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**Status of vaccination against  
seasonal influenza in pregnant  
Japanese women:  
effect on infection rate among  
primiparous and multiparous women**

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September 29, 2015

## Today's presentation

- 1. No maternal mortality from pandemic (H1N1) 2009 occurred in Japan (*Letter BMJ* 2010 Aug 6 )**
- 2. Pandemic (H1N1) 2009 in pregnant Japanese women in Hokkaido (*J Obstet Gynaecol Res* 38: 130–6, 2012)**
- 3. Vaccination during the 2013–2014 influenza season in pregnant Japanese women (*Eur J Clin Microbiol Infect Dis* 34:543-548, 2015)**
- 4. Influenza 2014 - 2015 among pregnant Japanese women: primiparous vs. multiparous women (manuscript in preparation)**



## Background

- ✓ **Pregnant women are at an increased risk of severe influenza-related complications.**
- ✓ **Evidence from several countries demonstrated increased hospitalization rates and higher rate of mortality in pregnant women during the influenza.**



# No maternal mortality from pandemic (H1N1) 2009 occurred in Japan (Letter BMJ 2010 Aug 6 ): **Our first report** 3

district/ country	Hokkaido, Japan	Japan	Australia	California, USA	Canada	China	
Study period	Dec,2009– May, 2010				2009 –Dec. 2009		
Admission	6 (2.25% of pregnant patients)					328	
ICU	0				593 (13.7% of admitted patients)	593 (13.7% of admitted patients)	
death	<b>0</b>	<b>0</b>	3(1.08% of admitted patients)	8(7.8% of admitted patients)	30 (5.89% of admitted patients)	4 (4.7% of admitted patients)	326 (7.5% of admitted patients)

What is the  
reasons for this  
lack of maternal  
deaths in Japan?



# Pandemic (H1N1) 2009 in pregnant Japanese women in Hokkaido (*J Obstet Gynaecol Res* 38: 130–6, 2012): 2<sup>nd</sup> report

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Background and Aims: The reasons for the lack of maternal deaths from pandemic (H1N1) 2009 remain unknown. This questionnaire survey was performed to investigate how many pregnant women were infected, how many women took antiviral drugs for prophylaxis or treatment, and the rate of vaccination effectiveness.

Methods:

Questionnaire study for 20,500 postpartum women

Study period:

Dec 2009 - May 2010

THE JOURNAL OF  
Obstetrics and Gynaecology Research



doi:10.1111/j.1447-0756.2011.01644.x

*J. Obstet. Gynaecol. Res.* Vol. 38, No. 1: 130–136, January 2012

Pandemic (H1N1) 2009 in pregnant Japanese women in Hokkaido

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## Maternal age and birth weight of infants

	Infected	Non-infected	p-value
No. of women	268*	7,267	
Age (years old)			0.1823
-19	6 (2.2%)	85 (1.2%)	
20-24	25 (9.3%)	816 (11.2%)	
25-29			
30-34			
35-39			
40+			
unknown			
Birth weight (kg)			
<1,500			
1,500-1,999	0 (0.0%)	51 (0.70%)	
2,000-2,499	21 (7.9%)	457 (6.3%)	
2,500-2,999	107 (39.9%)	2,809 (38.7%)	
3,000-3,499	135 (50.6%)	3,901 (53.7%)	
3,500-3,999			
4,000-4,499			
4,500-4,999			
5,000+			
unknown	2 (0.76%)	22 (0.30%)	

There were no significant differences in the distributions of maternal age or birth weight of infants between the infected and non-infected women.

## Influenza and preterm delivery

Influenza did not significantly increase the rate of preterm delivery.

However, if the hospitalization needed, the risk of preterm birth is increased.

(Nakai A et al., J Infect. 2011; 62:232-233)

Risk of preterm birth/abortion among 181 women who needed hospitalization.

Characteristics	Japan <sup>a</sup>	Overall	Pneumonitis	
			Absent	Present
No. of women	1,091,156	181	164	17
Abortion at <22w	NA	3/181(1.7)	2/164(1.2)	1/17(5.9)
Preterm birth				
22-31 weeks	7876/1,091,156 (0.7)	5/178 (2.8)*	5/162 (3.1) *	0/16 (0)
32-36 weeks	54,932/1,091,156 (5.0)	21/178 (11.8) *	16/162 (9.8) *	5/16 (29.4) *#
Term birth	1,028,348/1,091,156 (94.2)	152/178 (85.4) *	141/162 (86.0) *	11/16 (68.8) *

\*p < 0.01 vs Japan (national statistics)      #p < 0.05 vs women group without pneumonitis.

<sup>a</sup>National data of Japan in 2008 were presented as a comparison group.



## Vaccination, Antiviral drug

	Infected(268)	Non-infected(7267)	p-value
Vaccination †	11 (4.1%)	<b>4,910 (67.6%)</b>	<0.0001
Antiviral drug			
Prophylaxis only	4 (1.5%)	213 (2.9%)	0.1948
Treatment only	93 (34.3%)	–	
Both	<b>136 (50.8%)</b>	–	

More than 60% of candidates were vaccinated within 1.5 months after the availability of vaccine and half of all infected women had taken prophylactic antiviral drug after coming into close contact with an infected person





# Vaccination reduced infection by 89% in pregnant Japanese women

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Infection rate with pandemic (H1N1) 2009 according to the status of vaccination at after December in Hokkaido

	Vaccinated	Non-vaccinated	p-value
No. of women	4,921	2,407	
No. of infected	11 (0.224%)	50 (2.08%)	<0.0001



## Summery of first questionnaire survey

- ✓ **Pregnant Japanese women had a high level of concern regarding pandemin (H1N1) 2009, went to some effort to avoid contracting the influenza by taking antiviral drugs and vaccination.**
- ✓ **This behaviour may have contributed to the lack of maternal mortality associated with this pandemic in Japan.**
- ✓ **Vaccination reduced infection by 89% in pregnant Japanese women.**



**Vaccination during the 2013–2014 influenza season in pregnant Japanese women (Eur J Clin Microbiol Infect Dis 34:543-548, 2015): 3<sup>rd</sup> report** 10

- ✓ How many pregnant Japanese women are vaccinated against seasonal influenza?
- ✓ How many pregnant Japanese women contracted seasonal influenza before or after the pandemic (H1N1) 2009?
- ✓ The baseline level of concern regarding influenza among pregnant Japanese women?

**To prepare for future avian influenza epidemics.**

Eur J Clin Microbiol Infect Dis  
DOI 10.1007/s10096-014-2259-8

ARTICLE

**Vaccination during the 2013–2014 influenza season  
in pregnant Japanese women**

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# **Vaccination during the 2013–2014 influenza season in pregnant Japanese women (Eur J Clin Microbiol Infect Dis 34:543-548, 2015)**<sup>11</sup>

We conducted the multi-center study to determine vaccination coverage against seasonal influenza and the prevalence rate of influenza infection among pregnant Japanese women during the 2013 – 2014 influenza season.

This is the first study focusing on the behavior of pregnant Japanese women with regard to seasonal influenza.

## **Vaccination during the 2013–2014 influenza season in pregnant Japanese women**

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# Vaccination rates according to maternal age and experience of prior birth

Age (year)	Overall	Primiparous	Multiparous	<i>P</i> -value*
≤ 24	39/124 (31%)¶	29/92 (32%)¶	10/32 (31%)†	0.9772
25 – 29	171/332 (52%)	112/198 (57%)	59/134 (44%)	0.0249
30 – 34	305/571 (53%)	156/299 (52%)	149/272 (55%)	0.5330
35 – 39	260/501 (52%)	106/222 (48%)	154/279 (55%)	0.0974
≥ 40	101/185 (55%)	44/92 (48%)	57/93 (61%)	0.0659
<b>Overall</b>	<b>876/1713 (51%)</b>	<b>447/903 (50%)</b>	<b>429/810 (53%)</b>	<b>0.1525</b>

\* , Comparison between primiparous and multiparous women.

¶, *P* < 0.05 vs. any other age category.

†, *P* < 0.05 vs. any other age category except women aged 25 – 29 years.

✓ 876 (51%) reported having received vaccination against influenza in or after October 2013.

✓ Women aged ≤ 24 years had a significantly lower vaccination rate than those aged ≥ 25 years (31% vs 53%, respectively; *P*=0.0000).



## Comparison of women who did and did not contract influenza 13

	<u>Infection with influenza</u>		<i>P</i> -value
	Yes	No	
No. of women	87	1626	
Vaccinated	34 (39%)	842 (52%)	0.0210
<b>Primiparous</b>	<b>26 (30%)</b>	<b>877 (54%)</b>	<b>&lt;0.0001</b>
Maternal age (years)			
≤ 29	21 (24%)	435 (27%)	0.7088
30 – 35	34 (39%)	537 (33%)	0.2450
≥ 35	32 (37%)	654 (40%)	0.5235

87 (5.1%) and 1626 (94.9%) women did and did not contract influenza, respectively. Although prior birth did not affect overall vaccination coverage (50% for primiparous vs. 53% for multiparous), multiparous women had a significantly higher rate of contracting influenza than primiparous women irrespective of vaccination status (5.6% vs. 2.2% [ $P=0.0216$ ] with vaccination and 9.7% vs. 3.5% [ $P=0.0003$ ] without vaccination, respectively).



## A and B

	Vaccinated	Unvaccinated	<i>P</i> -value
No. of women	876	837	
Type of influenza virus			
A	24* (2.7%)	27* (3.2%)	0.5542
B	7 (0.8%)	16 (1.9%)	0.0455
Unknown	4 (0.5%)	11 (1.3%)	0.0569
<b>Overall</b>	<b>34 (3.9%)</b>	<b>53 (6.3%)</b>	<b>0.0272</b>

\* , One was also infected with influenza virus B.

- ✓ The vaccination program of this season significantly reduced influenza infection rate by 35% (3.9% vs. 6.3% for women with and without vaccination, respectively;  $P=0.0272$ ).
- ✓ 72 (83%) of the 87 infected women took antiviral agents for the treatment of influenza and 2 (2.3%) required hospitalization.



## Summary of second questionnaire survey

- ✓ **Pregnant Japanese women had a high level of concern regarding seasonal influenza .**
- ✓ **The higher vaccination level achieved during the pandemic (H1N1) 2009 was sustained.**
- ✓ **Campaigns targeting young pregnant Japanese women as well as multiparous women for vaccination are needed to further reduce the incidence of influenza among pregnant Japanese women.**





CQ. Why multiparous pregnant women are more susceptible to flu than primiparous pregnant women?

We conducted 4th study to address this issue during 2014-2015 flu season



## **Objective:**

- 1. To determine the reproducibility of the phenomenon, i.e., “multiparous pregnant Japanese women are more vulnerable to influenza than primiparous pregnant Japanese women”**
- 2. To test a hypothesis that the risk of influenza increases with increasing number of cohabitants among pregnant Japanese women**





## Result 1: Maternal age distribution among all 6694 candidates and 5197 respondents (78%)

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The 5197 women corresponded to approximately 1.2% of all expected 440,000 maternities occurring in the study period in Japan that has approximately population of 130,000,000.

	All candidates (primiparous)	Respondents (primiparous)
<b>Maternal age</b>		
– 19	83 (70), [1.2% (2.0%)]	56 (50), [1.1% (1.9%)]
20 – 29	2036 (1313), [30.4% (37.8%)]	1437 (933), [27.7% (35.4%)]
30 – 34	2200 (1049), [32.9% (30.2%)]	1728 (791), [33.2% (30.0%)]
35 – 39	1793 (749), [26.8% (21.6%)]	1456 (607), [28.0% (23.0%)]
40 –	582 (294), [8.7% (8.5%)]	515 (251), [9.9% (9.5%)]
Unknown	0 (0), [0.0% (0.0%)]	5(3), [0.1% (0.1%)]
Overall	6694 (3475), [100% (100%)]	5197 (2635), [100% (100%)]

Percentages of all women (primiparous women) are indicated in square brackets



## Result 2: Influenza infection rate in primiparous vs. multiparous women

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### Influenza infection during current pregnancy

	Yes	No	Total
No. of women	364	4833	5197
<b>Primiparous</b>	<b>131 (36.0%)</b>	<b>2504 (51.8%)</b>	<b>2635</b>
<b>Multiparous</b>	<b>233 (64.0%)</b>	<b>2329 (48.2%)</b>	<b>2562</b>
<b>Unknown</b>	<b>0 (0%)</b>	<b>0 (0%)</b>	<b>0</b>

Infection rate was significantly higher for multi- than for primiparous women

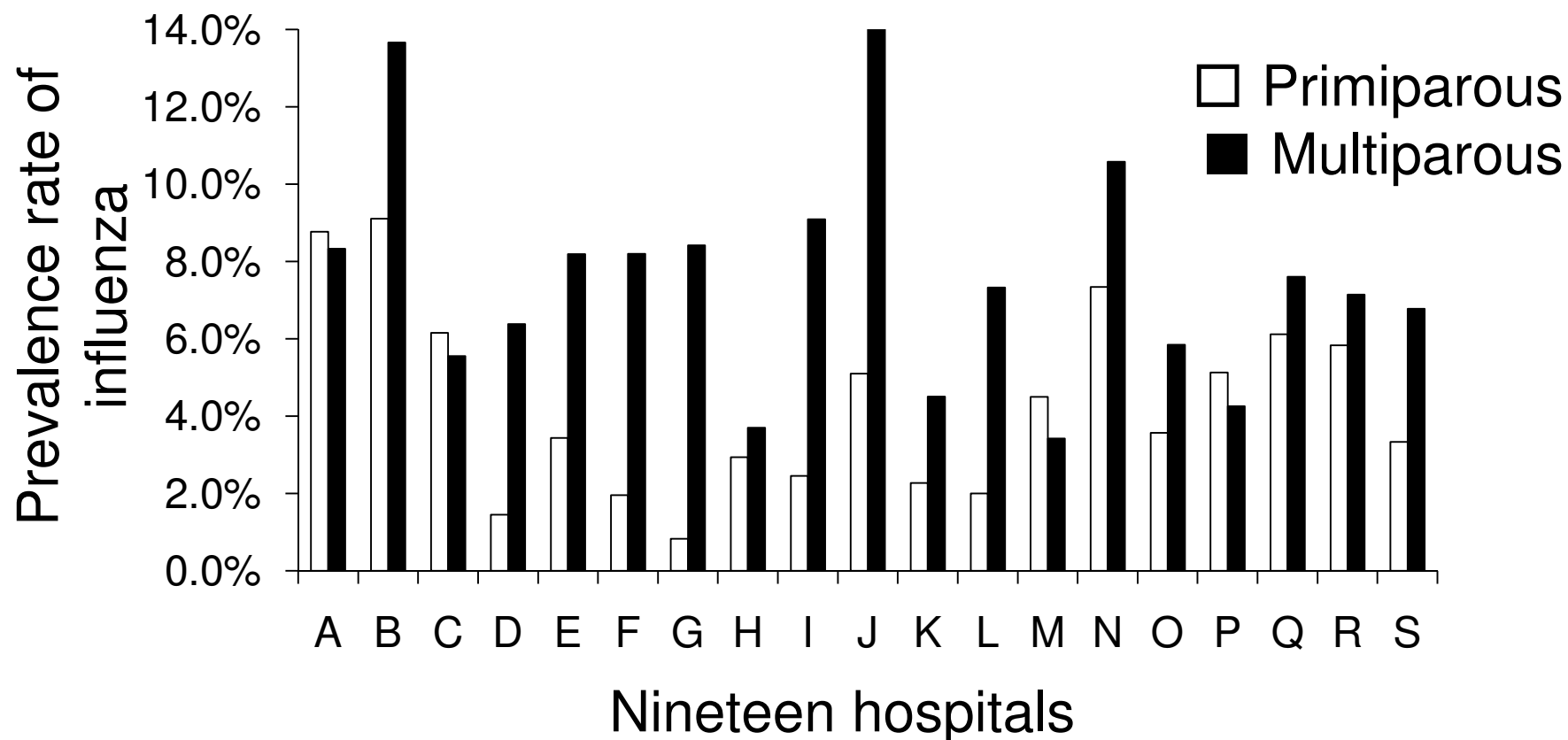
9.1% [233/2562] vs. 5.0% [131/2635],  $P=0.0000$

RR [95%CI]: 1.83 [1.49 – 2.25]



## Result 2: Influenza infection rate in primiparous vs. multiparous women

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The infection rate was higher in multi- than in primiparous women at 15 (79%) of the 19 hospitals



## Result 3: Vaccination coverage rate and effect of vaccination on influenza infection

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Overall vaccination coverage rate was 51% (2661/5197) and did not differ greatly between primi- and multiparous women.

### Influenza infection during current pregnancy

	Yes	No	total
Use of vaccination			
Yes	195 (53.6%)	2466 (51.0%)	2661
No	169 (46.4%)	2357 (48.8%)	2526
Unknown	0 (0%)	10 (0.2%)	10

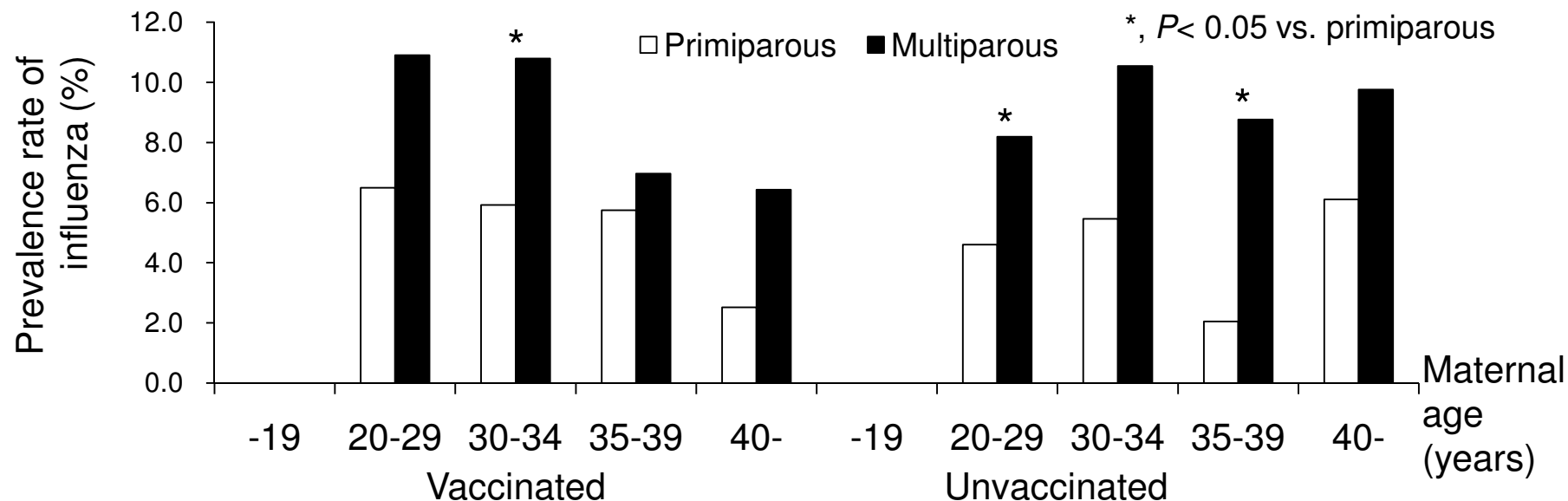
- ✓ Vaccines against influenza used in Japan in this season did not work at all to reduce number of pregnant women with influenza infection.
- ✓ Overall infection rate did not differ significantly between those with and without vaccination (7.3% [195/2661] vs. 6.7% [169/2526]).



## Result 3: Vaccination coverage rate and effect of vaccination on influenza infection

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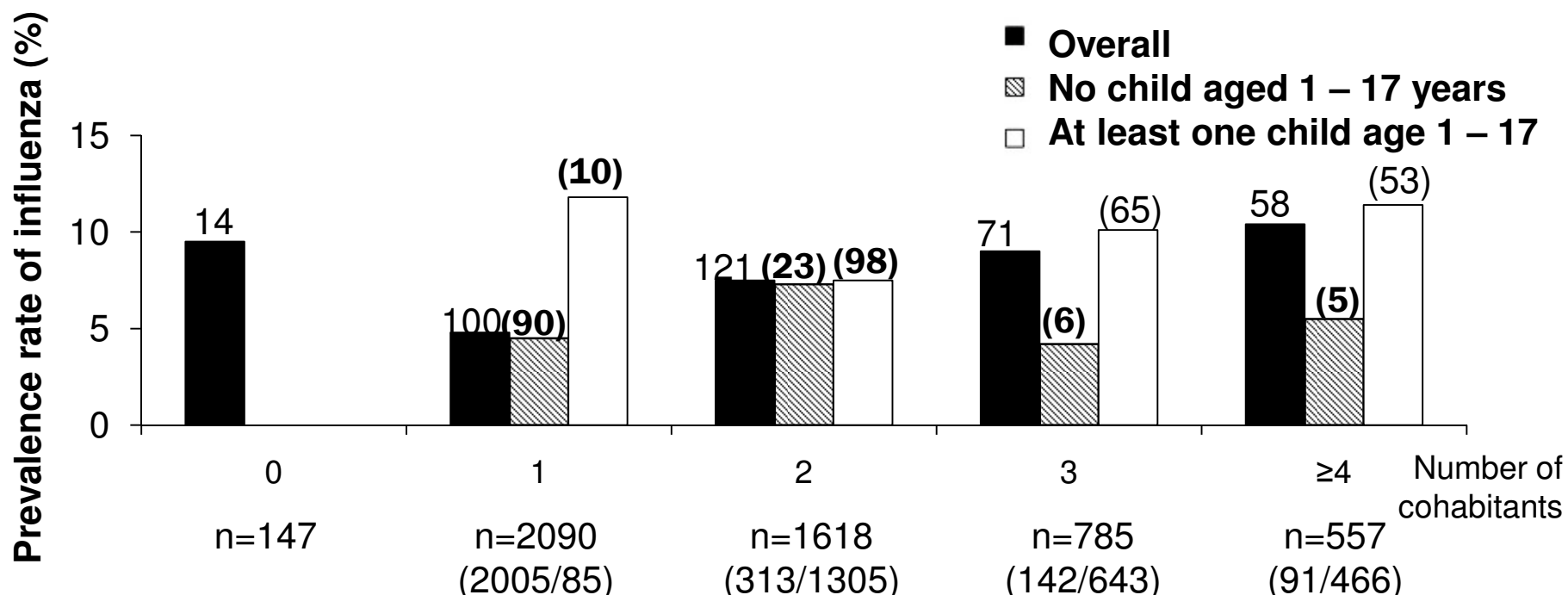
- ✓ Women aged less than 30 years received vaccination significantly less often than those aged 30 years or more.
- ✓ The infection rate did not differ significantly between those with and without vaccination among primiparous as well as multiparous women.
- ✓ Thus, multiparous women had a higher risk of influenza irrespective of vaccination status compared to primiparous.
- ✓ No consistent association was seen between maternal age and the risk of influenza infection.





## Result 4: Effect of cohabitant number on influenza infection rate

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- ✓ Number of cohabitants was greater in multiparous than in primiparous women.
- ✓ The influenza infection rate increased with increasing number of cohabitants among pregnant women with at least one cohabitant.
- ✓ The presence of at least one child aged 1 – 17 years increased consistently the risk of influenza in pregnancy at any family size.
- ✓ Overall infection rate was higher for those with at least one child aged 1 – 17 years than in those without such children (9.0% [226/2499] vs. 5.1% [138/2698],  $P < 0.0001$ ).



## Result 5: Risk of influenza infection in women whose main job was housekeeping during current pregnancy 25

### Influenza infection during current pregnancy

	Yes	No	Total
<b>Job</b>			
<b>Housekeeping</b>	<b>150 (41.2%)</b>	<b>2391 (49.5%)</b>	<b>2541</b>
<b>Outside home</b>	<b>212 (58.2%)</b>	<b>2404 (49.7%)</b>	<b>2616</b>
<b>Unknown</b>	<b>2 (0.5%)</b>	<b>38 (0.8%)</b>	<b>40</b>

- ✓ Neither maternal age nor number of cohabitants differed significantly between those who worked inside and outside home.
- ✓ However, women with housekeeping had a significantly reduced risk of influenza approximately by 27% (5.9% [150/2541] vs. 8.1% [212/2616]; RR [95%CI], 0.73 [0.60 – 0.89]).



## Summery of third questionnaire survey

- ✓ **Multiparous women had higher risk of influenza irrespective of vaccination status compared to primiparous women.**
- ✓ **Number of cohabitants was greater in multi- than in primiparous women.**
- ✓ **The risk of influenza increased with increasing number of cohabitants.**
- ✓ **The presence of at least one child aged 1 – 17 years increased consistently the risk of influenza in pregnancy at any family size.**
- ✓ **Women with housekeeping had a reduced risk of influenza.**
- ✓ **Vaccine coverage was low in younger pregnant Japanese women.**



# Highlights

- ✓ **Pregnant Japanese women had a high level of concern regarding influenza, went to some effort to avoid contracting the influenza by taking antiviral drugs and vaccination.**
- ✓ **This behavior may have contributed to the lack of maternal mortality associated with the pandemic in Japan.**
- ✓ **Vaccine coverage was low in **younger pregnant Japanese women.****
- ✓ ****Multiparous women** had higher risk of influenza compared to primiparous women.**
- ✓ **The risk of influenza increased with **increasing number of cohabitants.****
- ✓ **The presence of at least one **child aged 1 – 17 years** increased the risk of influenza in pregnancy.**
- ✓ **Women with housekeeping had a reduced risk of influenza**



**Campaigns targeting young pregnant Japanese women as well as multiparous women for vaccination are needed to further reduce the incidence of influenza among pregnant Japanese women.**



# Acknowledgements

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