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Strong Immune Response to a Monovalent non-Adjuvanted 2009 Influenza A/H1N1v Vaccine in Pregnant Women

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Background

- Physiological adaptations in the cardiac, respiratory, and immune systems predispose pregnant and post-partum women to severe illness for influenza, particularly pandemic flu

- Seasonal inactivated vaccine
  - is safe and immunogenic in pregnant women (*Englund J. Vaccine, 2003),*
  and reduces influenza illness in infants up to six months of age (*Zaman K, et al. N Engl J Med, 2008)*

- The CDC therefore recommends seasonal inactivated influenza vaccine in all pregnant women during the second or third trimester of pregnancy

- However, in pregnant women, there are:
  - only few data on immunogenicity of seasonal flu vaccine,
  - no available data on immunogenicity of pandemic flu vaccine

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Methods

- A phase 2 pilot clinical trial was conducted in five centers in France
- **Main objective : to evaluate the immunogenicity of a single 15 µg dose of a non-adjuvanted inactivated 2009 influenza A/H1N1v vaccine in pregnant women in the second or third trimester**
- *Inclusion criteria*:
  - aged 18–45
  - between 22 and 32 weeks gestation.

  inclusion after the ultrasonography for pregnancy monitoring planned at 21–23 weeks gestation to exclude malformation
- *Main exclusion criteria*;
  - allergy to eggs or other components in the vaccine,
  - history of premature delivery, or eclampsia
  - history of severe reaction following previous influenza vaccine,
  - H1N1 influenza during the last 6 months,
  - febrile episode within one week prior to vaccination

Study Design

Stratification:

***Group 1*: 22 – 26 weeks gestation**

***Group 2*: 27 – 32 weeks gestation**

Inclusion
Vaccination
(IM)

D0

Follow-up
Visits + samples

D0 **D21** **D42** **Delivery** **Delivery + 3 months**

Delivery: maternal and umbilical samples
Safety follow up of mothers and infants

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Characteristics of the women at inclusion

	Group 1 n=58	Group 2 n=49	All women n=107
Age, yr			
Median	31.9	32.2	32.0
(IQR)	(30.2 - 36.4)	(30.0 - 36.4)	(30.1 - 36.4)
Weeks gestation			
Median	23.0	30.0	26.0
(IQR)	(22.0 - 25.0)	(28.0 - 31.0)	(23.0 - 29.0)
Multiple pregnancy, n (%)	7 (12%)	2 (4%)	9 (8%)
Seasonal flu vaccine in the past 3 years, n (%)	**10 (17%)**	**9 (18%)**	**19 (18%)**

Inclusions were performed from 3rd November to 4th December 2009

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Hemagglutination-Inhibition (HI) Assay at baseline

Day 0	Group 1 n=58	Group 2 n=49	All women n=107
Geometric mean titer	**11.1**	**10.7**	**10.9**
95%CI	8.0 – 15.5	7.5 – 15.4	8.6 – 13.9
Seroprotection (HI titer ≥ 1:40)			
n	11	9	20
%	**19%**	**18%**	**19%**
95%CI	10 – 31	9 – 32	12 – 27

At baseline, 19% of women had protective hemagglutination-inhibition antibodies against A/California/7/2009(H1N1v) strain with titers ≥ 1:40

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Immunogenicity

Hemagglutination-Inhibition at day 21

Day 21	Group 1 n=55	Group 2 n=46	All the women n=101
Seroprotection, n	54	45	99
%	**98%**	**98%**	**98%**
95% CI	90 - 100	88 - 100	93 - 100
Seroconversion*, n	52	42	94
%	**95%**	**91%**	**93%**
95% CI	85 - 99	79 - 98	86 - 97
Geometric mean ratio	**64.8**	**70.6**	**67.4**
95% CI	42.9 – 97.8	43.0 – 115.9	49.3 – 92.1
Geometric mean titer	**753.9**	**635.2**	**697.3**
95% CI	522.0 – 1089.0	420.0 – 960.6	532.0 – 914.1

* Seroconversion rate is defined as the percentage of patients with a pre-vaccination HI titer < 1:10 and a post-vaccination titer ≥ 1:40, or showing a significant increase in antibody titer defined as a pre-vaccination titer ≥ 1:10 and at least a fourfold increase in post vaccination titer.

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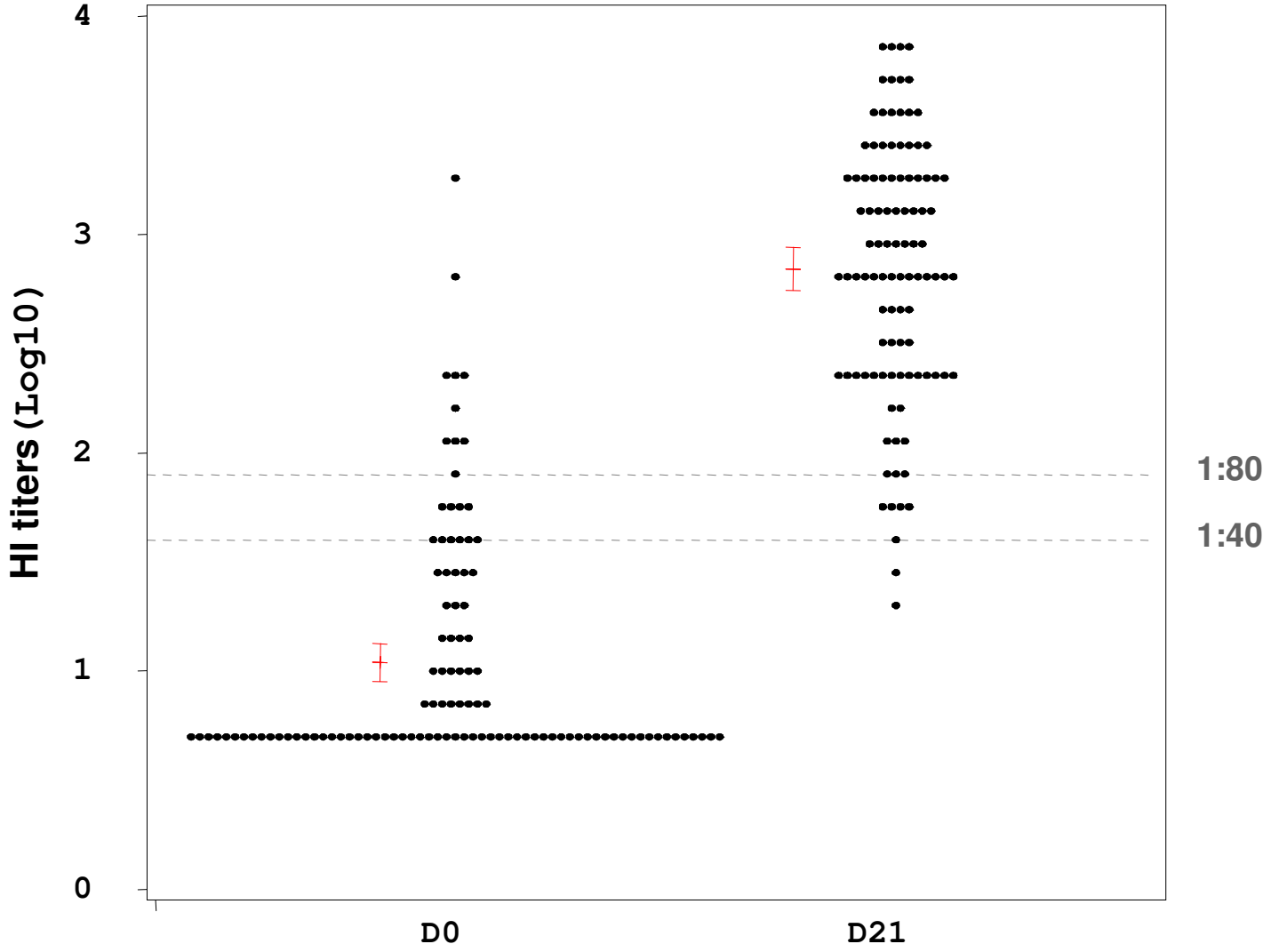
Immunogenicity

Individual patient HI titers at day 0 and day 21



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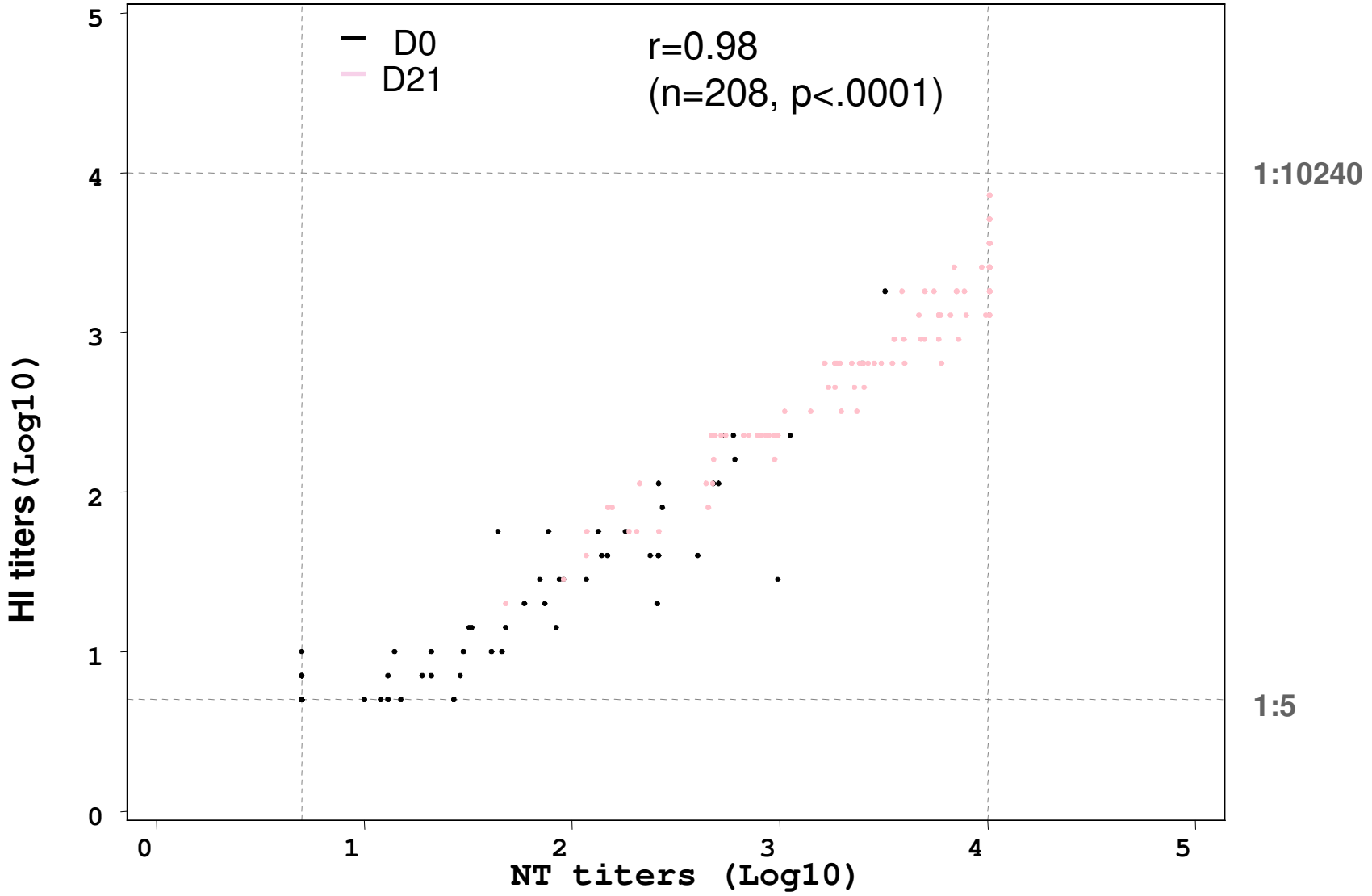
Immunogenicity

HI and Microneutralization assay (NT) titers



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Safety
Solicited adverse events

Number of women with at least one reaction	All women (n=107) n (%)
Local or systemic reaction	45 (42)
Local reaction	22 (21)
Mild	18 (17)
Moderate	3 (3)
Severe	1 (1)
Systemic reaction	33 (31)
Mild	16 (15)
Moderate	13 (12)
Severe	3 (3)

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Safety
Solicited adverse events

	All women (n=107) n (%)
Local solicited reactions	
Pain	20 (19)
Induration	3 (3)
Erythema	2 (2)
Systemic solicited reactions	
Asthenia	24 (22)
Headache	10 (9)
Myalgia	3 (3)
Arthralgia	2 (2)
Hyperhydrosis	2 (2)
Chills	2 (2)
Pyrexia	1 (1)

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Safety

- 116 live births
- 11 maternal Serious Adverse Events
  (5 in twin pregnancies)
  - all judged to be non associated
- 6 infants SAEs at birth
  - all judged to be non associated

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Pregnancy outcome

		Single (n=98)	Twin (n=9)	Total (n=107)
Weeks gestation	min-max	36 - 42	33 - 40	33 - 42
	median (IQR)	40 (39 - 40)	37 (36 - 37)	39 (38 - 40)
Preterm (<37 weeks)	n %	4 (4%)	5 (56%)	9 (8%)
Delivery	Vaginal, n %	82 (84%)	6 (67%)	88 (82%)
	Caesarean, n %	16 (16%)	3 (33%)	19 (18%)

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Conclusion

- A single 15 µg dose of a monovalent non-adjuvanted 2009 H1N1v vaccine administered in pregnant women in the second or third trimester :
  - induces a strong immune response,
  - has an acceptable safety profile

- Information on maternal persistence and placental transfer of antibodies is currently under evaluation

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