THE LANCET
Infectious Diseases

Supplementary appendix 5

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Dawood FS, Kittikraisak W, Patel A, et al. Incidence of influenza during pregnancy and association with pregnancy and perinatal outcomes in three middle-income countries: a multisite prospective longitudinal cohort study. *Lancet Infect Dis* 2020; published online Oct 29. https://doi.org/10.1016/S1473-3099(20)30592-2.

Supplemental Methods

Study site selection

Sites in low- or middle-income countries were evaluated and selected based on prior experience enrolling pregnant women into research studies; ability to access local data on pregnancy and birth outcomes to guide sample size assumptions; ability to enroll at least 1,000 pregnant women during a three month period as supported by previous study enrollment experiences and/or data on number of pregnancies or live-births in the study area; access to local real time reverse transcription polymerase chain reaction (RT-PCR) laboratory testing for influenza using Centers for Disease Control and Prevention (US CDC) protocols; ability to measure primary outcomes using standardized methods per study protocol; access to at least three years of local influenza surveillance data to establish the typical timing of seasonal influenza epidemics; and ability to implement real-time electronic data collection in the field. Sites were also selected based on an anticipated low uptake of influenza vaccine since effective influenza vaccination might be expected to impact influenza virus infection incidence.

Study sites

Women were enrolled at two tertiary level referral hospitals (12,000-13,000 deliveries/year) in Bangkok, four tertiary referral level hospitals (37,000 deliveries/year) in Lima, and one secondary level referral hospital (14,000-15,000 deliveries/year) in Nagpur. National or state-based influenza surveillance data from years preceding the study indicated that there was perennial influenza virus circulation with a larger peak in June-September and a second smaller peak in December-January in Bangkok, a single peak during May-August in Lima, and a single peak in influenza virus detection during July-October in Nagpur.[1-3] Although all three study sites had national or state-based recommendations for influenza vaccination for pregnant women during the study period, study sites were selected, in part, because historical data suggested that vaccine uptake among pregnant women was low (<10%) in recent years.

Abbreviated wealth index questionnaire

As part of the enrollment interview, women were asked about components of an abbreviated version of the World Health Organization (WHO) Demographic and Health Survey wealth index that included household

ownership of the following items: car or truck, motorcycle, toilet, refrigerator, electricity, separate room as a kitchen, television, telephone, clock/watch, and computer.[4]

Gestational age dating by ultrasound

Study ultrasonographers were required to have completed training in gestational age dating. Ultrasound machines were programmed to provide both gestational age and estimated delivery date using crown rump measurements before 14 weeks and using combinations of biparietal diameter, head circumference, abdominal circumference and femur length at 14 weeks or more. Estimated gestational age in weeks and days based on the ultrasound exam was recorded.

Respiratory illness surveillance

During enrollment participants were given information about how to contact study staff if they had influenza-like symptoms (ILS) 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 were encouraged to contact study staff directly if they were sick, similar to methods used in previous influenza cohort studies.[5-7] Participants were also asked to respond to twice weekly ILS surveillance contacts.

For participants for whom telephone call was the primary contact method, study staff attempted to reach non-respondents (those whom staff could not reach to complete the ILS screening questions) at least twice by telephone call within one day of the first missed call. If still unsuccessful, study staff attempted to reach participants' study proxies twice by telephone within two days of the originally scheduled telephone call.

For participants whose primary method of surveillance contact was home visit, study staff attempted to reach non-respondents with a telephone number on record at least two times within one day of the originally scheduled home visit. If the participant did not have a telephone number on record, study staff attempted a second home visit within one day of the originally scheduled home visit. Once ILS episodes ended or after a maximum of 13 days from symptom onset, study staff conducted standardized interviews with women to collect information about their symptoms, duration of fever and height of highest measured temperature, whether their illness disrupted their normal daily activities based on their subjective assessment, and receipt of medical care for ILS episodes.

Birthweight collection

At study hospitals or clinics, investigators assessed and approved scales in the labor and delivery area for acceptability for study purposes prior to study initiation. Scales had to be digital, designed to measure weight with accuracy to the nearest 10 grams, and be calibrated daily. Study staff and collaborating hospital staff were trained prior to study initiation and periodically throughout the study period on weight measurement procedures which included removing all clothing from the infant down to no clothing or a thin shirt and performing at least two birthweight measurements consecutively. Study staff measured a third weight if there was a difference of more than 20 grams between the first two measurements.

Birthweights were taken as close to the time of delivery as possible but no later than 48 hours after delivery. For infants born at non-study hospitals, study staff weighed infants with study digital scales when possible or abstracted birthweights from the medical record if direct measurement was not possible.

Chart abstraction

Overall, 96% of participants had chart abstractions completed (98% in India, 98% in Peru, and 90% in Thailand). Chart abstractions collected information on antenatal care, pregnancy course, delivery/perinatal outcomes, and any hospitalization for acute medical illnesses that occurred during the pregnancy. Participant reports of influenza vaccination during pregnancy were verified using medical and vaccination records.

Participant age, parity, educational level, household income, selected WHO wealth index indicators, smoking and alcohol use during pregnancy, psychosocial stressors (e.g. participant or partner lost a job, participant suffered serious illness or injury, death of a close family member), and pre-pregnancy height and weight for body mass index calculation were ascertained from participant interview. A combination of participant interview and chart abstraction was used to ascertain complications and outcomes during previous pregnancies, chronic medical conditions, and current pregnancy complications; participants were considered to have had a given event if it was reported from either source.

Study laboratories

Study laboratories completed WHO or CDC proficiency panels prior to the start of the study. Testing was performed at the Armed Forces Research Institute of Medical Sciences in Bangkok and the US Naval Medical Research Unit, No. 6 Virology and Emerging Infections Laboratory in Lima. In India, testing was performed by Dhruv Pathology and Diagnostic Laboratories, Nagpur; the All India Institute of Medical Sciences, New Delhi, and the Manipal Institute of Virology, Karnataka.

Sample size calculations

Sample size estimates were calculated *a priori* to assess the impact of influenza during pregnancy on the primary outcomes of preterm birth and birth weight of term singleton infants with a desired alpha of 5% and beta of 20% (80% power). For preterm birth, prevalence was assumed to be 10% among women without influenza based on WHO estimates of preterm birth prevalence in low- and middle-income countries.[8] For birthweight of term singleton infants, mean birthweight was assumed to be 3000 grams with a standard deviation of 500 grams among women without influenza based on published estimate from low- and middle-income countries.[9] Six thousand seven hundred women with complete birthweight data would be needed to provide 80% power to detect a mean difference in birthweight of 100 grams between women with influenza during pregnancy compared to those without.

Pregnancy and perinatal outcome definitions

ARI-associated hospitalizations and rRT-PCR-confirmed influenza-associated hospitalizations were defined as those with admission occurring within 13 days after symptom onset of an ARI or rRT-PCR-confirmed influenza episode. Pregnancy outcomes were defined according to definitions from the Global Alignment of Immunization Safety Assessment in Pregnancy.[10] Spontaneous abortion was defined as pregnancy loss without any preceding intervention at <22 weeks gestation. Stillbirth was defined as the death of a fetus at $\geq$22 weeks gestation. Preterm birth was defined as live birth occurring before 37 0/7 weeks gestation. Small for gestational age infant was defined as an infant with birthweight <10% for infants of the same gestational age and gender based on INTERGROWTH-21 Project Standards.[11] Birthweights measured at 12-48 hours after delivery were

adjusted to account for typical weight loss patterns among newborns in the first 48 hours after birth using published nomograms.[12]

Analytic time periods for incidence rate calculations

For incidence calculations, the full cohort period was defined as starting seven days prior to the first surveillance contact for each participant through the last surveillance contact for each participant, and the influenza season was defined at each site for analytic purposes as starting and ending on the date of symptom onset for the illnesses with the first and last nasal swabs that were positive for influenza virus by rRT-PCR.

Analytic methods for incidence rate calculations

Incidence rates were calculated as true rates with enumerated events (i.e. not women) as the numerator and person-months at risk for events as the denominator. Multiple events within the same individual were counted separately toward the numerator. It was assumed that recall of illness events over a period >14 days was not reliable, so intervals between successful surveillance contacts that exceeded 14 days were subtracted from the person-time denominator. A successful surveillance contact was defined as a contact in which study staff were able to speak with a participant and complete the screening questions pertaining to ILS symptoms. Crude incidence rates of rRT-PCR-confirmed influenza and influenza-associated hospitalization were adjusted for Peru to account for missed swab collection which exceeded 10% of ILS episodes in both years (13% in both 2017 and 2018); no adjustments were made for India and Thailand where missed swab collection was minimal (<1% and 3% of ILS episodes in India during 2017 and 2018, respectively, and 1% and 2% of ILS episodes in Thailand during 2017 and 2018, respectively). To calculate the adjusted incidence rate, the percent of ILS episodes with respiratory specimen collection that were positive for influenza during the time period of analysis was applied to the number of ILS episodes without respiratory specimen collection, and the product was added to the numerator.

Regression models

Model covariates were selected based on *a priori* identification of potential confounders from the published literature[8, 13-15] and/or if they were identified as confounders during data exploration, defined as variables associated with both the outcome and exposure status and not thought to be part of the causal pathway

between exposure and outcome. For each model, participants with missing data for model covariates were excluded (<10% of participants for any model). Participants with loss to follow-up for whom pregnancy and perinatal outcomes could not be ascertained from either participant interview or medical records were excluded from birthweight and SGA infant models.

In two-stage site stratified analyses, adjusted log relative risks or beta coefficients were first estimated separately for each study site and then combined using inverse-variance weights to assess effect heterogeneity. Variables were removed from site specific models if there was collinearity that otherwise prevented model convergence (Supplemental Table 2).

For all models, sensitivity analyses were performed excluding women with chronic medical conditions or infants with congenital anomalies. For ARI and febrile ARI models, sensitivity analyses were conducted for preterm birth and pregnancy loss in which cumulative exposures were assessed for women with multiple episodes of ARI or febrile ARI. For febrile ARI models, sensitivity analyses were conducted excluding women with ARI or influenza that did not meet the criteria for febrile ARI from the unexposed group to remove potential effects from these exposures from the comparison group which might bias model results towards the null. For models assessing the effect of influenza exposure, sensitivity analyses were conducted in which women with non-influenza ARI episodes were excluded from the unexposed group to remove potential effects of non-influenza ARI from the comparison group.

1. Chadha MS, Potdar VA, Saha S, Koul PA, Broor S, Dar L, Chawla-Sarkar M, Biswas D, Gunasekaran P, Abraham AM, et al. Dynamics of influenza seasonality at sub-regional levels in India and implications for vaccination timing. PLoS One 2015;10:e0124122.
2. Chittaganpitch M, Supawat K, Olsen SJ, Waicharoen S, Patthamadilok S, Yingyong T, Brammer L, Epperson SP, Akrasewi P, Sawanpanyalert P. Influenza viruses in Thailand: 7 years of sentinel surveillance data, 2004-2010. Influenza Other Respir Viruses 2012;6:276-83.
3. Tinoco YO, Azziz-Baumgartner E, Uyeki TM, Razuri HR, Kasper MR, Romero C, Silva ME, Simons MP, Soto GM, Widdowson MA, et al. Burden of Influenza in 4 Ecologically Distinct Regions of Peru: Household Active Surveillance of a Community Cohort, 2009-2015. Clin Infect Dis 2017;65:1532-41.
4. DHS Comparative Reports 6, The DHS Wealth Index. 2004. (Accessed November 27, 2019, at https://dhsprogram.com/pubs/pdf/CR6/CR6.pdf.)
5. Thompson MG, Li DK, Naleway AL, Ferber JR, Henninger ML, Shifflett P, Sokolow LZ, Odouli R, Kauffman TL, Fink RV, et al. Factors associated with recruitment, surveillance participation, and retention in an observational study of pregnant women and influenza. BMC Pregnancy Childbirth 2019;19:161.
6. Monto AS, Malosh RE, Evans R, Lauring AS, Gordon A, Thompson MG, Fry AM, Flannery B, Ohmit SE, Petrie JG, et al. Data resource profile: Household Influenza Vaccine Evaluation (HIVE) Study. Int J Epidemiol 2019;48:1040-g.
7. Thompson MG, Gaglani MJ, Naleway A, Ball S, Henkle EM, Sokolow LZ, Brennan B, Zhou H, Foster L, Black C, et al. The expected emotional benefits of influenza vaccination strongly affect pre-season intentions and subsequent vaccination among healthcare personnel. Vaccine 2012;30:3557-65.
8. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162-72.
9. Bose CL, Bauserman M, Goldenberg RL, Goudar SS, McClure EM, Pasha O, Carlo WA, Garces A, Moore JL, Miodovnik M, et al. The Global Network Maternal Newborn Health Registry: a multi-national, community-based registry of pregnancy outcomes. Reprod Health 2015;12 Suppl 2:S1.
10. Munoz FM, Eckert LO, Katz MA, Lambach P, Ortiz JR, Bauwens J, Bonhoeffer J. Key terms for the assessment of the safety of vaccines in pregnancy: Results of a global consultative process to initiate harmonization of adverse event definitions. Vaccine 2015;33:6441-52.
11. Villar J, Cheikh Ismail L, Victora CG, Ohuma EO, Bertino E, Altman DG, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 2014;384:857-68.
12. Flaherman VJ, Schaefer EW, Kuzniewicz MW, Li SX, Walsh EM, Paul IM. Early weight loss nomograms for exclusively breastfed newborns. Pediatrics 2015;135:e16-23.
13. Escanuela Sanchez T, Meaney S, O'Donoghue K. Modifiable risk factors for stillbirth: a literature review. Midwifery 2019;79:102539.
14. Cogswell ME, Yip R. The influence of fetal and maternal factors on the distribution of birthweight. Semin Perinatol 1995;19:222-40.
15. Edmonds K, Lees C, Bourne T. Dewhurst's Textbook of Obstetrics & Gynaecology, 9th Edition. 9 ed: Wiley-Blackwell; 2018.

Incidence of Influenza during Pregnancy and Impact on Pregnancy and Perinatal Outcomes: A Multi-Site Prospective Longitudinal Cohort Study in Three Middle-Income Countries

Supplemental Data Tables

Supplemental Table 1 Cohort enrollment, consent and participation characteristics overall and by site, PRIME Study, India, Peru, and Thailand, 2017 and 2018

	Years 1 and 2 Combined (2017 and 2018)			
	All Study Sites	**India**	**Peru**	**Thailand**
Enrollment and consent steps				
Women potentially eligible from ANC clinic visits	76,960	41139	16942	18879
Prescreened as ineligible	*49,270*	*32588*	*5651*	*11031*
Did not prescreen and unable to approach	*7,500*	*0*	*6964*	*536*
Approached for formal screening	20,190	8551	4327	7312
Refused screening	*3,240*	*3240*	*0*	*0*
Completed formal screening	16,950	5311	4327	7312
Did not meet eligibility criteria	*4,686*	*127*	*622*	*3937*
Eligible	12,264	5184	3705	3375
Did not consent	*699*	*1*	*133*	*565*
Consented	11,565	5183	3572	2810
Did not meet eligibility criteria based on ultrasound results	*267*	*171*	*50*	*46*
Fully enrolled	11,298	5012	3522	2764
Did not complete enrollment interview and >=1 surveillance contact	*14*	*1*	*17*	*3*
Fully enrolled, completed enrollment interview and >=1 surveillance contact	11277	5011	3505	2761
Lost to follow-up and/or withdrawn	*352*	*40*	*70*	*242*
Completed follow-up through end of pregnancy**	10925	4971	3435	2519
Participation measures				
Consented to screening	84%	62%	100%	100%
Consented to enrollment (among eligible)	94%	100%	96%	83%
Completed follow-up through end of delivery (among fully enrolled)	97%	99%	98%	91%

**Defined as having complete information on end of pregnancy/birth outcomes.

Supplemental Table 2 Covariates excluded from site-specific models evaluating small for gestational age infant as an outcome because of collinearity that otherwise prevented model convergence

Model	India	Peru	Thailand
Influenza	no exclusions	exposure to indoor air pollution from cooking fuels, highest educational level	HIV infection
Febrile acute respiratory illness	no exclusions	exposure to indoor air pollution from cooking fuels, highest educational level	HIV infection
Acute respiratory illness	no exclusions	exposure to indoor air pollution from cooking fuels, highest educational level	HIV infection

Supplemental Table 3 Influenza detection (with real time reverse transcription polymerase chain reaction (rRT-PCR))*, by subtype, site, and year among pregnant women in the Pregnancy and Influenza Multinational Epidemiologic (PRIME) Study, India, Peru, and Thailand, 2017 and 2018, N=310 women

	2017			2018		
	India n=59	Peru n=24	Thailand n=59	India n=57	Peru n=85	Thailand n=26
Influenza A	57 (97%)	16 (67%)	39 (66%)	57 (100%)	76 (89%)	25 (96%)
A(H1N1)pdm09	49 (83%)	0 (0%)	18 (31%)	13 (23%)	72 (85%)	15 (58%)
A(H3N2)	1 (2%)	15 (63%)	21 (36%)	44 (77%)	4 (5%)	10 (38%)
Unsubtypable	7 (12%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Influenza B	2 (3%)	8 (33%)	20 (34%)	0 (0%)	9 (11%)	1 (4%)
B(Yamagata)	2 (2%)	2 (8%)	19 (32%)	0 (0%)	7 (8%)	1 (4%)
B(Victoria)	0 (0%)	4 (17%)	1 (2%)	0 (0%)	2 (2%)	0 (0%)
Unsubtypable	1 (2%)	2 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Column n denotes the total number of women with influenza. One woman had two episodes of antenatal influenza, an infection with an A(H1N1)pdm09 virus and an infection with a B(Yamagata) virus (see Supplemental Table 3 for results by site and year).

Supplemental Table 4 Baseline characteristics of pregnant women enrolled in the PRIME Study by exposure to acute respiratory illness (ARI), febrile ARI, and influenza (confirmed with real time reverse transcription polymerase chain reaction, rRT-PCR)*, India, Peru, Thailand, 2017-2018, N=11,277

	No ARI n=6,486		ARI n=4,791			No Febrile ARI n=10,407		Febrile ARI n=870			No Influenza[a] n=10,967		Influenza n=310		
	n or mean	(% or SD)	n or mean	(% or SD)	p-value[b]	n or mean	(% or SD)	n or mean	(% or SD)	p-value[b]	n or mean	(% or SD)	n or mean	(% or SD)	p-value[b]
Pre-pregnancy characteristics															
Country															
India	2981	(46)	2030	(42)	<0.0001	4638	(45)	373	(43)	<0.0001	4895	(45)	116	(37)	0.0416
Peru	1332	(21)	2173	(45)		3113	(30)	392	(45)		3396	(31)	109	(35)	
Thailand	2173	(34)	588	(12)		2656	(26)	105	(12)		2676	(24)	85	(27)	
Age, median (interquartile range)	27	(23 - 31)	26	(23 - 30)	<0.0001	26	(23 - 31)	26	(22 - 30)	0.0004	26	(23 - 31)	27	(23 - 32)	0.0349
Education															
No formal education	120	(2)	46	(1)	<0.0001	161	(2)	5	(1)	<0.0001	163	(1)	3	(1)	0.0366
Primary	1447	(22)	649	(14)		1986	(19)	110	(13)		2048	(19)	48	(16)	
Secondary	2972	(46)	2511	(52)		5031	(48)	452	(52)		5344	(49)	139	(45)	
Post-secondary/University	1935	(30)	1578	(33)		3210	(31)	303	(35)		3394	(31)	119	(39)	
Health insurance	2910	(45)	1916	(40)	<0.0001	4470	(43)	356	(41)	0.3497	4686	(43)	140	(45)	0.7189
Works outside the home	2130	(33)	1257	(26)	<0.0001	3153	(30)	234	(27)	0.0361	3275	(30)	112	(36)	0.0168
Parity, median (interquartile range)	1	(1 - 2)	1	(0 - 2)	0.8684	1	(0 - 2)	1	(0 - 2)	0.1227	1	(0 - 2)	1	(0 - 2)	0.0109
Pre-pregnancy BMI, median (interquartile range)	22	(19 - 25)	23	(20 - 26)	<0.0001	22	(19 - 25)	23	(20 - 26)	0.0086	22	(19 - 25)	22	(19 - 26)	0.3218
≥1 medical conditions	852	(13)	785	(16)	<0.0001	1460	(14)	177	(20)	<0.0001	1588	(14)	49	(16)	0.5132
Respiratory	89	(1)	113	(2)	<0.0001	175	(2)	27	(3)	0.0024	199	(2)	3	(1)	0.2676
Blood	171	(3)	112	(2)	0.3161	249	(2)	34	(4)	0.0060	276	(3)	7	(2)	0.7741
Endocrine	323	(5)	259	(5)	0.3121	524	(5)	58	(7)	0.0366	564	(5)	18	(6)	0.6024
Heart (including hypertension)	105	(2)	75	(2)	0.8229	161	(2)	19	(2)	0.1499	175	(2)	5	(2)	0.9810
HIV	11	(0)	16	(0)	0.0775	23	(0)	4	(0)	0.1663	27	(0)	0	(0)	0.3818
Other	242	(4)	317	(7)	<0.0001	491	(5)	68	(8)	<0.0001	538	(5)	21	(7)	0.1350
Previous miscarriage/stillbirth (rate per # of previous pregnancies), median (interquartile range)	0	(0 - 0.5)	0	(0 - 0.5)	<.0001	0	(0 - 0.5)	0	(0 - 0.5)	0.0143	0	(0 - 0.5)	0	(0 - 0.5)	0.5324
Current pregnancy characteristics															
Year of enrollment															
2017	2876	(44)	1898	(40)	<0.0001	4486	(43)	288	(33)	<0.0001	4632	(42)	142	(46)	0.2096
2018	3610	(56)	2893	(60)		5921	(57)	582	(67)		6335	(58)	168	(54)	
Trimester at enrollment															
First (0 to 13 6/7 weeks gestation)	1233	(19)	1429	(30)	<0.0001	2365	(23)	297	(34)	<0.0001	2569	(23)	93	(30)	0.0028
Second (14 to 27 6/7 weeks gestation)	4573	(71)	3146	(66)		7183	(69)	536	(62)		7514	(69)	205	(66)	
Third (≥28 weeks gestation)	654	(10)	213	(4)		830	(8)	37	(4)		855	(8)	12	(4)	
GA at first antenatal care visit, median (interquartile range)	13	(9 - 18)	13	(9 - 17)	0.0411	13	(9 - 18)	12	(9 - 17)	0.0003	13	(9 - 18)	13	(9 - 18)	0.1451
Multiple gestation pregnancy	92	(1)	70	(1)	0.9882	148	(1)	14	(2)	0.7130	159	(1)	3	(1)	0.4658
Current smoker	99	(2)	164	(3)	<0.0001	235	(2)	28	(3)	0.0714	254	(2)	9	(3)	0.4993
Current alcohol user	665	(10)	894	(19)	<0.0001	1397	(13)	162	(19)	<0.0001	1514	(14)	45	(15)	0.7206
Gestational diabetes	329	(5)	191	(4)	0.0066	479	(5)	41	(5)	0.8819	506	(5)	14	(5)	0.9355
Pregnancy induced hypertension	544	(8)	422	(9)	0.4298	865	(8)	101	(12)	0.0008	938	(9)	28	(9)	0.7662
≥1 psychosocial stressors	1879	(31)	2361	(50)	<0.0001	3782	(38)	458	(53)	<0.0001	4119	(39)	121	(40)	0.7509
Influenza vaccine in the current year[c]	484	(7)	990	(21)	<0.0001	1284	(12)	190	(22)	<0.0001	1427	(13)	47	(15)	0.2682

ARI: Acute respiratory illness; BMI: Body mass index.

* Women with febrile ARI and women with influenza were subsets of women with ARI. Of the 11,277 in the cohort, 4,791 (42%) had ≥1 episode of ARI while pregnant in the cohort. Of these 4,791 women with ARI, 870 (8%) had ≥1 episode of febrile ARI and 310 (3%) had influenza.
a Women without real time reverse transcription polymerase chain reaction-confirmed influenza who were pregnant for at least two weeks during the influenza season.
b p-values for the comparison of exposed versus unexposed groups examining the following exposures: ARI versus no ARI, febrile ARI versus no febrile ARI, and influenza versus no influenza. p-values were calculated using chi-squared or Fisher's Exact test.
c Based on maternal report verified with source documents such as vaccination cards or medical records.

Supplemental Table 5 Months pregnant during the influenza season by year and site among women included in outcomes analyses*, India, Peru, and Thailand, N=10,561 pregnant women who were pregnant for at least two weeks during the influenza season

	2017								2018							
	India		Thailand		Peru		Total		India		Thailand		Peru		Total	
	n	IQR	n	IQR	n	IQR	n	IQR	n	IQR	n	IQR	n	IQR	n	IQR
Total women	1951		1122		1484		4530		2962		1210		1859		6031	
Months, mean (SD)	3.4	(1.1)	3.8	(1.7)	3.8	(1.8)	3.6	(1.5)	2.9	(1.1)	2.9	(1.0)	4.5	(1.8)	3.4	(1.5)

Supplemental Table 6 Incidences of confirmed influenza (with real-time reverse transcription polymerase-chain reaction) per 10,000 pregnant woman-months during influenza season[a] by study year and influenza subtype, N=11,108 pregnant women[b]

	2017			2018		
	Episodes	Incidence	95% CI	Episodes	Incidence	95% CI
Influenza A	112	67.6	(56.2-81.4)	158	72.8	(62.3-85.1)
A(H1N1)pdm09	67	40.5	(31.9-51.4)	100	46.1	(37.9-56.1)
A(H3N2)	37	22.3	(16.2-30.8)	58	26.7	(20.7-34.6)
Influenza B	30	18.1	(12.7-25.9)	10	4.6	(2.5-8.6)
B(Yamagata)	22	13.3	(8.8-20.2)	8	3.7	(1.8-7.4)
B(Victoria)	5	3.0	(1.3-7.3)	2	0.9	(0.2-3.7)

[a] Influenza season defined as starting and ending on the date of collection of the first and last nasal swabs that were positive for influenza virus by rRT-PCR.
[b] Excludes 169 women who were not pregnant for at least 2 weeks during the influenza season.

Supplemental Table 7 Incidences of confirmed influenza (by real time reverse transcription polymerase chain reaction) during influenza season per 10,000 pregnant woman-months during influenza season by trimester, N=11,084 pregnant women*

	2017			2018			Overall		
	Episodes	Incidence	95% CI	Episodes	Incidence	95% CI	Episodes	Incidence	95% CI
Trimester									
1st	4	104.3	(41.2-264.3)	16	178.2	(109.5-290.1)	20	149.9	(96.7-232.3)
2nd	43	69.1	(51.3-93.2)	57	65.5	(50.6-85.0)	100	67.0	(55.1-81.6)
3rd	95	95.8	(78.4-117.2)	97	80.2	(65.7-97.9)	192	87.2	(75.7-100.5)

*Excludes 193 women who were not pregnant for at least 2 weeks during the influenza season or were missing data required for incidence estimates by trimester. Influenza season defined as starting and ending on the date of collection of the first and last nasal swabs that were positive for influenza virus by rRT-PCR.

Supplemental Table 8 Pregnancy and perinatal outcomes by site, 2017-2018, India, Peru, and Thailand, N=10,826

	All Participants N=10,826		India n=4,956		Peru 3,367		Thailand n=2,503	
	n	%	n	%	n	%	n	%
Preterm birth[a]	1196	(11)	587	(12)	391	(12)	218	(9)
Small for gestational age infant[b]	2,385	(22)	2081	(42)	100	(3)	204	(8)
Early spontaneous abortion[c]	43	(<1)	5	(<1)	35	(1)	3	(<1)
Late spontaneous abortion[d]	46	(<1)	20	(<1)	22	(1)	4	(<1)
Stillbirth[e]	133	(1)	80	(2)	40	(1)	13	(1)
Late pregnancy loss[f]	179	(2)	100	(2)	62	(2)	17	(1)
Maternal death[g]	15	(<1)	12	(<1)	2	(<1)	1	(<1)
Birthweight of term singleton infants[h], grams (SD)	3092	(516)	2766	(388)	3497	(430)	3192	(413)

a Birth at <37 weeks gestation.
b Infant with birth weight <10% for infants of the same gestational age and gender in the same population.
c Defined as spontaneous abortion occurring at <13 weeks gestation.
d Defined as spontaneous abortion occurring at ≥13 weeks gestation.
e Defined as death of a fetus at >22 weeks gestation.
f Defined as late spontaneous abortion occurring from 13 through 21 weeks gestation or stillbirth occurring at >22 weeks gestation.
g Death during pregnancy or within 28 days postpartum.
h Adjusted to account for typical weight loss patterns among newborns in the first 48 hours after birth using published nomograms.

Supplemental Table 9 Inverse-variance weighted effect sizes of exposure to acute respiratory illness, febrile acute respiratory illness, or influenza (by real time reverse transcription polymerase chain reaction)* on pregnancy outcomes based on two-stage site-stratified[e] regression models, 2017-2018, India, Peru, and Thailand, N=10,826 pregnant women

	Acute Respiratory Illness			Febrile Acute Respiratory Illness			rRT-PCR-Confirmed Influenza		
	Effect size[a]	(95% CI)	p value	Effect size[a]	(95% CI)	p value	Effect size[a]	(95% CI)	p value
Preterm birth[b]	1.1	(0.99, 1.28)	0.0746	1.4	(1.1, 1.7)	0.0026	1.2	(0.8, 1.7)	0.4105
SGA infant[c]	1.0	(0.9, 1.1)	0.5047	1.1	(1.0, 1.3)	0.1755	1.0	(0.8, 1.2)	0.6854
Late pregnancy loss[d]	0.98	(0.7, 1.4)	0.9055	1.5	(0.5, 4.8)	0.5078	11.5	(4.4, 30.0)	<0.0001
Birthweights of term singleton infants (grams)[e]	-2.8	(-22.7, 17.2)	0.7846	-19.9	(-54.4, 14.6)	0.2588	-39.9	(-93.8, 14.0)	0.1468

SGA: Small for gestational age.

*To assess the impact of each exposure, women with ARI were compared to those without ARI; women with febrile ARI were compared to those without febrile ARI; and women with influenza were compared to women without influenza. For the comparison of women with influenza versus without influenza, the analysis was restricted to women who were pregnant for at least two weeks during the influenza season.

a Effect sizes are hazard ratios for pregnancy loss and preterm birth, relative risks for SGA infant, and mean differences for birthweight of term singleton infants. In general, 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; 18.5 to <25, 25 to <30, >=30), 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). In addition, 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 prior pregnancy loss; and models assessing birthweight and SGA included smoking, exposure to indoor air pollution from cooking fuels, prenatal vitamin use, number of antenatal clinic visits, or weeks pregnant in the cohort (for assessing impact of febrile ARI and ARI), and infant gender (birthweight models only). Covariates were removed from site-specific models evaluating SGA infant as an outcome if there was collinearity with other variables in the model that prevented model convergence (see Supplemental Table 2).

b Birth at <37 weeks gestation.

c SGA defined as an infant with birth weight <10% for infants of the same gestational age and gender using INTERGROWTH-21 Project Standards.

d Defined as late spontaneous abortion occurring from 13 through 21 weeks gestation or stillbirth occurring at >22 weeks gestation.

e Multivariable models restricted to term singleton infants with birthweights collected per study protocol. Birthweights adjusted to account for typical weight loss patterns among newborns in the first 48 hours after birth using published nomograms.