A Multi-Country Cohort to Estimate Vaccine Effectiveness against Hospitalized Influenza during Pregnancy

Allison L. Naleway*1 allison.naleway@kpchr.org

Sarah Ball 2 sarah_ball@abtassoc.com

Jeffrey C. Kwong 3,4,5,6,7 jeff.kwong@utoronto.ca

Brandy E. Wyant 2 brandy_wyant@abtassoc.com

Mark A. Katz 8 markakatz@gmail.com

Annette K. Regan 9 annette.regan@curtin.edu.au

Margaret L. Russell 10 mlrussel@ucalgary.ca

Nicola P. Klein 11 nicola.klein@kp.org

Hannah Chung 3 hannah.chung@ices.on.ca

Kimberley A. Simmonds 10,12 kimberley.simmonds@gov.ab.ca

Eduardo Azziz-Baumgartner 13 eha9@cdc.gov

Becca Feldman 8 beccafe@clalit.org.il

Avram Levy 14 avram.levy@health.wa.gov.au

Deshayne B. Fell 3,15,16 dfell@cheo.on.ca

Steven J. Drews 17,18 steven.drews@albertahealthservices.ca

Shikha Garg 13 izj7@cdc.gov

Paul Effler 19 paul.effler@health.wa.gov.au

Noam Barda 8 noamba@clalit.org.il

Stephanie A. Irving 1 stephanie.a.irving@kpchr.org

Pat Shifflett 2 pat_shifflett@abtassoc.com

Michael L. Jackson 20 jackson.ml@ghc.org
Mark G. Thompson  

on behalf of the PREVENT Investigators

1 Center for Health Research, Kaiser Permanente Northwest, Portland, OR United States
2 Abt Associates, Inc., Cambridge, MA United States
3 Institute for Clinical Evaluative Sciences, Toronto, ON Canada
4 Public Health Ontario, Toronto, ON Canada
5 Department of Family and Community Medicine, University of Toronto, Toronto, ON Canada
6 Dalla Lana School of Public Health, University of Toronto, Toronto, ON Canada
7 University Health Network, Toronto, ON Canada
8 Chief Physician’s Office, Clalit Research Institute, Tel Aviv, Israel
9 School of Public Health, Curtin University, Perth, WA Australia
10 Cumming School of Medicine, University of Calgary, Calgary, AB Canada
11 Kaiser Permanente Vaccine Study Center, Oakland, CA USA
12 Alberta Health, Edmonton, AB Canada
13 Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA United States
14 PathWest Laboratory Medicine WA, Perth, WA Australia
15 School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON Canada
16 Children’s Hospital of Eastern Ontario Research Institute, Ottawa, ON Canada
17 University of Alberta, Edmonton, AB Canada
18 ProvLab Alberta, Edmonton, AB Canada
19 Department of Health, Western Australia, Perth, WA Australia
20 Kaiser Permanente Washington Health Research Institute, Seattle, WA United States
* Corresponding Author: Allison Naleway, PhD; Center for Health Research, Kaiser Permanente Northwest, 3800 N. Interstate Ave., Portland, OR 97227, USA; tel: 503-335-6352; fax: 503-335-36311; allison.naleway@kpchr.org
ABSTRACT

2Background: Although pregnant women are believed to have elevated risks of severe influenza infection and are targeted for influenza vaccination, no study to date has examined influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza-associated hospitalizations during pregnancy, primarily because this outcome poses many methodological challenges.

6Methods: The Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) was formed in 2016 as an international collaboration with the Centers for Disease Control and Prevention, Abt Associates, and study sites in Australia, Canada, Israel, and the United States. The primary goal of this collaboration is to estimate IVE in preventing acute respiratory or febrile illness (ARFI) hospitalizations associated with laboratory-confirmed influenza virus infection during pregnancy. Secondary aims include: 1) estimating the incidence of influenza-associated ARFI hospitalization during pregnancy; 2) comparing the characteristics of ARFI-hospitalized pregnant women who were tested for influenza to those who were not tested; 3) describing the severity of influenza and non-influenza ARFI hospitalization during pregnancy; 4) describing the clinical course of respiratory syncytial virus (RSV)-associated hospitalization during pregnancy; 5) describing influenza vaccination coverage in pregnant women; and 6) comparing birth outcomes among women with laboratory-confirmed influenza-associated hospitalization vs. other non-influenza ARFI hospitalizations. For an initial assessment of IVE, sites identified a retrospective cohort of pregnant women aged 18 through 50 years whose pregnancies overlapped with local influenza seasons from 2010 through 2016. Pregnancies were defined as those that ended in a live birth or stillbirth of at least 20 weeks gestation. The analytic sample for the primary IVE analysis was restricted to pregnant women who were hospitalized for ARFI during site-specific influenza seasons and clinically tested for influenza virus infection using real-time reverse transcription polymerase chain reaction.
Discussion: In addition to addressing the primary question about the effectiveness of influenza vaccination, PREVENT data will address other important knowledge gaps including understanding the incidence, clinical course, and severity of influenza-related hospitalizations during pregnancy. The data infrastructure and international partnerships created for these analyses may be useful and informative for future influenza studies.

Keywords: influenza; pregnancy; hospitalization; epidemiology; vaccine effectiveness
BACKGROUND

Pregnant women are believed to be at greater risk of severe complications from influenza infection than non-pregnant women of childbearing age based on findings from studies primarily conducted during influenza pandemics [1, 2]. Anatomic, immunologic, and physiologic changes during pregnancy that affect respiratory, cardiovascular, and other organ systems may increase the risk and severity of infections, including influenza [3, 4]. The risk of hospitalization due to clinically diagnosed influenza or pneumonia appears to increase with each trimester of pregnancy [5-7]. The vulnerability of pregnant women to severe influenza disease was observed during the 2009 A(H1N1) pandemic [8-10] and at least two prior pandemics [11, 12]. However, there are substantial gaps in our knowledge regarding the seasonal burden of influenza among pregnant women.

Influenza vaccination is an effective method of influenza prevention, but the vaccine is widely underutilized during pregnancy [13-15]. Although there are ample data on the safety of inactivated influenza vaccination (IIV) during pregnancy [16-18], a major challenge to maternal immunization policymaking has been the paucity of data regarding the effectiveness of IIV in preventing severe influenza-related outcomes in pregnant women [2, 19]. Serologic studies have found a similar antibody response to the vaccine among pregnant and non-pregnant women [20, 21]. Several observational studies have compared rates of non-specific respiratory illness among vaccinated and unvaccinated pregnant women with mixed results [20, 22-25]. Randomized controlled trials [24, 26] and observational studies in pregnant women [27, 28] have reported that IIV reduces the risk of mild to moderately severe laboratory-confirmed influenza illness by about half.

No study to date has examined influenza vaccine effectiveness (IVE) against laboratory-confirmed influenza-associated hospitalization during pregnancy. This is an important gap in
knowledge for maternal immunization policy. Perhaps the greatest challenge in addressing this IVE question is identifying study populations with sufficient numbers of influenza-related hospitalizations during pregnancy in non-pandemic seasons. Randomized controlled trials and prospective observational studies are impractical due to the large number of women that would be required to observe a statistically meaningful number of hospitalizations. Additionally, randomized controlled trials may be unethical in high-income countries where influenza vaccination is recommended for pregnant women. Large-scale retrospective observational studies may be feasible, but no single public or private healthcare database with influenza testing results and influenza vaccination records is large enough to adequately address the question. After considering these limitations, the US Centers for Disease Control and Prevention (US CDC) reached out to international partners to build a collaboration capable of determining IVE against hospitalization in pregnant women. In addition to addressing the primary IVE question, the collaboration was envisioned as a way to explore other important gaps in our understanding of influenza infection and vaccination during pregnancy.

METHODS/DESIGN

The Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) was formed in 2016 as an international collaboration with the US CDC, Abt Associates, and study sites in four countries: Australia, Canada, Israel, and the United States. PREVENT was established to address multiple gaps in knowledge about influenza vaccination and infection during pregnancy (Table 1). The primary goal of this collaboration was to estimate IVE in preventing acute respiratory or febrile illness (ARFI) hospitalizations associated with laboratory-confirmed influenza virus infection during pregnancy.

Secondary aims include estimating the incidence of influenza-associated ARFI hospitalization during pregnancy, comparing the characteristics of ARFI-hospitalized pregnant
women who were tested for influenza to those who were not tested, describing the clinical course
and severity of influenza and non-influenza ARFI hospitalizations during pregnancy, and describing
the clinical course of respiratory syncytial virus (RSV)-associated hospitalizations during
pregnancy. Participating sites also will describe influenza vaccination rates in pregnant women, and
compare birth outcomes (such as low birth weight, preterm delivery, and small-for-gestational age
births) among women with laboratory-confirmed influenza-associated hospitalizations vs. other
non-influenza ARFI hospitalizations.

Study Sites and Enrollment

In 2015, study investigators conducted a series of telephone interviews and written surveys
to recruit potential international study sites. To be considered a potential PREVENT site,
institutions/regions were required to meet several inclusion criteria related to the underlying
characteristics of the source population, clinical and laboratory practices, and availability of high-
quality regional respiratory virus surveillance and electronic medical records (EMR) data (Table 2).
Based on these criteria, five study sites were recruited in four countries: Australia, Canada, Israel,
and the United States (Table 3). Each PREVENT study site developed methods to define local
influenza seasons, identify pregnant women, identify relevant ARFI hospitalizations and influenza
tests, and extract data about influenza vaccinations and important covariates. Influenza vaccination
is recommended and available at no cost to women in all study sites. A brief description of each
study site and the methods they used follows below.

Australia

Western Australia (WA) is the country’s largest state in total land area and has about 2.6
million residents, most of whom live in the capital city of Perth. The Western Australia Department
of Health has access to data on the annual birth cohort of approximately 34,000 through its state
perinatal data collection, the Midwives Notification System. This data collection includes
information on >99% of births in the state with gestation ≥20 weeks (live and stillborn), and was used to identify a cohort of pregnant women who gave birth between January 2012 and December 2015. Inpatient records for all public and private hospitals in WA are available in the Hospital Morbidity Data System, which collects information on hospital discharge and was used to identify ARFI hospitalizations. Public immunization providers report influenza vaccines administered to pregnant women to the WA Antenatal Influenza Vaccination Database; the number of pregnant women obtaining vaccines in the private market is thought to be small [29]. An evaluation of this dataset showed it was 46% sensitive to compared to self-reported influenza vaccination status [30]. Influenza surveillance data were obtained from two sources: i) the state’s public health reference laboratory (PathWest Laboratory Medicine WA) and ii) state notifications of laboratory-confirmed influenza infection (WA Notifiable Infectious Disease Database). Laboratory real-time reverse transcription polymerase chain reaction (rRT-PCR) testing data from the state’s public health reference laboratory were linked to the cohort to identify influenza and RSV testing results.

Canada

Two provinces in Canada are participating in PREVENT. The province of Alberta has about 4.1 million residents and 53,500 annual births. The Alberta Ministry of Health (Alberta Health) administers its publicly-funded healthcare system. Each resident registered in the insurance plan has a unique lifetime identifier that can be used to link the data sources described below, including the provincial vaccination repository and the vital statistics registry. All live and stillbirths of at least 20 weeks’ gestation are available through the provincial Vital Statistic Registry, which was used to identify pregnancies. The Canadian Institute for Health Information’s Discharge Abstract Database (DAD) captures administrative, clinical, and demographic information on hospital discharges directly from all 106 acute care facilities in the province and was used to identify ARFI hospitalizations. All Albertans are eligible to receive influenza vaccination free of charge, with less than 10% of influenza vaccinations not reported to the registry. Influenza surveillance is conducted
1 continuously in Alberta with year-round laboratory testing, and a community-based sentinel
2 physician network, hospital and emergency room surveillance. Information about clinician-ordered
3 influenza testing with rRT-PCR was obtained through the centralized Provincial Laboratory
4 Information System.
5 The province of Ontario has about 14 million residents and approximately 147,000 births
6 annually, and includes Canada’s capital (Ottawa) and Canada’s largest city (Toronto). The
7 sponsoring organization, The Institute for Clinical Evaluative Sciences, is a not-for-profit research
8 institute whose mandate is to enable health system evaluation and research within Ontario. Data
9 from the DAD were extracted to identify pregnant women (using their delivery hospitalization
10 abstract) and ARFI hospitalizations. Physician and pharmacist (starting in 2012) billing
11 claims contained in the Ontario Health Insurance Plan (OHIP) and Ontario Drug Benefits databases,
12 respectively, were used to identify influenza vaccinations. A previous validation study of one of
13 these sources (OHIP) found physician billing claims were 42% sensitive among pregnant women
14 compared to self-reported influenza vaccination status, since individuals can also receive influenza
15 vaccination through public health and workplace clinics [31]. Respiratory specimen results from
16 Public Health Ontario and eight academic hospital laboratories using rRT-PCR were individually
17 linked to the health administrative data using unique encoded identifiers.

18 Israel

19 Clalit Health Services is the largest healthcare fund in Israel, covering 53% of Israel’s
20 population. About 4.4 million people are covered by the fund, including about 93,000 births
21 annually. Nearly all patients (> 98%) remain in the fund from year to year, receiving all of their
22 publicly-funded healthcare through the fund. Clalit’s comprehensive EMR has been universally
23 adopted among all inpatient and outpatient healthcare facilities. All live births are captured through
24 hospital EMR data and a demographic registry that feeds into the Clalit data warehouse. An
algorithm based on diagnostic and procedure codes was employed to identify pregnancies ≥20 weeks’ gestation that did not end in live births. Hospitalizations of pregnant women associated with deliveries that occurred in non-Clalit hospitals (over half to two-thirds of all hospitalizations) were not captured by the EMR. Influenza vaccines are offered free of charge to healthcare fund members at Clalit clinics, and details regarding influenza vaccination are entered into the EMR. Influenza and RSV testing is conducted using rRT-PCR in Clalit hospitals at the discretion of the physician, and rRT-PCR results are captured in the EMR.

United States

Kaiser Permanente (KP) is an integrated healthcare delivery system serving over 12 million people in the United States. Three KP sites contributed data to PREVENT – KP Northwest (Portland, OR), KP Northern California (Sacramento, San Francisco Bay Area, Fresno), and KP Washington (Seattle, WA; formerly Group Health Cooperative). The combined population of the KP PREVENT sites is about 6.2 million people, including about 56,000 live births annually. KP Northern California provides inpatient care at 21 KP-owned hospitals, KP Northwest provides inpatient care at two KP-owned hospitals and contracts with several other regional hospitals, and KP Washington does not own any hospitals but contracts with regional hospitals for patient care. A common comprehensive EMR system is used at the KP sites. The KP sites identified pregnancies of at least 20 weeks’ gestation using a combination of local pregnancy registry data and a validated algorithm that uses diagnosis and procedure codes to identify pregnancy episodes [32]. Two sites, KP Washington and KP Northwest, further manually reviewed the medical record of women who were hospitalized with ARFI and excluded those not found to be pregnant. Influenza vaccination records were extracted from the EMR and from state immunization registries in Oregon and Washington states. A previous study found that KP EMR records were 89% sensitive among pregnant women compared to self-reported influenza vaccination status [27]. Influenza surveillance data for Region 10 of the United States were provided by CDC and were used to identify influenza
seasons for the KP sites (https://www.cdc.gov/flu/weekly/pastreports.htm). At KP Northern California and KP Northwest, clinical influenza and RSV rRT-PCR testing dates and results were extracted directly from the EMR. At KP Washington, test dates and results were manually abstracted from medical records.

**Influenza Seasons and Peak Period Definitions**

With study sites located around the globe and in both hemispheres, a necessary first step in developing the study protocol was to agree upon a shared method for defining influenza seasons and peak periods of circulation. Each site included up to six seasons of data starting with the northern hemisphere 2010-11 season as the earliest. Using a combination of regional surveillance and clinical laboratory records, each site identified the number of respiratory specimens tested and the number of laboratory-confirmed influenza positives identified among tested specimens.

Similar to previous efforts to define influenza seasons consistently across countries [33, 34], each study site identified criteria to delineate the start and end of sustained influenza circulation and to identify a period of peak influenza circulation (Table 4). Three sites (Australia, Ontario [Canada], and the United States) used the mean percentage of specimens that tested positive for influenza A or B virus infection across weeks for each surveillance year to define their threshold of increased or decreased activity. Two sites (Alberta [Canada] and Israel) used a weekly influenza positivity rate of greater than 5% of specimens tested as their threshold. With this information, each site determined for each study season:

1. the **start of each season**, defined as the Sunday of the first of three consecutive weeks in which the percentage of specimens testing positive for influenza A or B virus infection was higher than the determined threshold;
2. the **end of each season**, defined as the Saturday of the first of three consecutive weeks in which the percentage of specimens testing positive for influenza was below the threshold;
(3) the peak period, defined as the weeks that included ≥68% of influenza positives between the start and end of each season;

(4) the early season, defined as the weeks from the start of the season through the week before the peak period;

(5) the late season, defined as the week after the peak period through the end of the season.

Retrospective Cohort Identification

Pregnancies were defined as those that ended in a live birth or stillbirth of at least 20 weeks’ gestation. Sites began analysis by identifying all pregnancies during the study years (e.g., starting in July of the first year and ending in June of the last for northern hemisphere sites), with the exception of the California and Washington USA sites that could only examine pregnancies during influenza seasons. Nonetheless, among sites that attempted to identify all pregnancies during study years, 83% (1.72 million [M]/2.07 M) of the pregnancies overlapped with an influenza season.

Figure 1 summarizes the steps sites followed to create the retrospective PREVENT cohort, starting with pregnant women aged 18 through 50 years at the time of inpatient admission whose pregnancies overlapped with the site-specific influenza seasons. This population of 1,928,147 pregnant women will be used in secondary analyses describing vaccination coverage, influenza incidence, and birth outcomes.

Study sites subsequently limited their study population to 19,450 pregnant women who were hospitalized for ARFI during the site-specific influenza seasons. ARFI hospitalizations were identified using a shared list of International Classification of Diseases, 9th and 10th Revision (ICD-9/ICD-10) diagnosis codes applied in previous studies of medically-attended influenza illness and expanded to include acute illnesses with febrile only, non-respiratory, or sepsis-like
presentations that may be associated with severe influenza disease among adults [37, 38]. Canada and Australia used country-specific versions of these codes (Supplemental Table 1).

To define the analytic sample for the primary IVE analysis, we further limited the population to the 1,136 women who were clinically tested for influenza virus infection using rRT-PCR with respiratory specimens collected within three days prior to admission through hospital discharge. Women who were ineligible for influenza vaccination (e.g., were not covered by health insurance during the vaccination campaign period), those vaccinated within 14 days of admission, and (at some sites) those without documented influenza vaccination status were excluded. Ninety-five ARFI hospitalizations that were re-admissions within 14 days of discharge were combined with the index hospitalization and considered single events, leaving 1,030 hospitalizations in the IVE analytic sample. Of these, only 25 were repeated hospitalizations (>14 days between discharge and future admission) for the same woman; thus the IVE analytic sample consists of 1,005 women.

Data Collection

As an important early step, PREVENT investigators developed and refined a shared data dictionary (Supplemental Table 2). Each site developed a site-specific plan to measure the common data requirements for the project. These plans were then compared and harmonized into a common set of requirements and strategies. The shared data dictionary initially focused on variables that were key to the primary aim of estimating IVE. All participating sites were able to provide all of the variables in this core dataset. Additional data elements were added to support secondary aims of the study, and for some of these secondary variables, only a subset of sites were able to provide data.

For women in the retrospective cohort, we extracted the following data from records associated with the index AFRI hospitalization, and where possible from administrative records or ambulatory care records prior to hospitalization: 1) basic descriptive demographic information and maternal characteristics (e.g., age, race, ethnicity, socioeconomic status, height, weight, and
1) smoking; 2) underlying health conditions prior to pregnancy (e.g., asthma, diabetes, cancer); 3) pregnancy history and complications with the current pregnancy (e.g., gestational hypertension, gestational diabetes; 4) clinical signs and symptoms, course, and treatment during the ARFI hospitalization; 5) respiratory specimen collection and laboratory test results for influenza, RSV, and other pathogens; 6) disposition at hospital discharge (e.g., home, hospital transfer, death); 7) delivery date, gestational age of the infant at delivery, and birth outcomes (e.g., birth weight, small-for-gestational age); and 9) influenza vaccination records for the current season. When hospital or birth outcome information was not available in EMR or administrative databases, a limited medical record abstraction was performed by study sites that had direct access to medical records. During the study seasons, most sites only used trivalent inactivated influenza vaccine; quadrivalent inactivated influenza vaccine represented <5% of doses administered to pregnant women starting in 2012 in the United States and 2015 in Israel.

Data Management

Study datasets remain at participating sites and methods were developed to share standardized aggregated reports with Abt Associates and US CDC. Each site created a plan for checking data consistency and implementing other quality control checks prior to data analysis and data deliveries. Because individual-level data remain at the study sites, the investigators responsible for each proposed analysis must develop procedures for combining and analyzing aggregate data across sites. In most cases, sites will be asked to complete a series of descriptive tables that will be pooled by Abt, the study coordinating center. For some analyses, sites will be asked to conduct statistical modeling with their local data and then send the modeling results (e.g., beta estimates and standard errors) to Abt and US CDC to be used in a meta-analysis. Some sites have restrictions on the data they are allowed to share and report; in cases of small cell sizes, results will only be presented at the aggregate level or will be masked to protect the privacy of patient data.
1Ethical Approval & Considerations

The study protocol and procedures have been reviewed and approved by Institutional Review Boards (IRBs) (or their equivalents) at each study site and by Abt Associates (the coordinating institution on which US CDC relies). It was not possible to use a common IRB for this project because the institutional and regional human subjects protection policies and regulations varied for each PREVENT site.

Each site received a waiver of informed consent for all participants. The study presented minimal risk to participants, as there was no interaction or intervention with patients. Although patient information was extracted from existing administrative databases, no personal identifiers were shared between study sites, Abt Associates, or US CDC. Sites provided aggregate data tables that included summary statistics rather than individual-level data sets. As noted above, measures were taken to ensure subject privacy in reports with small cell sizes. There was no risk to the participants’ health from participation in this study, because data were collected either as part of patients’ routine care or for billing purposes. The study had no impact on patients’ current health care or therapeutic management plan. Consequently, patients were not provided information about their participation.

DISCUSSION

The PREVENT collaboration will provide important information about the effectiveness of influenza vaccination in preventing severe laboratory-confirmed influenza illness requiring hospitalization in pregnant women and will address additional pertinent knowledge gaps about influenza and pregnancy. Since hospitalization for ARFI with laboratory-confirmed influenza is a rare occurrence in pregnant women, an international collaboration was needed to address this question. Out of approximately 2 million women who were pregnant during influenza seasons 2010-11 through 2015-16 at seven study sites in four countries, we identified about 1,000 who were
hospitalized and tested for influenza by rRT-PCR for inclusion in the primary IVE analysis. This analysis to address this important gap in knowledge would not be possible without an international collaboration of this magnitude.

In addition to the magnitude and geographic diversity of the study cohort, this network has established resources valuable for antenatal influenza research. As part of this collaboration, PREVENT has brought together a pool of international expertise in influenza vaccination and infection during pregnancy. The study investigators worked together to develop methods to harmonize data collection, management, and analyses across different institutions and countries with differing underlying populations, data sources, and human subjects protection regulations. In addition to addressing the primary question about the effectiveness of influenza vaccination, PREVENT data will be used to address other important knowledge gaps including understanding the incidence, clinical course, and severity of hospitalized influenza during pregnancy. The data infrastructure and partnerships created for these analyses may be useful and informative for future studies.

Despite the strengths of this collaboration, there are a few limitations to the analyses within this cohort. Due to the nature of the data sources across sites, we were only able to include pregnancies ending in live birth or stillbirth of at least 20 weeks’ gestational age, because several sites were unable to extract reliable data on pregnancies ending in fetal loss prior to 20 weeks. We are therefore not able to examine the impact of influenza infection or influenza vaccination on outcomes early in pregnancy, such as spontaneous abortion. Additionally, we included study sites that routinely tested pregnant women for influenza and had maternal influenza immunization programs, which limited our study to the inclusion of four high-income countries. PREVENT study results therefore may not be generalizable to countries with fewer resources dedicated to testing and vaccination programs, or with different underlying population characteristics (e.g., high prevalence of HIV or malaria) that may impact IVE or influenza incidence and severity. Finally, there is the
potential for misclassification bias in some of our measurements. To ensure consistency across sites, chronic diseases are characterized solely by ICD code, which may underestimate the prevalence of these conditions in the women studied. Misclassification of influenza vaccination is of most concern for the primary IVE analysis; however, the participating sites generally have high rates of influenza vaccination capture, often using a combination of EMR data and regional and national immunization registries.

Due to methodological challenges in researching seasonal influenza infection and vaccination in pregnant women, we have several important unanswered questions, including understanding the effectiveness of influenza vaccination in preventing hospitalization during pregnancy. PREVENT will address this primary IVE question, as well as a number of other important gaps in our understanding of influenza and other respiratory infections during pregnancy. This work will be informative for strengthening global influenza prevention strategies and for improving the health of pregnant women.
1LIST OF ABBREVIATIONS

2ARFI: Acute respiratory or febrile illness

3DAD: Discharge Abstract Database

4EMR: Electronic medical record

5ICD-9: *International Classification of Diseases, 9th Revision*

6ICD-10: *International Classification of Diseases, 10th Revision*

7ICU: Intensive care unit

8IIV: Inactivated influenza vaccine

9IRB: Institutional Review Board

10IVE: Influenza vaccine effectiveness

11KP: Kaiser Permanente

12NH: Northern hemisphere

13OHIP: Ontario Health Insurance Plan

14PREVENT: *Pregnancy Influenza Vaccine Effectiveness Network*

15RSV: Respiratory syncytial virus

16rRT-PCR: Real-time reverse transcriptase polymerase chain reaction assay

17SH: Southern hemisphere

18US CDC: Centers for Disease Control and Prevention (United States)

19WA: Western Australia
1 DECLARATIONS

2 Ethics Approvals and Consent to Participate

3 The study protocol and procedures have been reviewed and approved by Institutional Review Boards by Abt Associates (the coordinating institution on which US CDC relies) and at each study site: Human Research Ethics Committee, Department of Health Western Australia; Conjoint Health Research Ethics Board, University of Calgary; University of Alberta Health Research Ethics Board; Sunnybrook Health Sciences Centre, Toronto, Canada; Kaiser Permanente Northwest Institutional Review Board; Clalit Health Services Research Ethics Committee.

4 Consent for Publication

5 Not applicable

6 Availability of Data and Materials

7 Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

8 Competing Interests

9 SJD reports that he is a content advisor to Johnson & Johnson (Janssen Pharmaceuticals) on respiratory virus testing.

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16Author Contributions

17Designed the study: MGT and ALN developed the original proposal for PREVENT. All named 18authors contributed to the development of the common protocol and procedures.

19Coordination of the study: SB, BEW, KAS, SAI, MAK, JCK, MGT, AKR

20Wrote the manuscript: ALN, MGT, and SB wrote the first draft. All named authors contributed to 21subsequent drafts. All authors read and approved the final manuscript.

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\(^4\)Israel Center for Disease Control, Israel Ministry of Health (Aharona Glatman-Freedman), Central
\(^5\)Virology Laboratory, Israel Ministry of Health (Michal Mandelboim), Clalit Research Institute
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Table 1. Study goals and features intended to address specific knowledge gaps

<table>
<thead>
<tr>
<th>Knowledge Gap</th>
<th>Study Feature</th>
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<tbody>
<tr>
<td>No study to date has examined IVE against laboratory-confirmed influenza hospitalization during pregnancy.</td>
<td>Assess IVE against laboratory-confirmed influenza-associated hospitalization using the test-negative design.</td>
</tr>
<tr>
<td>Information is limited on how IVE during pregnancy may vary across seasons and by influenza type and subtype.</td>
<td>Assess IVE by site and study season and across seasons by influenza type and subtype.</td>
</tr>
<tr>
<td>Information is needed on whether influenza vaccinations received in previous seasons (prior to pregnancy) affect IVE during pregnancy.</td>
<td>Where prior season vaccination records are available, assess IVE by combinations of current and prior season influenza vaccination status.</td>
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Secondary Analysis: Assess the frequency of hospitalization for acute respiratory and febrile illness (ARFI) associated with laboratory-confirmed influenza virus infection during pregnancy

<table>
<thead>
<tr>
<th>Knowledge Gap</th>
<th>Study Feature</th>
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<tbody>
<tr>
<td>Studies of influenza during pregnancy using laboratory-confirmed outcomes are scarce.</td>
<td>Identify hospitalizations during influenza season among pregnant women with clinical testing for influenza by rRT-PCR assay.</td>
</tr>
<tr>
<td>Studies of influenza-associated hospitalization during pregnancy have been predominantly limited to the USA.</td>
<td>Examine influenza-associated hospitalizations in regions of Australia, Canada, Israel, and USA.</td>
</tr>
<tr>
<td>Studies often enroll only during peak periods of virus circulation.</td>
<td>Examine influenza-associated hospitalizations during early, peak, and late periods of influenza circulation.</td>
</tr>
<tr>
<td>Information is limited on atypical and non-respiratory disease manifestations of influenza virus infection.</td>
<td>Assess the frequency of influenza virus infections among women hospitalized without influenza or pneumonia diagnoses, including febrile-only and sepsis-like syndromes.</td>
</tr>
<tr>
<td>Information on the burden of influenza disease associated with seasonal influenza viruses during pregnancy is limited, especially for severe disease requiring hospitalization.</td>
<td>Assess the incidence of influenza-associated hospitalization during pregnancy over multiple influenza seasons by study site.</td>
</tr>
</tbody>
</table>

Secondary Analysis: Describe the clinical features of influenza-associated hospitalization during pregnancy

<table>
<thead>
<tr>
<th>Knowledge Gap</th>
<th>Study Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency and application of clinical influenza testing among pregnant women hospitalized with</td>
<td>Assess the frequency of clinical influenza testing across healthcare systems and countries and</td>
</tr>
<tr>
<td>Knowledge Gap</td>
<td>Study Feature</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Acute respiratory illness during influenza season is unknown.</td>
<td>Compare characteristics of tested versus untested pregnant women and their reasons for hospitalization.</td>
</tr>
<tr>
<td>Information on the clinical epidemiology of severe influenza disease during pregnancy is scarce, especially for seasonal influenza.</td>
<td>Describe the characteristics of pregnant women (e.g., age, trimester, underlying health condition[s]) hospitalized with influenza virus infection and their clinical diagnoses.</td>
</tr>
<tr>
<td>Further research is needed to identify risk factors for very severe influenza disease during pregnancy that requires intensive care.</td>
<td>Assess the characteristics of pregnant women with influenza virus infection who are admitted to an intensive care unit (ICU) during hospitalization.</td>
</tr>
<tr>
<td>Information on the clinical course of influenza virus infections among pregnant women during hospitalization is limited, especially for those with laboratory-confirmed seasonal influenza.</td>
<td>Describe the length of stay in the general ward or ICU and the frequencies of pneumonia diagnosis, respiratory failure, and need for intensive care of pregnant women hospitalized with influenza.</td>
</tr>
<tr>
<td>Variation in illness severity and outcomes among influenza virus type and subtype has not been assessed among pregnant women with seasonal influenza.</td>
<td>Compare indicators of illness severity and selected hospitalization outcomes among women with laboratory-confirmed influenza by type and subtype.</td>
</tr>
<tr>
<td>Information on the frequency of deliveries among women hospitalized with influenza is limited.</td>
<td>Assess the frequency of deliveries during hospitalizations with AFRI diagnoses associated with maternal influenza virus infection.</td>
</tr>
</tbody>
</table>

**Secondary Analysis: Describe the frequency and clinical features of RSV-associated hospitalization during pregnancy**

<table>
<thead>
<tr>
<th>Knowledge Gap</th>
<th>Study Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Despite substantial evidence highlighting the burden of RSV in young children, little is known about RSV infection during pregnancy.</td>
<td>Describe the clinical characteristics of RSV infection during pregnancy.</td>
</tr>
<tr>
<td>Few studies have documented the impact of antenatal RSV infection on birth outcomes</td>
<td>Describe outcomes at birth for women testing positive for RSV during pregnancy compared to women who test negative.</td>
</tr>
</tbody>
</table>

**Secondary Analysis: Examine birth outcomes associated with hospitalized influenza infection during pregnancy**

<table>
<thead>
<tr>
<th>Knowledge Gap</th>
<th>Study Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal risks posed by antenatal influenza virus infection are unclear, especially for seasonal influenza.</td>
<td>Compare birth outcomes of women hospitalized with ARFI with laboratory-confirmed influenza virus infection to birth outcomes of women with ARFI hospitalizations confirmed as influenza negative and women without ARFI hospitalization during pregnancy.</td>
</tr>
<tr>
<td>Few comparative studies have accounted for gestational timing of influenza infection when</td>
<td>Compare birth outcomes by gestational age at influenza infection in women hospitalized with...</td>
</tr>
</tbody>
</table>
comparing birth outcomes in influenza infected and uninfected women. laboratory-confirmed influenza.

**Secondary Analysis: Assess the frequency of vaccination with inactivated influenza vaccine (IIV) during pregnancy across countries and healthcare systems.**

<table>
<thead>
<tr>
<th>Knowledge Gap</th>
<th>Study Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information is limited on the uptake of IIV during pregnancy across healthcare systems and countries.</td>
<td>Describe IIV coverage among women pregnant during influenza vaccine campaigns and/or influenza seasons across multiple years and study sites.</td>
</tr>
<tr>
<td>Information is limited on the timing of IIV vaccination, even though this has implications for the protection of the mother and the transfer of protective antibodies to the fetus.</td>
<td>Describe the frequency of IIV vaccination among pregnant women by stage of pregnancy and relative to influenza season timing.</td>
</tr>
<tr>
<td>More information is needed on the differences between IIV vaccinated versus unvaccinated pregnant women who are at greatest risk for influenza hospitalization.</td>
<td>Compare the socio-demographic and underlying health characteristics of pregnant women hospitalized for ARFI during influenza season by seasonal vaccination status.</td>
</tr>
</tbody>
</table>
### Table 2. Eligibility Criteria for PREVENT Study Site Selection

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza surveillance data to identify weeks of local influenza circulation for multiple years (ideally dating from 2010) were available</td>
</tr>
<tr>
<td>Women who were pregnant during hospitalization for acute respiratory or febrile illness could be identified with electronic medical records, administrative data, or laboratory records</td>
</tr>
<tr>
<td>Diagnostic hospital admission and/or discharge codes (ICD-9 or ICD-10 with Australian and Canadian variations) from the records described above were accessible</td>
</tr>
<tr>
<td>Demographic characteristics, underlying medical conditions prior to pregnancy, pregnancy history, and medical complications during pregnancy were available from medical records or routine registry data</td>
</tr>
<tr>
<td>Pregnant women with acute respiratory or febrile disease during influenza season were routinely tested for influenza with reverse transcriptase polymerase chain reaction (RT-PCR) at study facilities</td>
</tr>
<tr>
<td>Demographic characteristics, underlying medical conditions, influenza vaccination status and clinical diagnoses of pregnant women who received clinical virus testing could be compared with those of pregnant women who were not tested during influenza season</td>
</tr>
<tr>
<td>Influenza vaccine coverage among pregnant women in the catchment area was modest to high (10%-70%), but not universal, during the study period</td>
</tr>
<tr>
<td>Influenza vaccination records from electronic registries, electronic medical records, or public health records were available</td>
</tr>
</tbody>
</table>
Table 3. PREVENT study countries, sponsors, populations, and data sources

<table>
<thead>
<tr>
<th>Country (Region)</th>
<th>Sponsoring Institution</th>
<th>Local Population Served</th>
<th>Influenza seasons contributed</th>
<th>Cohort of Pregnant Women Hospitalized for ARFI</th>
<th>Estimated Seasonal Influenza Vaccination Coverage among Pregnant Women</th>
<th>Method of Identifying Pregnant Women</th>
<th>Source of Vaccination Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (Western)</td>
<td>Western Australia Dept. of Health</td>
<td>~2,600,000</td>
<td>2012-2015 (southern hemisphere)</td>
<td>1,639</td>
<td>27%</td>
<td>Midwives Notification System; Hospital Morbidity Data System</td>
<td>State immunization registry</td>
</tr>
<tr>
<td>Canada (Alberta)</td>
<td>Alberta Health</td>
<td>~4,100,000</td>
<td>2011-2015</td>
<td>5,042</td>
<td>15 - 30%</td>
<td>National Discharge Abstract Database; Provinicial vital statistic registry</td>
<td>Provincial vaccination registry</td>
</tr>
<tr>
<td>Canada (Ontario)</td>
<td>Institute for Clinical Evaluative Sciences</td>
<td>~14,000,000</td>
<td>2010-2016</td>
<td>7,738</td>
<td>10%</td>
<td>National Discharge Abstract Database</td>
<td>Billing claims to provincial health system</td>
</tr>
<tr>
<td>Israel</td>
<td>Clalit Health</td>
<td>~4,400,000</td>
<td>2010-11, 2012-2016</td>
<td>1,424*</td>
<td>20%</td>
<td>EMR</td>
<td>EMR</td>
</tr>
<tr>
<td>Services</td>
<td>~6,200,000</td>
<td>2011-2016</td>
<td>2,709</td>
<td>49%</td>
<td>EMR</td>
<td>EMR; state immunization registries</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<td></td>
</tr>
</tbody>
</table>

1*Hospitalizations of pregnant women associated with deliveries that occurred in non-Clalit hospitals were not captured by the EMR
Table 4. Weeks of local early, peak, and late influenza seasons, earliest and latest week of clinical influenza positives, and predominant local circulating influenza strains by year and study sites

<table>
<thead>
<tr>
<th></th>
<th>Early Season</th>
<th>Peak Season</th>
<th>Late Season</th>
<th>Sum Weeks</th>
<th>Predominant Local Strains *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Range of Weeks (Total Weeks)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NH 2010-11</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada (Alberta)</td>
<td>50-3 (6)</td>
<td>4-8 (5)</td>
<td>9-15 (7)</td>
<td>18</td>
<td>A(H3N2)</td>
</tr>
<tr>
<td>Canada (Ontario)</td>
<td>48-49 (2)</td>
<td>50-6 (9)</td>
<td>7-15 (9)</td>
<td>20</td>
<td>A(H3N2)</td>
</tr>
<tr>
<td>Israel</td>
<td>48-50 (3)</td>
<td>51-5 (7)</td>
<td>6-14 (9)</td>
<td>19</td>
<td>A(H1N1)pdm; A(H3N2); B viruses</td>
</tr>
<tr>
<td>USA (West)</td>
<td>51-3 (5)</td>
<td>4-11 (8)</td>
<td>12-15 (4)</td>
<td>17</td>
<td>A(H3N2); A(H1N1)pdm; B viruses</td>
</tr>
<tr>
<td><strong>NH 2011-12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada (Alberta)</td>
<td>2-7 (6)</td>
<td>8-17 (10)</td>
<td>18-26 (9)</td>
<td>25</td>
<td>A(H3N2)</td>
</tr>
<tr>
<td>Canada (Ontario)</td>
<td>5-7 (3)</td>
<td>8-15 (8)</td>
<td>16-21 (6)</td>
<td>17</td>
<td>B viruses</td>
</tr>
<tr>
<td>USA (West)</td>
<td>6-8 (3)</td>
<td>9-20 (12)</td>
<td>21-25 (5)</td>
<td>20</td>
<td>A(H3N2)</td>
</tr>
<tr>
<td><strong>SH 2012</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia (West)</td>
<td>27-30 (4)</td>
<td>31-37 (7)</td>
<td>38-40 (3)</td>
<td>14</td>
<td>A(H3N2)</td>
</tr>
<tr>
<td><strong>NH 2012-13</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada (Alberta)</td>
<td>46-49 (4)</td>
<td>50-10 (13)</td>
<td>11-23 (13)</td>
<td>30</td>
<td>A(H3N2), B(Yamagata)</td>
</tr>
<tr>
<td>Canada (Ontario)</td>
<td>46-48 (3)</td>
<td>49-4 (8)</td>
<td>5-12 (8)</td>
<td>19</td>
<td>A(H3N2); A(H1N1)pdm</td>
</tr>
<tr>
<td>Israel</td>
<td>2-3 (2)</td>
<td>4-8 (5)</td>
<td>9-14 (6)</td>
<td>13</td>
<td>A(H1N1)pdm; A(H3N2)</td>
</tr>
<tr>
<td>USA (West)</td>
<td>48-51 (4)</td>
<td>52-10 (12)</td>
<td>11-20 (10)</td>
<td>26</td>
<td>A(H3N2)</td>
</tr>
<tr>
<td><strong>SH 2013</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia (West)</td>
<td>33-35 (3)</td>
<td>36-45 (10)</td>
<td>46-47 (2)</td>
<td>15</td>
<td>A(H3N2); A(H1N1)pdm</td>
</tr>
<tr>
<td><strong>NH 2013-14</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>SH 2014</td>
<td>NH 2014-15</td>
<td>NH 2015-16</td>
<td></td>
<td></td>
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<td>----------------------</td>
<td>----------------------------------------</td>
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<td>--------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A(H1N1)pdm; B (Yamagata)</td>
<td>A(H1N1)pdm; A(H3N2)</td>
<td>A(H1N1)pdm; B viruses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada (Alberta)</td>
<td>48-51 (4) 52-6 (7) 7-10 (4) 21</td>
<td>41-48 (8) 49-7 (12) 8-17 (10) 30</td>
<td>3-5 (3) 6-13 (8) 14-20 (7) 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada (Ontario)</td>
<td>49 - 49 (1) 50-11 (14) 12-22 (11) 26</td>
<td>49- 49 (1) 50-5 (9) 6-19 (14) 24</td>
<td>49-51 (3) 52-5 (6) 6-14 (9) 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>52-4 (5) 5-11 (7) 12-18 (7) 19</td>
<td>45-3 (11) 4-9 (6) 10-10 (1) 18</td>
<td>49-51 (3) 52-5 (6) 6-14 (9) 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA (West)</td>
<td>50-50 (1) 51-9 (11) 10-10 (1) 13</td>
<td>45-48 (4) 49-5 (10) 6-6 (1) 15</td>
<td>52-4 (5) 5-13 (9) 14-21 (8) 22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SH 2014**
- Australia (West): 29-31 (3) 32-40 (9) 41-44 (4) 16

**NH 2014-15**
- Canada (Alberta): 41-48 (8) 49-7 (12) 8-17 (10) 30
- Canada (Ontario): 49- 49 (1) 50-5 (9) 6-19 (14) 24
- Israel: 45-3 (11) 4-9 (6) 10-10 (1) 18
- USA (West): 45-48 (4) 49-5 (10) 6-6 (1) 15

**SH 2015**
- Australia (West): 25-28 (4) 29-40 (12) 41-45 (5) 21

**NH 2015-16**
- Canada (Ontario): 3-5 (3) 6-13 (8) 14-20 (7) 18
- Israel: 49-51 (3) 52-5 (6) 6-14 (9) 18
- USA (West): 52-4 (5) 5-13 (9) 14-21 (8) 22

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*a* - Conclusions regarding prominent strains (believed to represent >20% of circulating viruses) came primarily from rRT-PCR (sub)type results from clinical isolates from this study for Australia and Canada (Alberta and Ontario); for USA (West) where A subtype results were not available from clinical rRT-PCR results, we referenced US CDC west coast Regional reports; for Israel, where A(H1N1)pdm virus subtyping is consistently done but A(H3N2) virus subtyping is not, we supplemented our data with a review of clinical rRT-PCR results with WHO EURO and EMRO reports.

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1

2**Figure 1. PREVENT retrospective cohort inclusion and exclusion criteria**

3
Supplemental Table 1. *International Classification of Diseases* (ICD) version used by study site and influenza season

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (Western)</td>
<td>ICD-10-AM</td>
<td>ICD-10-AM</td>
<td>ICD-10-AM</td>
<td>ICD-10-AM</td>
<td>ICD-10-AM</td>
<td>ICD-10-AM</td>
</tr>
<tr>
<td>Canada (Alberta)</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
</tr>
<tr>
<td>Canada (Ontario)</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
<td>ICD-10-CA</td>
</tr>
<tr>
<td>Israel</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>ICD-9</td>
</tr>
<tr>
<td>United States (California, Oregon, Washington)</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>ICD-9</td>
<td>ICD-10</td>
</tr>
</tbody>
</table>
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