



Title	Vaccination during the 2013-2014 influenza season in pregnant Japanese women
Author(s)	Yamada, Takahiro; Abe, Kanako; Baba, Yosuke; Inubashiri, Eisuke; Kawabata, Kosuke; Kubo, Takahiko; Maegawa, Yuka; Fuchi, Naoki; Nomizo, Mari; Shimada, Manabu; Shiozaki, Arihiro; Hamada, Hiromi; Matsubara, Shigeki; Akutagawa, Noriyuki; Kataoka, Soromon; Maeda, Makoto; Masuzaki, Hideaki; Sagawa, Norimasa; Nakai, Akihito; Saito, Shigeru; Minakami, Hisanori
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1 **Title: Vaccination during the 2013 – 2014 influenza season in pregnant Japanese**
2 **women**

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4 Takahiro Yamada^{1*}, Kanako Abe², Yosuke Baba³, Eisuke Inubashiri⁴, Kosuke
5 Kawabata⁵, Takahiko Kubo⁶, Yuka Maegawa⁷, Naoki Fuchi⁸, Mari Nomizo⁹, Manabu
6 Shimada¹⁰, Arihiro Shiozaki¹¹, Hiromi Hamada², Shigeki Matsubara³, Noriyuki
7 Akutagawa⁴, Soromon Kataoka⁵, Makoto Maeda⁷, Hideaki Masuzaki⁸, Norimasa
8 Sagawa⁹, Akihito Nakai¹⁰, Shigeru Saito¹¹, Hisanori Minakami¹

9
10 **Running title: Influenza vaccine in pregnancy**

11
12
13 1 Department of Obstetrics and Gynecology, Hokkaido University Graduate School of
14 Medicine, N15W7, Kita-ku, Sapporo, 060-8638, Japan

15 2 Department of Obstetrics and Gynecology, Faculty of Medicine, University of
16 Tsukuba, Tsukuba, Japan

17 3 Department of Obstetrics and Gynecology, Jichi Medical University, Tochigi, Japan

18 4 Department of Obstetrics and Gynecology, Sapporo Toho Hospital, Sapporo, Japan

19 5 Department of Obstetrics and Gynecology, Hakodate Central General Hospital,
20 Hakodate, Japan

21 6 Division of Obstetrics, National Center for Child Health and Development, Tokyo,
22 Japan

23 7 Department of Obstetrics and Gynecology, Mie Chuo Medical Center, Tsu, Japan

24 8 Department of Obstetrics and Gynecology, Nagasaki University Graduate School of

25 Medicine, Nagasaki, Japan
26 9 General Women's Medical and Health Science Center, Rakuwakai Otowa Hospital,
27 Kyoto, Japan
28 10 Department of Obstetrics and Gynecology, Nippon Medical School Tama-Nagayama
29 Hospital, Tokyo, Japan
30 11 Department of Obstetrics and Gynecology, University of Toyama, Toyama, Japan
31
32
33 * Correspondence to Takahiro Yamada, MD, PhD.
34 Department of Obstetrics, Hokkaido University Graduate School of Medicine,
35 N15W7, Kita-ku, Sapporo, 060-8638, Japan
36 Phone: +81-11-706-5941
37 Fax: +81-11-706-7711
38 E-mail address: taka0197@med.hokudai.ac.jp
39
40

41 **ABSTRACT**

42 This questionnaire survey was conducted at 11 hospitals in Japan to determine
43 vaccination coverage against seasonal influenza and the prevalence rate of influenza
44 among pregnant Japanese women. Of 2808 postpartum women who gave birth at the 11
45 hospitals during the study period from March 1, 2014, to July 31, 2014, 1713 (61%)
46 participated in this study and 876 (51%) reported having received vaccination against
47 influenza in or after October 2013. Women aged < 25 years had a significantly lower
48 vaccination rate than those aged ≥ 25 years (31% vs. 53%, respectively; $P=0.0000$).
49 Eighty-seven (5.1%) and 1626 (94.9%) women did and did not contract influenza,
50 respectively. Although prior birth did not affect overall vaccination coverage (50% for
51 primiparous vs. 53% for multiparous), multiparous women had a significantly higher
52 rate of contracting influenza than primiparous women irrespective of vaccination status
53 (5.6% vs. 2.2% [$P=0.0216$] and 9.7% vs. 3.5% [$P=0.0003$] for women with and without
54 vaccination, respectively). The 2013 – 2014 vaccination program significantly reduced
55 influenza infection rate by 35% (3.9% vs. 6.3% for women with and without
56 vaccination, respectively; $P=0.0272$). Seventy-two (83%) of the 87 women took
57 antiviral agents for the treatment of influenza and two (2.3%) required hospitalization.
58 These results suggested that pregnant Japanese women had a high level of concern
59 regarding seasonal influenza. However, campaigns targeting young pregnant Japanese
60 women as well as multiparous women for vaccination are needed to further reduce the
61 incidence of influenza among pregnant Japanese women.

62

63 **Key words:** Influenza, vaccine, pregnancy, pandemic

64 **Introduction**

65 Pregnant women are at an increased risk of severe influenza-related complications (1 –
66 9). Evidence from several countries demonstrated increased hospitalization rates and
67 disproportionately higher rate of mortality in pregnant women during the previous
68 seasonal influenza and pandemic (H1N1) 2009 (1 – 9). However, there were no
69 mortalities among pregnant women during the pandemic (H1N1) 2009 in Japan (10, 11).
70 At that time of pandemic (H1N1) 2009, pregnant Japanese women had a high level of
71 concern regarding pandemic influenza because the Japan Society of Obstetrics and
72 Gynecology aggressively intensified outreach to pregnant women, policy-makers, and
73 medical workers, including medical doctors, midwives, and nurses, to minimize the
74 number of cases of infection among pregnant women (10, 12). Indeed, more than 60%
75 of candidates were vaccinated within 1.5 months after the availability of vaccine against
76 the pandemic (H1N1) 2009 virus and half of all women infected with influenza had
77 taken prophylactic antiviral drug after coming into close contact with an infected person
78 in Hokkaido, the northernmost and the second largest island of Japan (13).

79

80 However, to our knowledge, there have been no studies regarding how many pregnant
81 Japanese women are vaccinated against seasonal influenza and how many pregnant
82 Japanese women contracted seasonal influenza before or after the pandemic (H1N1)
83 2009. It may be important to determine the baseline level of concern regarding
84 influenza among pregnant Japanese women to prepare for future avian influenza
85 epidemics. Therefore, we conducted this multi-center study to determine vaccination
86 coverage against seasonal influenza and the prevalence rate of influenza infection
87 among pregnant Japanese women during the 2013 – 2014 influenza season.

88

89 **Materials and Methods**

90 This multi-center observational study was conducted with the approval of the
91 Institutional Review Boards of Hokkaido University Hospital and the following 11
92 hospitals widely dispersed throughout Japan that participated in this study: Nagasaki
93 University Hospital, Rakuwakai Otowa Hospital, Toyama University Hospital, Mie
94 Chuo Medical Center, Nippon Medical School Tama-Nagayama Hospital, National
95 Center for Child Health and Development, University of Tsukuba Hospital, Jichi
96 Medical University Hospital, Hakodate Central General Hospital, Sapporo Toho
97 Hospital, and Hokkaido University Hospital.

98

99 In Japan, women usually remain at obstetric facilities for 4 to 8 days after giving birth.
100 We conducted an anonymous questionnaire study (Table 1) among all postpartum
101 women who gave birth at and after gestational week 22 and within 5 days after delivery
102 before leaving the obstetric facility during the study period from March 1, 2014, to July
103 31, 2014. Therefore, the majority of these postpartum conceived in or before October
104 2013.

105

106 All data are presented as means \pm SD. For statistical analysis of categorical data, χ^2 or
107 Fisher's exact test was applied. The statistical software package StatView 5.0 for
108 Macintosh (SAS Institute Inc. Cary, NC) was used for data analysis. In all analyses, $P <$
109 0.05 was taken to indicate statistical significance.

110

111 **Results**

112 During the 5-month study period, 2808 women gave birth on and after gestational week
113 22 at the 11 participating hospitals. Preterm birth (at < 37 weeks of gestation) occurred
114 in 373 (13%) women. A total of 1713 (61%) of the 2808 women participated in this
115 study (Table 2). Although the response rate and vaccination coverage differed
116 considerably between hospitals, the mean (SD) response rate was 62% (22%), and mean
117 vaccination rate was 53% (13%) for the 11 hospitals. The age-specific response rate was
118 as follows: 54% (124/229), 59% (332/559), 62% (571/927), 63% (501/793), and 62%
119 (185/300) for women aged 24 years or less, 25 – 29, 30 – 34, 35 – 39, and 40 years or
120 more, respectively. Of the 1713 respondents, 876 (51%) and 837 (49%) women did and
121 did not receive a vaccine against influenza in or after October 2013, respectively.

122

123 Maternal age affected vaccination coverage—women aged 24 years or less received
124 vaccination significantly less often than those in other age categories (Table 3).
125 However, experience of prior birth did not affect the overall vaccination coverage (50%
126 for primiparous vs. 53% for multiparous women), although a significantly larger
127 number of primiparous women aged 25 – 29 years old received the vaccination
128 compared to multiparous women in the same age group (57% vs. 44%, respectively). In
129 contrast, among women 35 years old or more, multiparous women tended to have a
130 greater vaccination rate than primiparous women.

131

132 Eighty-seven (5.1%) and 1626 (94.9%) women did and did not contract influenza,
133 respectively (Table 4). The prevalence of influenza did not differ markedly between
134 hospitals, ranging from 3.4% (10/298) in Jichi Medical University Hospital to 8.9%
135 (10/112) in Nagasaki University Hospital (mean \pm SD, 5.5% \pm 1.8%). In the 1626

136 women without influenza than in the 87 with influenza, the fraction size of women with
137 vaccination and that of primiparous women were significantly greater (Table 4). As this
138 suggested that the experience of childbirth was a risk factor for contracting influenza,
139 we analyzed the differences in prevalence rate of influenza between primiparous and
140 multiparous women according to maternal age (Fig. 1). The infection rate was
141 consistently higher for multiparous than primiparous women irrespective of vaccination
142 status. Maternal age was not associated with the infection rate (Fig. 1, Table 4).

143

144 The effects of vaccination on prevention of influenza were analyzed (Table 5). Two
145 women (one was vaccinated and the other was unvaccinated) contracted both influenza
146 A and B viruses. The number of women infected with influenza virus A did not differ
147 significantly between the 876 and 837 women with and without vaccination (2.7% vs.
148 3.2%, respectively), while that of women with influenza virus B infection was
149 significantly lower among women with than without vaccination (0.8% vs. 1.9%,
150 respectively; $P = 0.0455$). Overall, the 2013 – 2014 vaccination program against
151 influenza reduced the risk of influenza infection by 35% ($[54 - 35]/54$) among pregnant
152 Japanese women.

153

154 Among the 87 women with influenza, 72 (83%) reported having taken antiviral agents
155 for treatment of influenza. Antiviral agents administered for these 72 women were oral
156 tablets in 34 (47%) women and inhalation drugs for the remaining 38 (53%) women.
157 Two (2.3%) women required hospitalization for treatment of the influenza—both were
158 multiparous, one with vaccination contracted both influenza viruses A and B, and the
159 other without vaccination contracted influenza virus A.

160

161 **Discussion**

162 To our knowledge, this is the first study focusing on the behavior of pregnant Japanese
163 women with regard to seasonal influenza.

164

165 It may be important to determine the attitudes of pregnant women toward vaccination
166 and antiviral drugs. A survey conducted in the 2006 – 2007 influenza season in the USA
167 indicated that almost one third of health care workers not believe that vaccines are a
168 safe and effective way to decrease infections, although the Advisory Committee on
169 Immunization Practices began recommending routine influenza vaccination for healthy
170 pregnant women during the influenza season in 2004 (14). A meeting designed to
171 integrate scientific evidence and expert opinion (13) in 2008 in the USA concluded that
172 pregnant women should be considered a high-priority group for receipt of vaccine and
173 that increased seasonal influenza vaccine coverage may improve vaccine uptake in a
174 pandemic (13). Indeed, at the pandemic (H1N1) 2009, 7.8% of 102 obstetric patients
175 who required hospitalization for pandemic (H1N1) 2009 died in California (15). In
176 Australia and New Zealand, pregnant women accounted for 9.1% of 722 patients who
177 required treatment at an intensive care unit (ICU) (7) and 11% of 64 pregnant women
178 who required ICU treatment died (8). Pregnant women accounted for 5%, 7.5%, and
179 8.3% of hospitalized cases in Canada, the UK, and Brazil, respectively (16), although
180 pregnant women account for approximately 1.0% of the total population.

181

182

183 Approximately half of pregnant Japanese women were vaccinated against seasonal
184 influenza. As this figure was similar to those at and after the pandemic (H1N1) 2009 in
185 the USA (17, 18), it may have been brought about by the pandemic (H1N1) 2009.
186 Before the pandemic (H1N1) 2009, estimated influenza vaccination coverage among
187 pregnant women in the USA was consistently low (approximately 15%) (18 - 20),
188 although there is no significant increase in adverse reactions in mothers or neonates
189 related to the vaccine and side effects are similar to those in the general population (19,
190 20). Women offered influenza vaccination by a health care provider are more likely to
191 be vaccinated and are more likely to have positive attitudes about vaccine effectiveness
192 and safety (18). The Healthy People 2020 initiative of the United States Department of
193 Health and Human Services has set a goal of 80% vaccine coverage among pregnant
194 women in the USA (21). As the maternal influenza immunization is a highly
195 cost-effective intervention to reduce disease rates and severity corresponding to both
196 seasonal influenza epidemics and occasional pandemics (22), continued efforts are
197 needed to encourage pregnant women to receive influenza vaccination.

198

199 Eighty-three percent of infected Japanese women reported having taken antiviral drugs.
200 An early treatment of pregnant women with antiviral medications is associated with
201 fewer ICU admissions and fewer maternal deaths (23). No harmful effects of
202 neuraminidase inhibitors, including oseltamivir, zanamivir, and laninamivir, on fetuses
203 exposed *in utero* have been reported (24, 25), and they are believed to have contributed
204 to the lack of maternal mortality during the pandemic (H1N1) 2009 in Japan (10 – 12).

205

206
207 Multiparous women had an approximately twofold higher risk of influenza infection
208 than primiparous women in this study. To our knowledge, this phenomenon has not
209 been reported to date. The reason for this phenomenon is not yet clear. However, these
210 observations may be explained by the greater number of cohabitants for multiparous
211 than primiparous women, which may be associated with higher risk of infection.

212
213 In conclusion, although it was difficult to verify that respondents answered questions
214 correctly due to the nature of this questionnaire study, our results suggested that
215 influenza vaccine coverage was approximately 50% among pregnant women in Japan
216 and approximately 1 in 20 pregnant women contracted influenza in the 2013 – 2014
217 influenza season. These observations indicated that the higher vaccination level
218 achieved during the pandemic (H1N1) 2009 was sustained. However, the vaccination
219 coverage was insufficient in younger pregnant women, and multiparous women had an
220 approximately twofold higher risk of infection compared with primiparous women.
221 Continued efforts are needed to encourage pregnant women, especially those less than
222 25 years old and multiparous women, to receive the vaccination to further reduce the
223 number of pregnant women with influenza in Japan.

224

225 **Disclosure**

226 All authors declare that they have no financial relationships with biotechnology
227 manufacturers, pharmaceutical companies, or other commercial entities with an interest
228 in the subject matter or materials discussed in this manuscript.

229

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300 [ization%20and%20Infectious%20Diseases&objective=IID-12.10&anchor=578826](http://www.healthypeople.gov/2020/Data/SearchResult.aspx?topicid=23&topic=Immunization%20and%20Infectious%20Diseases&objective=IID-12.10&anchor=578826)
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314

315

316

317 **Figure legend**

318

319 **Figure 1. Prevalence rate of influenza infection according to maternal age among**
320 **primiparous and multiparous women**

321

322 *, $P < 0.05$ vs. primiparous women. Figures on top of bars indicate actual numbers of
323 women with influenza/designated population. The prevalence rate of influenza was
324 consistently higher for multiparous (closed bars) than primiparous (open bars) women
325 in all age categories irrespective of vaccination status. Overall, the infection rate was
326 significantly higher in multiparous than primiparous women for both vaccinated (5.6%
327 [24/429] vs. 2.2% [10/427], $P=0.0216$) and unvaccinated women (9.7% [37/381] vs.
328 3.5% [16/456], $P=0.0003$). Among primiparous women, the infection rate did not differ
329 between those with without vaccination in any age category. Among multiparous
330 women, the infection rate was significantly lower in those with vaccination and aged 30
331 – 34 years than in their counterparts (5.4% [8/149] vs. 13.0% [16/123], respectively; P
332 = 0.0321). Overall, the infection rate did not differ significantly between primiparous
333 women with and without vaccination (2.2% [10/447] vs. 3.5% [16/456], respectively),
334 whereas it was significantly lower in multiparous women with than without vaccination
335 (5.6% [24/429] vs. 9.7% [37/381], respectively; $P = 0.0324$)

336

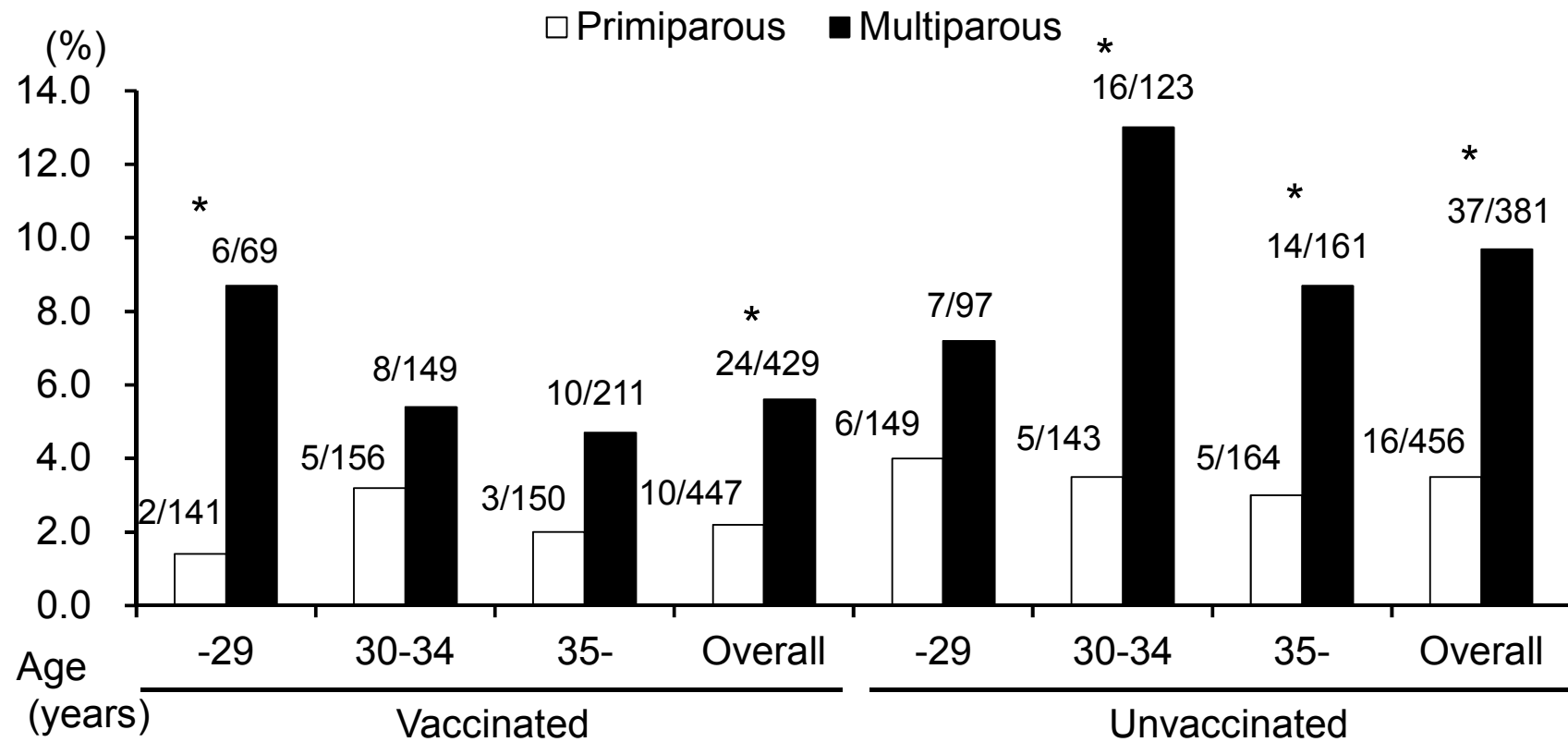


Table 1. Questionnaire form given to women within 5 days after delivery during the study period (March 1, 2014, to July 31, 2014)

Q1: When did you give birth?

March, April, May, June, July in 2014

Q2: How old are you?

≤ 19, 20 – 24, 25 – 29, 30 – 34, 35 – 39, 40 – 44, ≥ 45

Q3: Was this your first experience of birth?

Yes, No

Q4: Were you vaccinated against influenza on or after October 2013?

Yes, No

Q5: Did you contract influenza during the current pregnancy?

Yes, No

The following questions are for women with “Yes” in response to Q5

Q6: Were you hospitalized for treatment of influenza?

Yes, No

Q7: What was the type of influenza?

A, B, Unknown

Q8: Did you receive antiviral agent for the treatment of influenza?

Yes, No

The following question is for women with “Yes” in response to Q8

Q9: What was the type of antiviral agent given?

Oral tablet, Inhalation drug

Table 2. Number of participants, response rates, and vaccination rates according to institution

Institution	No. of women		
	Candidates*	Participants	Vaccinated
NUH	132	112 (85%)	55 [49%]
ROH	136	97 (71%)	31 [32%]
TUH	131	60 (46%)	36 [60%]
MCMC	190	124 (65%)	82 [66%]
NMSTH	252	77 (31%)	33 [43%]
NCCHD†	318	139 (44%)	97 [70%]
UTH	392	382 (97%)	166 [43%]
JMUH	338	298 (88%)	127 [43%]
HCGH	259	140 (54%)	81 [58%]
STH	480	166 (35%)	80 [48%]
HUH	180	118 (66%)	88 [75%]
Overall	2808	1713 (61%)	876 [51%]
Overall (mean±SD)	255±116	156±98 (62%±22%)	80±41 [53%±13%]

*, Number of women who gave birth during the study period; †, study subjects were women who gave birth in March and April only. Percentage response rate (participants/candidates) to this questionnaire survey and vaccination rate (vaccinated/participants) are indicated in parentheses and square brackets, respectively.

NUH, Nagasaki University Hospital; ROH, Rakuwakai Otowa Hospital; TUH, Toyama University Hospital; MCMC, Mie Chuo Medical Center; NMSTH, Nippon Medical School Tama-Nagayama Hospital; NCCHD, National Center for Child Health and Development; UTH, University of Tsukuba Hospital; JMUH, Jichi Medical University Hospital; HCGH, Hakodate Central General Hospital; STH, Sapporo Toho Hospital, HUH, Hokkaido University Hospital.

Table 3. Vaccination rates according to maternal age and experience of prior birth

<u>Age (year)</u>	<u>Overall</u>	<u>Primiparous</u>	<u>Multiparous</u>	<u>P-value*</u>
≤ 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
Overall	876/1713 (51%)	447/903 (50%)	429/810 (53%)	0.1525

* , 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.

Table 4. Comparison of women who did and did not contract influenza

	Infection with influenza		<i>P</i> -value
	Yes	No	
No. of women	87	1626	
Vaccinated	34 (39%)	842 (52%)	0.0210
Primiparous	26 (30%)	877 (54%)	0.0000
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

Table 5. Vaccination and infection with influenza virus 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
Overall	34 (3.9%)	53 (6.3%)	0.0272

*, One was also infected with influenza virus B.