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| Author(s) | Yamada, T.; Kawakami, S.; Yoshida, Y.; Kawamura, H.; Ohta, S.; Abe, K.; Hamada, H.; Dohi, S.; Ichizuka, K.; Takita, H.; Baba, Y.; Matsubara, S.; Mochizuki, J.; Unno, N.; Maegawa, Y.; Maeda, M.; Inubashiri, E.; Akutagawa, N.; Kubo, T.; Shiota, T.; Oda, Y.; Yamada, T.; Yamagishi, E.; Nakai, A.; Fuchi, N.; Masuzaki, H.; Urabe, S.; Kudo, Y.; Nomizo, M.; Sagawa, N.; Maeda, T.; Kamitomo, M.; Kawabata, K.; Kataoka, S.; Shiozaki, A.; Saito, S.; Sekizawa, A.; Minakami, H. |
| Citation | European journal of clinical microbiology & infectious diseases, 35(4), 665-671 https://doi.org/10.1007/s10096-016-2585-0 |
| Issue Date | 2016-04 |
| Doc URL | http://hdl.handle.net/2115/64949 |
| Rights | The final publication is available at link.springer.com |
| Type | article (author version) |
| File Information | EurJClInMicrobiolInfectDis35_665.pdf |



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Title: Influenza 2014 – 2015 among pregnant Japanese women: primiparous vs. multiparous women

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Running title: Influenza in pregnancy

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Abstract

Objectives: This study was performed to determine whether multiparous pregnant women are prone to influenza.

Methods: A questionnaire survey was conducted at 19 centres located throughout Japan, targeting all 6694 postpartum women within 7 days after birth before leaving the hospital. All women gave birth during the study period between March 1, 2015, and July 31, 2015. Data regarding vaccination and influenza infection in or after October 2014, age, previous experience of childbirth, and number and ages of cohabitants were collected.

Results: Seventy-eight percent ($n = 5,197$) of women given questionnaires responded. Of these, 2,661 (51%) and 364 (7.0%) women reported having been vaccinated and having contracted influenza, respectively. Multiparous women had a higher risk of influenza regardless of vaccination status (8.9% [121/1,362] vs. 5.7% [74/1,299], relative risk [95% confidence interval], 1.80 [1.36 to 2.38] for vaccinated and 9.3% [112/1,198] vs. 4.3% [57/1,328], 2.18 [1.60 to 2.97] for unvaccinated women) compared to primiparous women. The risk of influenza increased with increasing number of cohabitants: 4.8% (100/2,089), 7.5%, (121/1,618), 9.0%, (71/785), and 10.4% (58/557) for women with 1, 2, 3, and ≥ 4 cohabitants, respectively.

Conclusions: Family size is a risk factor for influenza infection in pregnancy.

Key words: influenza pandemic, influenza vaccine effectiveness, pregnancy and infection

Introduction

Pregnant women are at increased risk of severe influenza-related complications (1, 2). Despite accounting for approximately 1.0% of the total population, pregnant women accounted for 5%, 7.5%, and 8.3% of hospitalised cases in Canada, the UK, and Brazil, respectively (3), and 9.1% of 722 patients requiring treatment at an intensive care unit (ICU) in Australia and New Zealand (4) during the previous influenza H1N1 pandemic in 2009.

A meeting designed to integrate scientific evidence and expert opinion (5) in 2008 in the USA concluded that pregnant women should be considered a high-priority group for receipt of vaccine, and that increased seasonal influenza vaccine coverage may improve vaccine uptake in a pandemic (5). The WHO recommends that pregnant women should be given the highest vaccination priority (6). Therefore, it is important to determine the attitudes of pregnant women toward vaccination. During the 2013 – 2014 influenza season in Japan, approximately half of all pregnant Japanese women received influenza vaccination, which reduced the risk of influenza infection by 35% among these women (7).

This previous investigation indicated multiparous pregnant women had an approximately twofold higher risk of influenza infection compared with primiparous pregnant women regardless of vaccination status in any age category (7).

The present multicentre questionnaire survey was conducted among postpartum Japanese women who gave birth during a 5-month period between March 1, 2015, and

July 31, 2015, to determine the reproducibility of this phenomenon, i.e., that multiparous pregnant women are more vulnerable to influenza than primiparous pregnant women, and to test the hypothesis that the risk of influenza in pregnant women is related to number of cohabitants.

Materials and Methods

This multicentre observational study was conducted with the approval of the Institutional Review Boards of Hokkaido University Hospital (No. 014-0265) and each of following 19 participating hospitals widely dispersed throughout Japan: Kagoshima City Hospital (designated as A in Fig. 1), Fukuda Hospital (B), Nagasaki University Hospital (C), Hiroshima University Hospital (D), Osaka Medical Center and Research Institute for Maternal and Child Health (E), Rakuwakai Otowa Hospital (F), Mie Chuo Medical Center (G), Toyama University Hospital (H), Kitasato University Hospital (I), Nippon Medical School Tama-Nagayama Hospital (J), Shirota Obstetrical and Gynecological Hospital (K), Showa University Northern Yokohama Hospital (L), Showa University Hospital (M), University of Tsukuba Hospital (N), Jichi Medical University Hospital (O), Hakodate Central General Hospital (P), JCHO Hokkaido Hospital (Q), Sapporo Toho Hospital (R), and Hokkaido University Hospital (S).

In Japan, women usually remain at obstetric facilities for 4 – 8 days after giving birth. We conducted an anonymous questionnaire study (Table 1) among all postpartum women who gave birth at and after gestational week 22 and within 7 days after delivery before leaving the obstetric facility during the study period from March 1, 2015, to July 31, 2015. Therefore, the majority of these women conceived in or before October 2014.

All data are presented as the median (range). For statistical analysis of categorical data, the χ^2 , Fisher's exact test, or Mann–Whitney U-test was applied for comparison of medians. The statistical software package StatView 5.0 for Macintosh (SAS Institute Inc., Cary, NC, USA) was used for data analysis. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

During the 5-month study period, a total of 6,694 women, including 3,475 primiparous and 3,219 multiparous women, gave birth on or after gestational week 22 at the 19 participating hospitals (Table 2). Of these, 5,197 (78%) women, consisting of 2,635 (76%) of the 3,475 primiparous women and 2,562 (80%) of the 3,219 multiparous women, responded to the questionnaire and participated in this study (Table 2). The 5,197 women corresponded to approximately 1.2% of all expected 440,000 maternities occurring in the study period in Japan, which has population of approximately 130,000,000. Younger primiparous women aged < 30 years were less likely to participate in this study (Table 2). The response rate at each hospital is shown in the legend for Fig. 1.

Influenza infection rate in primiparous vs. multiparous women

A total of 364 women (7.0%) reported having contracted influenza during the current pregnancy (Table 3). The infection rate was significantly higher for multiparous than for primiparous women (9.1% [233/2,562] vs. 5.0% [131/2,635], $P = 0.0000$; relative risk [RR] with 95% confidence interval [95%CI], 1.83 [1.49 to 2.25]). Indeed, the infection

rate was higher in multiparous than in primiparous women at 15 (79%) of the 19 hospitals (Fig. 1) in which the median (range) infection rate was significantly higher for multiparous than for primiparous women (7.5% [3.4% – 13.7%] vs. 4.0% [0.8% – 13.6%], $P = 0.0034$).

Vaccination coverage rate and effect of vaccination on influenza infection

The overall vaccination coverage rate was 51% (2,661/5,197) (Table 3) and did not differ markedly between primiparous and multiparous women (49% [1,299/2,635] vs. 53% [1,362/2,562], respectively). Maternal age affected vaccination coverage—women aged < 25 years received vaccination significantly less often than those aged ≥ 25 years (see legend for Fig. 2). Vaccines against influenza used in Japan in 2014 – 2015 did not work to reduce number of pregnant women with influenza (Table 3, Fig. 2). Overall infection rate did not differ significantly between those with and without vaccination (7.3% [195/2,661] vs. 6.7% [169/2,526], respectively) (Table 3). The infection rate did not differ significantly between those with and without vaccination among primiparous (5.7% [74/1,299] vs. 4.3% [57/1,328], respectively) as well as multiparous women (8.9% [121/1,362] vs. 9.3% [112/1,198], respectively). Thus, multiparous women had a higher risk of influenza regardless of vaccination status compared to primiparous women (8.9% vs. 5.7%; RR [95% CI], 1.80 [1.36 to 2.38] for vaccinated women and 9.3% vs. 4.3%; 2.18 [1.60 to 2.97] for unvaccinated women).

There was no consistent association between maternal age and the risk of influenza infection (Fig. 2). The median (range) vaccination coverage rate among 19 hospitals was 49% (27% – 72%) vs. 52% (31% – 70%) for primiparous vs. multiparous women.

No significant correlation was seen between vaccination coverage rates and influenza infection rates (data not shown).

Effect of cohabitant number on influenza infection rate (Fig. 3)

As expected, the number of cohabitants was significantly greater for multiparous than primiparous women (2 [0 – 9] vs. 1 [0 – 11], respectively, $P < 0.0001$). The influenza infection rate increased with increasing number of cohabitants among pregnant women with at least one cohabitant (Fig. 3). The presence of at least one child aged 1 – 17 years consistently increased 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% [226/2,499] vs. 5.1% [138/2,698], $P < 0.0001$). Although the median cohabitant number was 2 for both women with and without influenza (Table 3), the distribution of number of cohabitants differed significantly between women with and without influenza ($P < 0.0001$). The number of women with ≥ 3 cohabitants was significantly greater for those with than without influenza (35% [129/364] vs. 25% [1,213/4,833], respectively, $P < 0.0001$).

Risk of influenza infection in women whose main occupation was housekeeping during the current pregnancy

Housekeeping was the main occupation in 49% (2,541) of the 5,197 women (Table 3). Neither maternal age nor number of cohabitants differed significantly between those who worked within and outside the home (33.0 [15 – 48] vs. 32.5 [16 – 48] years for maternal age, respectively; 2 [0 – 11] vs. 2 [0 – 9] for number of cohabitants,

respectively). However, women with housekeeping had a significantly reduced risk of influenza by approximately 27% (5.9% [150/2,541] vs. 8.1% [212/2,616] (Table 3); RR [95%CI], 0.73 [0.60 to 0.89]).

Discussion

To our knowledge, this is the first study demonstrating family size as a risk factor for influenza infection in pregnancy. The risk of influenza infection in pregnancy increased with increasing number of cohabitants among women with at least one cohabitant, while pregnant women living alone (no cohabitant) were at higher risk of influenza comparable to that of pregnant women with ≥ 3 cohabitants in this study. Women with at least one child aged 1 – 17 years had a consistently higher risk of influenza at any family size. In addition, this study demonstrated that pregnant homemakers were at lower risk of influenza compared to women working outside home. Taken together, these results suggested that pregnant women with a greater chance of encountering individuals possibly carrying influenza virus have higher risk of influenza. It was speculated that pregnant women living alone may have had more opportunities to go out compared to those with one cohabitant, and that nursery- and school-aged children were responsible for bringing influenza viruses into most families of multiparous pregnant women.

Our previous study conducted during the 2013 – 2014 influenza season indicated a seasonal influenza vaccine coverage rate among pregnant Japanese women of approximately 50% (7), which was similar to those during and after pandemic (H1N1)

2009 in the USA (8, 9) and was nearly equivalent between primiparous and multiparous women (50% and 53%, respectively (7), consistent with the results of 49% and 53%, respectively, in this study). However, multiparous women had a significantly higher rate of contracting influenza than primiparous women, regardless of vaccination status (5.6% vs. 2.2% for vaccinated women and 9.7% vs. 3.5% for unvaccinated women, respectively)(7). This information was considered important and useful to aid national policy makers and health programme planners in making decisions about target groups for vaccination if this phenomenon would be reproducible. This study confirmed the reproducibility of the higher risk of influenza in multiparous than primiparous women; multiparous women had a higher risk of influenza regardless of vaccination status (RR of 1.80 [1.36 – 2.38] for vaccinated women and 2.18 [1.60 – 2.97] for unvaccinated women) compared to primiparous women.

We hypothesised that multiparous pregnant women have a greater number of cohabitants than primiparous women, and therefore the chance of influenza viruses being brought into the home is greater in families of multiparous than primiparous pregnant women. This hypothesis was verified in this study; indeed, family size was greater for multiparous than for primiparous women, and the risk of influenza among pregnant women increased with increasing number of cohabitants. Thus, the higher risk of influenza in multiparous than primiparous women could be explained by the greater numbers of cohabitants in families of multiparous women. In addition, nursery- and school-aged children were suggested to be responsible for bringing influenza viruses into most families of multiparous pregnant women.

Low vaccine effectiveness can occur as a result of mismatch between vaccine strains and circulating strains (10), and was a concern in the 2014 – 2015 Northern hemisphere influenza season (11 – 13). Indeed, vaccines used in Japan in the 2014 – 2015 influenza season were ineffective in reducing the number of pregnant women with influenza, with influenza prevalence rates of 7.3% vs. 6.7% for those with and without vaccination, respectively, in this study.

It was difficult to verify that respondents answered questions correctly due to the nature of this questionnaire study. However, the prevalence rate of influenza among unvaccinated pregnant women, 6.7% (169/2,526) in this study, was consistent with the corresponding rate of 6.3% in the 2013 – 2014 influenza season (7). Eighty-four percent (306/364) and 77% (282/364) of women who reported having contracted influenza specified the types of influenza and took antiviral agents, respectively, in this study. These figures were also consistent with those in the 2013 – 2014 influenza season (83% for influenza type specification and 83% for use of antiviral agents) (7). In addition, low vaccine coverage in younger pregnant women was also a reproducible phenomenon; 28% (95/336) for women aged < 25 years in this study and 31% in the 2013 – 2014 influenza season (7). The use of influenza rapid diagnostic tests capable of differentiating between influenza A and influenza B is a common clinical practice in febrile patients in Japan, and the use of anti-influenza drugs for treatment of influenza is widely accepted in pregnant Japanese women (14).

In conclusion, this study demonstrated that multiparous women were at increased risk of influenza infection. The risk of influenza in pregnancy increased with increasing

number of cohabitants. Children aged 1 – 17 years were suggested to be responsible for bringing viruses into the homes of most families of multiparous pregnant women. Vaccine coverage was low in younger pregnant Japanese women. This information will be useful to aid national policy makers and health programme planners in making decisions about target groups for vaccination and intensified campaigns. Although mismatch between vaccine strains and circulating strains resulted in low vaccine effectiveness in the 2014 – 2015 influenza season in the Northern hemisphere (10 – 13), including Japan, maternal influenza immunization is a highly cost-effective intervention to reduce disease rates and severity in seasonal influenza epidemics as well as occasional pandemics (15). Continued efforts are required to avoid the mismatch between vaccine strains and circulating strains and to encourage pregnant women to receive influenza vaccination.

Disclosure

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

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Figure legends

Figure 1. Influenza infection rates among primiparous vs. multiparous women in 19 hospitals located throughout Japan

A, Locations of 19 hospitals that participated in this study on a map of Japan; B, Influenza infection rates at the 19 hospitals. Although the infection rate was slightly higher among primiparous than multiparous women at 4 (21%) hospitals (A, C, M, and P), the median (range) infection rate at the 19 hospitals was significantly higher for multiparous than for primiparous women (7.5% [3.4% – 13.7%] vs. 4.0% [0.8% – 13.6%], respectively, $P = 0.00338$). The influenza infection rates at these hospitals for primiparous vs. multiparous women were as follows: 8.8% (5/57) vs. 8.3% (4/48) at hospital A, 9.1% (46/505) vs. 13.7% (85/622) at B, 6.2% (4/65) vs. 5.6% (3/54) at C, 1.4% (1/69) vs. 6.4% (3/47) at D, 3.4% (10/291) vs. 8.2% (24/293) at E, 2.0% (1/51) vs. 8.2% (5/61) at F, 0.8% (1/120) vs. 8.2% (8/95) at G, 2.9% (1/34) vs. 3.7% (1/27) at H, 2.5% (4/163) vs. 9.1% (14/154) at I, 5.1% (3/59) vs. 18.3% (13/71) at J, 2.3% (2/88) vs. 4.5% (5/111) at K, 2.0% (4/200) vs. 7.3% (14/191) at L, 4.5% (9/200) vs. 3.4% (5/146) at M, 7.3% (16/218) vs. 10.6% (20/189) at N, 3.6% (6/168) vs. 5.8% (10/171) at O, 5.1% (2/39) vs. 4.3% (2/47) at P, 6.1% (6/98) vs. 7.6% (7/92) at Q, 5.8% (7/120) vs. 7.1% (6/84) at R, and 3.3% (3/90) vs. 6.8% (4/59) at hospital S, respectively. The response rates to our questionnaire among primiparous vs. multiparous women at these hospitals were as follows: 49% (57/117) vs. 36% (48/134) at hospital A, 100% (505/505) vs. 100% (622/622) at B, 96% (65/68) vs. 84% (54/64) at C, 100% (69/69) vs. 100% (47/47) at D, 87% (291/333) vs. 88% (293/334) at E, 86% (51/59) vs. 80% (61/76) at F, 88% (120/136) vs. 90% (95/106) at G, 38% (38/89) vs. 38% (27/72) at H,

82% (163/200) vs. 81% (154/190) at I, 54% (59/110) vs. 59% (71/121) at J, 67% (88/132) vs. 80% (111/138) at K, 60% (200/335) vs. 76% (191/250) at L, 71% (200/280) vs. 66% (146/220) at M, 93% (218/235) vs. 94% (189/201) at N, 88% (168/191) vs. 94% (171/181) at O, 61% (39/64) vs. 64% (47/73) at P, 82% (98/120) vs. 81% (92/114) at Q, 36% (120/336) vs. 39% (84/214) at R, and 94% (90/96) vs. 95% (59/62) at S, respectively.

Figure 2. Influenza infection rates according to maternal age and vaccination status among primiparous vs. multiparous women

For primiparous vs. multiparous women, overall vaccination coverage rate was 49% (1,299/2,635) vs. 53% (1,362/2,562) respectively, and was 24% (12/50) vs. 33% (2/6) for those aged < 20 years, 29% (70/239) vs. 26% (25/97) for 20 – 24 years, 52% (361/694) vs. 46% (186/407) for 25 – 29 years, 53% (422/791) vs. 52% (491/937) for 30 – 34 years, 52% (313/607) vs. 61% (517/849) for 35 – 39 years, and 47% (119/251) vs. 53% (140/264) for those aged ≥ 40 years, respectively. Influenza was consistently more prevalent for multiparous than primiparous women in all age categories regardless of vaccination status. No influenza infection occurred in teenage pregnant women (0.0% [0/50] vs. 0.0% [0/6] for primiparous vs. multiparous women, respectively).

Figure 3. Effects of number of cohabitants on the risk of influenza infection

The numbers of women with influenza are indicated at the tops of the bars. Compared to women with one cohabitant, women with 0, 2, 3, and ≥ 4 cohabitants had RR (95% CI) of 1.99 (1.17 to 3.39), 1.56 (1.21 to 2.02), 1.89 (1.41 to 2.53), and 2.18 (1.60 to 2.96) for contracting influenza, respectively. Women with cohabitant(s) were divided

into two groups according to the presence or absence of at least one child aged 1 – 17 years. The presence of a child aged 1 – 17 years consistently increased the risk of influenza in pregnancy at all family sizes.

Fig. 1

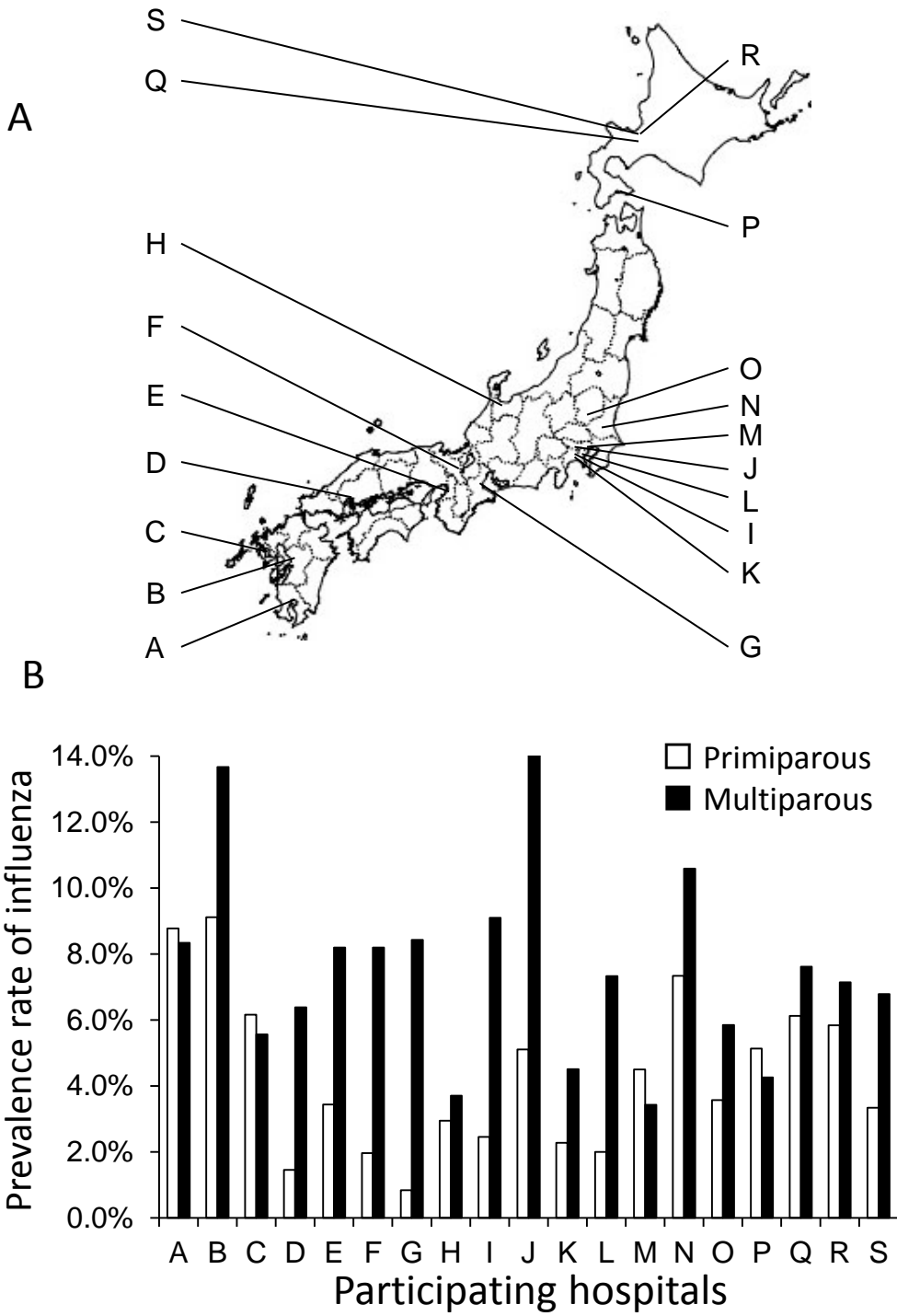
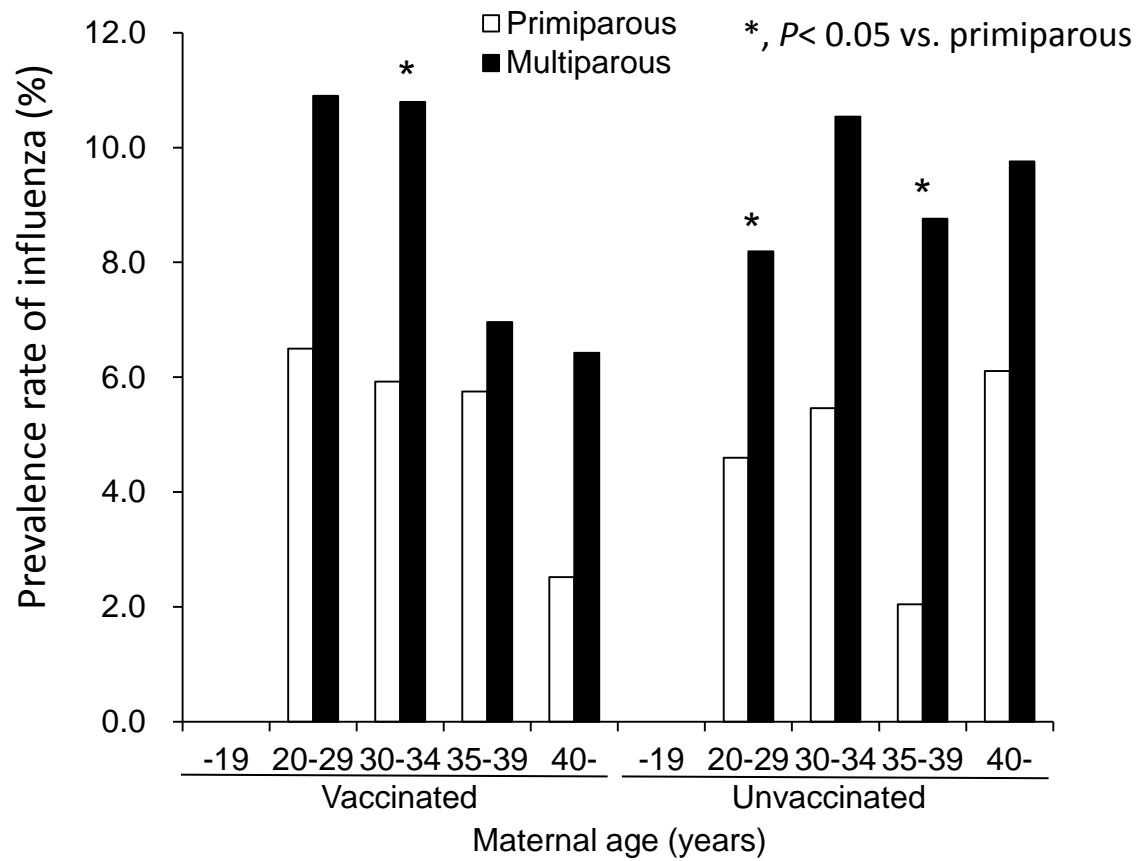


Fig. 2



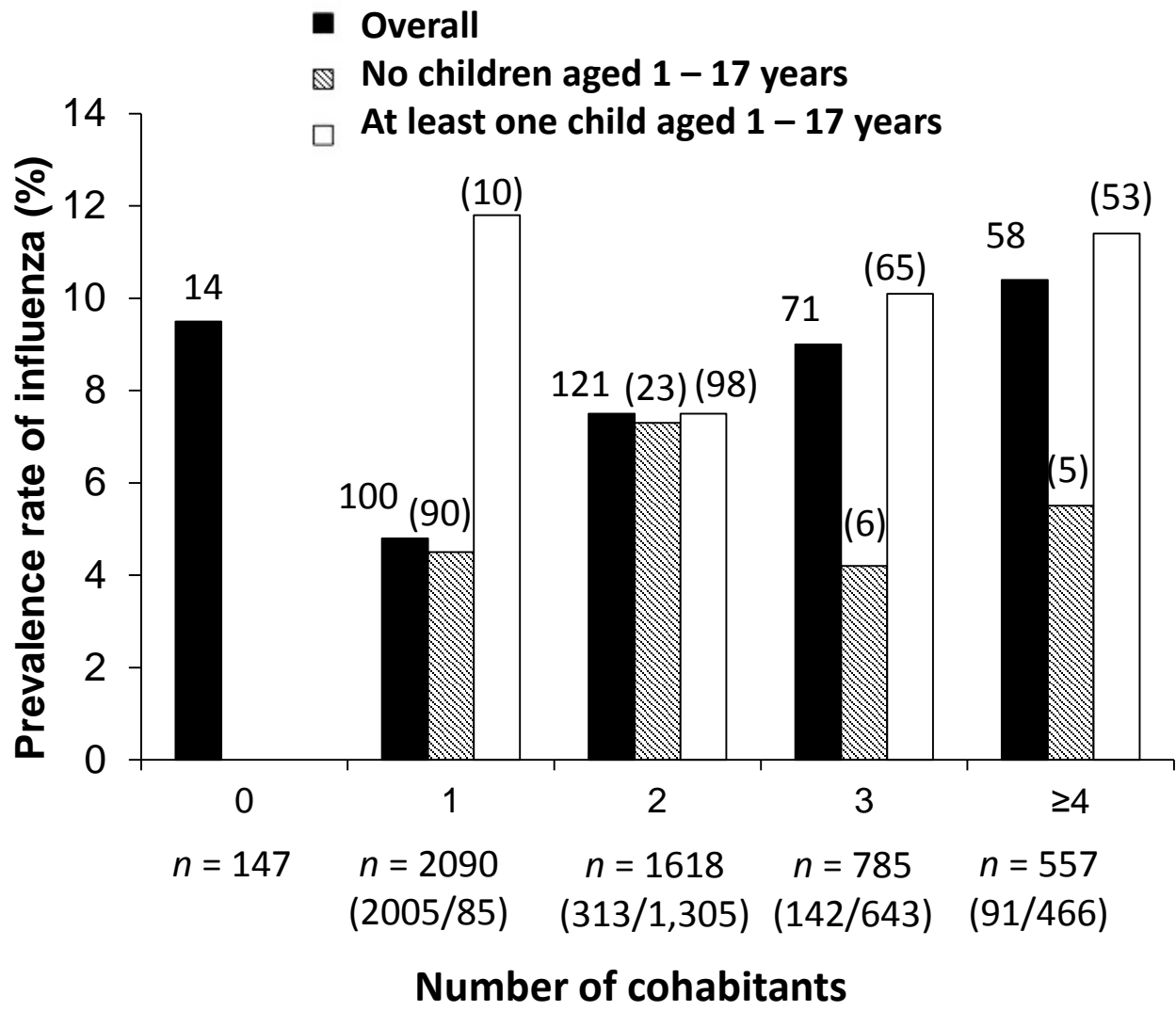


Table 1. Questionnaire form given to postpartum women with deliveries during the study period (March 1, 2015, to July 31, 2015)

Q1: Please specify your age in parenthesis.

I am (____) years old.

Q2: Was the current childbirth your first experience of childbirth?

Yes, No

Q3: Were you vaccinated against influenza on or after October 2014?

Yes, No

Q4: Please specify number of cohabitants according to their age in parentheses.

- Infants aged less than 1 year: () persons
- Children aged 1 to 17years: () persons
- adults aged 18 years of more: () persons

Q5: What was your job that accounted for most time of your pregnancy?

mainly housekeeping

mainly jobs done outside your home

Q6: Did you contract influenza during the current pregnancy?

Yes, No

The following questions are for women answering “Yes” in response to Q6

Q7: What was the type of influenza?

A, B, Unknown

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

Yes, No

Table 2 Maternal age distribution among all 6,694 candidates and 5,197 respondents

| | All candidates (primiparous) | Respondents (primiparous) |
|---------------------|--------------------------------|------------------------------|
| Maternal age (year) | | |
| ≤19 | 83 (70), [1.2% (2.0%)] | 56 (50), [1.1% (1.9%)] |
| 20–29 | 2,036 (1,313), [30.4% (37.8%)] | 1,437 (933), [27.7% (35.4%)] |
| 30–34 | 2,200 (1,049), [32.9% (30.2%)] | 1,728 (791), [33.2% (30.0%)] |
| 35–39 | 1,793 (749), [26.8% (21.6%)] | 1,456 (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 | 6,694 (3,475), [100% (100%)] | 5,197 (2,635), [100% (100%)] |

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

Table 3 Demographic characteristics of 5,197 participants

| | Influenza infection during current pregnancy | |
|------------------------|--|----------------|
| | Yes | No |
| No. of women | 364 | 4,833 |
| Primiparous | 131 (36.0%) | 2,504 (51.8%) |
| Multiparous | 233 (64.0%) | 2,329 (48.2%) |
| Unknown | 0 (0%) | 0 (0%) |
| Maternal age (year) | 32.0 (20 - 45) | 33.0 (15 - 48) |
| ≤ 19 | 0 (0%) | 56 (1.2%) |
| 20–34 | 243 (66.8%) | 2,922 (60.5%) |
| 35–39 | 89 (24.4%) | 1,367 (28.3%) |
| ≥ 40 | 32 (8.8%) | 483 (10.0%) |
| Unknown | 0 (0%) | 5 (0.1%) |
| No. of cohabitants | 2.0 (0–8) | 2.0 (0–11) |
| 0 | 14 (3.8%) | 133 (2.8%) |
| 1 | 100 (27.5%) | 1,990 (41.2%) |
| 2 | 121 (33.2%) | 1,497 (31.0%) |
| 3 | 71 (19.5%) | 714 (14.8%) |
| ≥ 4 | 58 (15.9%) | 499 (10.3%) |
| Unknown | 0 (0%) | 0 (0%) |
| Job | | |
| Housekeeping | 150 (41.2%) | 2,391 (49.5%) |
| Outside home | 212 (58.2%) | 2,404 (49.7%) |
| Unknown | 2 (0.5%) | 38 (0.8%) |
| Vaccination | | |
| Yes | 195 (53.6%) | 2,466 (51.0%) |
| No | 169 (46.4%) | 2,357 (48.8%) |
| Unknown | 0 (0%) | 10 (0.2%) |
| Type of influenza | | |
| A | 270 (74.2%) | |
| B | 36 (9.9%) | |
| Unknown | 58 (15.9%) | |
| Use of antiviral agent | | |
| Yes | 282 (77.5%) | 2 (0.0%) |
| No | 74 (20.3%) | 4,831 (100.0%) |
| Unknown | 8 (2.2%) | 0 (0%) |