Influenza Vaccine Effectiveness in Preventing Influenza-Associated Hospitalizations during Pregnancy: A Multi-Country Retrospective Test Negative Design Study, 2010-2016

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on behalf of the
Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) Network
and the
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Background

- Pregnant women are believed to be at increased risk of severe influenza disease, including influenza hospitalization

- 44% of WHO member states recommend influenza vaccination for pregnant women
  - Some with trimester restrictions
  - Contraindicated in some countries
  - Even high-income countries underutilize

- Inactivated influenza vaccines reduce the risk of mild to moderately severe PCR-confirmed influenza illness by about half

- Scarce data on severe outcomes; RCTs or existing IVE platforms cannot address this gap

“Policy-makers from LMICs are likely to place higher value on vaccines with demonstrated impact on severe influenza disease.”
PREVENT Network

- US CDC funded Pregnancy Influenza Vaccine Effectiveness Network (PREVENT)
  - HHSD20022013M53890B (200-2014-F-60406) to Abt Associates, Inc.

- Collaboration among public health and healthcare systems with integrated medical, laboratory, and vaccination records

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Study Sites and Seasons

**Australia (Western):** Western Australia Dept. of Health (Annette Regan)

**Canada (Alberta):** Alberta Health (Kim Simmonds, Margaret Russell, Steve Drews)

**Canada (Ontario):** Institute for Clinical Evaluative Sciences (Jeff Kwong, Deshayne Fell)

**Israel:** Clalit Health Research Institute (Becca Feldman, Mark Katz)

**USA (West):** Kaiser Permanente (Allison Naleway, Nicky Klein, Mike Jackson)

Abt Associates was the coordinating center; IRBs approved the study protocol and procedures.

### Sites or Subgroups

**Sites or Subgroups** | **Seasons**
--- | ---
**All Sites** | 2010-11 to 2015-16

### By Site

**Australia (West)** | 2013 to 2015
**Canada (Alberta)** | 2010-11 to 2014-15
**Canada (Ontario)** | 2010-11 to 2015-16
**Israel** | 2010-11, 2012-13 to 2015-16
**USA (West)** | 2010-11 to 2015-16

### By Season

**All NH Sites** | NH 2010-11
**NH Sites (except Israel)** | NH 2011-12
**All Sites** | NH 2012-13 & SH 2013
**All NH Sites** | NH 2013-14
**All Sites** | SH 2014 & NH 2014-15
**All Sites (except Alberta)** | SH 2015 & NH 2015-16

**Sites contributed data for 3 to 6 seasons, for a total of 25 study seasons**

**Median season length was 19 weeks (IQR = 17, 23)**
Acute Respiratory or Febrile Illness (ARFI) Hospitalizations

- Pregnant women aged 18-50 years with records of live or still birth with gestations ≥20 weeks
- ARFI hospitalizations identified by ICD-9/ICD-10 discharge diagnosis codes
  - Influenza, pneumonia, and other acute respiratory codes
  - Febrile only, sepsis-like, and other acute conditions associated with influenza
- Clinician ordered real-time reverse transcription polymerase chain reaction (rRT-PCR) testing for influenza within 3 days prior to admission through discharge
  - Focus on any A or B influenza positive (since subtyping was not done consistently on clinical specimens)
- Excluded small number with missing influenza vaccination records or vaccination 0-14 days prior to admission
Test Negative Design (TND)

- **Cases**: rRT-PCR confirmed influenza positives
- **Controls**: influenza negatives
- **Influenza Vaccine Effectiveness (IVE)** equals 100% × (1 – odds ratio [ratio of odds of vaccination among influenza-positive cases to the odds of vaccination among influenza-negative controls]) using logistic regression
- **Minimizes bias** due to access to IIV and healthcare seeking
- **Adjusted** for site, season, season period (early, peak, vs. late), and the presence of high risk medical conditions (not pregnancy complications)
  - Standard TND adjustments
  - Were associated with both influenza positivity and vaccination status in our sample
  - Other potential confounders (ARFI primary diagnosis, pneumonia or influenza diagnosis, pregnancy complication, ICU, or delivery during hospitalization) did not change the adjusted VE by ≥5% and thus were not included
Results
PREVENT’s Analytic Sample: Pregnancies during Flu Seasons

Sites quantifying denominator of all pregnancies (≥20 weeks gestation)

- 2,068,648 Pregnancies for Full Years (e.g., July to June for NH years)
- 1,717,354 Pregnancies Overlapping with Flu Seasons (84%)
- 331,853 pregnancies outside of flu seasons

No overlap, 16%
PREVENT’s Analytic Sample: Acute Respiratory or Febrile Illness (ARFI)

All Study Sites Examining Hospitalizations of Pregnant Women During Flu Seasons

- 587,204 Hospitalizations during Flu Seasons
- 567,754 No ARFI discharge diagnosis
- 19,450 Hospitalizations with ARFI during Flu Seasons (3%)
Clinical PCR Testing and Flu Positivity: ARFI Primary Discharge Diagnosis

- 64% PCR Flu Positive
- 19% PCR Tested
- ARFI was primary diagnosis, 15%
- 3% PCR Tested
- 52% PCR Flu Positive
- ARFI was not primary diagnosis, 85%

85% ARFI primary diagnosis, 15% ARFI not primary diagnosis.
Clinical PCR Testing and Flu Positivity: ARFI at Delivery

- 60% PCR Flu Positive
- 14% PCR Tested
- 2% PCR Tested
- 51% PCR Flu Positive

ARFI not with delivery, 33%
ARFI identified at delivery, 67%
PREVENT’s Analytic Sample: 1,030 PCR-tested ARFI Hospitalizations

All Study Sites Examining Hospitalizations of Pregnant Women During Flu Seasons

587,204 Hospitalizations during Flu Seasons

567,754 No ARFI discharge diagnosis

19,450 ARFI Hospitalizations during Flu Seasons (3%)

18,314 No rRT-PCR testing for influenza

11 flu vaccinated 0-14 days prior or missing

1,125 Admissions (corrected for 95 re-admissions); Resulting in 1,030 Hospitalizations
ARFI Hospitalizations with rRT-PCR Flu Testing

- **1,030 ARFI hospitalizations with rRT-PCR testing**
  - Only 25 of these are repeated hospitalizations for the same woman

- **Most of the PCR-tested ARFI hospitalized women were:**
  - Aged <35 years (79%)
  - In their third trimester (65%)
  - Had no high risk medical conditions (66%)

- **598 PCR-flu positives**
  - 83% A flu positives
  - A(H1N1)pdm prominent in half of seasons
  - A(H3N2) prominent in >70% seasons
Characteristics Associated with Influenza Detection and Vaccination

**Influenza Positives vs. Negatives**

- 598/1030 (58%) influenza positive
- **Influenza positives were more likely**
  - Third trimester
  - Pneumonia or influenza diagnosis
  - ARFI was primary diagnosis
- **Influenza positives were less likely**
  - Had a high risk medical condition
  - Diagnosed with a pregnancy complication
  - Delivery during hospitalization

**Influenza Vaccinated vs. Unvaccinated**

- 169/1030 (16%) influenza vaccinated
- **Influenza vaccination was higher**
  - Varied across season (8-21%)
  - Highest in USA (50%) compared to other sites (8-14%)
- **Influenza vaccination was lower**
  - Pneumonia or influenza diagnosis
  - ARFI was primary diagnosis
  - Have a high risk medical condition
  - Delivery during hospitalization
  - Diagnosed with a pregnancy complication
IVE against Influenza-Associated Hospitalization during Pregnancy

Number and percentage influenza vaccinated (vacc.) among women hospitalized for acute respiratory or febrile illness (ARFI) by influenza virus test result with influenza vaccine effectiveness (IVE) against all influenza A and B viruses

- IVE adjusted for site, season, season timing, and high risk medical conditions was 40% (95% CI = 12-59%)
- IVE varied across sites and seasons
- Only significant IVE estimate by site was for USA (West): 55% (95% CI = 7-78%)
- If we exclude SH 2014 and NH 2014-15 (poor vaccine match), IVE is 49% (95% CI = 22-67%)
- IVE is similar when stratified by season timing, high risk medical conditions, and pneumonia/influenza diagnosis
- IVE point estimates were higher if ARFI was the primary diagnosis

<table>
<thead>
<tr>
<th>Sites or Subgroups</th>
<th>Seasons</th>
<th>Influenza Positives</th>
<th>Influenza Negatives</th>
<th>Unadjusted IVE</th>
<th>Adjusted IVE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total V acc. N ( % )</td>
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<td>IVE ( 95% CI )</td>
<td>IVE ( 95% CI )</td>
</tr>
<tr>
<td>All Sites</td>
<td>2010-11 to 2015-16</td>
<td>598 75 ( 13 )</td>
<td>432 94 ( 22 )</td>
<td>48 ( 28 , 63 )</td>
<td>40 ( 12 , 59 )</td>
</tr>
</tbody>
</table>
Discussion

**Strengths**

- Applies best practices in observational VE assessment
  - Highly sensitive and specific rRT-PCR influenza outcome
  - Vaccination status confirmed by medical records and registries
  - TND with standard adjustments
- Describes the average field performance of IIV across multiple seasons and settings
  - Mixture of A and B influenza viruses
  - Good and sub-optimal vaccine matches
  - Similar IVE estimates to meta-analyses

**Limitations**

- Limits to generalizability
  - Clinician ordered testing (only 6%) may favor more severe patients
  - High income settings may not generalize to LMICs
- Pooled estimate cannot disentangle sources of IVE variations
  - Lack influenza A subtype data
  - Variation in vaccine-virus match
- Registries may miss some vaccinations
  - Unlikely to bias as long as not differential to cases vs. controls
Summary

- Across sites and seasons (2010-2016), influenza vaccines had the potential to prevent 40% (95% CI = 12-59%) of influenza-associated hospitalizations during pregnancy
  - Likely a conservative estimate
Consistent with Prior Studies

Two prospective RCTs of vaccine efficacy in preventing symptomatic PCR-influenza illness during pregnancy and post-partum of:

- 70% in a 2011–2014 RCT in Mali
- 50% in a 2011–2012 RCT in South Africa

44% VE against symptomatic non-hospitalized PCR-influenza among pregnant women in a prospective TND study during 2010–11 and 2011–12 in the United States
Summary

- Across sites and seasons (2010-2016), influenza vaccines had the potential to prevent 40% (95% CI = 12-59%) of influenza-associated hospitalizations during pregnancy
  - Further strengthens international rationale for maternal influenza vaccination programs

- Substantial hidden burden of influenza virus infection among hospitalized pregnant women
  - 84% of pregnancies overlap with influenza season
  - Half of rRT-PCR confirmed influenza was among those without clinical influenza or pneumonia diagnoses
  - Influenza infections may be frequent among women who deliver or suffer from pregnancy complications while ill with ARFI
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