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Incidence of influenza during pregnancy and association with pregnancy and perinatal outcomes in three middle-income countries: a multisite prospective longitudinal cohort study

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Summary

Background Influenza vaccination during pregnancy prevents influenza among women and their infants but remains underused among pregnant women. We aimed to quantify the risk of antenatal influenza and examine its association with perinatal outcomes.

Methods We did a prospective cohort study in pregnant women in India, Peru, and Thailand. Before the 2017 and 2018 influenza seasons, we enrolled pregnant women aged 18 years or older with expected delivery dates 8 weeks or more after the season started. We contacted women twice weekly until the end of pregnancy to identify illnesses with symptoms of myalgia, cough, runny nose or nasal congestion, sore throat, or difficulty breathing and collected mid-turbinate nasal swabs from symptomatic women for influenza real-time RT-PCR testing. We assessed the association of antenatal influenza with preterm birth, late pregnancy loss (≥13 weeks gestation), small for gestational age (SGA), and birthweight of term singleton infants using Cox proportional hazards models or generalised linear models to adjust for potential confounders.

Findings Between March 13, 2017, and Aug 3, 2018, we enrolled 11 277 women with a median age of 26 years (IQR 23–31) and gestational age of 19 weeks (14–24). 1474 (13%) received influenza vaccines. 310 participants (3%) had influenza (270 [87%] influenza A and 40 [13%] influenza B). Influenza incidences weighted by the population of women of childbearing age in each study country were 88·7 per 10 000 pregnant woman-months (95% CI 68·6 to 114·8) during the 2017 season and 69·6 per 10 000 pregnant woman-months (53·8 to 90·2) during the 2018 season. Antenatal influenza was not associated with preterm birth (adjusted hazard ratio [aHR] 1·4, 95% CI 0·9 to 2·0; p=0·096) or having an SGA infant (adjusted relative risk 1·0, 95% CI 0·8 to 1·3, p=0·97), but was associated with late pregnancy loss (aHR 10·7, 95% CI 4·3 to 27·0; p<0·0001) and reduction in mean birthweight of term, singleton infants (–55·3 g, 95% CI –109·3 to –1·4; p=0·0445).

Interpretation Women had a 0·7–0·9% risk of influenza per month of pregnancy during the influenza season, and antenatal influenza was associated with increased risk for some adverse pregnancy outcomes. These findings support the added value of antenatal influenza vaccination to improve perinatal outcomes.

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For the Thai translation of the abstract see **Online** for appendix 1

For the Hindi translation of the abstract see **Online** for appendix 2

For the Marathi translation of the abstract see **Online** for appendix 3

For the Spanish translation of the abstract see **Online** for appendix 4

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Introduction

Influenza viruses cause annual epidemics of respiratory infection globally. Pregnant women are thought to be at increased risk for morbidity and mortality from respiratory infections due to changes in anatomy and the immune and cardiovascular systems that accompany pregnancy. In 2012, WHO recommended that countries prioritise pregnant women for influenza vaccination when developing national influenza vaccination policies.[1] Multiple clinical trials and observational studies, including studies done in high-income and low-income countries, have shown that antenatal influenza vaccination prevents influenza illness in pregnant women[2–5] and provides protection against influenza to infants of vaccinated women for the first few months of life.[2–4,6] However, influenza vaccines remain underused or are not used at all among pregnant women in many countries, particularly in low-income and middle-income countries (LMICs).[7]

The underuse of influenza vaccines for pregnant women in LMICs is likely driven by multiple factors, one of which is the scarcity of data on the burden and

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Research in context

Evidence before this study

Data from seasonal epidemics indicate that pregnant women are at increased risk of hospitalisation due to seasonal influenza compared with non-pregnant women of childbearing age. However, few data are available on the effect of antenatal seasonal influenza on adverse pregnancy and perinatal outcomes. Such data would provide evidence for evaluation of the potential benefits of maternal influenza vaccination beyond protection of mothers and infants from influenza illness. Shortly before this study was done, a WHO systematic review of literature published up to December, 2014, concluded that existing studies of the effects of antenatal seasonal influenza on key pregnancy outcomes were of inadequate quality. Of 21 comparative studies included, no study assessed the effect of antenatal laboratory-confirmed seasonal influenza on outcomes using a prospective design. We searched PubMed for articles published between Dec 1, 2014, and Dec 31, 2019, in English with the terms "influenza, human" AND "pregnancy complications" AND "prospective". The search identified 20 publications. There were no prospective comparative studies assessing the effects of laboratory-confirmed influenza on adverse pregnancy or perinatal outcomes.

Added value of this study

This multinational prospective study was designed to assess the effect of antenatal influenza on pregnancy outcomes, including preterm birth, small for gestational age, late pregnancy loss, and birthweight. The study was designed to achieve an adequate sample size to assess the effects of influenza on preterm birth for effect sizes that might be of public health significance. It is one of few studies to provide estimates of influenza incidence during pregnancy among women in middle-income countries representing multiple patterns of influenza seasonality. Our findings that antenatal influenza was associated with late pregnancy loss and a reduction in birthweight and that women had a 0·7–0·9% risk of influenza for each month of pregnancy spent in the influenza season provide evidence of the effects of antenatal influenza on key perinatal outcomes. Findings from this study provide inputs needed to model potential illnesses and adverse pregnancy outcomes averted by influenza vaccination programmes.

Implications of all the available evidence

Clinical trials and observational studies have established that maternal influenza vaccination prevents influenza illness in mothers and their infants during the first few months of life. This study contributes evidence that maternal influenza vaccination may have benefit beyond protecting mothers and infants from influenza.

effects of seasonal influenza among pregnant women in these settings. A WHO systematic review about the effect of antenatal influenza on pregnancy and perinatal outcomes, such as preterm birth and stillbirth, concluded that existing studies were of inadequate quality, largely limited to high-income countries, and had mixed findings that precluded conclusions about the effects of influenza.[8]

See Online for appendix 5

Data on the effect of antenatal influenza on birth and perinatal outcomes associated with increased infant morbidity and mortality might inform decisions about influenza vaccine use in pregnant women by policy makers, health-care workers, and pregnant women themselves. Antenatal influenza has been hypothesised to result in inflammatory responses or immune dysregulation that might increase the risk for spontaneous abortion, stillbirth, and preterm birth and alter placental transfer of nutrients and cytokines to the developing fetus, which might affect fetal growth.[9] We aimed to estimate the incidence of all-cause acute respiratory illness (ARI), febrile ARI, and influenza during pregnancy and assess their association with pregnancy and perinatal outcomes.

Methods

Study design and participants

We did a prospective, multi-season cohort study of pregnant women in Bangkok, Thailand, Lima, Peru, and Nagpur, India. A detailed description of study site selection criteria and characteristics and the study protocol were published previously (appendix 5 p 1).[10] Women were eligible for enrolment if they were pregnant, as confirmed by urine pregnancy test or abdominal ultrasound; were 18 years of age or older; had an estimated date of delivery (based on last menstrual period or ultrasound) that allowed for 8 weeks of observation during the influenza season, assuming a 40 week gestation; planned to remain in the study area until delivery and deliver at a study hospital; and were willing to be contacted twice weekly for study surveillance. All enrolled women had an ultrasound before 28 weeks gestation to establish estimated date of delivery as part of clinical care or study procedures.

In 2017 and 2018, cohorts of pregnant women were enrolled starting up to 10 weeks before the anticipated start of the influenza season until the fourth week of the influenza season. For enrolment purposes, the influenza season was defined as the 16-week period in which influenza epidemics are most likely to occur as predicted by local influenza virus surveillance data.[10]

The study protocol was reviewed and approved by ethical review committees in each country[10] and the Abt Associates Institutional Review Board. The US Centers for Disease Control and Prevention (CDC) relied on the review of the Abt Associates Institutional Review Board. Informed consent was obtained from all study participants.

Procedures

At enrolment, participants completed interviews about their sociodemographic characteristics, including an abbreviated wealth index questionnaire (appendix 5 p 1), medical and pregnancy histories, and antenatal care for their current pregnancies. If participants had not had an ultrasound for gestational age dating as part of routine clinical care, a transabdominal ultrasound was done according to study standard operating procedures (appendix 5 p 2). Participants were provided with digital thermometers and symptom diary cards to use during illness episodes. Participants were also asked to designate proxies (eg, husband or partner or mother) to answer surveillance screening questions if participants were not available.

For the duration of participants' pregnancies, study staff attempted to contact them twice weekly by phone or home visit to ascertain whether women had influenza-like symptoms during the preceding 7 days or since the last successful contact (appendix 5 p 2). Influenza-like symptoms were defined as new onset or sudden worsening of one or more of myalgia, cough, runny nose or nasal congestion, sore throat, or difficulty breathing. Participants with influenza-like symptoms with illness onset within the preceding 7 days had mid-turbinate nasal swabs collected by study staff in Lima and Nagpur or self-collected in Bangkok. The influenza-like symptoms case definition was used to capture a broad range of influenza symptoms during surveillance to allow for evaluation of several outcomes using analytic definitions.

At delivery, infants were weighed at study hospitals according to study standard operating procedures using digital scales (appendix 5 p 3).[10] Within 7 days after the end of pregnancy, study staff interviewed participants to collect information about pregnancy complications, antenatal care and health behaviours since enrolment, end-of-pregnancy complications and outcomes, and influenza vaccination status during pregnancy. Postpartum maternal deaths were ascertained through postpartum interviews with participants' proxies at 6–8 weeks after end of pregnancy or through review of medical records and local death documents.[10] When medical records were available, study staff also completed chart abstractions after the end of pregnancy (appendix 5 p 3). Women were considered vaccinated against influenza if influenza vaccination status could be verified from available medical or vaccination records.

Respiratory swabs were tested by real-time RT-PCR (rtPCR) for influenza A and B viruses, including subtyping for influenza A(H1N1)pdm09 and A(H3N2) and lineage testing for B(Yamagata) and B(Victoria) using CDC protocols and primers and probes (appendix 5 p 4).

Outcomes

Incidence outcomes of interest were ARI, ARI-associated hospitalisation, febrile ARI, and rtPCR-confirmed influenza during pregnancy. ARI was defined as influenza-like symptoms with at least one of the following symptoms: cough, runny nose or nasal congestion, sore throat, or difficulty breathing. Febrile ARI was defined as influenza-like symptoms meeting criteria for ARI with chills or measured fever (≥38·0°C) or subjective fever. rtPCR-confirmed influenza was defined as influenza-like symptoms with a mid-turbinate nasal swab specimen positive for an influenza virus by rtPCR testing.

The primary pregnancy and perinatal outcomes of interest were preterm birth and birthweights of term singleton infants. Secondary outcomes were spontaneous abortion (<22 weeks gestation), stillbirth (≥22 weeks gestation), and small for gestational age (SGA) infants (appendix 5 p 4).[11] Owing to small numbers of spontaneous abortions and stillbirths, late spontaneous abortions (at 13–21 weeks gestation) and stillbirths (at ≥22 weeks gestation) were assessed together as a composite outcome of late pregnancy loss for multivariable models since gestational cut-offs for determining stillbirth vary by setting,[11] and early spontaneous abortion was not assessed. Gestational age for outcomes were calculated using gestational age dating by the earliest available ultrasound done according to study standard operating procedures. Because local growth curves were not available, INTERGROWTH-21 Project Standards[12] were used to determine SGA status.

Statistical analysis

A-priori sample size estimates indicated that 10 700 pregnant women with complete outcome data would be needed to detect a relative risk of preterm birth of 1·5 among women with antenatal influenza if the influenza attack rate among the cohort was 3% or a relative risk of 1·4 with a 5% attack rate (appendix 5 p 4).

The full analytic population for incidence calculations was defined as participants who consented to study participation, met eligibility criteria, completed the enrolment interview, and completed at least one surveillance contact. For incidence analyses restricted to the influenza season, the analytic population was restricted to participants at risk for influenza, defined as women pregnant for 2 weeks or more during the influenza season. Crude incidence rates per 10 000 person-months were calculated for each incidence outcome by site and trimester for the full cohort period and the influenza season (appendix 5 p 5). An aggregate incidence across all sites and all trimesters of pregnancy, weighted by population of women of childbearing age (15–44 years) for the country (obtained from the 2017 revision of the UN's World Population Prospects), was also calculated to give a representative estimate for women in middle-income countries. 95% CIs were calculated using standard formulas assuming a binomial distribution.

For **World Population Prospects** see https://population.un.org/wpp/

The associations of ARI, febrile ARI, and rtPCR-confirmed influenza with pregnancy and perinatal outcomes was assessed using Cox proportional-hazards

	Population restrictions	Model covariates
All outcomes	Women without elective or therapeutic terminations and without missing data on gestational age by ultrasound at <28 weeks gestation; all models assessing influenza exposure were further restricted to participants who were at risk for influenza virus infection, defined as women pregnant and enrolled for at least 2 weeks during the influenza season	Study site (multisite cohort models only); year; age (18–20 years, 21–34 years, ≥35 years); parity; highest educational level; psychosocial stressor score based on responses to a 17-question interview (0, 1, >1); body-mass index (<18·5 kg/m²; 18·5 kg/m² to <25 kg/m², 25 kg/m² to <30 kg/m², ≥30 kg/m²); HIV infection; chronic endocrine conditions; chronic heart disease; gestational diabetes; gestational hypertension; gestational age at first antenatal care visit; weeks pregnant during the influenza season (for assessing impact of influenza)
Preterm birth	Women without pregnancy losses	Smoking; alcohol use; abbreviated wealth index score
Small for gestational age	Women with livebirths and complete information on infant birthweights collected according to the study protocol	Smoking; exposure to indoor air pollution from cooking fuels*; antenatal vitamin use; number of antenatal clinic visits; weeks pregnant in the cohort (for assessing impact of febrile ARI and ARI)
Pregnancy loss†	Women without early spontaneous abortion (at <13 weeks gestation)	Alcohol use; abbreviated wealth index score; rate of previous pregnancy loss
Birthweight (g), term singleton infants	Women with live, term, singleton births and complete information on infant birthweights collected according to the study protocol	Smoking; exposure to indoor air pollution from cooking fuels*; antenatal vitamin use; number of antenatal clinic visits; infant sex; weeks pregnant in the cohort (for assessing impact of febrile ARI and ARI)

*Indoor air pollution defined as exposure to the following: polluting cooking fuels: animal dung, charcoal, candles, kerosene, sawdust, and wood. This was a potential confounder identified post hoc during data exploration. All other covariates were identified as potential confounders a priori from published literature on risk factors for the given outcome. †Pregnancy loss defined as late spontaneous abortion occurring from 13 to 21 weeks gestation or stillbirth occurring at ≥22 weeks gestation.

Table 1: **Analytic populations and multivariable model covariates by outcome**

regression for preterm birth and late pregnancy loss, SGA infant using modified Poisson regression, and birthweight among term singleton infants using multiple linear regression (appendix 5 p 5). For Cox proportional-hazards models, the time scale was weeks since date of conception and began at week 13 for late pregnancy loss models and week 0 for preterm birth models. Censoring was defined as a livebirth or loss to follow-up for pregnancy loss models and loss to follow-up for preterm birth models. For models assessing preterm birth, women with pregnancy losses were excluded and full-term pregnancies exited the risk-set after completing 36 weeks of gestation. Women were considered exposed from the date of illness onset of their first ARI, febrile ARI, or rtPCR-confirmed influenza episode. The association of antenatal influenza with birthweight was assessed by trimester using stratified regression models in which women with exposure in a given trimester were compared with women without the exposure after excluding women with influenza exposure in other trimesters. Table 1 shows the analytic populations and covariates in each model. Both two-stage site-stratified analyses and combined analyses were done for each outcome (appendix 5 p 6). χ^2 tests or independent-samples *t* tests were used to evaluate statistical significance. Statistical significance was defined by a two-tailed p value of less than 0·05.

Analyses were done in SAS version 9.1

Role of the funding source

CDC-affiliated authors were involved in study design, data collection, analysis, and interpretation, report writing, and the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 13, 2017, and Aug 3, 2018, 16 950 women consented to screening (figure 1; appendix 5 p 9), of whom 12 264 (72%) were eligible for study participation. 11 565 (94%) of 12 264 consented to study participation, and 11 277 (98%) were fully enrolled (ie, met gestational age criteria by ultrasound and completed an enrolment interview and at least one surveillance contact) and included in the analytic population for incidence calculations. Of these 11 277 women, 10 925 (97%) completed follow-up up to the end of pregnancy, and 10 826 (96%) had complete information for assessment of end-of-pregnancy outcomes. Women in the cohort contributed a mean of 4·3 pregnant woman-months of observation time (SD 1·6), and 11 108 (99%) of the 11 277 women were pregnant for at least 2 weeks during the influenza season and contributed to influenza incidence estimates.

Of the 11 277 fully enrolled women, 5011 were from India, 3505 from Peru, and 2761 from Thailand (table 2). The median age at enrolment was 26 years (IQR 23–31), 8996 (80%) of 11 277 women had completed some secondary school education or higher, and 4826 (43%) had health insurance (table 2). 1637 (15%) of 11 277 women had at least one chronic medical condition. 7719 (69%) women were enrolled during their second trimester of pregnancy at a median gestational age of 19 weeks (IQR 14–24 weeks) and had their first antenatal care clinic visit at a median of 13 gestational weeks (IQR 9–18). 1474 (13%) of 11 277 received an influenza vaccine during the current influenza season, although the proportion of

vaccinated women varied by site (11 [<1%] of 5011 in India, 1449 [43%] of 3505 in Peru, and 14 [1%] of 2761 in Thailand).

4791 (42%) of 11 277 women had at least one episode of ARI while pregnant. 870 (8%) had at least one episode of febrile ARI, including 202 (2%) with febrile ARI with measured fever of 38·0°C or higher, and 310 (3%) had influenza (142 [3%] of 4774 women in 2017 and 168 [3%] of 6503 women in 2018). 270 (87%) of 310 women with influenza had influenza A virus infection (167 [62%] A(H1N1)pdm09, 95 [35%] A(H3N2), and eight [3%] influenza A not subtyped) and 40 (13%) had influenza B virus infection (30 [75%] B(Yamagata), seven [18%] B(Victoria), and three [8%] without lineage typing). One woman had two episodes of antenatal influenza, an infection with an A(H1N1)pdm09 virus, and an infection with a B(Yamagata) virus (appendix 5 p 11). Compared with women without ARI, febrile ARI, or influenza episodes, women with these exposures were similar in age, health insurance status, parity, and pre-pregnancy body-mass index (appendix 5 p 12). However, women with ARI and febrile ARI were more likely to have chronic medical conditions, smoke and use alcohol, report at least one psychosocial stressor during their current pregnancies, and have received an influenza vaccine than women without episodes; there were no differences in these characteristics between women with and without influenza episodes.

Women in the cohort contributed 50 075 pregnant woman-months of cohort observation time. Incidence of ARI during the full cohort period, weighted for country population of women of childbearing age, was 1104·1 per 10 000 and of febrile ARI was 118·8 per 10 000 pregnant woman-months in the 2017 cohort and 1340·0 per 10 000 and 210·1 per 10 000 pregnant woman-months in the 2018 cohort (table 3). There were 3·7 ARI-associated hospitalisations per 10 000 pregnant woman-months in the 2017 cohort and 12·0 per 10 000 pregnant woman-months in the 2018 cohort.

Women in the cohort contributed 39 136 pregnant woman-months of observation time during influenza seasons (appendix 5 p 14). The weighted incidence of influenza was 88·7 per 10 000 pregnant woman-months and of influenza-associated hospitalisation was 1·6 per 10 000 pregnant woman-months during the influenza

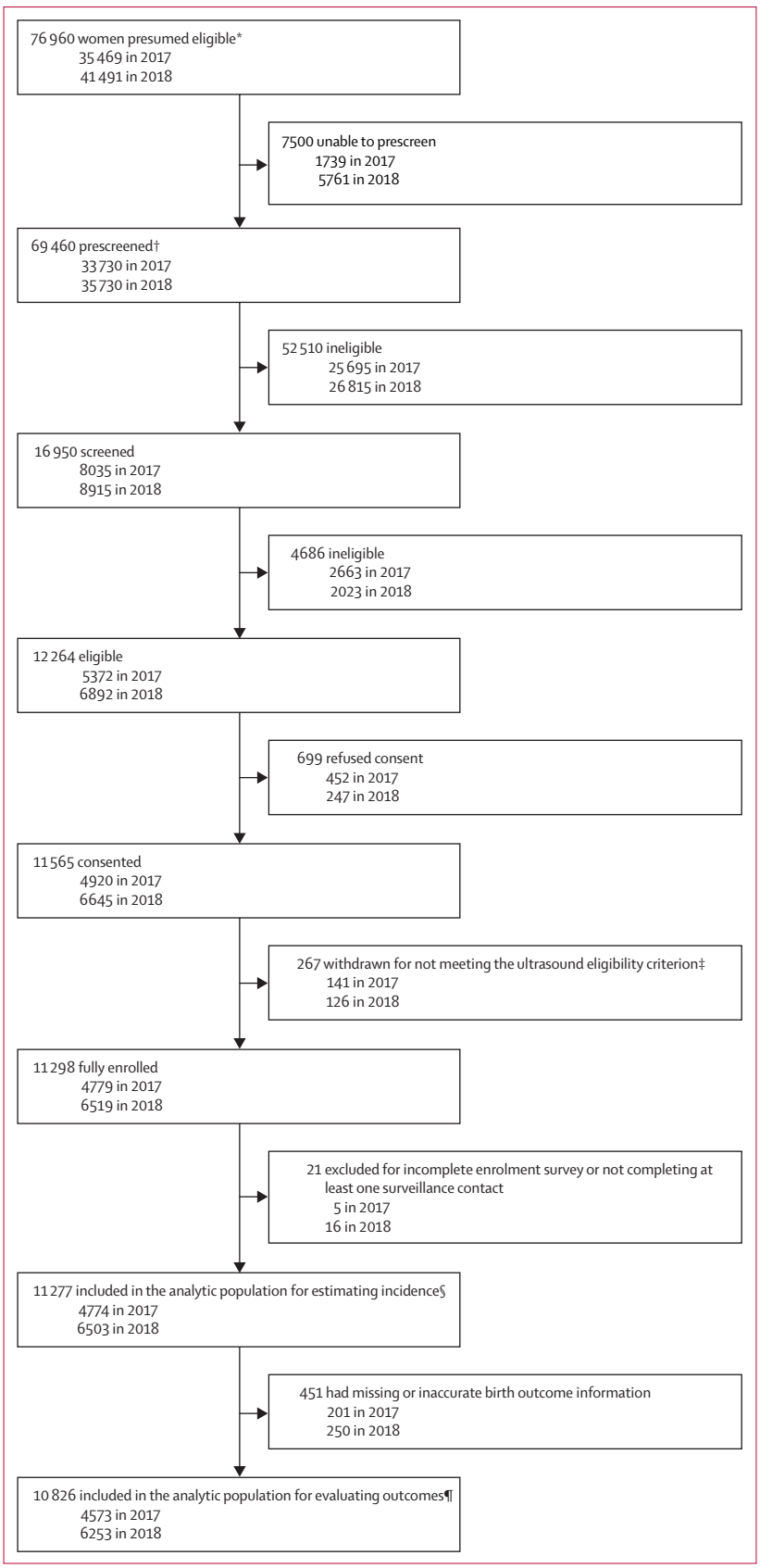

Figure 1: **Study profile**

*Includes all women who presented to the antenatal clinics for antenatal care during the enrolment period. †Includes all women who study staff screened for selected eligibility criteria, such as age, before formal eligibility screening. ‡If participants did not have ultrasounds for gestational dating that met study protocol standards, ultrasounds were done as part of the study. If participants were found to be at gestational age of more than 28 weeks by ultrasound, they were withdrawn due to ineligibility. §Met gestational age criteria by ultrasound and completion of an enrolment interview and at least one surveillance contact. ¶Excluded women who had missing data on gestational age dating by ultrasound at less than 28 weeks or pregnancy outcome (pregnancy loss or livebirth) and women who had elective terminations.

	Participants, N=11 277
Pre-pregnancy characteristics	
Country	
India	5011 (44%)
Peru	3505 (31%)
Thailand	2761 (24%)
Age, years	26 (23–31)
Highest educational level*	
No formal education	166 (1%)
Primary	2096 (19%)
Secondary	5483 (49%)
Post-secondary or university	3513 (31%)
Health insurance	4826 (43%)
Works outside the home	3387 (30%)
Parity	1 (0–2)
Pre-pregnancy body-mass index	22 (19–26)
One or more chronic medical conditions	1637 (15%)
Respiratory	202 (2%)
Blood	283 (3%)
Endocrine	582 (5%)
Heart (including hypertension)	180 (2%)
HIV	27 (<1%)
Other	559 (5%)
Previous miscarriage or stillbirth, per number of previous pregnancies	0·0 (0·0–0·5)
Current pregnancy characteristics	
Year of enrolment	
2017	4774 (42%)
2018	6503 (58%)
Trimester at enrolment†	
First (0 weeks to 13 weeks 6 days gestation)	2662 (24%)
Second (14 weeks to 27 weeks 6 days gestation)	7719 (68%)
Third (≥28 weeks gestation)	867 (8%)
Gestational age at first antenatal care visit	13 (9–18)
Multiple gestation pregnancy	162 (1%)
Current smoker	263 (2%)
Current alcohol user	1559 (14%)
Gestational diabetes	520 (5%)
Pregnancy-induced hypertension	966 (9%)
One or more psychosocial stressors	4240 (38%)
Influenza vaccine in the current year‡	1474 (13%)

Data are n (%) or median (IQR). *19 women were missing data on highest educational level. †29 women were missing data on trimester at enrolment. ‡Based on maternal report verified with source documents such as vaccination cards or medical records.

Table 2: **Cohort characteristics**

season in the 2017 cohort and 69·6 per 10 000 pregnant woman-months and 2·2 per 10 000 pregnant woman-months in the 2018 cohort. Incidences varied by season and site (figure 2). In Peru, where 1449 (43%) of 3505 women received influenza vaccine, the incidence of influenza was similar among the whole cohort compared with unvaccinated women during both years (data not shown). Among the 2017 and 2018 cohorts in all countries combined, the highest incidences of influenza were attributable to influenza A(H1N1)pdm09 virus infection (40·5 per 10 000 pregnant woman-months in 2017 and 46·1 per 10 000 pregnant woman-months in 2018), followed by influenza A(H3N2) virus infection (22·3 per 10 000 pregnant woman-months in 2017 and 26·7 per 10 000 pregnant woman-months in 2018) and influenza B virus infection (18·1 per 10 000 pregnant woman-months in 2017 and 4·6 per 10 000 pregnant woman-months in 2018; appendix 5 p 15). Incidences of influenza were highest in the first trimester (149·9 per 10 000 pregnant woman-months, 95% CI 96·7–232·3), followed by the third (87·2 per 10 000 pregnant woman-months, 75·7–100·5) and second (67·0 per 10 000 pregnant woman-months, 55·1–81·6) trimesters (appendix 5 p 16).

Among 310 women with influenza, the mean duration of illness was 7 days (SD 3) based on reported end of symptoms from illness follow-up interviews. 110 (35%) of 310 women reported subjective fever or chills and 101 (33%) had measured fever of 38·0°C or higher. The median duration of measured fever was 1 day (IQR 1–2) among the subset of women with complete data on fever start and end dates (n=56). 148 (48%) of 310 prompted medical attention, and seven episodes (2%) were associated with hospitalisation within 13 days of illness onset.

Among 10 826 women with complete data on pregnancy and perinatal outcomes, 1196 (11%) had preterm births, 2385 (22%) had SGA infants, and 222 (2%) had pregnancy losses, including 89 spontaneous abortions (43 at ≤13 weeks and 46 at 13–21 weeks) and 133 stillbirths (appendix 5 p 17). The mean birthweight adjusted for time from birth to birthweight collection was 3012 g (SD 565) among all infants and 3092 g (SD 516) among term singleton infants. Of 10 726 liveborn infants, 7903 (74%) had birthweights measured per study protocol. The prevalence of adverse pregnancy outcomes and mean infant birthweight varied by site (appendix 5 p 17). There were 15 maternal deaths (five before delivery and ten within 28 days after delivery); three occurred during pregnancy and were associated with ARI. Of the three ARI-associated deaths, all occurred in women tested for influenza in the study, and one was positive.

ARI exposure during pregnancy was not associated with an increased risk of preterm birth, having an SGA infant, late pregnancy loss, or a difference in mean birthweight among term singleton infants after controlling for potential confounders (table 4). Febrile ARI also was not associated with an increased risk of any of these outcomes except preterm birth (adjusted hazard ratio (aHR) 1·4, 95% CI 1·1–1·6; p=0·0067). Findings were consistent across multisite and two-stage site-stratified models (appendix 5 p 18) and in sensitivity analyses described in the supplemental study methods (data not shown). Findings were also consistent when

	Full cohort period		Influenza season*	
	2017	2018	2017	2018
ARI				
Overall, crude	2842; 1423·8 (1372·6–1477·0)	4146; 1376·7 (1335·5–1419·2)	2261; 1338·5 (1284·6–1394·7)	3265; 1467·8 (1418·5–1518·9)
Overall, weighted	858; 1104·1 (1033·5–1179·6)	1889; 1340·0 (1241·8–1401·7)	722; 1099·8 (1023·3–1182·1)	1060; 1219·0 (1148·1–1294·3)
India	824; 1035·3 (967·1–1108·3)	1920; 1309·7 (1252·6–1369·5)	702; 1036·3 (962·6–1115·7)	1029; 1175·4 (1105·9–1249·3)
Peru	1702; 2592·6 (2472·9–2718·2)	1967; 2288·7 (2190·2–2391·7)	1263; 2485·9 (2353·1–2626·2)	1957; 2292·5 (2193·6–2395·9)
Thailand	316; 581·3 (520·7–649·0)	259; 377·5 (334·2–426·3)	296; 587·6 (524·4–658·4)	279; 563·3 (501·0–633·4)
Febrile ARI				
Overall, crude	310; 150·4 (134·5–168·1)	630; 202·4 (187·2–218·8)	234; 134·3 (118·1–152·6)	506; 219·5 (201·2–239·5)
Overall, weighted	95; 118·8 (97·3–145·2)	308; 210·1 (187·9–235·0)	81; 118·9 (95·6–147·8)	189; 210·1 (182·2–242·4)
India	92; 113·0 (92·1–138·6)	315; 208·3 (186·5–232·6)	80; 115·3 (92·6–143·5)	187; 207·7 (179·9–239·6)
Peru	164; 235·6 (202·1–274·5)	279; 307·0 (273·0–345·2)	105; 195·1 (161·1–236·2)	276; 305·6 (271·6–343·9)
Thailand	54; 98·0 (75·1–128·0)	36; 52·0 (37·5–72·1)	49; 96·0 (72·5–127·0)	43; 85·8 (63·6–115·7)
rtPCR-confirmed influenza†				
Overall, crude	143; 73·7 (62·5–86·8)	168; 55·3 (47·6–64·4)	142; 85·8 (72·8–101·1)	168; 77·4 (66·6–90·1)
Overall, weighted	58; 73·7 (57·0–95·4)	58; 41·7 (32·3–53·8)	58; 88·7 (68·6–114·8)	58; 69·6 (53·8–90·2)
India	60; 74·8 (58·1–96·3)	57; 38·7 (29·9–50·2)	60; 90·3 (70·1–116·3)	57; 68·4 (52·8–88·7)
Peru	27; 45·9 (31·5–66·8)	96; 111·1 (90·9–135·6)	27; 54·3 (37·3–79·2)	96; 112·2 (91·9–137·1)
Thailand	59; 107·8 (83·5–139·1)	26; 37·2 (25·3–54·6)	58; 117·7 (91·0–152·2)	26; 54·0 (36·8–79·4)
ARI-associated hospitalisation				
Overall, crude	10; 4·8 (2·6–9·0)	28; 8·9 (6·2–12·9)	10; 5·7 (3·1–10·6)	20; 8·6 (5·6–13·4)
Overall, weighted	3; 3·7 (1·2–11·6)	18; 12·0 (7·5–19·1)	3; 4·3 (1·4–13·6)	11; 12·7 (7·1–22·7)
India	3; 3·7 (1·2–11·4)	19; 12·5 (8·0–19·6)	3; 4·3 (1·4–13·4)	12; 13·2 (7·5–23·3)
Peru	1; 1·4 (0·2–10·1)	4; 4·4 (1·6–11·6)	1; 1·8 (0·3–13·1)	4; 4·4 (1·6–11·7)
Thailand	6; 10·9 (4·9–24·2)	5; 7·2 (3·0–17·3)	6; 11·7 (5·3–26·1)	4; 8·0 (3·0–21·2)
rtPCR-confirmed influenza-associated hospitalisation†				
Overall, crude	5; 2·6 (1·1–6·2)	2; 0·7 (0·2–2·6)	5; 3·0 (1·3–7·2)	2; 0·9 (0·2–3·7)
Overall, weighted	1; 1·4 (0·2–9·1)	2; 1·3 (0·3–5·0)	1; 1·6 (0·2–11·0)	2; 2·2 (0·6–8·9)
India	1; 1·2 (0·2–8·8)	2; 1·4 (0·3–5·4)	1; 1·5 (0·2–10·7)	2; 2·4 (0·6–9·6)
Peru	1; 1·7 (0·2–12·0)	0; 0	1; 2·0 (0·3–14·2)	0; 0
Thailand	3; 5·5 (1·8–17·0)	0; 0	3; 6·1 (2·0–18·8)	0; 0

Data are episodes; incidence per 10 000 pregnant woman-months (95% CI). ARI=acute respiratory illness. rtPCR=real-time RT-PCR. *Excludes 169 women who were not pregnant for at least 2 weeks during the influenza season. The influenza season was defined as starting and ending on the date of collection of the first and last nasal swabs that were positive for influenza virus by rtPCR. †Crude incidence rates of rtPCR-confirmed influenza and influenza-associated hospitalisation were adjusted for Peru to account for missed swab collection, which exceeded 10% of episodes of influenza-like symptoms in both years (13% in both 2017 and 2018); no adjustments were made for India and Thailand where missed swab collection was minimal (<1% of episodes of influenza-like symptoms in 2017 and 3% in 2018 in Nagpur and 1% and 2% in Bangkok). To calculate the adjusted incidence rate, the proportion of episodes of influenza-like symptoms with respiratory specimen collection that were positive for influenza during the period of analysis was multiplied by the number of episodes of influenza-like symptoms without respiratory specimen collection, and the product was added to the numerator.

***Table 3*: Incidence per 10 000 pregnant woman-months of ARI, febrile ARI, and confirmed influenza (N=11 277)**

modelling the effects of multiple episodes of exposure separately (data not shown).

Having an influenza episode during pregnancy was not associated with an increased risk of preterm birth (aHR 1·4, 95% CI 0·9 to 2·0; p=0·096) or having an SGA infant (adjusted relative risk 1·0, 95% CI 0·8 to 1·3; p=0·97). However, having an influenza episode was associated with an increased risk of late pregnancy loss (aHR 10·7, 95% CI 4·3 to 27·0; p<0·0001) and a reduction in mean birthweight (–55·3 g, 95% CI –109·3 to –1·4; p=0·045) among term singleton infants (table 4). Findings were consistent in sensitivity analyses (data not shown). In analyses stratified by trimester, there was a significant reduction in mean birthweight for second trimester exposures (β coefficient –113·9, 95% CI –207·9 to –19·9; p=0·018) but not first trimester (–117·9, –406·9 to 171·0; p=0·42) and third trimester exposures (–22·8, –89·5 to 44·0; p=0·50).

Discussion

We prospectively evaluated the association of influenza, ARI, and febrile ARI during pregnancy with pregnancy and perinatal outcomes among a large and diverse cohort of more than 11 000 pregnant women from three middle-income countries. Influenza was not associated with preterm birth but was associated with a decrease in birthweight of singleton, full-term, liveborn infants. Influenza also conferred an increased risk of late pregnancy

loss (at ≥13 weeks gestation). ARI was not associated with any adverse pregnancy outcomes assessed in this study, but febrile ARI conferred an increased risk of preterm birth.

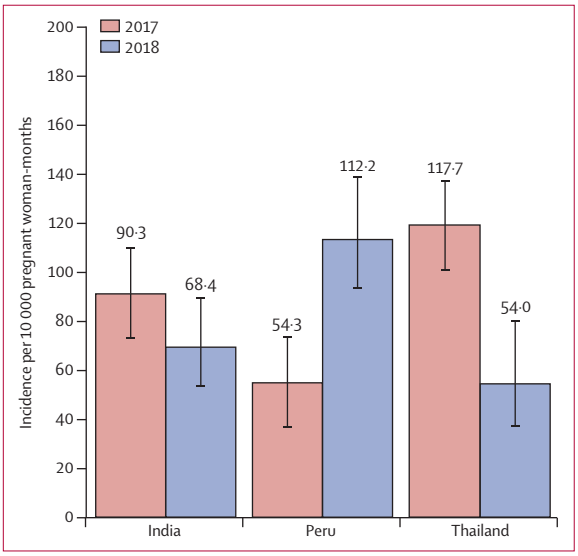

Figure 2: **Incidence of confirmed influenza in pregnant women (N=11 108)**
Error bars represent 95% CI. 169 women who were not pregnant for at least 2 weeks during the influenza season were excluded. Influenza season was defined as starting and ending on the date of collection of the first and last nasal swabs that were positive for influenza virus by real-time RT-PCR.

Pregnant women in the cohort had 0·7–0·9% risk of influenza per month of pregnancy spent in the influenza season. Among women with rtPCR-confirmed influenza, half reported seeking medical care for their illnesses, and one in 50 had an associated hospitalisation. Pregnant women in the cohort also had an 11–13% risk of ARI and 1–2% risk of febrile ARI per month of pregnancy.

Adverse pregnancy and perinatal outcomes can result in substantial psychosocial and economic costs[13–15] and might be associated with adverse long-term health sequelae for mothers or their infants.[16–18] Our finding that antenatal influenza was associated with an increased risk of late pregnancy loss is consistent with the few published studies without systematic influenza testing done during influenza pandemics.[19,20] Small numbers of participants precluded our assessment of influenza subtype-specific effects or effects by trimester of influenza exposure. The mechanisms leading to late spontaneous abortion and stillbirths are unknown,[21,22] but it has been hypothesised that immunological changes during pregnancy could result in a heightened inflammatory response to systemic infections that might have a role in both outcomes.[21,22] In our study, ARI and febrile ARI were not associated with late pregnancy loss, suggesting that pathogen-specific effects might be involved in respiratory infection-induced pregnancy loss. We did not find an association between antenatal

	Illness*	No illness*	Crude		Multisite cohort model	
			Effect size (95% CI)	p value	Effect size (95% CI)†	p value
Acute respiratory illness						
Preterm birth‡	691/6359 (11%)	494/4467 (11%)	1·0 (0·9 to 1·1)	0·34	1·1 (1·0 to 1·3)	0·13
SGA§	1411/6147 (23%)	974/4679 (21%)	0·9 (0·9 to 1·0)	0·0082	1·0 (0·9 to 1·1)	0·44
Late pregnancy loss¶	135/6147 (2%)	44/4679 (1%)	0·6 (0·4 to 0·7)	<0·0001	0·9 (0·6 to 1·3)	0·62
Birthweights of term singleton infants, g‖	2966 (568)	3066 (588)	99·5 (77·4 to 121·7)	<0·0001	−4·4 (−24·4 to 15·6)	0·67
Febrile acute respiratory illness						
Preterm birth‡	1075/9989 (11%)	110/837 (13%)	1·2 (1·0 to 1·5)	0·038	1·4 (1·1 to 1·6)	0·0067
SGA§	2187/9980 (22%)	198/846 (23%)	1·1 (0·9 to 1·3)	0·32	1·1 (0·9 to 1·2)	0·39
Late pregnancy loss¶	170/9980 (2%)	9/846 (1%)	0·6 (0·3 to 1·2)	0·20	1·2 (0·6 to 2·4)	0·59
Birthweights of term singleton infants, g‖	3010 (576)	3006 (605)	−3·3 (−44·3 to 37·6)	0·87	−20·4 (−55·0 to 14·2)	0·25
rtPCR-confirmed influenza**						
Preterm birth‡	1129/10285 (11%)	31/276 (11%)	1·0 (0·7 to 1·5)	0·85	1·4 (0·9 to 2·0)	0·096
SGA§	2320/10 263 (23%)	58/298 (19%)	0·8 (0·6 to 1·1)	0·23	1·0 (0·8 to 1·3)	0·97
Late pregnancy loss¶	133/10 263 (1%)	5/298 (2%)	1·3 (0·5 to 3·1)	0·60	10·7 (4·3 to 27·0)	<0·0001
Birthweights of term singleton infants, g‖	3010 (576)	3031 (540)	21·8 (−45·2 to 88·7)	0·52	−55·3 (−109·3 to −1·4)	0·045

SGA=small for gestational age. *Data are n/N (%) or mean (SD). †Effect sizes are hazard ratios for pregnancy loss and preterm birth, relative risks for SGA, and mean differences for birthweight of term singleton infants. All models adjusted for study site and year, age (18–20 years, 21–34 years, ≥35 years), parity, highest educational level, psychosocial stressor score based on responses to a 17-question interview (0–17), body-mass index (<18·5 kg/m², 18·5 kg/m² to <25 kg/m², 25 kg/m² to <30 kg/m², ≥30 kg/m²), HIV infection, chronic endocrine conditions, chronic heart disease, gestational diabetes, gestational hypertension, gestational age at first antenatal care visit, and weeks pregnant during the influenza season (for assessing impact of influenza). Additionally, models assessing prematurity included smoking, alcohol use, and abbreviated wealth index score; models assessing pregnancy loss included alcohol use, abbreviated wealth index score, and rate of previous pregnancy loss; and models assessing birthweight and SGA included smoking, exposure to indoor air pollution from cooking fuels, antenatal vitamin use, number of antenatal clinic visits, weeks pregnant in the cohort (for assessing impact of febrile ARI and ARI), and infant gender (birthweight models only). ‡Birth at <37 weeks gestation. Denominators differ for the preterm birth outcome because women were considered exposed if exposure occurred at <37 weeks gestation when women were at risk for preterm birth. §Defined as an infant with birthweight <10% for infants of the same gestational age and sex using INTERGROWTH-21 Project Standards. ¶Defined as late spontaneous abortion occurring at 13–21 weeks gestation or stillbirth occurring at >22 weeks gestation. ‖Of 9352 term singleton infants. Multivariable models restricted to term singleton infants with birthweights collected per study protocol. Adjusted to account for typical weight loss patterns among newborns in the first 48 h after birth using published nomograms. **Analysis restricted to 10 561 women who were pregnant for at least 2 weeks during the influenza season and had complete outcome data.

Table 4: **Pregnancy and perinatal outcomes**

influenza and preterm birth or having an SGA infant, although the sample size of this study might have been inadequate to detect a smaller effect of influenza on preterm birth than assumed for sample size calculations. These results are consistent with the findings for seasonal influenza from a WHO meta-analysis.[8] Although some previous studies found an association between antenatal influenza and preterm birth, these studies were retrospective, did not include systematic testing for influenza, and focused on effects of severe pandemic influenza requiring hospitalisation.[8]

To date, studies evaluating the effects of influenza on birthweight have yielded mixed results, with most data originating from studies that indirectly assessed these effects by evaluating the effect of vaccination on low birthweight.[2–4,23] Although it is unclear whether birthweight alone is a predictor of infant survival, independent of preterm birth, decreased birthweight might provide an indication of underlying problems during pregnancy that are linked to both fetal growth and future risks for the newborn.[24] Furthermore, effects on birthweight might have larger effects on infant health in settings where maternal and infant malnutrition also affect early infant weight gain. We found that antenatal influenza was associated with an average reduction in birthweight of about 55 g, with the largest reduction observed with influenza during the second trimester.

This study was designed to provide data to inform decisions by policy makers in middle-income countries about influenza vaccination policies for pregnant women. Data from the cohort quantify the risk of influenza per month of pregnancy spent in the influenza season and show that the risk of influenza was highest in the first trimester. These findings, coupled with the observed increased risks of late pregnancy loss and decreased infant birthweight among women with influenza, support influenza vaccination of pregnant women before the influenza season in settings with seasonal circulation and in the first trimester in settings with perennial circulation to optimise protection of the mother and fetus. At present, opportunities for first trimester vaccination are missed in some LMICs where influenza vaccination recommendations for pregnant women are limited to the second or third trimesters.

This study has several strengths. We enrolled a large and diverse cohort representative of pregnant women with access to antenatal care in middle-income countries. We followed the cohort prospectively to minimise recall bias and surveilled with a broad case definition for influenza-like illness and systematic influenza testing with molecular diagnostic techniques. We also had high cohort retention, with ascertainment of study outcomes in more than 95% of participants, and used rigorous procedures to ensure accurate outcome measurement. Limitations of our study include the absence of systematic testing for other infections that could increase risk for adverse perinatal outcomes, although other infections would only be confounders if they were associated with both the outcome and risk for influenza virus infection; the absence of placental histopathology studies to assess for alternative causes of pregnancy loss; inability to assess effects of ARIs and febrile ARIs that women may have had before cohort enrolment, which might bias results towards null effects for these exposures; and inability to rule out the possibility that cohort participants had antenatal influenza episodes before enrolment, although local surveillance data from Peru and Thailand indicated sparse influenza virus detection in the months before cohort enrolment. The small number of pregnancy losses among women with antenatal influenza resulted in wide confidence limits around the estimates of influenza effects. Findings from this study might not be generalisable to women without access to antenatal care or populations with high rates of HIV infection, which was relatively uncommon in our study population (<1% of women).

In conclusion, this study quantifies the incidence of antenatal influenza among women in three diverse middle-income countries using a standardised and broad case definition. Antenatal influenza was associated with late pregnancy loss at 13 weeks or more gestation and reduction in birthweight of singleton term infants but was not associated with preterm birth. Our findings suggest the potential added value of influenza vaccination during pregnancy to improve perinatal outcomes in addition to the established benefits of protecting mothers and their infants.

Contributors

FSD, WK, ArP, DRH, PS, MGT, GS, CSA, EA-B, HHC, SL, and YT designed the study. FSD, DRH, MGW, and TB oversaw data collection across the study network, and WK, ArP, PS, GS, ShM, SC, MD, DE, RF, OG, KK, SK, BR, EL, JAM, SS, AmP, CS, and YT oversaw data collection at study sites. FSD, MGW, TB, and SaM analysed the data, with statistical support from HHC. All authors participated in data interpretation. FSD wrote the first draft of the manuscript, and all authors critically reviewed the manuscript and approved the final manuscript for submission.

Declaration of interests

We declare no competing interests.

Data sharing

Data are available upon request to the corresponding author. Researchers interested in collaborations should contact the corresponding author. We welcome proposals to use this data from potential collaborators or from researchers interested in investigating specific questions independently.

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publication. The opinions or assertions contained herein are the private views of the author, and are not to be construed as official, or as reflecting true views of the Department of the Army or the Department of Defense. The investigators have adhered to the policies for protection of human participants as prescribed in AR 70–25. FSD, WK, MGT, GS, CSA, EA-B, DE, SL, JAM, SS, CS, and YT are employees of the US Government. This work was prepared as part of their official duties. Title 17 USC § 105 provides that "Copyright protection under this title is not available for any work of the United States Government". Title 17 USC § 101 defines a US Government work as a work prepared by a military service member or employee of the LUSTER-1 and LUSTER-2 as part of that person's official duties. The authors wish to acknowledge Eric Griggs at the Centers for Disease Control and Prevention for analytic support.

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