Pregnancy and Vaccines –History, safety and current recommendations

Kevin A. Ault, MD

April 5, 2022

KU WOMEN'S HEALTH SPECIALTY CENTERS
The University of Kansas Medical Center

THE UNIVERSITY OF KANSAS HEALTH SYSTEM

Conflicts of Interest Etc.

- I have no conflicts of interests with the content of this talk.
- I am a voting member of the federal vaccine policy committee "ACIP" and a consultant to the CDC, FIGO and ACOG. Today's lecture is my own thoughts and opinions.

THE NATIONAL WWI MUSEUM AND MEMORIAL

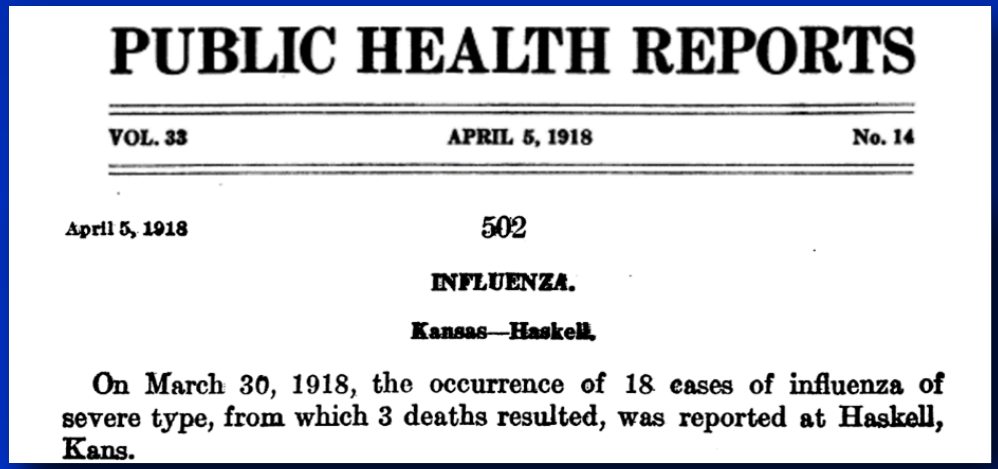
Objectives Today

- Be aware of the history of 20th century pandemics and how this led to maternal immunization recommendations
- Know safety data concerning current vaccines recommended during pregnancy and
- Discuss the data concerning safety and efficacy of COVID vaccines during pregnancy.

Origin of the 1918 "Spanish Flu" Pandemic

More than 25 percent of the U.S. population became sick and 675,000 Americans died. Worldwide deaths 21 to 100 million.

Photo from US Army archives taken at Camp Funiston, KS 1918.



PUBLIC HEALTH REPORTS

VOL. 33 APRIL 5, 1918 No. 14

April 5, 1918 502

INFLUENZA.

Kansas—Haskell.

On March 30, 1918, the occurrence of 18 cases of influenza of severe type, from which 3 deaths resulted, was reported at Haskell, Kans.

"Spanish Flu" Timeline Fall 1918 Philadelphia

- Sept 7 – Three hundred sailors arrive at Philadelphia Navy Yard from Boston.
- Sept 11 – Four sailors hospitalized with influenza. By the 15th, 600 cases and 2 deaths confined to sailors.
- Sept 28 – Liberty Bond Parade with 200,000 people.
- Oct 1 – 117 influenza death on one day. Maximum 711 on October 17.

Source – "The Great Influenza" by JM Barry, 2004

Fall Philadelphia 1918 part 2

"What are the authorities trying to do? Scare everyone to death? … What then should a man do to prevent panic and fear? Live a clean life. Do not even discuss influenza. … Talk of cheerful things."

The Philadelphia Inquirer

ALLIES SMASHING HUN DEFENSES ON FOUR VITAL SECTORS ALONG 250 MILE FRONT

WORKERS AND FIGHTERS IN LOAN PAGEANT

FIGHTING MEN OF NAVY THRILL VAST CROWDS AS THEY MARCH ALONG BROAD STREET

GERMANS FACING WORST SITUATION SINCE WAR BEGAN

'YANKS ARE COMING!' TIMES 20,000 FEET N LIBERTY PAGEANT

CONGRESS VOTES $1,000,000 TO CURB SPANISH INFLUENZA

ENGLAND REFUSES BULGARIA'S REQUEST FOR AN ARMISTICE

PERSHING'S BIG GUNS HURLING SHELLS FAR BEYOND HUNS' LINES

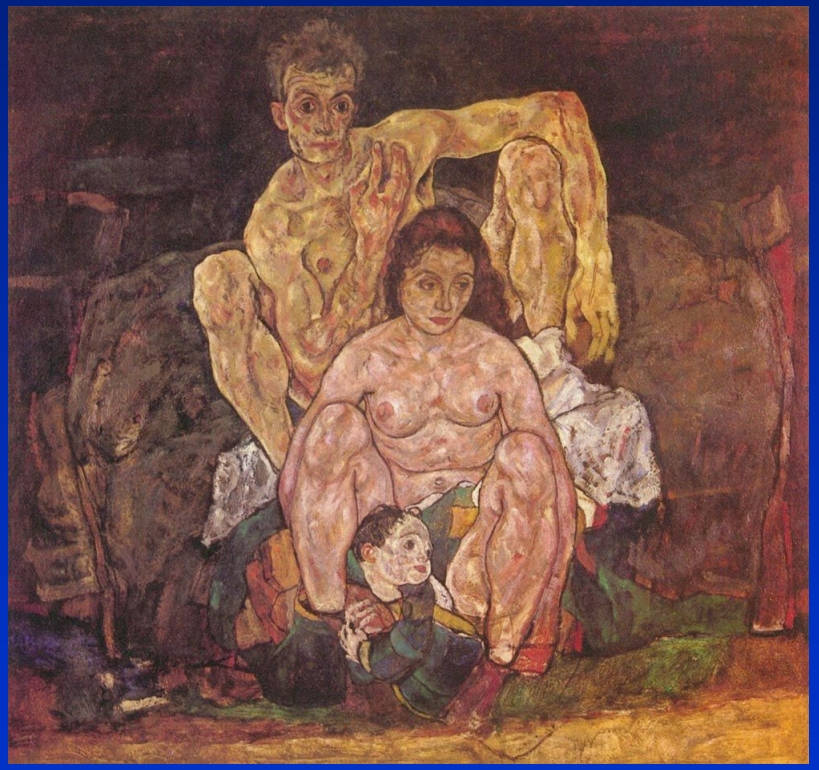
Philadelphia Inquirer - October 4, 1918.

Plague, war and revolution in 1918

"Shut your eyes," said Miss Tanner.

"Oh no," said Miranda, "for then I see worse things…"

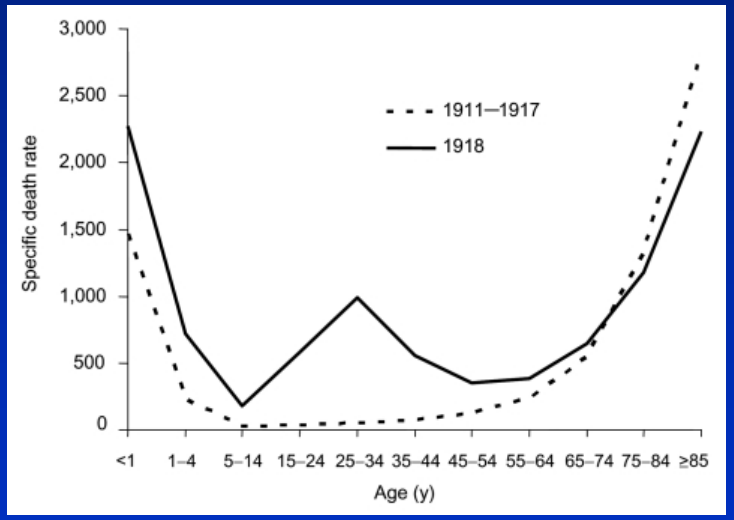
— Katherine Anne Porter in Pale Horse, Pale Rider (1939)



for more about Egon Schiele see Potter 2013

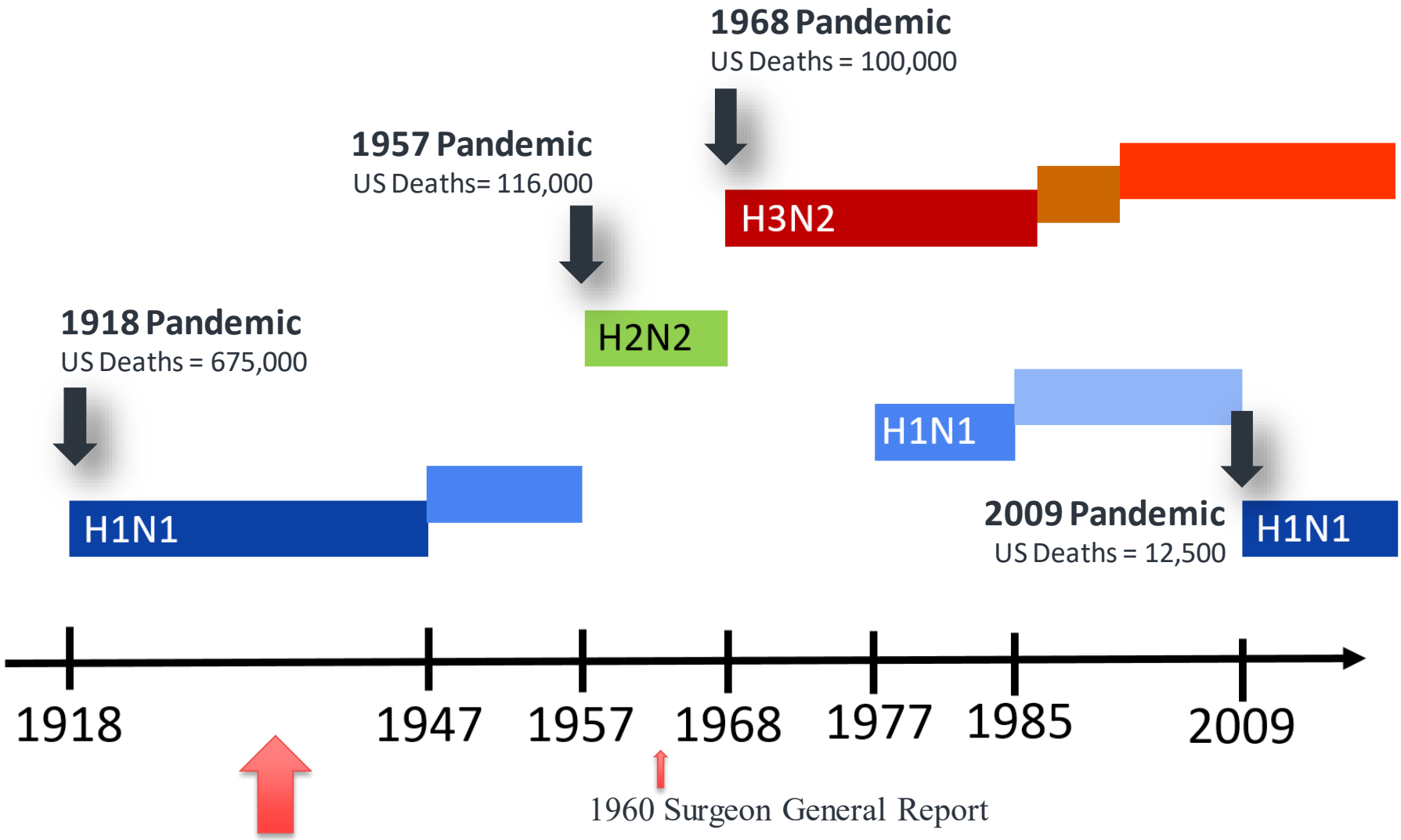
Morbidity and Mortality of Influenza during Pregnancy

- "Cytokine storm"
- 1918 cases series – 50% mortality with pneumonia, 52% pregnancy complication
- "Highly predisposed to and fatally afflicted by this malady"
- 2009 pandemic with six fold increase mortality during pregnancy



Sources Harris 1919, Jordan 1927, Jamieson et al 2009, Rasmussen & Jamieson 2014

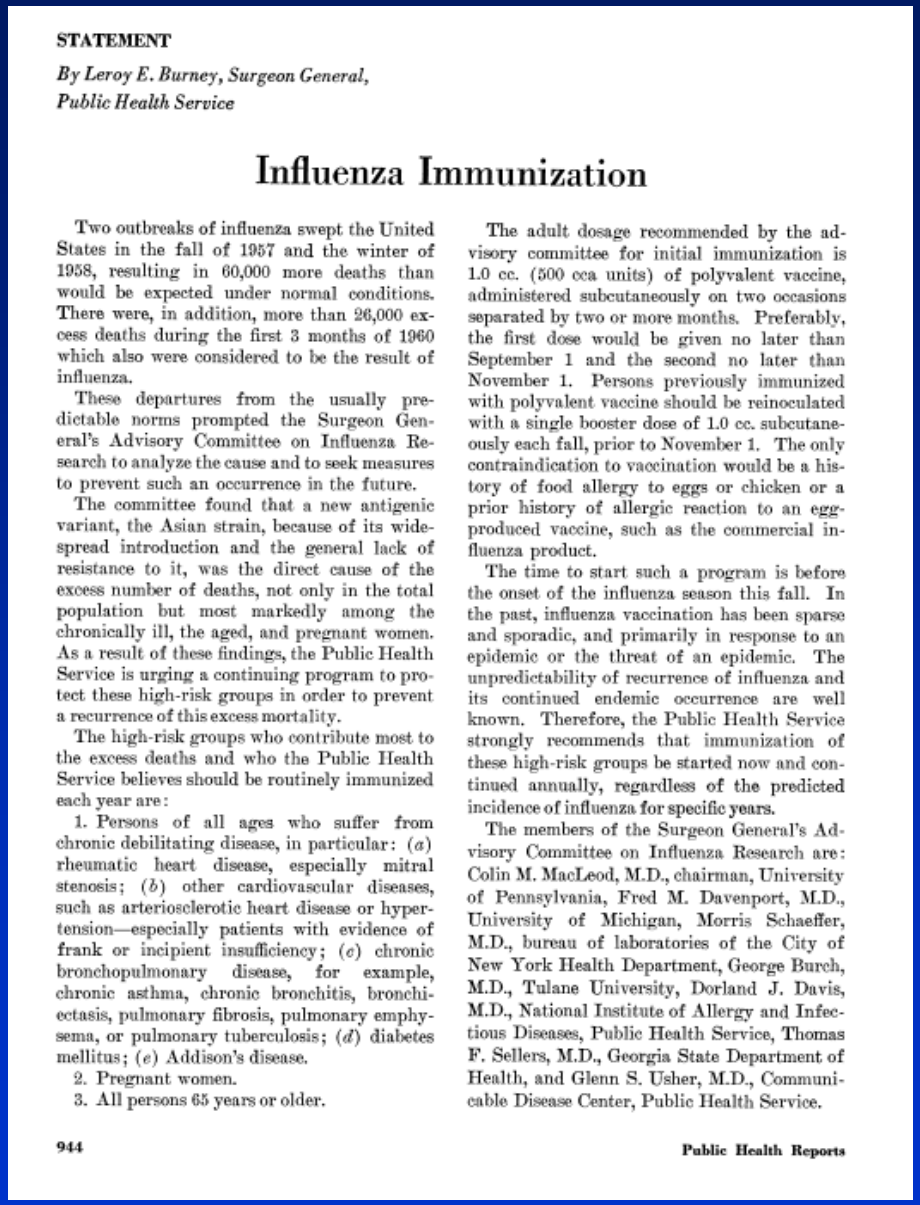
Influenza A Viruses Since 1918



Isolation of viruses (A/B) 1930s, egg/cell culture 1940s, vaccines mid 1940s

Surgeon General 1960

- 60,000 deaths in 1957 – 58 flu season
- Pandemic "Asian" strain – new antigenic variant
- Routine yearly immunization of "at risk groups" including pregnant women



STATEMENT

By Leroy E. Burney, Surgeon General, Public Health Service

Influenza Immunization

Two outbreaks of influenza swept the United States in the fall of 1957 and the winter of 1958, resulting in 60,000 more deaths than would be expected under normal conditions. There were, in addition, more than 26,000 excess deaths during the first 3 months of 1960 which also were considered to be the result of influenza.

These departures from the usually predictable norms prompted the Surgeon General's Advisory Committee on Influenza Research to analyze the cause and to seek measures to prevent such an occurrence in the future.

The committee found that a new antigenic variant, the Asian strain, because of its widespread introduction and the general lack of resistance to it, was the direct cause of the excess number of deaths, not only in the total population but most markedly among the chronically ill, the aged, and pregnant women. As a result of these findings, the Public Health Service is urging a continuing program to protect these high-risk groups in order to prevent a recurrence of this excess mortality.

The high-risk groups who contribute most to the excess deaths and who the Public Health Service believes should be routinely immunized each year are:

1. Persons of all ages who suffer from chronic debilitating disease, in particular: (*a*) rheumatic heart disease, especially mitral stenosis; (*b*) other cardiovascular diseases, such as arteriosclerotic heart disease or hypertension—especially patients with evidence of frank or incipient insufficiency; (*c*) chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, or pulmonary tuberculosis; (*d*) diabetes mellitus; (*e*) Addison's disease.
2. Pregnant women.
3. All persons 65 years or older.

The adult dosage recommended by the advisory committee for initial immunization is 1.0 cc. (500 cca units) of polyvalent vaccine, administered subcutaneously on two occasions separated by two or more months. Preferably, the first dose would be given no later than September 1 and the second no later than November 1. Persons previously immunized with polyvalent vaccine should be reinoculated with a single booster dose of 1.0 cc. subcutaneously each fall, prior to November 1. The only contraindication to vaccination would be a history of food allergy to eggs or chicken or a prior history of allergic reaction to an egg-produced vaccine, such as the commercial influenza product.

The time to start such a program is before the onset of the influenza season this fall. In the past, influenza vaccination has been sparse and sporadic, and primarily in response to an epidemic or the threat of an epidemic. The unpredictability of recurrence of influenza and its continued endemic occurrence are well known. Therefore, the Public Health Service strongly recommends that immunization of these high-risk groups be started now and continued annually, regardless of the predicted incidence of influenza for specific years.

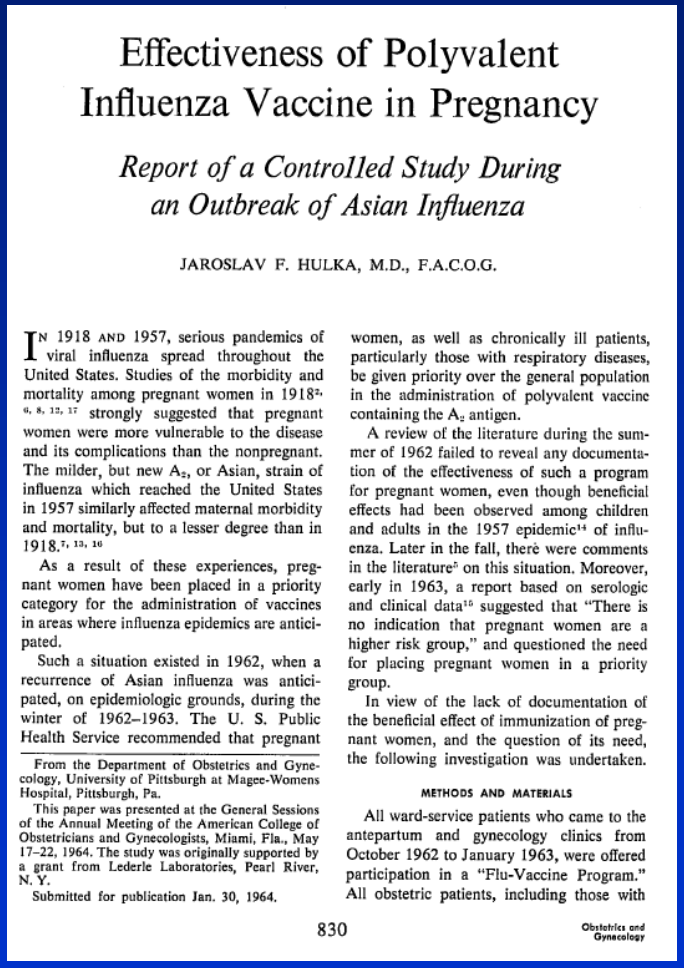
The members of the Surgeon General's Advisory Committee on Influenza Research are: Colin M. MacLeod, M.D., chairman, University of Pennsylvania, Fred M. Davenport, M.D., University of Michigan, Morris Schaeffer, M.D., bureau of laboratories of the City of New York Health Department, George Burch, M.D., Tulane University, Dorland J. Davis, M.D., National Institute of Allergy and Infectious Diseases, Public Health Service, Thomas F. Sellers, M.D., Georgia State Department of Health, and Glenn S. Usher, M.D., Communicable Disease Center, Public Health Service.

944 **Public Health Reports**

Public Health Reports October 1960

Safety of a 'polyvalent' flu vaccine - 1964

- Similar antibody responses in pregnant and non pregnant volunteers
- ~ 40 % reduction in influenza like illnesses with decreased sick days
- No increased pregnancy complications



Effectiveness of Polyvalent Influenza Vaccine in Pregnancy

Report of a Controlled Study During an Outbreak of Asian Influenza

JAROSLAV F. HULKA, M.D., F.A.C.O.G.

IN 1918 AND 1957, serious pandemics of viral influenza spread throughout the United States. Studies of the morbidity and mortality among pregnant women in 1918[2, 6, 8, 12, 17] strongly suggested that pregnant women were more vulnerable to the disease and its complications than the nonpregnant. The milder, but new A_2, or Asian, strain of influenza which reached the United States in 1957 similarly affected maternal morbidity and mortality, but to a lesser degree than in 1918.[7, 13, 16]

As a result of these experiences, pregnant women have been placed in a priority category for the administration of vaccines in areas where influenza epidemics are anticipated.

Such a situation existed in 1962, when a recurrence of Asian influenza was anticipated, on epidemiologic grounds, during the winter of 1962–1963. The U. S. Public Health Service recommended that pregnant women, as well as chronically ill patients, particularly those with respiratory diseases, be given priority over the general population in the administration of polyvalent vaccine containing the A_2 antigen.

A review of the literature during the summer of 1962 failed to reveal any documentation of the effectiveness of such a program for pregnant women, even though beneficial effects had been observed among children and adults in the 1957 epidemic[14] of influenza. Later in the fall, there were comments in the literature[5] on this situation. Moreover, early in 1963, a report based on serologic and clinical data[15] suggested that "There is no indication that pregnant women are a higher risk group," and questioned the need for placing pregnant women in a priority group.

In view of the lack of documentation of the beneficial effect of immunization of pregnant women, and the question of its need, the following investigation was undertaken.

METHODS AND MATERIALS

All ward-service patients who came to the antepartum and gynecology clinics from October 1962 to January 1963, were offered participation in a "Flu-Vaccine Program." All obstetric patients, including those with

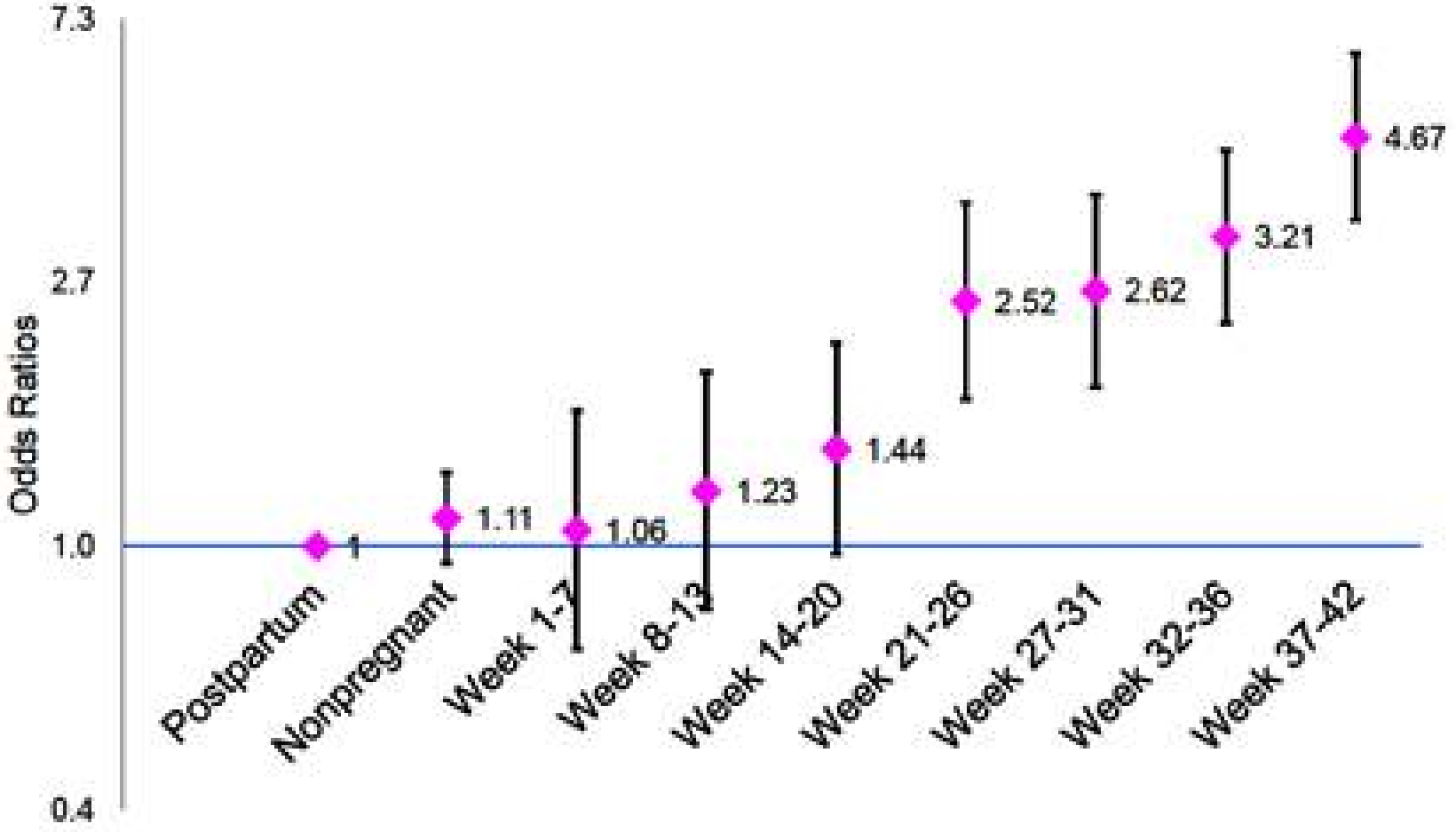
From the Department of Obstetrics and Gynecology, University of Pittsburgh at Magee-Womens Hospital, Pittsburgh, Pa.

This paper was presented at the General Sessions of the Annual Meeting of the American College of Obstetricians and Gynecologists, Miami, Fla., May 17–22, 1964. The study was originally supported by a grant from Lederle Laboratories, Pearl River, N. Y.

Submitted for publication Jan. 30, 1964.

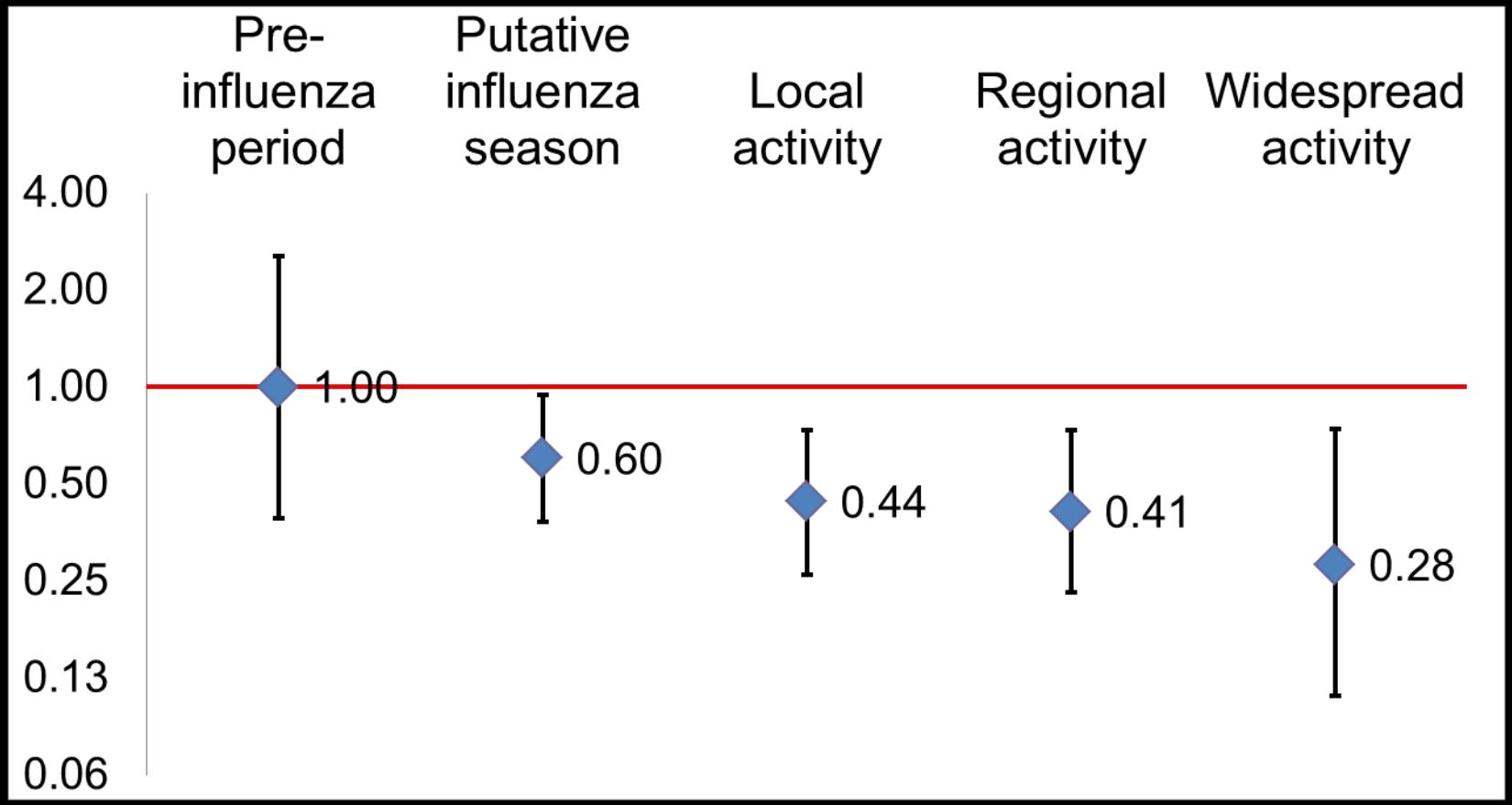
Odds Ratios of Cardiopulmonary Events by Pregnancy Status

Tennessee Medicaid Program 1974-1993



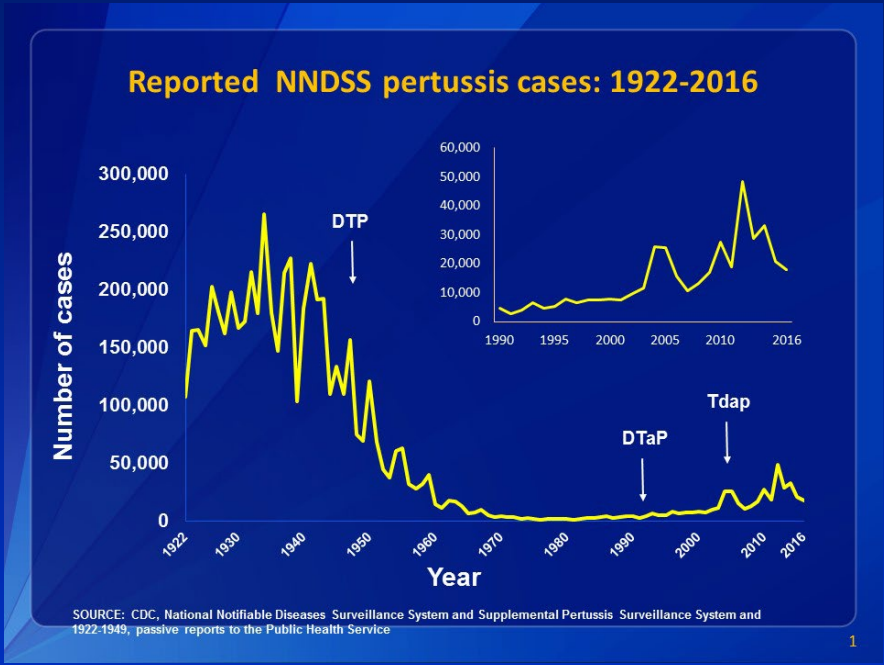
Data Source: Neuzil et al, AJE, 1998

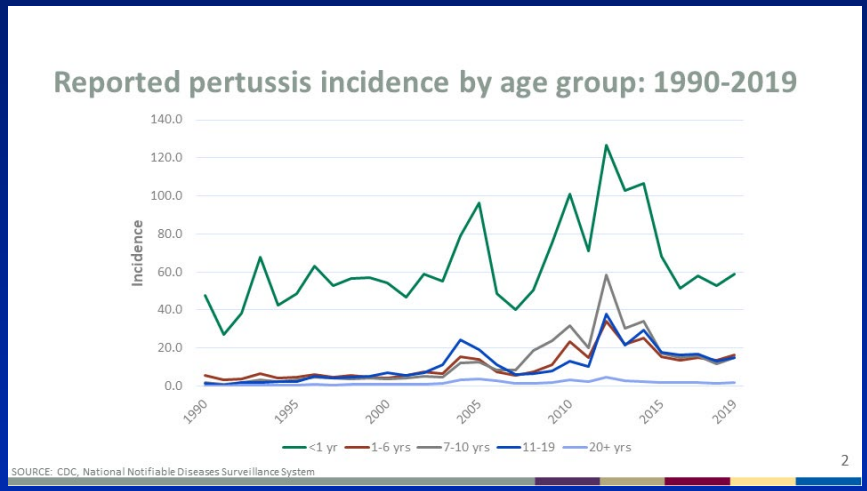
Adjusted Odds Ratios of Prematurity by Maternal Influenza Vaccine Status



Omer et al., PLoS Medicine, 2011

History of Pertussis and Pertussis Vaccines

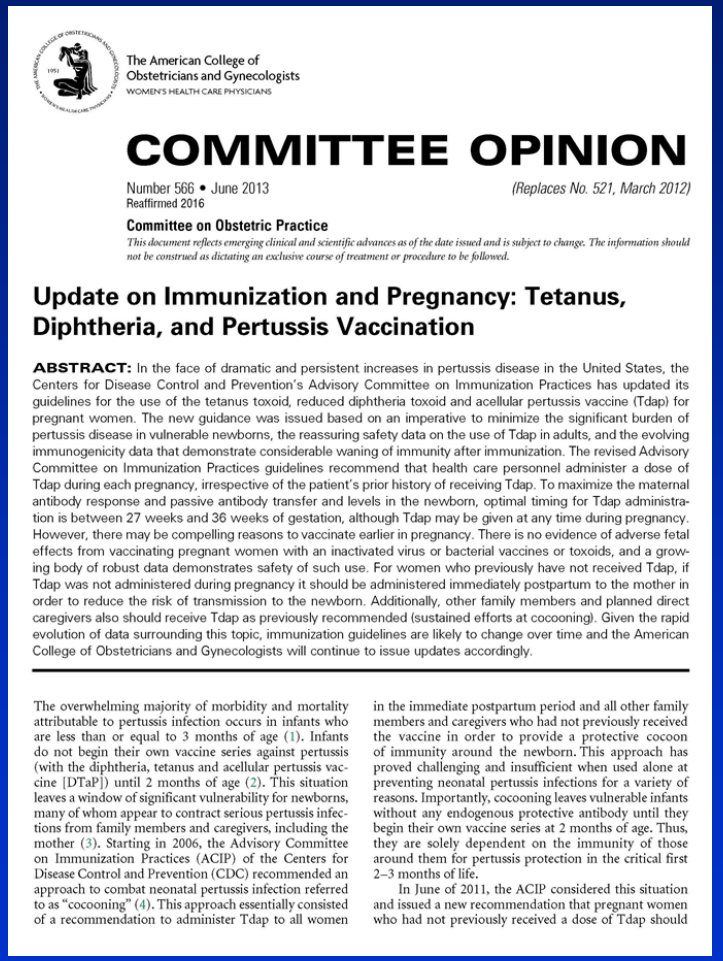




Similar to influenza, mortality concentrated in youngest ages group. Source – CDC.

Pertussis Vaccination during pregnancy

- "dramatic and persistent increase in pertussis disease" lead to pregnancy recommendation
- Should be given every pregnancy at 27-36 weeks gestation
- Goal – prevention of newborn morbidity and mortality



The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 566 • June 2013 *(Replaces No. 521, March 2012)*
Reaffirmed 2016

Committee on Obstetric Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Update on Immunization and Pregnancy: Tetanus, Diphtheria, and Pertussis Vaccination

ABSTRACT: In the face of dramatic and persistent increases in pertussis disease in the United States, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices has updated its guidelines for the use of the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) for pregnant women. The new guidance was issued based on an imperative to minimize the significant burden of pertussis disease in vulnerable newborns, the reassuring safety data on the use of Tdap in adults, and the evolving immunogenicity data that demonstrate considerable waning of immunity after immunization. The revised Advisory Committee on Immunization Practices guidelines recommend that health care personnel administer a dose of Tdap during each pregnancy, irrespective of the patient's prior history of receiving Tdap. To maximize the maternal antibody response and passive antibody transfer and levels in the newborn, optimal timing for Tdap administration is between 27 weeks and 36 weeks of gestation, although Tdap may be given at any time during pregnancy. However, there may be compelling reasons to vaccinate earlier in pregnancy. There is no evidence of adverse fetal effects from vaccinating pregnant women with an inactivated virus or bacterial vaccines or toxoids, and a growing body of robust data demonstrates safety of such use. For women who previously have not received Tdap, if Tdap was not administered during pregnancy it should be administered immediately postpartum to the mother in order to reduce the risk of transmission to the newborn. Additionally, other family members and planned direct caregivers also should receive Tdap as previously recommended (sustained efforts at cocooning). Given the rapid evolution of data surrounding this topic, immunization guidelines are likely to change over time and the American College of Obstetricians and Gynecologists will continue to issue updates accordingly.

The overwhelming majority of morbidity and mortality attributable to pertussis infection occurs in infants who are less than or equal to 3 months of age (1). Infants do not begin their own vaccine series against pertussis (with the diphtheria, tetanus and acellular pertussis vaccine [DTaP]) until 2 months of age (2). This situation leaves a window of significant vulnerability for newborns, many of whom appear to contract serious pertussis infections from family members and caregivers, including the mother (3). Starting in 2006, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended an approach to combat neonatal pertussis infection referred to as "cocooning" (4). This approach essentially consisted of a recommendation to administer Tdap to all women in the immediate postpartum period and all other family members and caregivers who had not previously received the vaccine in order to provide a protective cocoon of immunity around the newborn. This approach has proved challenging and insufficient when used alone at preventing neonatal pertussis infections for a variety of reasons. Importantly, cocooning leaves vulnerable infants without any endogenous protective antibody until they begin their own vaccine series at 2 months of age. Thus, they are solely dependent on the immunity of those around them for pertussis protection in the critical first 2–3 months of life.

In June of 2011, the ACIP considered this situation and issued a new recommendation that pregnant women who had not previously received a dose of Tdap should

ACOG CO # 566 2013

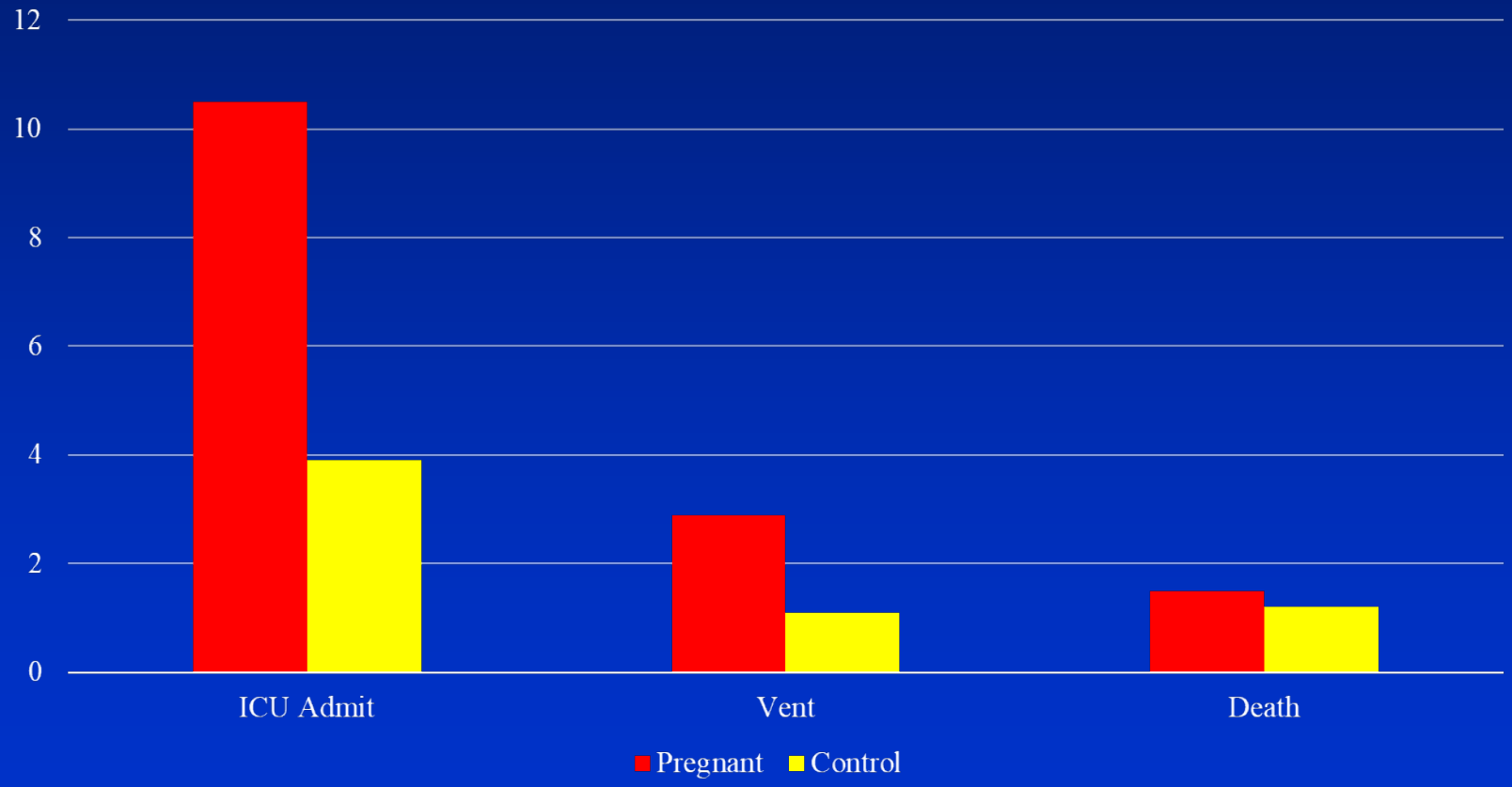
Vaccine*	Indicated During Every Pregnancy	May Be Given During Pregnancy in Certain Populations	Contraindicated During Pregnancy	Can Be Initiated Postpartum or When Breastfeeding or Both
Inactivated influenza	X[†,1,2]			X[‡]
Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap)	X[†,3,4]			X[‡]
Pneumococcal vaccines		X[§,5,6]		X[§,5,6]
Meningococcal conjugate (MenACWY) and Meningococcal serogroup B		X[‖,7]		X[‖,7]
Hepatitis A		X[¶,8]		X[¶,8]
Hepatitis B		X[#,9,10]		X[#,9,10]
Human papillomavirus (HPV)**				X[**,11,12]
Measles–mumps–rubella			X[††,13,14]	X[††]
Varicella			X[††,13,15,16]	X[††]

*An "X" indicates that the vaccine can be given in this window. See the corresponding numbered footnote for details.

[†]Inactivated influenza vaccination can be given in any trimester and should be given with each influenza season as soon as the vaccine is available. The Tdap vaccine is given at 27–36 weeks of gestation in each pregnancy, preferably as early in the 27–36-week window as possible. The Tdap vaccine should be given during each pregnancy in order to boost the maternal immune response and maximize the passive antibody transfer to the newborn. Women who did not receive Tdap during pregnancy (and have never received the Tdap vaccine) should be immunized once in the immediate postpartum period.[1–3]

ACOG Committee Opinion 741 June 2018

Morbidity and Mortality in Women Admitted for COVID-19



Zambrano *et al* 2020 – Y Axis is cases per 1,000 cases, n = 409,462

Is COVID safe in pregnancy?

- No evidence for reduced female fertility or increased risk of miscarriage in early pregnancy
- Later in pregnancy, increased risk of
  - Preterm birth (OR 1.48)
  - Pre-eclampsia (OR 1.6)
  - Stillbirth (OR 2.36)
  - Neonatal death (OR 3.35)

Is COVID vaccination safe in pregnancy?

- 211,000 pregnant people vaccinated in the USA and more than 100,000 in the UK, with no safety signal appearing in passive reporting.
- 16 studies, in 5 countries, including a total of 185,309 people vaccinated in pregnancy found
  - no increased risk of miscarriage
  - no increased risk of preterm birth
  - no increased risk of stillbirth
  - no increased risk of SGA
  - no increased risk of congenital abnormalities
  - no increased risk of NICU admission
  - no health problems in babies up to six months old

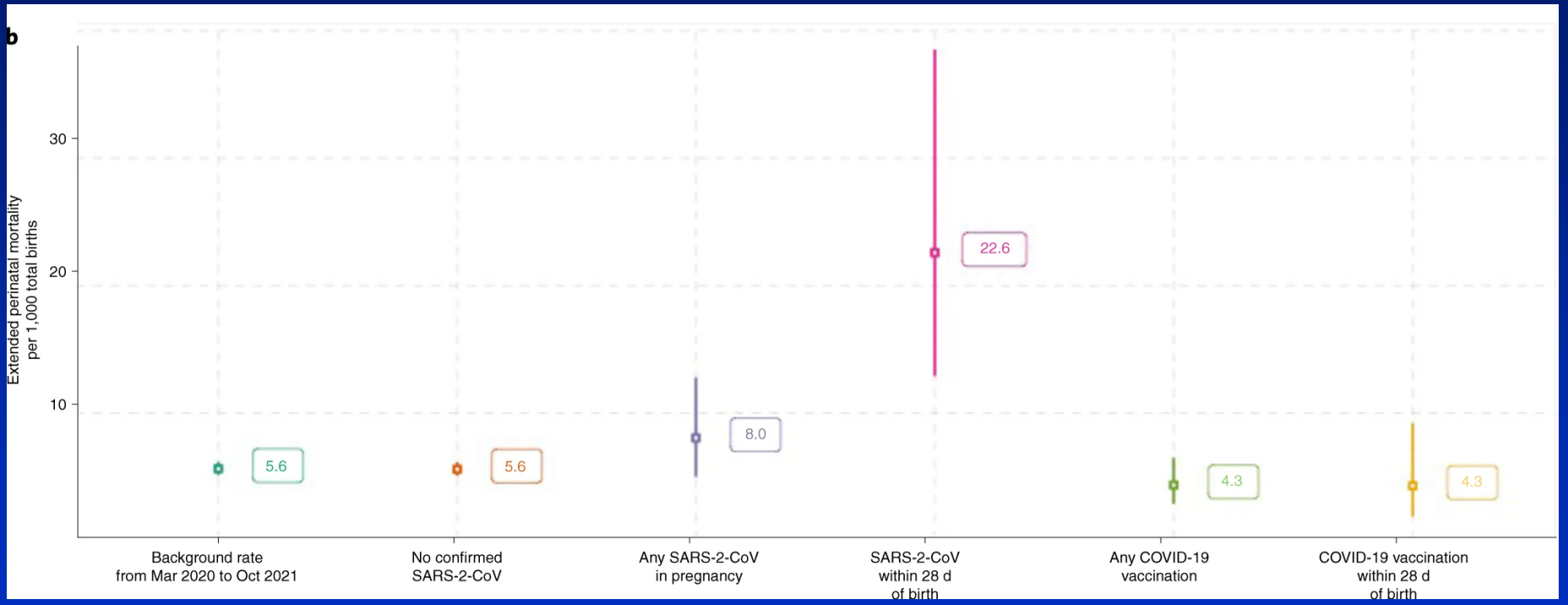
following COVID vaccination

Say hi!
@VikiLovesFACS

https://tinyurl.com/pregnancydata

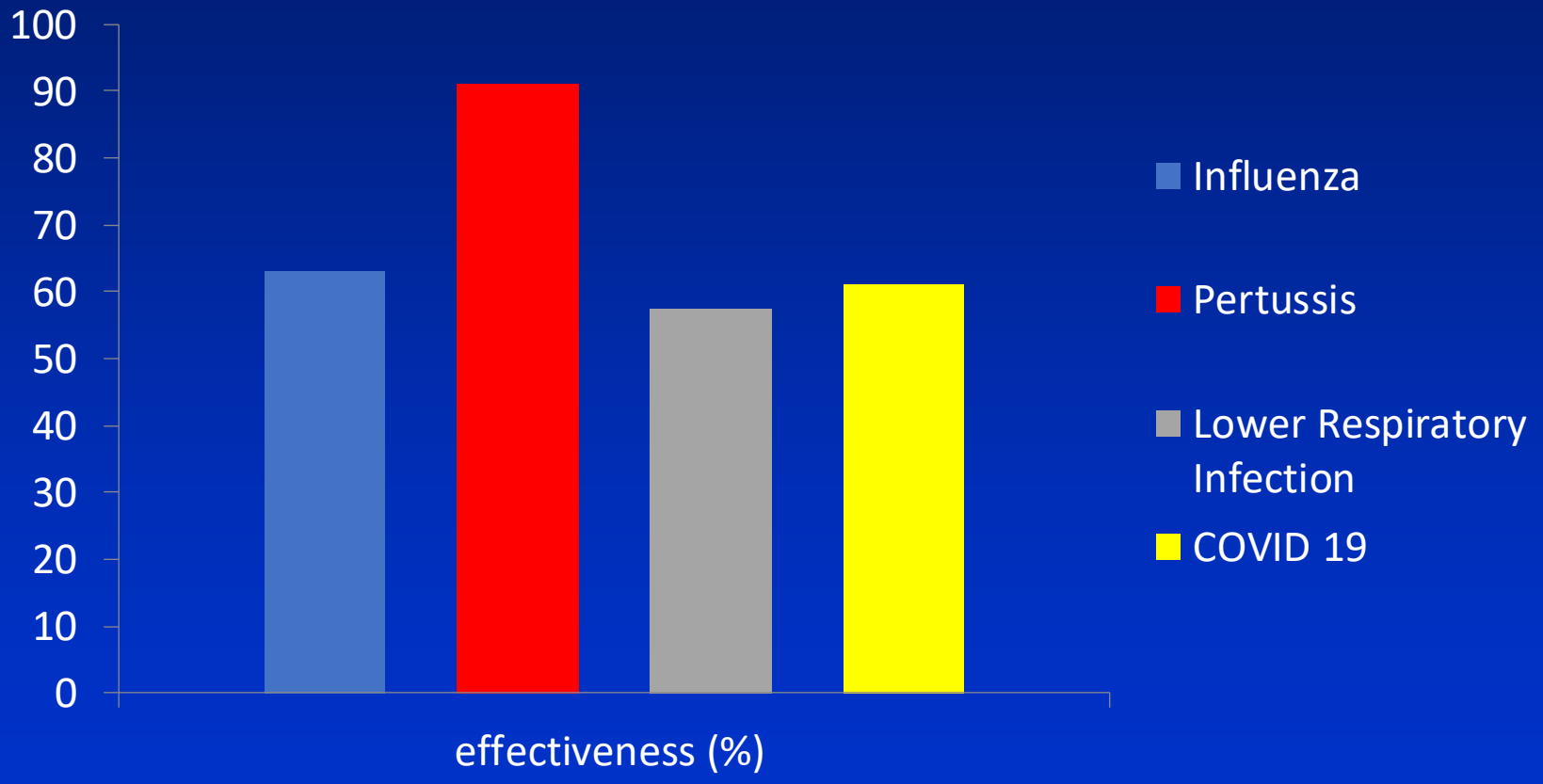
Male 2022, also Ma *et al* shows 87 % vaccine effectiveness

COVID – Preterm Birth and Perinatal Mortality Scotland



Stock *et al* 2022

Effectiveness of Maternal Immunization to prevent Neonatal Infection



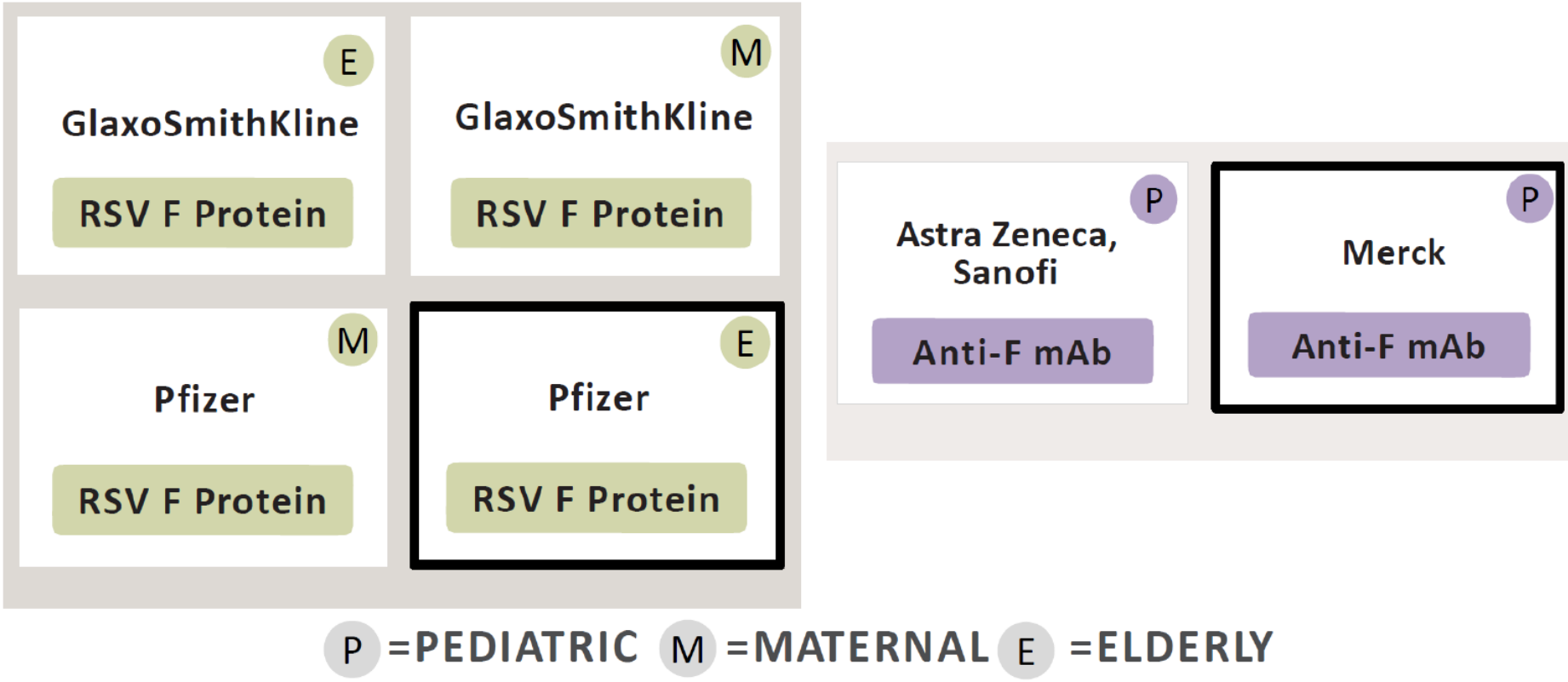
Zaman *et al* 2008, Baxter *et al* 2017, Nunes *et al* 2017 and Halasa et al 2022

Respiratory Syncytial Virus (RSV) Vaccines

- Common respiratory pathogen
  - 2 to 3 % require hospitalization
  - 30 to 40 % primary infections result in lower respiratory infection
  - 20 % of newborn hospitalizations
- Maternal immunization to provide newborn protection
- Multiple vaccines in clinical trials including phase III pregnancy trials.

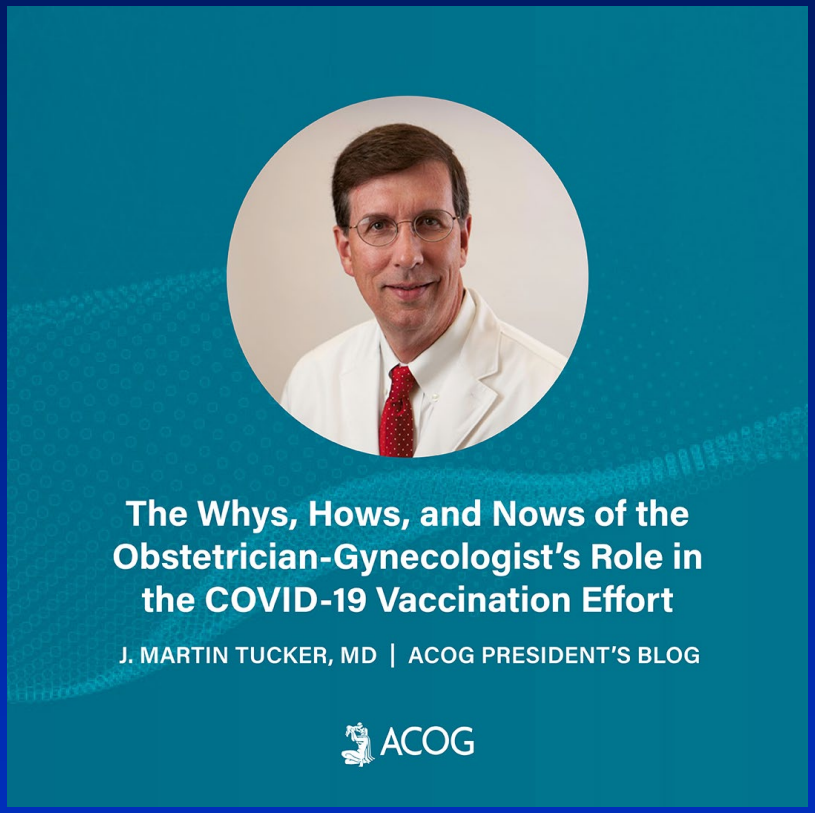
Mazur et al 2018

RSV Vaccine and Monoclonal Antibody Products in Phase 3 Trials



Current & Future Vaccines - Maternal Immunization

	Maternal	**Fetal / Pregnancy**	**Newborn**
Flu	x	x	x
Tdap			x
RSV	?		x
COVID 19	x	x	x



Major professional and public health groups recommend vaccination of pregnant people

Conclusions

- Three vaccines are currently recommended during every pregnancy – influenza, pertussis and COVID-19.

- Vaccine safety and effectiveness for these three vaccines have been extensively studied.

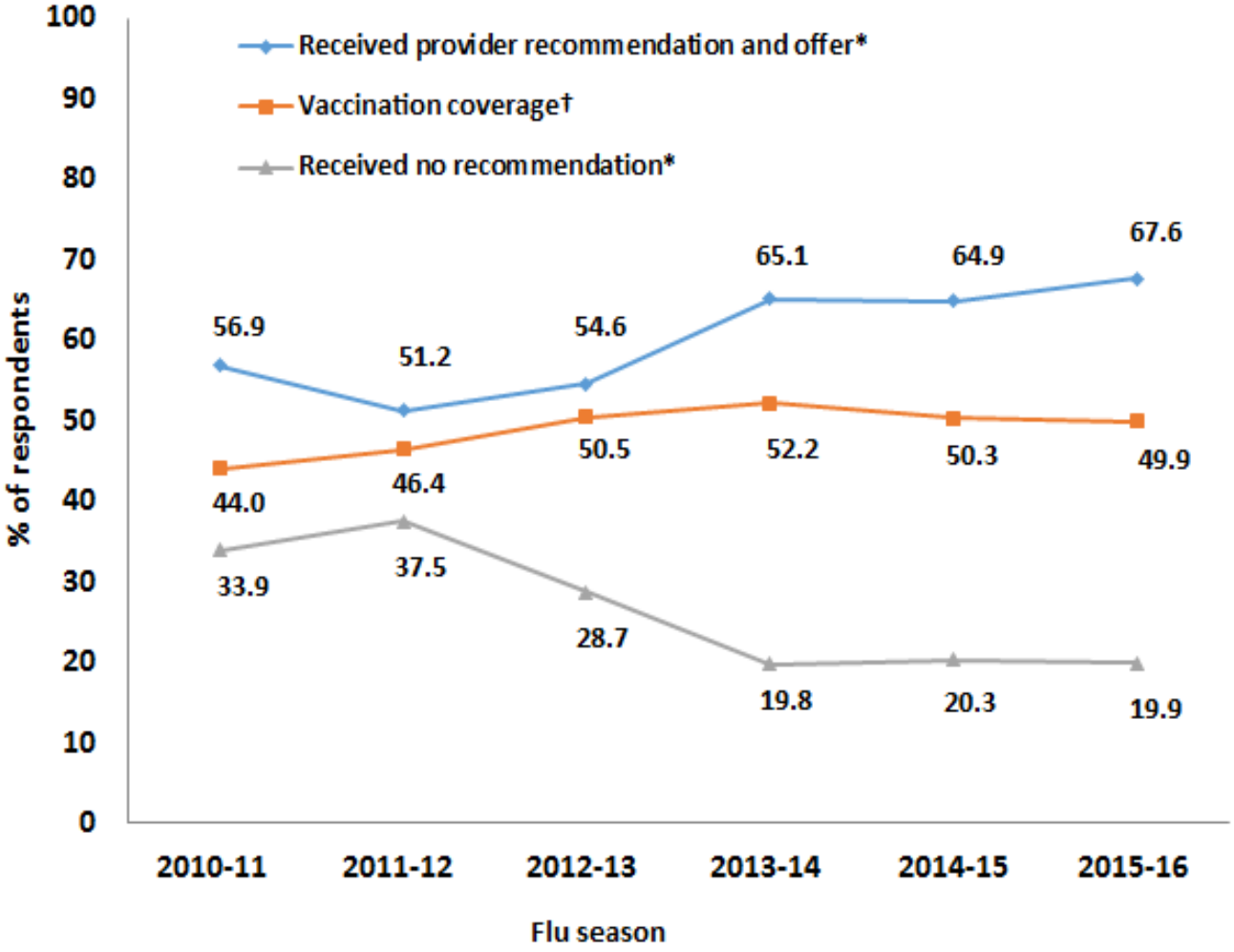
Back up slides

Potential Group B Strep Vaccines

- Leading cause of invasive bacterial disease with early and late onset disease.
- Approximately 0.5 cases/1000 live births with global variation
- Potential neonatal & maternal benefits
- Difficult study design

Heath et al 2017

Figure 1. Trend of flu vaccination coverage before and during pregnancy and prevalence of provider recommendation / offer or no recommendation for vaccination among women pregnant anytime October through January, Internet panel survey, United States, 2010-11 through 2015-2016 flu seasons



https://www.cdc.gov/flu/fluvaxview/pregnant-coverage_1516estimates.htm