UPDATE
SULLE VACCINAZIONI IN GRAVIDANZA

23 SETTEMBRE 2016
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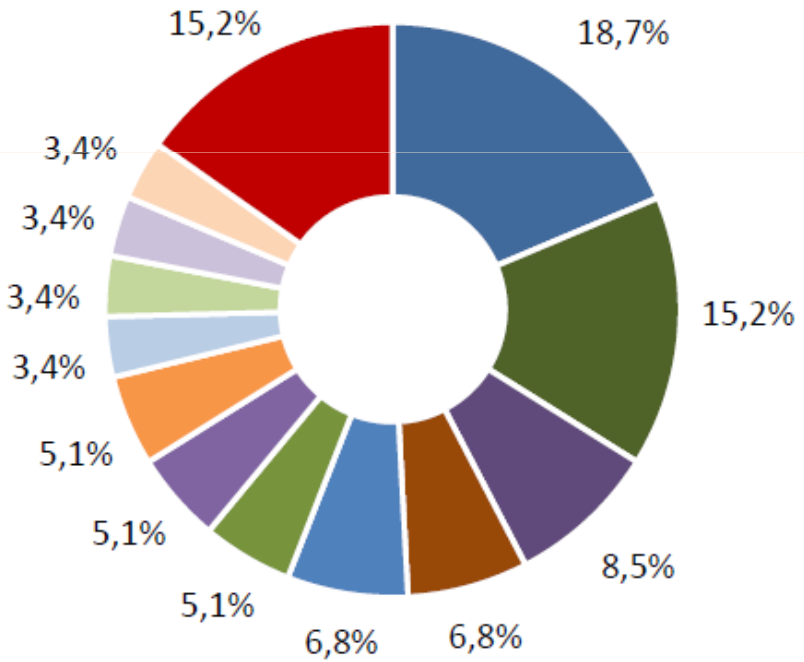
UNIVERSITÀ DEGLI STUDI DI PARMA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Parma

I rischi dell'influenza in gravidanza e nella paziente con comorbilità

S. Fieni

Mortalità materna entro 42 giorni in 8 Regioni



- Emorragia ostetrica (N=11)
- Sepsi (N=9)
- Influenza H1N1 (N=5)
- Disordini ipertensivi (N=4)
- Emoperitoneo da rottura vasi (N=4)
- Embolia da liquido amniotico (N=3)
- Infarto acuto del miocardio (N=3)
- Neoplasie (N=3)
- Suicidio (N=2)
- Tromboembolia (N=2)
- Malattie infettive (N=2)
- Altra causa* (N=2)
- Causa non definibile (N=9)

** Altra causa: Cardiomiopatia e Emorragia cerebrale*

Morti materne da influenza H1N1

Età della donna	Esito gravidanza	vaccinazione	ricovero	antivirale
39 anni	gravidanza 27+5 sett.	no	si	si
29 anni	puerperio	no	si	si
33 anni	gravidanza 22 sett.	no	si	si
37 anni	gravidanza 33 +4 sett.	no	si	si
35 anni	gravidanza 26 sett.	no	si	si

1 donna su 13 è morta a causa dell'influenza
Nessuna era stata vaccinata durante la gravidanza

In Italia la copertura vaccinale in gravidanza è pari a 0,5-1%
Nel Regno Unito la copertura vaccinale è pari al 40% in Inghilterra, 71% nel Galles e 58% nell'Irlanda del Nord.
Nel 2011-2013 in UK non è stata segnalata alcuna morte da influenza in gravidanza.

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Impact of Influenza on Acute Cardiopulmonary Hospitalizations in Pregnant Women

Kathleen Maletic Neuzil,[1,3] George W. Reed,[2] Edward F. Mitchel,[2] Lone Simonsen,[4] and Marie R. Griffin[1,2]

TABLE 2. Odds ratio* for any cardiopulmonary event occurring during influenza season among women aged 15–44 years enrolled in the Tennessee Medicaid program, by pregnancy status, 1974–1993

Pregnancy status	Prevalence (%)		OR†	95% CI†
	Cases (*n* = 4,369)	Controls (*n* = 21,845)		
Postpartum	4.4	7.7	1.0‡	
Nonpregnant	86.6	85.3	1.11	0.94–1.32

- Women in the second and third trimesters had excess hospital admission rates of 6 ·32 and 10 ·48 per 10 000 woman-months, respectively.
- Women in the fi rst trimester and women in the postpartum period had excess hospital admission rates of only 3 ·06 and 1 ·16 per 10 000
- The excess hospital admission rate attributable to influenza in healthy women in the last trimester was equivalent to that seen in non-pregnant women with chronic medical conditions.

* Referent.

UNIVERSITÀ DEGLI STUD DI PARMA

RESEARCH

VIZIO SANITARIO REGIONALE
IA-ROMAGNA
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Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women

Linda Dodds, Shelly A. McNeil, Deshayne B. Fell, Victoria M. Allen, Ann Coombs, Jeffrey Scott, Noni MacDonald

Excess hospital admission rates attributable to influenza in a 1990–2002 134 188 pregnant women from Nova Scotia.

Table 2: Hospital admissions because of respiratory illness during the influenza season in the year before pregnancy and during pregnancy, by presence of comorbidities

	Women with no comorbidity			Women with ≥ 1 comorbidity		
Period	No. of admissions during influenza season	Rate per 10 000 woman-months	Rate ratio (95% CI)*	No. of admissions during influenza season	Rate per 10 000 woman-months	Rate ratio (95% CI)*
Year before pregnancy	49	1.4	1.0	23	5.7	1.0
Pregnancy						
First trimester	22	2.4	1.7 (1.0-2.8)	17	16.3	2.9 (1.5-5.4)
Second trimester	30	3.0	2.1 (1.3-3.3)	22	19.4	3.4 (1.9-6.0)
Third trimester	76	7.4	5.1 (3.6-7.3)	49	44.9	7.9 (5.0-12.5)

1. Pregnant women with a **comorbidities condition** were three times more likely to have a respiratory illness (OR 3·2 [3·0–3·5]
2. Pregnant women with a history of **asthma** had the highest rate of respiratory hospital admission at 597 per 10 000 (OR 10·63)
3. pregnant women with comorbidities should receive influenza vaccination regardless of their stage of pregnancy during the influenza season.
4. Since hospital admissions because of respiratory illness were also increased among pregnant women without comorbidities, all pregnant women are likely to benefit from influenza vaccination.

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REVIEW

Risk management of seasonal influenza during pregnancy: current perspectives

Mark H Yudin

1. In the 1918 H1N1 influenza pandemic, half of all pregnant patients had pneumonia and there was a 27% case fatality rate among pregnant women.
2. In the H2N2 influenza pandemic in 1957–1958, one half of women of reproductive age who died from pandemic influenza were pregnant.
3. Pregnant women were again overrepresented among cases of illness and death in the 2009 global H1N1 influenza pandemic.

Tab. II. Chronic diseases that increase the risk of contracting influenza, for which influenza vaccination is strongly recommended (mod. from Ministero della Salute, 2016 [21]).

Chronic diseases
Respiratory and pulmonary diseases (COPD, asthma, cystic fibrosis etc.)
Heart diseases (all congenital or acquired heart conditions)
Diabetes mellitus or any other metabolic diseases (including individuals with BMI > 30)
Chronic renal or adrenal gland failure
Any type of cancer (also during radio- and chemotherapy)
Hematological diseases or hemoglobinopathies
Congenital or acquired immunodeficiency (pharmacological, AIDS etc.)
Chronic inflammatory bowel disease and inadequate intestinal absorption syndrome
Chronic hepatic diseases
Neuromuscular diseases or any disease at risk for aspiration of respiratory secretions

2. **Malattie cardiovascolari croniche (ipertensione lieve esclusa)**
3. **Malattie metaboliche croniche (in particolare il diabete)**
4. **Malattie croniche renali ed epatiche**
5. **Deficienze immunitarie congenite e acquisite**
6. **Malattie neurologiche o neuromuscolari croniche**
7. **Qualsiasi altra condizione che comprometta la competenza immunitaria o pregiudichi la funzione respiratoria, inclusa l'obesità grave o patologica**
8. **É consideratala collocazione nell'ambito dei gruppi a rischio : gravide**

ECDC Pandemic 2009 Risk Assessment.
DisponibileDisponibileininhttp://www.ecdc.europa.eu/en/Health_topics/novel_influenza_virus /200 9_Outbreak : virus/

LE

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OBSTETRICS

2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature

Laura G. Mosby, BA; Sonja A. Rasmussen, MD, MS; Denise J. Jamieson, MD, MPH

TABLE 1
Relative risk of hospitalization, intensive care unit admission, death, or any severe outcome in pregnant women due to 2009 H1N1 influenza

Paper	Risk of hospitalization	Risk of ICU admission	Risk of death	Risk of severe disease
New South Wales Public Health Network[110]		RR, 5.8[a]	RR, 10.2[a]	
ANZIC[8]		RR, 7.4[a]		
Campbell et al[123]		RR, 0.7 (0.4–1.2)[a]	RR, 1.1 (0.3–4.1)[a]	RR, 0.7 (0.4–1.3)
Creanga et al[13]	RR, 7.2[a]			RR, 4.3[a]
Fuhrman et al[62]			aOR, 0.3 (0.04–3.0)	aOR, 0.5 (0.2–0.8)
Gérardin et al[46]		RR, 0.4 (0–2.6)[a]		
Hanslik et al[23]		OR, 5.2 (4.0–6.9)	OR, 1.4 (0.3–4.2)	
Jamieson et al[3]	RR, 4.3 (2.3–7.8)[b]			
Kelly et al[28]	RR, 5.2 (4.6–5.8)[b]	RR, 6.5 (4.8–8.8)[b]	RR, 1.4 (0.4–4.5)[b]	
Koegelenberg et al[29]				
Oliveira et al[81]				
Yang et al[53]				
Zarychanski et al[106]		OR, 3.64 (0		

ANZIC, ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System; *aO*

[a] Compared to nonpregnant women of reproductive age; [b] Compared to general population; [c] This nu require only outpatient treatment.

Mosby. 2009 H1N1 and pregnancy. Am J Obstet Gynecol 2011.

ESITI MATERNI

Popolazione gravida in America 1%

-6.3% ospedalizzazione

- 5.9% ICU

- 5.7% decesso

ANTIVIRALI

-5 studi riportano che il trattamento < 48h riduce il rischio di malattia severa
- non RCT
- tutti gli studi riconoscono un beneficio
- tutti gli studi concordano nell'importanza della tempestività

COMORBILITA'

•Asma
•Diabete
•Obesità

MODALITA' DEL PARTO

•PPT >30% (9.6%---15%)
•TC urgenti (58%)
•Indicazioni al TC : ipossiemia materna, scompenso materno

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 60 / No. 35
September 9, 2011

Maternal and Infant Outcomes Among Severely Ill Pregnant and Postpartum Women with 2009 Pandemic Influenza A (H1N1) — United States, April 2009–August 2010

TABLE 1. Characteristics of pregnant women with 2009 pandemic influenza A (H1N1) severe illness (i.e., ICU admission or death) — United States, April 15, 2009–August 10, 2010

	Died (n = 75)		Admitted to ICU and survived (n = 272)		
Characteristic	No.	(%)	No.	(%)	p value
Maternal age (yrs)					
Mean age at illness onset (range)	26.9 (18–43)	—	25.9 (16–43)	—	0.17*
Unknown/Missing	1	—	13	—	
Race/Ethnicity					0.89†
White, non-Hispanic	21	(35.6)	88	(36.8)	
Black, non-Hispanic	12	(20.3)	44	(18.4)	
Hispanic	20	(33.9)	88	(36.8)	
Other race	6	(10.2)	19	(8.0)	
Missing	16		33		
Trimester at symptom onset					0.23†
First trimester (0–13 wks)	5	(6.9)	16	(6.5)	
Second trimester (14–28 wks)	22	(30.6)	103	(41.7)	
Third trimester (≥29 wks)	45	(62.5)	128	(51.8)	
Unknown/Missing	3		25		
Underlying illness/condition					0.04†
None of the following underlying conditions	25	(38.5)	129	(53.3)	
Any of the following underlying conditions	40	(61.5)	113	(46.7)	
Asthma	22		55		
Obesity	19		39		
Diabetes (gestational or pregestational)	11		16		
Other medical conditions§	19		40		
Unknown/Missing	10		30		
Antiviral medication prescribed					0.02†
No neuraminidase antiviral treatment	10	(13.9)	13	(5.2)	
Any neuraminidase antiviral treatment¶	62	(86.1)	238	(94.8)	
Unknown/Missing	3		21		
Total	**75**	**100.0**	**272**	**100.0**	
Days from symptom onset until treatment**					<0.01†
≤2	4	(7.0)	76	(40.6)	
3–4	11	(19.3)	47	(25.1)	
>4	42	(73.7)	64	(34.2)	
Unknown/Missing	8		72		
Total	**65**	**100.0**	**259**	**100.0**	

TABLE 2. Outcomes for live births to pregnant women with 2009 pandemic influenza A (H1N1) severe illness (i.e., ICU admission or death) — United States, April 15, 2009–August 10, 2010

Outcome	Delivery during maternal hospitalization for 2009 H1N1 illness		Delivery after discharge from 2009 H1N1 illness hospitalization		Estimated % in U.S. population
	No.	(%)	No.	(%)	
Gestational age at delivery (wks)					
Very preterm (<32)	17	(22.1)	0	—	
Preterm (32–36)	32	(41.6)	10	(20.8)	
Very preterm and preterm (<37)	49	(63.6; CI = 51.8–74.3)	10	(20.8; CI = 10.5–35.0)	12.3*
Term (≥37)	28	(36.4)	38	(79.2)	
Unknown/Missing	8	—	6	—	
Small for gestational age					
≤10th centile for gestational age†	3	(4.1; CI = 0.0–11.5)	13	(25.0; CI = 14.0–39.0)	10.0†
>10th centile for gestational age	70	(95.9)	39	(75.0)	
Unknown/Missing	12	—	2	—	
Birthweight (g)					
Low (<2,500)	32	(43.8; CI = 32.2 –56.0)	10	(19.2; CI = 9.6–32.5)	8.2*
Normal (≥2,500)	41	(56.2)	42	(80.8)	
Unknown/Missing	12	—	2	—	
Admission to neonatal ICU					
No admission	22	(30.6)	39	(78.0)	
Admission	50	(69.4; CI = 57.5–79.8)	11	(22.0; CI = 11.5–36.0)	6.1§
Unknown/Missing	13	—	4	—	
5-minute Apgar scores					
Low (≤6)	21	(29.2; CI = 19.1–41.1)	1	(2.0; CI = 0.1–10.7)	1.6¶
Normal (>6)	51	(70.8)	49	(98.0)	
Unknown/Missing	13	—	4	—	
Total	**85****	**100.0**	**54****	**100.0**	

Centers for Disease Control and Prevention
MMWR
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September 9, 2011

1. Based on data from seasonal influenza and the 2009 H1N1 pandemic, pregnant women are **more severely affected** with influenza than the general population.
2. During the 2009 H1N1 pandemic, **early treatment of pregnant** women with antiviral medications was associated with fewer admissions to an intensive-care unit (ICU) and fewer deaths.

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 60 / No. 35
September 9, 2011

1. These data emphasize the importance of **influenza vaccination** for pregnant women, regardless of pregnancy trimester, and of **prompt, empiric treatment** with appropriate antiviral medications for pregnant women with suspected or confirmed influenza
2. Infants were more likely to be **preterm and of lower birth weight** than the general population,

TABLE 2
Number of deliveries, gestational age, mode of delivery, and neonatal outcome in pregnancies affected by 2009 H1N1 influenza

Paper	No. of deliveries[a]	Proportion of preterm deliveries	Proportion of cesarean deliveries	Fetal/neonatal survival
United States				
CDC[7]	9	5/9	At least 2/9	1 stillbirth; 1 neonatal death
Creanga et al[13]	22 while ill 22 after recovery	While ill: 3/22 (2 in women with severe disease) After recovery: 3/22	While ill: 11/22 After recovery: 7/22	2 neonatal deaths
Jamieson et al[3]	6	6/6	6 (5 in cases with maternal death)	
Louie et al[35]	35	25-28 wks: 3 >28 wks: 32 Of severe maternal illness: 11/13	Of severe maternal illness: 10/12	
Miller et al[49]	6	4/6	5/6	1 neonatal death
Siston et al[41]	169	30.2%	109/188	
Australia				
ANZIC[8]	59	36%	While ill: 14/22 After recovery: 6/23	4 stillbirths; 2 neonatal deaths: 1 postneonatal

Mosby. 2009 H1N1 and pregnancy. Am J Obstet Gynecol 2011.

1. Pregnancy was associated with increased risk of hospital and intensive care unit admission and of death.
2. Pregnant women who received delayed treatment with neuraminidase inhibitors or who had additional risk factors were more likely to develop severe disease.
3. Preterm and emergency cesarean deliveries were frequently reported.
4. These results reinforce the importance of early identification and treatment of suspected influenza in this high-risk population

ORIGINAL CONTRIBUTION

Pandemic 2009 Influenza A(H1N1) Virus Illness Among Pregnant Women in the United States

Siston et al JAMA 2010

1. Health conditions typically associated with risk for seasonal influenza complications were also found among individuals with 2009 influenza A(H1N1) admitted to an intensive care unit (ICU), **including chronic lung disease, neurological disorders, diabetes, and pregnancy**
2. Changes in the immune, cardiac, and respiratory systems are likely reasons that pregnant women are at increased risk for severe illness with influenza.

Table 1. Characteristics of Pregnant Women With 2009 Influenza A(H1N1) Illness Through August 21, 2009, United States[a]

Characteristics	No. (%) of Pregnant Women			
	Total (n = 788)	Hospitalized (n = 509)[b]	Intensive Care Unit Admission (n = 115)[c]	Maternal Deaths (n = 30)
Race/ethnicity				
White, non-Hispanic	167 (22.7)	89 (18.2)	31 (29.0)	13 (44.8)
Black, non-Hispanic	141 (19.1)	103 (21.0)	15 (14.0)	2 (6.9)
Hispanic	242 (32.8)	175 (35.7)	39 (36.4)	8 (27.6)
Asian/Pacific Islander	42 (5.7)	28 (5.7)	9 (8.4)	4 (13.8)
Alaskan Native/American Indian	9 (1.2)	7 (1.4)	0	0
Multiracial	4 (0.5)	2 (0.4)	0	0
Other/unknown	132 (17.9)	86 (17.6)	13 (12.1)	2 (6.9)
Missing	51	19	8	1
Maternal age, y				
<20	124 (16.0)	80 (15.9)	12 (10.4)	2 (6.7)
20-24	249 (32.2)	164 (32.5)	36 (31.3)	10 (33.3)
25-29	195 (25.2)	133 (26.4)	31 (27.0)	8 (26.7)
30-34	122 (15.8)	73 (14.5)	22 (19.1)	6 (20.0)
35-39	69 (8.9)	42 (8.3)	12 (10.4)	3 (10.0)
≥40	15 (1.9)	12 (2.4)	2 (1.7)	1 (3.3)
Unknown/missing	14	5	0	0
Age, median (range)	25 (14-43)	25 (15-43)	26 (17-43)	25 (18-43)
Trimester of pregnancy at symptom onset (wk)				
First trimester (0-13)	67 (11.3)	30 (7.6)	8 (8.2)	3 (10.0)
Second trimester (14-28)	250 (42.2)	151 (38.3)	38 (39.2)	9 (30.0)
Third trimester (≥29)	275 (46.5)	213 (54.1)	51 (52.6)	18 (60.0)
Unknown/missing	196	115	18	0
Month of symptom onset				
April (14 to 30 only)	28 (3.9)	10 (2.2)	2 (1.8)	1 (3.3)
May	182 (25.6)	103 (22.2)	22 (20.0)	9 (30.0)
June	296 (41.6)	182 (39.1)	39 (35.5)	9 (30.0)
July	149 (20.9)	126 (27.1)	35 (31.8)	8 (26.7)
August (1 to 21 only)	57 (8.0)	44 (9.5)	12 (10.9)	3 (10.0)
Unknown/missing	76	44	5	0
Underlying illness/condition				
Asthma	99 (22.9)	73 (23.0)	22 (25.6)	10 (43.5)
Obesity[d]	56 (13.0)	53 (16.7)	19 (22.1)	9 (39.1)
Pregestational diabetes	17 (3.9)	14 (4.4)	3 (3.5)	1 (4.3)
Anemia	15 (3.5)	15 (4.7)	4 (4.7)	0
Hypertension	13 (3.0)	9 (2.8)	3 (3.5)	1 (4.3)
Gestational diabetes	12 (2.8)	10 (3.1)	1 (1.2)	1 (4.3)
Cardiovascular disease (excluding hypertension)	10 (2.3)	10 (3.1)	6 (7.0)	3 (13.0)
Thyroid disease	8 (1.9)	5 (1.6)	2 (2.3)	2 (8.7)
Immune suppression (due to underlying disease or meds)	8 (1.9)	8 (2.5)	5 (5.8)	2 (8.7)
Neurological disease	7 (1.6)	7 (2.2)	4 (4.7)	2 (8.7)
Chronic lung disease (excluding asthma)	7 (1.6)	7 (2.2)	4 (4.7)	1 (4.3)
Autoimmune disease	3 (0.7)	3 (0.9)	3 (3.5)	2 (8.7)
Other	33 (7.6)	30 (9.4)	10 (11.6)	4 (17.4)
Any of the above underlying conditions	213 (49.3)	176 (55.3)	54 (62.8)	18 (78.3)
No underlying conditions	219 (50.7)	142 (44.7)	32 (37.2)	5 (21.7)
Unknown/missing	356	191	29	7

Table 1. Characteristics of Pregnant Women With 2009 Influenza A(H1N1) Illness Through August 21, 2009, United States (continued)[a]

Characteristics	No. (%) of Pregnant Women			
	Total (n = 788)	Hospitalized (n = 509)[b]	Intensive Care Unit Admission (n = 115)[c]	Maternal Deaths (n = 30)
Antiviral medication prescribed				
Oseltamivir only	476 (81.0)	329 (82.5)	71 (73.2)	21 (70.0)
Zanamivir only	13 (2.2)	8 (2.0)	3 (3.1)	0
Oseltamivir and zanamivir	12 (2.0)	11 (2.8)	4 (4.1)	1 (3.3)
Oseltamivir and adamantine	4 (0.7)	3 (0.8)	2 (2.1)	1 (3.3)
Antiviral prescribed, but not specified	4 (0.7)	3 (0.8)	2 (2.1)	2 (6.7)
Refused treatment	5 (0.9)	0	0	0
No treatment	74 (12.6)	45 (11.3)	15 (15.5)	5 (16.7)
Unknown/missing	200	110	18	0
Antiviral treatment timing from symptom onset, d[e]				
≤2	219 (43.0)	148 (41.8)	13 (15.9)	1 (4.0)
3-4	84 (16.5)	66 (18.6)	15 (18.3)	4 (16.0)
>4	81 (15.9)	67 (18.9)	37 (45.1)	20 (80.0)
Antiviral treatment, but timing not known	125 (24.6)	73 (20.6)	17 (20.7)	0
Median (range)[f]	2 (–2 to 21)	2 (–2 to 21)	5 (–1 to 21)	6 (2 to 21)
Unknown/missing	200	110	18	0

[a] Percentages are based on women with complete information in the respective categories.
[b] Includes intensive care unit admission and maternal deaths.
[c] Includes maternal deaths.
[d] Data are based on reports to Centers for Disease Control and Prevention from state and local health departments; prepregnancy body mass index was not available.
[e] Does not include "no treatment."
[f] Negative numbers represent prophylaxis administered before symptom onset.

Table 3. Comparison of Maternal Outcomes by Timing of Antiviral (Oseltamivir or Zanamivir) Treatment[a]

Treatment	No. (%) of Women							
	Hospital Admission[b]		ICU Admission Among Hospitalized Patients[c]		Mechanical Ventilation Among Hospitalized Patients[c]		Maternal Death[b]	
	Yes (n = 509)	No (n = 263)	Yes (n = 115)	No (n = 350)	Yes (n = 77)	No (n = 332)	Yes (n = 30)	No (n = 662)
Timing after symptom onset, d								
≤2	148 (67.6)	71 (32.4)	13 (9.4)	125 (90.6)	6 (4.6)	125 (95.4)	1 (0.5)	197 (99.5)
3-4	66 (78.6)	18 (21.4)	15 (22.7)	51 (77.3)	10 (17.2)	48 (82.8)	4 (5.0)	76 (95.0)
>4	67 (82.7)	14 (17.3)	37 (56.9)	28 (43.1)	32 (56.1)	25 (43.9)	20 (27.0)	54 (73.0)
No treatment	45 (57.7)	33 (42.3)	15 (34.9)	28 (65.1)	9 (21.4)	33 (78.6)	5 (6.9)	67 (93.1)
Treated, timing unknown[d]	73	52	17	47	10	41	0	115
Unknown treatment status[d]	110	75	18	71	10	60	0	153
Treatment Timing Comparisons								
3-4 vs ≤2 d								
Relative risk (95% CI)	1.2 (1.0-1.3)		2.4 (1.2-4.8)		3.8 (1.4-9.9)		9.9 (1.1-87.2)	
P Value	.06		.01		.008[e]		.03[e]	
>4 vs ≤2 d								
Relative risk (95% CI)	1.2 (1.1-1.4)		6.0 (3.5-10.6)		12.3 (5.4-27.7)		53.5 (7.3-391.7)	
P Value	.01		<.001		<.001		<.001	
None vs ≤2 d								
Relative risk (95% CI)	0.8 (0.7-1.0)		3.7 (1.9-7.2)		4.7 (1.8-12.4)		13.8 (1.6-115.7)	
P Value	.12		<.001		.002[e]		.006[e]	

Table 4. Impact of Trimester and Timing of Antiviral Treatment on Admission to an Intensive Care Unit Among Hospitalized Patients

Trimester and Treatment Timing[a]	No. (%) of Women: Intensive Care Admission (n = 61)	No. (%) of Women: No Intensive Care Admission (n = 192)	Relative Risk (95% CI)	*P* Value
Any trimester ≤2 d after symptom onset	13 (9.4)	125 (90.6)	1.0 [Referent]	
3-4 d after symptom onset, trimester				
First	1 (16.7)	5 (83.3)	1.8 (0.3-11.4)	.47[b]
Second	3 (14.3)	18 (85.7)	1.5 (0.5-4.9)	.45[b]
Third	9 (33.3)	18 (66.7)	3.5 (1.7-7.4)	.003[b]
>4 d after symptom onset, trimester				
First	3 (75.0)	1 (25.0)	8.0 (3.7-17.1)	.004[b]
Second	14 (58.3)	10 (41.7)	6.2 (3.3-11.5)	<.001[b]
Third	18 (54.5)	15 (45.5)	5.8 (3.2-10.6)	<.001

Table 2. Clinical Outcomes Among Pregnant Women With Pandemic 2009 Influenza A(H1N1) Illness Through August 21, 2009, United States[a]

Outcome	No. (%) of Pregnant Women
All Pregnant Women (n = 788)	
Hospital admission	
Yes	509 (65.9)
No	263 (34.1)
Unknown/missing	16
Maternal death	
Yes	30 (4.3)
No	662 (95.7)
Unknown/missing	96
Preterm delivery[b]	
Yes (<37 wk gestation)	51 (30.2)
No (≥37 wk gestation)	118 (69.8)
Delivery type	
Spontaneous abortion	8 (1.4)
Therapeutic abortion	4 (0.7)
Vaginal delivery	79 (13.5)
Cesarean delivery	109 (18.6)
Among Hospitalized Pregnant Women (n = 509)	
Hospital length of stay, d	
Median (range)	3 (1-73)
Unknown/missing	122
Admission to intensive care unit	
Yes	115 (24.7)
No	350 (75.3)
Unknown/missing	44
Mechanical ventilation	
Yes	77 (18.8)
No	332 (81.2)
Unknown/missing	100

Preparing for influenza after 2009 H1N1: special considerations for pregnant women and newborns

Sonja A. Rasmussen, MD, MS; Dmitry M. Kissin, MD, MPH; Lorraine F. Yeung, MD, MPH; Kitty MacFa
Susan Y. Chu, PhD, MSPH; Reina M. Turcios-Ruiz, MD; Elizabeth W. Mitchell, PhD; Jennifer Williams,
Alicia M. Fry, MD, MPH; Jeffrey Hageman, MHS; Timothy M. Uyeki, MD, MPH, MPP; Denise J. Jamies
and the Pandemic Influenza and Pregnancy Working Group

TABLE

Areas of expertise and organizations that were represented at the "Pandemic Influenza Revisited: Special Considerations for Pregnant Women and Newborns" meeting in Atlanta, GA, on August 12-13, 2010 *(continued)*

Organizations
Academy of Breastfeeding Medicine
Advisory Committee on Immunization Practices
American Academy of Family Physicians
American Academy of Pediatrics
American College of Nurse Midwives
American College of Obstetricians and Gynecologists
American Medical Association
American Nurses Association
American Pharmacists Association
Association for Professionals in Infection Control and Epidemiology
Association of Maternal and Child Health Programs
Association of Women's Health, Obstetric and Neonatal Nurses
California Department of Public Health
Centers for Disease Control and Prevention
Centers for Medicare & Medicaid Services
Food and Drug Administration
Georgia Division of Public Health
Indian Health Service
International Lactation Consultant Association
March of Dimes
Memphis County (TN) Health Department
National Association of County and City Health Officials
National Institutes of Health
National Medical Association
National Vaccine Program Office
New York City Department of Health and Mental Hygiene
New York State Department of Health
Nurses for Newborns Foundation
Organization of Teratology Information Specialists
Shelby County (TN) Health Department
Society for Healthcare Epidemiology of America
World Health Organization

Rasmussen. Preparing for Influenza after 2009 H1N1. Am J Obstet Gynecol 2011.

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Preparing for influenza after 2009 H1N1: special considerations for pregnant women and newborns

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1. CDC recommended that pregnant women with H1N1 receive prompt empiric antiviral treatment with oseltamivir.
2. 6 studies showed that **early (2 days** after symptom onset) treatment was associated with fewer intensive care unit admissions and fewer deaths, when compared with late
3. Rapid influenza diagnostic tests do not have sufficient sensitivity clinical decisions to initiate antiviral treatment should be based on clinical suspicion of influenza.

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Preparing for influenza after 2009 H1N1: special considerations for pregnant women and newborns

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4. **Oseltamivir i**s preferred over zanamivir, assuming that the prevalence of oseltamivir resistance is low among circulating influenza viruses
5. **Vaccination** with inactivated influenza vaccine during pregnancy is the **best way** to protect the mother from influenza and its complications; however, uptake among pregnant women has been low.

1. In addition, influenza vaccination of pregnant women and of household contacts and caregivers of **infants who are 6 months old** can help prevent influenza in these infants
2. Continued surveillance and research to address gaps in the understanding of influenza and its **treatment and prevention** among pregnant women and ways to best **communicate public health messages** to pregnant women and their health care providers are critically needed.

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AOGS
ACTA Obstetricia et Gynecologica Scandinavica

AOGS REVIEW ARTICLE

Influenza virus infection in pregnancy: a review

WOUTER J. MEIJER[1], ALEID G.A. VAN NOORTWIJK[2], HEIN W. BRUINSE[1] & ANNEMARIE M.J. WENSING[3]

[1]Perinatal Center, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, [2]Department of Obstetrics and Gynecology, Ikazia Hospital, Rotterdam, and [3]Department of Virology, Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands

- 100 papers
- 32 MD
- 26 pregnant outcome
- 2055 patients

1. Maternal morbidity
2. Pregnancy outcome
3. Treatment of pregnant women with influenza infection
4. Vaccination

MATERNAL MORBIDITY

1. Pregnant women appear to be at an **increased risk** of influenza virus infection or influenza-like illness, especially during the **third trimester** of pregnancy
2. **Severe maternal disease** is associated with poor pregnancy outcome.
3. RR to be **admitted to a hospital** due to influenza virus infection is increased with a median RR of **6.8** (range 3.5– 25.3)
4. RR to be **admitted to an ICU** is **6.5**
5. **Mortality** also emphasize the considerable burden of influenza infection in pregnancy

ANTIVIRAL DRUGS

1. **No RCT** on the benefits and/or risks of treatment of pregnant women with **antiviral** medication were found.
2. Four cohort studies showed an association of severe disease (ICU admission or maternal death) with delayed (>48 h after symptom onset) compared with prompt (≤48 h) initiation of **treatment with antiviral** drugs
3. **Oseltamivir** was the drug mainly used in these studie
4. Safety reports on the outcome of pregnancy after oseltamivir use during pregnancy are reassuring.
5. There was no increased risk of congenital malformations or other adverse pregnancy outcomes for both mother and neonate.

VACCINATION

1. **Vaccination** of pregnant women is probably the best option to reduce morbidity from influenza infection in pregnant women.
2. Studies on the **immunological response** to influenza vaccination in pregnancy have shown that seroconversion rates in pregnancy are comparable to non-pregnant women
3. The **stage of gestation** does not seem to influence the response rate and neither does a second dose of vaccine seem to add an additional antibody response
4. **Vaccination should be recommended** to pregnant women, because it is safe and reduces both maternal and neonatal morbidity from influenza virus infection.

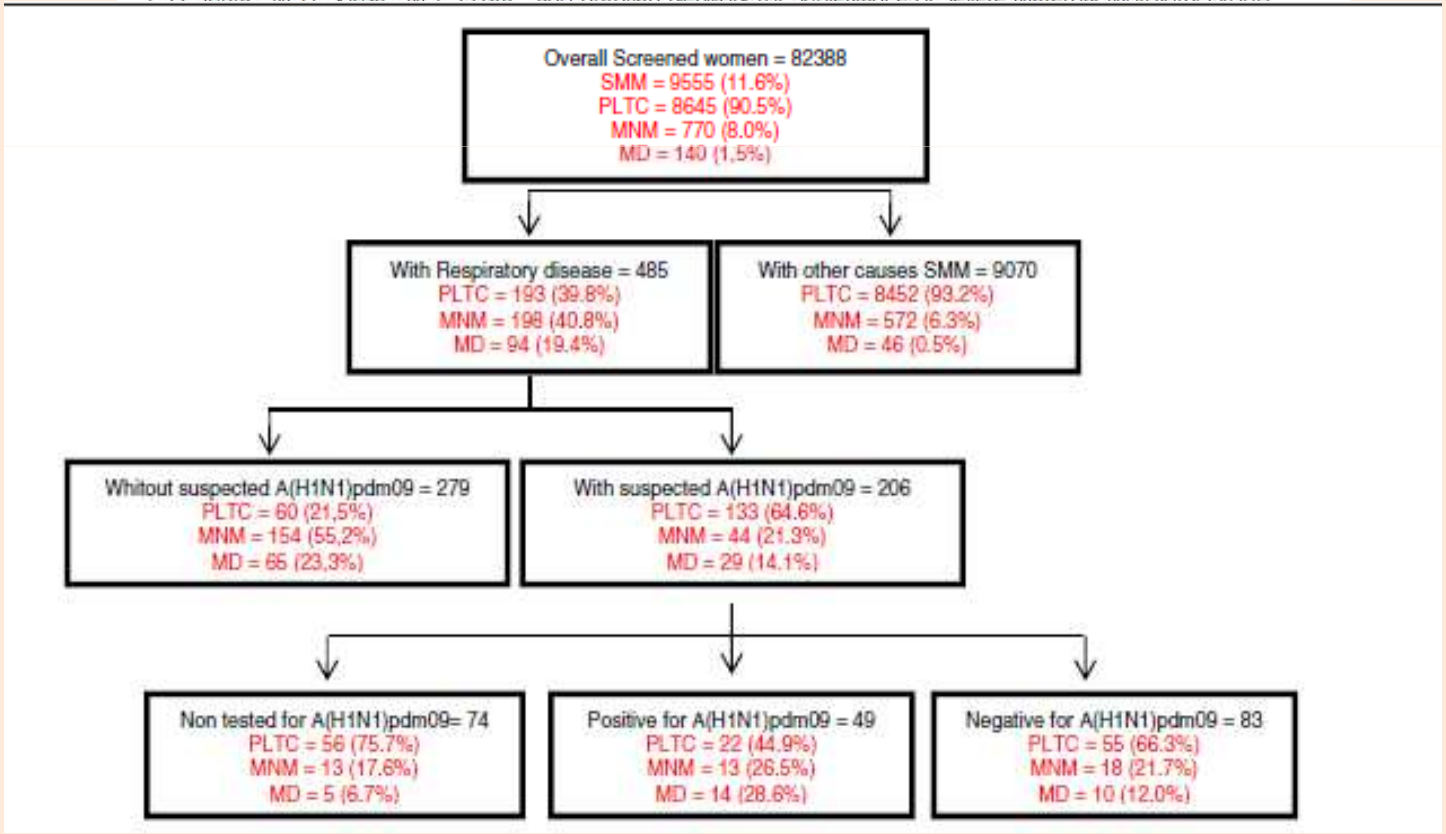
Pfitscher *et al. BMC Infectious Diseases* (2016) 16:220
DOI 10.1186/s12879-016-1525-z

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Severe maternal morbidity due to respiratory disease and impact of 2009 H1N1 influenza A pandemic in Brazil: results from a national multicenter cross-sectional study

L. C. Pfitscher[1], J. G. Cecatti[1], R. C. Pacagnella[1], S. M. Haddad[1], M. A. Parpinelli[1], J. P. Souza[1,2], S. M. Quintana[2], F. G. Surita[1], M. H. Sousa[1], M. L. Costa[1*] and Brazilian Network for Surveillance of Severe Maternal Morbidity Group

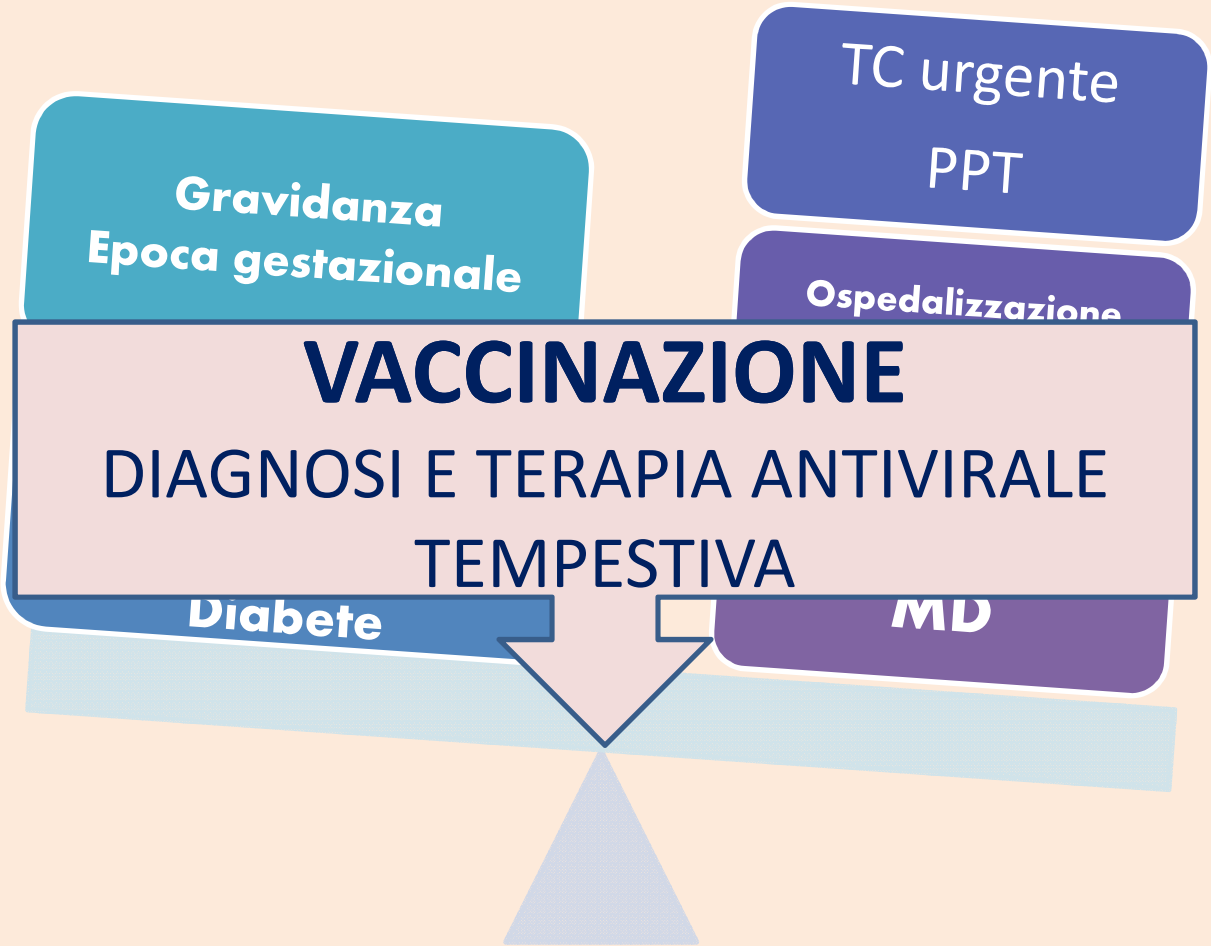


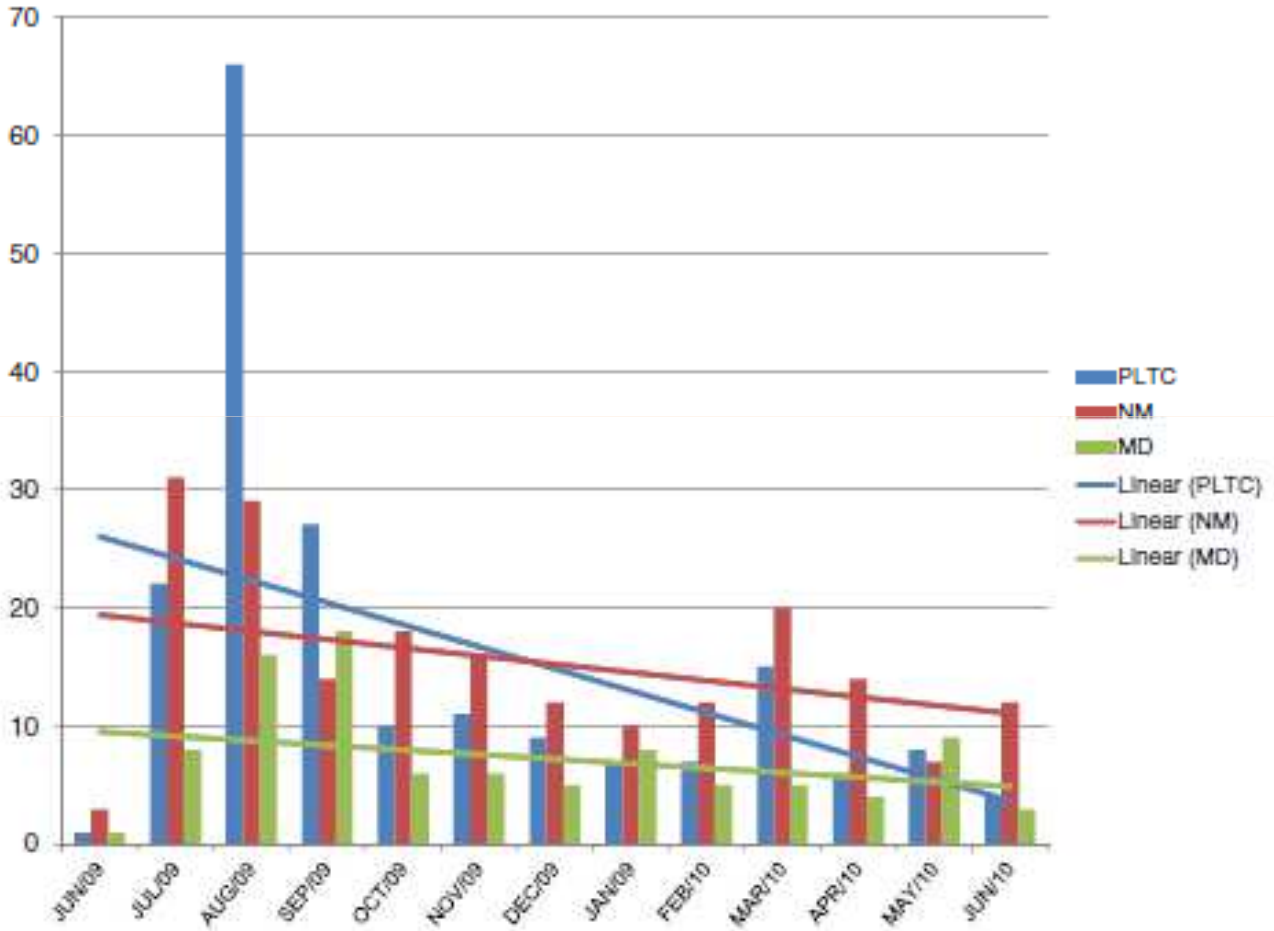
1. Respiratory disease occurred in **one-quarter of MNM** cases and two-thirds of MD.
2. **Asthma** is the most common medical condition that worsen during pregnancy and it is often underdiagnosed and under-treated
3. **Confirmed H1N1** influenza cases had worse adverse outcomes

1. **Delay in medical** care was associated with SMO in all cases considered, with a two-fold increased risk among respiratory disease patients.
2. **Perinatal outcome** was worse in cases complicated by respira disease, with increased prematurity, stillbirth, low birth and Apgar score<7.
3. **Preventive** vaccination during pregnancy, early diagnosis and treatment are required to improve maternal health

FATTORI DI RISCHIO

ESITI AVVERSI





g. 2 Distribution of cases with severe respiratory disease, according to progression of severity during the study period

Changes in physiology and immune function in pregnancy include:
increased heart rate, stroke volume, and oxygen consumption;
a decrease in lung capacity;
alterations in cell-mediated immunity.

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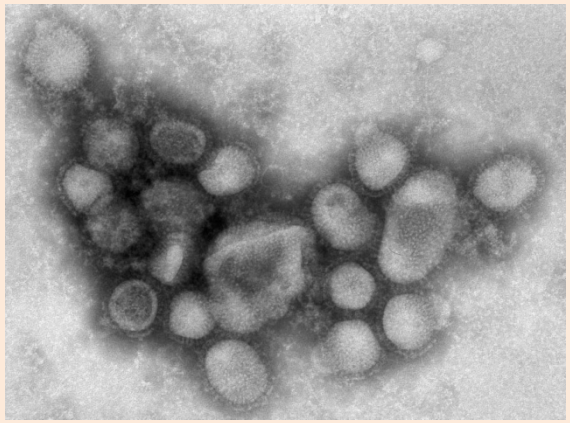

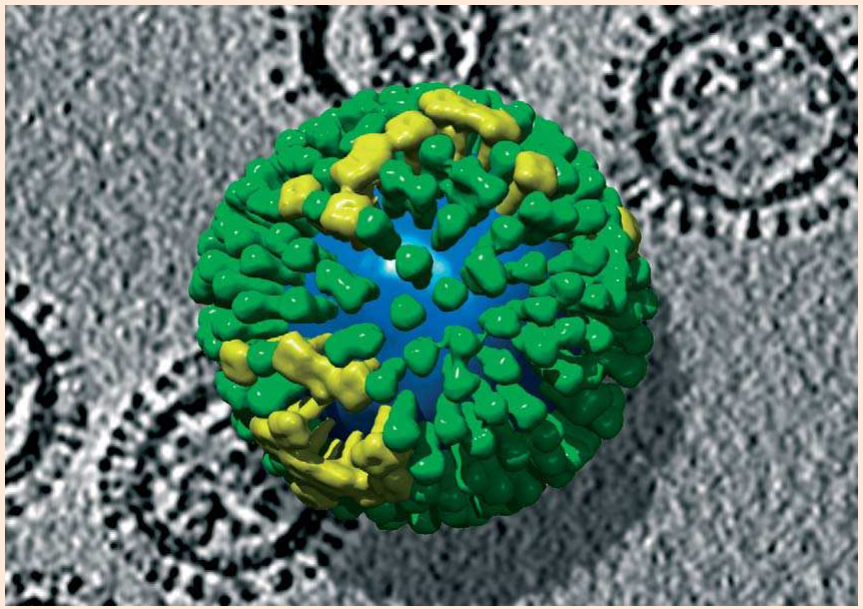

Tabella 1. Elenco delle categorie per le quali la vaccinazione stagionale è raccomandata.

	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 cronico 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 carente produzione di anticorpi, immunosoppressione indotta da farmaci o da HIV h) malattie infiammatorie croniche e sindromi da malassorbimento intestinali i) patologie per le quali sono programmati importanti interventi chirurgici j) patologie associate a un aumentato rischio di aspirazione delle secrezioni respiratorie (ad es. malattie neuromuscolari) 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 e terzo trimestre di gravidanza.	
5	Individui di qualunque età ricoverati presso strutture per lungodegenti.	
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

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Cochrane Library
Cochrane Database of Systematic Reviews

Impact of Haemophilus influenzae type B (Hib) and viral influenza vaccinations in pregnancy for improving maternal, neonatal and infant health outcomes

Comparison 2. Viral influenza vaccine versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	1	2116	Risk Ratio (M-H, Fixed, 95% CI)	4.96 [0.24, 103.24]
2 Infant death (up to 175 days)	1	2049	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.37, 1.37]
3 Perinatal death (stillbirth + death in first week of life)	1	2083	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.73, 2.38]
4 RT-PCR confirmed influenza in infants	1	2049	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.30, 0.88]
5 RT-PCR confirmed influenza in women	1	2116	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.29, 0.86]
6 Influenza-like illness in infants	1	2049	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.94, 1.09]
7 Any respiratory illness in women	1	2116	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.91, 1.04]
8 Any respiratory illness in infants	1	2049	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
9 Influenza-like illness in women	1	2116	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.79, 1.16]
10 Maternal hospitalisation for respiratory infection	1	2116	Risk Ratio (M-H, Fixed, 95% CI)	8.93 [0.48, 165.70]
11 Infant hospitalisation for respiratory infection	1	2049	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.52, 1.39]
12 Preterm labour	1	2116	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.53, 1.59]
13 Miscarriage (24-28 weeks)	1	2116	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.14, 2.49]
14 Stillbirth	1	2116	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.73, 3.76]
15 Adverse events: at least one systemic reaction	1	353	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.87, 1.30]
16 Maternal hospitalisation for any infection	1	2116	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [0.94, 5.49]
17 Neonatal hospitalisation due to sepsis within 28 days of birth	1	2049	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.73, 3.50]

Analysis 2.10. Comparison 2 Viral influenza vaccine versus control, Outcome 10 Maternal hospitalisation for respiratory infection.

Review: Impact of *Haemophilus influenzae* type B (Hib) and viral influenza vaccinations in pregnancy for improving maternal, neonatal and infant health outcomes

Comparison: 2 Viral influenza vaccine versus control

Outcome: 10 Maternal hospitalisation for respiratory infection

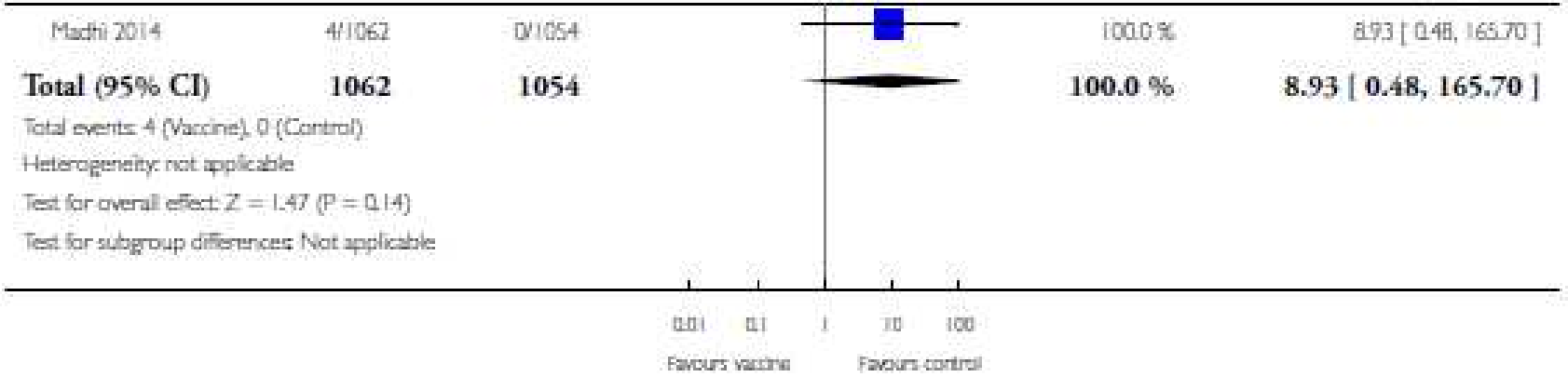
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Madhi 2014	4/1062	0/1054		100.0 %	8.93 [0.48, 165.70]
Total (95% CI)	**1062**	**1054**		**100.0 %**	**8.93 [0.48, 165.70]**

Total events: 4 (Vaccine), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.47 (P = 0.14)

Test for subgroup differences: Not applicable

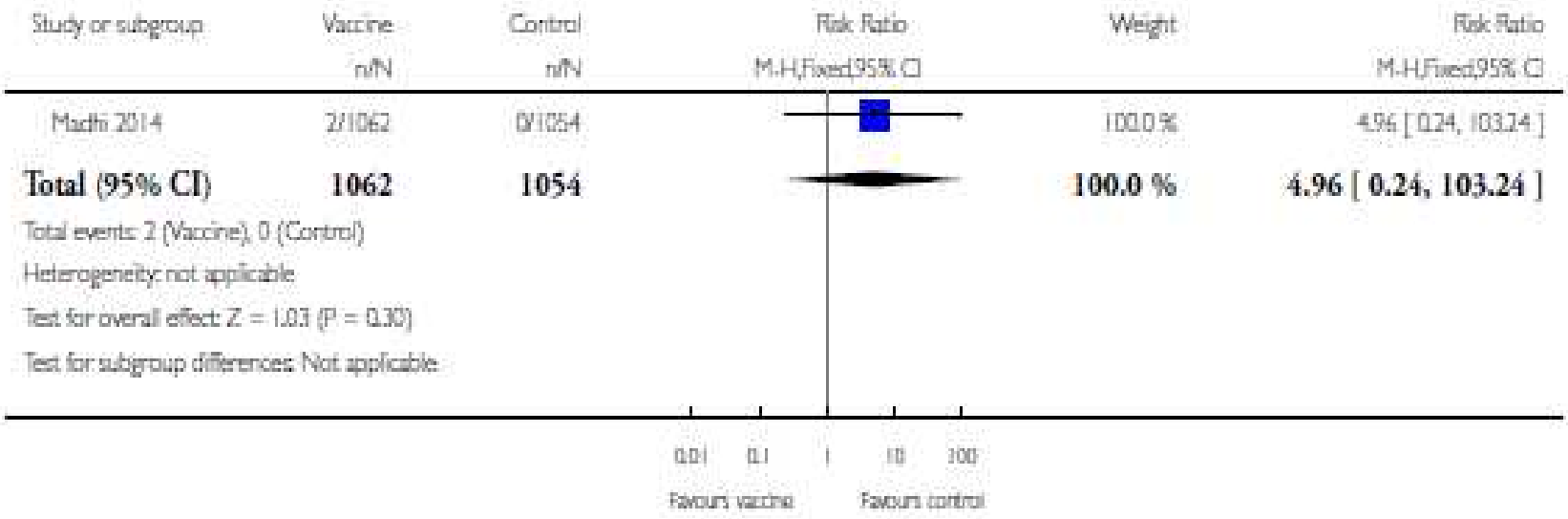


Analysis 2.1. Comparison 2 Viral influenza vaccine versus control, Outcome 1 Maternal death.

Review: Impact of *Haemophilus influenzae* type B (Hib) and viral influenza vaccinations in pregnancy for improving maternal, neonatal and infant health outcomes

Comparison: 2 Viral influenza vaccine versus control

Outcome: 1 Maternal death

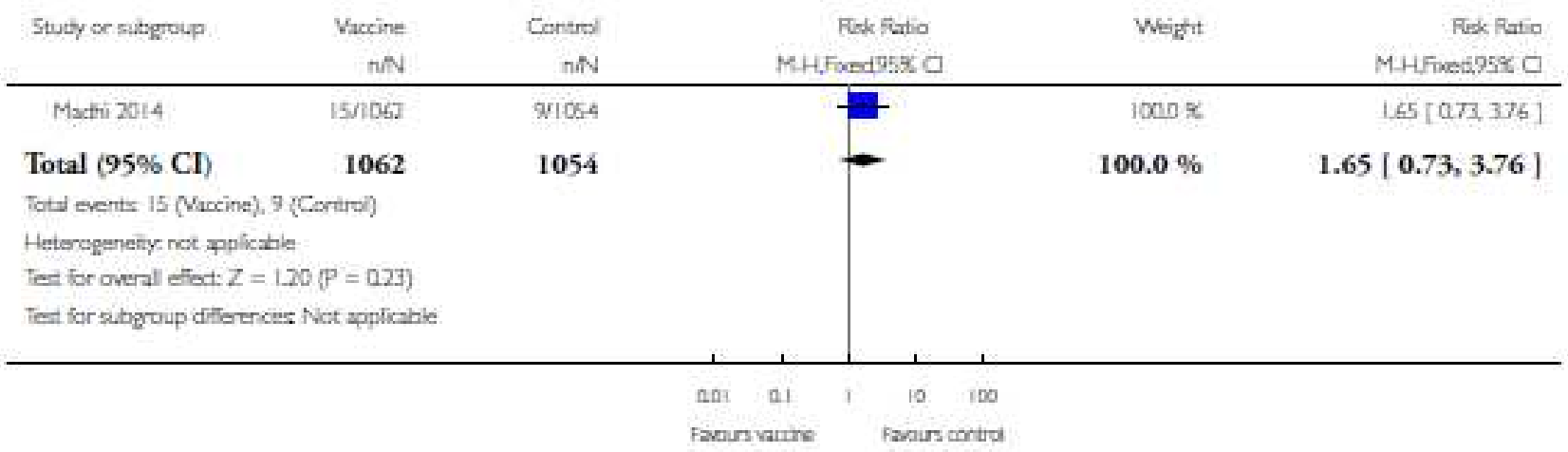


Analysis 2.14. Comparison 2 Viral influenza vaccine versus control, Outcome 14 Stillbirth.

Review: Impact of *Haemophilus influenzae* type B (Hib) and viral influenza vaccinations in pregnancy for improving maternal, neonatal and infant health outcomes

Comparison: 2 Viral influenza vaccine versus control

Outcome: 14 Stillbirth



SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Viral influenza vaccine compared with control in pregnancy for improving maternal, neonatal and infant health outcomes

Patient or population: Pregnant women aged 18 to 38 years and an estimated gestation of 20 to 36 weeks.
Settings: South Africa. (All data from a single trial, Madhi 2014).
Intervention: Viral influenza vaccine
Comparison: Placebo vaccine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo vaccine	Viral influenza vaccine				
Maternal death	Study population		RR 4.95 (0.24 to 103.24)	2116 (1 RCT)	⊕⊕⊕○ MODERATE [1]	
	0 per 1000	0 per 1000 (0 to 0)				
Infant death (up to 175 days)	Study population		RR 0.71 (0.37 to 1.37)	2049 (1 RCT)	⊕⊕⊕○ MODERATE [2]	
	21 per 1000	15 per 1000 (8 to 28)				
Perinatal death (stillbirth + death in first week of life)	Study population		RR 1.32 (0.73 to 2.38)	2083 (1 RCT)	⊕⊕⊕○ MODERATE [2]	
	18 per 1000	24 per 1000 (13 to 43)				
Any respiratory illness in women	Study population		RR 0.97 (0.91 to 1.04)	2116 (1 RCT)	⊕⊕⊕⊕ HIGH	
	632 per 1000	632 per 1000 (593 to 678)				
Any respiratory illness in infants	Study population		RR 1.01 (0.95 to 1.07)	2049 (1 RCT)	⊕⊕⊕⊕ HIGH	
	681 per 1000	688 per 1000 (647 to 729)				
Maternal hospitalisation for any infection	Study population		RR 2.27 (0.94 to 5.49)	2116 (1 RCT)	⊕⊕⊕○ MODERATE [1]	
	7 per 1000	15 per 1000 (6 to 35)				
Neonatal hospitalisation due to sepsis within 28 days of birth	Study population		RR 1.60 (0.73 to 3.50)	2049 (1 RCT)	⊕⊕⊕○ MODERATE [1]	
	10 per 1000	16 per 1000 (7 to 34)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** risk ratio

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Deaths From Seasonal Influenza Among Pregnant Women in the United States, 1998–2005

William M. Callaghan, MD, MPH, Susan Y. Chu, PhD, MSPH, and Denise J. Jamieson, MD, MPH

RESULTS:
4,693 pregnancy related deaths.
78 women died from influenza or pneumonia;
40 of these deaths occurred during an influenza season.
CONCLUSION:
On average, five possible influenza related deaths among pregnant women were reported per year before the emergence of pregnancy-related deaths due to the current H1N1 pandemic compared with the 28 laboratory-confirmed, pregnancy-related deaths reported for the first 4 months of the 2009 pandemic. This highlights the excess mortality among pregnant women resulting from this pandemic influenza virus.
(Obstet Gynecol 2010;115:919–23)

Review

Influenza vaccination in pregnancy: current evidence and selected national policies

Tippi K Mak, Punam Mangtani, Jane Leese, John M Watson, Dina Pfeifer

Lancet Infect Dis 2008; 8: 44-52

In several countries, pregnant women are recommended seasonal influenza vaccination and identified as a priority gro

11% of 1659 women in the 1993–94
infl uenza season in the UK had a four-fold rise in
antibody titres indicative of new infl uenza infections.9
Following the 1989–90 severe infl uenza season in the
UK, a one in 15 random sample of records of all fatal
cases was compared with a “regular” season in 1985–86.10
Using these methods, eight deaths in pregnant women
were counted in the severe season and two in the regular
season, suggesting a four times higher risk of death
during a severe infl uenza season. These fi gures were
extrapolated to an excess of 90 deaths in pregnant women
out of the 25 185 total excess deaths estimated in the
1989–90 infl uenza season