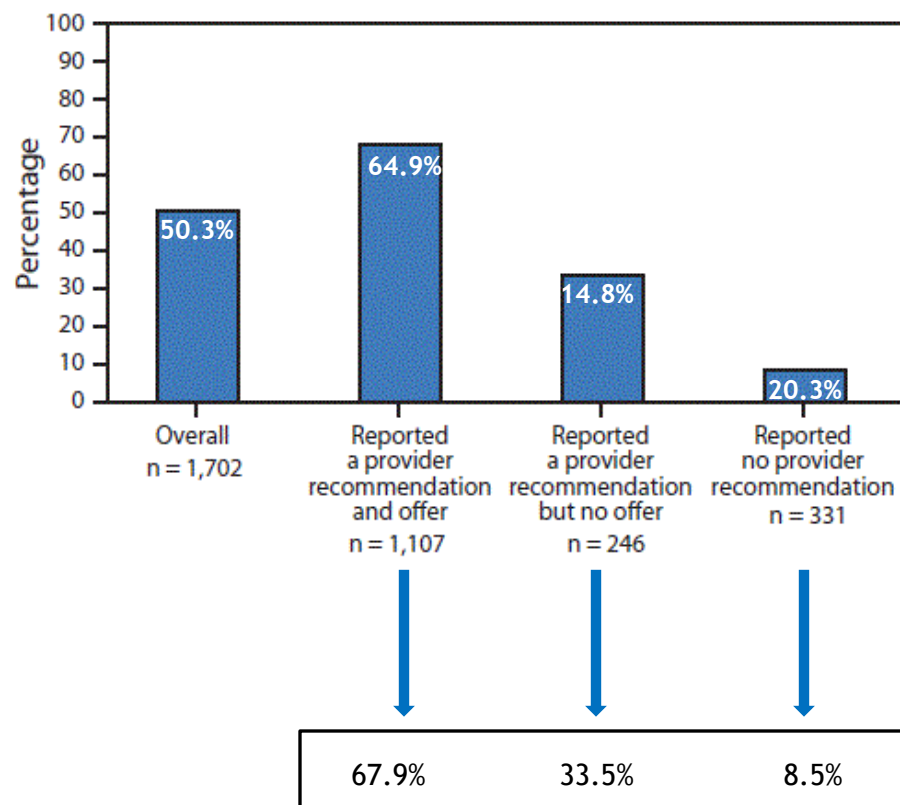
“As pregnant women are at a higher risk from severe complications from influenza than non-pregnant women, yet are expected to benefit similarly from immunization, it is desirable to optimize immunization strategies...”

Percentage of women vaccinated for influenza before and during pregnancy, overall and by health care provider recommendation and offer* of influenza vaccination, Colorado and United States

Colorado PRAMS, 2012-13 and 2013-14



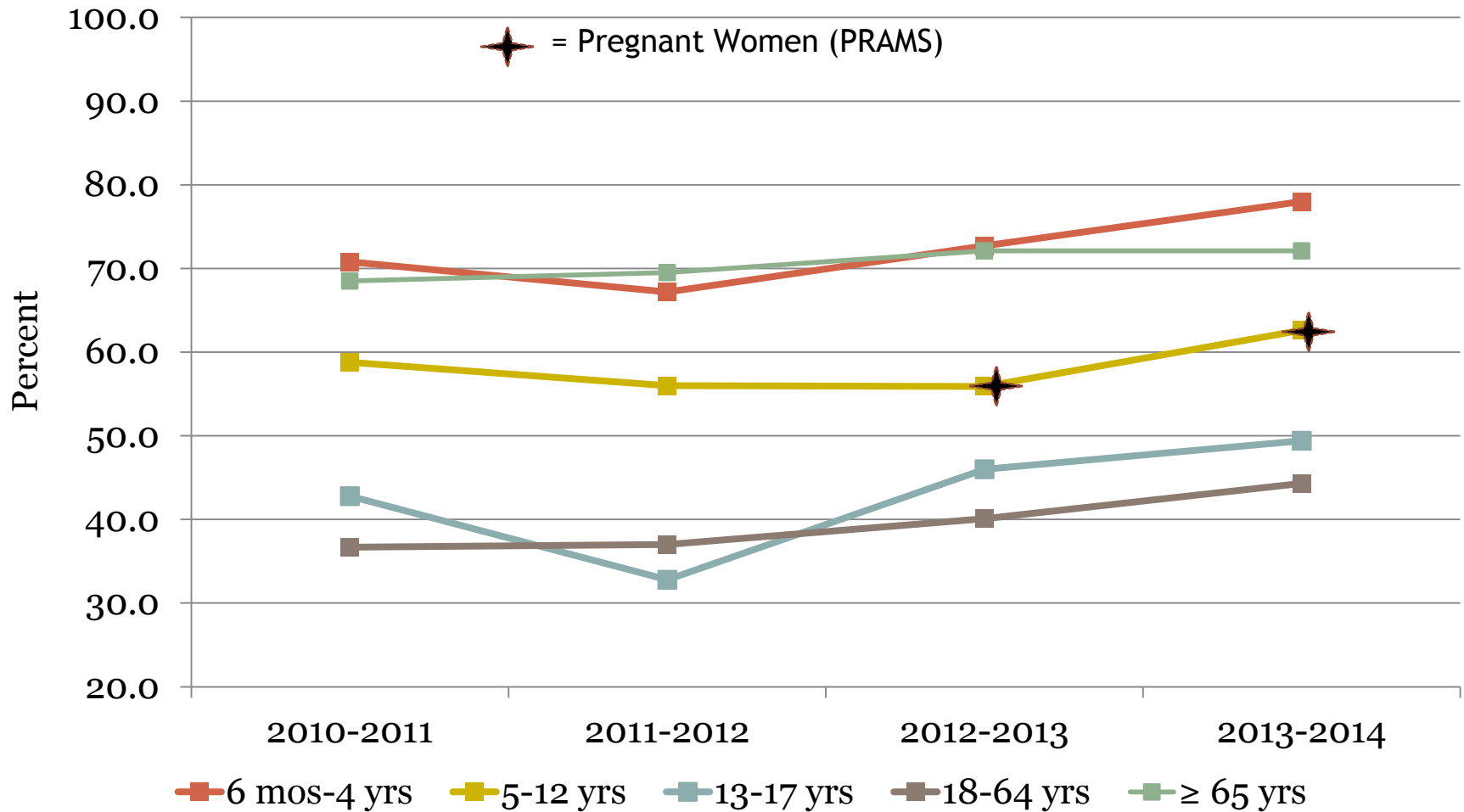
U.S. Internet Panel Survey 2014-15



Vaccination Rates



Colorado Influenza Vaccination Coverage, by Age Group, 2010–2013 (BRFSS)



*There are no significant differences in the immunization rate across years for each age group

Benefits of Maternal IIV Vaccine for Neonates and Young Infants



- Reduces risk of prematurity by 40%¹
- Reduces influenza-related hospitalization during the first 6 months by 90%²



What about breastfeeding?



- Independently decreases risk or severity of respiratory illness^{1,2,3,4,5}
- Maternal influenza vaccination results in sustained high levels of actively produced anti-influenza IgA in breast milk that may provide local mucosal protection for the infant for at least 6 months⁶
- Maternal IIV positively modifies effect of breast feeding on prevention of influenza infection
- Quantified benefit of transplacental IgG vs. local mucosal IgA?

Breastfeeding (IgA)	Maternal IIV (IgG)	Overall Protection
+		+
+	++	+++
	++	++



Influenza Vaccine Safety

Vaccine Safety Monitoring



- **Vaccine Adverse Event Reporting System-**
 - National vaccine safety surveillance program run by CDC and FDA
 - Early warning system, detect signals to investigate
 - Healthcare providers are required by law to report any conditions on the RET (Reportable Events Table) to VAERS, and are strongly encouraged to report clinically significant or unexpected events following vaccination.
- **Vaccine Safety Datalink**
 - CDC and health care organization collaborative
 - Kaiser Permanente Colorado
 - Population-based risk, rates of Adverse Events
 - Population of 7 million, 500,000 children less than 6



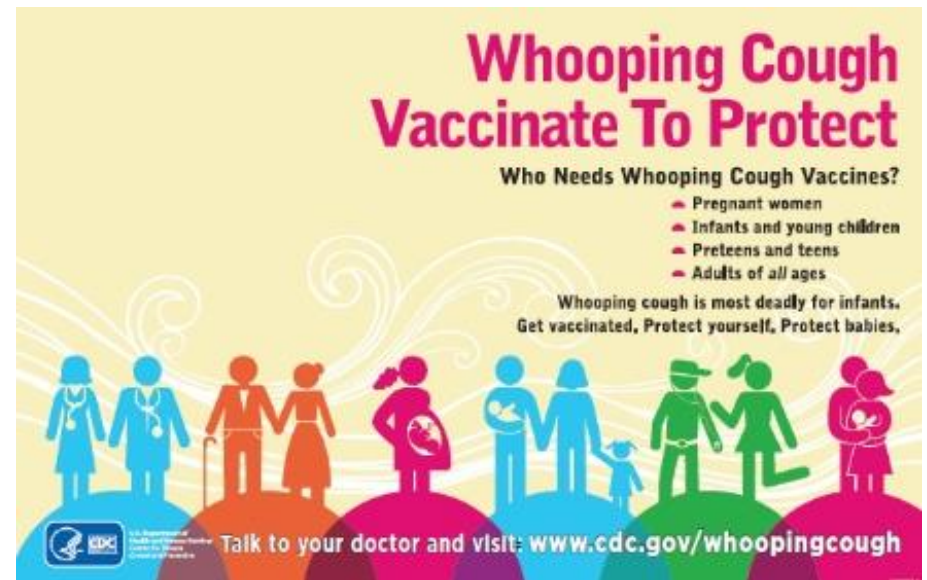
Influenza Vaccine Safety Studies



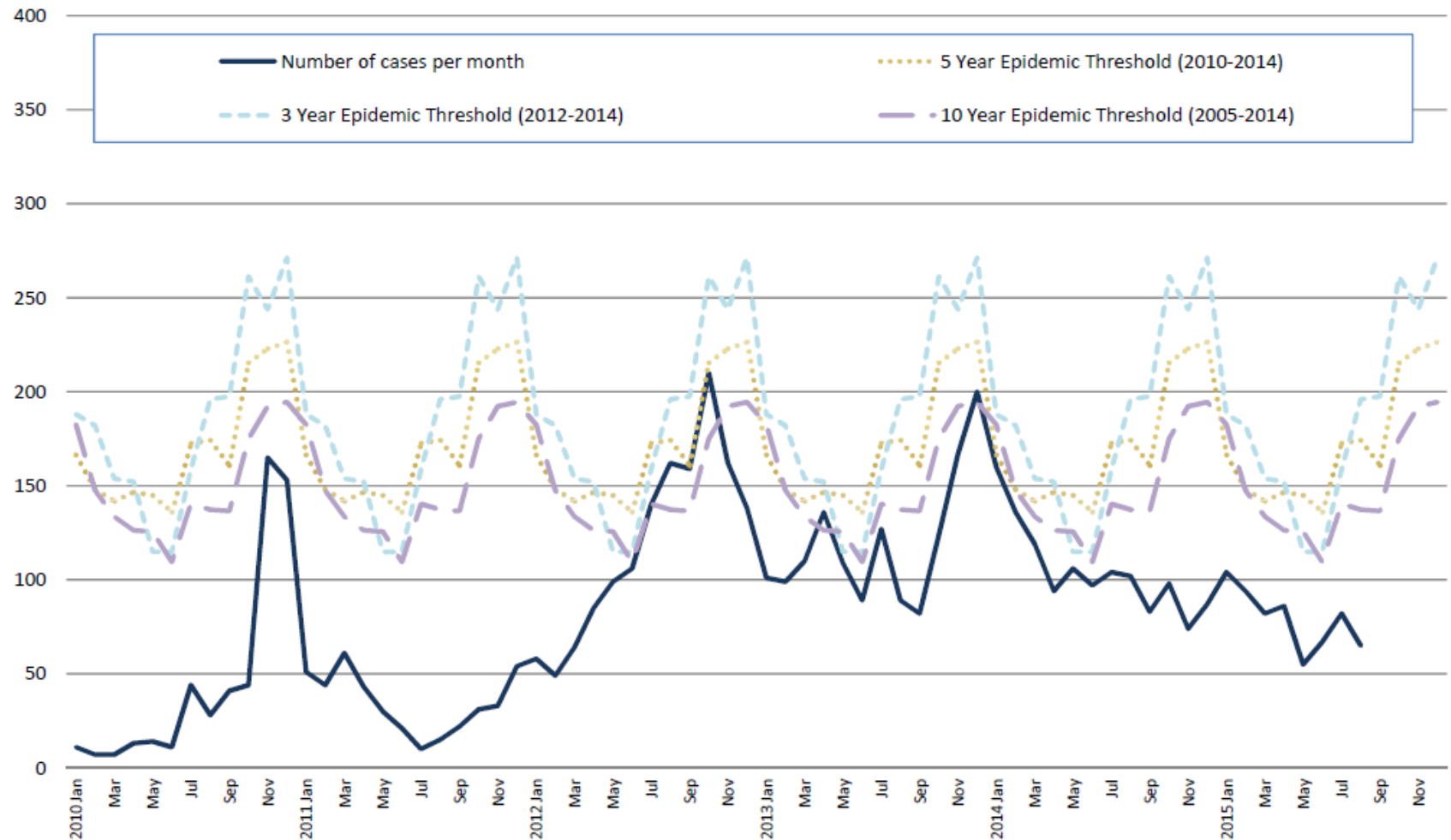
- Review of reports to the Vaccine Adverse Reporting System ([VAERS](#)) ([Moro et al, 2011](#)) found no link between pregnancy complications or adverse fetal outcomes among pregnant women and flu shots or nasal spray flu vaccine.
 - While the nasal spray is not recommended for pregnant women, researchers were reassured to find that the accidental administration of the nasal spray vaccine to pregnant women did not result in any complications.
- Study using Vaccine Safety Datalink ([VSD](#)) data ([Irving et al, 2013](#)) found no increased risk of miscarriage among pregnant women who received flu vaccines in the 2005-06 or 2006-07 flu seasons.
- A large study using [VSD](#) data ([Kharbanda et al, 2013](#)) found no increased risk for adverse obstetric events (like chorioamnionitis, pre-eclampsia, or gestational hypertension) for pregnant women who received the flu vaccine from 2002 to 2009 when compared to pregnant woman who were not vaccinated.
- A [VSD](#) study ([Nordin et al, 2014](#)) compared pregnant women who received the flu shot with an equal number of pregnant women who did not receive the flu shot during the 2004-05 and 2008-09 flu seasons, and found no differences between the two groups in the rates of premature delivery or small for gestational age infants.



Pertussis

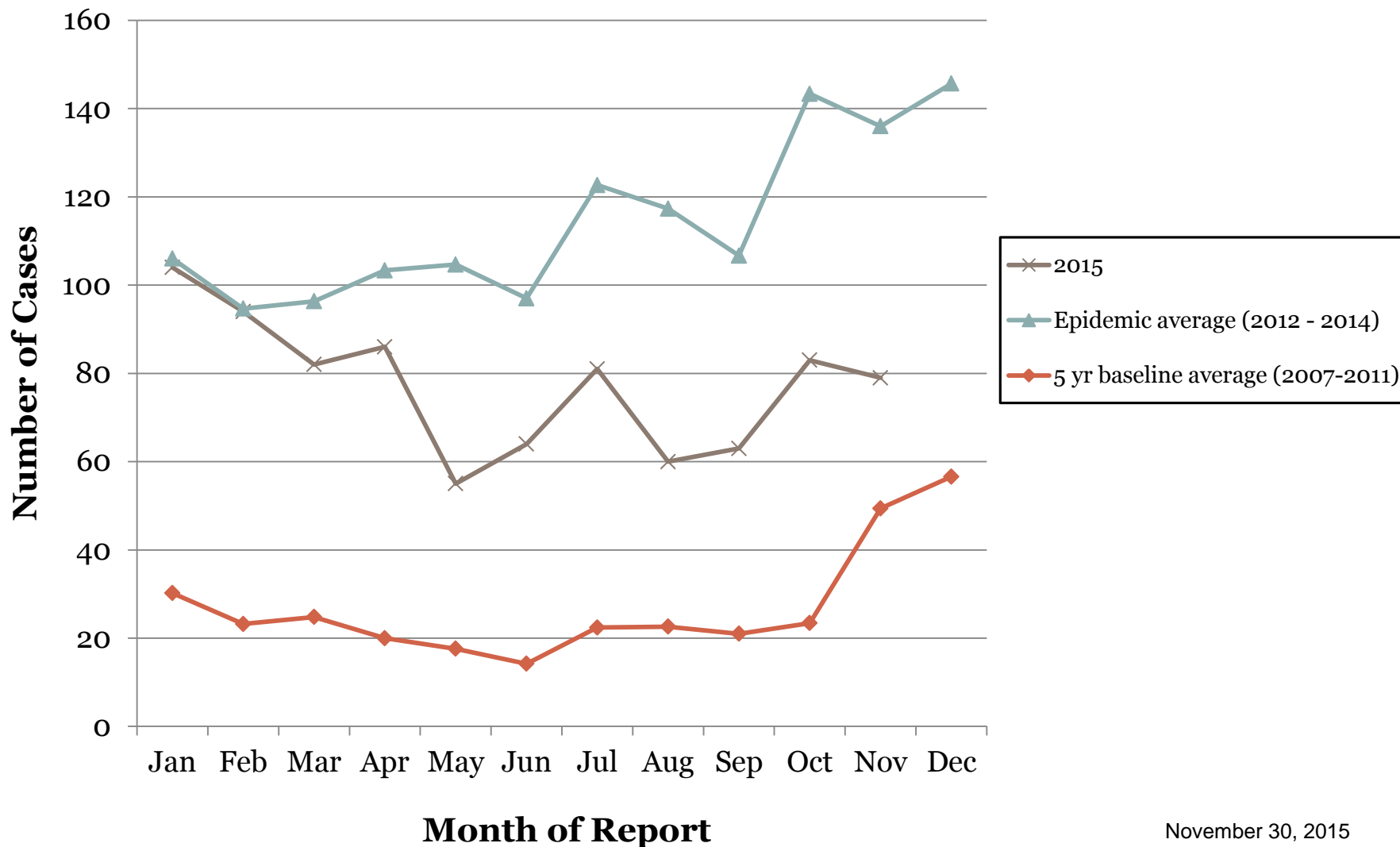


Reported Pertussis Cases by Month and Year with Projected Baseline and Epidemic Thresholds, Colorado, 2005-2015 (provisional)



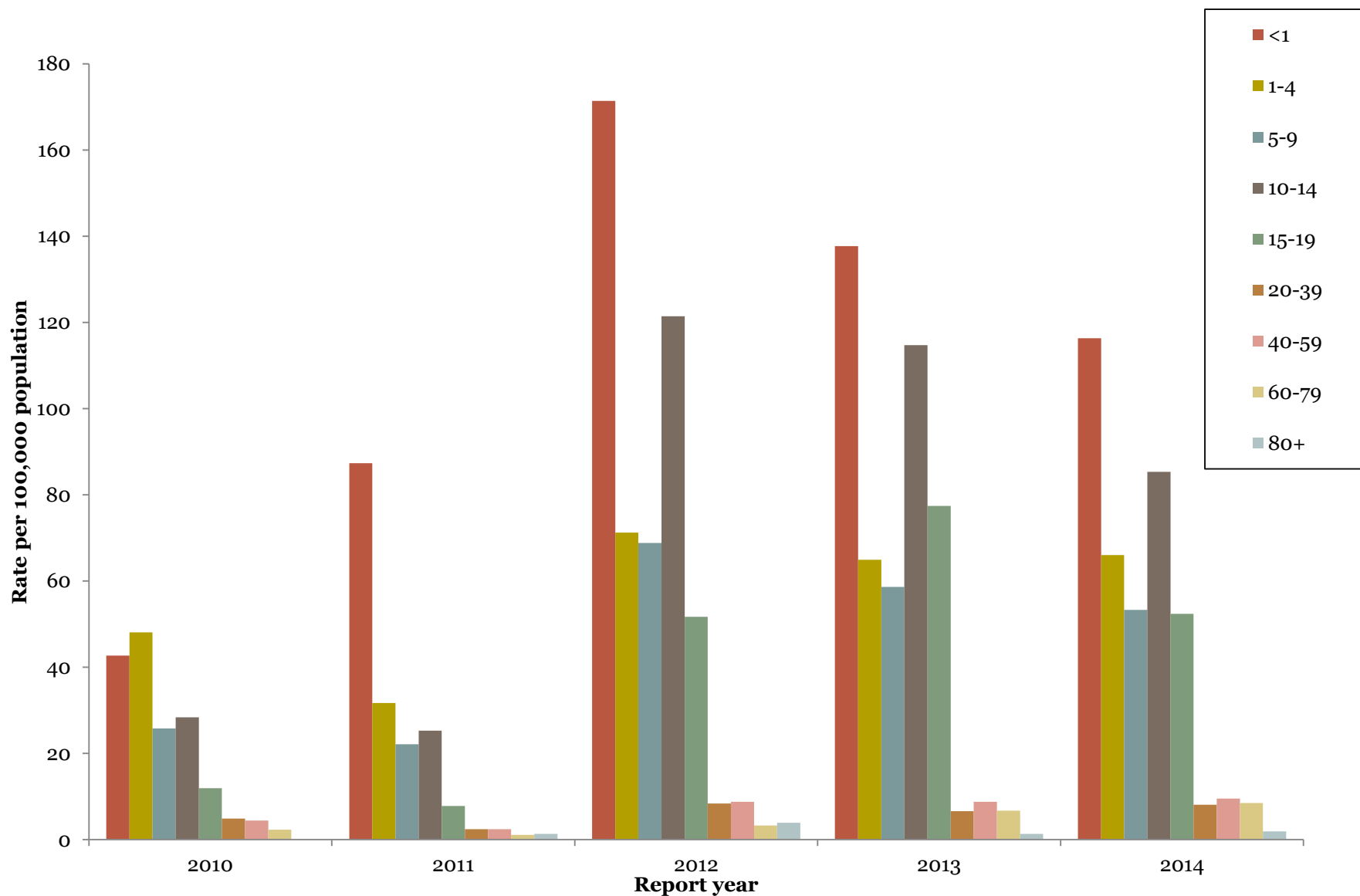
Updated 9/9/2015

Pertussis Cases by Month of Report, Colorado Provisional 2015 (year-to-date) vs. Epidemic Average (2012 - 2014) vs. 5-Year Baseline Average (2007-2011)



November 30, 2015

Rates of Pertussis by Age Group, Colorado, 2010 - 2014



Severity of Illness in Infants



- Infants <6 months are at highest risk of pertussis infection, hospitalization, and death
- Pertussis deaths occur almost exclusively in infants <3 months of age
- Among infants <12 months who get pertussis, 50% are hospitalized
 - Among hospitalized infants:
 - ✦ 67% experience apnea
 - ✦ 23% develop pneumonia
 - ✦ 1.6% die
- 10-20 infant deaths per year in the U.S.



Infant Sources of Infection

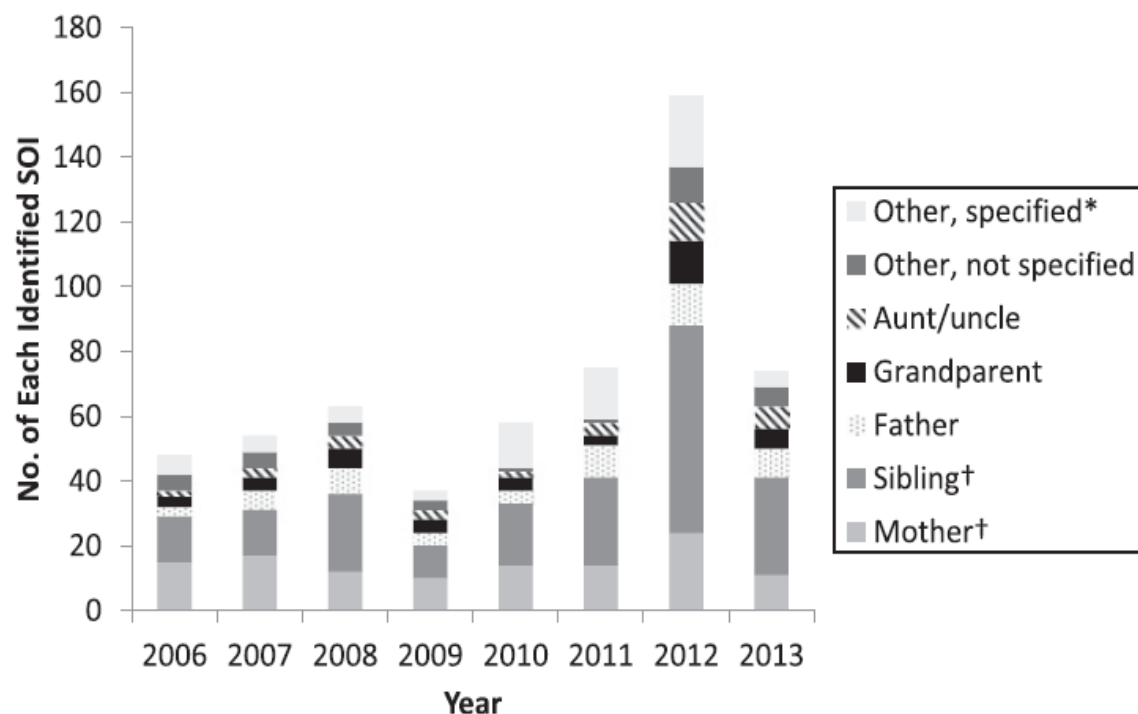
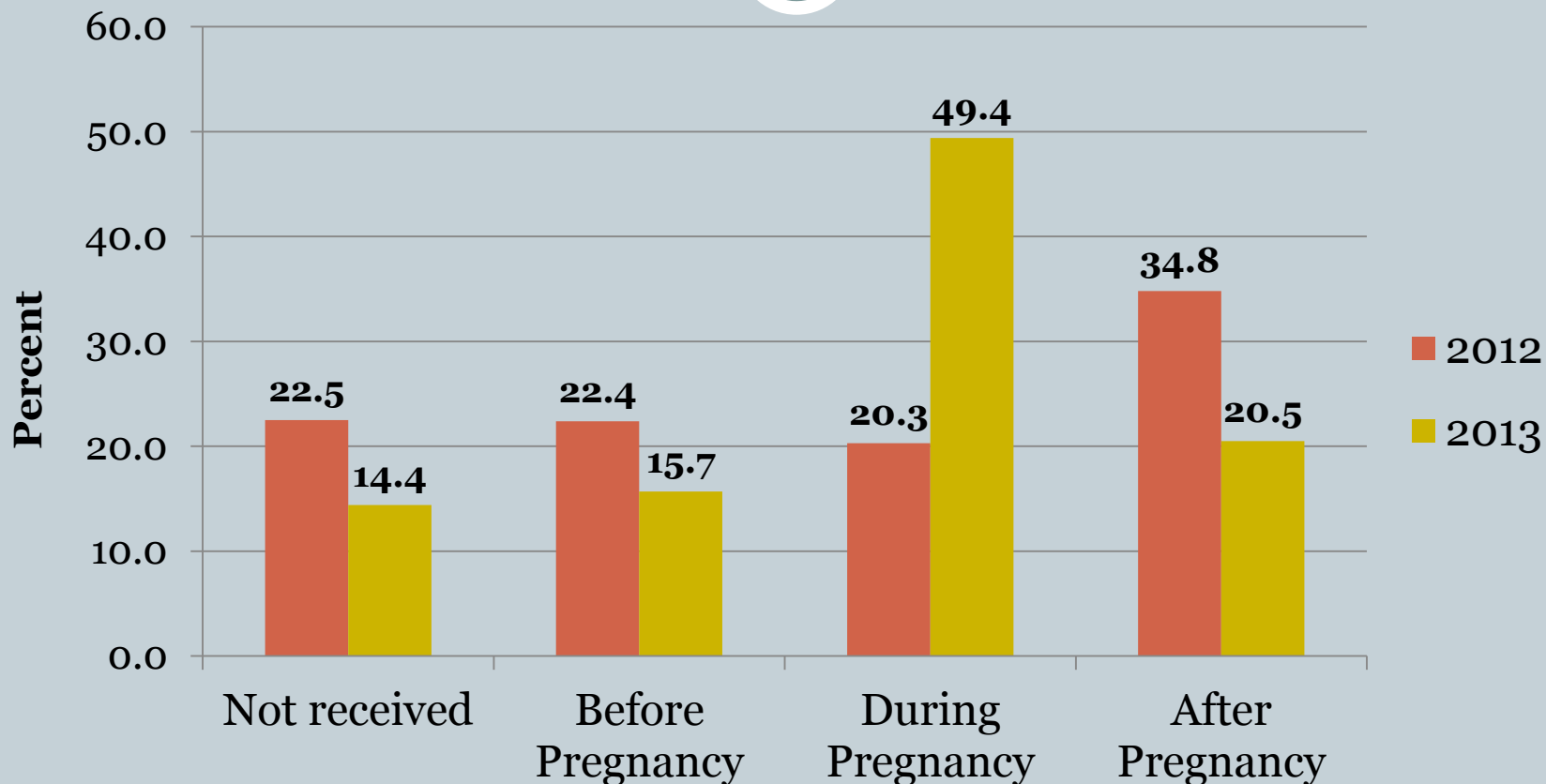


FIGURE 2

Relationship of identified sources of infection, by year, 2006–2013. * Includes day-care contacts, cousins, friends, babysitters, and nieces/nephews, unknown source ($n = 1$). † $P < .05$.

Tdap Immunization, Colorado Pregnancy Risk Assessment and Monitoring System (PRAMS), 2012/2013*



*Mothers receiving a Tdap shot during pregnancy increased significantly between 2012 and 2013



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2005- Single dose of Tdap before or after pregnancy
Oct 2011- Single dose of Tdap during pregnancy if previously unvaccinated
Oct 2012- dose of Tdap during every pregnancy

Timing of Tdap



- Healy *et al.* found that infants of mothers immunized preconception or in early pregnancy had insufficient pertussis-specific IgG at 2 months of age
- Munoz *et al.* observed higher pertussis-specific IgG at birth and 2 months among infants whose mothers received vaccine at 30-32 weeks vs. postpartum. No difference following 4th DTaP dose.
- Raya *et al.* found that women vaccinated at 27-30 week had higher pertussis specific IgG than those vaccinated at 31-36 and >36 weeks
- Amirthalingam *et al.* measured vaccine effectiveness at 91% when mothers were vaccinated at least 4 weeks prior to birth. VE was 38% when vaccination was 0-6 day before or 1-13 days after birth



Pertussis Vaccine Safety

Tdap Safety



- Randomized trial¹ and several observational studies^{2,3,4} have not identified increase in significant maternal, infant, or pregnancy outcomes.
- Available data have not shown increased risk of AEs after two doses of Tdap. Data for >2 doses are limited but reassuring⁵
- Cohort study found small but statistically significant increased risk of chorioamnionitis diagnosis⁶



Co-administration of Tdap and IIV



- Skumaran *et al.* (Obstet Gynecol Nov 2015) compared concomitant and sequential vaccination of Tdap and IIV
- 36,844 pregnancies in the Vaccine Safety Datalink
- Concomitant administration was not associated with higher risk of adverse acute outcomes or birth outcomes compared with sequential.



Best Practices



- Standing orders
- Routinize in office- 28 wks
- Immunization Registry- CIIS
- Obstetrical care provider recommendation
- Obstetrical care provider offer onsite
 - “...if the provider states the influenza vaccine is important and it is not available, this contradicts the original message of the vaccine’s importance”
- Recommendation and offer can overcome other barriers

Talking to patients



- Informing patients of the risks of being unvaccinated
- “Regret Avoidance”- inaction may feel safer
- Another way to avoid unnecessary risks
- Invite questions & address misinformation
 - Vaccine uptake positively associated with vaccine knowledge¹
- ACOG scripts

Resources



- ACOG Resources

<http://www.immunizationforwomen.org/>



- CDC Resources

<http://www.cdc.gov/vaccines/spec-grps/default.htm#preg>

Pregnant Women



- **Vaccines Before, During, and After Pregnancy**
Vaccine safety, your vaccine history, important vaccines to consider for women planning a pregnancy
- **Clinical guidelines for vaccinating pregnant women**
Includes routine and travel
- **Print materials about immunizations and pregnancy (flu specific)**
Vaccines help keep a pregnant woman and her growing family healthy.

More Resources



- **Billing and coding resources**
 - ACOG tools & on-demand webinar
 - ✦ <http://immunizationforwomen.org/>
- **Administration guidance**
 - Screening for contraindications
 - Storage and handling
 - Dose, Route, Site, Needle size
 - ✦ <http://www.immunize.org/clinic/>



Vaccines in Development



- **RSV**
 - Novavax, GSK, Novartis
 - Immunization of pregnant women with single dose during 3rd trimester to prevent RSV (subtypes A and B) associated LRTI in infants
 - Safe, well-tolerated, immunogenic in mothers & infants in phase II
 - Gates Foundation funding large Phase 3 Novavax study to measure clinical efficacy beginning 2016
- **Group B Strep**
 - Novartis
 - Multi-center (UCD) phase 2 study evaluating safety and immunogenicity in healthy pregnant women



Summary



- Tremendous rationale
 - More severe illness in pregnancy
 - Burden of disease greatest in young infants
 - Maternal-fetal physiology
 - Safe & highly effective intervention
- Evidence-based tools & resources
- Additional opportunity to build on maternal immunization platform in the future



Thank you!



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