

Impact of influenza on respiratory-related hospitalizations and office visits in pregnant women: From evidence to public health practice

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Thanks to the Co-investigators and Collaborators

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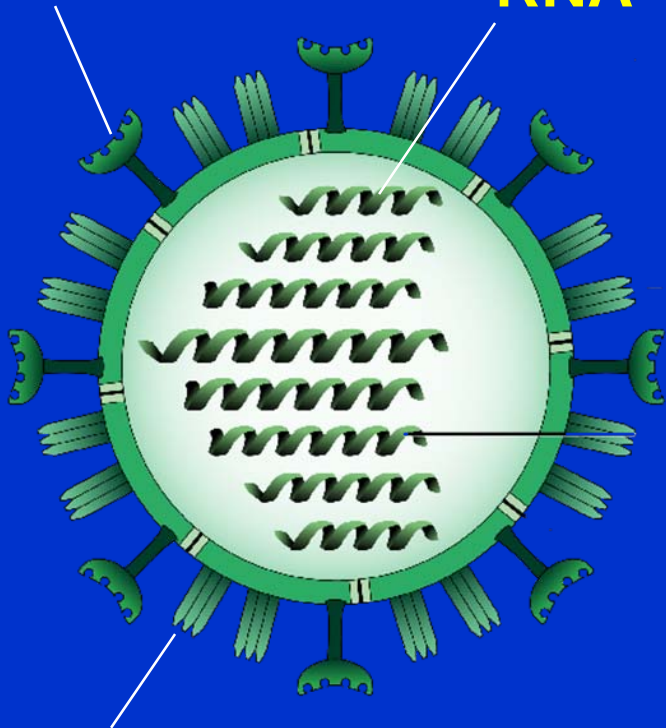
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Deshayne Fell: data analyst

Thanks to RCP and PHRU for access to data!

Background

Neuraminidase **RNA**



Hemagglutinin

- Enveloped RNA virus with 8 different segments
- Types A, B, and C: Significant differences in structure, genetics, organization, host range, epidemiologic and clinical characteristics
- Covered with surface projections or spikes -- Hemagglutinin and neuraminidase-- used to subtype influenza A virus types.

INFLUENZA – Virology



Amazing ability to change:

- **Antigenic Drift (A and B)**
 - Comparatively minor antigenic change
 - Why we need a new vaccine each year
 - Causes epidemics: a higher than normal level in the population, usually much higher than endemic, and usually short-term
- **Antigenic Shift (A only)**
 - Major antigenic change
 - Leads to pandemics—novel strain, little immunity, epidemic spreading between continents



Epidemiology

- Each year in Canada up to 75,000 people are admitted to hospital with influenza and 6700 die
- 90% of deaths occur in patients > 65years
- 50% of influenza-related deaths occur in nursing homes
- During outbreaks, attack rates of 5-20% in general public - attack rates as high as 30-50% during severe Influenza A epidemics

INFLUENZA IS THE SINGLE MOST COMMON VACCINE PREVENTABLE DISEASE



Influenza- associated Morbidity and Mortality During Pregnancy

- Excess deaths among previously healthy pregnant women documented during influenza pandemics in 1918-19 and 1957-58
- Pneumonia reported in 50% cases in pregnant women with 50% associated maternal mortality
 - Maternal deaths accounted for 10% of all deaths in 57-58
 - 50% of all women of childbearing age who died were pregnant

Influenza- associated Morbidity and Mortality During Pregnancy

- High rate of pregnancy loss observed during 1918-19 pandemic (52%)
- Contributions of other risk factors for severe disease not explored

Influenza-associated Morbidity and Mortality During Pregnancy

- Impact of influenza on pregnant women in non-pandemic years less clear
- **NYC**- ↑ rate of maternal death with first appearance of H2N2 in 1957-58 (antigenic shift) but no ↑ risk in the 3 subsequent seasons when only drift occurred resulting in non-pandemic seasons

Widelock. Public Health Rep 1963;78:1-11

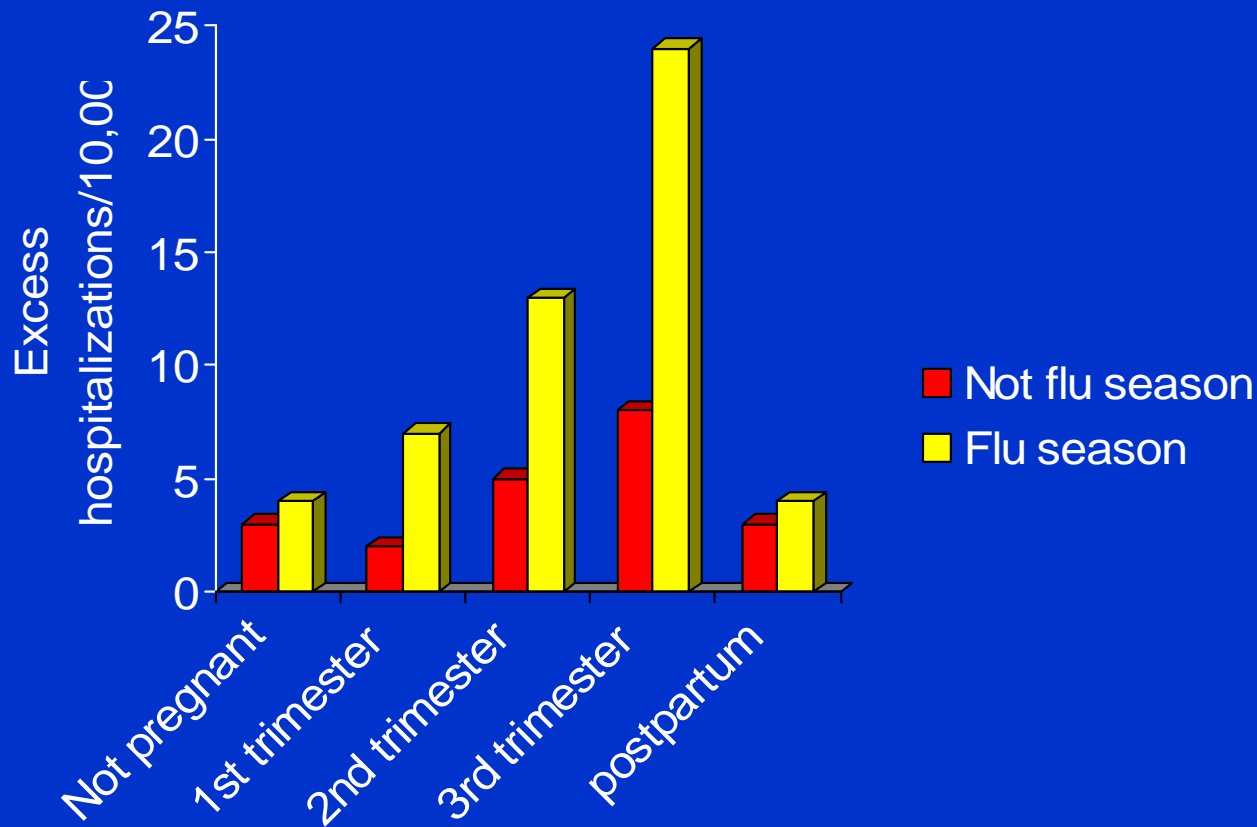
Influenza-associated Morbidity and Mortality During Pregnancy

- **Oregon**- 5,518 women for 5 years- ↑ medical visits for aRTI in pregnant women during a flu season with significant antigenic shift but not during seasons when only drift occurred

Mullooly. Public Health Rep 1986;101:205

- **Nottingham, UK**- 14 month case control - no differences in individual complications, but increased composite endpoint of fetal, obstetrical, and medical complications (106/181 vs 73/180; $p < .001$)

Irving. Br J Obstet Gynecol 2000;107:1282-9



Adapted from Neuzil Am J Epidemiol 1998;148:1094

- More recent 9-year matched cohort study demonstrated that those with asthma, a known risk factor for severe disease, accounted for half of all respiratory-related hospitalizations during influenza season
- 6% of women with asthma required hospitalization during flu season
- No increases in adverse perinatal outcomes were seen in either study

Influenza-associated Morbidity and Mortality During Pregnancy

- Black (Am J Perinatol 2004) examined influenza-related morbidity and impact of vaccine in a California cohort of ~50K mother-baby pairs over 5 flu seasons
 - rate of hospital admissions among pregnant women for flu or pneumonia was very low (8.2/100,000)
 - Despite recommendation for flu vaccine for all women in the 2nd or 3rd trimester during flu season, only 7.5% were immunized
 - Rates of OPD visits, hospitalization, and adverse perinatal outcome did not differ between vaccinated and unvaccinated women or their babies

Influenza Immunization Recommendations During Pregnancy

- ACIP (USA)- recommendation expanded in 2004 to include all women who will be pregnant during flu season regardless of trimester
- NACI (Canada)- all women at high risk for influenza complications, regardless of trimester

So, why the debate?

- NACI has raised concerns that the US data may not be generalizable to the Canadian population:
- Tennessee study population included predominantly young urban, African-Americans of low SES
- California study population included only HMO patients

So, why the debate?

- Presence and magnitude of increased maternal or neonatal morbidity associated with influenza in non-pandemic years not yet proven
- Although large studies may demonstrate increased risk, absolute disease risk is very low
- No studies designed to address protection of newborns
- Absolute potential public health impact of prenatal influenza immunization may be very low
- Robust Canadian data on which to base public health policy is needed

The Nova Scotia Influenza Study



Overall Objective

- To provide evidence for (or against) a recommendation for universal influenza immunization for pregnant women, irrespective of risk status

Specific Objectives

- To determine if rates of hospitalizations and office visits differ between flu season and peri-and non-influenza seasons, and if these rates differ by trimester of pregnancy
- To determine if underlying comorbidities predispose pregnant women to higher rates of hospitalization and office visits during flu season compared to healthy pregnant women

Specific Objectives

- To determine whether the rates of respiratory morbidity differ among women between the influenza season during pregnancy and the influenza season 1 year prior to pregnancy
- To determine whether fetal or neonatal outcomes differ among women with, and without, maternal respiratory morbidity
- To describe the rates and characteristics of women who receive influenza vaccine during pregnancy

Retrospective Cohort Study

- Cohort: Women who delivered an infant between 1990 and 2002
- Primary Exposure Variable:
 - Flu season
 - Peri-flu season
 - Non-flu season
- Primary Outcome Variable
 - Hospitalization for respiratory disease
 - Physician visits for respiratory disease

Defining Flu Seasons

Information obtained from Department of Health

- Start date: defined as the date when 2 or more isolates of influenza were identified in Nova Scotia in sequential weeks or 3 or more isolates identified in a single week
- Stop date: defined as the date when no influenza isolates were identified in Nova Scotia in 2 or more sequential weeks

Examples of Flu Seasons

1994-1995 March 5 to May 6

1997-1998 January 25 to April 11

1999-2000 December 12 to May 13

2001-2002 January 27 to June 15

2003-2004 November 1 to April 6

Defining Peri-flu and Non-flu Seasons

Peri-flu season:

- November 1 to start of flu season and 2 weeks following flu season

Non-flu season:

- Day following end of peri-flu season until October 31st

Databases

Atlee Perinatal Database used for:

- Defining the cohort (women who gave birth between 1990 and 2002)
- Determining “high-risk” women
- Deriving dates of each trimester of pregnancy
- Obtaining information on potential confounders
- Obtaining information on neonatal outcomes

Administrative Databases

Hospital Discharge Abstract Database and the Physician Billing Database (includes emergency room visits)

Primary Outcome: Cardio-respiratory conditions

- Pneumonia
- Influenza
- Acute respiratory conditions (such as bronchitis, bronchiolitis, acute laryngitis, etc)
- Heart failure and myocarditis

Definition of High Risk

High risk women, identified by Atlee Database, were women with any of the following:

- Pre-existing diabetes
- Asthma or other pulmonary disease
- Heart disease
- Renal disease
- Anemia during pregnancy

Analyses

Only the first hospital admission of the pregnancy was used

Date of hospital admission lagged by 4 days

Respiratory-related hospital admissions that included the birth were not counted as an admission

Analyses

Calculate rates of hospitalization/physician visits:

For: flu season, peri-flu season, non-flu season

By: trimester of pregnancy and year before pregnancy

? How do we account for the varying amount of time women may be pregnant in a particular season?

Nov 1st

Jan 24th

May 30th

June 14th

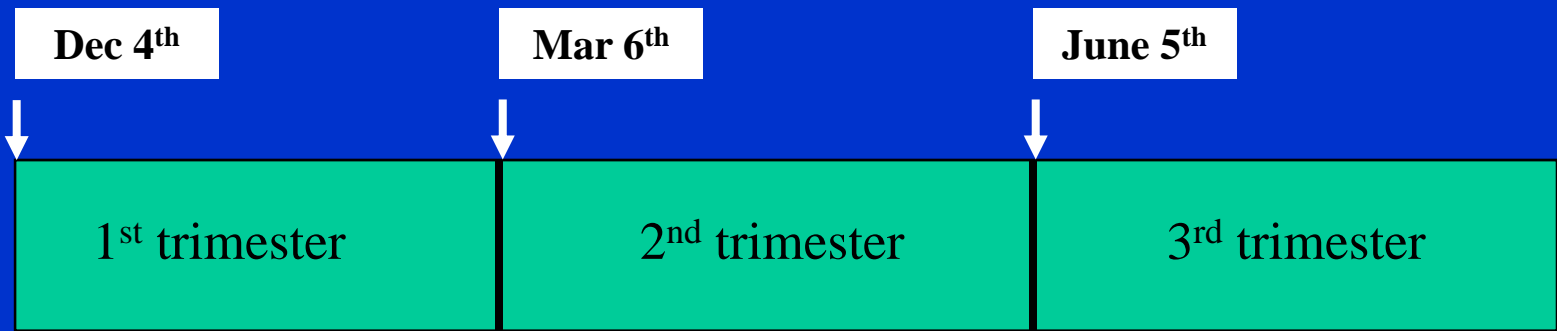
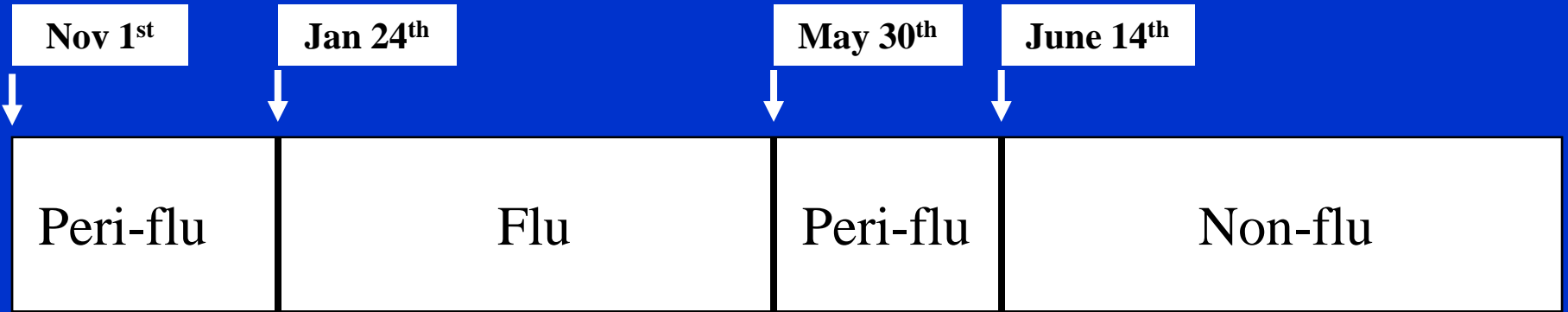


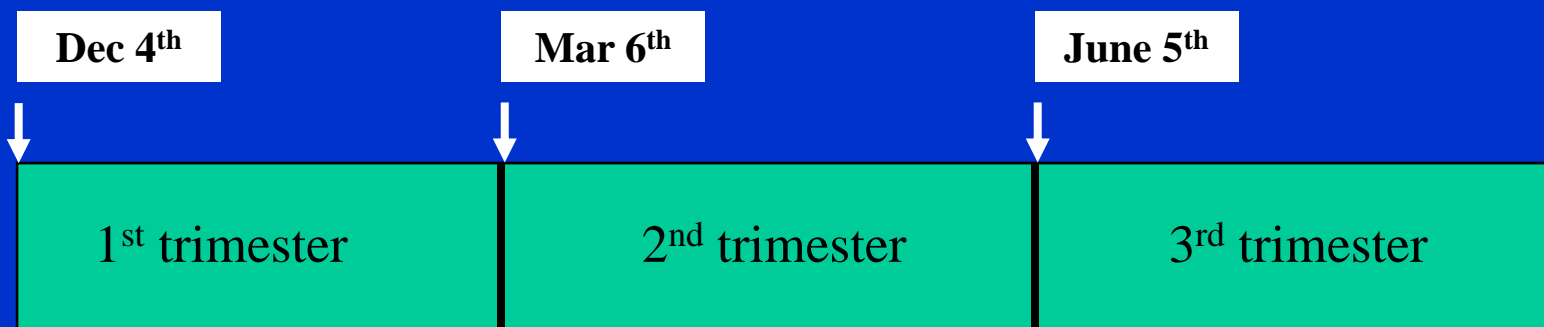
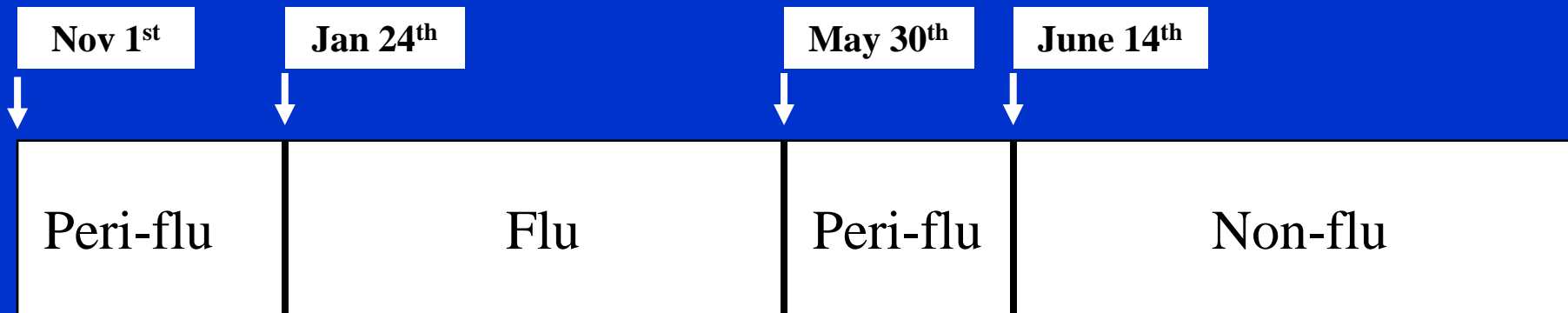
Peri-flu

Flu

Peri-flu

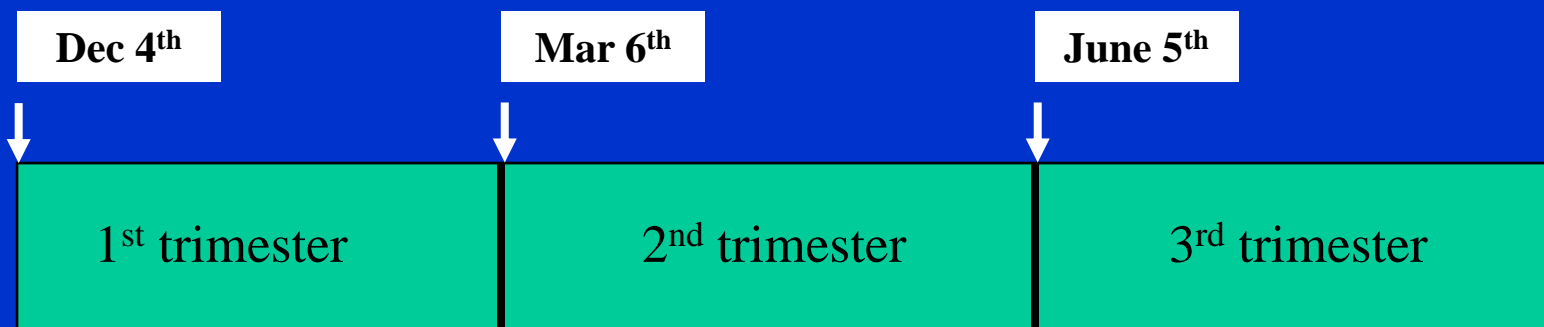
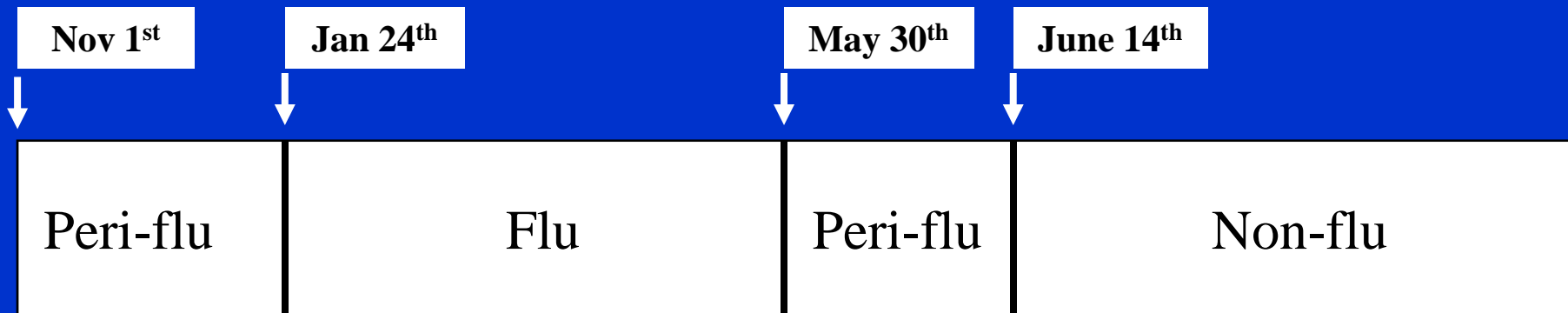
Non-flu





Peri-flu = 51 days
(1.8 WM)

Flu = 41 days
(1.4 WM)

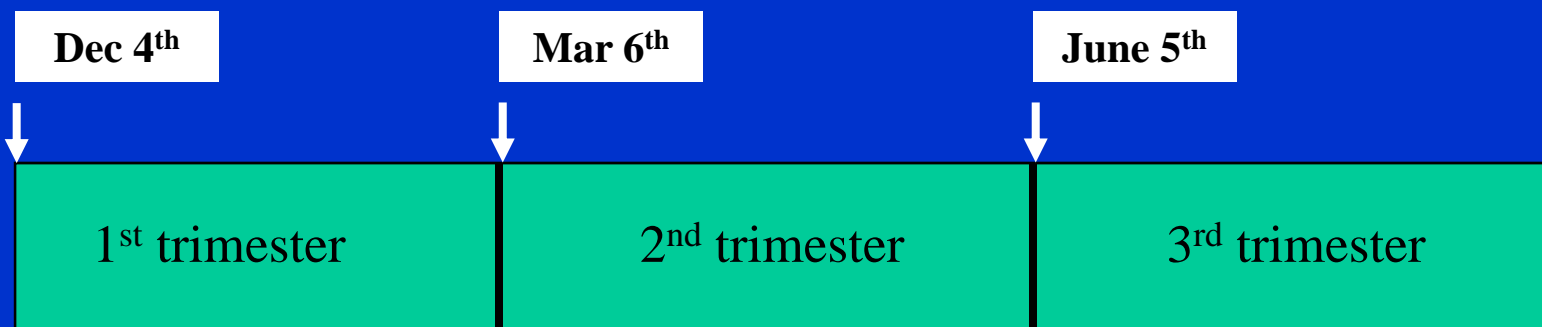
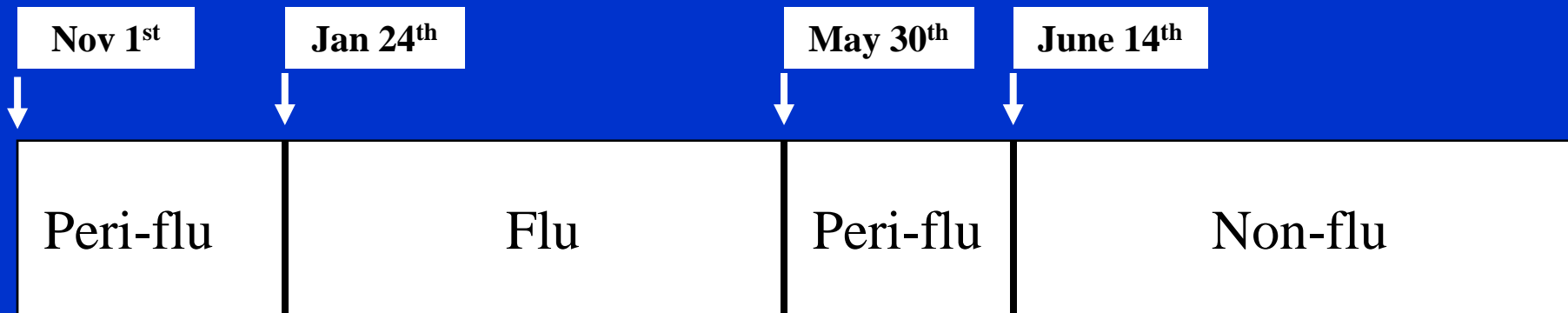


Peri-flu = 51 days
 (1.8 WM)

Flu = 41 days
 (1.4 WM)

Flu = 85 days
 (2.8 WM)

Peri-flu = 5 days
 (0.2 WM)



Peri-flu = 51 days
 (1.8 WM)

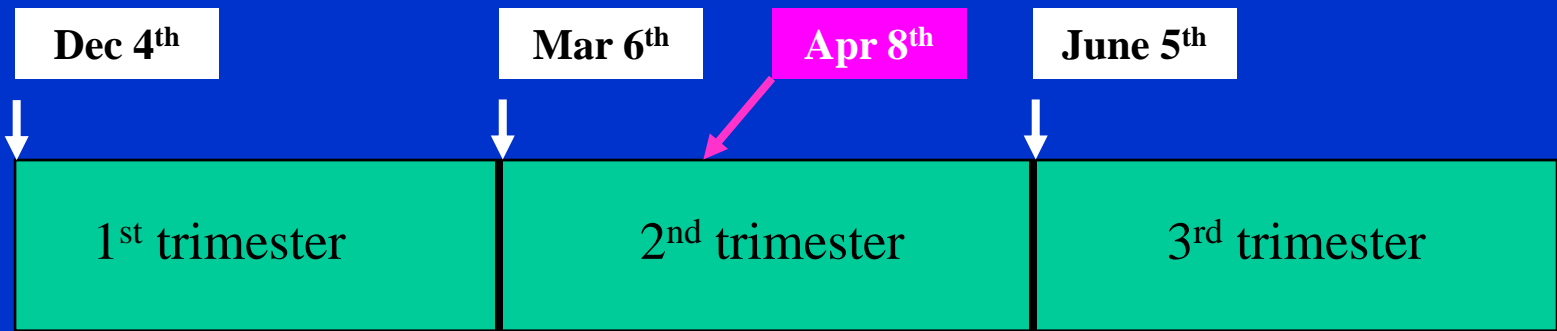
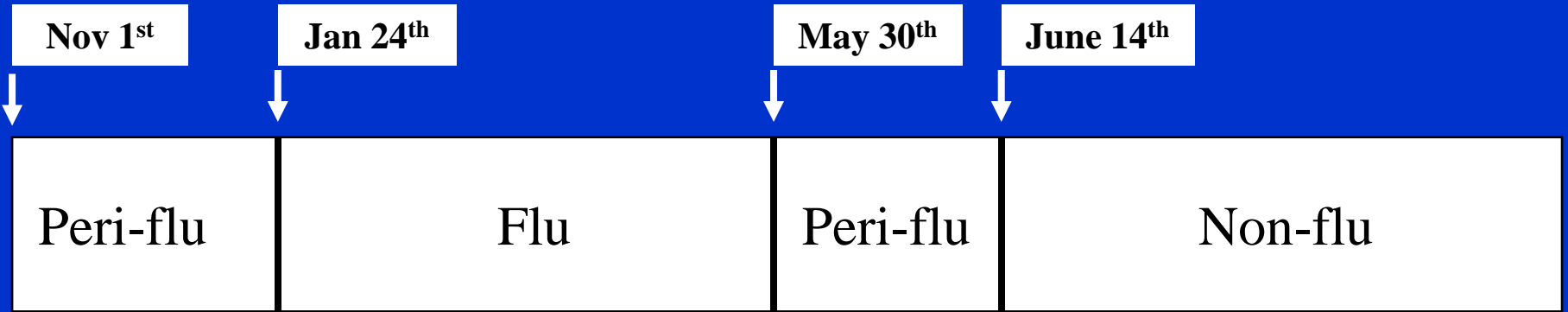
Flu = 41 days
 (1.4 WM)

Flu = 85 days
 (2.8 WM)

Peri-flu = 5 days
 (0.2 WM)

Peri-flu = 9 days
 (0.3 WM)

Non-flu = 88 days
 (2.9 WM)



Peri-flu = 51 days
(1.8 WM)

Flu = 41 days
(1.4 WM)

Flu = 85 days
(2.8 WM)

Peri-flu = 5 days
(0.2 WM)

Peri-flu = 9 days
(0.3 WM)

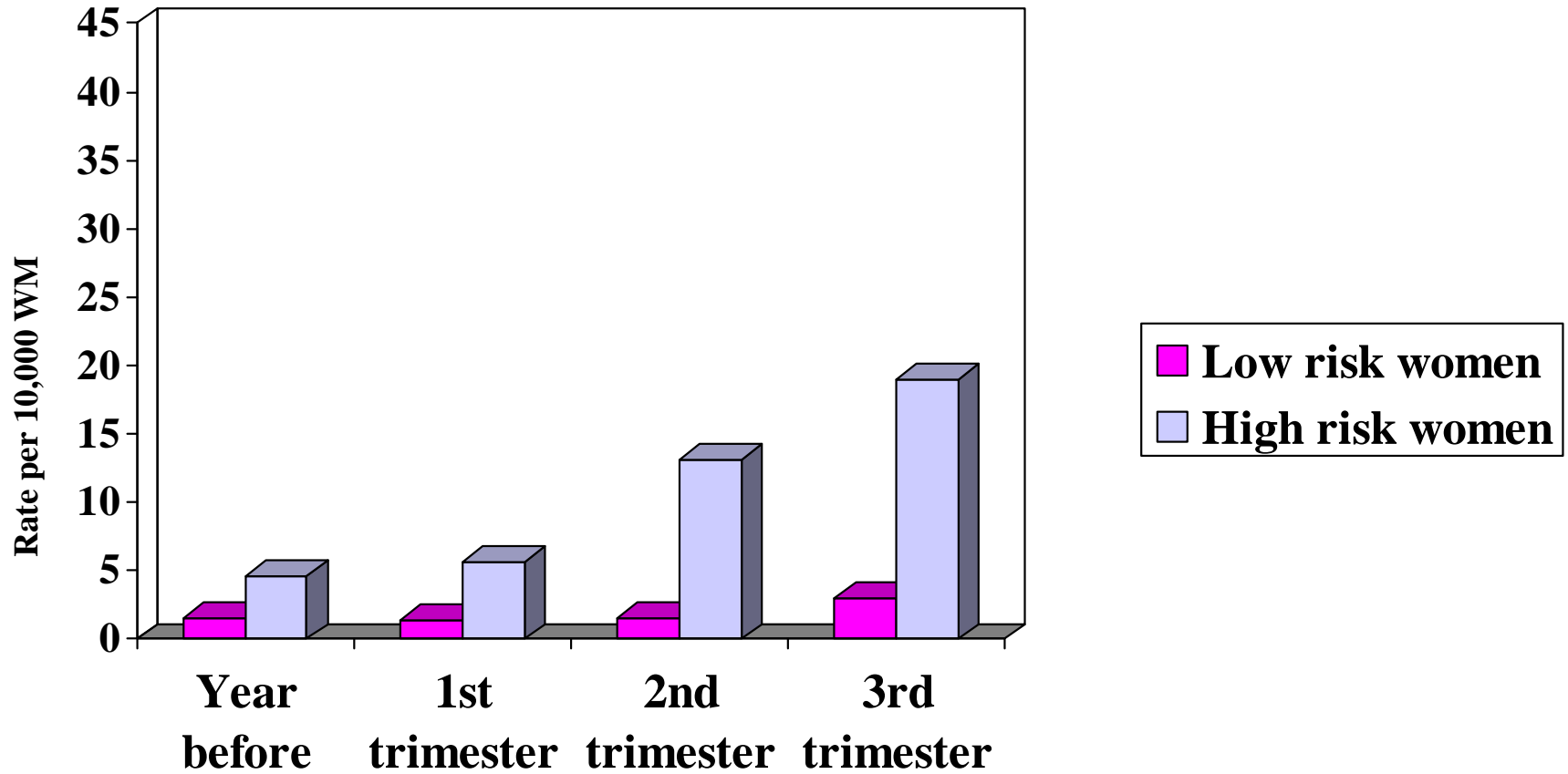
Non-flu = 88 days
(2.9 WM)

Respiratory admission

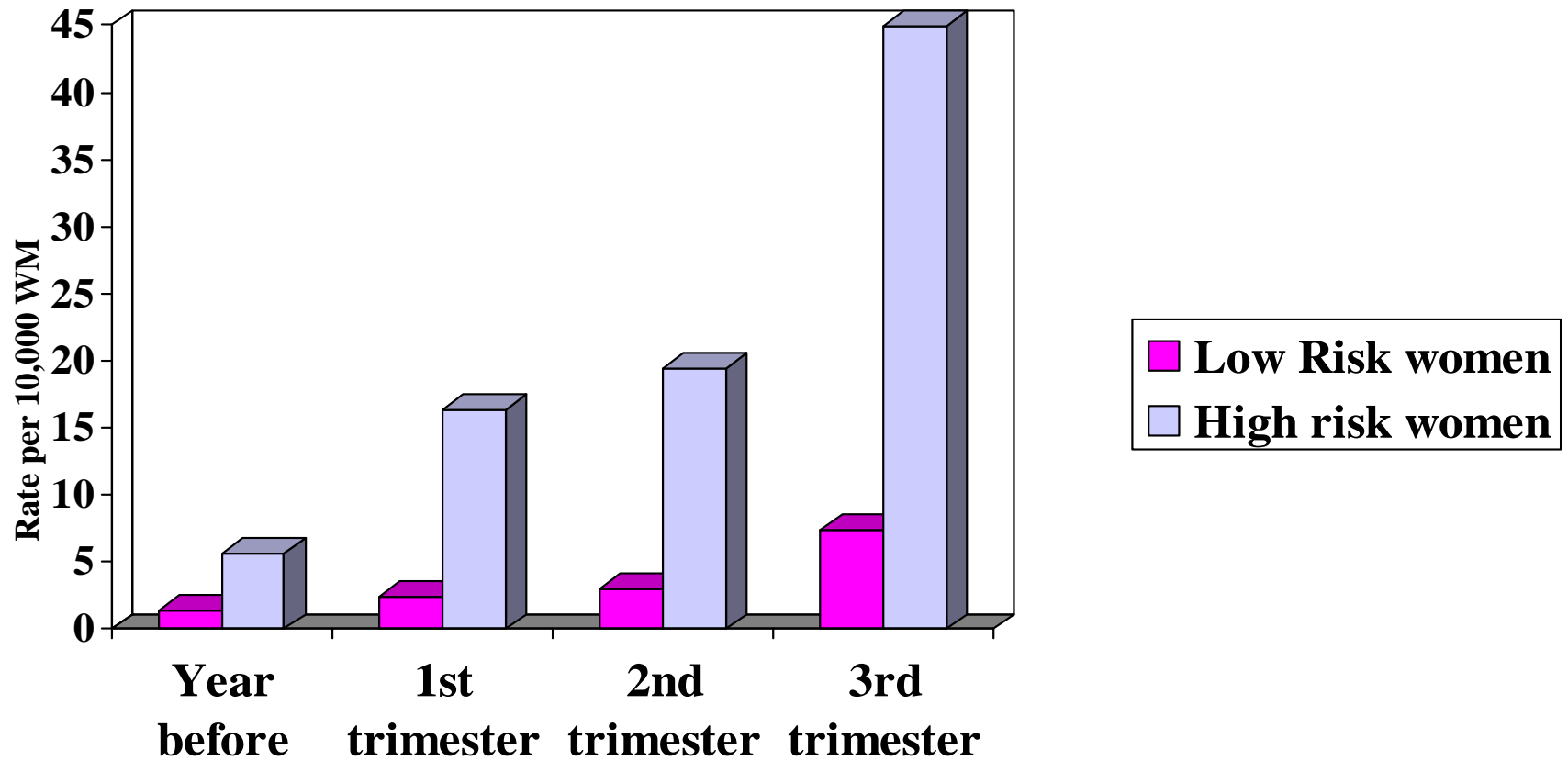
Results

- 134,188 women in cohort
 - 10% “high risk”
- 510 (0.4%) women had a respiratory-related hospital admission (not including their delivery admission)
- 33,775 (25.2%) women had at least one respiratory- related physician visit at some time during their pregnancy

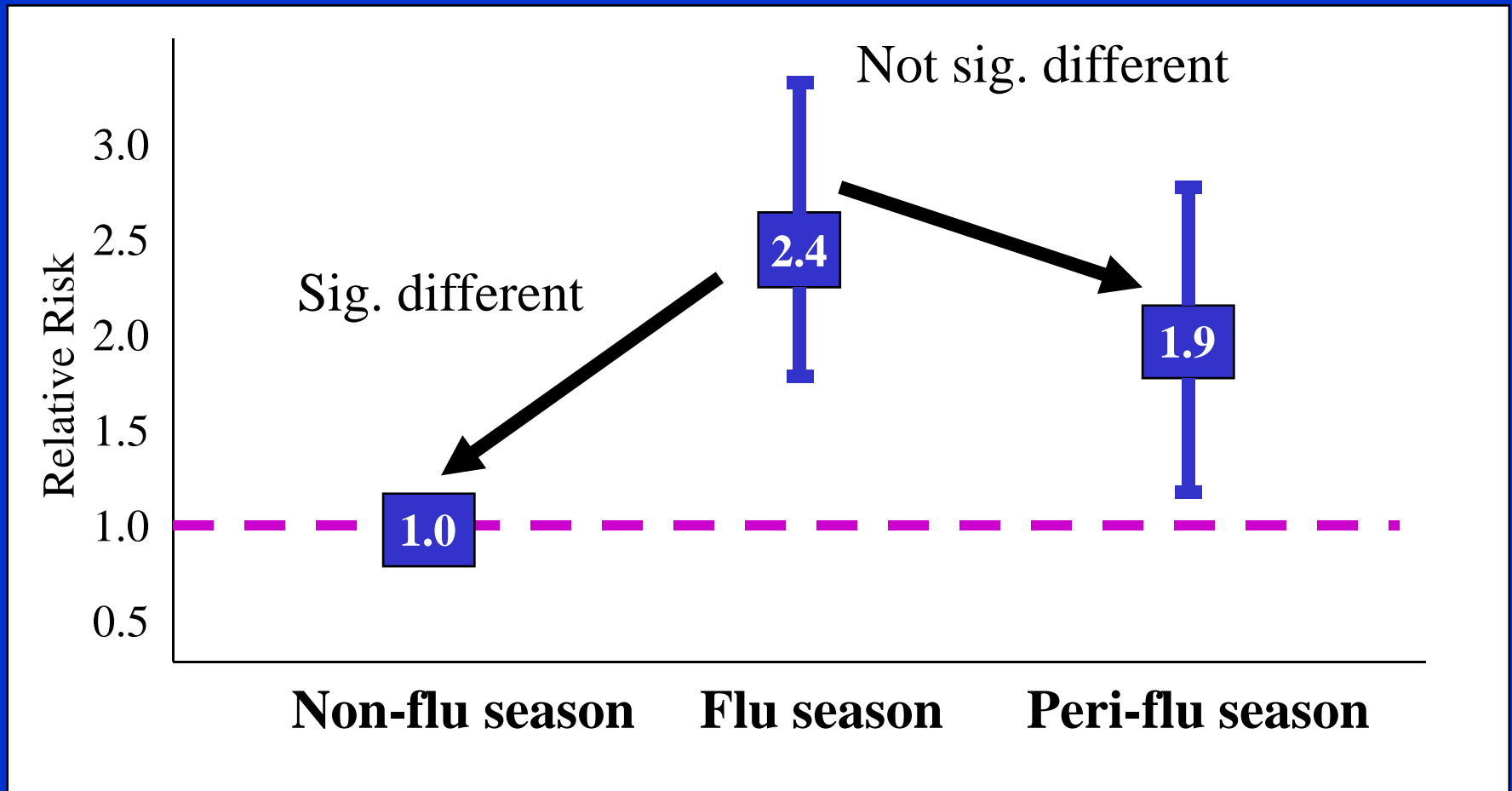
Rates of Respiratory-Related Hospitalizations in the Non-flu seasons



Rates of Respiratory-related Hospitalizations in the Flu Seasons

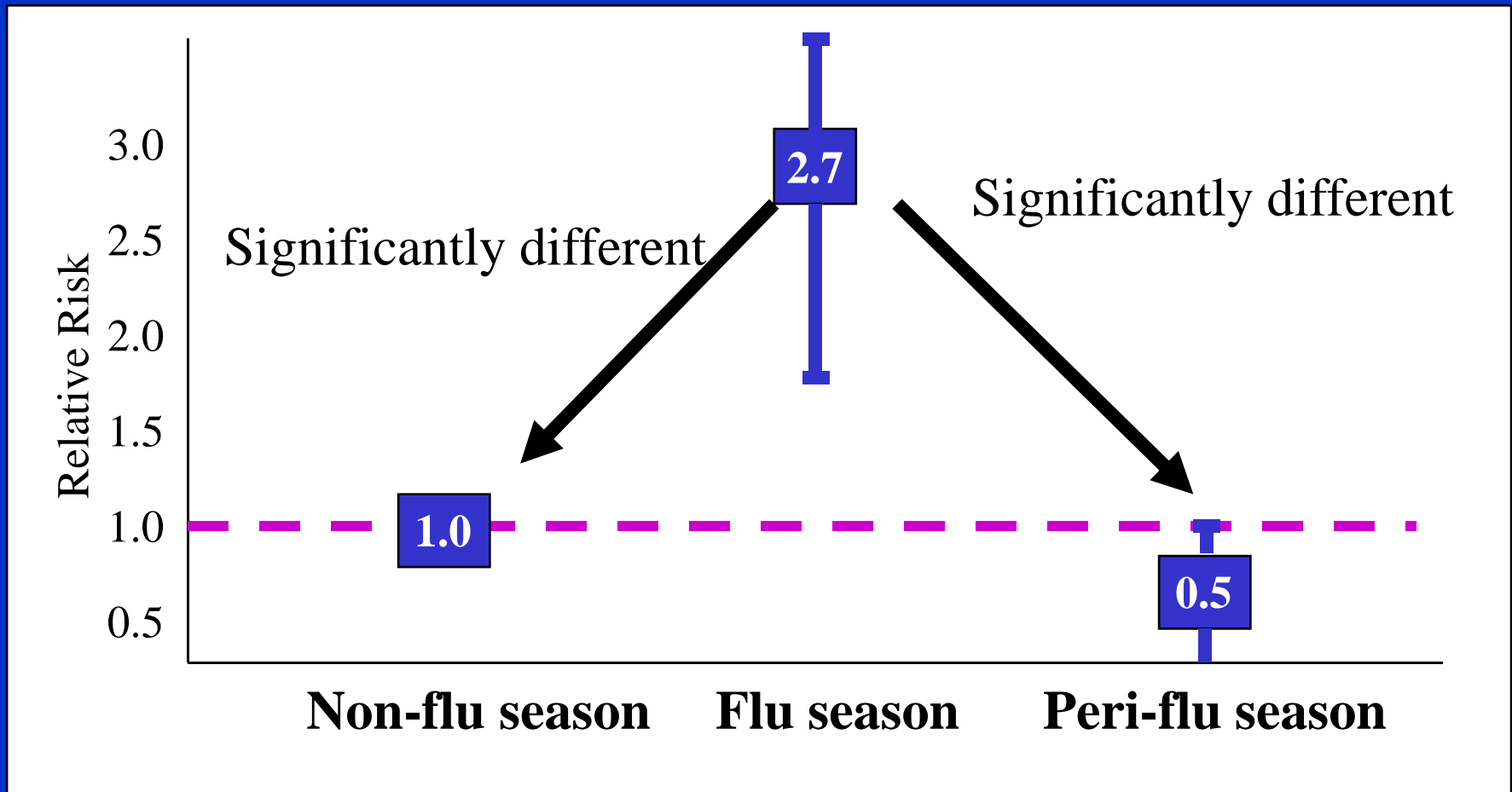


Relative risk of 3rd trimester hospitalization during flu and peri-flu season compared to non-flu season: Low-risk women



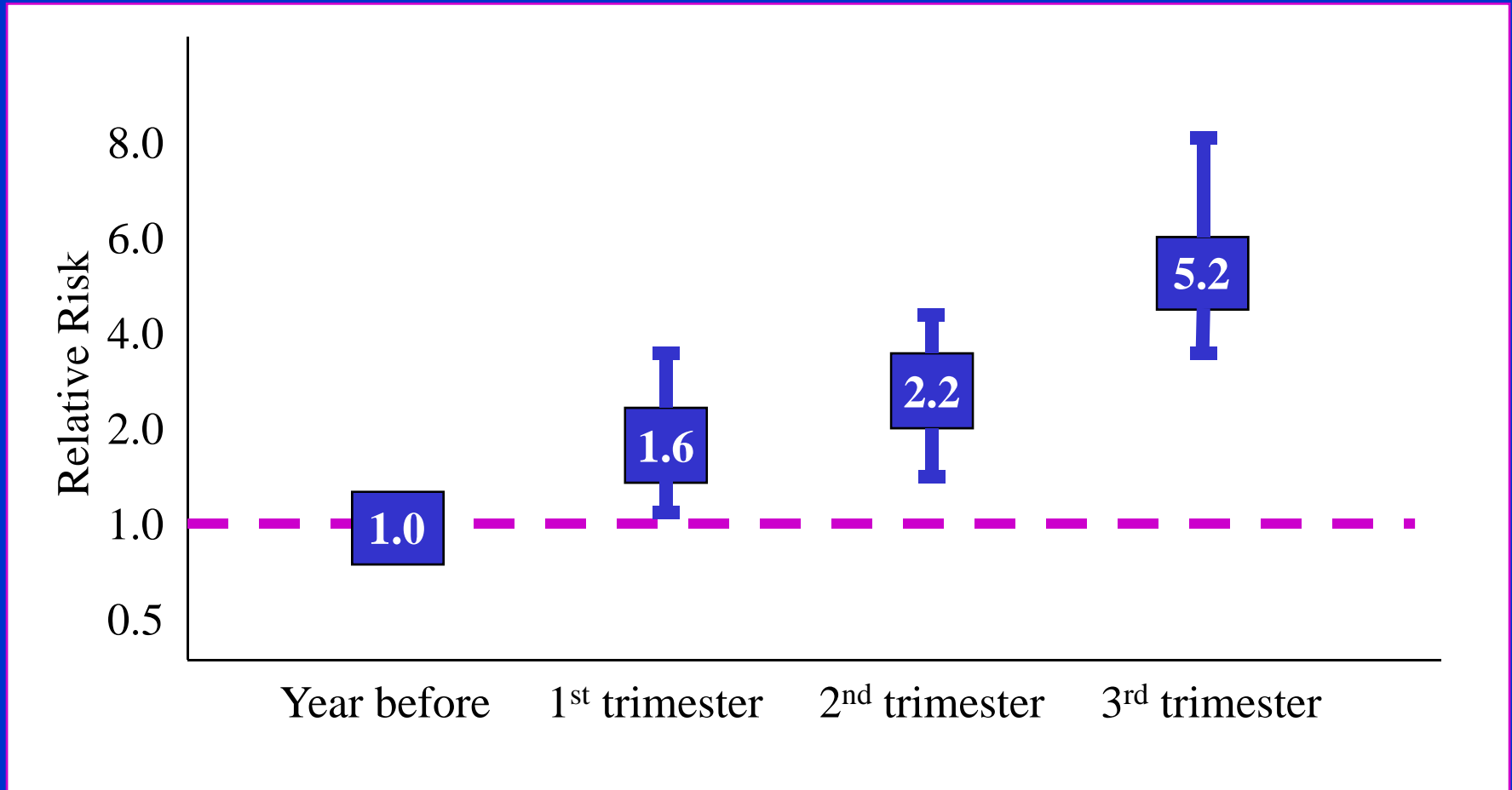
Adjusted for maternal age, maternal smoking total number of siblings less than 5 and income support in birth year

Relative risk of 3rd trimester hospitalization during flu and peri-flu season compared to non-flu season: High-risk women



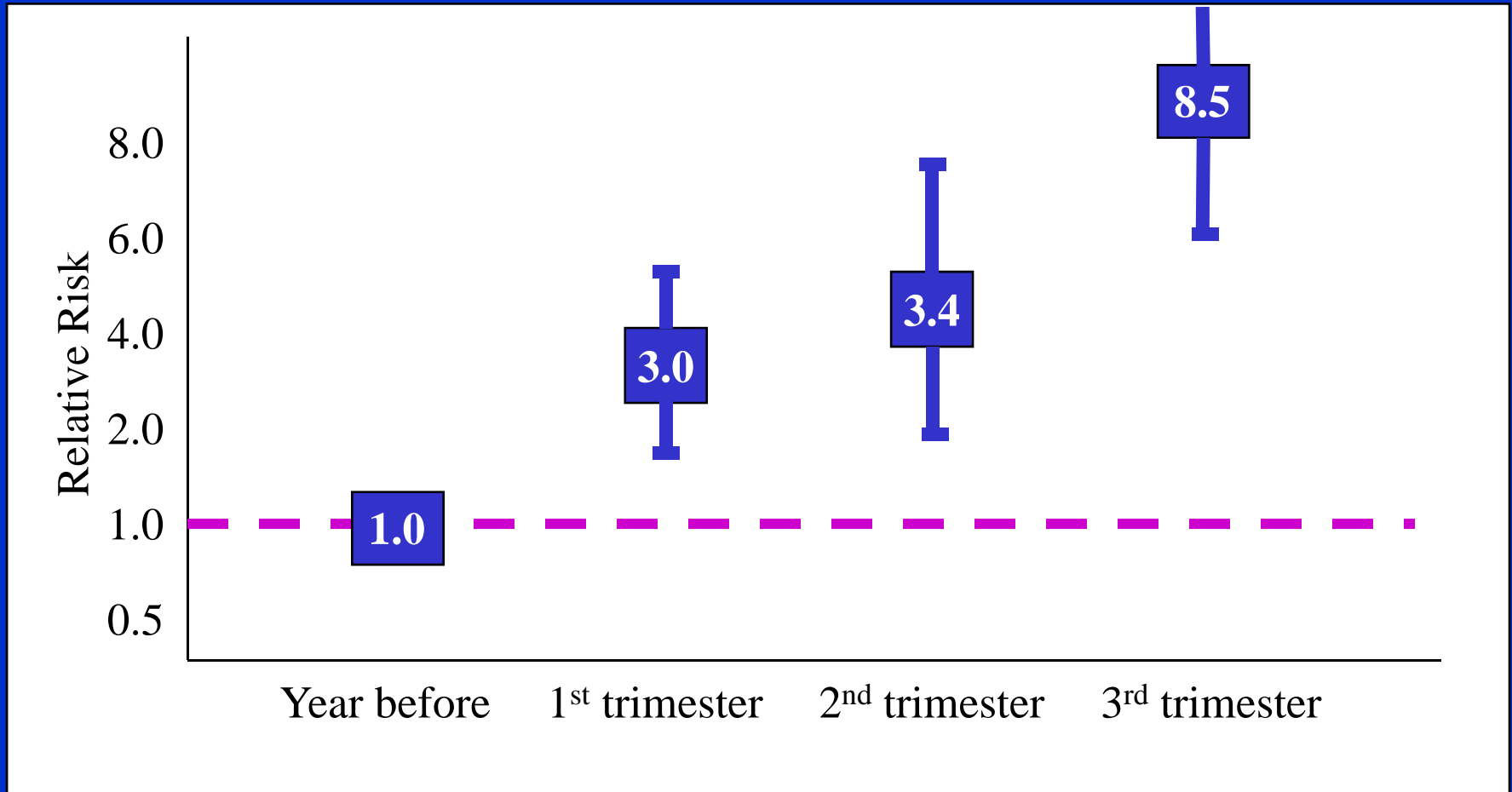
Adjusted for maternal age, maternal smoking total number of siblings less than 5 and income support in birth year

Relative risk of hospitalization in the flu season for each trimester compared to the year before pregnancy: Low risk women



Adjusted for maternal age, maternal smoking total number of siblings less than 5 and income support in birth year

Relative risk of hospitalization in the flu season for each trimester compared to the year before pregnancy: High risk women



Adjusted for maternal age, maternal smoking total number of siblings less than 5 and income support in birth year

Sensitivity Analysis

Issue: Respiratory illness may not have been the primary reason for hospital admission

The respiratory illness was the primary reason for admission in about 1/3 of the admissions

Analysis limited to hospital admissions with a respiratory illness as the primary reason for admission:

3rd trimester admissions:

<u>Low Risk</u>	Rate per 10,000 women months	# of women hospitalized
Flu Season	1.94	20
Peri-Flu Season	1.00	9
Non-Flu Season	0.81	14
<u>High Risk</u>		
Flu Season	14.66	16
Peri-Flu Season	2.06	2
Non-Flu Season	3.68	7

Physician Visits or Hospitalization for Respiratory Illness

Third Trimester:

	Rate per 10,000 women months
Flu Season	522.1
Peri-flu Season	425.6
Non-flu Season	319.0

What is the Effect on the Newborn?

	<u>Season of Birth</u>		
	Flu	Peri-flu	Non-flu
Preterm	6.1%	6.3%	5.7%
Mortality (1-year)	0.8%	0.9%	0.8%
Neonatal Morbidity (composite)	6.4%	6.9%	6.6%

Influenza Vaccination During Pregnancy

Data available from 1998- onwards (for vaccines given at a physician office)

- Overall, 2% of women received a flu vaccine in the year of their pregnancy
- 3.5% of high risk women received a flu vaccine in the year of their pregnancy

Conclusions

- Strong evidence of increased hospitalization rates among high risk women during flu seasons
- Even in the absence of pre-existing risk factors, women at all stages of pregnancy (and particularly the third trimester) are at increased risk of serious respiratory morbidity during influenza seasons
- Most high risk pregnant women are not being immunized for influenza

Policy Implications

Assuming an average length of flu season of 3.4 months:

High Risk Women:

 30 excess hospitalizations, in flu season,
per 10,000 high risk, third trimester
women per year

Low Risk Women:

 1-2 excess hospitalizations, in flu season,
per 10,000 low risk, third trimester
women per year

But, many more low risk women than high risk women each year...

Policy Implications

- This study provides robust, population-based Canadian data which demonstrates that pregnant women, with or without co-morbid medical conditions, represent an important influenza risk group
- While the data represents women in a single Canadian province, the population studied is clearly more representative of Canadian women than the Tennessee Medicaid population, making the data more generalizable to Canadians.
- Data clearly support need for aggressive efforts to ensure that all pregnant women with comorbidities receive influenza vaccine

Policy Implications-

Guiding Principles for Maternal Immunization

- The benefits of vaccinating a pregnant woman usually outweighs the risk for potential adverse effects in the woman or the developing offspring when:
 - The risk for disease exposure is high
 - Infection poses a special risk to mother and/or fetus
 - A vaccine is available and is unlikely to cause harm

ACOG Technical Bulletin 1991;160

Maternal Vaccine Safety: Collaborative Perinatal Project 1957-1966, USA*

- NIH-sponsored 7 year longitudinal study of >50,000 pregnant women; all exposure to immunization recorded
- Offspring assessed for malformations, learning problems, hearing loss, and cancer
- # doses of vaccines administered:
 - IPV 18,000
 - OPV 3,000
 - Influenza 2,291
 - Other- tetanus and diphtheria toxoids
- No significant increase in adverse reactions in mothers or adverse outcomes in neonates

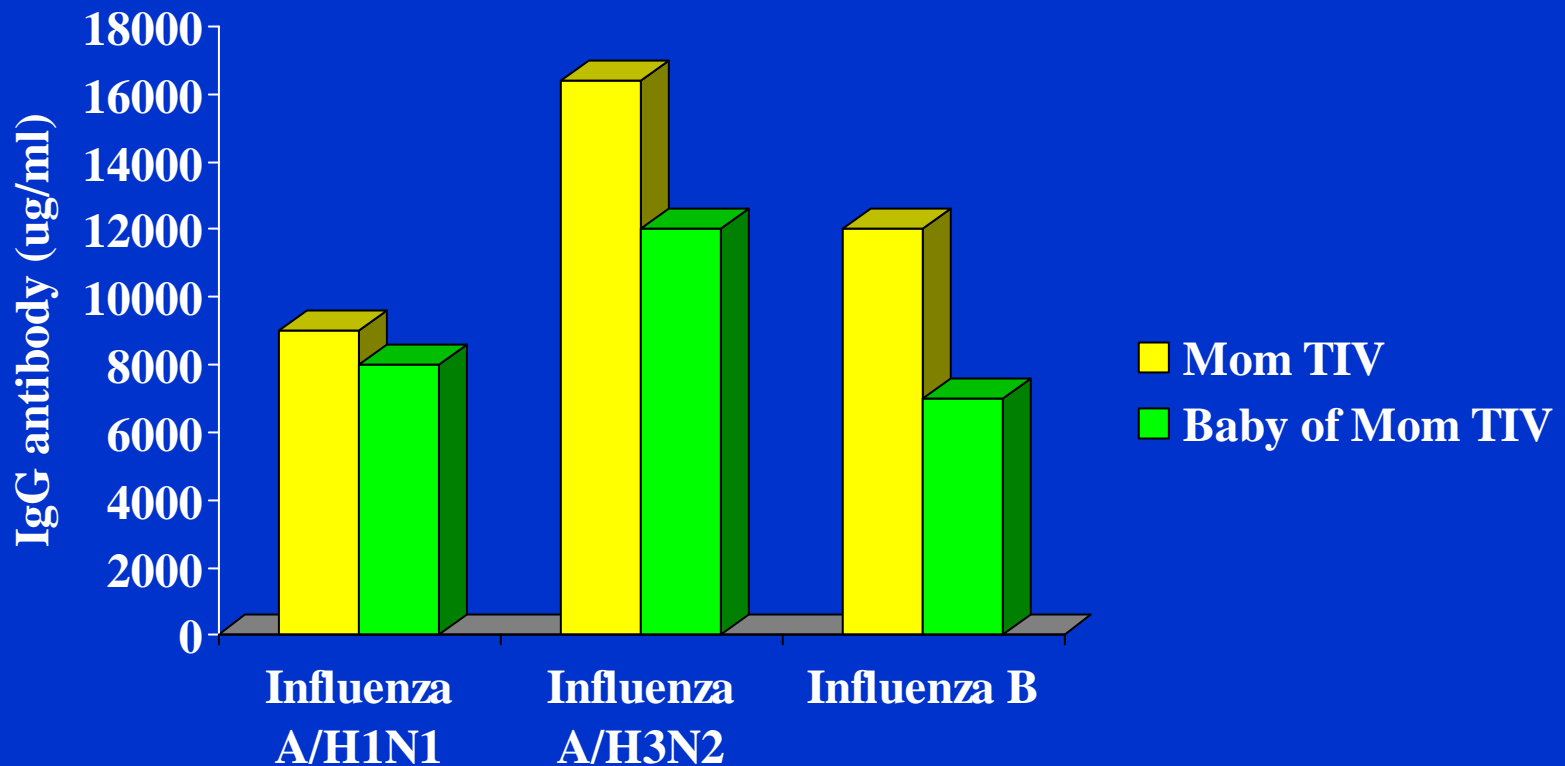
**Heinonen et al. Immunizing Agents. In Kaufman DW (ed): Birth Defects and Drugs in Pregnancy. Publishing Sciences Group, 1977, pp 314-21.*

Maternal Vaccine Safety

- “To date there is no documented evidence of reproductive toxic effects in humans caused by the use of any approved vaccines”

Gruber. Maternal Immunization: US FDA Regulatory Considerations. Vaccine 2003;21:3487-91

Influenza IgG Following Maternal Immunization with TT or Inactivated Influenza Vaccine



Policy Implications

- Given the increased risk of respiratory-related hospitalization and office visits in healthy women during all trimesters compared to the year prior to pregnancy, consideration should be given to broadening the Canadian influenza immunization recommendation to include all pregnant women