

WHO Working Group to Evaluate Influenza Data to Inform Vaccine Impact and Economic Modelling

Bradford D. Gessner, Chair

On behalf of Working Group Activity Leads
– Niranjana Bhat, Mark Loeb, Deshayne Fell

Outline

- WHO Working Group
- Risk of severe influenza in pregnancy
- Adverse fetal outcomes associated with maternal influenza
- Pending evaluations
- Conclusion

WHO Working Group

- WHO IVR working group to advise on influenza disease burden and vaccine impact assessment relevant to maternal immunization
- Subgroup of Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC)

Working Group Objectives

1. Determine key parameters for influenza vaccine impact and health economic modelling studies
 - focus on immunization in low-resource settings, pregnant women
2. Determine evidence-based estimates for key parameters
3. Evaluate quality of data informing these estimates
4. Recommend research to address data gaps

Working Group Composition

Members

- 26 people
- Expertise in modelling, influenza epidemiology, perinatal epidemiology, health economics
- IVIR-AC members

Work streams

- Pregnant women
- Fetus
- <6 month old infants

Process

- Work stream leads conducted systematic literature reviews
- Findings presented to the full working group for feedback

Time period: November 2014 through June 2015

Association between pregnancy and severe influenza outcomes

Objectives

- To quantify the effect of pregnancy on severe influenza-associated disease

Eligibility

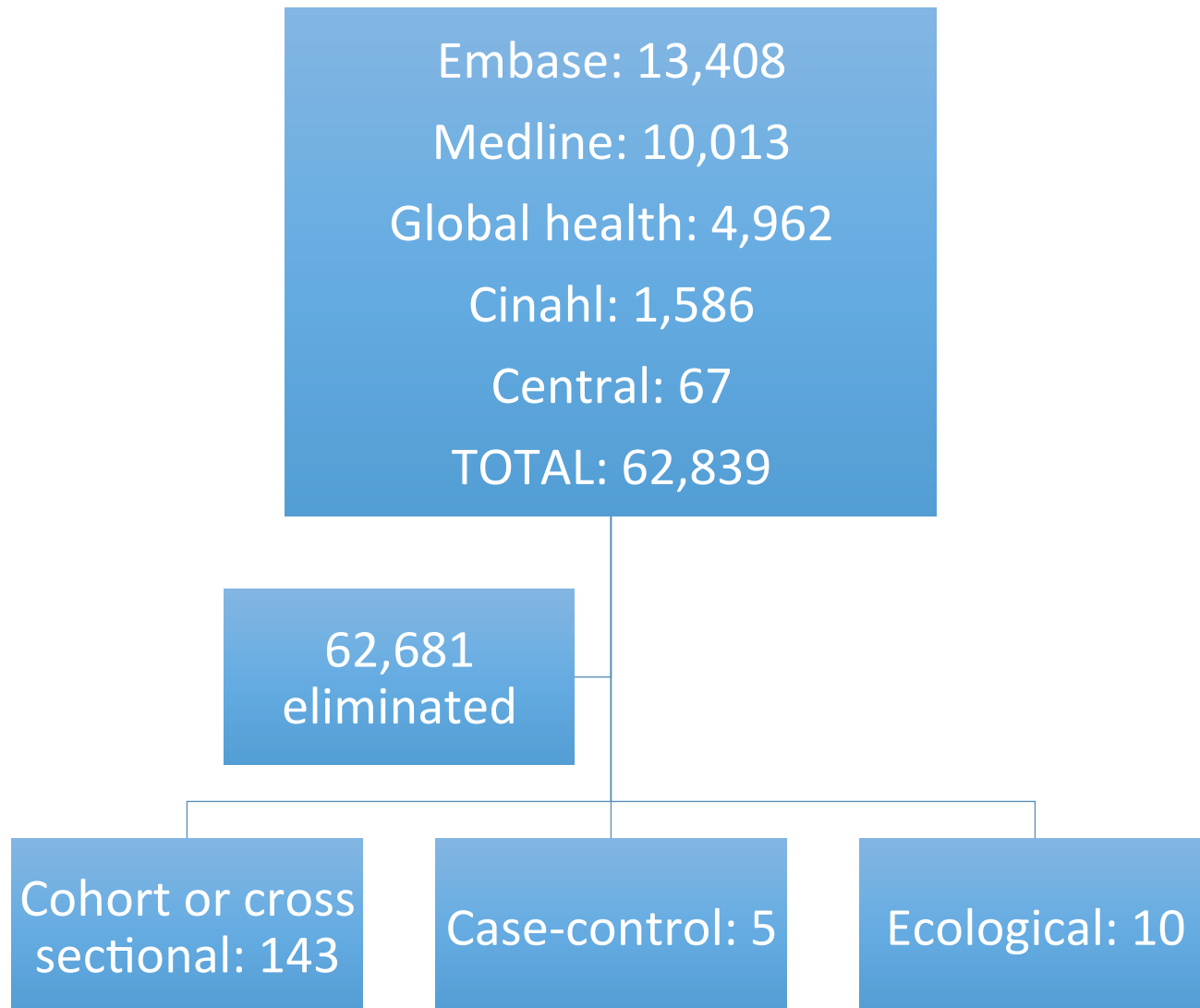
- Observational studies reporting on pregnancy as a risk factor for severe influenza
- Studies with no comparator arm were excluded
- Compare pregnant women to all other persons; sub-analysis women child-bearing age
- All subjects had influenza infection

Outcomes

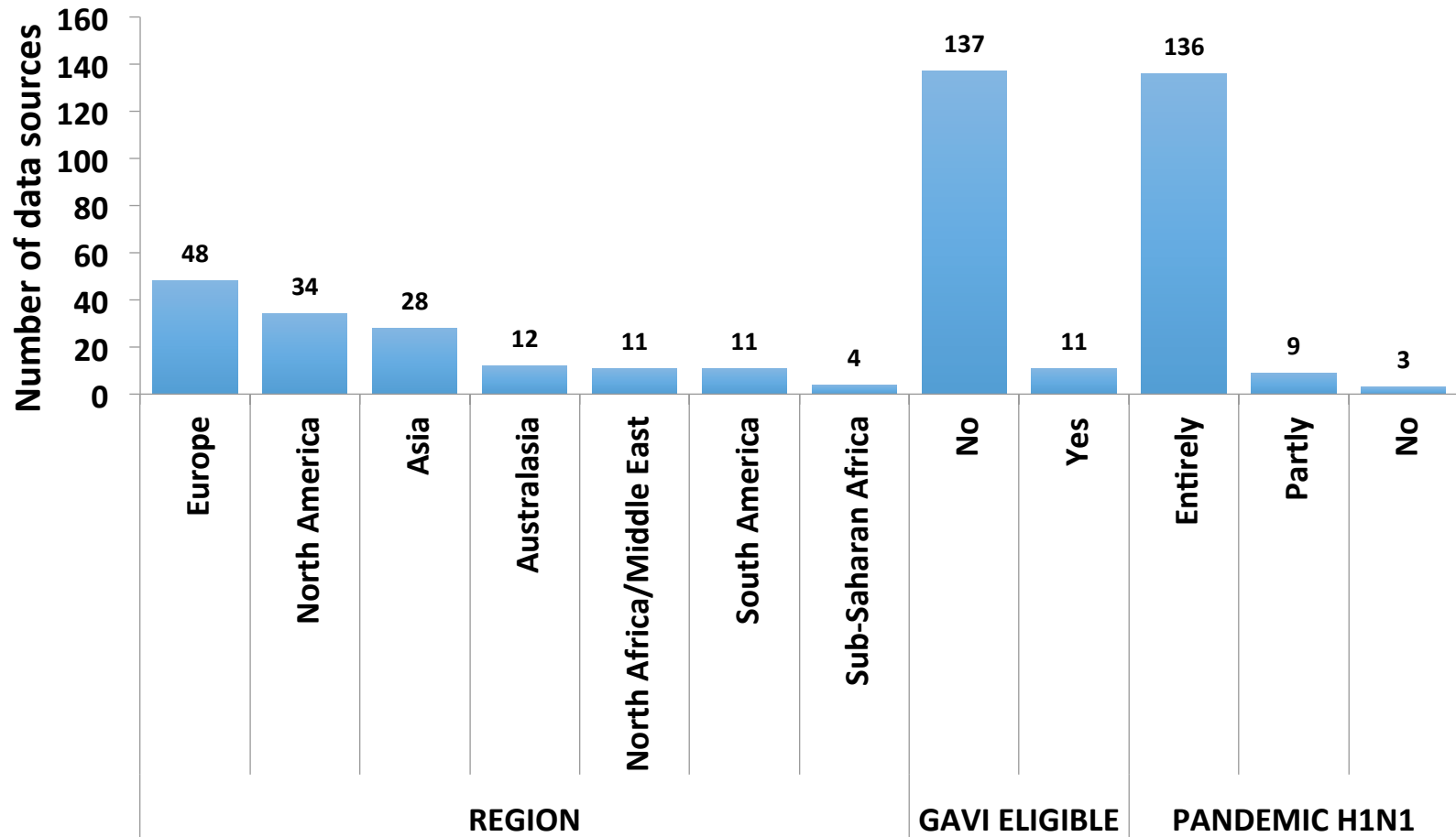
- Community-acquired pneumonia
- All-cause, influenza-associated, or pneumonia-associated mortality
- All cause, influenza-associated, or pneumonia-associated hospitalization
- ICU admission and need for ventilator support

Risk of Bias and Quality of Evidence Assessed

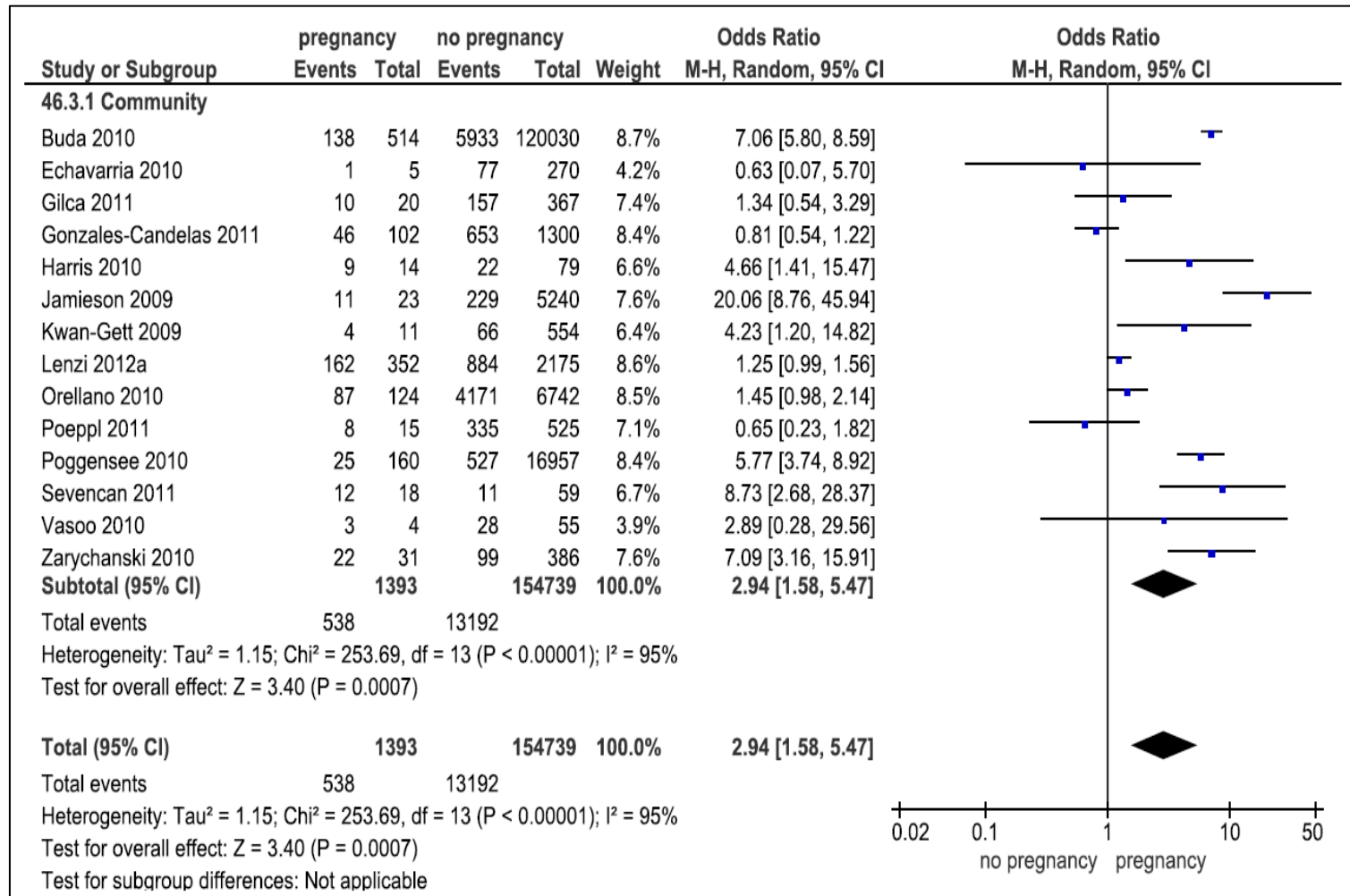
Flow diagram for systematic review of association between pregnancy and severe influenza outcomes



Data source distribution



Association between pregnancy and flu hospitalization (n=14)



- Two studies with Women of Reproductive Age as comparator: OR 3.3 (0.52 to 20)
- Three studies limited to LMIC: OR 2.1 (0.49 to 9.0)

Association between pregnancy and other influenza-associated severe outcomes

- **Mortality**

- 92 studies total: OR 1.0 (0.81 to 1.3)
- 17 studies Women of Reproductive Age as comparator: OR 0.94 (0.52 to 1.7)
- 36 studies from LMIC: OR 1.6 (1.1 to 2.2)

- **Mechanical ventilator support**

- 26 studies total: OR 1.21 (0.70 to 2.08)
- 5 studies Women of Reproductive Age as comparator: OR 0.88 (0.62 to 1.3)
- 4 studies from LMIC: OR 1.2 (0.41 to 3.2)

- **Community acquired pneumonia**

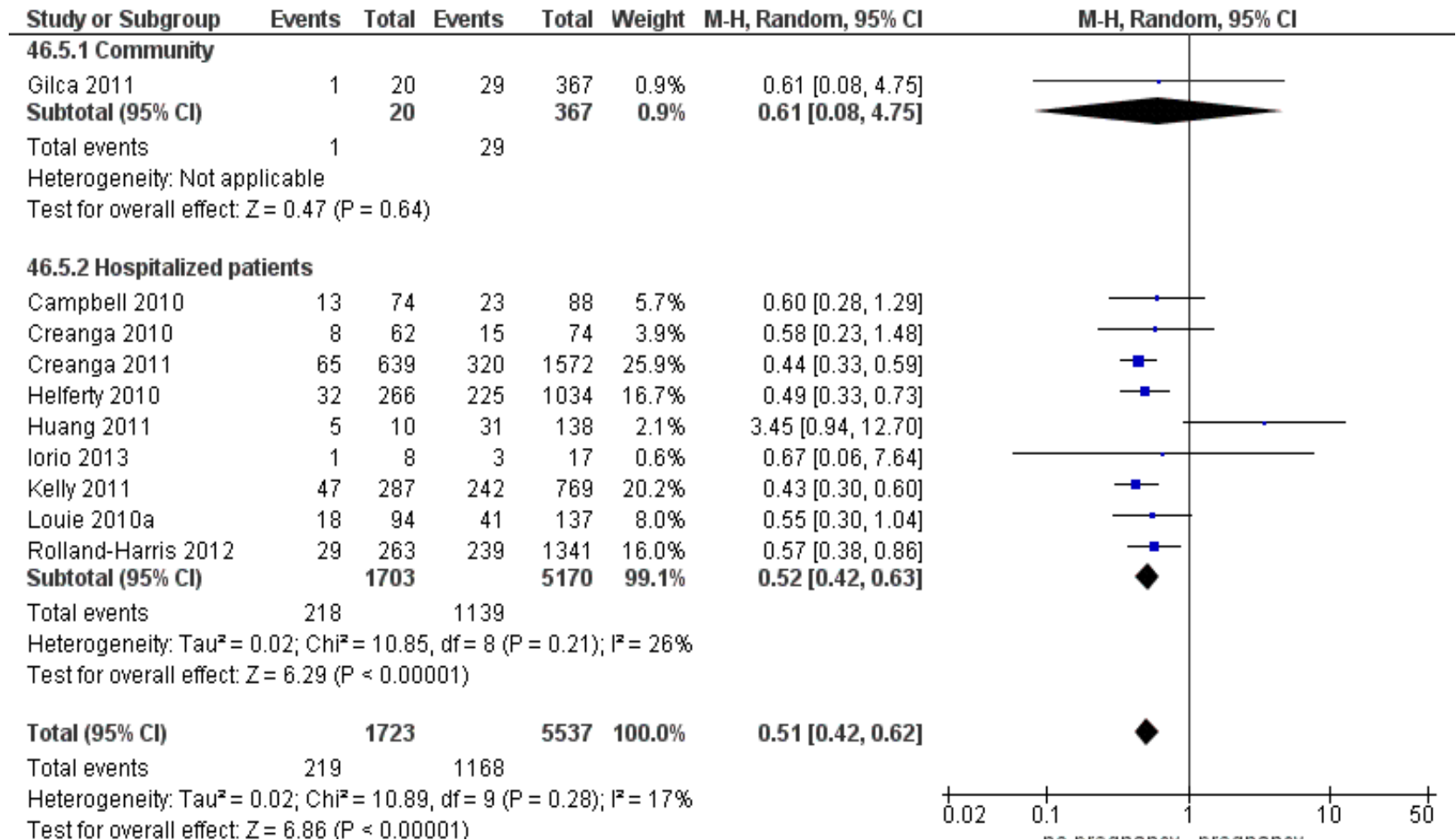
- 9 studies total: OR 1.80 (0.72 to 4.49)
- 3 studies Women of Reproductive Age as comparator: OR 1.1 (0.29 to 4.1)
- 3 studies from LMIC: OR 2.1 (0.49 to 9.0)

- **ICU admission**

- 45 studies total: OR 0.89 (0.65 to 1.2)
- 10 studies Women of Reproductive Age as comparator: OR 0.51 (0.42 to 0.62)
- 8 studies from LMIC: OR 1.4 (0.78 to 2.4)

*High heterogeneity for each analysis

Association between pregnancy and influenza associated ICU admissions; women of reproductive age as comparator



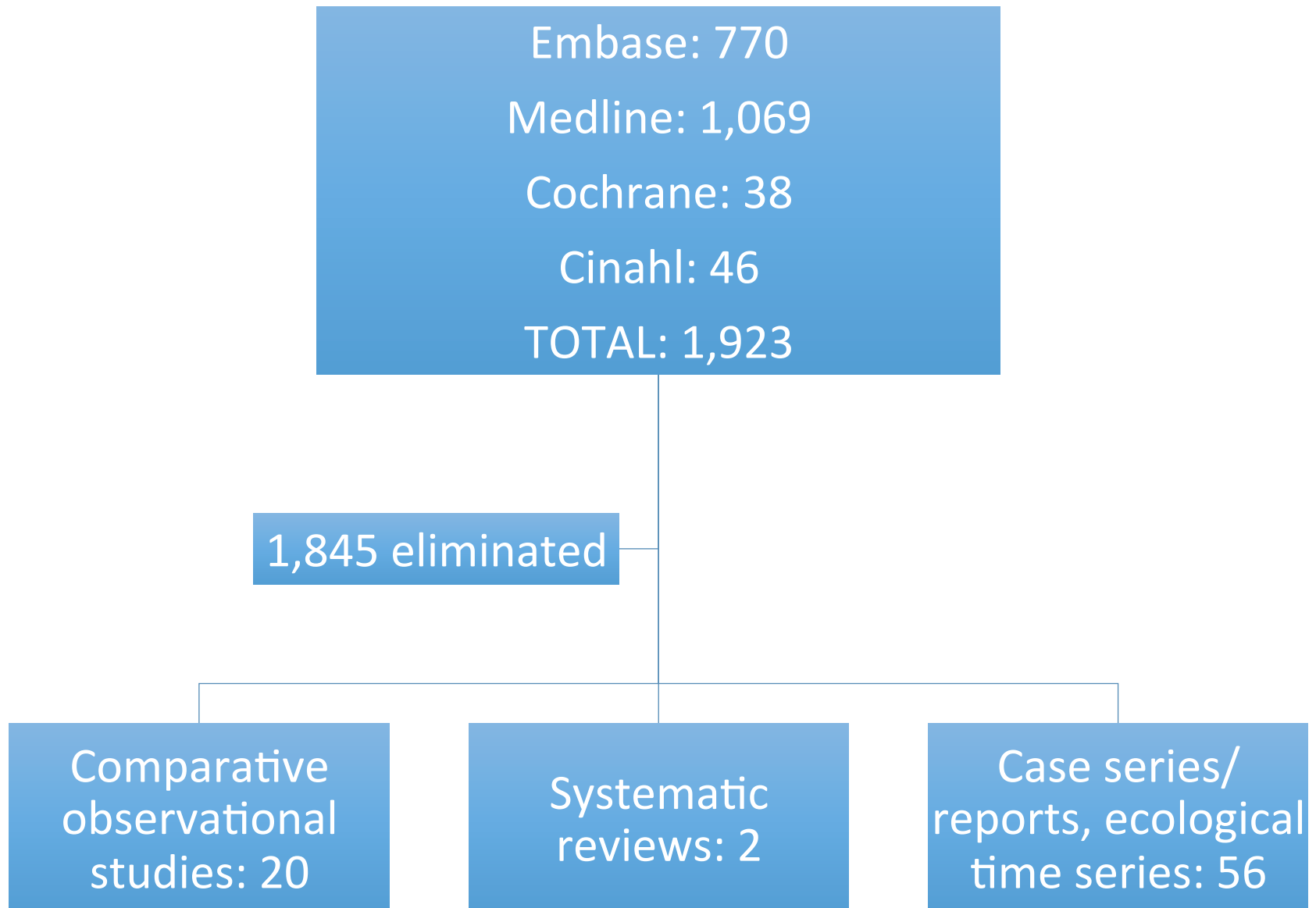
Conclusions and interpretation

- Among persons with primarily pH1N1 infection:
 - Pregnant women had a higher risk of influenza-associated hospitalization than the general population
 - Pregnant women did not have a higher risk of severe outcomes than the general population or WRA
 - Pregnant women in LMIC had a higher risk of mortality than the general population
 - Pregnant women had less risk of ICU admissions than other WRA
- Quality of evidence low with significant heterogeneity between studies for most analyses
- Hospitalization a marker of access and not severity?
- Women in LMIC more fragile state during pregnancy; reason for association rather than flu?

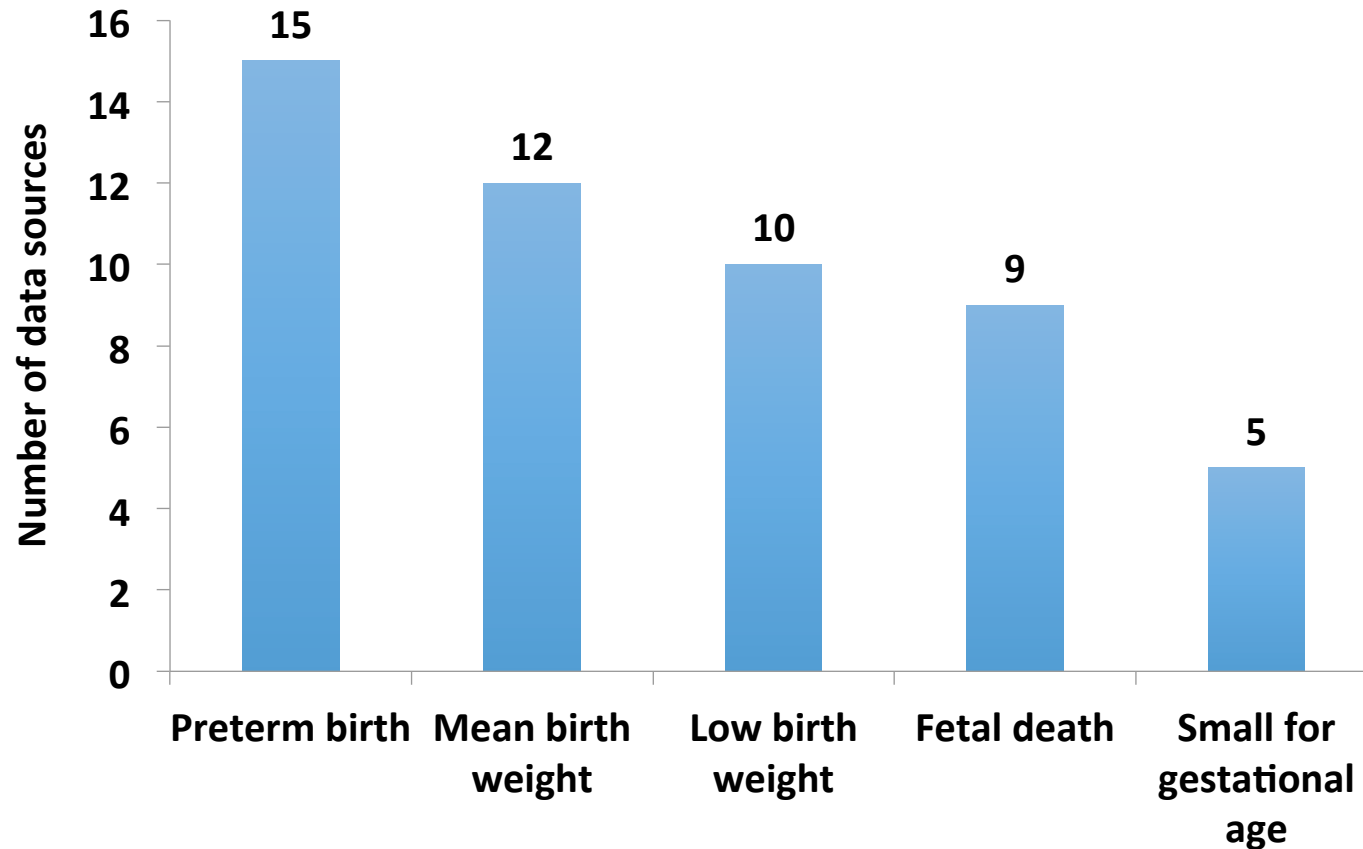
Adverse fetal outcomes associated with maternal influenza illness and infection

- **Objective:** Assess association between maternal influenza illness/ILI during pregnancy, as compared with no maternal influenza illness during pregnancy, on the risk of adverse fetal outcomes
- **Eligibility:** Observational studies of outcomes among pregnant women with influenza compared to pregnant women without influenza
- **Exposure**
 - Lab-confirmed influenza
 - Non-lab confirmed influenza (diagnostic codes, self-reported influenza or ILI)

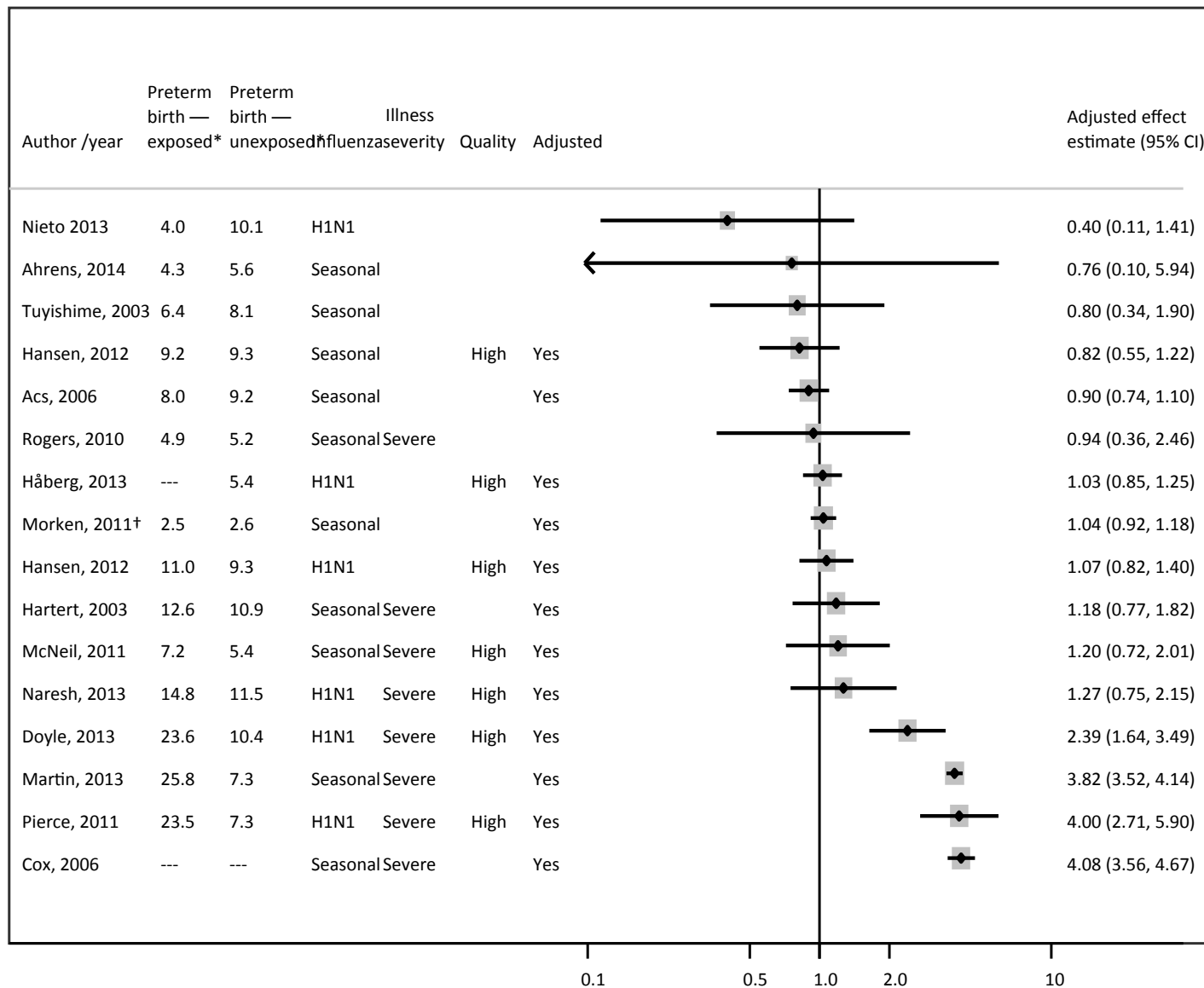
Flow diagram for systematic review of adverse fetal outcomes associated with maternal influenza



Studies reporting outcomes



Preterm birth (n=15 Studies)

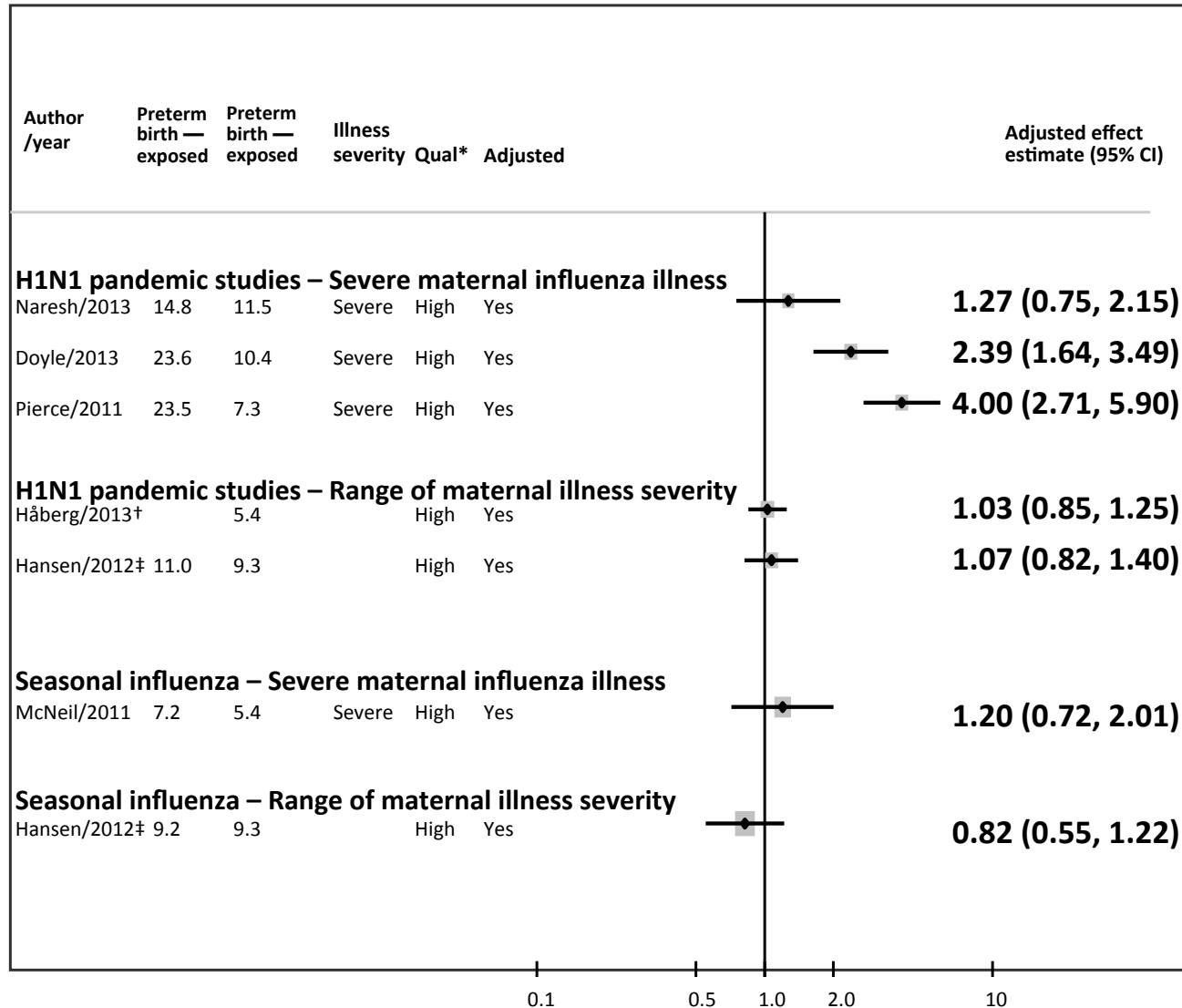


* Risk of preterm birth per 100 among women classified as having or not having influenza illness during pregnancy

† Morken et al. studied spontaneous preterm birth only

‡ Hansen, 2012 is shown twice: one estimate for each season (first line=seasonal influenza, second line=H1N1 influenza)

Subgroup analysis to reduce clinical and statistical heterogeneity (n=6 Studies)



* Highest quality based on Newcastle Ottawa Score of 8 or 9 AND adjustment for at least some covariates AND exposure not measured using self-reported questionnaire
 ‡ Hansen, 2012 provided estimates for both the 2009-2010 pandemic and one non-pandemic influenza season

SGA/LBW/mean birth weight

- Small for gestational age
 - Definitions differed (e.g., different reference standards)
 - RR range: 0.74 to 2.4 (3 studies no effect, 3 studies positive effect)
- Low birth weight
 - No consistent effect with/without adjustment for gestational age
 - RR range: 0.4 to 3.2
- Mean birth weight
 - Adjustment for GA:
 - 2 studies increased, 2 decreased with influenza
 - Range: -99g to 70g
 - No adjustment for GA:
 - 5 studies increased, 4 decreased, 1 no change with influenza
 - -255g to 117g

Fetal death (n=9 studies)

First author, year of publication	Fetal death among exposed per 1,000 (n/N)	Fetal death among unexposed per 1,000 (n/N)	Crude risk difference per 100 (95% CI)	Effect measure reported	Crude effect measure (95% CI)	Adjusted effect measure (95% CI)
Nieto-Pascual 2013 ¹	13.2‰ (1/76)	32.6‰ (3/92)	-19.5 (-63.9 to 25)	RR	0.40 (0.04–3.80)	---
Nieto-Pascual 2013 ¹	13.3‰ (1/75)	11.2‰ (1/89)	2.1 (-31.9 to 36.1)	RR	1.19 (0.08–18.65)	---
Martin 2013 ²	19.1‰ (333/17,468)	6.5‰ (102,993/15,825,557)	12.6 (10.5 to 14.6)	OR	---	2.50 (1.97–3.18)
Håberg 2013 ³	---	4.3‰ (492/113,331)	---	HR	2.00 (1.20–3.32)	1.91 (1.07–3.41)
Pierce 2011	27.3‰ (7/256)	5.7‰ (7/1,233)	21.7 (1.3 to 42.1)	OR	4.9 (1.7–14.2)	4.2 (1.4–12.4)
Hartert 2003	10.2‰ (3/293)	3.4‰ (2/587)	6.8 (-5.6 to 19.3)	OR	---	3.03 (0.50–18.2)
Irving 2000	5.6‰ (1/180)	0 (0/180)	---	---	---	---
Stanwell-Smith 1994 ⁴	91% cases had history of ILI	44% controls had history of ILI	---	OR	12.5 (1.09–143)	---
Stanwell-Smith 1994 ⁴	100% cases were seropositive	0 controls were seropositive	---	---	---	---
Korones 1970	19.6‰ (1/51)	19.6‰ (1/51)	0 (-53.8 to 53.8)	RR	1.00 (0.06–15.56)	---
Wilson 1969	30.1‰ (9/299)	13.3‰ (2.5/188)	16.8 (-8.6 to 42.2)	RR	2.26 (0.56–9.08)	---

¹ Nieto-Pascual, 2013 is shown twice: the first estimate is for abortion, and the second is for intrauterine fetal death (detailed definitions not provided)

² Martin, 2013 only measured influenza if it was present at the time of the delivery

³ Håberg, 2013 did not provide the risk of fetal death by exposure group. Overall risk in the study population was 4.3 fetal deaths per 1,000 singleton pregnancies

⁴ Stanwell-Smith, 1994 is shown twice: the first estimate is for a self-reported history of influenza-like illness, and the second for serologic evidence of influenza A infection

⁵ Crude risk differences calculated by review authors

Fetal death

- Inadequate documentation of outcome definitions
- Most studies had inadequate number of events for meaningful analysis
- Most studies pH1N1, including 2/3 with adequate event number

Prevalence of pre-existing maternal co-morbidities

First author, year of publication	Diabetes	Asthma	Obesity	Hypertension
Acs 2006	0.1%	--	--	--
Naresh 2013	1.3%	11.3%	--	3.8%
Hartert 2003	2.2%	4.4%	--	--
Rogers 2010	3.0%	1.0%	--	5%
Hansen 2012	13.2%	2.9%	22%	--
Ahrens 2014	--	--	14.5% (BMI ≥ 30)	--
Pierce 2011	--		17.0% (BMI ≥ 30)	--
Doyle 2013	--	--	19.0% (BMI ≥ 30)	--
Irving 2000	--	--	--	7.5%
11 STUDIES NO DATA	--	--	--	--

Summary

- **Few studies**
 - Particularly non-pH1N1
 - None from resource poor settings
- **Notable deficits in methodologies**
- **High heterogeneity in exposure measurement and outcome definitions**
- **Some evidence for increased risk of preterm birth and fetal death associated with pH1N1, particularly severe illness; magnitude unclear**
- **Uncertainty**
 - Existence of effect
 - Magnitude of effect
 - Contribution of contextual factors: influenza serotype, illness severity, underlying illness, trimester of infection
 - Contribution of nuances in outcome definition: fetal death, gestational age

Pending evaluations

- **Topics**

- Incidence of severe influenza during pregnancy
- Incidence of severe influenza age <6 months

- **Methods**

- Systematic literature review
- Re-analysis of Nair Lancet study for <6 month disease burden

- **Influenza-associated incidence outcomes**

- Pneumonia
- Hospitalization
- ICU admissions
- DALYs
- Mortality

- **Progress to date**

- Pregnancy: all dates, 11 relevant studies have been found
- Age <6 months: from 1995-2014, 22 relevant studies have been found
- Most studies from pH1N1 pandemic and high resource settings

Overall Summary

- Influenza disease burden data (particularly in pregnant women) may not be sufficient to inform definitive decisions regarding routine immunization of pregnant women in some locales
- Few data for low-resource settings, where results may differ
- Lack of data prevents assessment of the impact of a maternal influenza vaccine program on severe maternal, fetal, and newborn outcomes
- Absence of evidence is not evidence of absence
- Some analyses are still ongoing

Next steps

- Work group final report expected June 2015
- Systematic reviews will be finalized and submitted for publication in 2015
- Plan to continue the fetal effects workstream to further assess observational literature, mechanisms of disease and protection, clinical significance of observed effects

Acknowledgements

Taskforce

- Michael Baker
- Maneesh Batra
- Julien Beaute
- Philippe Beutels
- Niranjan Bhat
- Zulfiqar Bhutta
- Simon Cauchemez
- Nathorn Chaiyakunapruk
- Cheryl Cohen
- Deshayne Fell
- Brad Gessner
- Michael Gravett
- Mark Katz
- Marian Knight
- Michael Kramer
- Anand Krishnan
- Vernon Lee
- Mark Loeb
- Johannes Luteijn
- Helen Marshall
- Harish Nair
- Rehana Salam
- David Savitz
- Becky Skidmore
- Yot Teerawattananon
- Marc-Alain Widdowson

Secretariat

- Bremen De Mucio
- Chiara Gerardi
- Rodolfo Gomez Ponce de Leon
- Joachim Hombach
- Raymond Hutubessy
- Jeanene Johnson
- Philipp Lambach
- Nataliya Shapovalova
- Suzanne Suruyya
- Özge Tuncalp
- Justin Ortiz
- Katelijn Vandemaele