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MAJOR ARTICLE

Influenza Vaccine Effectiveness in Preventing Influenza-associated Hospitalizations During Pregnancy: A Multi-country Retrospective Test Negative Design Study, 2010–2016

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(See the Editorial Commentary by Munoz on pages 1454-5.)

Background. To date, no study has examined influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza-associated hospitalizations during pregnancy.

Methods. The Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) consisted of public health or healthcare systems with integrated laboratory, medical, and vaccination records in Australia, Canada (Alberta and Ontario), Israel, and the United States (California, Oregon, and Washington). Sites identified pregnant women aged 18 through 50 years whose pregnancies overlapped with local influenza seasons from 2010 through 2016. Administrative data were used to identify hospitalizations with acute respiratory or febrile illness (ARFI) and clinician-ordered real-time reverse transcription polymerase chain reaction (rRT-PCR) testing for influenza viruses. Overall IVE was estimated using the test-negative design and adjusting for site, season, season timing, and high-risk medical conditions.

Results. Among 19 450 hospitalizations with an ARFI discharge diagnosis (across 25 site-specific study seasons), only 1030 (6%) of the pregnant women were tested for influenza viruses by rRT-PCR. Approximately half of these women had pneumonia or influenza discharge diagnoses (54%). Influenza A or B virus infections were detected in 598/1030 (58%) of the ARFI hospitalizations with influenza testing. Across sites and seasons, 13% of rRT-PCR-confirmed influenza-positive pregnant women were vaccinated compared with 22% of influenza-negative pregnant women; the adjusted overall IVE was 40% (95% confidence interval = 12%–59%) against influenza-associated hospitalization during pregnancy.

Conclusion. Between 2010 and 2016, influenza vaccines offered moderate protection against laboratory-confirmed influenza-associated hospitalizations during pregnancy, which may further inform the benefits of maternal influenza vaccination programs.

Keywords. pregnant women; pregnancy; influenza; vaccine effectiveness; hospitalization.

Pregnant women are at increased risk of severe complications from influenza virus infections, including hospitalization [1–3]. Consequently, the World Health Organization and many national public health agencies recommend that pregnant women receive influenza vaccination [2, 4, 5]. Although randomized controlled trials [6, 7] and observational studies of pregnant women [8, 9] suggest influenza vaccination may reduce the risk of mild to moderately severe influenza illness by half, no study to date has examined influenza vaccine effectiveness (IVE) in preventing severe influenza illness associated with hospitalization during pregnancy. The paucity of data on IVE in preventing severe influenza-related outcomes in pregnant women has been a major challenge to maternal immunization policymaking [2, 10], especially in low- and middle-income countries (LMICs) [5]. Even in high-income countries, influenza vaccines are widely underutilized during pregnancy [11, 12].

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Addressing this knowledge gap with observational studies poses challenges because of the large number of women needed to evaluate IVE against influenza hospitalization, and randomized placebo-controlled trials would be unethical. Therefore, the US Centers for Disease Control and Prevention (US CDC) in collaboration with national and international partners with integrated medical, laboratory, and vaccination records established the *Pre*gnancy Influenza *V*accine *E*ffectiveness *Net*work (PREVENT) to assess IVE in preventing laboratory-confirmed influenza (LCI) hospitalizations during pregnancy.

METHODS

Study Sites

PREVENT comprises 5 study sites in 4 countries (see Supplementary Table A). Regional public health and medical records were examined for residents in Western Australia and the provinces of Alberta and Ontario, Canada, whereas electronic medical records of large integrated care systems were examined for health plan members in the United States (Kaiser Permanente in Northern California, Oregon, and Washington) and Israel (Clalit Health Services). All sites reported high data capture rates for influenza vaccination from their review of medical records (Israel and USA), billing claims (Ontario), and/or regional immunization registries (Western Australia, Alberta, USA). At all study sites, influenza vaccination was recommended for pregnant women and available free of cost. Almost all influenza vaccines were trivalent and inactivated. Institutional Review Boards of the participating organizations approved the study protocol and procedures.

Influenza Seasons

Sites contributed data for 3 to 6 seasons, for a combined total of 25 site-specific study seasons. Southern hemisphere (SH) data from Western Australia were combined with northern hemisphere (NH) seasons with homologous influenza vaccine components and similar circulating strains (Table 1 and Supplementary Table B). Israel did not contribute data for NH 2011–12 due to limited clinical testing during that season. Similar to previous studies that defined influenza seasons consistently across countries [13, 14], sites used regional laboratory surveillance data to identify early, peak, and late periods for each season (Supplementary Table C). The peak period contained weeks during which ≥68% of the entire season's influenza positives were identified [15]. Median season length was 19 weeks (interquartile range [IQR] = 17–23); prominent influenza virus strains (>20% of tested specimens) were identified from a combination of clinical testing results and regional surveillance (described in Supplementary Table C).

Inclusion and Exclusion Criteria

Pregnant women aged 18–50 years were identified by records of live births or stillbirths with gestations ≥20 weeks. Hospitalization records were extracted for these women if their pregnancy overlapped with the local influenza season.

Hospitalizations for acute respiratory or febrile illness (ARFI) were identified using a shared list of *International Classification of Diseases, 9th and 10th Revision* (ICD-9/ICD-10) diagnosis codes (Supplementary Methods). These codes have been applied in previous studies of medically attended influenza illness [8, 16, 17] and were expanded to include other acute illnesses, such as febrile disease and sepsis-like presentations, that may also be associated with severe influenza disease among adults [18, 19]. A pregnant woman could contribute more than 1 hospital event if the admission occurred >14 days after the previous hospital discharge date; a second admission within 14 days of discharge was combined with the first event (i.e., the initial hospitalization) for analytic purposes.

We included ARFI hospitalizations among pregnant women only if there was also a clinician-ordered real-time reverse transcription polymerase chain reaction (rRT-PCR) test for influenza virus that occurred within 3 days prior to admission (to include ambulatory or emergency care testing that preceded admission) through the discharge date. ARFI hospitalizations among pregnant women with influenza results obtained only through non-PCR laboratory testing were excluded. Patients who were vaccinated <14 days prior to hospital admission and those for whom influenza vaccination status could not be documented were also excluded.

Statistical Analysis

IVE was assessed using the test-negative design (TND), whereby IVE equals 1 − odds ratio [ratio of odds of vaccination among influenza-positive cases to the odds of vaccination among influenza-negative controls] × 100% using logistic regression. The TND is believed to minimize biases associated with access to influenza vaccines and healthcare seeking [20, 21]. Nonetheless, IVE estimates were adjusted for site, season, season timing at hospital admission (early, peak, vs. late), and the presence of high-risk medical conditions (Supplementary Methods), because of the associations between these covariates and both influenza virus-positivity and vaccination status as well as to aid in comparability with IVE estimates from other studies [22]. Other variables that appeared to be potential confounders in our data (trimester at admission, ARFI primary diagnosis, pneumonia or influenza ICD-coded diagnosis, pregnancy complication, delivery during hospitalization, or intensive care unit [ICU] admission) and/or have been shown to be confounders in previous TND studies (age and race) [16, 23] did not change the adjusted VE by ≥5%, in our study, and thus were not included in the IVE models.

We estimated IVE using a model that combined all data, but adjusted for covariates including site and season; this approach has been used in previous studies that estimated IVE among relatively small populations or against rarer influenza outcomes

Table 1. Characteristics of Pregnant Women Hospitalized With Acute Respiratory or Febrile Illness (ARFI) Who Were Positive vs. Negative With Real-time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) Confirmed Influenza Virus Infections and Percentage Vaccinated

	Sample		Negatives		Positives[a]			Vaccinated		
	N	(Col. %)	N	(Col. %)	N	(Col. %)	*P*-value	N	(Row %)	*P*-Value
All hospitalizations	1030	(100)	432	(100)	598	(100)		169	(16)	
Site and Season Characteristics										
Site							0.0002			<.0001
Australia (Western)	74	(7)	39	(9)	35	(6)		7	(9)	
Canada (Alberta)	186	(18)	84	(19)	102	(17)		23	(12)	
Canada (Ontario)	354	(34)	132	(31)	222	(37)		27	(8)	
Israel	265	(26)	94	(22)	171	(29)		37	(14)	
USA (Western)	151	(15)	83	(19)	68	(11)		75	(50)	
Season							0.55			.004
NH 2010–11	167	(16)	70	(16)	97	(16)		14	(8)	
NH 2011–12	84	(8)	41	(9)	43	(7)		17	(20)	
NH 2012–13 and SH 2013	192	(19)	73	(17)	119	(20)		31	(16)	
NH 2013–14	200	(19)	81	(19)	119	(20)		25	(13)	
SH 2014 and NH 2014–15	171	(17)	78	(18)	93	(16)		36	(21)	
SH 2015 and NH 2015–16	216	(21)	89	(21)	127	(21)		46	(21)	
Season timing of hospital admission[b]							<0.0001			.02
Early season	116	(11)	61	(14)	55	(9)		25	(22)	
Peak season	582	(57)	207	(48)	375	(63)		104	(18)	
Late season	332	(32)	164	(38)	168	(28)		40	(12)	
Descriptive Characteristics										
Age at admission							0.12			.30
<35 years	811	(79)	330	(76)	481	(80)		128	(16)	
≥35 years	219	(21)	102	(24)	117	(20)		41	(19)	
Parity[c]							0.65			.92
0	313	(30)	130	(30)	183	(31)		51	(16)	
1	357	(35)	151	(35)	206	(34)		56	(16)	
≥2	360	(35)	151	(35)	209	(35)		62	(17)	
Trimester at index admission							0.03			.16
First (0–13 weeks)	60	(6)	33	(8)	27	(5)		≤5	(≤8)	[h]
Second (14–27 weeks)	298	(29)	134	(31)	164	(27)		46	(15)	
Third (≥28 weeks)	672	(65)	265	(61)	407	(68)		118	(18)	
Health Status										
Any high risk medical condition[d]							<0.0001			<.0001
No high risk	680	(66)	236	(55)	444	(74)		83	(12)	
One or more high risk	350	(34)	196	(45)	154	(26)		86	(25)	
Asthma							0.01			<.0001
No asthma	926	(90)	376	(87)	550	(92)		138	(15)	
Asthma	104	(10)	56	(13)	48	(8)		31	(30)	
Cardio-pulmonary condition							<0.0001			.001
No cardiac or pulmonary	868	(84)	327	(76)	541	(90)		128	(15)	
One or more cardiac or pulmonary	162	(16)	105	(24)	57	(10)		41	(25)	
Index Hospitalization										
ARFI was first or primary diagnosis							0.0001			<.0001
ARFI not primary	498	(48)	239	(55)	259	(43)		106	(21)	
ARFI was primary	532	(52)	193	(45)	339	(57)		63	(12)	
Delivery at index hospitalization							0.01			.02
No delivery	807	(78)	322	(75)	485	(81)		121	(15)	
Delivery	223	(22)	110	(25)	113	(19)		48	(22)	

(Continued)

Table 1. Continued

	Sample		Negatives		Positives[a]			Vaccinated		
	N	(Col. %)	N	(Col. %)	N	(Col. %)	*P*-value	N	(Row %)	*P*-Value
ICU							0.0002			.52
No ICU admission	931	(90)	374	(87)	557	(93)		159	(17)	
ICU admitted	75	(7)	47	(11)	28	(5)		10	(13)	
Unknown	24	(2)	11	(3)	13	(2)		0	(0)	
Pneumonia or influenza diagnosed							<0.0001			.01
No pneumonia or influenza	470	(46)	263	(61)	207	(35)		87	(19)	
Pneumonia or influenza diagnosed	560	(54)	169	(39)	391	(65)		82	(15)	
Febrile disease diagnosed							<0.0001			.80
No febrile disease	920	(89)	365	(84)	555	(93)		150	(16)	
Febrile disease diagnosed	110	(11)	67	(16)	43	(7)		19	(17)	
Pregnancy complications[e]							0.003			<.0001
No high risk	504	(49)	188	(44)	316	(53)		58	(12)	
One or more high risk	526	(51)	244	(56)	282	(47)		111	(21)	
Influenza Vaccination										
Current season influenza vaccination status[f]							<0.0001			
Unvaccinated	861	(84)	338	(78)	523	(87)				
Vaccinated	169	(16)	94	(22)	75	(13)				
Influenza RT-PCR Results										
A or B influenza result										<.0001
Negative	432	(42)						94	(22)	
Positive	598	(58)						75	(13)	
Influenza type and subtype[g]										<.0001
A unsubtyped					207	(35)		31	(15)	
A(H3N2) virus					113	(19)		17	(15)	
A(H1N1)pdm09 virus					179	(30)		16	(9)	
B virus					102	(17)		12	(12)	

P-values are from χ^2 tests of association.

Abbreviations: ARFI, acute respiratory or febrile illness; ICU, intensive care unit; NH, Northern Hemisphere; RT-PCR, reverse transcription polymerase chain reaction; SH, Southern Hemisphere.

[a]All hospitalizations for ARFI included clinical rRT-PCR testing for influenza within 3 days of admission through discharge

[b]Period of influenza circulation was defined by regional surveillance of laboratory-confirmed influenza (Supplementary Table C); peak period contained the weeks during which ≥68% of the entire season's influenza positives were identified.

[c]A small number ≤5 with unconfirmed parity were assumed to have 0 parity.

[d]High-risk medical conditions include underlying medical conditions (not pregnancy complications) recognized as increasing risk of secondary influenza complications; identified from discharge codes at index hospitalization.

[e]Pregnancy complications identified from discharge codes at index hospitalization.

[f]Current season vaccination documented by medical record or registry; those known to have received vaccination 0–14 days prior to admission are excluded from study sample as indeterminate immunization status.

[g]The total by (sub)type is higher than the total influenza positives due to influenza A and B coinfections.

[h]Small cells had to be expressed as a range of possible values due to site-specific data use rules.

[8, 24, 25]. In exploratory examinations of data heterogeneity, neither Cochran's χ^2 (or Q-test) nor the I^2 index rejected the null hypothesis of homogeneity in adjusted IVE between study sites (Q[4] = 1.19, P = .95; I^2 = 0) or between seasons (Q[5] = 4.40, P = .51; I^2 = 0) though both indicators were underpowered to detect heterogeneity with small numbers of observations [26]. Nonetheless, to aid in the interpretation of the overall adjusted IVE estimate, IVE results are reported by strata for all adjusted model covariates and by trimester at admission, ICU admission, the presence of an ICD-coded pneumonia or influenza diagnosis, and whether ARFI was the primary diagnosis. IVE is also reported excluding SH 2014 and NH 2014–15 given poor antigenic and genetic match between the A(H3N2) vaccine component and circulating strains during these seasons [23, 27, 28]. For the purposes of hypothesis generation, we examined statistical indications that IVE varied by certain subgroups by estimating interaction terms for vaccination status by all stratification variables.

Because our sample was relatively small, and because influenza A virus subtyping results were not available for Israel or the United States, we were not able to report IVE by influenza subtype. Site-specific estimates could not be calculated for Western Australia, and small cells had to be expressed as a range of possible values due to site-specific data use requirements.

RESULTS

Sample Characteristics

Among the sites that we were able to identify all recorded pregnancies (≥20 weeks gestation) during the study years, 84% (1.72 million [M]/2.05 M) of the pregnancies occurred during an influenza season (Supplementary Table D). Across all sites and seasons, 19 450 ARFI hospitalizations were identified; of these, 6% (1235) had rRT-PCR influenza virus testing; an additional 0.5% (99) had non-PCR influenza test results only and were excluded. After excluding 11 ARFI hospitalizations with recent or missing vaccination status, and combining 95 readmissions (<14 days of discharge) into single hospitalizations, the analytic sample was 1030 hospitalizations, which included only 25 repeated hospitalizations from the same woman.

Most of the ARFI hospitalizations occurred among women who were aged <35 years (79%), were in their third trimester (65%), and had no high-risk medical conditions (66%) (Table 1). An ARFI diagnosis was the primary discharge diagnosis for 52% of the hospitalizations; 7% included an ICU admission, and delivery occurred in 22% of the hospitalization. About half (54%) of the hospitalizations included an ICD-coded discharge diagnosis of pneumonia or influenza, and half (51%) included a pregnancy complication diagnosis.

Influenza-associated ARFI Hospitalizations

Among the ARFI hospitalizations with PCR-influenza testing, 58% (598/1030) were positive for influenza virus infection. Influenza positivity ranged from 51% to 62% across seasons and from 45% to 65% across sites. The number of influenza positives identified per season was similar for most seasons (ranges, n = 93–127) except for NH 2011–12, which was considerably lower (n = 43) (Supplementary Figure A). Of 25 site-specific study seasons, A(H3N2) viruses were most prominent in 18 (72%); A(H1N1)pdm09 viruses were prominent in 13 (52%); B viruses were prominent in 10 (40%) of the seasons (Supplementary Table C).

Compared to influenza-negative pregnant women hospitalized with ARFI, influenza-positive pregnant women were more likely to be in their third trimester and less likely to have a high-risk medical condition (Table 1). Influenza-positive pregnant women were also more likely to have an ICD-coded pneumonia or influenza diagnosis and have an ARFI ICD code as their primary discharge diagnosis; however, they were less likely to have a febrile disease diagnosis, have a pregnancy complication diagnosis, deliver during their ARFI hospitalization, or be admitted to an ICU. Nonetheless, influenza positivity was high even in these groups. For example, influenza positivity was highest for women with a pneumonia or influenza diagnosis (70%) but was also high among those with a febrile disease diagnosis (39%). Similarly, influenza positivity was >50% among women when ARFI was not their primary diagnosis, when they were diagnosed with a pregnancy complication, or when they delivered in hospital. Site-level associations are summarized in Supplementary Table E.

Influenza Vaccination

Across all sites and seasons, 16% of women were vaccinated against influenza prior to their ARFI hospitalization. Vaccination coverage varied across seasons (range = 8%–21%), but was significantly higher after SH 2014 (21%) than before (14%) ($P = .002$). Vaccination coverage was much higher in the USA (50%) compared to the other four sites (range = 8%–14%). With the combined data from all sites, vaccination coverage did not differ significantly by maternal age group, parity, or trimester at ARFI hospitalization; however, coverage was higher among women with a high-risk medical condition (including asthma or any cardiopulmonary conditions) (Table 1). Vaccination coverage was higher among women who delivered or had a pregnancy complication during their ARFI hospitalization and was lower if ARFI was the primary discharge diagnosis or if there was a diagnosis of pneumonia or influenza.

Vaccine Effectiveness

Across study seasons, 13% of rRT-PCR-confirmed influenza-positive pregnant women were vaccinated compared with 22% of influenza-negative pregnant women, which corresponds to an unadjusted IVE of 48% (95% confidence interval [CI]: 28%–63%). Adjusted for site, season, season timing, and the presence of any high-risk medical condition, IVE was 40% (95% CI: 12%–59%) against LCI hospitalization during pregnancy.

Confidence intervals overlapped for all stratified IVE estimates by site, season, season timing, and patient diagnoses. Adjusted IVE point estimates by site were lowest for Alberta (8%) and Israel (17%) and highest for Ontario (40%) and the United States, which was the only site with a statistically significant IVE estimate: 55% (95% CI: 7%–78%) (Table 2). IVE point estimates by season ranged from −24% (SH 2014 and NH 2014–15) to 72% (NH 2010–11); when SH 2014 and NH 2014–15 seasons were excluded, the combined adjusted IVE estimate for all other seasons was 49% (95% CI: 22–67%).

IVE point estimates were similar when stratified by season timing of admission or by the presence of high-risk medical conditions. IVE point estimates were lower for women hospitalized in their third trimester and when their ARFI hospitalization discharge included an ICD-coded pneumonia or influenza diagnosis. IVE point estimates were higher for hospitalizations with an ICU admissions and for hospitalizations where an ARFI diagnoses was the primary discharge code; this corresponded to an interaction term for vaccination status by ARFI primary diagnosis that was statistically significant ($P = .028$). Interaction terms for all other variables, including site and season, were not statistically significant ($P > .28$).

Table 2. Number and Percentage Influenza Vaccinated (vacc.) Among Women Hospitalized for Acute Respiratory or Febrile Illness by Influenza Virus Test Result With Influenza Vaccine Effectiveness Against All Influenza A and B Viruses

		Influenza Positives			Influenza Negatives			Unadjusted IVE		Adjusted IVE[a]	
Sites or Subgroups	Seasons	Total	Vacc. N	(%)	Total	Vacc. N	(%)	IVE	(95% CI)	IVE	(95% CI)
All sites	2010–11 to 2015–16	598	75	(13)	432	94	(22)	48	(28,63)	**40**	**(12, 59)**
By site[e]											
Canada (Alberta)	2010–11 to 2014–15	102	11	(11)	84	12	(14)	28	(-74,70)	8	(−132, 64)
Canada (Ontario)	2010–11 to 2015–16	222	14	(6)	132	13	(10)	38	(-36,72)	40	(−40, 74)
Israel	2010–11, 2012–13 to 2015–16	171	22	(13)	94	15	(16)	22	(-58,62)	17	(−75, 61)
USA (West)	2010–11 to 2015–16	68	25	(37)	83	50	(60)	62	(26,80)	**55**	**(7, 78)**
By season											
All NH sites	NH 2010–11	97	≤5	(≤5)[e]	70	9	(13)	63	(-15,88)	72	(−5, 93)
NH sites (except Israel)	NH 2011–12	43	6	(14)	41	11	(27)	56	(-34,85)	47	(−98, 86)
All sites	NH 2012–13 and SH 2013	119	16	(13)	73	15	(21)	40	(-30,72)	23	(−85, 68)
All NH sites	NH 2013–14	119	9	(8)	81	16	(20)	67	(21,86)	51	(−30, 82)
All sites	SH 2014 and NH 2014–15	93	20	(22)	78	16	(21)	-6	(-122,49)	-24	(−189, 47)
All sites (except Alberta)	SH 2015 and NH 2015–16	127	19	(15)	89	27	(30)	60	(22,79)	40	(−33, 72)
Season timing of admission[b]	2010–11 to 2015–16										
Early		55	8	(15)	61	17	(28)	56	(-12,83)	33	(−156, 82)
Peak		422	54	(13)	230	50	(22)	47	(19,65)	**37**	**(0, 60)**
Late		121	13	(11)	141	27	(19)	49	(-3,75)	37	(−42, 72)
All sites by trimester	2010–11 to 2015–16										
1st or 2nd trimester		191	17	(9)	167	34	(20)	62	(29,80)	**55**	**(10, 78)**
3rd trimester at admission		407	58	(14)	265	60	(23)	43	(15,62)	35	(−3, 59)
All sites by medical conditions	2010–11 to 2015–16										
No high risk conditions		443	46	(10)	237	37	(16)	37	(3,61)	38	(−2, 63)
≥1 medical condition[c]		155	29	(19)	195	57	(29)	44	(7,67)	44	(−1, 69)
All sites by primary diagnosis	2010–11 to 2015–16										
ARFI not primary		259	48	(19)	239	58	(24)	29	(-9,54)	23	(−28, 54)
ARFI primary diagnosis		339	27	(8)	193	36	(19)	62	(36,78)	**54**	**(17, 75)**
All sites by diagnosis	2010–11 to 2015–16										
Not pneumonia or influenza		207	27	(13)	263	60	(23)	50	(17,69)	**49**	**(9, 72)**
Pneumonia or influenza		391	48	(12)	169	34	(20)	44	(10,66)	25	(−32, 57)

(Continued)

Table 2. Continued

Sites or Subgroups	Seasons	Influenza Positives			Influenza Negatives			Unadjusted IVE		Adjusted IVE[a]	
		Total	Vacc. N	(%)	Total	Vacc. N	(%)	IVE	(95% CI)	IVE	(95% CI)
All sites by ICU[d]	2010–11 to 2015–16										
Not ICU		374	85	(23)	557	74	(13)	48	(27,63)	**37**	**(7, 58)**
ICU admitted		47	9	(19)	28	(≤5)[e]	(≤18)[e]	84	(-31,98)	NC	
All sites	All (exclude SH 2014 and NH 2014–15)	505	55	(11)	354	78	(22)	57	(38,71)	**49**	**(22, 67)**

Abbreviations: ARFI, acute respiratory or febrile illness; CI, confidence interval; ICU, intensive care unit; IVE, influenza vaccine effectiveness; NC, not calculated due to insufficient sample size; NH, Northern Hemisphere; SH, Southern Hemisphere.

[a]Adjusted models include site, season/year, season period (early, late, or peak), and presence of a high risk medical condition. Statistically significant estimates are bolded.

[b]Period of influenza circulation was defined by regional surveillance of laboratory-confirmed influenza (Supplementary Table C); peak period contained the weeks during which ≥68% of the entire season's influenza positives were identified.

[c]High-risk medical conditions include underlying medical conditions (not pregnancy complications) recognized as increasing risk of secondary influenza complications; identified from discharge codes at index hospitalization

[d]ICU admission documentation was missing for 24 hospitalizations; adjusted IVE model for ICU admitted could not be calculated due to sparse data.

[e]Site-specific numbers could not be calculated for Australia and small cells had to be expressed as a range of possible values due to site-specific data use requirements.

DISCUSSION

Across influenza seasons and study sites from 2010–11 to 2015–16, influenza vaccines were 40% (95% CI: 12%–59%) effective in preventing LCI hospitalizations in pregnant women. This moderate protection was noted during a period when A(H1N1) pdm09 viruses were a prominent strain in about half of the study seasons, A(H3N2) viruses were a prominent strain in >70% of study seasons, and the match between vaccine strains and circulating A(H3N2) viruses varied from good to poor [29, 30].

Our adjusted 40% overall IVE estimate in preventing LCI hospitalizations in pregnant women is similar to, though slightly lower than, a recent pooled IVE estimate of 51% against LCI hospitalizations across TND studies of all adults aged 18–64 years during the 2010–11 to 2014–15 seasons [29]. Our finding is also similar to the 44% IVE against symptomatic non-hospitalized LCI among pregnant women in a prospective TND study during 2010–11 and 2011–12 in the United States [8]. The only prospective RCTs to date reported influenza vaccine efficacy in preventing symptomatic LCI illness during pregnancy and post-partum of 70% in a 2011–2014 RCT in Mali [7] and 50% in a 2011–2012 RCT in South Africa [6]. It is reassuring that our IVE point estimates appeared to be consistent throughout the early, peak, and late weeks of influenza seasons and were similar for those with and without underlying high-risk medical conditions.

Our findings are potentially relevant to several public health policy and research debates. Indeed, the lack of evidence for IVE against severe LCI during pregnancy has been described as an obstacle to the expansion of maternal influenza vaccination programs in LMICs, where vaccine policy and investment decisions generally favor vaccines with demonstrated benefits against more severe outcomes [2, 5]. The generalizability of findings from PREVENT's high-income countries to LMICs is not clear. Access to hospital care and the severity threshold for admission likely differs for LMICs; though, it is noteworthy that IVE unadjusted point estimates trended higher (though not significant statistically) when we limited analyses to women with ICU admissions. Nonetheless, our IVE estimates may help inform planning models for LMICs and increase confidence in the preventive benefits of maternal influenza vaccination programs even if the IVE estimates are not directly generalizable [2]. Our findings could also support the expanded use of influenza vaccine among pregnant women in high-income countries; in our study, influenza vaccination coverage among hospitalized pregnant women during influenza seasons was well below national and international goals [11, 12]. Our finding of a significant IVE of 55% among women who were hospitalized in their first and second trimester may also contribute to research and policy discussions about the benefits and possible risks of early maternal vaccination [10], especially during the first trimester [31].

Strengths of this study include the relatively large sample size from 5 sites in 4 countries, the use of the extensively validated TND [20–22] with influenza virus infection confirmed by highly sensitive and specific rRT-PCR assay, and vaccination status documented in medical records and vaccination registries. We also used a broad ARFI case definition that included diagnoses beyond typical acute respiratory illnesses. Our findings suggest that there may be a broader vaccine-preventable laboratory-confirmed influenza burden among hospitalized pregnant women, including laboratory-confirmed influenza with febrile disease or at delivery, which may have been missed by the use of narrower ARI definitions in previous studies [3, 32].

Our overall IVE estimate is a function of the match between vaccine and circulating viruses of the specific study sites and seasons we examined. Despite the lack of statistical heterogeneity between study sites, there is certainly visible heterogeneity in stratified IVE estimates between study sites and seasons. Nonetheless, the direction of the effects with higher vaccination coverage among influenza-negatives compared to influenza-positives across sites and most seasons is consistent with expectations. The findings of low IVE point estimates in NH 2012–13 and SH 2013 seasons and negative IVE in SH 2014 and NH 2014–15 seasons fit with previous reports that the A(H3N2) vaccine components in those years were antigenically and/or genetically mismatched with the prominent A(H3N2) circulating viruses [23, 27, 28, 33, 34]. Israel and Canada (Alberta) had relatively low IVE estimates, which may be due in part to the fact that they both contributed data for seasons with particularly low IVE (2012–13 and 2014–15) and did not contribute data from a season with relatively high IVE (2011–12 for Israel and 2015–16 for Canada [Alberta]).

The interpretation of our IVE findings are limited because we were unable to stratify IVE based on influenza types and subtypes. Thus, we could not examine whether IVE may have been higher against A(H1N1)pdm09 compared to A(H3N2) viruses, which was observed among hospitalized adults during this time period in a recent review [29]. Similarly, we lacked information on the genetic sequencing of viruses, which may have aided in interpreting IVE differences even between neighboring regions [35].

In addition to those already mentioned, this study has other limitations. First, we could not extract date of illness onset from medical records and thus could not exclude women with prolonged illnesses and reduced influenza virus shedding. The higher IVE observed among hospitalizations when ARFI was the primary diagnosis may reflect that there was less misclassification of LCI among these women who had a clinically urgent illness. Second, PREVENT relied on clinician-ordered rRT-PCR testing of only 6% of ARFI hospitalizations; clinician-ordered testing can bias IVE results if they are influenced by vaccination status, although findings on the association between clinical testing and vaccination status are mixed [36, 37]. Third, we likely misclassified some women as unvaccinated at some sites; however, this likely biases IVE estimates toward the null as vaccination ascertainment is unlikely to differ substantially for influenza positives versus negatives [22, 38]. Fourth, without full influenza vaccination histories, we were unable to examine whether prior vaccination offered cross-season protection and/or negatively interfered with IVE, as observed by other studies in some of our study seasons [8, 39–41].

CONCLUSION

In this retrospective cohort of over 2 million pregnancies that we assembled from 2010 to 2016 across 5 regions in 4 countries, 84% of the pregnancies overlapped with an influenza season. Thus, the risk of influenza virus infection is relevant to most pregnant women. In addition to the ample data on the safety of inactivated influenza vaccination during pregnancy [42, 43], mounting evidence that influenza vaccination reduces the risk of mild to moderately severe LCI disease during pregnancy [6–8], and evidence that maternal vaccination offers secondary protection to infants during the first months of life [6, 7, 44, 45], our finding of 40% IVE in preventing LCI hospitalization during pregnancy further strengthens the rationale for influenza vaccination programs for pregnant women.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol **2012**; 207:S3–8.
2. Fell DB, Azziz-Baumgartner E, Baker MG, et al.; WHO taskforce to evaluate influenza data to inform vaccine impact and economic modelling. Influenza epidemiology and immunization during pregnancy: final report of a World Health Organization working group. Vaccine **2017**; 35:5738–50.
3. Mertz D, Geraci J, Winkup J, Gessner BD, Ortiz JR, Loeb M. Pregnancy as a risk factor for severe outcomes from influenza virus infection: a systematic review and meta-analysis of observational studies. Vaccine **2017**; 35:521–8.
4. Jamieson DJ, Kissin DM, Bridges CB, Rasmussen SA. Benefits of influenza vaccination during pregnancy for pregnant women. Am J Obstet Gynecol **2012**; 207:S17–20.
5. Ortiz JR, Neuzil KM. Influenza immunization of pregnant women in resource-constrained countries: an update for funding and implementation decisions. Curr Opin Infect Dis **2017**; 30:455–62.
6. Madhi SA, Cutland CL, Kuwanda L, et al.; Maternal Flu Trial (Matflu) Team. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med **2014**; 371:918–31.
7. Tapia MD, Sow SO, Tamboura B, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. Lancet Infect Dis **2016**; 16:1026–35.
8. Thompson MG, Li DK, Shifflett P, et al. Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010–2011 and 2011–2012 influenza seasons. Clin Infect Dis **2014**; 58:449–57.
9. Manske JM. Efficacy and effectiveness of maternal influenza vaccination during pregnancy: a review of the evidence. Matern Child Health J **2014**; 18:1599–609.
10. Skowronski DM, De Serres G. Is routine influenza immunization warranted in early pregnancy? Vaccine **2009**; 27:4754–70.
11. Wong VW, Lok KY, Tarrant M. Interventions to increase the uptake of seasonal influenza vaccination among pregnant women: a systematic review. Vaccine **2016**; 34:20–32.
12. Ding H, Black CL, Ball S, et al. Influenza vaccination coverage among pregnant women—United States, 2016–17 Influenza Season. MMWR Morb Mortal Wkly Rep **2017**; 66:1016–22.
13. Durand LO, Cheng PY, Palekar R, et al. Timing of influenza epidemics and vaccines in the American tropics, 2002–2008, 2011–2014. Influenza Other Respir Viruses **2016**; 10:170–5.
14. Hirve S, Newman LP, Paget J, et al. Influenza seasonality in the tropics and subtropics: when to vaccinate? PLoS One **2016**; 11:e0153003.
15. Azziz Baumgartner E, Dao CN, Nasreen S, et al. Seasonality, timing, and climate drivers of influenza activity worldwide. J Infect Dis **2012**; 206: 838–46.
16. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012–2013: variable protection by age and virus type. J Infect Dis **2015**; 211(10): 1529–40.
17. Sokolow LZ, Naleway AL, Li DK, et al. Severity of influenza and noninfluenza acute respiratory illness among pregnant women, 2010–2012. Am J Obstet Gynecol **2015**; 212:202 e1–e11.
18. Reed C, Chaves SS, Perez A, et al. Complications among adults hospitalized with influenza: a comparison of seasonal influenza and the 2009 H1N1 pandemic. Clin Infect Dis **2014**; 59:166–74.
19. Oboho IK, Reed C, Gargiullo P, et al. Benefit of early initiation of influenza antiviral treatment to pregnant women hospitalized with laboratory-confirmed influenza. J Infect Dis **2016**; 214:507–15.
20. Foppa IM, Haber M, Ferdinands JM, Shay DK. The case test-negative design for studies of the effectiveness of influenza vaccine. Vaccine **2013**; 31:3104–9.
21. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine **2013**; 31:2165–8.
22. Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. Expert Rev Vaccines **2014**; 13:1571–91.
23. Zimmerman RK, Nowalk MP, Chung J, et al. 2014–2015 influenza vaccine effectiveness in the United States by vaccine type. Clin Infect Dis **2016**; 63(12): 1564–73.
24. Ferdinands JM, Olsho LE, Agan AA, et al. Effectiveness of influenza vaccine against life-threatening RT-PCR-confirmed influenza illness in US children, 2010–2012. J Infect Dis **2014**; 210(5): 674–83.
25. Thompson MG, Clippard J, Petrie JG, et al. Influenza vaccine effectiveness for fully and partially vaccinated children 6 months to 8 years old during 2011–2012 and 2012–2013: the importance of two priming doses. Pediatr Infect Dis J **2015**.
26. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med **2002**; 21:1539–58.
27. Skowronski DM, Chambers C, Sabaiduc S, et al. Interim estimates of 2014/15 vaccine effectiveness against influenza A(H3N2) from Canada's Sentinel Physician Surveillance Network, January 2015. Euro Surveill **2015**; 20(4).
28. Pierse N, Kelly H, Thompson MG, et al. Influenza vaccine effectiveness for hospital and community patients using control groups with and without non-influenza respiratory viruses detected, Auckland, New Zealand 2014. Vaccine **2015**.
29. Rondy M, El Omeiri N, Thompson MG, Levêque A, Moren A, Sullivan SG. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies. J Infect **2017**; 75:381–94.
30. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis **2016**; 16:942–51.
31. Donahue JG, Kieke BA, King JP, et al. Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010-11 and 2011-12. Vaccine **2017**; 35:5314–22.
32. Katz MA, Gessner BD, Johnson J, et al. Incidence of influenza virus infection among pregnant women: a systematic review. BMC Pregnancy Childbirth **2017**; 17:155.
33. Skowronski DM, Janjua NZ, De Serres G, et al. Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses. PLoS One **2014**; 9:e92153.
34. McLean HQ, Meece JK, Belongia EA. Influenza vaccination and risk of hospitalization among adults with laboratory confirmed influenza illness. Vaccine **2014**; 32:453–7.

35. Skowronski DM, Chambers C, Sabaiduc S, et al. Interim estimates of 2016/17 vaccine effectiveness against influenza A(H3N2), Canada, January 2017. Euro Surveill **2017**; 22(6).
36. Kwong JC, Campitelli MA, Gubbay JB, et al. Vaccine effectiveness against laboratory-confirmed influenza hospitalizations among elderly adults during the 2010–2011 season. Clin Infect Dis **2013**; 57(6): 820–7.
37. Ferdinands JM, Belongia EA, Nwasike C, Shay DK. Influenza vaccination status is not associated with influenza testing among children: implications for observational studies of vaccine effectiveness. Vaccine **2011**; 29: 1935–40.
38. Ohmit SE, Thompson MG, Petrie JG, et al. Influenza vaccine effectiveness in the 2011–2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. Clin Infect Dis **2014**; 58(3): 319–27.
39. Skowronski DM, Chambers C, De Serres G, et al. Serial vaccination and the antigenic distance hypothesis: effects on influenza vaccine effectiveness during A(H3N2) epidemics in Canada, 2010–2011 to 2014–2015. J Infect Dis **2017**; 215(7): 1059–99.
40. Belongia EA, Skowronski DM, McLean HQ, Chambers C, Sundaram ME, De Serres G. Repeated annual influenza vaccination and vaccine effectiveness: review of evidence. Expert Rev Vaccines **2017**; 16:1–14.
41. McLean HQ, Thompson MG, Sundaram ME, et al. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. Clin Infect Dis **2014**; 59:1375–85.
42. Keller-Stanislawski B, Englund JA, Kang G, et al. Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. Vaccine **2014**; 32:7057–64.
43. Sukumaran L, McCarthy NL, Kharbanda EO, et al. Safety of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis and influenza vaccinations in pregnancy. Obstet Gynecol **2015**; 126:1069–74.
44. Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med **2008**; 359:1555–64.
45. Steinhoff MC, Katz J, Englund JA, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. Lancet Infect Dis **2017**; 17:981–9.