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Risk of fetal death after pandemic influenza infection or vaccination during pregnancy

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Abstract

Background—During the 2009 influenza pandemic, pregnant women were at particular risk of serious influenza illness. This concern was further complicated by questions about vaccine safety in pregnant women raised by anecdotal reports of fetal deaths following vaccination.

Methods—We explored the safety of influenza vaccination of pregnant women by linking Norwegian national registries and medical consultation data to determine influenza diagnosis, vaccination status, birth outcomes, and background information for pregnant women before, during, and after the pandemic. We used Cox regression models to estimate hazard ratios of fetal death, with gestational day as the time metric and vaccination and pandemic exposure as time-dependent exposure variables.

Results—There were 117,347 eligible pregnancies in Norway in 2009–2010. Fetal mortality was 4.9/1000. 54% of pregnant women in their second or third trimester during the pandemic were vaccinated. Vaccination in pregnancy substantially reduced the risk of influenza diagnosis (adjusted hazard ratio, 0.30; 95% confidence interval [CI], 0.25 to 0.34). A clinical diagnosis of influenza in the mother increased the risk of fetal death (adjusted hazard ratio, 1.91; 95% CI, 1.07 to 3.41). Among pregnant women, the risk of fetal death was lower with vaccination, although this reduction was not statistically significant (adjusted hazard ratio, 0.88; 95% CI, 0.66 to 1.17).

Conclusions—Pandemic influenza in pregnancy was associated with increased risk of fetal death. Vaccination during pregnancy reduced the risk of influenza diagnosis. Vaccination itself did not increase fetal mortality, and may have reduced the risk of influenza-related fetal death during the pandemic.

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Keywords

Pandemic vaccination; influenza; influenza A(H1N1)pdm09; pandemic; pregnancy; fetal death; miscarriage; abortions; stillbirth; Norway; registry; register; population

BACKGROUND

During the influenza pandemic of 2009, pregnant women were particularly vulnerable to severe influenza illness, with heightened risk of adverse pregnancy outcomes and maternal death.[1–4] This susceptibility of pregnant women to influenza has also been observed in the past.[5–12]

The WHO recommendation for seasonal influenza vaccine, which includes vaccination of pregnant women, did not change during the H1N1pandemic.[13] In addition, pregnant women were recommended a pandemic vaccine.[14] Before 2009, pregnant women in Norway were not routinely advised to be vaccinated against seasonal influenza. During the pandemic, a trivalent seasonal influenza vaccine and an adjuvanted H1N1 vaccine were recommended to high-risk groups, except that pregnant women were recommended the pandemic vaccine only, in the second or third trimesters of pregnancy. Animal trials and results provided by the vaccine manufacturer indicated no excess risk of miscarriage or stillbirth after vaccination.[15] Still, anecdotal reports of fetal deaths occurring shortly after vaccination raised public concern about vaccine safety.[15]

Following the 2009 pandemic, we made use of national health registries and primary care reimbursement data in Norway to assess the effectiveness of the vaccine in pregnant women and the impact of vaccination or influenza on fetal survival.

METHODS

Data sources and study population

We linked information on women of reproductive age in Norway to various national health registries and to national primary-care physician-reimbursement data. Data were obtained from the National Population Register,[16] the Norwegian Immunisation Register,[17] the Surveillance System for Communicable Diseases,[18] the Medical Birth Registry of Norway,[19] and the Directorate of Health (reimbursement data). The Norwegian Patient Registry provided the number of hospitalized pregnant women during the pandemic. Of 1,153,738 women living in Norway in 2009 who were 13–49 years of age, 117,026 women gave birth in 2009 or 2010. We restricted our sample to women who became pregnant 43 weeks before 31 December 2010, so as not to oversample short pregnancies during the latter part of 2010. We excluded from the main analysis children who were part of a plural birth, those with invalid vaccination dates, and the few women vaccinated with Celvapan only, leaving 113,331 women in analyses. Details on number and type of information from each data source, and a flow chart showing eligibility, are provided in the Supplementary Appendix (Methods and Figure S1).

The study was approved by the Regional Committee for Medical and Health Research Ethics and the Norwegian Data Protection Authority. All authors contributed to the design, collection of data, writing of the paper, and all agreed to publish the paper. SEH, NG, HKG, SOS, and AS were responsible for the data analyses. The first author vouches for data integrity and accuracy of the analysis.

Outcome and exposure information

We defined fetal death as any recorded miscarriage or stillbirth after 12 completed weeks of pregnancy. Based on both laboratory-confirmed cases of pandemic influenza and physician visits for influenza reported to the Norwegian Institute of Public Health,[20] the main pandemic wave in Norway occurred between 1 October and 31 December 2009. For women already pregnant on 1 October, "exposure to the pandemic" was defined as from 1 October to day of delivery. Women whose first day of last menstrual period (LMP) fell between 1 October and 31 December were considered "exposed to the pandemic" from LMP to delivery.

"Exposure to influenza" was defined as a primary-care-physician contact leading to a diagnosis of influenza (International Classification of Primary Care code R80; criteria listed in Supplementary Appendix). Pregnant women were considered "exposed to influenza" from day of diagnosis until delivery. If there were multiple consultation dates during the main pandemic, the first visit was used.

Pregnant women were defined as "unexposed to the vaccine" from LMP to day of vaccination, and as "exposed to the vaccine" from day of vaccination until delivery. The Norwegian Institute of Public Health recommended one dose of Pandemrix. For the few pregnant women (n=266) receiving two doses, exposure was defined as starting with the first dose. Fetuses whose mothers were unvaccinated, vaccinated before pregnancy, or vaccinated on the day of delivery or thereafter, were considered unexposed to vaccine.

Statistical analyses

The analysis requires methods that handle time-dependent exposures and censoring.[21] We used a Cox proportional-hazards model[22] with gestational day as the underlying time metric. Hazard ratios with 95% confidence intervals were estimated. Pregnancies entered into analysis on day 84 (pregnancy week 12) and were censored at delivery. Pregnancies longer than 84 days as of 1 January 2009 entered at gestational age as of that date. Pregnancy days prior to 1 January 2009 were not included in the risk set. Figure 1 illustrates the study design, eligible pregnancies, observed pregnancy days and exposure to the pandemic wave.

The study had three specific aims: to investigate the risk of fetal death after exposure to the pandemic, the risk after clinical diagnosis of influenza, and the risk after vaccination in pregnancy. In the first model, we used a binary time-dependent variable for exposure to the pandemic wave during pregnancy. In the second model, we analyzed clinical influenza diagnosis during pregnancy as a time-dependent variable, using the same reference as in the first model ("no exposure to the pandemic" [reference group], "exposed, *without* a clinical diagnosis", and "exposed, *with* a clinical diagnosis"). Exposure to vaccination during pregnancy was a binary time-dependent variable.

Exposure variables were first analyzed separately with fetal death as outcome to obtain crude estimates. We then adjusted the models with influenza exposures for vaccination status. Finally, we added potential confounders to the models to estimate adjusted hazard ratios for fetal death. Possible confounders included chronic diseases, previous pregnancy history, BMI, use of nutritional supplements, and smoking. To further explore whether pandemic influenza had different effects in vaccinated versus unvaccinated pregnant women, we used a third model that combined exposure to the pandemic and vaccination status in four mutually exclusive categories: "*not* pregnant during the pandemic and vaccinated" (only 38 women), "pregnant during the pandemic *and not* vaccinated", "pregnant during the pandemic *and* vaccinated" and "*not* pregnant in the main pandemic wave *and not* vaccinated (reference group)." A separate model was used to examine the risk of influenza diagnosis after vaccination during the pandemic period. In this model, only

pregnancy days within the main pandemic wave (1 October to 31 December 2009) were included, and the outcome was physician consultation for influenza. Women were regarded as becoming at risk one week after vaccination. The time metric was gestational day, and women entered analysis on 1 October 2009 or on their LMP if this was within the pandemic window. Women were censored at delivery if before 31 December, or on the day of influenza diagnosis.

There were 3,208 women who had two pregnancies during the study period. To handle dependency between the two pregnancy outcomes, we used a sandwich estimator to obtain confidence intervals that take the dependence into account. We conducted sensitivity analyses that included plural births, and that excluded women vaccinated in the first trimester of pregnancy. We also performed analyses in which women vaccinated before pregnancy were defined as vaccinated on their first pregnancy day. Body mass index (BMI) was available for only 39% of the women, and therefore analyzed in a separate model. The remaining confounder data were complete for 98% of women, and were included in the fully adjusted models. The assumption of proportional hazards was assessed using Schoenfeld residuals and found valid. Analyses were done using SPSS version 19 (SPSS Inc., Chicago, IL) and STATA version 11 (StataCorp, College Station, TX).

RESULTS

There were 117,347 deliveries in Norway in 2009–2010 among women with LMP in the eligible time-window, including 570 fetal deaths (4.9/1000). There were 113,331 eligible singleton pregnancies, of which 492 ended in fetal death (4.3/1000). Among the 99,539 women who delivered outside the pandemic, there were 410 fetal deaths. Pandemic influenza vaccinations were offered starting 19 October 2009, and nearly all vaccinations (97%) were given by 31 December 2009. There were 25,976 children born after their mother was vaccinated during pregnancy, with almost all vaccinations occurring during the second or third trimester. Among the vaccinated women there were 78 fetal deaths. Among women pregnant during the pandemic but unvaccinated (n= 87,335) there were 414 fetal deaths. Vaccination status of eligible women is shown in Table S1 (Supplementary Appendix), together with the distribution of gestational age at vaccination (Figure S2). Of the 46,491 women in their second or third trimester during the pandemic wave (1 October to 31 December 2009), 54% were vaccinated. Characteristics of these pregnancies are provided in Table 1, with an extended list in Table S2 (Supplementary Appendix). Vaccination coverage of pregnant women was higher in those with chronic diseases, and lower in daily smokers and younger women.

A clinical diagnosis of influenza during the pandemic wave was recorded for 2,278 eligible pregnant women, in whom there were 16 fetal deaths. There were 516 women laboratory-positive for A(H1N1)pdm09, of which fewer than 5 experienced fetal death (too few to estimate risk). The time distribution of vaccinations and positive laboratory tests in pregnant women are illustrated in Figure 2. Vaccination in pregnancy reduced the risk of receiving a clinical diagnosis of influenza (adjusted hazard ratio, 0.30; 95% CI, 0.25 to 0.34).

Using women who were pregnant outside the pandemic as reference, pregnant women exposed to the pandemic had an increased risk of fetal death (adjusted hazard ratio, 1.26; 95% CI, 1.02 to 1.55)(Table 2). Risk of fetal death was higher among women with a clinical diagnosis of influenza (adjusted hazard ratio, 1.91; 95% CI, 1.07 to 3.41). Pregnant women who were vaccinated had a slightly lower risk of fetal death compared with unvaccinated women (regardless of infection), although this was not statistically significant (hazard ratio, 0.88; 95% CI, 0.66 to 1.17). Since nearly all vaccinations occurred during the pandemic period, the estimated hazard ratio in effect compares vaccinated and unvaccinated women

who were pregnant during the pandemic period. Unvaccinated women had higher risk of fetal death during the pandemic (hazard ratio, 1.25; 95% CI, 1.02 to 1.55) (Table 3).

Adjustment for covariates did not substantially influence the estimates, which were likewise similar in models that included women with plural births or excluded women with first-trimester vaccinations, that adjusted for BMI, or that re-defined women who were vaccinated prior to pregnancy as "exposed" on their first pregnancy day.

The Norwegian Patient Registry reported that a total of 40 pregnant women were hospitalized with influenza during the pandemic wave, of whom only one had a fetal death. We also considered non-fatal birth outcomes (preterm delivery, term low birth weight, and Apgar score), and found no suggestion of adverse effects of vaccination on pregnancy (Table S3, Supplementary Appendix).

DISCUSSION

Pandemrix is an inactivated virus vaccine against influenza AH1N1pdm09, with an AS03 adjuvant. Although safety data for use of Pandemrix in pregnant women were lacking at the time of the pandemic, data from animal studies showed no reproductive toxicity, and it was considered safe for use in pregnancy[15]. Nevertheless, early reports of fetal losses after vaccination with Pandemrix, including 30 reports in Norway,[23] raised public concern about the safety of vaccination in pregnancy. Using national registries and health care reimbursement records in Norway, we found no evidence that influenza vaccination of pregnant women increased the risk of fetal death. However, influenza infection itself posed a major risk: among pregnant women who were clinically diagnosed with influenza, the risk of fetal death was increased nearly two-fold. Vaccination appeared to provide some protection against excess fetal mortality during the pandemic.

A strength of this study is the use of nationwide mandatory registries containing dates of events, combined with relatively high vaccination coverage. Due to the organization of health care in Norway, nearly all consultations for influenza symptoms are in primary care or emergency outpatient settings, for which physicians are reimbursed by the government. Pregnant women in Norway receive free prenatal care and deliver free of charge in hospitals. During the pandemic, vaccines were offered to all Norwegian residents for free or with a small administration fee. It is therefore unlikely that vaccine availability influenced the uptake of vaccination by pregnant women.

The birth registry data have been found to have adequate validity,[24, 25] and validity is not expected to be influenced by vaccination status. However, if awareness after vaccination triggered more reporting of early losses in vaccinated women, it could exaggerate adverse effects and attenuate potential protective effects of the vaccine. Registration of vaccination was mandatory, although around 10% of the 2.43 million doses given in Norway were not registered. If some women who were classified in our analysis as unvaccinated had been vaccinated without registration, this could mean that the benefits of vaccination are stronger than we estimate.

Estimates could be confounded if women with known risk factors for fetal death, for example diabetes or a history of previous fetal death, were more (or less) likely to accept vaccination. The vaccination coverage was higher among women with chronic conditions and obesity (which were high risk groups for influenza illness), and lower in smoking women, indicating that lifestyle factors may confound associations. However, adjusting for known potential confounding factors had little impact on the associations.

The main pandemic wave and the vaccination period had substantial overlap (Figure 2), and women could have been exposed to influenza before being vaccinated (or before the vaccine became effective), which could attenuate potential protective effects of the vaccine. We used three approaches to assess exposure to influenza virus. First, we accessed all reported cases of laboratory-confirmed pandemic influenza. The Norwegian Institute of Public Health issued recommendations on laboratory testing during the pandemic. Until 20 July 2009, physicians were encouraged to sample widely. After this date, for capacity reasons, it was recommended to restrict testing to prioritized groups including pregnant women. However, too few women were tested during pregnancy to make analyses of fetal death meaningful. Secondly, we had data on physician contacts leading to a diagnosis of influenza. Approximately 20–30% of the Norwegian population had clinical influenza during the pandemic.[26] In our study of women who gave birth in 2009–2010, the number was 8.9%. The women who contacted a physician regarding influenza symptoms were probably women with more severe symptoms, so our results may reflect effects related to more severe clinical illness. However, only one woman hospitalized with influenza had a fetal death during the pandemic, so our fetal loss data represent almost entirely non-hospitalized women. Women with a clinical diagnosis of influenza had nearly a two-fold increase of subsequent fetal death. Our third approach was to use the time period of the main pandemic wave as a proxy for exposure to the pandemic influenza virus. Pregnant women exposed to the main pandemic wave had elevated risks of fetal death (Table 2). Risk of fetal death was slightly lower in vaccinated than in unvaccinated women (Table 3). Taken together, these results are consistent in suggesting a harmful effect of pandemic influenza virus on fetal survival.

Recent smaller studies (from Denmark and Canada) have likewise found no evidence that influenza vaccination during the 2009 pandemic increased the risk of stillbirth[27,28] or other adverse birth outcomes.[29] Unlike these earlier studies, we also show an increased risk of fetal death after maternal infection by influenza, especially in women with clinical diagnosis of influenza. This consequence of influenza infection has been suggested by data from the influenza pandemic of 1918,[5, 7, 8] and been reported in women hospitalized during the 2009 pandemic.[4] However, maternal infection with influenza has not generally been recognized as a risk to the survival of the fetus in the absence of hospitalized maternal illness.

Given the danger posed by maternal influenza to fetal survival, our study adds to growing evidence for lack of harm – and a possible benefit – that accrues to the fetus from vaccination of pregnant women during an influenza pandemic. Based on these data, there is no basis for withholding influenza vaccinations from pregnant women in their second or third trimester – an important group, given that these women can be particularly vulnerable to the severe effects of influenza infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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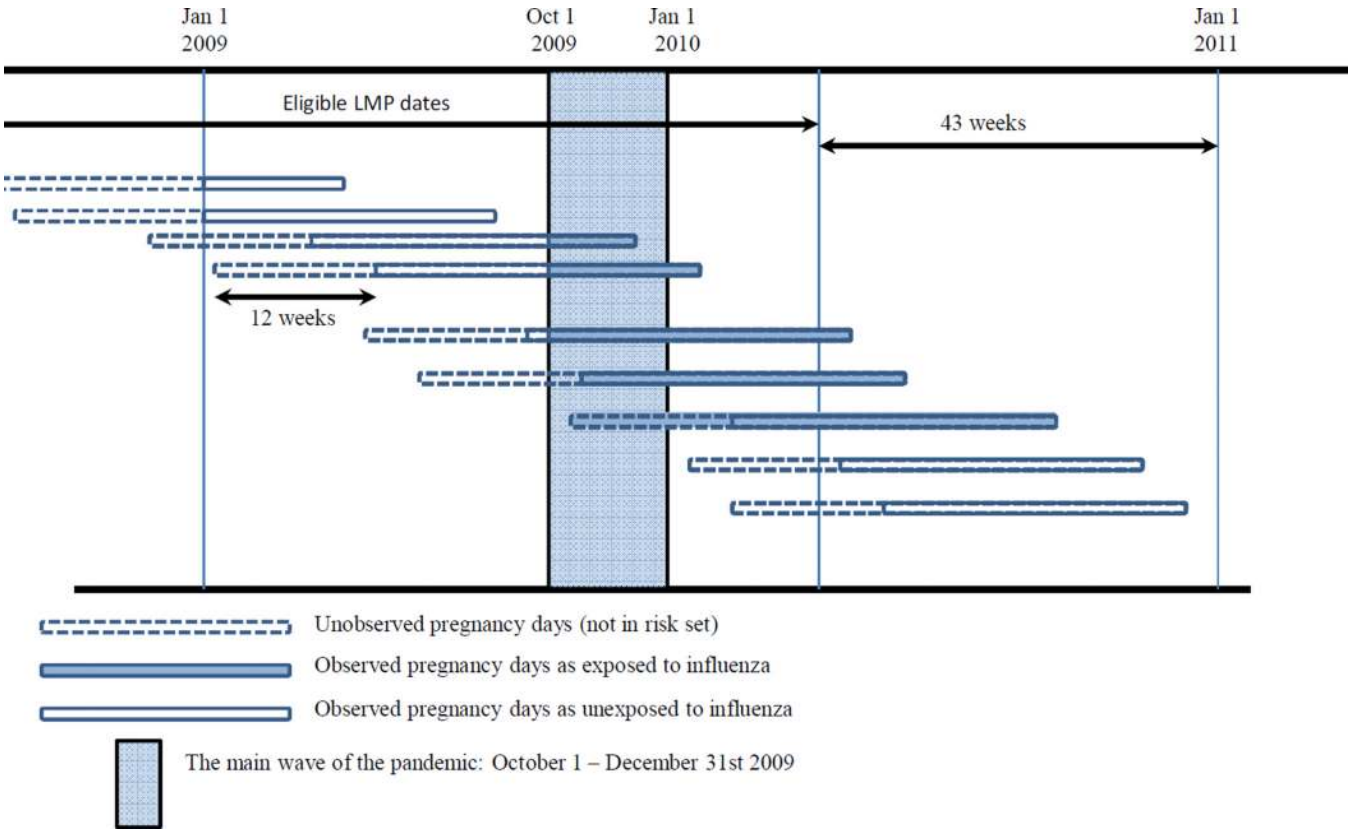

Figure 1.

Live births in Norway occurring in 2009 and 2010 were eligible for study if the date of last menstrual period occurred in or before the first 9 weeks of 2010 (43 weeks before 31 December 2009). Eligible pregnancies were defined as exposed to the influenza pandemic if any days between the date of the last menstrual period and birth occurred between 1 October and 31 December 2009. For a given pregnancy, days at risk are pregnancy days after week 12 occurring after 1 January 2009, and exposure days are defined as all pregnancy days from first day of exposure to delivery. For simplicity, the figure shows all pregnancies as lasting 9 months; study includes all registered pregnancies lasting at least 12 weeks. The period of the main wave of the influenza pandemic is shaded.

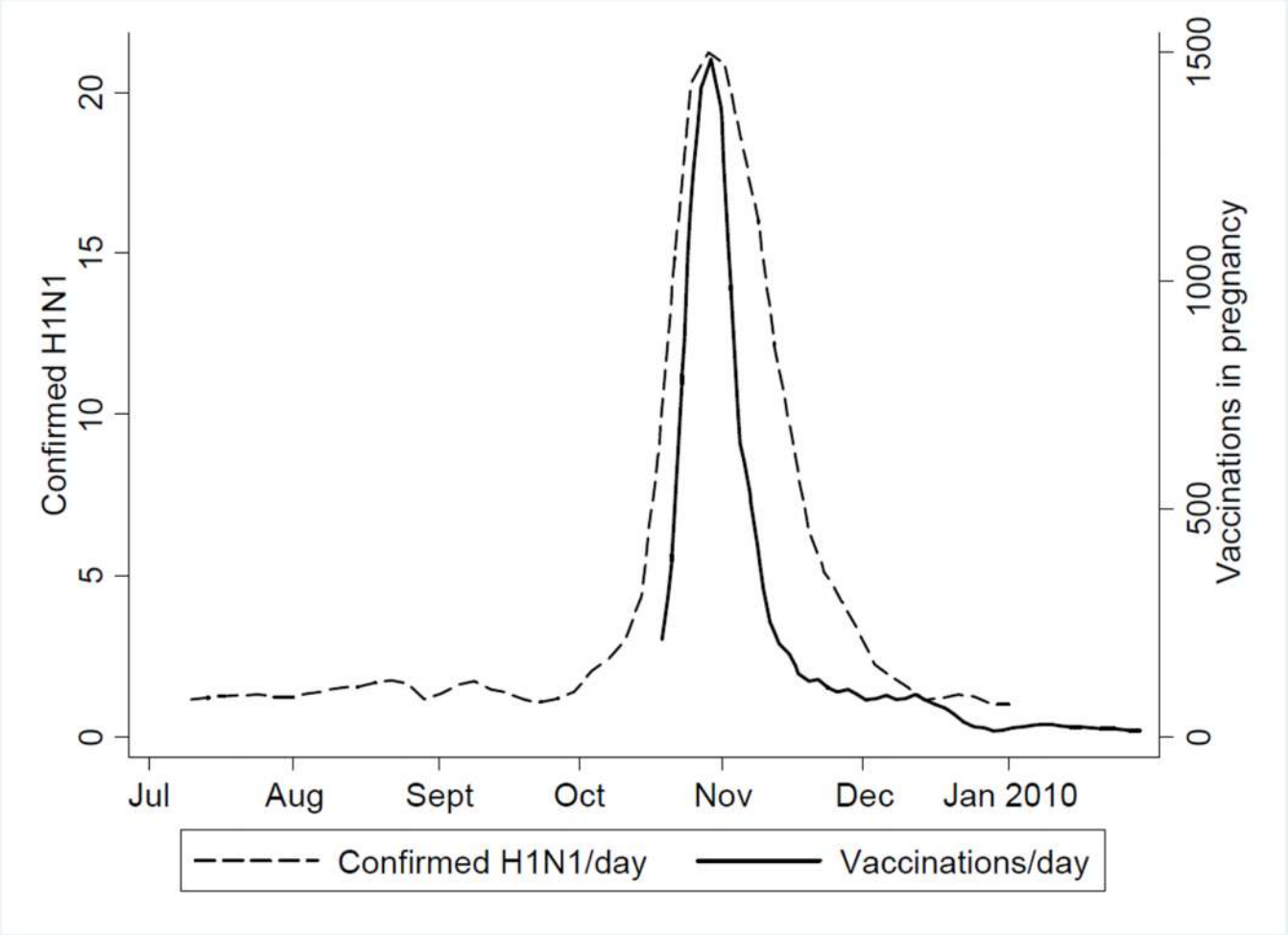

Figure 2.
Number of pregnant women in Norway with laboratory confirmed cases of pandemic influenza (dashed line) and number of vaccinations between 19 October, 2009 through February 2010 (solid line).

Table 1

Characteristics and vaccination coverage among women in Norway who were pregnant in the 2nd or 3rd trimester* during the main pandemic wave (1 October 2009 through 31 December 2009) of the 2009 influenza pandemic.

		Number of women	Vaccinated† (%)
Total		46,491	54
Age			
	<20	1,008	42
	20 – 24	6,723	48
	25 – 29	14,373	54
	30 – 34	15,191	57
	35 – 39	7,661	55
	≥40	1,535	54
Parity			
	0	19,640	52
	1	16,719	55
	2	7,171	56
	≥3	2,961	50
Smoking in pregnancy			
	No	32,148	55
	Occasionally	1,266	57
	Daily	6,291	50
	Refused to give information	6,397	52
	Missing	389	46
Chronic illness			
	No	41,146	53
	Yes	5,345	57

*Women with at least one day in 2nd of 3rd trimester between 1 October 2009 and 31 December 2009.

†Vaccination at any time in pregnancy.

Table 2

Crude and adjusted hazard ratios [*] (HRs) of fetal death [†] (n=492) among 113,331 women who gave birth to singletons in Norway in 2009 or 2010, according to influenza vaccination status and being pregnant during the pandemic [‡], with or without a clinical diagnosis of influenza.

	Pregnancy days at risk[§]	Crude HR	(95% CI)	Adjusted[▱] HR	(95% CI)	Adjusted[¶] HR	(95% CI)
Total	18,970,404						
Vaccinated in pregnancy							
No	15,942,324	1		1		1	
Yes	3,028,152	0.95	(0.74 – 1.21)	0.84	(0.64 – 1.10)	0.88	(0.66 – 1.17)
Pregnant during the pandemic							
No	10,422,035	1		1		1	
Yes	8,548,369	1.15	(0.96 – 1.37)	1.21	(1.00 – 1.48)	1.26	(1.02 – 1.55)
Pregnant during the pandemic							
No	10,422,035	1		1		1	
Yes, without a influenza diagnosis	8,221,514	1.11	(0.93 – 1.33)	1.18	(0.96 – 1.44)	1.23	(0.99 – 1.52)
Yes, with a influenza diagnosis	326,855	2.00	(1.20 – 3.32)	2.10	(1.27 – 3.49)	1.91	(1.07 – 3.41)

[*] Hazard ratios were estimated with gestational day as the time metric.

[†] Any fetal death/stillbirth after 12 completed pregnancy weeks.

[‡] At least one day in pregnancy between 1 October and 31 December 2009.

[§] Each woman may contribute days at risk as both unexposed and exposed.

[▱] Vaccination status adjusted for being pregnant during the main pandemic wave (Yes/No) but not for other covariates. Influenza exposures adjusted for vaccination status but not for other covariates.

[¶] Adjusted for age, parity, marital status, use of nutritional supplements in pregnancy, smoking in pregnancy, history of earlier fetal death, and chronic health conditions (asthma, hypertension, kidney disease, rheumatoid arthritis, epilepsy, thyroid disease, or diabetes).

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Table 3

Crude and adjusted hazard ratios [*] (HRs) of fetal death [†] (n=492) among 113,331 women who gave birth to singletons in Norway in 2009 or 2010, according to combinations of influenza vaccination status and being pregnant in the main wave of the 2009 influenza pandemic [‡].

Pregnant during the pandemic	Vaccinated in pregnancy	Pregnancy days at risk [§]	Crude		Adjusted [▱]	
			HR	(95% CI)	HR	(95% CI)
No	No	10,414,633	1	-	1	-
No	Yes	7402	-	-	-	-
Yes	No	5,527,619	1.21	(1.00 – 1.48)	1.25	(1.02 – 1.55)
Yes	Yes	3,020,750	1.02	(0.79 – 1.32)	1.10	(0.84 – 1.45)

[*] Hazard ratios were estimated with gestational day as the time metric.

[†] Fetal death was any fetal death/stillbirth after 12 completed pregnancy weeks.

[‡] At least one day in pregnancy between 1 October and 31 December 2009.

[§] Each woman may contribute days at risk as both unexposed and exposed.

[▱] Adjusted for age, parity, marital status, use of nutritional supplements in pregnancy, smoking in pregnancy, history of earlier fetal death, and chronic health conditions (asthma, hypertension, kidney disease, rheumatoid arthritis, epilepsy, thyroid disease, or diabetes).