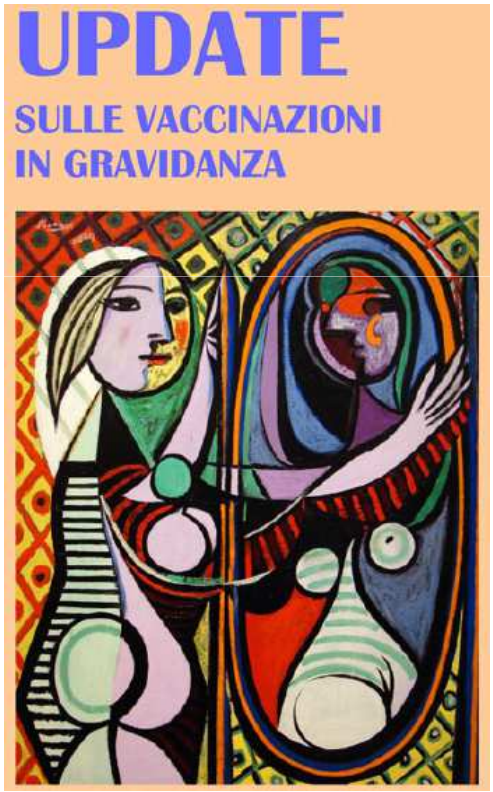
Parma, 23 settembre 2016

I rischi del feto di madre con infezione influenzale



tullio.ghi@unipr.it

Schema

- Rischi fetali da influenza
- Effetti della terapia/profilassi

Rischi fetali dell'influenza

- Trasmissione verticale per via transplacentare rara (viremia bassa)
- Complicazioni fetali in larga misura dipendenti dalla severità dell'infezione materna (polmonite) o dalla prematurità (iatrogena > spontanea)
- Eventi acuti (aborto, morte in utero) a fisiopatologia incerta
- Risposta immunologica (citochine) puo' influenzare la funzione placentare

Human Reproduction, Vol.29, No.4 pp. 809–823, 2014
Advanced Access publication on December 22, 2013 doi:10.1093/humrep/det455

human reproduction

META-ANALYSIS Reproductive epidemiology

Influenza and congenital anomalies: a systematic review and meta-analysis

J.M. Luteijn*, M.J. Brown, and H. Dolk

Institute of Nursing Research/School of Nursing, University of Ulster, Jordanstown Campus, Shore Road, Newtownabbey BT37 0QB, UK

Table II First trimester maternal influenza exposure and risk of congenital anomalies: studies, total number of cases of congenital anomaly (CA), pooled OR and heterogeneity.

Group	Participating studies (*n*)	I^2 statistic for heterogeneity (%)	Pooled OR (95% CI)	Total number of CA (*n*)
Any congenital anomaly	22	64	2.00 (1.62–2.48)	29 945[c]
Susceptible to differential recall bias	9	65	1.92 (1.35–2.72)	5426
Not susceptible to differential recall bias	13	64	2.12 (1.54–2.91)	24 519[c]
Case–control studies	13	60	1.84 (1.49–2.27)	29 542[c]
Cohort studies	9	62	2.12 (1.21–3.72)	403
Any type, published 1955–1969	11	58	2.47 (1.50–4.70)	1171
Any type, published 1975–2011	11	55	1.71 (1.41–2.08)	28 774
Adjusted estimates only[a]	4	87	2.15 (1.05–4.42)	3865
Crude estimates only[a]	21	61	2.22 (1.78–2.77)	27 584
Neural tube defects	11	50	3.33 (2.05–5.40)	2500
Anencephaly	10	44	3.52 (1.69–7.32)	608
Encephalocele	4	63	2.95 (0.78–11.13)	225
Spina bifida	7	0	2.20 (1.48–3.28)	1093
Hydrocephaly	5	45	5.74 (1.10–30.00)	323
Congenital heart defects	10	41	1.56 (1.13–2.14)	7715
Aortic valve atresia/stenosis	3	31	2.59 (1.21–5.54)	167
Atrial septal defect	3	0	0.82 (0.45–1.51)	429
Hypoplastic left heart	3	0	1.58 (0.94–2.64)	203
Transposition of the great vessels	3	0	1.40 (0.90–2.17)	321
Ventricular septal defect	4	0	1.59 (1.24–2.04)	1434
Orofacial clefts	10	37	1.96 (1.33–2.91)	2773[d]
Cleft lip + palate[b]	7	0	3.12 (2.20–4.42)	1404
Cleft palate[b]	3	0	1.05 (0.60–1.84)	584
Digestive system[b]	4	0	1.71 (1.09–2.69)	1195
Urinary	5	0	1.45 (0.90–2.34)	48
Hypospadias[b]	4	0	1.02 (0.75–1.39)	3041
Limb reduction	3	0	2.03 (1.27–3.27)	1002
Club foot[b]	4	0	1.11 (0.93–1.34)	2430
Hip dislocation/dysplasia	3	0	0.31 (0.00–37.62)	37
Polydactyly[b]	4	0	1.72 (0.85–3.48)	1094
Syndactyly	3	71	1.98 (0.19–20.563)	662
Musculoskeletal	3	0	1.05 (0.16–6.97)	776

The Association of H1N1 Pandemic Influenza with Congenital Anomaly Prevalence in Europe An Ecological Time Series Study

Epidem 2015

Anomaly		2009–2010 Pandemic Influenza Season Versus Nonpandemic Nonseasonal Periods (2007–2011)		2007–2011 Any Influenza Season (Including the 2009–2010 Pandemic Influenza Season) Versus Nonpandemic Nonseasonal Periods (2007–2011)		Critical Period (Postconception Age, Weeks)
Prior Hypothesis of Association with Influenza[1]	N Total	N Exposed[b]	Prevalence Rate Ratio[c]	N Exposed[b]	Prevalence Rate Ratio[c]	
Any nonchromosomal	26,967	1,879	1.00 (0.93–1.08)	5,363	0.99 (0.95–1.03)	3–11[b]
Any prior hypothesis	16,425	1,174	1.01 (0.92–1.11)	3,282	0.99 (0.94–1.04)	3–11[b]
Neural tube defects	1,436	85	1.22 (0.94–1.58)	213	1.10 (0.96–1.27)	3–4[22,24]
Anencephaly	584	34	1.24 (0.80–1.94)	86	1.12 (0.89–1.42)	3–4[20,22,24]
Encephalocele	170	10	1.00 (0.42–2.36)	23	0.90 (0.59–1.37)	3–4[20,22,24]
Spina Bifida	682	41	1.25 (0.95–1.65)	104	1.14 (0.96–1.34)	3–4[20,22,24]
Anophthalmos/microphthalmos	109	5	0.97 (0.31–3.05)	12	0.97 (0.45–2.08)	4–6[20]
Congenital heart defect	8,545	364	1.05 (0.92–1.20)	985	0.99 (0.92–1.07)	3–7[26]
Ventricular septal defect	4,358	173	1.23 (1.02–1.49)	448	1.08 (0.95–1.23)	3–6[22]
Tricuspid atresia and stenosis	93	9	2.46 (1.19–5.07)	14	1.30 (0.77–2.21)	3–7[26]
Pulmonary valve atresia	575	6	0.71 (0.18–2.84)	22	1.08 (0.51–2.30)	3–7[25]
Aortic valve atresia and/or stenosis	192	9	1.16 (0.63–2.14)	21	0.95 (0.61–1.49)	3–7[26]
Coarctation of aorta	467	30	1.31 (0.93–1.85)	73	0.98 (0.68–1.42)	3–9[26]
Orofacial clefts	1,946	136	1.02 (0.76–1.36)	352	0.98 (0.85–1.12)	3–10[22]
Cleft lip ± palate	1,158	49	0.92 (0.70–1.21)	131	0.95 (0.78–1.16)	3–5[22]
Cleft palate	788	53	1.10 (0.73–1.66)	138	0.97 (0.78–1.20)	3–10[22]
Oesophageal atresia	352	15	0.93 (0.62–1.39)	40	0.82 (0.61–1.10)	3–4[22]
Anorectal atresia and stenosis	401	13	1.20 (0.59–2.43)	36	1.03 (0.64–1.65)	3–6[22]
Diaphragmatic hernia	357	11	0.79 (0.39–1.59)	31	0.88 (0.55–1.39)	3–6[22]
Omphalocele	336	25	1.19 (0.68–2.07)	68	1.15 (0.81–1.64)	3–10[22]
Congenital hydronephrosis	1,507	85	1.03 (0.89–1.20)	227	1.05 (0.91–1.21)	6–12[20]
Limb reduction	757	40	1.04 (0.70–1.54)	102	0.97 (0.83–1.14)	4–5[20]
Syndactyly	483	13	0.86 (0.51–1.46)	36	0.81 (0.61–1.09)	3–6[22]
Situs inversus[3,4]	104	6	2.15 (0.58–8.03)	14	1.45 (0.64–3.30)	4–6[20]

Influenza e malformazioni

- Lieve aumento del rischio di difetti tubo neurale, labiopalatoschisi e cardiopatie
- Teratogenesi favorita da ipertermia (?)
- Possibili fattori di confondimento
- Dati contrastanti

BMJ

RESEARCH

Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study

Matthias Pierce, medical statistician,[1] Jennifer J Kurinczuk, reader in perinatal epidemiology and deputy director,[1] Patsy Spark, programmer,[1] Peter Brocklehurst, clinical epidemiologist and director,[1] Marian Knight, senior clinical research fellow,[1] on behalf of UKOSS

2011

Outcome	No (%)		Odds ratio (95% CI)		National data, 2008	
	Infected cohort (n=256)	Comparison cohort (n=1220)	Unadjusted	Adjusted*	No (%)	Unadjusted odds ratio (95% CI)
Outcome of pregnancy:						
Live birth†	249 (95)	1226 (99)	1	1	795 004 (99)	1
Stillbirth	7 (3)	7 (1)	4.9 (1.7 to 14.2)	4.2 (1.4 to 12.4)	4 043 (1)	5.5 (2.6 to 11.7)
Loss of pregnancy before 24 weeks	5 (2)	NA	NA	NA	NA	NA
Neonatal death:						
Yes	3 (1)	2 (0)	7.4 (1.2 to 44.7)	5.6 (0.5 to 64.2)	2 557 (0)	3.8 (1.2 to 11.8)
No	246 (99)	1218 (100)	1	1	792 487 (100)	1
Perinatal death:						
Yes	10 (4)	8 (1)	6.2 (2.4 to 15.9)	5.7 (2.2 to 15.1)	6 025 (1)	5.4 (2.8 to 10.1)
No	246 (96)	1219 (99)	1	1	793 022 (99)	1
Mean (SD) birth weight (kg)	3073 (774)	3342 (614)	−270 (−356 to −183)‡	−255 (−353 to −156)‡	NA	NA
Low birth weight (<2500 g):						
Yes	50 (20)	94 (8)	2.9 (2.0 to 4.3)	3.2 (2.1 to 4.9)	57 072 (7)§	3.0 (2.2 to 4.1)
No	206 (80)	1137 (92)	1	1	713 201 (93)	1
Very low birth weight (<1500 g):						
Yes	14 (5)	22 (2)	3.2 (1.6 to 6.3)	2.9 (1.3 to 6.4)	10 955 (1)§	4.0 (2.3 to 6.9)
No	242 (95)	1209 (98)	1	1	759 318 (99)	1
Preterm (<37 weeks):						
Yes	59 (24)	89 (7)	3.9 (2.7 to 5.6)	4.0 (2.7 to 5.9)	36 283 (8)	3.6 (2.7 to 4.8)
No	192 (76)	1129 (93)	1	1	423 475 (92)	1
Very preterm (<32 weeks):						
Yes	18 (7)	18 (1)	5.2 (2.6 to 10.0)	4.9 (2.4 to 10.0)	10 932 (2)	3.2 (2.0 to 5.1)
No	233 (93)	1200 (99)	1	1	449 101 (98)	1
Delivered by caesarean section:						
Yes	100 (40)	299 (25)	2.1 (1.5 to 2.7)	2.3 (1.7 to 3.2)	139 449 (24)	2.2 (1.7 to 2.8)
No	150 (60)	921 (75)	1	1	453 951 (76)	1

Characteristic	Preterm (n=59)	Not preterm (n=131)*	P value
Trimester of infection:			
First (0-11 weeks)	0 (0)	10 (8)	0.046†
Second (12-23 weeks)	8 (14)	24 (18)	
Third (≥24 weeks)	51 (86)	97 (74)	
Median (interquartile range) No of symptoms‡ at presentation	4 (3-5)	5 (3-6)	0.09§
Median (interquartile range) days before start of treatment	3 (1-7)	3 (1-6)	0.46†
Treated within 2 days of infection:			
Yes	28 (53)	69 (57)	0.61
No	25 (47)	52 (43)	
Immunised against 2009/H1N1:			
Yes	2 (4)	7 (6)	0.72§
No	54 (96)	119 (94)	
Admitted to intensive care unit:			
Yes	32 (54)	16 (12)	<0.001
No	27 (46)	115 (88)	
Pneumonia as secondary infection:			
Yes	12 (20)	5 (4)	0.001†
No	47 (80)	126 (96)	
Asthma:			
Yes	9 (15)	18 (14)	0.78
No	50 (85)	113 (86)	
Other comorbidity:			
Yes	15 (25)	23 (18)	0.21
No	44 (75)	108 (82)	
Delivered by caesarean section:			
Yes	42 (72)	39 (30)	<0.001
No	16 (28)	92 (70)	
Indication for caesarean section:			
Maternal influenza infection	22 (52)	3 (8)	<0.001†
Other	20 (48)	36 (92)	

Fetal hemodynamic changes in pregnant women with influenza AH1N1 infection and <arterial partial pressure of oxygen

Hernandez-Andrade Ultras Ob Gyn 2014

Doppler parameter	*Hypoxic* ($P_aO_2 < 60$ *mmHg*) (n = 5)	*Non-hypoxic* ($P_aO_2 \geq 60$ *mmHg*) (n = 10)	P
Within 24 h of admission			
UA-PI Z-score	1.26 ± 0.43	0.30 ± 0.64	0.01
MCA-PI Z-score	−0.56 ± 0.77*	0.39 ± 0.59	0.03
MPI	0.42 ± 0.01	0.35 ± 0.03	0.02
DV-PI Z-score	0.65 ± 0.7*	0.45 ± 0.6	0.61
3 days after admission			
UA-PI Z-score	1.24 ± 0.32	0.32 ± 0.8	0.03
MCA-PI Z-score	−0.46 ± 0.8*	0.67 ± 0.9	0.04
MPI	0.42 ± 0.04	0.34 ± 0.02	0.03
DV-PI Z-score	0.64 ± 0.8*	0.56 ± 0.63	0.84
4 weeks after admission			
UA-PI Z-score	0.29 ± 0.8†	0.14 ± 0.8	0.78
MCA-PI Z-score	−0.66 ± 0.5*	0.48 ± 0.68	0.008
MPI	0.39 ± 0.03†	0.38 ± 0.04	0.86
DV-PI Z-score	0.30 ± 0.67*	0.18 ± 0.82	0.79

DOI: 10.1111/1471-0528.14143
www.bjog.org

Systematic review

Maternal influenza and birth outcomes: systematic review of comparative studies

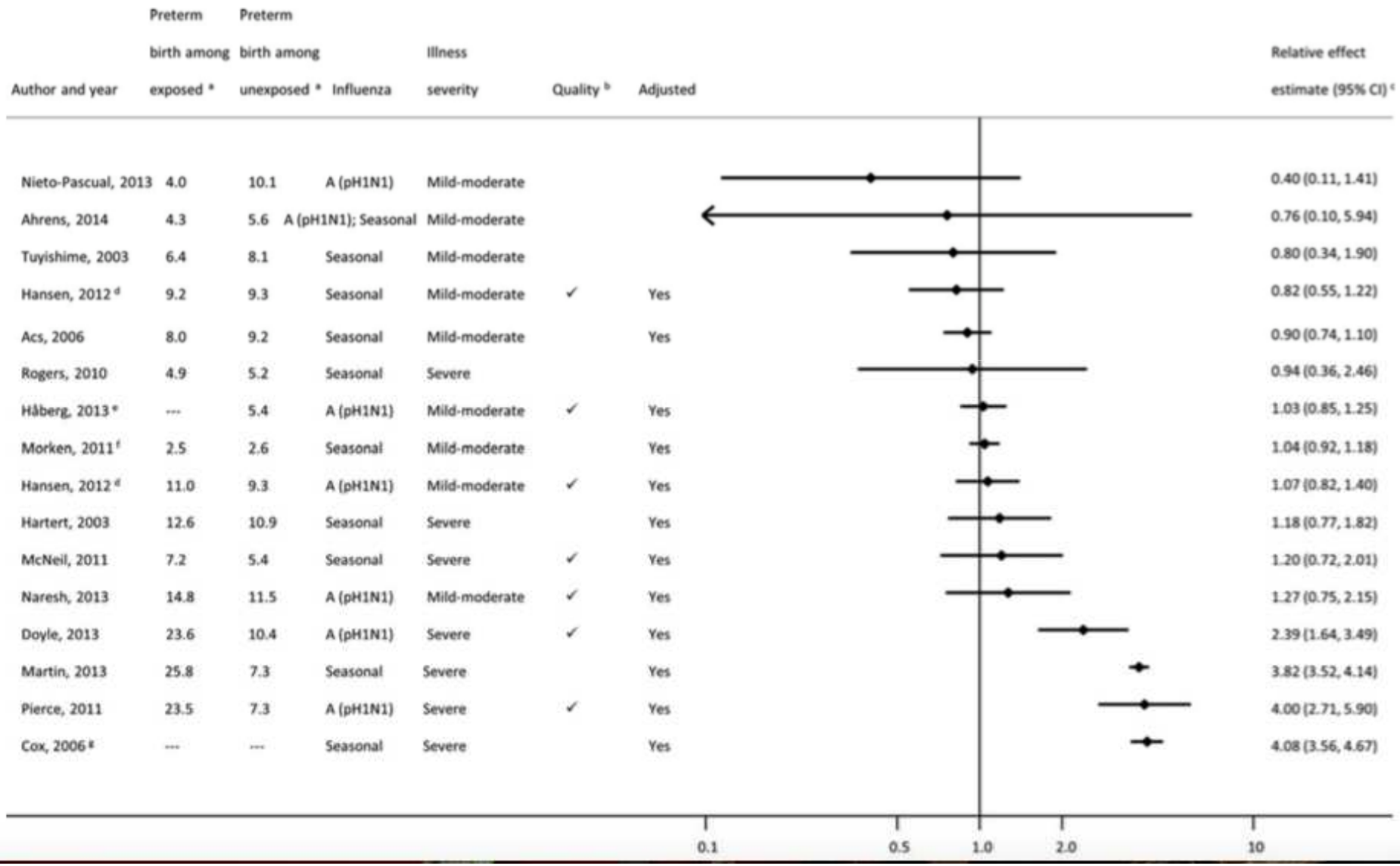
DB Fell,[a,b] DA Savitz,[c,d] MS Kramer,[a,e] BD Gessner,[f] MA Katz,[g] M Knight,[h] JM Luteijn,[i] H Marshall,[j,k,l] N Bhat,[m] MG Gravett,[n,o] B Skidmore,[p] JR Ortiz[q]

[a] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada [b] Better Outcomes Registry & Network (BORN), CHEO Research Institute, Ottawa, ON, Canada [c] Department of Epidemiology, Brown University, Providence, RI, USA [d] Department of Obstetrics and Gynecology, Brown University, Providence, RI, USA [e] Department of Pediatrics, McGill University Faculty of Medicine, Montreal, QC, Canada [f] Agence de Médecine Préventive, Paris, France [g] Independent Consultant, Tel Aviv, Israel [h] National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK [i] Queen Mary University of London, London, UK [j] Vaccinology and Immunology Research Trials Unit, Women's and Children's Hospital, North Adelaide, SA, Australia [k] School of Medicine, University of Adelaide, North Adelaide, SA, Australia [l] Robinson Research Institute, University of Adelaide, North Adelaide, SA, Australia [m] PATH, Seattle, WA, USA [n] Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, USA [p] Global Alliance to Prevent Prematurity and Stillbirth, Seattle Children's, Seattle, WA, USA [p] Independent Consultant, Ottawa, ON, Canada [q] Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Correspondence: DB Fell, Better Outcomes Registry & Network (BORN), CHEO Research Institute, 401 Smyth Road, Ottawa, ON K1H 8L1 Canada. Email deshayne.fell@mail.mcgill.ca

Accepted 15 April 2016. Published Online 31 May 2016.

Influenza and Preterm birth

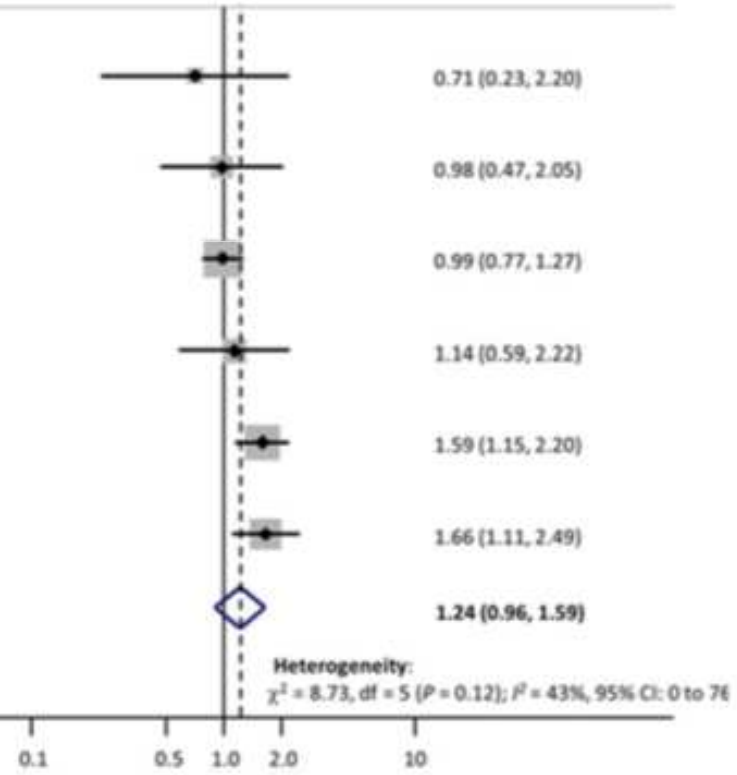


Influenza and SGA

Author and year	SGA among exposed [a]	SGA among unexposed [a]	Influenza	Illness severity	Quality [b]	Adjusted	Relative effect estimate (95% CI) [c]
Irving, 2000	2.8	3.9	Seasonal	Mild-moderate	✓	Yes	0.71 (0.23, 2.20)
Nieto-Pascual, 2013	14.4	14.1	A (pH1N1)	Mild-moderate			0.98 (0.47, 2.05)
Hansen, 2012 [d]	7.3	7.2	A (pH1N1)	Mild-moderate	✓	Yes	0.99 (0.77, 1.27)
Naresh, 2013	8.5	7.4	A (pH1N1)	Mild-moderate	✓	Yes	1.14 (0.59, 2.22)
Hansen, 2012 [d]	12.0	7.2	Seasonal	Mild-moderate	✓	Yes	1.59 (1.15, 2.20)
McNeil, 2011	15.3	9.7	Seasonal	Severe	✓	Yes	1.66 (1.11, 2.49)
Overall							**1.24 (0.96, 1.59)**

NOTE: Weights are from random effects analysis

Heterogeneity: $\chi^2 = 8.73$, df = 5 ($P = 0.12$); $I^2 = 43\%$, 95% CI: 0 to 76



Influenza and fetal death

Author and year	Fetal death among exposed *	Fetal death among unexposed *	Influenza	Illness severity	Quality [b]	Adjusted	Relative effect estimate (95% CI) [c]	Definition of fetal death
Nieto-Pascual, 2013 [d]	13.2	32.6	A (pH1N1)	Mild-moderate			0.40 (0.04, 3.80)	Abortion *
Korones, 1970	19.6	19.6	Seasonal	Mild-moderate			1.00 (0.06, 15.56)	Stillbirth *
Nieto-Pascual, 2013 [d]	13.3	11.2	A (pH1N1)	Mild-moderate			1.19 (0.08, 18.65)	Intrauterine fetal death *
Håberg, 2013 [f]	---	4.3	A (pH1N1)	Mild-moderate	✓	Yes	1.91 (1.07, 3.41)	Fetal death ≥12 weeks
Wilson 1969	30.1	13.3	Seasonal	Mild-moderate			2.26 (0.56, 9.08)	Fetal death *
Martin, 2013	19.1	6.5	Seasonal	Severe		Yes	2.50 (1.97, 3.18)	Intrauterine fetal demise or stillbirth [g]
Hartert, 2003	10.2	3.1	Seasonal	Severe		Yes	3.03 (0.50, 18.20)	Fetal death *
Pierce, 2011	27.3	5.7	A (pH1N1)	Severe	✓	Yes	4.20 (1.42, 12.40)	Fetal death ≥24 weeks
Stanwell-Smith, 1994	--- [h]	--- [h]	Seasonal	Mild-moderate			12.50 (1.09, 142.99)	Spontaneous abortion or stillbirth *
Irving, 2000	5.6	0.0	Seasonal	Mild-moderate			--- [i]	Fetal death *

Influenza e rischi fetali

- Bassa qualita’ e grande eterogeneita’ degli studi (diversa modalita’ di accertamento degli esiti)
- Per le forme di influenza severa H1N1 (2009) associazione consistente con parto prematuro e probabile con SGA/IUGR
- Incerta associazione con morte fetale
- Incerta associazione tra forme influenza lieve moderata o stagionale ed esiti avversi

Schema

- Rischi fetali da influenza
- Effetti della terapia/profilassi

Pregnancy and pandemic influenza A (H1N1) 2009: Information for programme managers and clinicians

Management of influenza during pregnancy

The following points are to be considered during pregnancy:

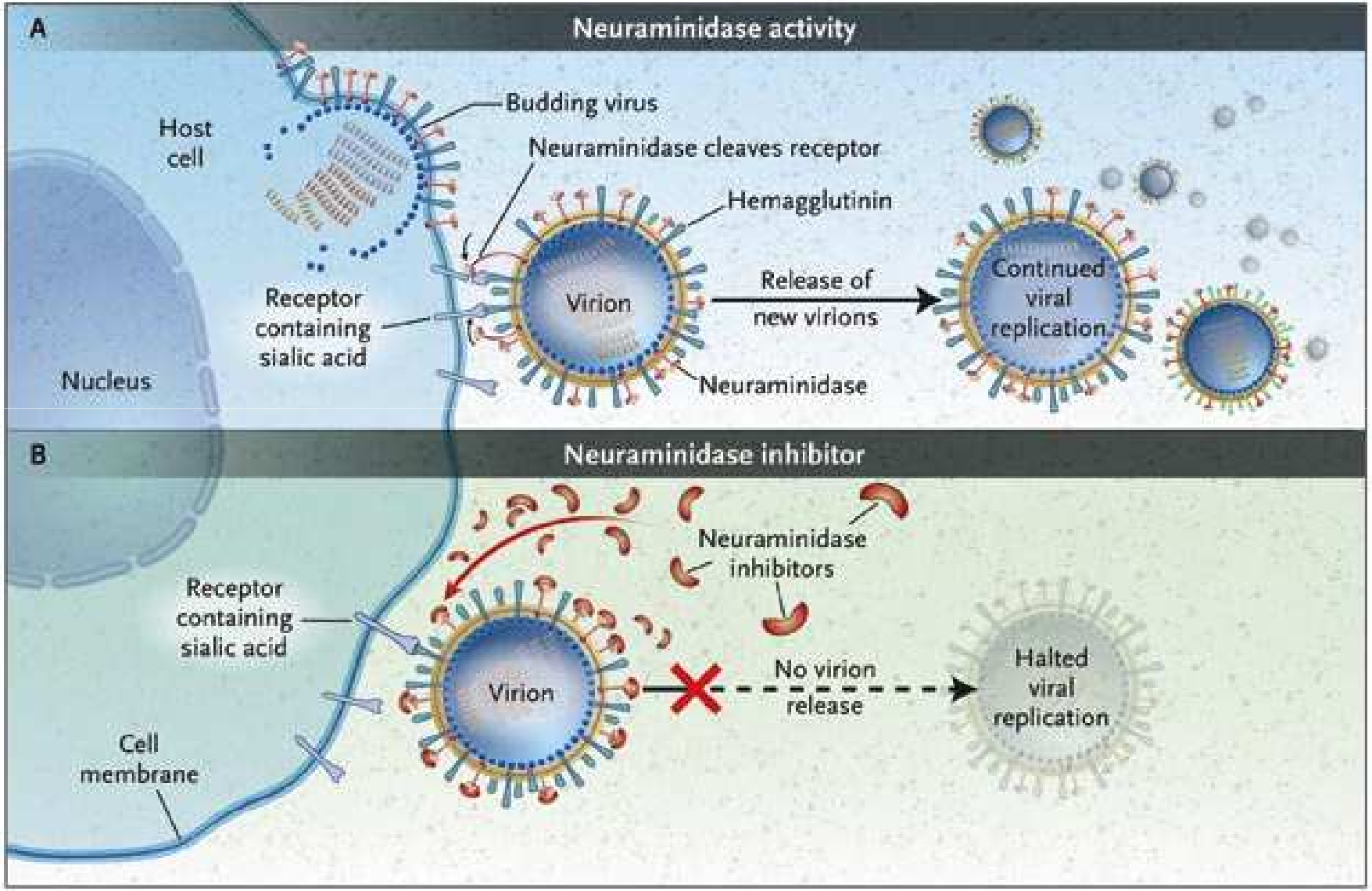
• Pregnant women who meet the current case definition for uncomplicated illness with confirmed or suspected pandemic (H1N1) 2009 virus should be treated early with the antiviral medications **oseltamivir** or **zanamivir**. The regimen is the same as the regimen for other adults. Treatment is for five days.

• Treatment with antiviral medications should begin as soon as possible and without waiting for results of diagnostic testing. A negative laboratory test should not stop treatment in a patient with clinical suspicion of influenza.

• Patients who have severe or progressive clinical illness should be treated with**oseltamivir**. This recommendation applies to all patient groups, including pregnant women. Currently, there are no data supporting administration of oseltamivir in doses higher than 75 mg twice daily for pregnant women.


Tamiflu® 75 mg
Hartkapseln
Oseltamivir
10 Kapseln
Roche


GlaxoSmithKline
NDC 0173-0681-01
RELENZA
(ZANAMIVIR FOR INHALATION)
Each blister contains 5 mg zanamivir with lactose.
Use RELENZA with the DISKHALER® inhalation device only.
See enclosed "Patient Information" and "Patient Instructions for Use."
Store at 25°C (77°F); excursions permitted to
15° to 30°C (59° to 86°F) (see USP Controlled
Room Temperature).
Contains 5 RELENZA ROTADISKS® each containing
four 5-mg blisters and one DISKHALER inhalation device.
℞ only
See package insert for Dosage and Administration.
5mg
10 Doses
FOR ORAL INHALATION ONLY
RELENZA
(ZANAMIVIR FOR INHALATION)
DISKHALER


A
Neuraminidase activity
Budding virus
Host cell
Neuraminidase cleaves receptor
Hemagglutinin
Virion
Release of new virions
Continued viral replication
Receptor containing sialic acid
Nucleus
Neuraminidase
B
Neuraminidase inhibitor
Neuraminidase inhibitors
Receptor containing sialic acid
Virion
No virion release
Halted viral replication
Cell membrane

DOI: 10.1111/1471-0528.12640
www.bjog.org

Pregnancy outcome following maternal use of zanamivir or oseltamivir during the 2009 influenza A/H1N1 pandemic: a national prospective surveillance study

HJ Dunstan,[a] AC Mill,[b] S Stephens,[a] LM Yates,[a,c] SHL Thomas[a,d]

[a]United Kingdom Teratology Information Service, Wolfson Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK [b] School of Biology, Newcastle University, Newcastle upon Tyne, UK [c] Institute of Human Genetics, International Centre for Life, Newcastle upon Tyne, UK [d] Wolfson Unit of Clinical Pharmacology, Institute of Cellular Medicine and Medical Toxicology Centre, Newcastle University, Newcastle upon Tyne, UK

Correspondence: L Yates, UKTIS, Wolfson Unit, Newcastle upon Tyne, NE2 4HH, UK. Email Laura.Yates@nuth.nhs.uk

Accepted 2 December 2013. Published Online 7 March 2014.

Methods Pregnancy outcomes were collected for prospectively reported pregnancies exposed to zanamivir (n = 180) or oseltamivir (n = 27), and compared with a reference group of 575 prospectively reported pregnancies exposed to non-teratogenic drugs over the same period.

Results No significant differences in overall rates of major malformation in live-born infants [adjusted odds ratios (aOR): zanamivir 0.37 (95% confidence interval 0.02–2.70); oseltamivir aOR 0.81 (0.05, 14.15)], preterm delivery [aOR: zanamivir 0.95 (0.45, 1.89); oseltamivir aOR 1.68 (0.38, 5.38)] or low birth weight [aOR: zanamivir 0.94 (0.25, 2.90); oseltamivir aOR 4.12 (0.59, 17.99)] were observed following exposure at any gestation. No major malformations were reported in 37 zanamivir or eight oseltamivir first trimester exposures.

RESEARCH www.AJOG.org

OBSTETRICS

Infant outcomes among pregnant women who used oseltamivir for treatment of influenza during the H1N1 epidemic

Hai-yan Xie, MSc; Abdool S. Yasseen III, MSc; Ri-hua Xie, PhD; Deshayne B. Fell, MSc; Ann E. Sprague, PhD; Ning Liu, MSc; Graeme N. Smith, PhD; Mark C. Walker, MD; Shi Wu Wen, PhD

Am J Obstet Gynecol 2013

Association between maternal use of oseltamivir and infant outcomes during 2009 H1N1 pandemic in Ontario, Canada

Outcome[a]	No antiviral use (n = 53,875)	Oseltamivir use (n = 1232)
Small for gestational age (<10th percentile)		
n (%)	4975 (9.2)	85 (6.9)
Unadjusted RR (95% CI)	1.00 (Reference)	0.75 (0.61–0.92)
Adjusted RR (95% CI)	1.00 (Reference)	0.77 (0.61–0.98)
Adjusted RR (95% CI)[b]	1.00 (Reference)	0.77 (0.60–0.98)
Small for gestational age (<3rd percentile)		
n (%)	1287 (2.39)	27 (2.2)
Unadjusted RR (95% CI)	1.00 (Reference)	0.92 (0.63–1.34)
Adjusted RR (95% CI)	1.00 (Reference)	0.86 (0.54–1.38)
Adjusted RR (95% CI)[b]	1.00 (Reference)	0.83 (0.51–1.35)
Preterm birth (<37 wk)		
n (%)	3306 (6.1)	86 (7.0)
Unadjusted RR (95% CI)	1.00 (Reference)	1.14 (0.93–1.40)
Adjusted RR (95% CI)	1.00 (Reference)	1.24 (0.97–1.58)
Adjusted RR (95% CI)[b]	1.00 (Reference)	1.26 (0.99–1.61)
Very preterm birth (<32 wk)		
n (%)	379 (0.7)	8 (0.7)
Unadjusted RR (95% CI)	1.00 (Reference)	0.92 (0.50–1.86)
Adjusted RR (95% CI)	1.00 (Reference)	1.39 (0.62–3.11)
Adjusted RR (95% CI)[b]	1.00 (Reference)	1.46 (0.65–3.27)
5-min Apgar score <7		
n (%)	637 (1.2)	16 (1.3)
Unadjusted RR (95% CI)	1.00 (Reference)	1.10 (0.67–1.79)
Adjusted RR (95% CI)	1.00 (Reference)	1.20 (0.67–2.12)
Adjusted RR (95% CI)[b]	1.00 (Reference)	1.22 (0.68–2.16)

CI, confidence interval; *RR*, risk ratio.

World Health Organization

Pregnancy and pandemic influenza A (H1N1) 2009: Information for programme managers and clinicians

- From May 2010 the new seasonal influenza vaccines (e.g. those prepared for the 2010 southern hemisphere influenza season) will include protection against pandemic (H1N1) 2009 and can be given to pregnant women. Older seasonal vaccines not containing a pandemic 2009 strain will not protect against the pandemic (H1N1) 2009 virus[14].

- Only inactivated influenza vaccine is suitable for pregnant women and children less than 24 months of age. Live attenuated influenza vaccine should not be used in this population.

The NEW ENGLAND JOURNAL of MEDICINE
2013

ORIGINAL ARTICLE

Risk of Fetal Death after Pandemic Influenza Virus Infection or Vaccination

Siri E. Håberg, M.D., Ph.D., Lill Trogstad, M.D., Ph.D.,
Nina Gunnes, Ph.D., Allen J. Wilcox, M.D., Ph.D., Håkon K. Gjessing, Ph.D.,
Sven Ove Samuelsen, Ph.D., Anders Skrondal, Ph.D., Inger Cappelen, Ph.D.,
Anders Engeland, Ph.D., Preben Aavitsland, M.D., Steinar Madsen, M.D.,
Ingebjørg Buajordet, Ph.D., Kari Furu, Ph.D., Per Nafstad, M.D., Ph.D.,
Stein Emil Vollset, M.D., Dr.P.H., Berit Feiring, M.Sc.Pharm.,
Hanne Nøkleby, M.D., Per Magnus, M.D., Ph.D.,
and Camilla Stoltenberg, M.D., Ph.D.

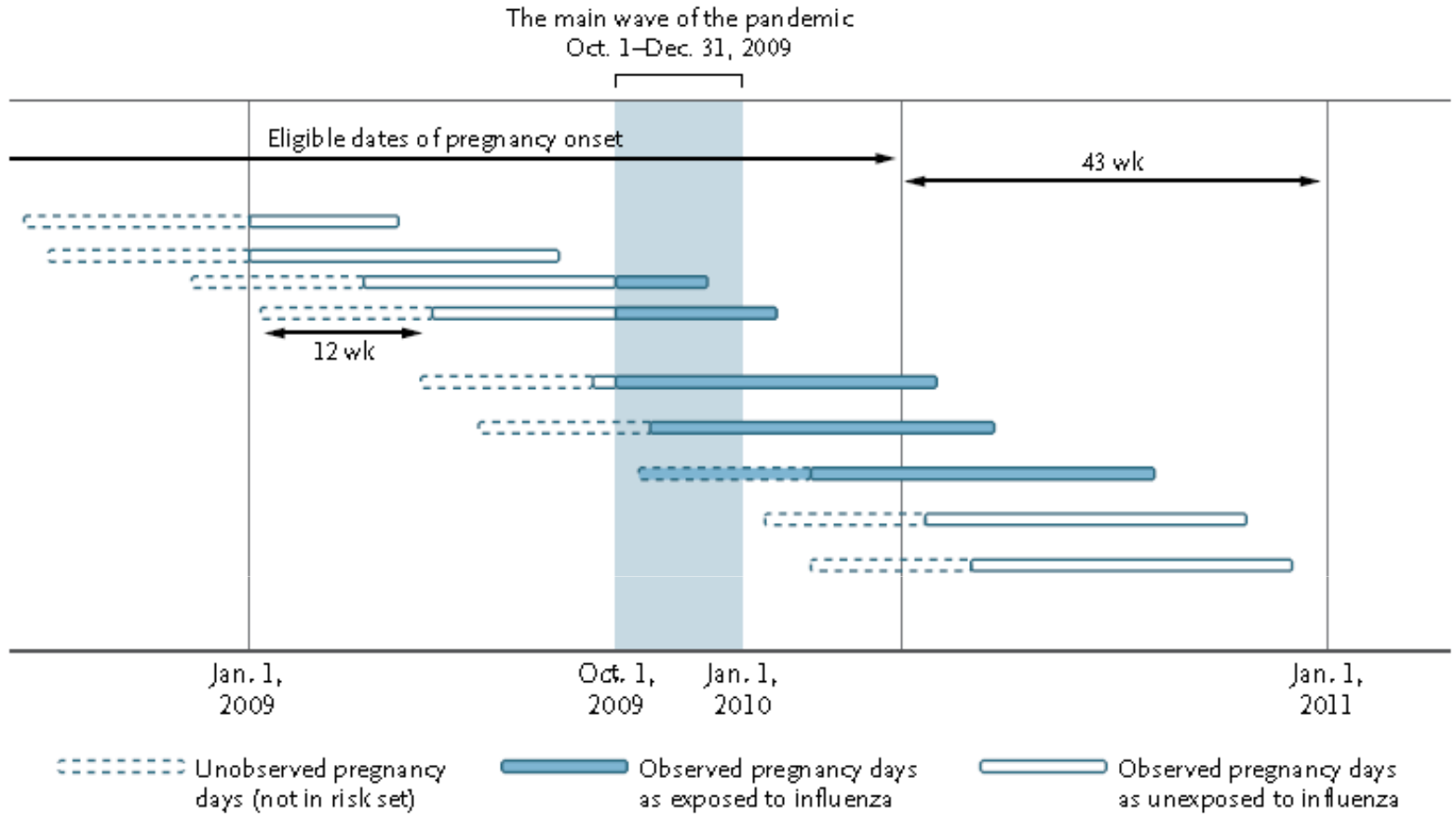


Figure 1. Eligible Pregnancies, Observed Pregnancy Days, and Exposure to the Main Pandemic Wave.

Births in Norway that occurred in 2009 and 2010 were eligible for the study if women had become pregnant at least 43 weeks before December 31, 2010. Eligible pregnancies were classified as involving maternal exposure to the influenza pandemic if any day of pregnancy occurred between October 1, 2009, and December 31, 2009. For a given pregnancy, days at risk were defined as pregnancy days after week 12 that occurred starting on January 1, 2009, and exposure days were defined as all pregnancy days from the first day of exposure until delivery. For simplicity, the figure shows all pregnancies as lasting 9 months. The study included all registered pregnancies lasting at least 12 weeks. The period of the main wave of the influenza pandemic is shaded.

Table 3. Hazard Ratios for Fetal Death, According to Pregnancy during the Pandemic Wave and Vaccination Status.*

Pregnancy and Vaccination Status during Pandemic	No. of Pregnancy-Days at Risk†	Hazard Ratio (95% CI)	
		Unadjusted	Adjusted‡
Not pregnant during the pandemic			
Not vaccinated during pregnancy	10,414,633	1.00	1.00
Vaccinated during pregnancy	7,402	NA	NA
Pregnant during the pandemic			
Not vaccinated during pregnancy	5,527,619	1.21 (1.00–1.48)	1.25 (1.02–1.55)
Vaccinated during pregnancy	3,020,750	1.02 (0.79–1.32)	1.10 (0.84–1.45)

DOI: 10.1111/1471-0528.12977
www.bjog.org

Systematic review

Fetal death and preterm birth associated with maternal influenza vaccination: systematic review

DB Fell,[a,b] RW Platt,[a] A Lanes,[c] K Wilson,[d,e,f] JS Kaufman,[a] O Basso,[a] D Buckeridge[a]

[a] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada [b] Better Outcomes Registry & Network (BORN) Ontario, Ottawa, ON, Canada [c] Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, ON, Canada [d] Department of Medicine, University of Ottawa, Ottawa, ON, Canada [e] Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada [f] Institute for Clinical Evaluative Sciences, Ottawa, ON, Canada

Correspondence: DB Fell, Better Outcomes Registry & Network (BORN) Ontario, Children's Hospital of Eastern Ontario Research Institute, 401 Smyth Road, Centre for Practice Changing Research, Ottawa, Ontario, Canada K1H 8L1. Email dfell@bornontario.ca

Accepted 13 May 2014. Published Online 10 July 2014.

Vaccinazione and fetal death

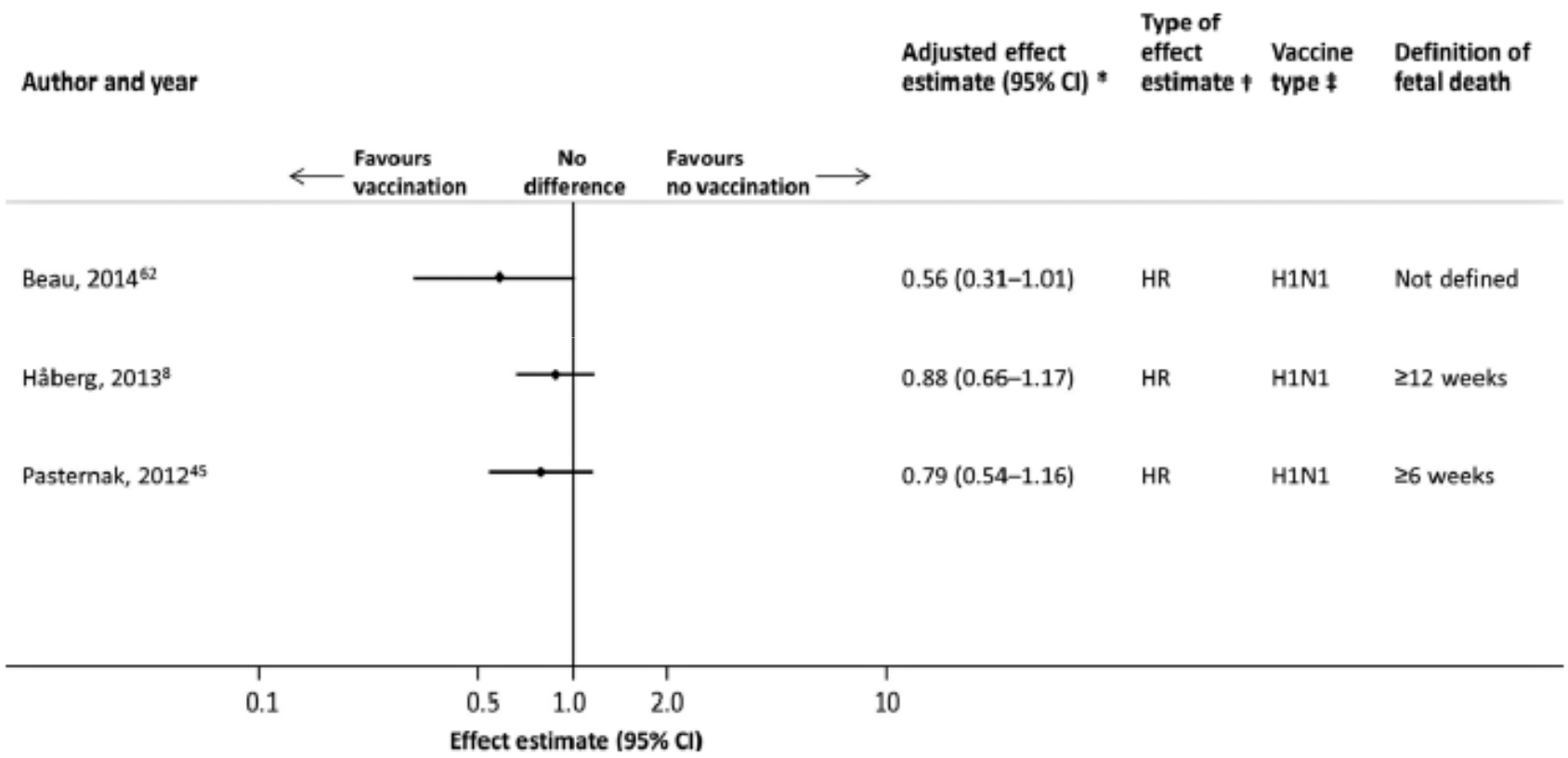
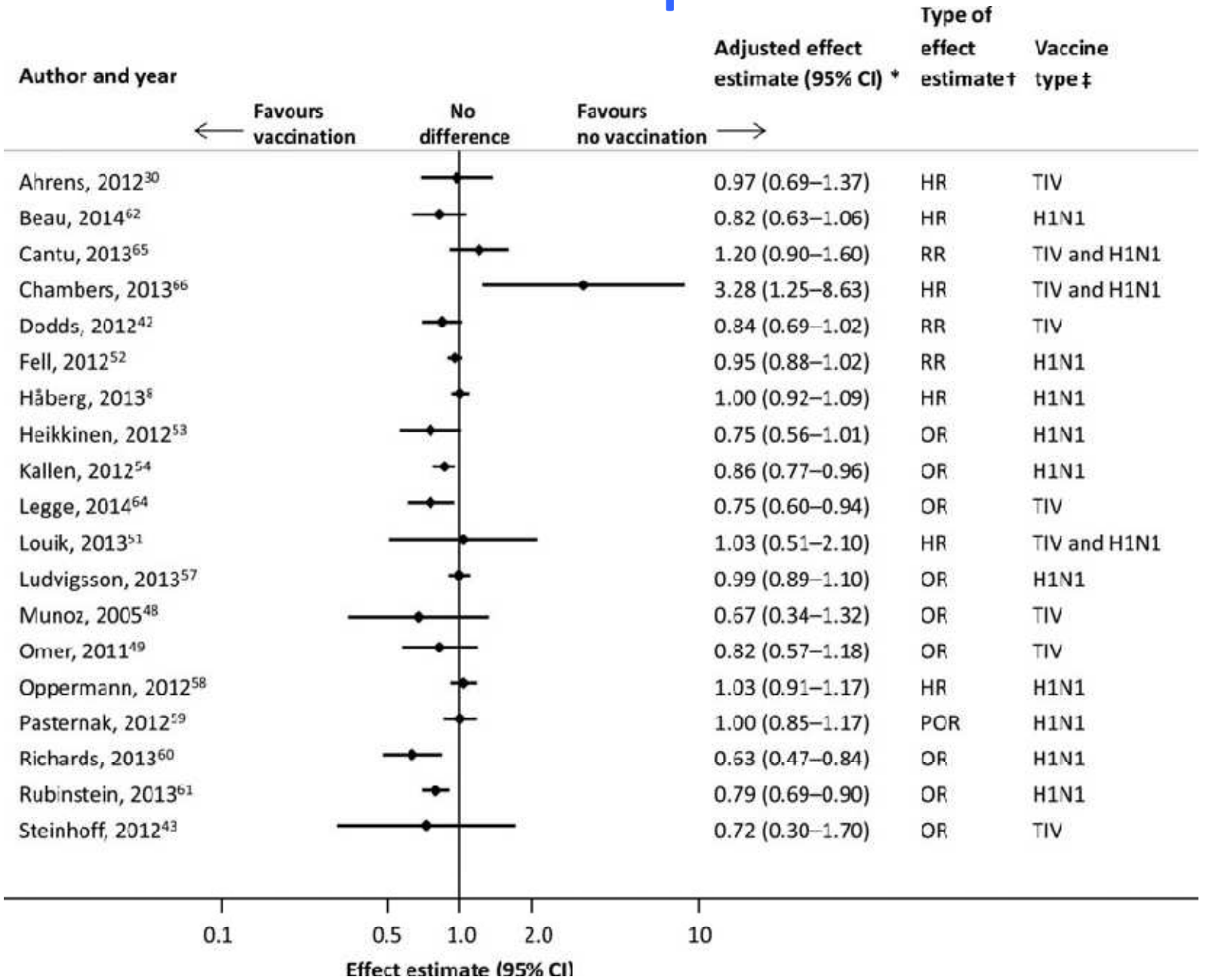


Figure 2. Individual study adjusted effect estimates for fetal death at any time during gestational follow up associated with influenza vaccination during pregnancy. Small, black diamond markers indicate individual study estimates, with corresponding 95% confidence intervals (CIs) represented by horizontal bars. *Adjusted estimate from original study. †HR, hazards ratio. ‡H1N1, monovalent H1N1 influenza vaccine.

Vaccinazione and preterm birth



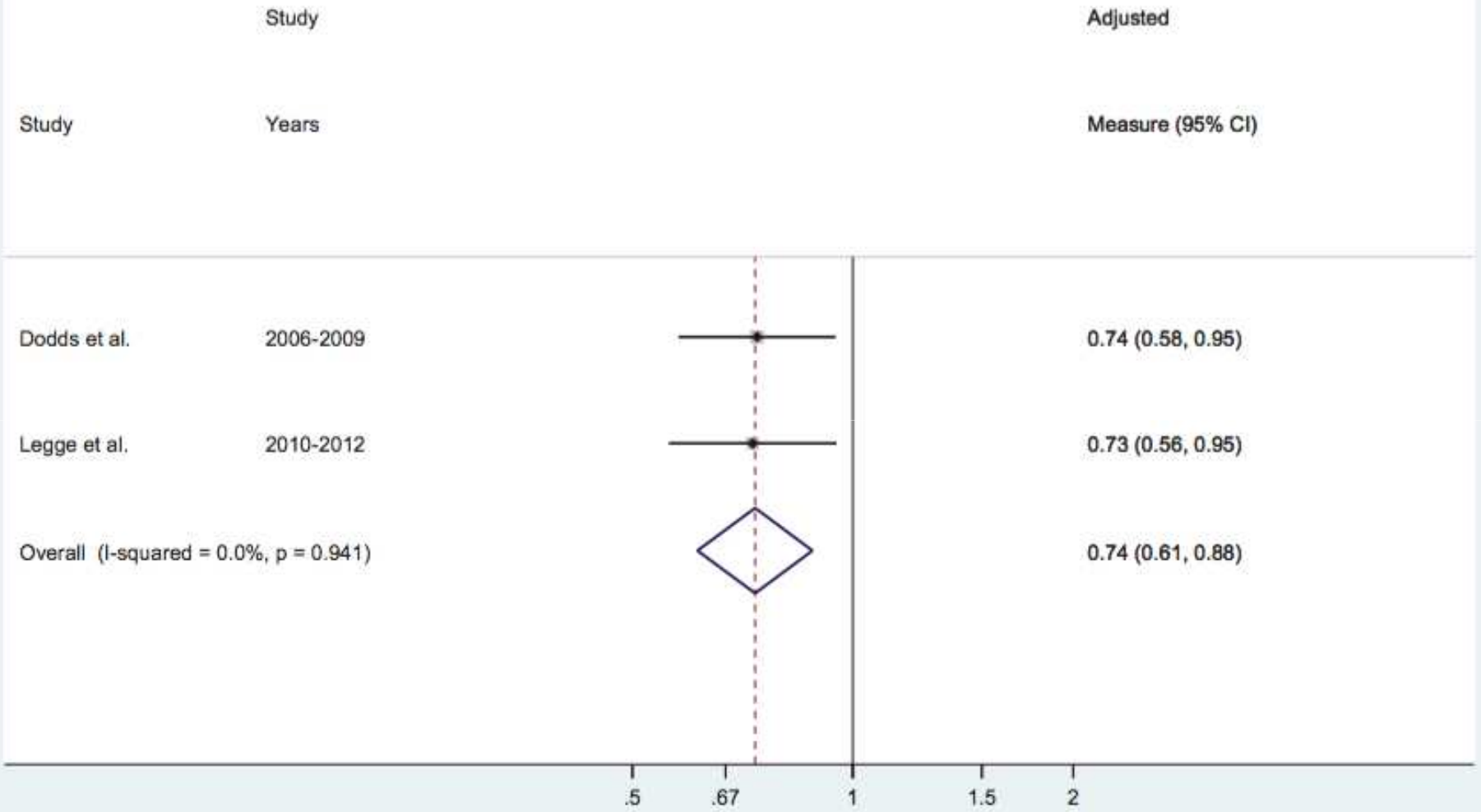
The Effects of Influenza Vaccination during Pregnancy on Birth Outcomes: A Systematic Review and Meta-Analysis

Marta C. Nunes, PhD[1,2,*] Anushka R. Aqil, MPH[3,*] Saad B. Omer, MBBS, MPH, PhD[3,4,5] Shabir A. Madhi, MD, PhD[1,2,6]

[1] Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, University of the Witwatersrand, Johannesburg, South Africa
[2] Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, University of the Witwatersrand, Johannesburg, South Africa
[3] Hubert Department of Global Health, Emory University Rollins School of Public Health, Atlanta, Georgia
[4] Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia
[5] Emory Vaccine Center, Emory University, Atlanta, Georgia
[6] Division of National Health Laboratory Service, Centre for Vaccines and Immunology, National Institute for Communicable Diseases, Johannesburg, South Africa

Address for correspondence Marta C. Nunes, PhD, Respiratory and Meningeal Pathogens Research Unit, Chris Hani-Baragwanath Hospital, Chris Hani Road, New Nurses Residence, 11th Floor West Wing, 2013 Bertsham, South Africa (e-mail: nunesm@rmpru.co.za).

Am J Perinatol 2016;33:1104–1114.



Forest plot for low birth weight births with seasonal influenza vaccine.

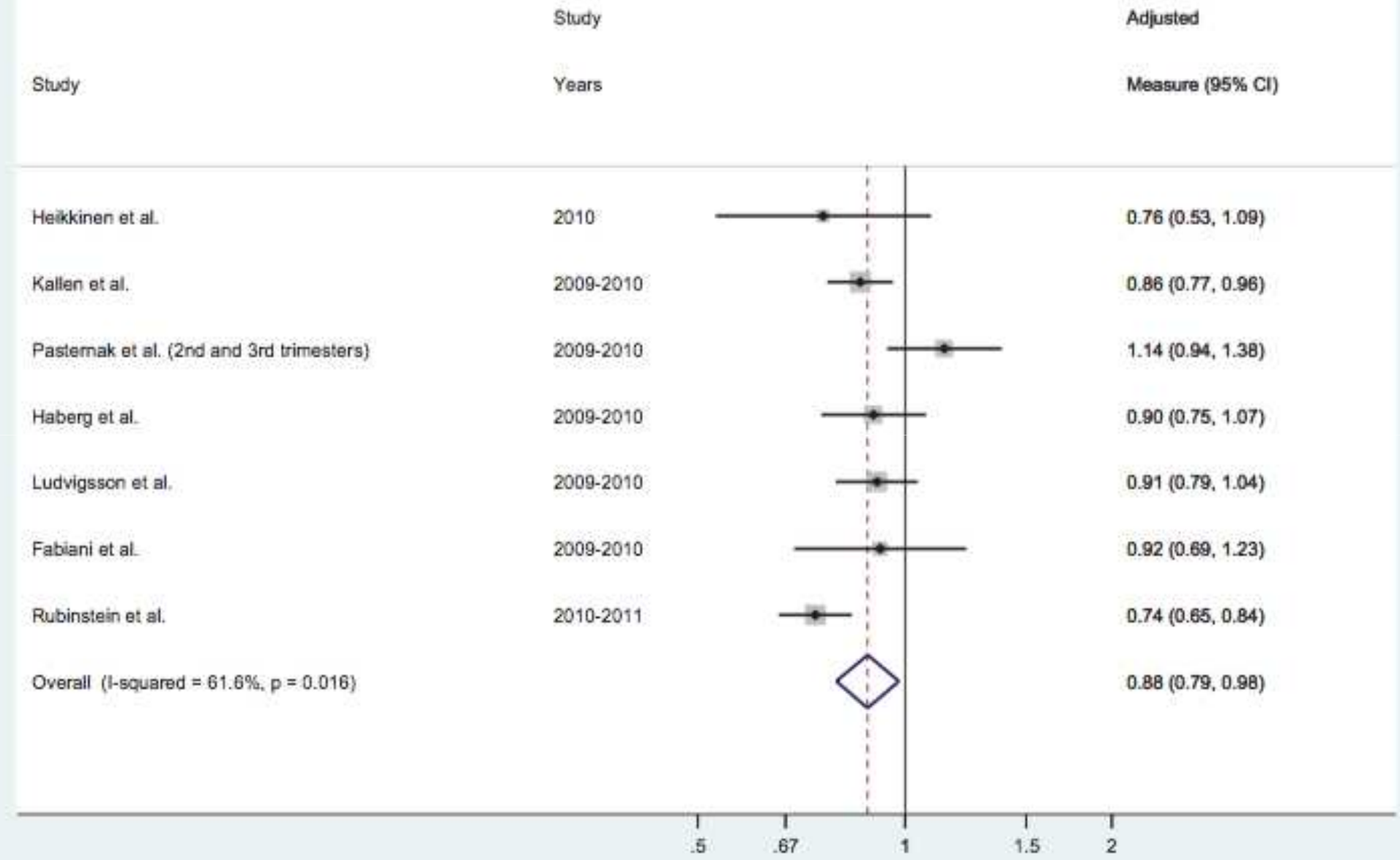


Fig. 7 Forest plot for low birth weight births with monovalent A/H1N1pdm09 influenza vaccine.

Vaccinazione ed outcome fetale

- Riduzione apparente di parto prematuro, basso peso neonatale, morte fetale e complicazioni ostetriche
- Studi prevalentemente osservazionali retrospettivi
- Bias di selezione non controllabile
- Le pazienti che si vaccinano sono di stato sociale piu' elevato, piu' motivate ai controlli in gravidanza e quindi a rischio piu basso di esiti avversi

CMAJ RESEARCH

Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial

Mark C. Steinhoff MD, Saad B. Omer PhD, Eliza Roy DCH, Shams El Arifeen DrPH, Rubhana Raqib PhD, Caitlin Dodd MS, Robert F. Breiman MD, K. Zaman PhD

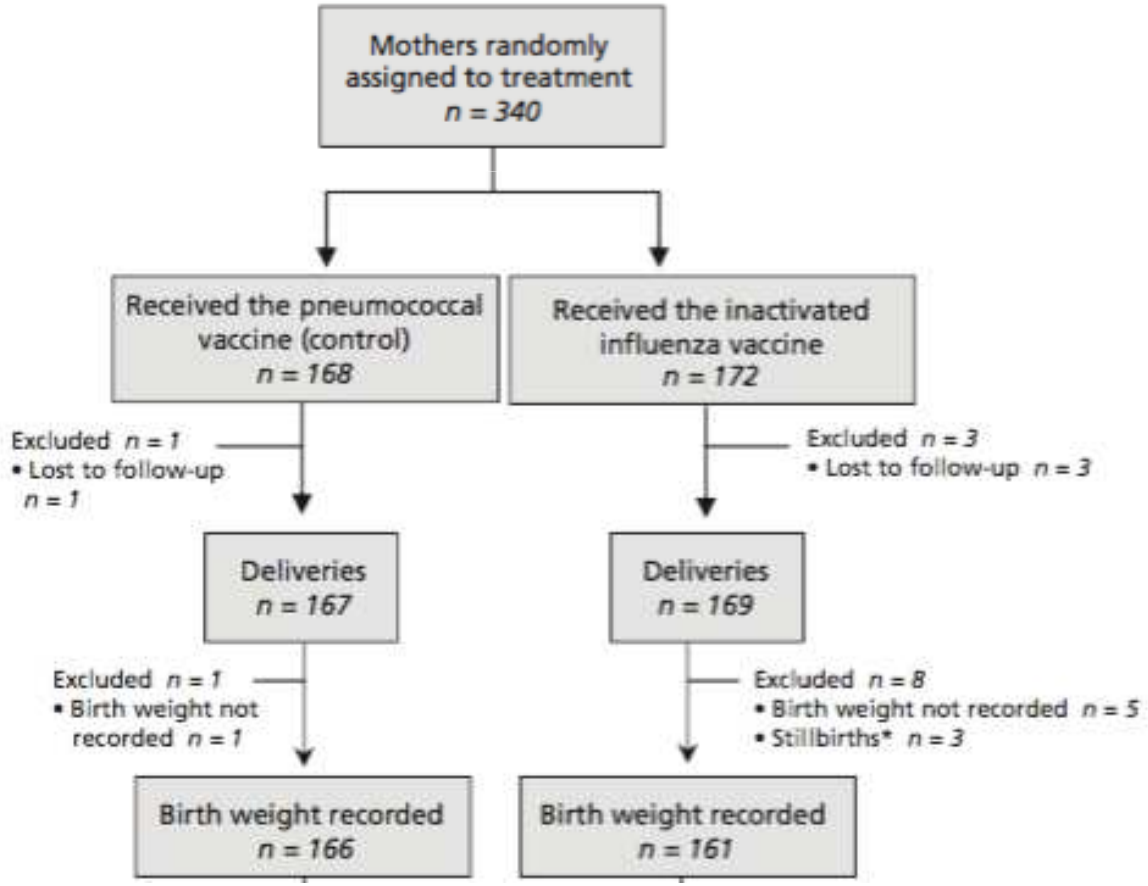


Table 4: Neonatal outcomes, by study period

Variable	Control vaccine		Influenza vaccine		OR (95% CI)*	p value	Adjusted OR (95% CI)*†	p value‡
	No.	% (95% CI)*	No.	% (95% CI)*				
No influenza virus circulating (Sept. 2004–Jan. 2005)		*n = 108*		*n = 103*				
Birth weight, g, mean	–	3053 (2967 to 3139)	–	3083 (3000 to 3176)	30 (–98 to 157)**	0.9††	–	
Small for gestational age§	37	34.3 (25.1 to 42.9)	30	29.1 (20.2 to 37.8)	0.79 (0.44 to 1.41)	0.4	–	
Born before 37 weeks' gestation	10	9.3 (3.8 to 14.8)	8	7.8 (2.6 to 13.0)	0.83 (0.31 to 2.18)	0.7	–	
Weight < 2500 g	8	7.4 (2.5 to 12.3)	6	5.8 (1.3 to 10.3)	0.77 (0.26 to 2.31)	0.6	–	
Apgar score at 1 min, mean	–	7.7 (7.3 to 8.1)	–	7.6 (7.3 to 8.1)	–	0.7	–	
Female	46¶	42.9 (32.7 to 51.3)	43	41.8 (31.5 to 50.5)	0.97 (0.56 to 1.67)	0.9	–	
Influenza virus circulating (Feb. 2005–Oct. 2005)		*n = 58*		*n = 58*				
Birth weight, g, mean	–	2978 (2849 to 3107)	–	3178 (3058 to 3298)	200 (191 to 209)**	0.02††	193 (9 to 378)‡‡	0.01
Small for gestational age§	26	44.8 (31.2 to 56.8)	15	25.9 (13.9 to 36.1)	0.43 (0.20 to 0.94)	0.03	0.44 (0.19 to 0.99)	0.05
Born before 37 weeks' gestation	4	6.9 (0.4 to 13.4)	2	3.5 (0 to 8.2)	0.48 (0.08 to 2.74)	0.4	0.32 (0.05 to 2.29)§§	0.3
Weight < 2500 g	5	8.6 (1.4 to 15.8)	1	1.7 (0 to 5.0)	0.19 (0.02 to 1.64)	0.09	0.17 (0.02 to 1.63)	0.1
Apgar score at 1 min, mean	–	7.3 (6.6 to 8.0)	–	7.7 (7.3 to 8.2)	–	0.3	–	
Female	26	44.8 (31.2 to 56.8)	27	46.6 (33.2 to 58.9)	1.07 (0.52 to 2.23)	0.9	1.12 (0.53 to 2.39)	0.8

European Journal of Obstetrics & Gynecology and Reproductive Biology 187 (2015) 14–19

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Adjuvanted vaccines in pregnancy: no evidence for effect of the adjuvanted H1N1/09 vaccination on occurrence of preeclampsia or intra-uterine growth restriction☆

Alies Coenders [a], Nienke K. Koopmans [a], Kim Broekhuijsen [b], Henk Groen [c], Janna M.A. Karstenberg-Kramer [d], Kim van Goor [d], Mariette Groenewout [a], Aren J. van Loon [b], Marijke M. Faas [d], Maria G. van Pampus [e,*]

	Vaccinated *N* (%)				OR	95% CI	p-value[a]
	Cases		Controls				
Total group							
PE and/or IUGR (*N* = 254 cases, 247 controls)	90	(35.4)	87	(35.2)	1.009	0.70–1.46	0.961[b]
Intra-uterine growth restriction							
Total IUGR < p10 (*N* = 184 cases, 247 controls)	67	(36.4)	87	(35.2)	1.053	0.71–1.57	0.799[b]
IUGR < p5 (*N* = 101 cases, 247 controls)	34	(33.7)	87	(35.2)	0.933	0.57–1.52	0.782[b]
IUGR < p3 (*N* = 55 cases, 247 controls)	19	(34.5)	87	(35.2)	0.971	0.53–1.79	0.924[b]
Preeclampsia							
Total PE (*N* = 78 cases, 247 controls)	24	(30.8)	87	(35.2)	0.817	0.47–1.41	0.470[b]
Early PE (delivery <34 weeks) (*N* = 24 cases, 247 controls)	5	(20.8)	87	(35.2)	0.484	0.18–1.34	0.155[b]
Late PE (delivery ≥34 weeks) (*N* = 54 cases, 247 controls)	19	(35.2)	87	(35.2)	0.998	0.54–1.85	0.996[b]

Ministero della Salute

DIREZIONE GENERALE DELLA PREVENZIONE SANITARIA – CCM
Ufficio V ex DGPREV - Malattie Infettive e Profilassi Internazionale

Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2015-2016

Tabella 1. Elenco delle categorie per le quali la vaccinazione stagionale è raccomandata.

	Categoria	Dettaglio
1	Soggetti di età pari o superiore a 65 anni	
2	Bambini di età superiore ai 6 mesi, ragazzi e adulti fino a 65 anni di età affetti da patologie che aumentano il rischio di complicanze da influenza	a) malattie croniche a carico dell'apparato respiratorio (inclusa l'asma grave, la displasia broncopolmonare, la fibrosi cistica e la broncopatia cronica ostruttiva-BPCO) b) malattie dell'apparato cardio-circolatorio, comprese le cardiopatie congenite e acquisite c) diabete mellito e altre malattie metaboliche (inclusi gli obesi con BMI >30) d) insufficienza renale/surrenale cronica e) malattie degli organi emopoietici ed emoglobinopatie f) tumori g) malattie congenite o acquisite che comportino [illegible] i) patologie per le quali sono programmati importanti interventi chirurgici j) [illegible] k) epatopatie croniche
3	Bambini e adolescenti in trattamento a lungo termine con acido acetilsalicilico, a rischio di Sindrome di Reye in caso di infezione influenzale	
4	Donne che all'inizio della stagione epidemica si trovino nel secondo o terzo trimestre di gravidanza	
5	Individui [illegible]	
6	Medici e personale sanitario di assistenza	
7	Familiari e contatti di soggetti ad alto rischio	
8	Soggetti addetti a servizi pubblici di primario interesse collettivo e categorie di lavoratori	a) Forze di polizia b) Vigili del fuoco c) Altre categorie socialmente utili potrebbero avvantaggiarsi della vaccinazione, per motivi vincolati allo svolgimento della loro attività lavorativa; a tale riguardo, è facoltà delle Regioni/PP.AA. definire i principi e le modalità dell'offerta a tali categorie. d) Infine, è pratica internazionalmente diffusa l'offerta attiva e gratuita della vaccinazione antinfluenzale da parte dei datori di lavoro ai lavoratori particolarmente esposti per attività svolta e al fine di contenere ricadute negative sulla produttività.
9	Personale che, per motivi di lavoro, è a contatto con animali che potrebbero costituire fonte di infezione da virus influenzali non umani	a) allevatori b) addetti all'attività di allevamento c) addetti al trasporto di animali vivi d) macellatori e vaccinatori e) veterinari pubblici e libero-professionisti

4. Donne che all'inizio della stagione epidemica si trovino nel secondo e terzo trimestre di gravidanza.

THE END