The safety of influenza vaccination during pregnancy

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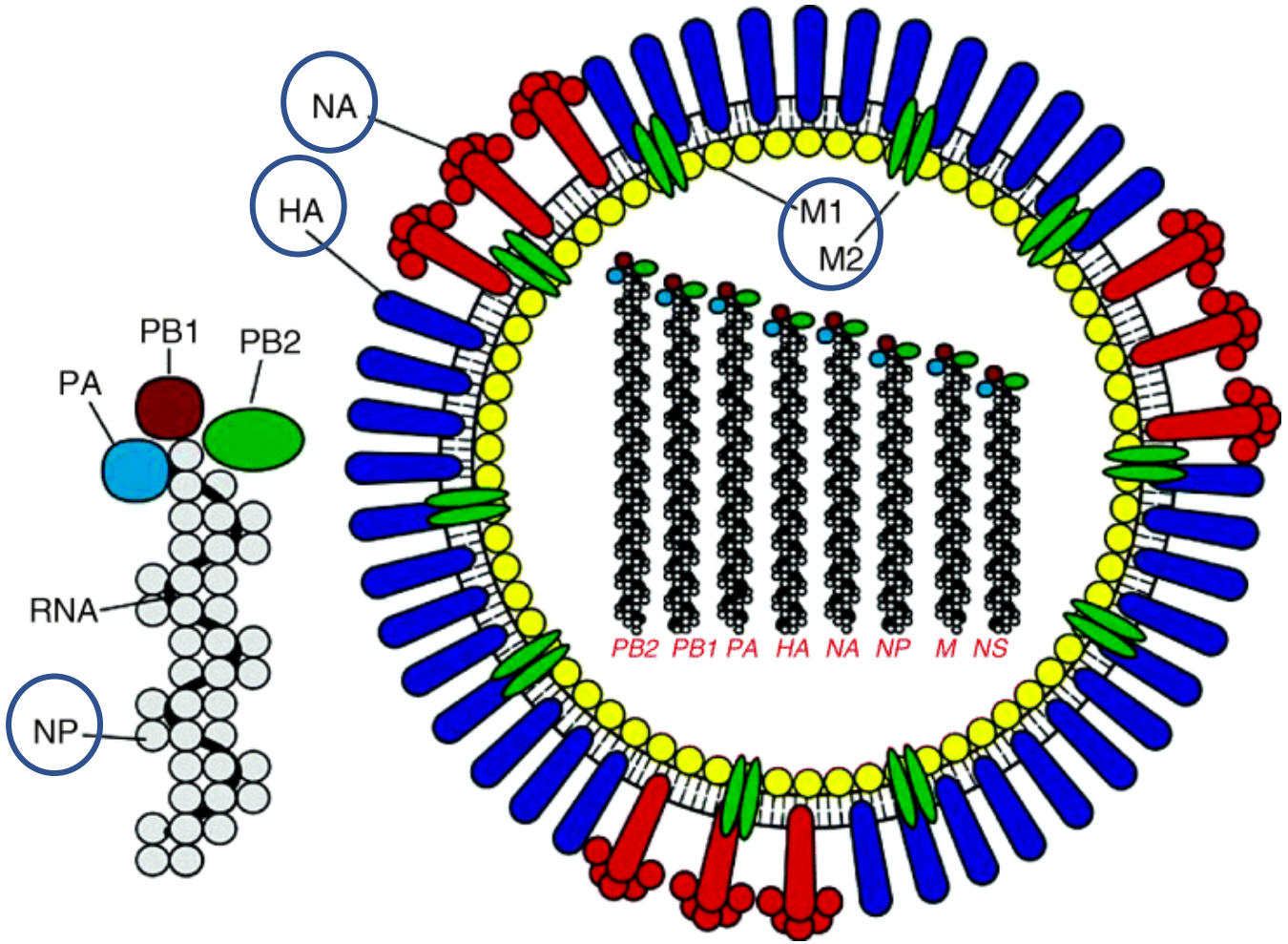
The influenza virus

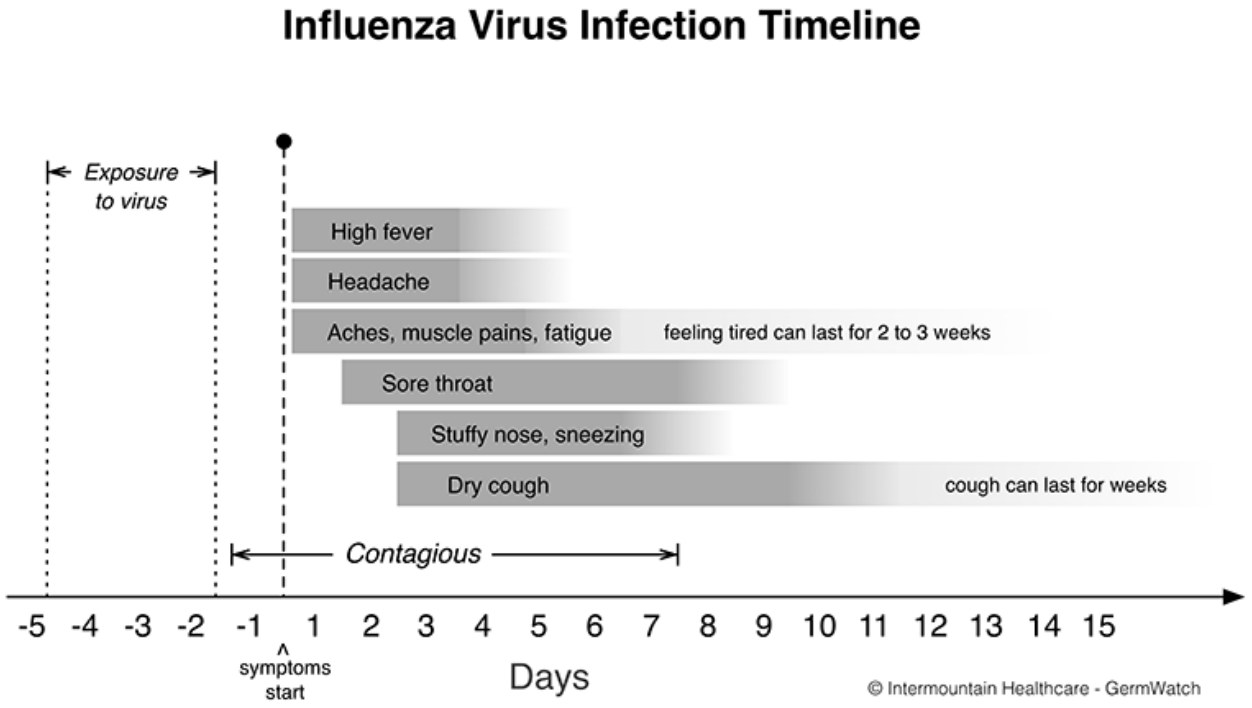
- Family: Orthomyxoviridae
- Influenza virus A, B & C
- Influenza A virus
  - HA
    - Virulence of the virus
    - Role in viral life cycle
  - NA
    - Cleaves sialic acid
    - Role in viral entry and release
- Virus undergoes antigenic change



Cox RJ et al. 2004: Influenza A virus

Pathology of influenza

- Characterized by
  - Systemic symptoms
  - Respiratory symptoms
- High-risk subjects
  - Hospitalization
  - Death
- Epidemic
  - 1:300 elderly hospitalized
  - 1:1500 elderly die



Cox RJ et al. 2004




Persons at risk

The priority groups for influenza immunization are drawn from the 2012 **WHO** position paper on influenza vaccines and include:

- Aged over 65
- Chronic medical conditions
- Caregivers
- Pregnant women
- Children aged 6-59 months

WHO. 2012

Changes during pregnancy

WHO: Pregnant women are a priority group

- Increased susceptibility to severe influenza from the second trimester to the early postpartum period
  - Physiologic changes
    - Lung capacity / cardiac output / oxygen consumption
  - Immuneresponse changes
    - T-helper-type 1 cell-mediated immunity is suppressed → Impairs maternal response to infection
  - 1-2:1000 hospitalized
    (18-fold above nonpregnant women)

Del Rio C et al. 2009

Pregnancy and vaccination

Table Influenza vaccination coverage rates in 2014/2015

	Netherlands
Vaccine coverage rate	(%)
Elderly	64.6
Healthcare professionals	ND
Living with medical condition	27.4
Pregnant*	63

* Influenza vaccination coverage rates in 2009

- Europe: 42.8%

- USA: 15% < 2009 > 50%

- Vaccination reduced the incidence of maternal influenza by 50.4%

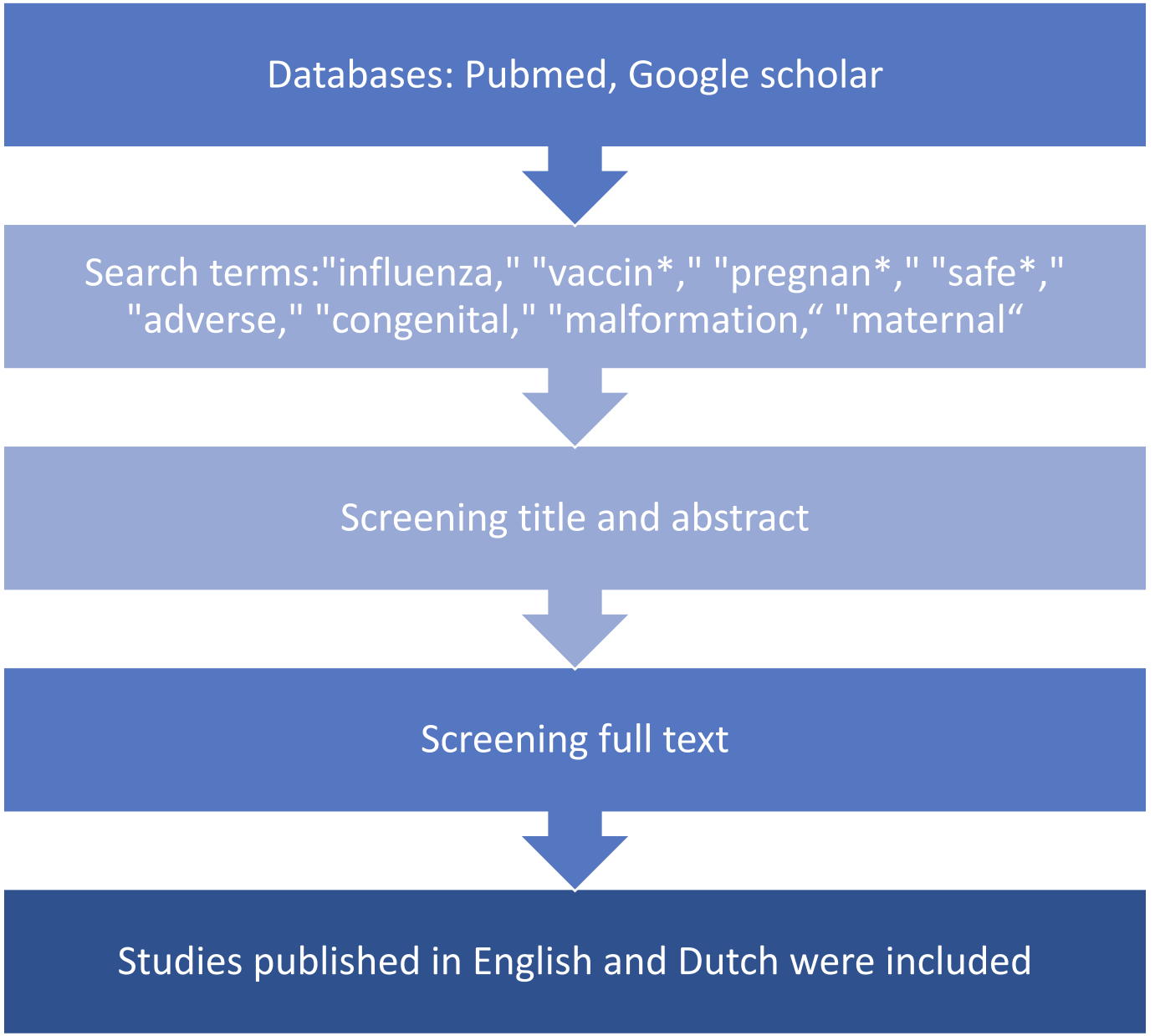
Blank PR et al. 2018
Van Lier A et al. 2012
Jamieson DJ et al. 2012

Do the safety concerns justify low vaccination rates in pregnant women?

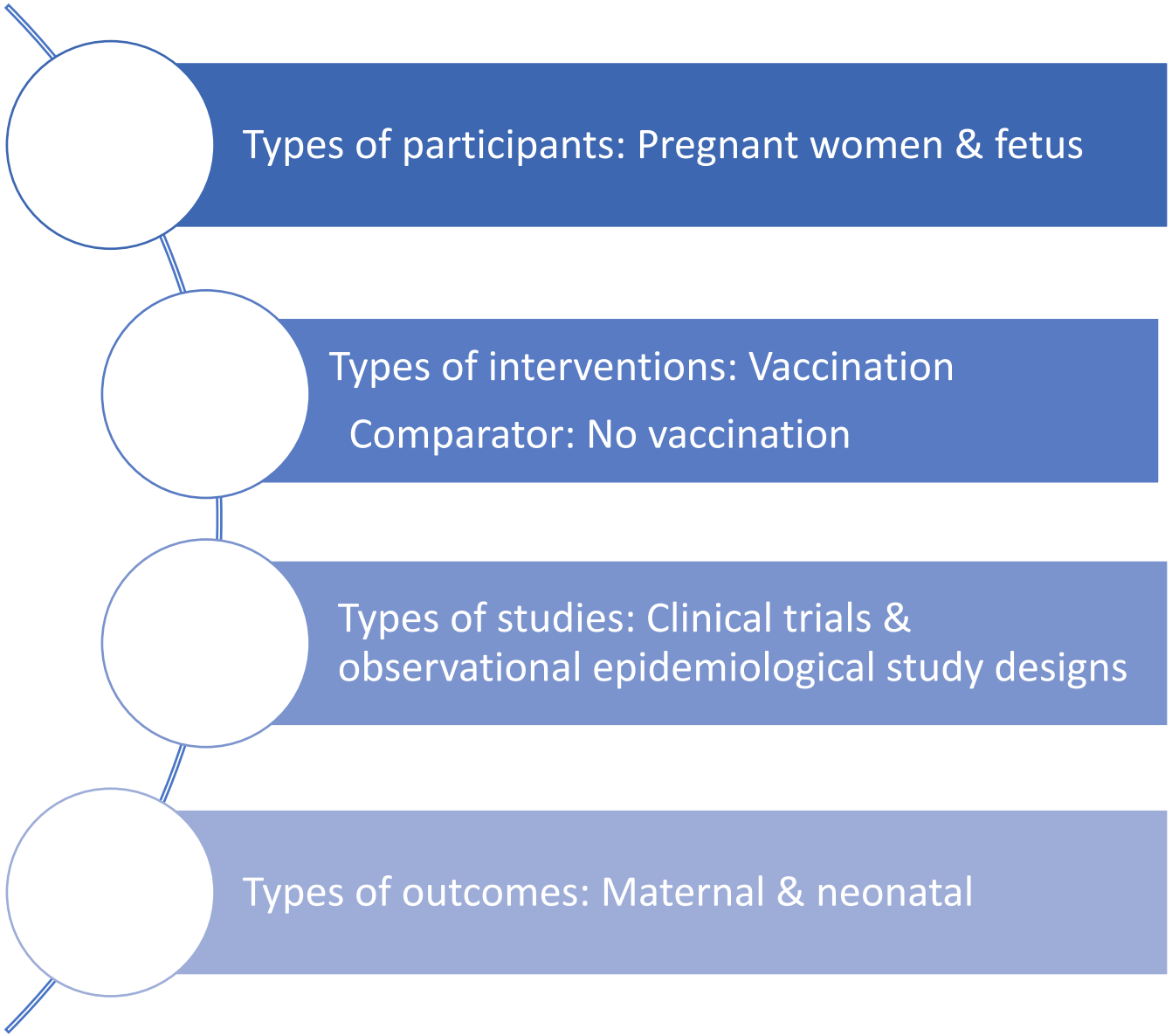
If they do not: What is the best trimester to get vaccinated + What are the benefits of vaccination?

If they do: What has to be done to create a safe vaccine during pregnancy?

Search strategies



Inclusion criteria



Types of vaccines

- Inactivated Influenza Vaccine (IIV)
- Recombinant Influenza Vaccine (RIV)
- Live attenuated Influenza Vaccine (LAIV)

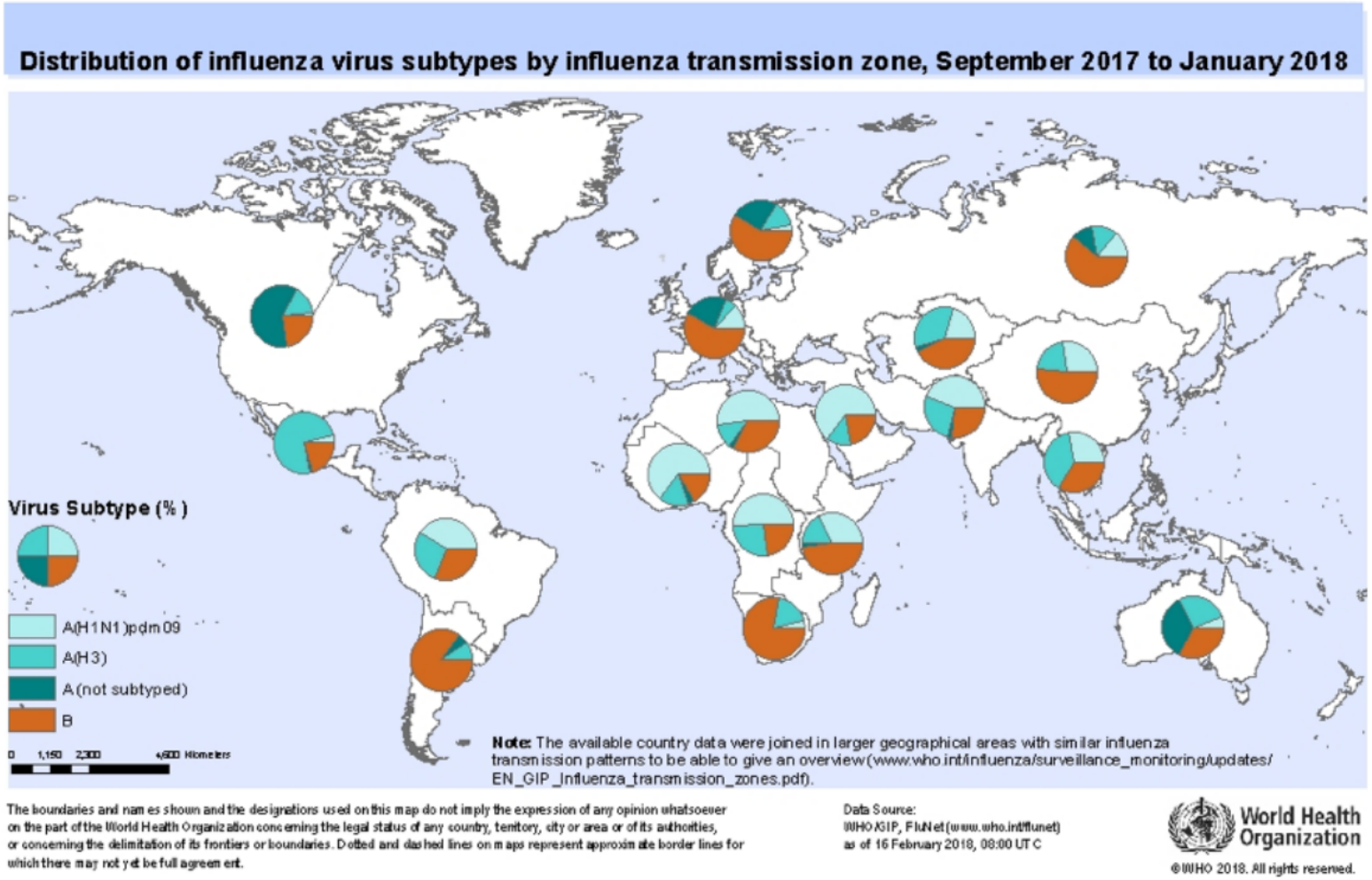
TABLE 1. Influenza vaccines — United States, 2018–19 influenza season*

Trade name (Manufacturer)	Presentation	Age indication
Quadrivalent IIVs (IIV4s)—Standard Dose—Contain inactivated virus		
Afluria Quadrivalent (Seqirus)	0.5 mL PFS	≥5 yrs
	5.0 mL MDV	≥5 yrs (needle/ syringe)
		18 through 64 yrs (jet injector)
Fluarix Quadrivalent (GlaxoSmithKline)	0.5 mL PFS	≥6 mos
Flulaval Quadrivalent (ID Biomedical Corp. of Quebec)	0.5 mL PFS	≥6 mos
	5.0 mL MDV	
Fluzone Quadrivalent (Sanofi Pasteur)	0.25 mL PFS	6 through 35 mos
	0.5 mL PFS	≥3 yrs
	0.5 mL SDV	≥3 yrs
	5.0 mL MDV	≥6 mos
Flucelvax Quadrivalent (Seqirus)	0.5 mL PFS	≥4 yrs
	5.0 mL MDV	
Trivalent IIV (IIV3)—Standard Dose—Contains inactivated virus		
Afluria (Seqirus)	0.5 mL PFS	≥5 yrs
	5.0 mL MDV	≥5 yrs (needle/ syringe)
		18 through 64 yrs (jet injector)
Trivalent IIV3—High-Dose—Contains inactivated virus		
Fluzone High-Dose (Sanofi Pasteur)	0.5 mL PFS	≥65 yrs
Trivalent IIV3—Adjuvanted—Contains inactivated virus		
Fluad (Seqirus)	0.5 mL PFS	≥65 yrs
Quadrivalent RIV (RIV4)—Contains recombinant HA		
Flublok Quadrivalent (Sanofi Pasteur)	0.5 mL PFS	≥18 yrs
Quadrivalent LAIV (LAIV4)—Contains live, attenuated, cold-adapted virus		
FluMist Quadrivalent (AstraZeneca)	0.2 mL prefilled single-use intranasal sprayer	2 through 49 yrs

CDCP week report. 2018

Types of vaccines

- Influenza Vaccines 2018-2019
  - IIV3: H1N1 pdm09–like virus **(A)**, H3N2-like virus **(A)**, B/Colorado/06/2017–like virus **(B)**
  - IIV4 / RIV4: IIV3 + B/Phuket/3073/2013–like virus **(B)**
- Influenza B (2001 -2011) responsible for 22-44% of influenza deaths each season (0-18 years)



Rondy M et al. 2018
Ambrose CS et al. 2012

SMPC

Trivalent vaccines — Influvac / Vaxigrip

Safe for mother and child

Quadrivalent vaccines — Fluzone / Fluquadri

Should be given to pregnant women only if clearly needed and following an assessment of the risks and benefits. However, there is no evidence to suggest a risk to the fetus or the pregnancy from maternal immunization with Quadrivalent vaccines

Safety / efficacy of influenza vaccines in pregnant woman

Table: Association between influenza vaccination during pregnancy and prenatal outcomes.

Outcomes	**Unvaccinated N = 116,040**	**Vaccinated N = 130,996**	**Crude**	**Adjusted**	**P-Value**
	n (%)		OR (95% CI)		
Maternal fever > 100.4 °F	858 (0.74)	412 (0.31)	0.42 (0.38, 0.48)	0.40 (0.35, 0.45)	<0.001
Chorioamnionitis	6226 (5.37)	7600 (5.80)	1.09 (1.05, 1.12)	1.00 (0.96, 1.04)	0.994
Preeclampsia/eclampsia	6730 (5.80)	8040 (6.14)	1.06 (1.03, 1.10)	0.93 (0.90, 0.96)	<0.001
Placental abruption	1270 (1.09)	1297 (0.99)	0.90 (0.84, 0.98)	0.89 (0.82, 0.96)	<0.001

Abbreviations: N, total birth; n, number of birth with the outcome; OR, odds ratios; CI, confidence intervals

**Adjustments were made for maternal age, race/ethnicity, education, smoking during pregnancy, parity, prenatal care, median family household income, pre-pregnancy BMI, and year of vaccination.*

Getahun D et al. 2019

Post-licensure surveillance of Quadrivalent vaccines (VAERS)

- Available since the 2013–2014 influenza season
- 36 reports of women who have recieved IIV4 during pregnancy are available
- Three reports described an adverse event related to pregnancy: spontaneous abortion, uterine bleeding, and trisomy (one report each)
- Twelve reports described adverse events that were not directly related to the pregnancy, e.g. injection site reactions, allergic reactions, and musculoskeletal symptoms
- Twenty-one reports did not describe an adverse event
- VAERS did not identify any safety concerns

Haber P et al. 2016

Recombinant Influenza Vaccine RIV4

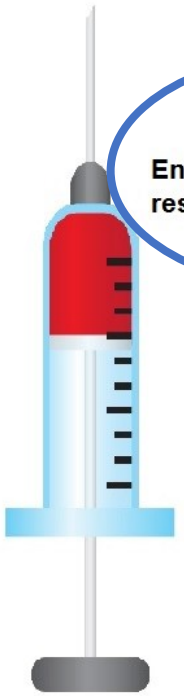
- Available since the 2013–2014 influenza season
- Experience with the use of RIVs in pregnant women 18 years and older is limited
- RIV4 had comparable safety and immunogenicity to IIV4

Dunkle LM et al. 2018

Different components of vaccines

ACTIVE COMPONENT

- **Antigen**
  - Weakened microbes
  - Inactivated microbes
  - Parts of microbes
  - Modified microbial toxins

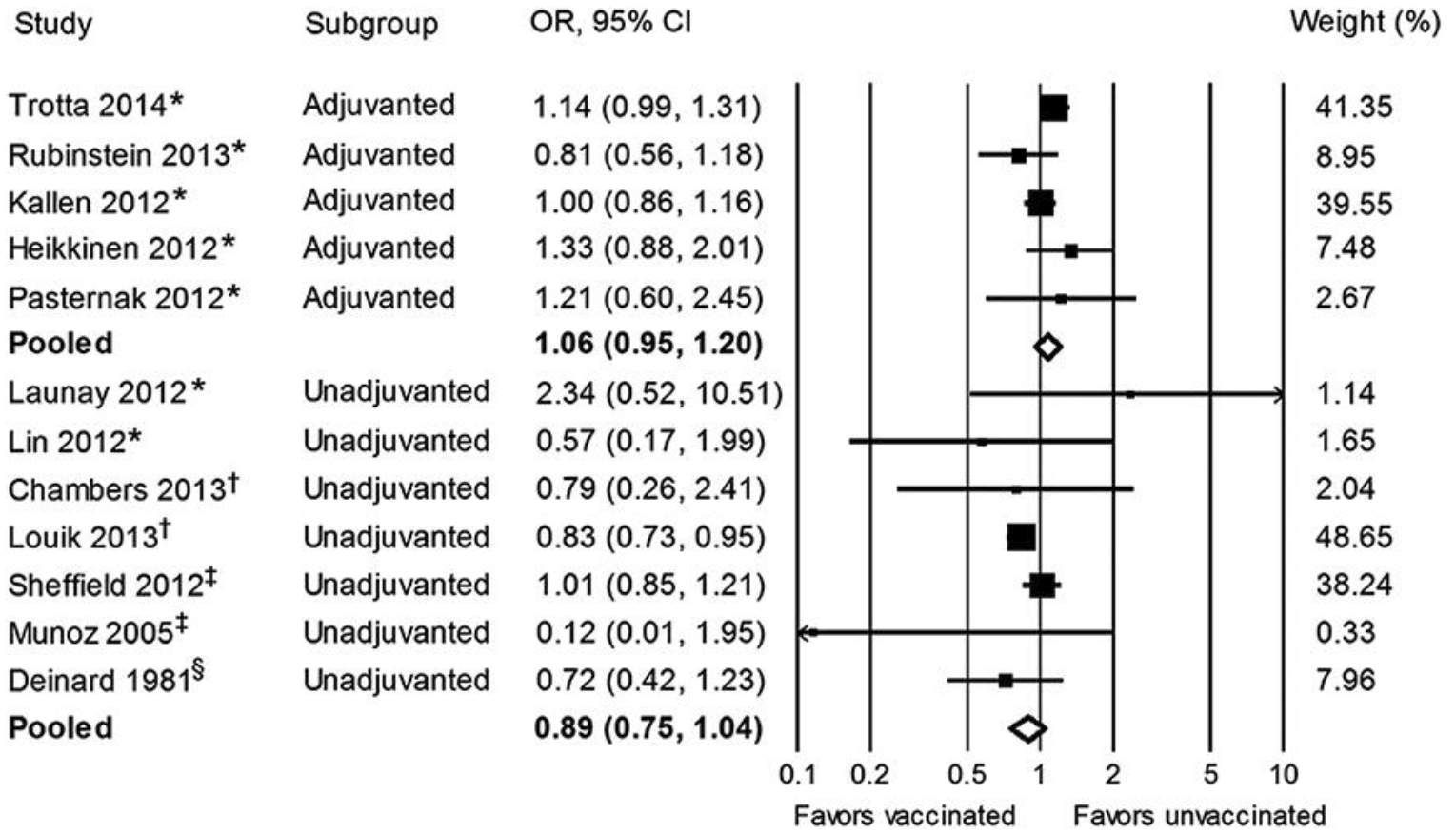


EXCIPIENTS

- **Adjuvants**
  - Enhance body's immune response towards antigens
- **Stabilizers**
  - Protect vaccine from harsh processing conditions
- **Antibiotics**
  - Prevent microbial contamination during manufacture
- **Preservatives**
  - Prevent contamination during use of multiple-dose preparations
- Used to inactivate microbes in toxoid vaccines
- **Trace Components**
  - Minute quantities of residual components used during manufacture (ie: inactivating agents, antibiotics, egg proteins etc)

Adjuvants

Forest plot for congenital anomalies associated with any-trimester influenza immunization
Adjuvanted with MF59 / AS03



Polyzos KA et al. 2015

Safety of maternal influenza vaccination for the fetus | Fetal death

Table: Influenza vaccine versus no vaccine, outcome of fetal death.

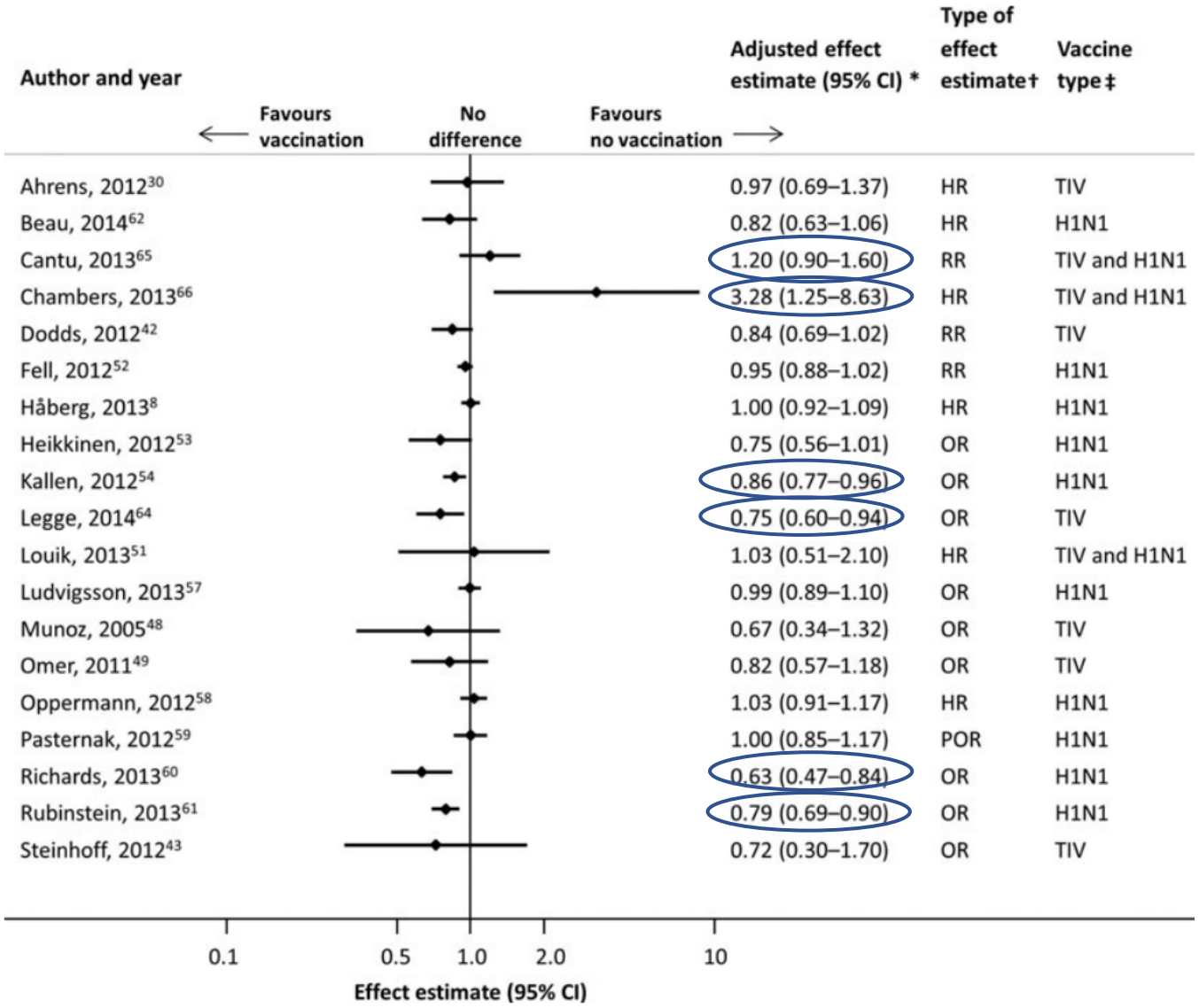
Study	Composition	Vaccine group	Control group	Effect estimate subtotals (95% CI)
Hårberg et al.	Mono H1N1	25976	87335	HR 0.88 (0.66 to 1.17)
Fell et al.	Mono H1N1	23340	32230	OR 0.66 (0.47 to 0.91)
Lin et al.	Mono H1N1	202	206	OR 0.34 (0.01 to 8.39)†
Heikkinen et al.	Mono H1N1	2295	2213	OR 1.44 (0.23 to 8.90)
Rubinstein et al.	Mono H1N1	7293	23195	OR 0.71 (0.46 to 1.10)‡
Kallen	Mono H1N1	18 844	84 484	OR 0.81 (0.59 to 1.12)
Pasternak et al.	Mono H1N1	7062	47524	HR 0.44 (0.20 to 0.94)
Launay et al.	Mono H1N1	320	422	OR 0.58 (0.06 to 5.59)‡
Sammon et al.	Mono H1N1	9445	26993	HR 1.56 (0.73 to 3.34)
Deinard	Mono Hsw1N1	176	517	OR 2.95 (0.18 to 47.39)‡
Sheffield et al.	TIV	8864	76919	OR 0.60 (0.41 to 0.86)‡
		439	76919	OR 2.54 (0.36 to 18.10)‡
Chambers et al.	TIV+/- Mono H1N1	1032	191	RR 0.23 (0.01 to 3.93)§
		348	191	RR 0.57 (0.03 to 9.57)‡
Cantu et al.	TIV+/- Mono H1N1	979	2010	OR 1.10 (0.46 to 2.59)‡

† Crude raw data used to estimate unadjusted odds ratio and 95% confidence interval by review authors.
‡ Analysis of women vaccinated during the first trimester.
§ Analysis of women vaccinated during their 2nd and 3rd trimester

McMillan M et al. 2015

Safety of maternal influenza vaccination for the fetus

Preterm birth



effect estimates for preterm birth at <37 weeks associated with influenza vaccination during pregnancy.
Small, black diamond markers indicate individual study estimates, with corresponding 95% confidence intervals (CIs) represented by horizontal bars

Fell DB et al. 2014

Safety of maternal influenza vaccination for the fetus | Congenital malformation

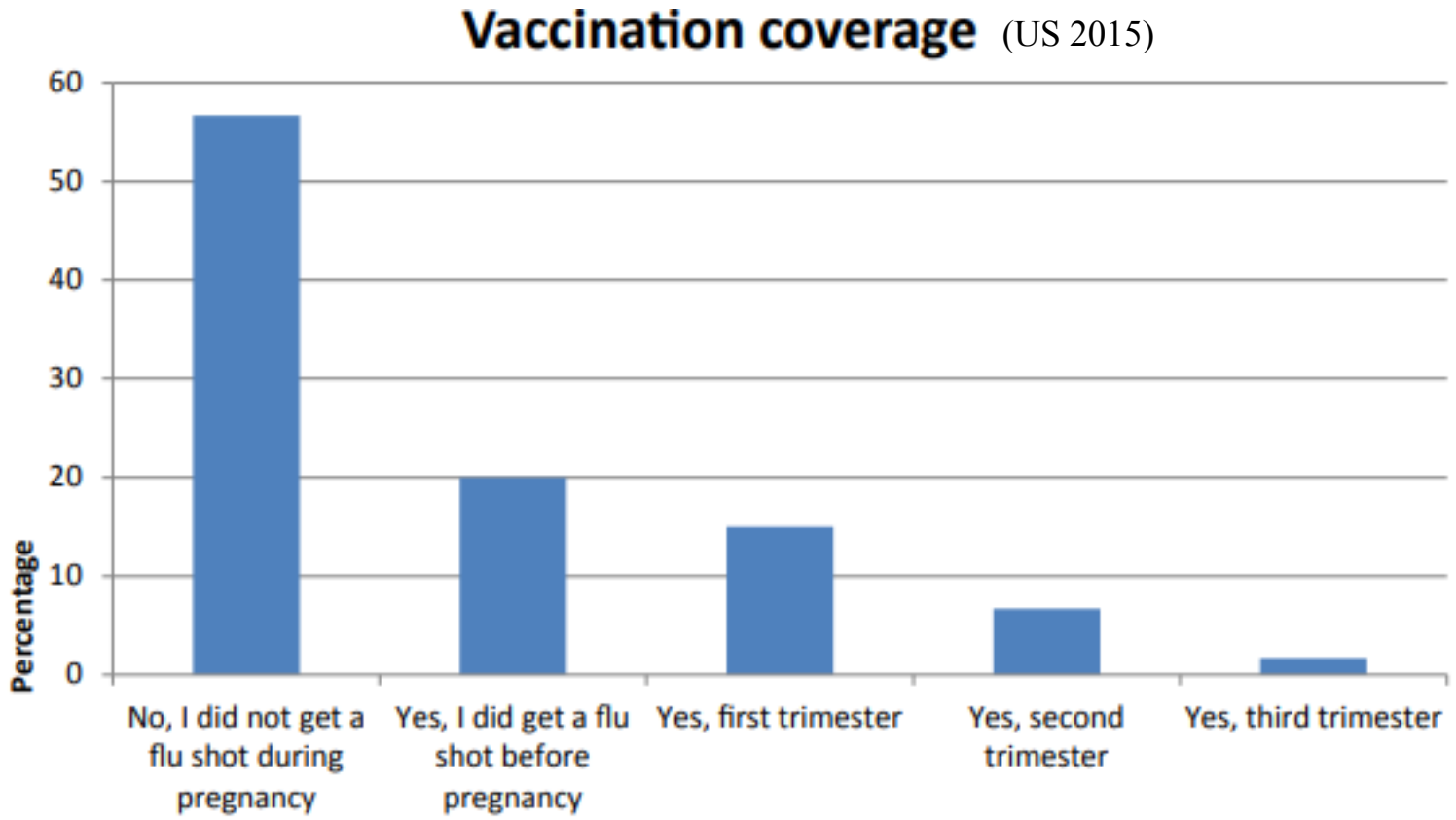
Table: Any trimester influenza vaccination versus no vaccine, outcome of congenital malformation.

Study	Composition	Vaccine group	Control group	Effect estimate subtotals (95% CI)
All malformation				
Opperman et al.	Mono H1N1	321	1198	OR 0.92 (0.58 to 1.46)
Heikkinen et al.	Mono H1N1	2295	2213	OR 1.33 (0.88 to 2.00)
Mackenzie et al.	Mono H1N1	97	13	OR 1.60 (0.08 to 30.70)†
Rubinstein et al.	Mono H1N1	7293	23195	OR 0.81 (0.55 to 1.19) †
Deinard	Mono Hsw1N1	176	517	OR 0.58 (0.32 to 1.06) †
Munoz et al.	TIV	225	825	OR 0.12 (0.01 to 1.95) †
Major malformation				
Opperman et al.	Mono H1N1	321	1198	OR 1.11 (0.51 to 2.42)
Launay et al.	Mono H1N1	320	557	OR 2.34 (0.52 to 10.51)†
Sheffield et al.	TIV	8425	76919	OR 1.01 (0.84 to 1.22)¥

† Crude raw data used to estimate unadjusted odds ratio and 95% confidence interval by review authors.
¥ 2nd and 3rd trimester vaccination only.

McMillan M et al. 2015

Timing of the influenza vaccine



Puchalski S et al. 2015

Timing of the influenza vaccine

Mother

Table: Association between influenza vaccination and perinatal outcomes based on timing of vaccination.

Outcomes	**Pre-pregnancy N = 9298**		**First trimester N = 42250**		**Second trimester N = 40823**		**Third trimester N = 38625**	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Maternal fever	63 (0.7)	0.88 (0.68, 1.14)	226 (0.5)	0.68 (0.58, 0.79)	91 (0.2)	0.29 (0.24, 0.37)	32 (0.1)	0.11 (0.08, 0.15)
Preeclampsia	566 (6.1)	0.92 (0.84, 1.01)	2679 (6.3)	0.95 (0.91, 1.00)	3008 (6.2)	0.97 (0.93, 1.02)	2730 (5.8)	0.89 (0.85, 0.94)
Placental abruption	102 (1.1)	0.96 (0.78, 1.18)	439 (1.0)	0.95 (0.85, 1.06)	522 (1.1)	1.00 (0.90, 1.12)	360 (0.8)	0.71 (0.62, 0.80)

Abbreviations: n, number of birth with the outcome; OR, odds ratios; CI, confidence intervals.

Getahun D et al. 2019

Timing of the influenza vaccine

Fetus

Table: Association between influenza vaccination and perinatal outcomes based on timing of vaccination.

Outcomes	**Pre-pregnancy N = 9298**		**First trimester N = 42250**		**Second trimester N = 40823**		**Third trimester N = 38625**	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Influenza illness	5 (0.1)	0.26 (0.11, 0.64)	47 (0.1)	0.57 (0.41, 0.79)	55 (0.1)	0.70 (0.52, 0.96)	16 (0.14)	0.22 (0.13, 0.37)
SGA	845 (9.1)	0.98 (0.91, 1.05)	4116 (9.7)	1.01 (0.97, 1.05)	4114 (10.1)	1.04 (0.99, 1.08)	3965 (10.3)	1.06 (1.02, 1.11)
Stillbirth	47 (0.5)	0.85 (0.62, 1.18)	231 (0.6)	0.87 (0.73, 1.03)	243 (0.6)	0.96 (0.81, 1.13)	146 (0.4)	0.77 (0.63, 0.93)
NICU admission	941 (10.1)	0.96 (0.89, 1.03)	4367 (10.3)	0.96 (0.92, 1.00)	4419 (10.8)	1.00 (0.96, 1.04)	3108 (8.1)	0.71 (0.68, 0.74)

Abbreviations: n, number of birth with the outcome; SGA, small for gestational age birth; NICU, neonatal intensive care unit; OR, odds ratios; CI, confidence intervals.

Getahun D et al. 2019

Benefits of the influenza vaccination for the neonate

- Transplacental influenza antibody is suggested to provide indirect protection in newborns
  - Increased H1-specific passive antibody titers
    - Delayed onset
    - Shorter duration

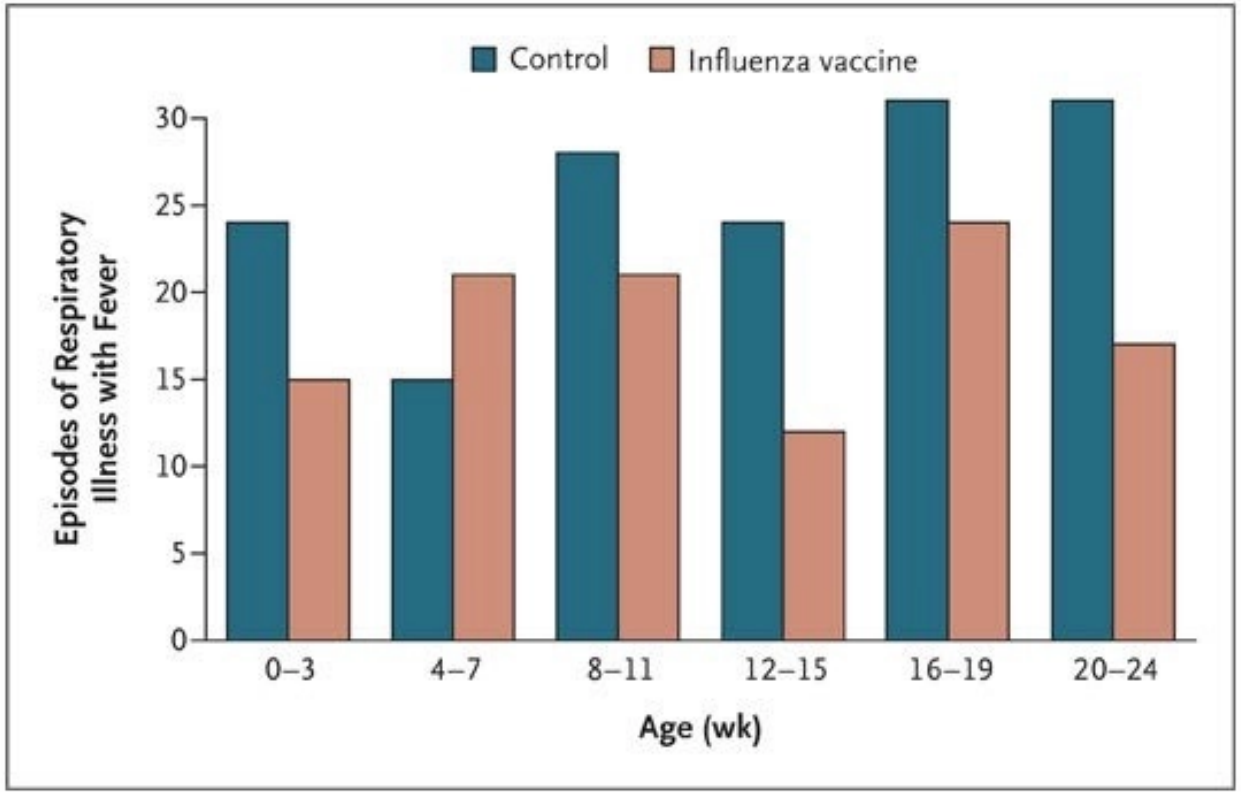


Figure: Episodes of Respiratory Illness with Fever in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects, According to Age.

Zaman K et al. 2008

Benefits of breastfeeding after vaccination

- Strongly recommended
  - activates innate antiviral mechanisms (type 1 interferons)
- Timing: Third trimester vaccination
  - Higher levels of influenza-specific immunoglobulin A
- Breastfeeding in first 6 months decreases respiratory illness with fever

American Academy of Pediatrics. 2018

Costs

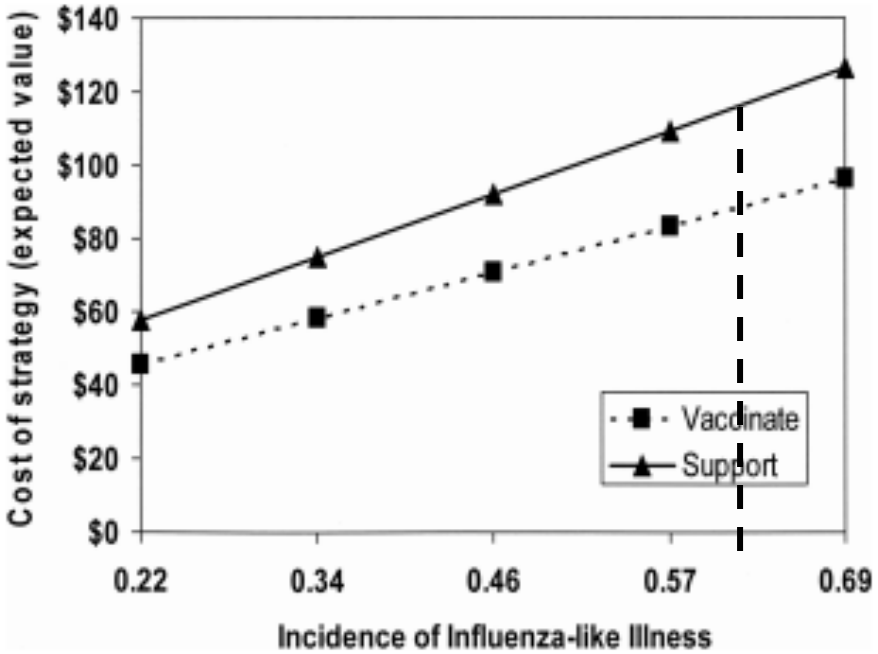


Fig. Sensitivity analysis for average cost-effectiveness of supportive care compared with vaccination for different incidences of influenza-like illness.

Table Costs, Effectiveness, and Incremental Cost-effectiveness of the 2 Interventions Studied Among 18–44-Year-Old Females

Measure	Total Cost ($)	Incremental Cost ($)	Total Effectiveness	Incremental Effectiveness	C ($)/E*	Incremental C/E (ICER)
Vaccinate†	81.38		0.89676 HRQL		91/QALY	
Support	106.60	25.22	0.89420 HRQL	–0.00256 HRQL	119/QALY	(Dominated)

ICER, incremental cost-effectiveness ratio; HRQL, health-related quality of life; QALY, quality-adjusted life years.
Total cost is the cost (in dollars) per pregnant woman in dollars for 1 pregnant woman who either receives vaccination or supportive care only during the evaluated pregnancy. Incremental cost is the difference in cost (in dollars) between total costs for 1 pregnant woman who receives vaccination or supportive care only during the evaluated pregnancy.
* Cost-effectiveness is the cost (in dollars) per pregnant woman relative to health-related quality of life during the evaluated pregnancy for 1 year.
† Probability of vaccination is 50% for calculation of cost/effectiveness in table.

Sheffield J et al. 2006

Conclusion

Do the safety concerns justify low vaccination rates in pregnant women?

No increased risk for maternal complications
No increased risk for adverse events in adjuvant containing vaccines
No increased risk for adverse event in neonates

They do not!

What is the best trimester to get vaccinated + What are the benefits of vaccination?

Third trimester vaccination best for mother & infant
Benefits are decreased risk for maternal & neonatal influenza
Vaccinating all pregnant women aged 18 – 44 years old would result in $50,- savings per women

Advice

- Consequences of influenza vaccination during pregnancy are less harmful compared to the consequences of getting the influenza virus during pregnancy
- Higher vaccination rates of mothers should further reduce viral exposure to infants
- Research should continue
  - Antigenic differences per season
  - Large study on quadrivalent vaccines
- Assess and compare the different formulations of vaccines available for pregnant women
- Better registration of administered vaccines

Questions?