

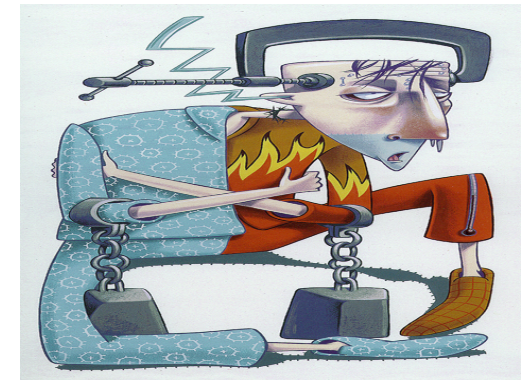
# Grippe grave et femmes enceintes

Matthieu Revest,  
Maladies Infectieuses et Réanimation Médicale, CHU Rennes



Gericco

La Rochelle, le 31 mars 2016



# Mme A, 32 ans

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- **Aucun ATCD, tabagisme = 0**
- **Non vaccinée contre la grippe**
- **A 28 semaines d'une première grossesse**
- **Toxo +, rubéole + (tunisienne)**
- **Consultation du médecin traitant le 13/02/2014:**
  - Courbatures, céphalées, myalgies
  - Toux non productive
  - Fièvre à 39°C
  - Mari: mêmes symptômes 3 jours avant

# Mme A, 32 ans

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- **Amoxicilline: 1g x 3/j**
- **17/02/2014 (J4):**
  - Persistance des symptômes
  - Amox remplacée par Cefpodoxime 100 mg x 2/j
- **18/02/2014:**
  - Apparition d'une dyspnée
  - Consulte aux urgences d'une clinique

# Mme A, 32 ans

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- **A l'entrée, cliniquement:**
  - T°: 39,5°C
  - FR: 40/min, SpO<sub>2</sub>: 85% en AA, tirage
  - Crépitants de base gauche avec souffle tubaire
  - TA: 100/60, FC: 130/min
  - Rythme cardiaque fœtal: 170/min, oscillant, pas de contraction
- **Bilan:**
  - Ionos, créat: N
  - NFS: N (Hb: 10,6 g/dL)
  - CRP: 102 mg/L
  - Ag<sub>u</sub> légionnelle et pneumocoque: négatifs

# Mme A, 32 ans

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- **Mise sous Amoxicilline 1 g x 3/j**
- **Transfert en gynécologie**
- **Transfert le lendemain matin en réanimation médicale**

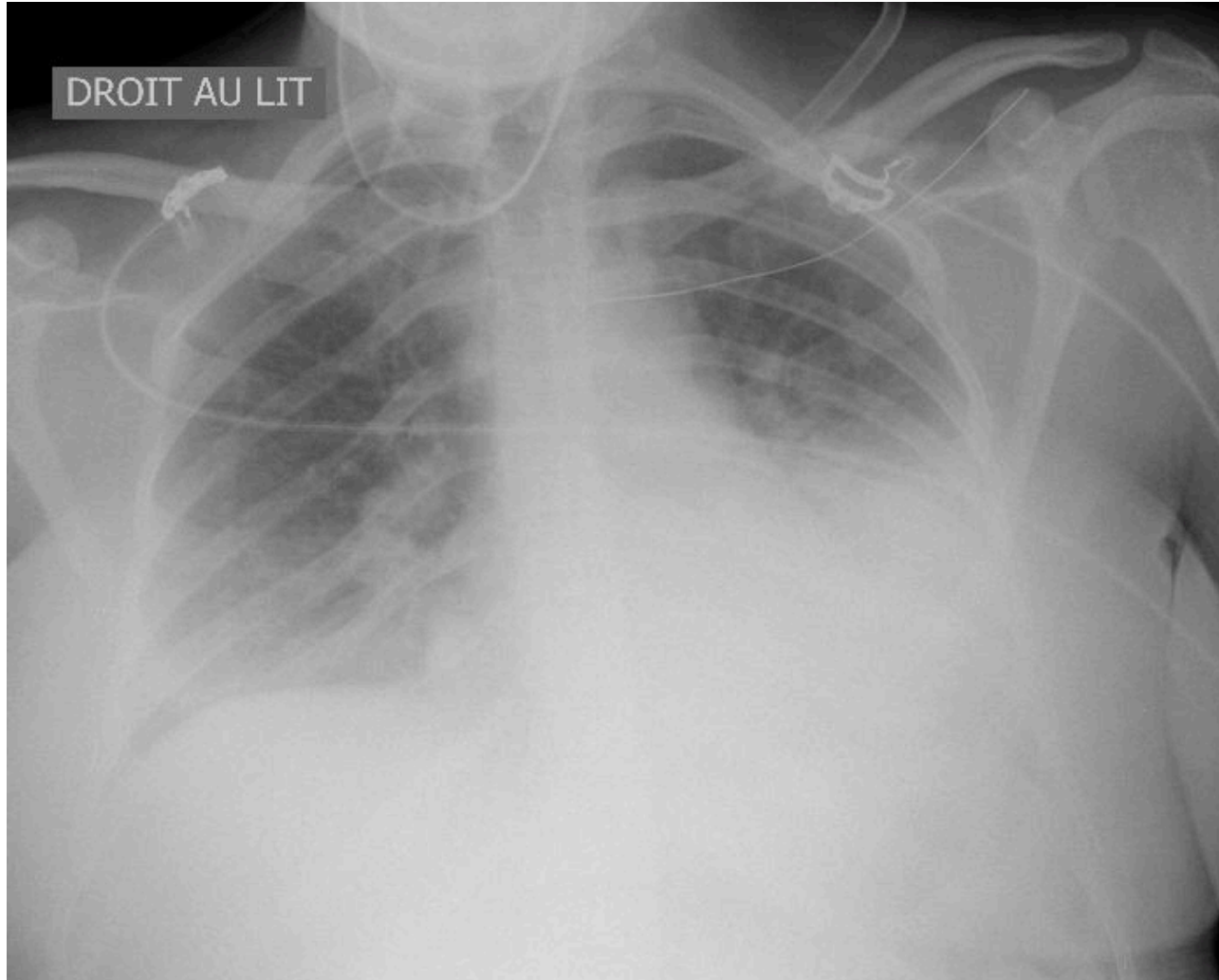
# Mme A, 32 ans

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- **A l'entrée, en réanimation:**
  - Apyrétique
  - FR: 42/min, SpO<sub>2</sub>: 91% sous 12 L/min O<sub>2</sub>, tirage
  - Crépitants de base gauche avec souffle tubaire
  - TA: 105/60, FC: 120/min, pas de signe d'hypoperfusion périphérique
  - Bilan foetal: RAS
- **Bilan:**
  - Ionos, créat: N
  - NFS: N (Hb: 10,6 g/dL)
  - GDS: PaO<sub>2</sub>: 64 mmHg, PaCO<sub>2</sub>: 38 mmHg, pH: 7,47, lactate: 2,1 mmol/L

# Mme A, 32 ans

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A l'entrée en réa

# Mme A, 32 ans

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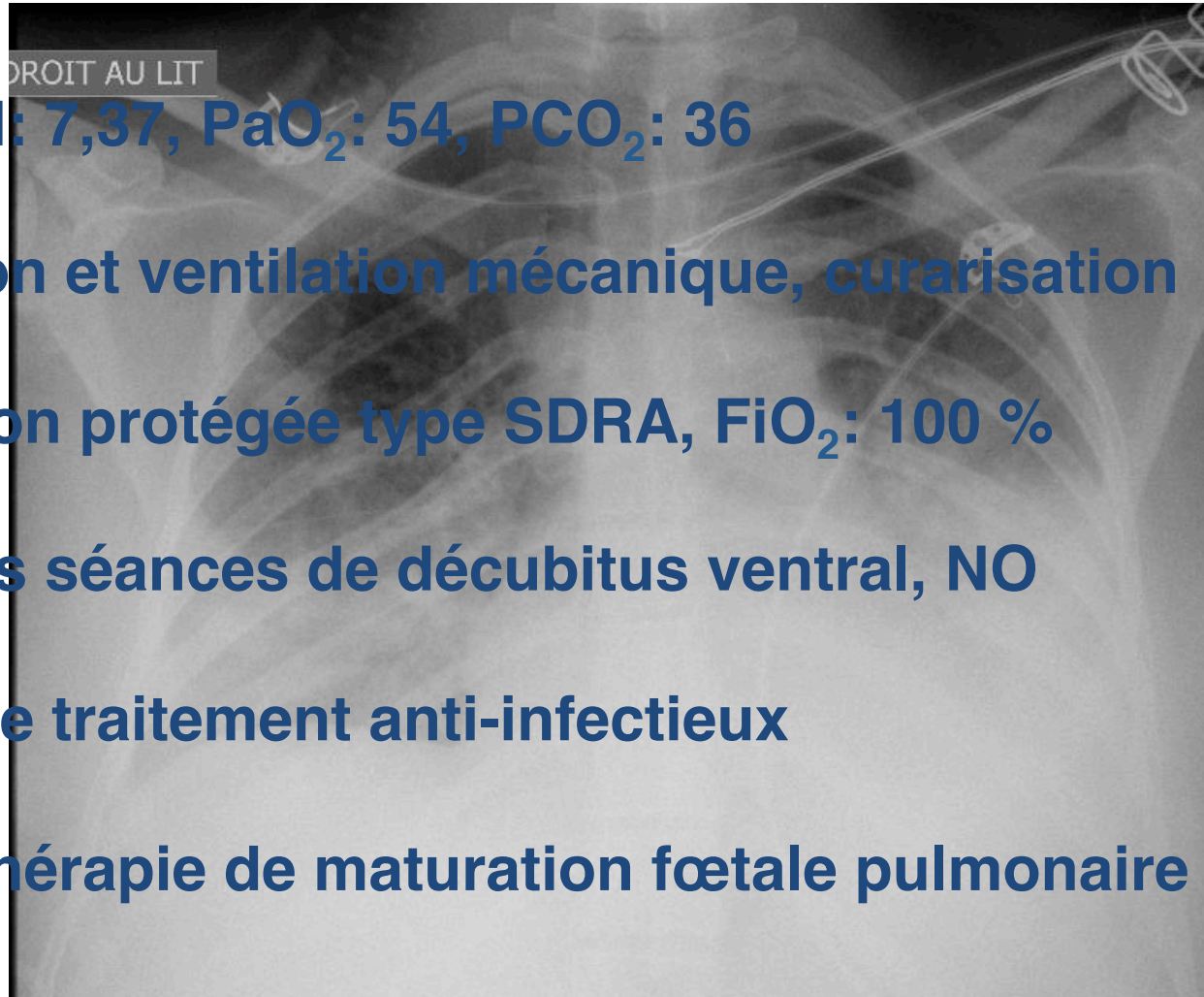
- **Traitement initié:**
  - Céfotaxime – Clarithromycine
  - Oseltamivir
- **Pas de prélèvement endo-bronchique possible**
- **Prélèvement naso-pharyngé: PCR Grippe A +**
- **Poursuite du traitement anti-infectieux à l'identique**
- **Optiflow 50 L/min, FiO2 100%**



# Mme A, 32 ans

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J + 1: épuisement respiratoire

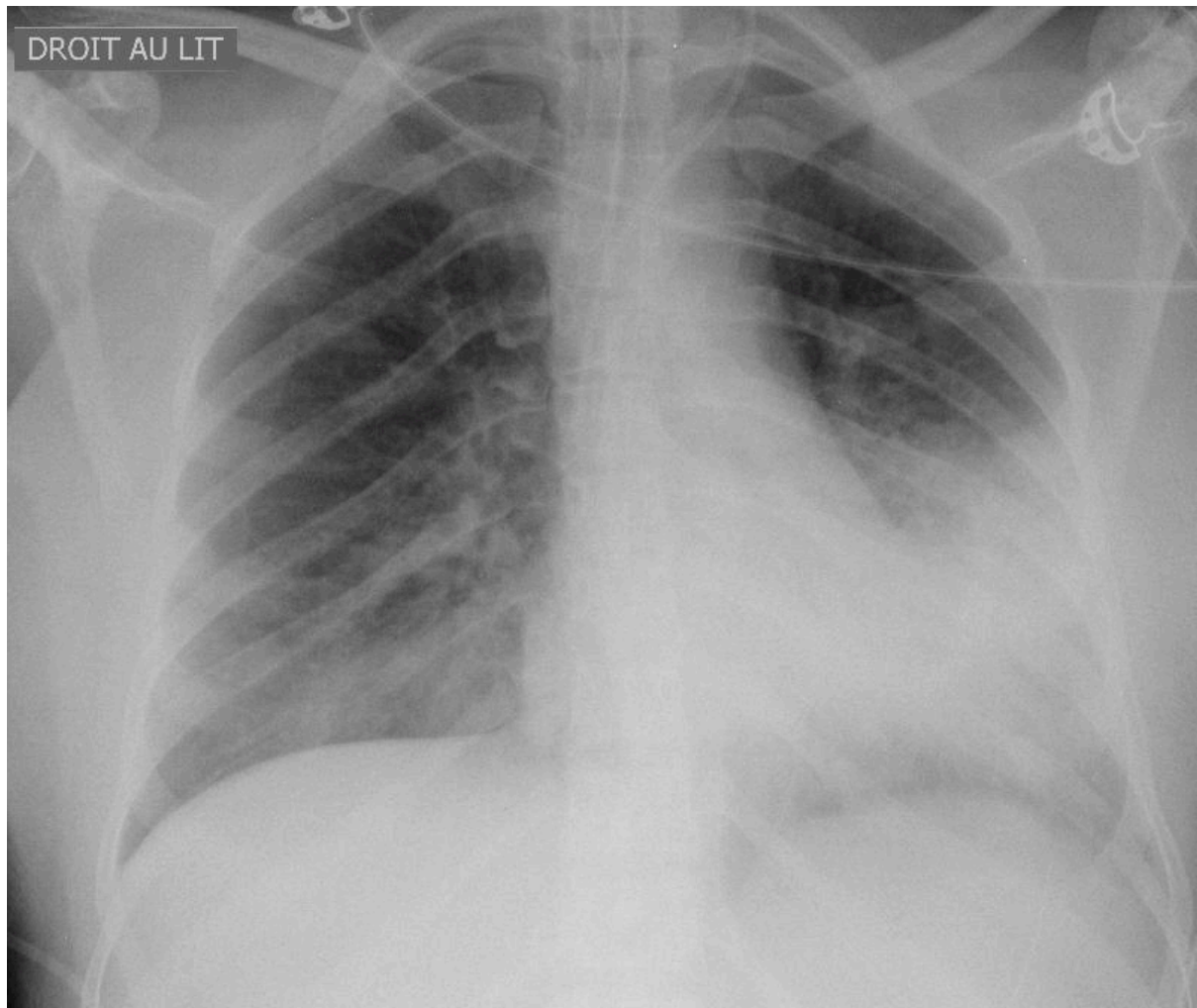


- **GDS: PH: 7,37, PaO<sub>2</sub>: 54, PCO<sub>2</sub>: 36**
- **Intubation et ventilation mécanique, curarisation**
- **Ventilation protégée type SDRA, FiO<sub>2</sub>: 100 %**
- **Plusieurs séances de décubitus ventral, NO**
- **Poursuite traitement anti-infectieux**
- **Corticothérapie de maturation foétale pulmonaire**

# Mme A, 32 ans

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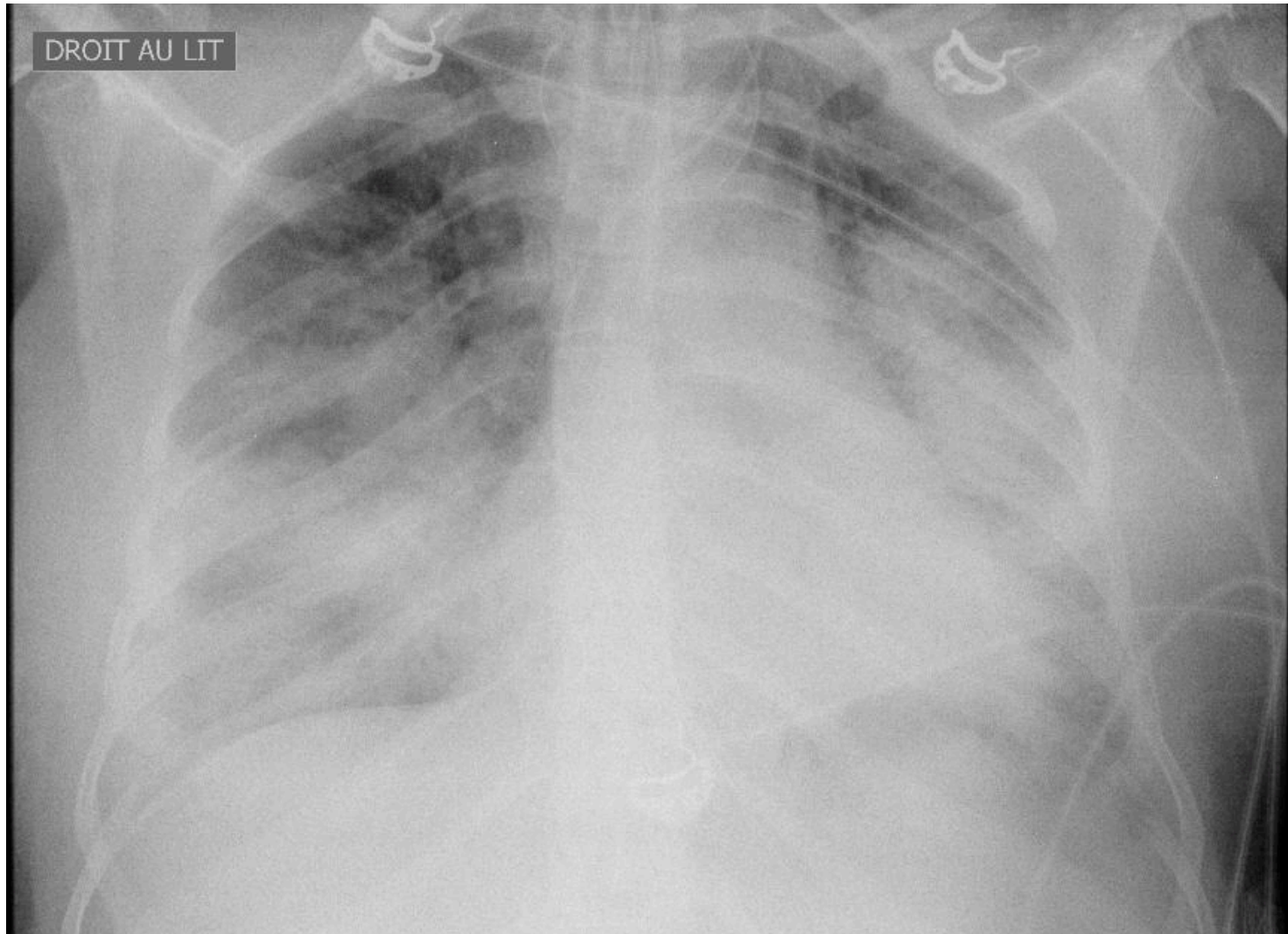
J + 3



# Mme A, 32 ans

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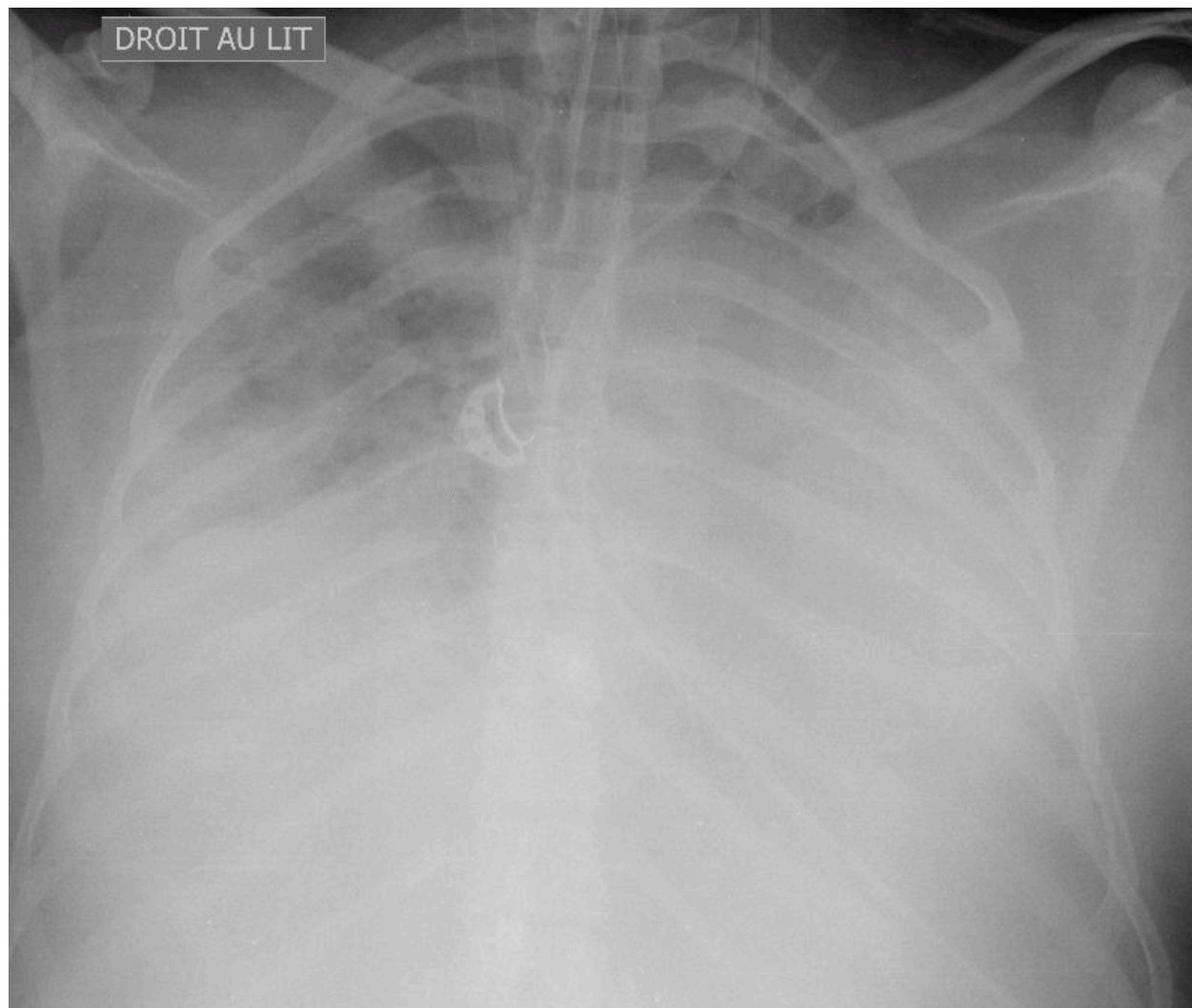
J + 6



# Mme A, 32 ans

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J + 8

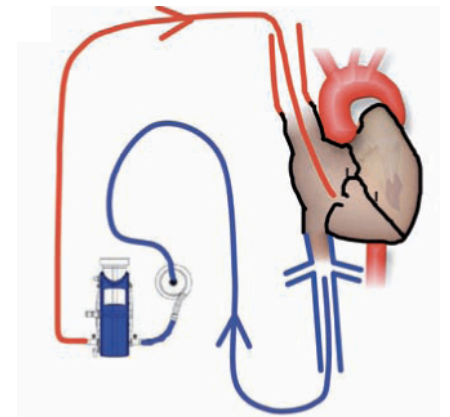


# Mme A, 32 ans

---

J + 8

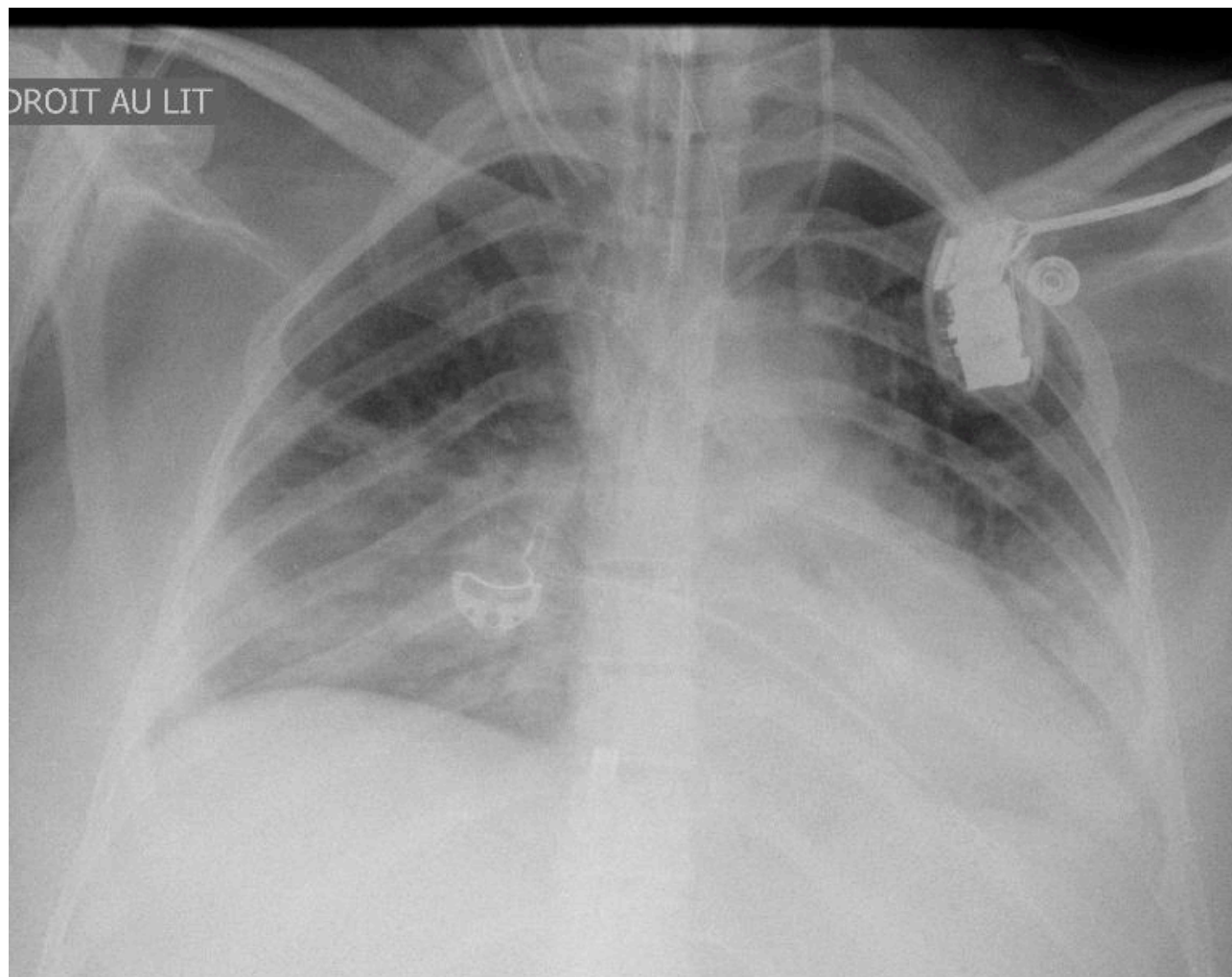
- Mise en place d'une ECMO veino-veineuse continue
- En concertation avec les obstétriciens
- Arrêt des ATB à J8
- Poursuite oseltamivir car PCR grippe restant positive (15 jours au total)



# Mme A, 32 ans

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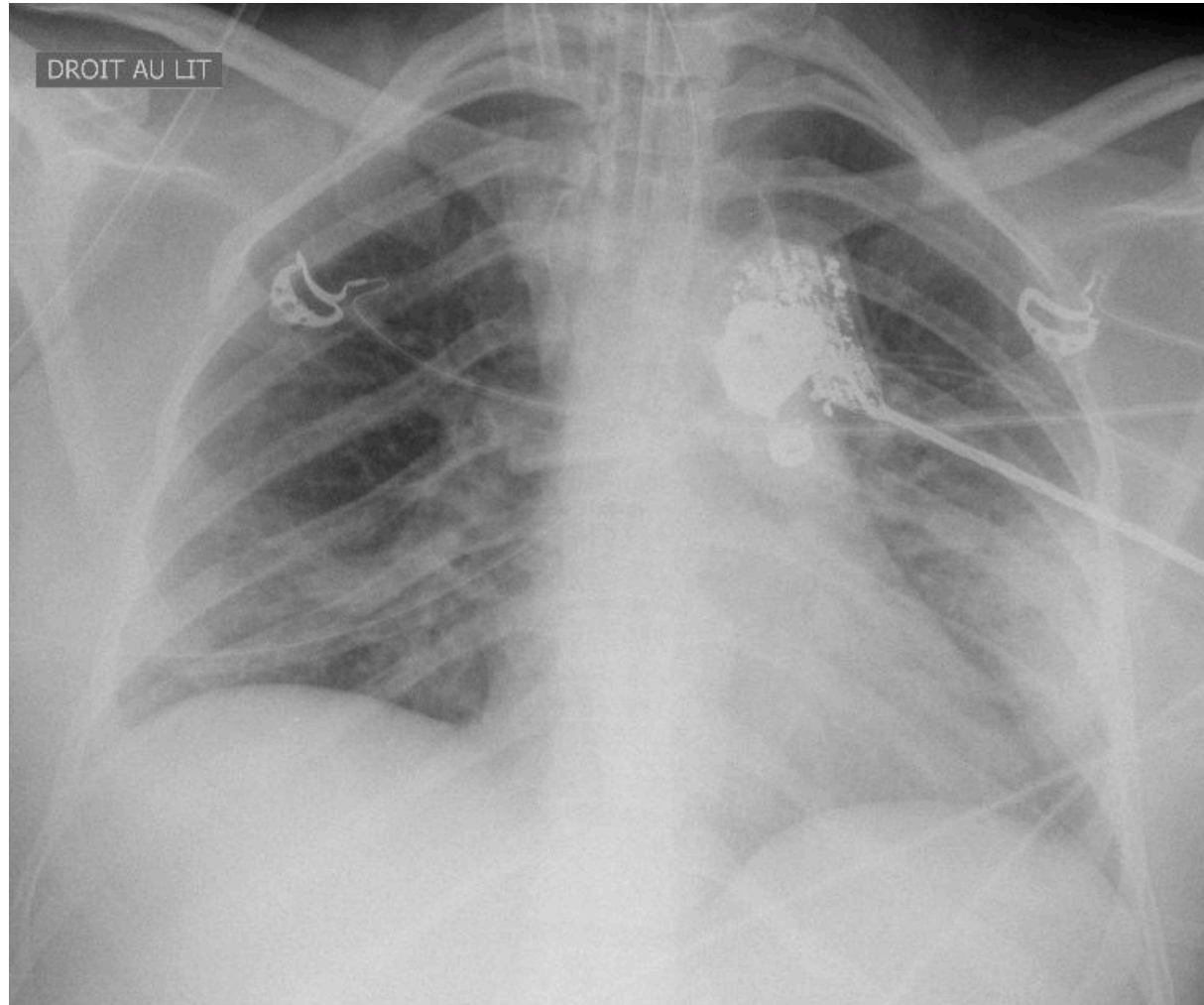
J + 15



# Mme A, 32 ans

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J + 23



# Mme A, 32 ans

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## Evolution

- 15 jours oseltamivir
- 12 jours d'ECMO
- 25 jours de ventilation mécanique
- Sortie de réanimation à J31
- Sortie d'hospitalisation sans séquelle à J43
- Naissance à 38,6 SA d'un garçon de 2,72 kg en bonne santé !





# Grippe et femmes enceintes

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- **Grippe saisonnière<sup>1,2</sup>:**
  - Risque de formes graves
  - Complications cardio-respiratoires plus fréquentes
- **Pandémies avant 2009:**
  - Grippe espagnole (1918): 1350 femmes enceintes<sup>3</sup>
    - **50 %**: pneumonies
    - Dont plus de la moitié sont décédées (3ème trimestre)
  - Grippe asiatique (1957): **50 %** des décès des femmes en âge de procréer touchaient des femmes enceintes<sup>4</sup>

<sup>1</sup>Dodds, CMAJ, 2007

<sup>2</sup>Neuzil, Am J Epidemiol, 1998

<sup>3</sup>Harris, JAMA, 1919

<sup>4</sup>Freeman, Am J Obstet Gynecol, 1959

Décès A(H1N1)						
Pays	Nombre de décès confirmés	Sexe (% F)	Age médian	% co-morbidité	Co-morbidité et facteurs de risque les plus fréquents	Grossesse (**)
Argentine	439 (28/08/09)	45%	34 ans	19% (56/296)	Path. respiratoires (7,1%), path. cardio-vasculaires (2,5%), cancer (1,5%), IS (1,5%), VIH (1%)	5,5% (16/296)
Australie	106 (15/08/09)	50%	56 ans		Origine indigène (13% (14/106)), cancer, diabète et obésité morbide	4% (4/106)
Bolivie	13	31%	29 ans	50% (6/12)	Path. hématologiques, IS, path. métaboliques	
Brésil	368			50% (185/368)	Path. métaboliques, path. respiratoires, cardiopathies, IS	12,5% (46/368)
Canada (Québec)	24	71%	53 ans	au moins 71% (17/24)	Path. pulmonaires (45%) et cardiaques (30%), IS (32%), diabète (29%), > 60 ans (38%), origine amérindienne	8% (2/24)
Chili	132	48%	49 ans	61% (78/128)		
Costa Rica	28	54%	41 ans		Obésité (43%), diabète (25%), asthme (21%), BPCO (11%), HTA (23/23)	11%
Ecosse	5					
Etats-Unis (Californie)	104					
Malaisie	68					
Mexique	170	49%	[30-34] ans		Path. métaboliques (35%), tabagisme (23%), path. cardiovasculaires (16,5%), path. respiratoires (9%)	
Pérou	62	50%	35 ans	82% (51/62)	Obésité (16%), HTA (14%), cardiopathie (10%), troubles neurologiques (10%), path. pulmonaire (8%)	

Décès dans le monde en septembre 2009, source INVS

# H1N1 2009 influenza virus infection during pregnancy in the USA

*Denise J Jamieson, Margaret A Honein, Sonja A Rasmussen, Jennifer L Williams, David L Swerdlow, Matthew S Biggerstaff, Stephen Lindstrom, Janice K Louie, Cara M Christ, Susan R Bohm, Vincent P Fonseca, Kathleen A Ritger, Daniel J Kuhles, Paula Eggers, Hollianne Bruce, Heidi A Davidson, Emily Lutterloh, Meghan L Harris, Colleen Burke, Noelle Cocoros, Lyn Finelli, Kitty F MacFarlane, Bo Shu, Sonja J Olsen, and the Novel Influenza A (H1N1) Pregnancy Working Group\**

[www.thelancet.com](http://www.thelancet.com) Vol 374 August 8, 2009

- Du 15 avril au 18 mai 2009 aux USA
- **34** femmes enceintes atteintes de grippe A
  - 0,62% des cas confirmés (34/5469)
  - 1 pour 100 000 femmes enceintes
- **11 hospitalisées** (32 %) vs 4,2 % de la population générale
- Taux d'hospitalisation: **RR= 4,3**
  - 0,32 pour 100 000 femmes enceintes
  - 0,076 pour 100 000 dans la population générale
  - 0,04 pour 100 000 chez les femmes en âge de procréer non enceintes
- Décès:
  - 6 femmes enceintes sur 42 décès (13% des décès)
  - Pneumonie grippale

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

JAMA, April 21, 2010—Vol 303, No. 15

Alicia M. Siston, PhD  
for the Pandemic H1N1 Influenza  
in Pregnancy Working Group

Outcome	No. (%) of Pregnant Women
<b>All Pregnant Women (n = 788)</b>	
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 <sup>b</sup>	
Yes (<37 wk gestation)	51 (30.2)
No (≥37 wk gestation)	118 (69.8)

## Among Hospitalized Pregnant Women (n = 509)

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



# Severe 2009 A/H1N1v influenza in pregnant women in Spain\*

Crit Care Med 2011 Vol. 39, No. 5

Enrique Maraví-Poma, MD, PhD, HonProf, FCCS, ERC, FCCM; Ignacio Martin-Loeches, MD, PhD;

Table 2. Results of the logistic multivariate analysis in women aged 15–44 yrs admitted to the intensive care unit for A/H1N1v influenza, in relation to primary pneumonia and death

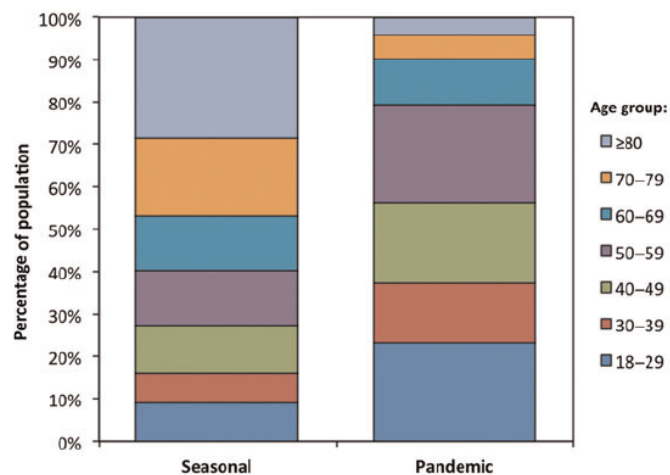
Diagnosis or Outcome	Odds Ratio (95% Confidence Interval) <sup>a</sup>	<i>p</i>
Primary pneumonia (n = 231)		
Variables in the model		
Pregnancy	4.90 (1.40–17.19)	.013
Obesity	2.03 (.93–4.41)	.076
Time from onset influenza symptoms to hospital admission (days)	1.30 (1.08–1.56)	.005
Asthma	0.34 (.16–.74)	.007
Death (n = 155)		
Variables in the model		
Acute Physiology and Chronic Health Evaluation II	1.15 (1.07–1.24)	<.001
Obesity	2.78 (1.04–7.44)	.042
Pregnancy	1.86 (.61–5.73)	.279

20% des femmes en  
âge de procréer  
admises en  
réanimation étaient  
enceintes

# Complications Among Adults Hospitalized With Influenza: A Comparison of Seasonal Influenza and the 2009 H1N1 Pandemic

Clinical Infectious Diseases 2014;59(2):166–74

Carrie Reed,<sup>1</sup> Sandra S. Chaves,<sup>1</sup> Alejandro Perez,<sup>1</sup> Tiffany D'Mello,<sup>1</sup> Pamala Daily Kirley,<sup>2</sup> Deborah Aragon,<sup>3</sup>



**Table 1. Characteristics of Adults Hospitalized With Laboratory-Confirmed Seasonal or Pandemic Influenza**

Characteristic	Seasonal 2005–2009 (n = 5270)		Pandemic 2009–2010 (n = 4962)		P Value
	No.	%	No.	%	
Pregnant	165	3.1	430	8.7	<.01

# French Experience of 2009 A/H1N1v Influenza in Pregnant Women



PLOS ONE October 2010 | Volume 5 | Issue 10 | e13112

Grégory Dubar<sup>1</sup>, Elie Azria<sup>2</sup>, Antoine Tesnière<sup>1</sup>, Hervé Dupont<sup>3</sup>, Camille Le Ray<sup>4</sup>, Thomas Baugnon<sup>5</sup>, Sophie Matheron<sup>6</sup>, Dominique Luton<sup>7</sup>, Jean-Christophe Richard<sup>8</sup>, Odile Launay<sup>9</sup>, Vassilis Tsatsaris<sup>4</sup>, François Goffinet<sup>4</sup>, Alexandre Mignon<sup>1\*</sup>, for the French Registry on 2009 A/H1N1v during pregnancy<sup>¶</sup>

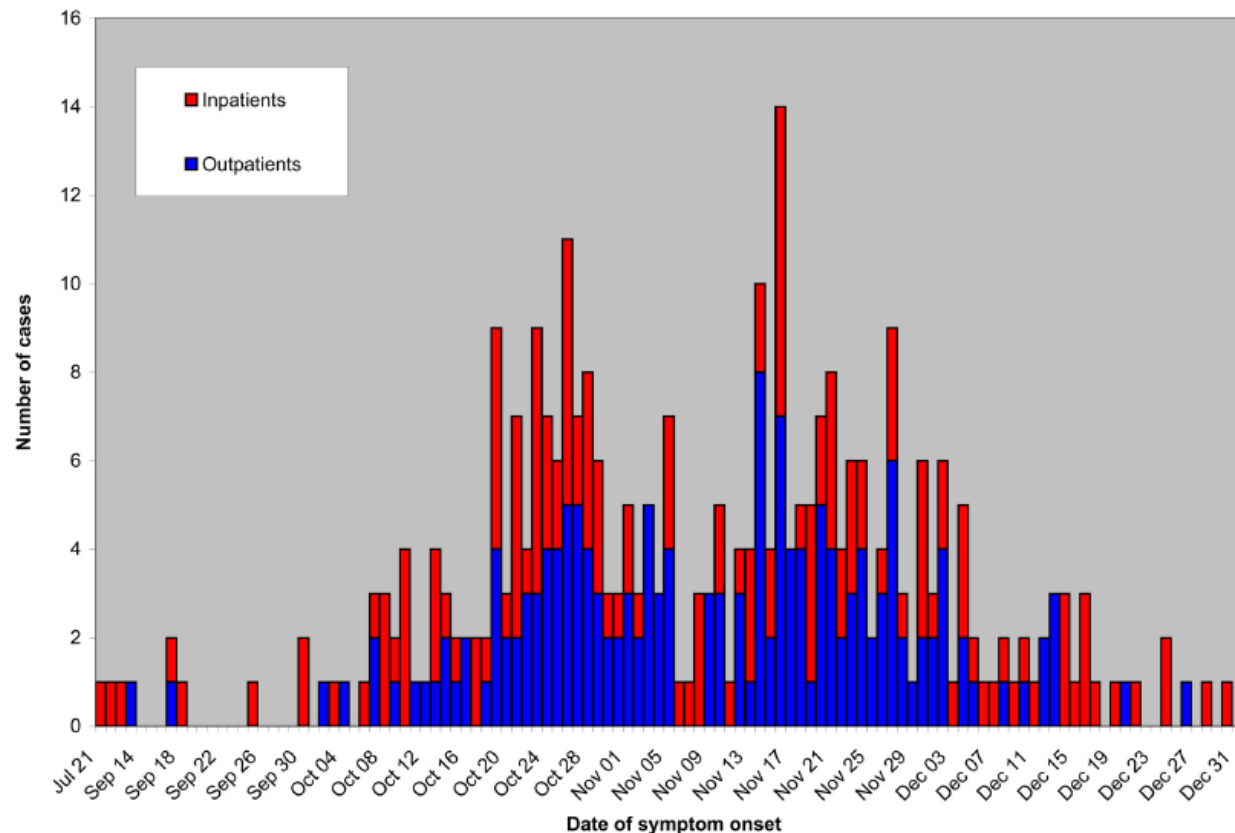


Figure 1. Temporal repartition of laboratory-confirmed 2009 A/H1N1v infection among pregnant women in the French registry according to patient status.

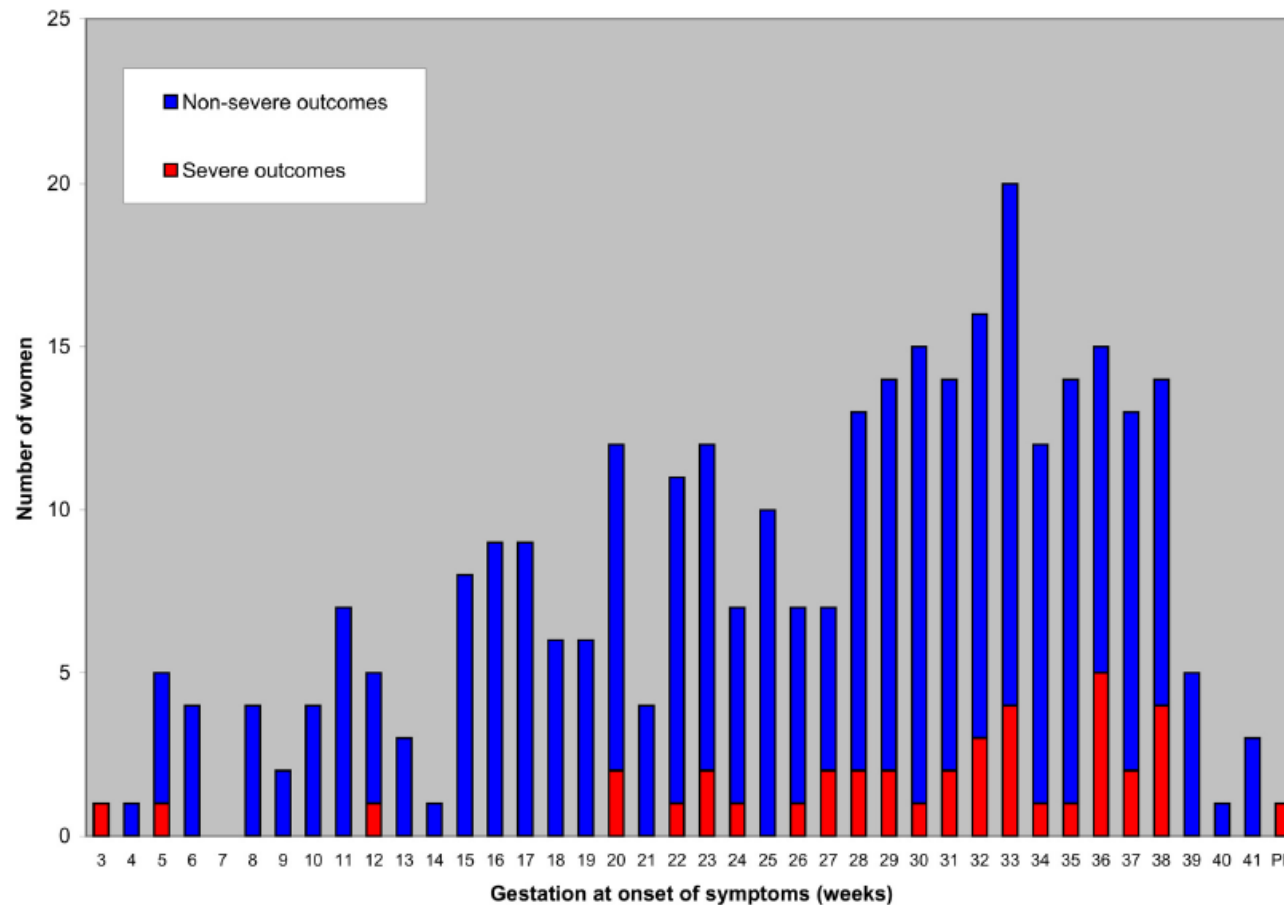
# French Experience of 2009 A/H1N1v Influenza in Pregnant Women



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$P < 0,001$

Figure 2. Gestational age at onset of symptoms according to the severity of symptoms.



# French Experience of 2009 A/H1N1v Influenza in Pregnant Women



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**Table 1.** Characteristics of pregnant or postpartum women with 2009 A/H1N1v influenza infection.

	ICU patients (severe) (n = 40)	Hospitalized non-severe patients (moderate) (n = 111)	Outpatients (mild) (n = 164)	p value
Chronic pre-existing disease	23 (58)	32 (29)	44 (27)	<0.001

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	ICU patients (severe) (n = 40)	Hospitalized non severe patients (moderate) (n = 111)	Outpatients (mild) (n = 164)	p value
<b>Antiviral treatment</b>	40 (100)	109 (98)	150 (91)	0.01
≤2 days	18 (45)	87 (80)	132 (88)	
3-5 days	10 (25)	16 (15)	13 (9)	<0.001
>5 days	12 (30)	6 (6)	5 (3)	

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## Ultimate respiratory care:

Oxygen therapy	15 (38)
Non-invasive ventilation	5 (13)
Mechanical ventilation (with or without ECMO)	20 (50)
ECMO	11 (28)
Median duration of ECMO – days [min-max]	8 [4–38]
Median length of ventilation, days [min-max]	13 [2–55]
Median ICU length of stay, days [min-max]	10 [2–80]
Death	3 (8)

**Table 5. Perinatal outcome.**

	ICU patients (severe) (n = 33)	Hospitalized non-severe patients (moderate) (n = 66)	Outpatients (mild) (n = 47)	p value
<b>A. PREGNANCY OUTCOME</b>				
Vaginal delivery (live birth)	11 (33)	48 (73)	40 (85)	<0.001
Cesarean delivery (live birth)	20 (61)	16 (24)	5 (11)	<0.001
Intra-uterine fetal death	1 (3)	1 (2)	0 (0)	NS
<b>B. NEONATAL OUTCOME*</b>				
Median birth weight - grams [min-max]	2780 [1215–4110]	3270 [550–4670]	3350 [1520–4380]	0.01
<1500	2/31 (6)	1/63 (2)	0 (0)	
1500–2499	12/31 (39)	6/63 (10)	1/44 (2)	
≥2500	17/31 (55)	56/63 (89)	43/44 (98)	
Newborn resuscitation in the L&D unit	15/31 (48) <sup>†,‡</sup>	8/61 (13)	3/45 (7)	<0.001
Admission to neonatal intensive care unit	14/31 (45)	4/61 (7)	1/45 (2)	<0.001
Neonatal death (in the L&D unit or in the neonatal intensive care unit)	1/31 (3)	1/61 (2)	0/45 (0)	NS

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**Table 4.** Impact of coexisting illnesses and the timing of antiviral treatment on admission to an intensive care unit.

	Adjusted OR	95% CI	p value
Coexisting illness	5.11	2.22–11.78	<0.001
Delay of treatment <3 days after symptom onset	Reference	-	-
Delay of treatment 3–5 days after symptom onset	4.78	1.89–12.09	0.001
Delay of treatment >5 days after symptom onset	61.24	14.35–261.25	<0.001

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

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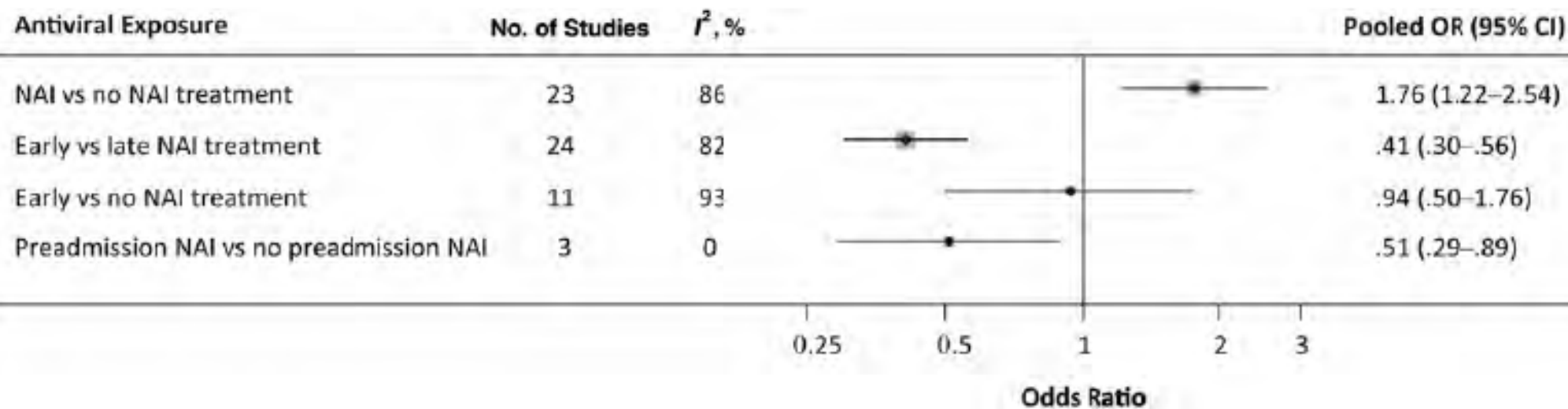
**Table 3.** Comparison of Maternal Outcomes by Timing of Antiviral (Oseltamivir or Zanamivir) Treatment<sup>a</sup>

Treatment	No. (%) of Women							
	Hospital Admission <sup>b</sup>		ICU Admission Among Hospitalized Patients <sup>c</sup>		Mechanical Ventilation Among Hospitalized Patients <sup>c</sup>		Maternal Death <sup>b</sup>	
	Yes (n = 509)	No (n = 263)	Yes (n = 115)	No (n = 350)	Yes (n = 77)	No (n = 332)	Yes (n = 30)	No (n = 662)
<b>Treatment Timing Comparisons</b>								
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 <sup>e</sup>		.03 <sup>e</sup>	
>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 <sup>e</sup>		.006 <sup>e</sup>	

# Impact of Neuraminidase Inhibitor Treatment on Outcomes of Public Health Importance During the 2009–2010 Influenza A(H1N1) Pandemic: A Systematic Review and Meta-Analysis in Hospitalized Patients

The Journal of Infectious Diseases 2013;207:553–63

Stella G. Muthuri,<sup>1</sup> Puja R. Myles,<sup>1,a</sup> Sudhir Venkatesan,<sup>1</sup> Jo Leonardi-Bee,<sup>2</sup> and Jonathan S. Nguyen-Van-Tam<sup>1</sup>



# Antivirals for Treatment of Influenza

*Ann Intern Med.* 2012;156:512-524.

## A Systematic Review and Meta-analysis of Observational Studies

Jonathan Hsu, BHSc; Nancy Santesso, MLIS, RD; Reem Mustafa, MD, MPH; Jan Brozek, MD; Yao Long Chen, MSc; Jessica P. Hopkins, MD, MHSc; Adrienne Cheung, BHSc; Gayane Hovhannisyan, MD; Liudmila Ivanova, MD, MPH, MSc; Signe A. Flottorp, MD, PhD; Ingvil Sæterdal, MSc, PhD; Arthur D. Wong, BHSc; Jinhui Tian, MSc; Timothy M. Uyeki, MD, MPH, MPP; Elie A. Akl, MD, MPH, PhD; Pablo Alonso-Coello, MD, PhD; Fiona Smaill, MB, ChB, MSc; and Holger J. Schünemann, MD, MSc, PhD

*Table 2.* GRADE Evidence Profile for Oral Oseltamivir Received Within or After 48 Hours

Outcome	Quality Assessment		Summary of Findings				
	Patients (Studies), n*	Overall Quality of Evidence	Study Event Rates, n/N (%)		Relative Effect (95% CI)	Anticipated Absolute Effects	
			Oseltamivir Received >48 h	Oseltamivir Received ≤48 h		Risk With Oseltamivir Received >48 h	Absolute Effect With Oseltamivir Received ≤48 h (95% CI)
Mortality	2141 (8)	Very low due to imprecision and risk of bias†§	1163	978	OR, 0.33 (0.12–0.86)	200 deaths per 1000 patients	124 fewer deaths (23 to 169 fewer deaths) per 1000 patients
Hospitalization	597 (2)	Very low due to risk of bias†§	144/316 (45.6)	151/281 (53.7)	OR, 0.52 (0.33–0.81)	456 hospitalizations per 1000 patients	152 fewer hospitalizations (52 to 239 fewer hospitalizations) per 1000 patients
ICU admission, mechanical ventilation, or respiratory failure	1102 (4)	Very low due to risk of bias†§	120/474 (25.3)	44/628 (7)	OR, 0.22 (0.15–0.33)	253 admissions per 1000 patients	184 fewer admissions (153 to 205 fewer admissions) per 1000 patients

# Benefit of Early Initiation of Influenza Antiviral Treatment to Pregnant Women Hospitalized With Laboratory-Confirmed Influenza

The Journal of Infectious Diseases® Sous presse

Ikwo K. Oboho,<sup>1,2a</sup> Carrie Reed,<sup>2</sup> Paul Gargiullo,<sup>2</sup> Michelle Leon,<sup>2</sup> Deborah Aragon,<sup>3</sup> James Meek,<sup>4</sup> Evan J. Anderson,<sup>5,6</sup> Patricia Ryan,<sup>7</sup> Ruth Lynfield,<sup>8</sup> Craig Morin,<sup>8</sup> Marisa Bargsten,<sup>9</sup> Shelley M. Zansky,<sup>10</sup> Brian Fowler,<sup>11</sup> Ann Thomas,<sup>12</sup> Mary Lou Lindegren,<sup>13</sup> William Schaffner,<sup>13</sup> Ilene Risk,<sup>14</sup> Lyn Finelli,<sup>2a</sup> and Sandra S. Chaves<sup>2</sup>

Saisons 2010-2014  
 865 Femmes enceintes, 63 sévères  
 Risque plus élevé de sévère si T3 ( $P = 0,04$ )

**Table 3. Clinical Outcomes Among Pregnant Women Hospitalized With Laboratory-Confirmed Influenza During the 2010–2014 Influenza Seasons, Overall and by Disease Severity**

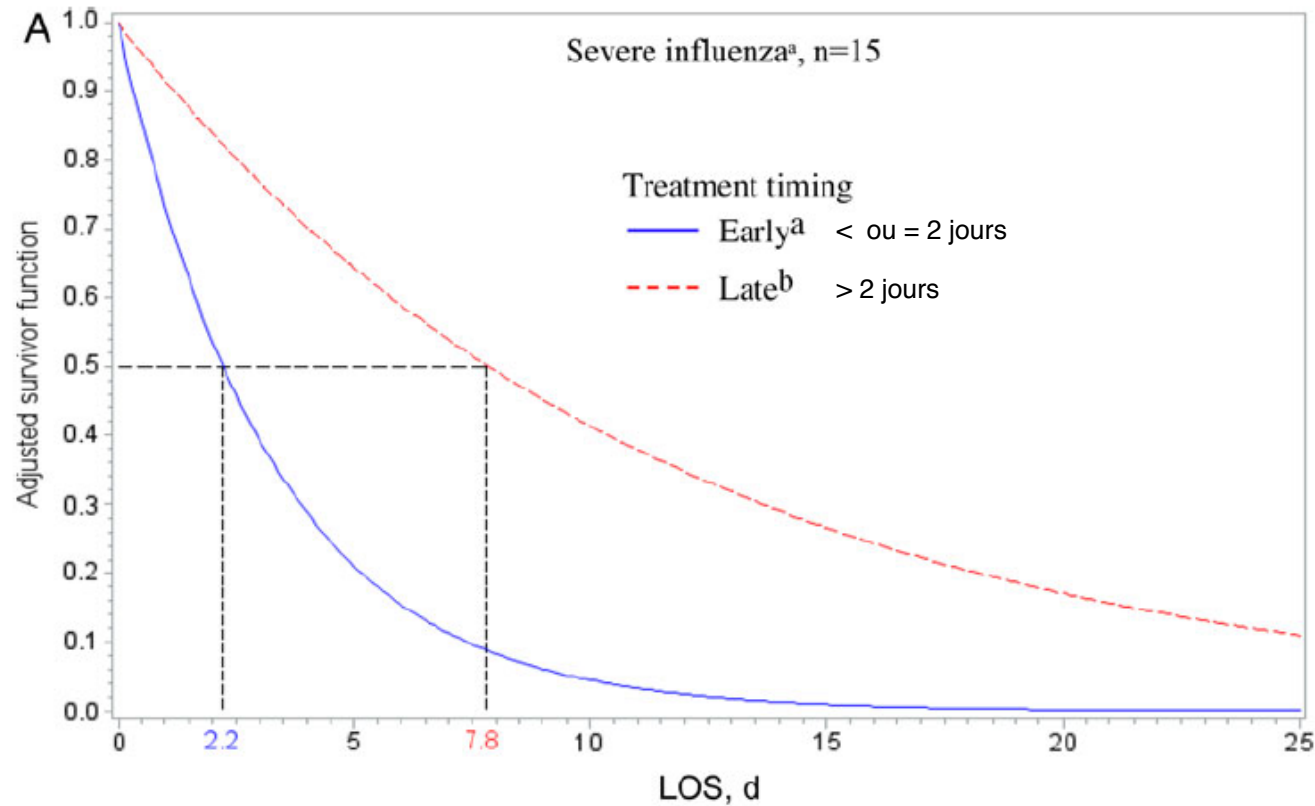
Characteristic	Overall (n = 865)	Severe <sup>a</sup> (n = 63)	Nonsevere (n = 802)	<i>P</i> Value <sup>b</sup>
Live birth	188 (22)	7 (11)	181 (23)	<b>.03</b>
Preterm delivery, proportion (%) <sup>c</sup>	41/188 (22)	5/7 (71)	36/181 (20)	<b>&lt;.01</b>
Fetal loss	4 (0.4)	3 (5)	1 (0.1)	<b>&lt;.01</b>
LOS, d, median (IQR)	2 (1–3)	5 (2–7)	2 (1–3)	<b>&lt;.01</b>
ICU admission	38 (4)	38 (60)	NA <sup>d</sup>	
Mechanical ventilation	16 (2)	16 (25)	NA <sup>d</sup>	
Death	4 (<1)	4 (6)	NA <sup>d</sup>	



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# Conclusions

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- **Un sur-risque probable**
- **Surtout au 3<sup>ème</sup> trimestre**
- **Surtout si autre comorbidité**
- **Plus important au moment de la grippe pandémique**
- **Intérêt du traitement par Oseltamivir dans les 48 heures**
- **Pronostic foetal impacté**
- **Mais des résultats assez bons**