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

Mark G. Thompson, Ph.D.
on behalf of the
Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) **Network**
and the
Influenza Division
US Centers for Disease Control and Prevention
Atlanta, GA USA

Background and Methods

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

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

WHO Report

Influenza epidemiology and immunization during pregnancy: Final report of a World Health Organization working group

Deshayne B. Fell [a,1], Eduardo Azziz-Baumgartner [b,2], Michael G. Baker [c,3], Maneesh Batra [d,4], Julien Beauté [e,5], Philippe Beutels [f,6], Niranjan Bhat [g,7], Zulfiqar A. Bhutta [h,i,8,9], Cheryl Cohen [j,k,10,11], Bremen De Mucio [l,12], Bradford D. Gessner [m,13], Michael G. Gravett [n,14], Mark A. Katz [o,p,15,16], Marian Knight [q,17], Vernon J. Lee [r,18], Mark Loeb [s,19], Johannes M. Luteijn [t,20], Helen Marshall [u,21], Harish Nair [v,22], Kevin Pottie [w,23], Rehana A. Salam [x,y,24,25], David A. Savitz [z,26], Suzanne J. Serruya [l,27], Becky Skidmore [aa,28], Justin R. Ortiz [ab,*], on behalf of the WHO taskforce to evaluate influenza data to inform vaccine impact and economic modelling

Vaccine (2017)

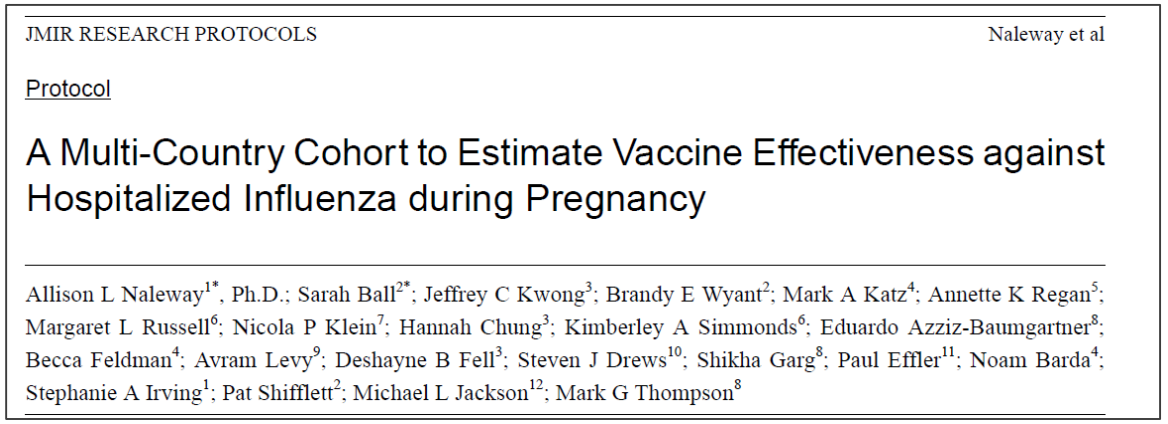
"Policy-makers from LMICs are likely to place higher value on vaccines with demonstrated impact on severe influenza disease."

- 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

PREVENT Network

- US CDC funded Pregnancy Influenza Vaccine Effectiveness Network (PREVENT)
  - HHSD2002013M53890B (200-2014-F-60406) to Abt Associates, Inc.
- Collaboration among public health and healthcare systems with integrated medical, laboratory, and vaccination records



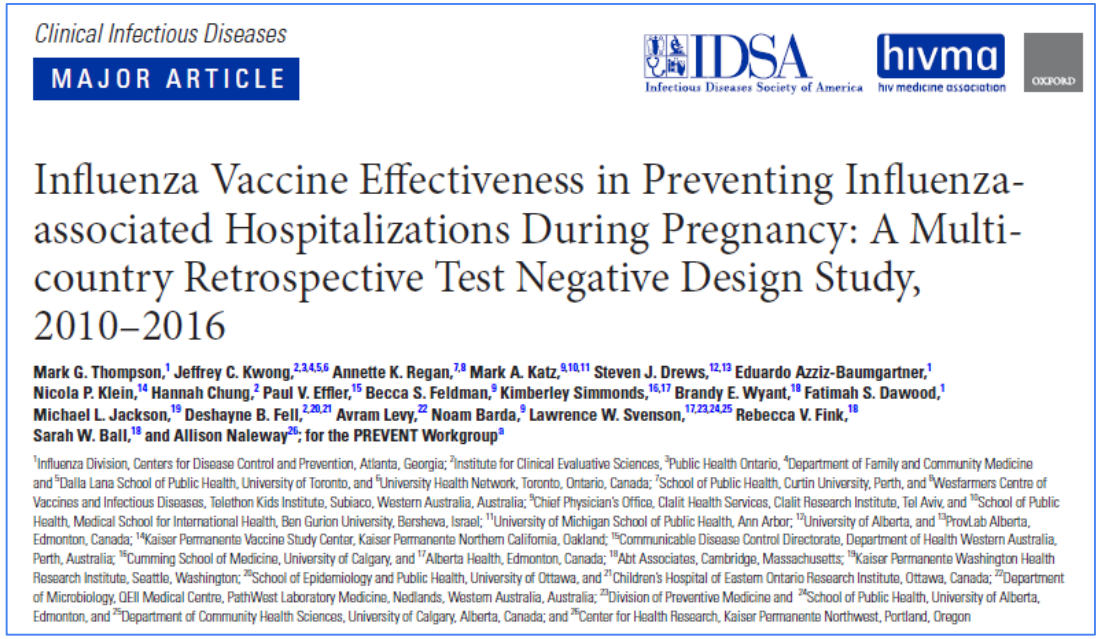
JMIR RESEARCH PROTOCOLS Naleway et al

Protocol

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

Allison L Naleway[1*], Ph.D.; Sarah Ball[2*]; Jeffrey C Kwong[3]; Brandy E Wyant[2]; Mark A Katz[4]; Annette K Regan[5]; Margaret L Russell[6]; Nicola P Klein[7]; Hannah Chung[3]; Kimberley A Simmonds[6]; Eduardo Azziz-Baumgartner[8]; Becca Feldman[4]; Avram Levy[9]; Deshayne B Fell[3]; Steven J Drews[10]; Shikha Garg[8]; Paul Effler[11]; Noam Barda[4]; Stephanie A Irving[1]; Pat Shifflett[2]; Michael L Jackson[12]; Mark G Thompson[8]

JMIR 2018



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

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

Mark G. Thompson,[1] Jeffrey C. Kwong,[2,3,4,5,6] Annette K. Regan,[7,8] Mark A. Katz,[8,10,11] Steven J. Drews,[12,13] Eduardo Azziz-Baumgartner,[1] Nicola P. Klein,[14] Hannah Chung,[2] Paul V. Effler,[15] Becca S. Feldman,[9] Kimberley Simmonds,[16,17] Brandy E. Wyant,[18] Fatimah S. Dawood,[1] Michael L. Jackson,[19] Deshayne B. Fell,[2,20,21] Avram Levy,[22] Noam Barda,[9] Lawrence W. Svenson,[17,23,24,25] Rebecca V. Fink,[18] Sarah W. Ball,[18] and Allison Naleway[26]; for the PREVENT Workgroup[a]

[1]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Institute for Clinical Evaluative Sciences, [3]Public Health Ontario, [4]Department of Family and Community Medicine and [5]Dalla Lana School of Public Health, University of Toronto, and [6]University Health Network, Toronto, Ontario, Canada; [7]School of Public Health, Curtin University, Perth, and [8]Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Subiaco, Western Australia, Australia; [9]Chief Physician's Office, Clalit Health Services, Clalit Research Institute, Tel Aviv, and [10]School of Public Health, Medical School for International Health, Ben Gurion University, Bersheva, Israel; [11]University of Michigan School of Public Health, Ann Arbor; [12]University of Alberta, and [13]ProvLab Alberta, Edmonton, Canada; [14]Kaiser Permanente Vaccine Study Center, Kaiser Permanente Northern California, Oakland; [15]Communicable Disease Control Directorate, Department of Health Western Australia, Perth, Australia; [16]Cumming School of Medicine, University of Calgary, and [17]Alberta Health, Edmonton, Canada; [18]Abt Associates, Cambridge, Massachusetts; [19]Kaiser Permanente Washington Health Research Institute, Seattle, Washington; [20]School of Epidemiology and Public Health, University of Ottawa, and [21]Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada; [22]Department of Microbiology, QEII Medical Centre, PathWest Laboratory Medicine, Nedlands, Western Australia, Australia; [23]Division of Preventive Medicine and [24]School of Public Health, University of Alberta, Edmonton, and [25]Department of Community Health Sciences, University of Calgary, Alberta, Canada; and [26]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon

CID 2018 https://doi.org/10.1093/cid/ciy737

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	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

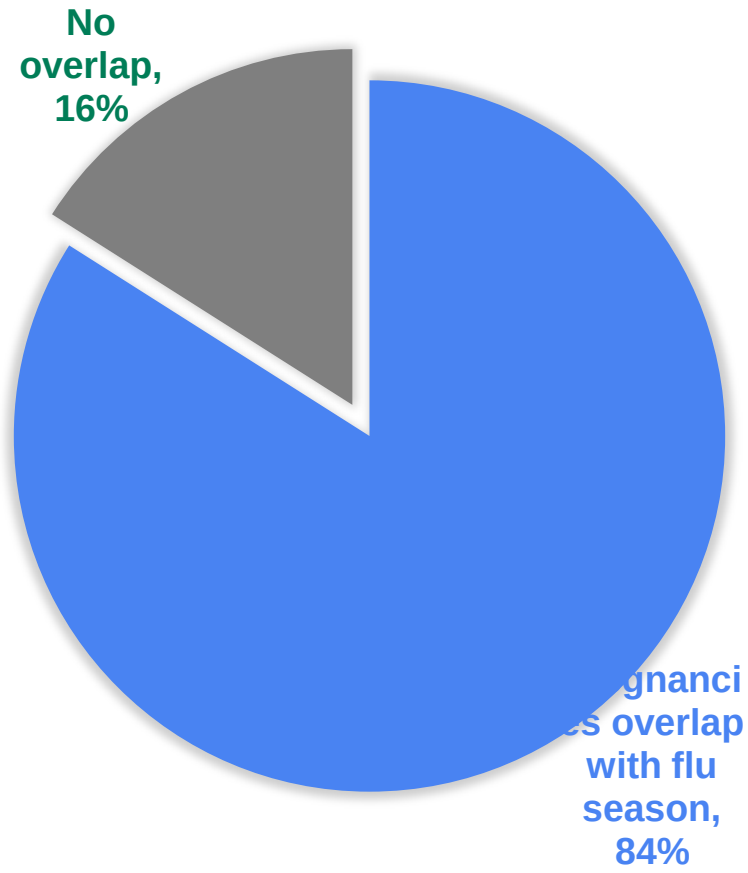
PREVENT's Analytic Sample: Pregnancies during Flu Seasons

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

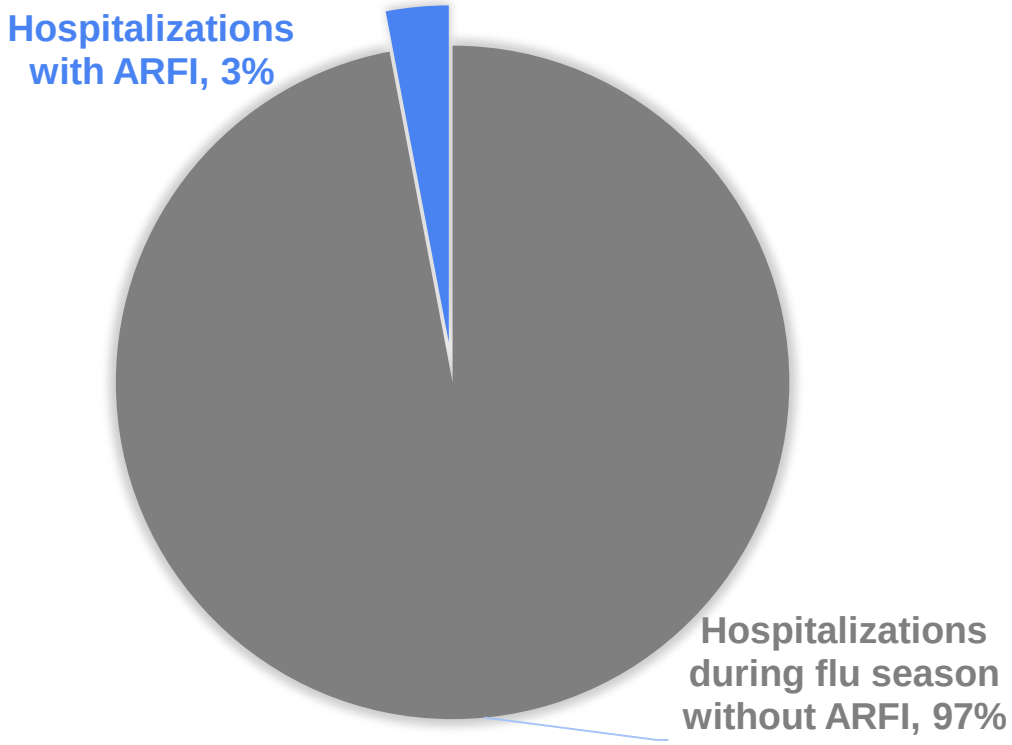
2,068,648 Pregnancies for Full Years
(e.g., July to June for NH years)

→ 331,853 pregnancies outside of flu seasons

1,717,354 Pregnancies
Overlapping with Flu Seasons (84%)



PREVENT's Analytic Sample: Acute Respiratory or Febrile Illness (ARFI)



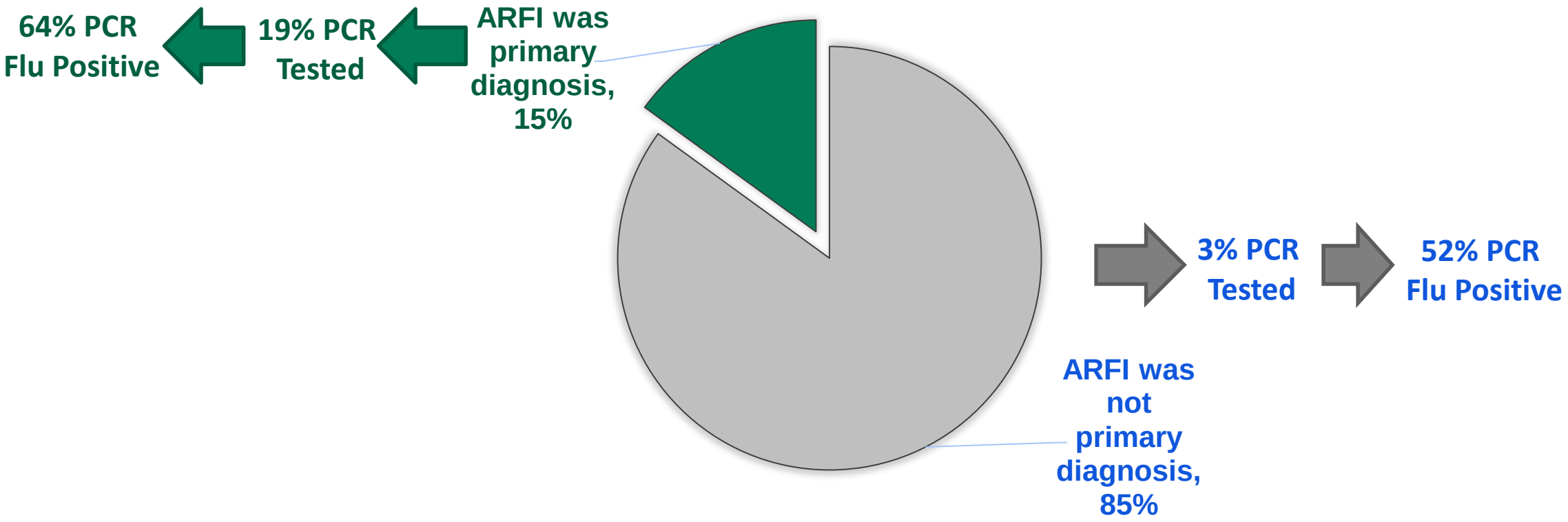
All Study Sites Examining Hospitalizations of Pregnant Women During Flu Seasons

587,204 Hospitalizations during Flu Seasons

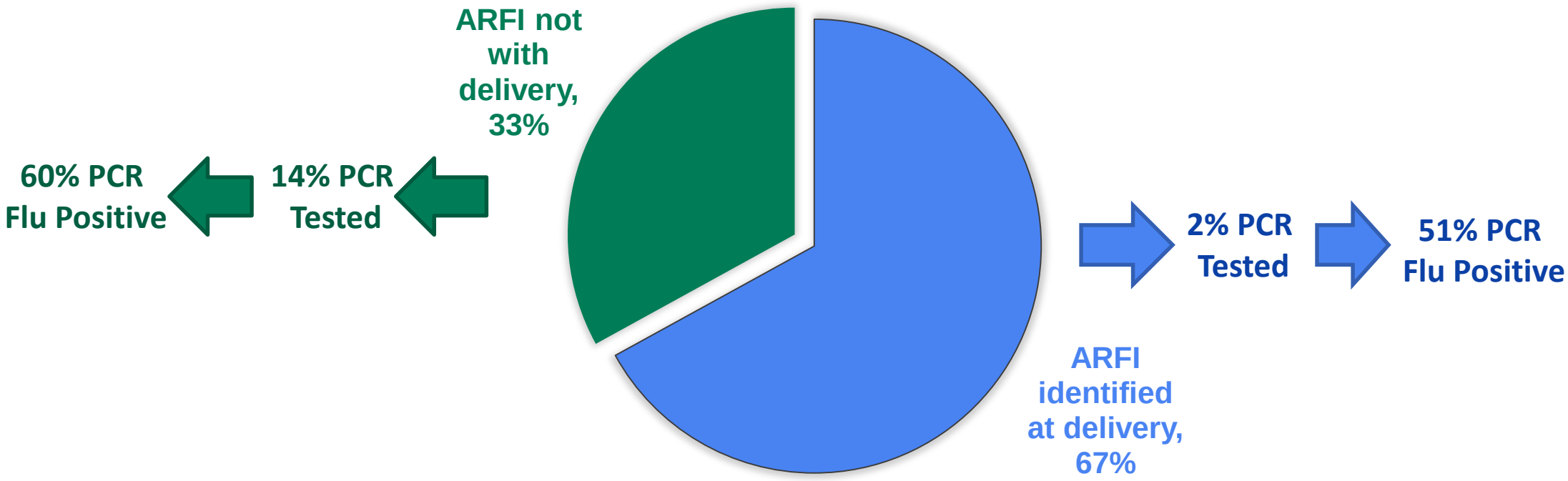
→ 567,754 No ARFI discharge diagnosis

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

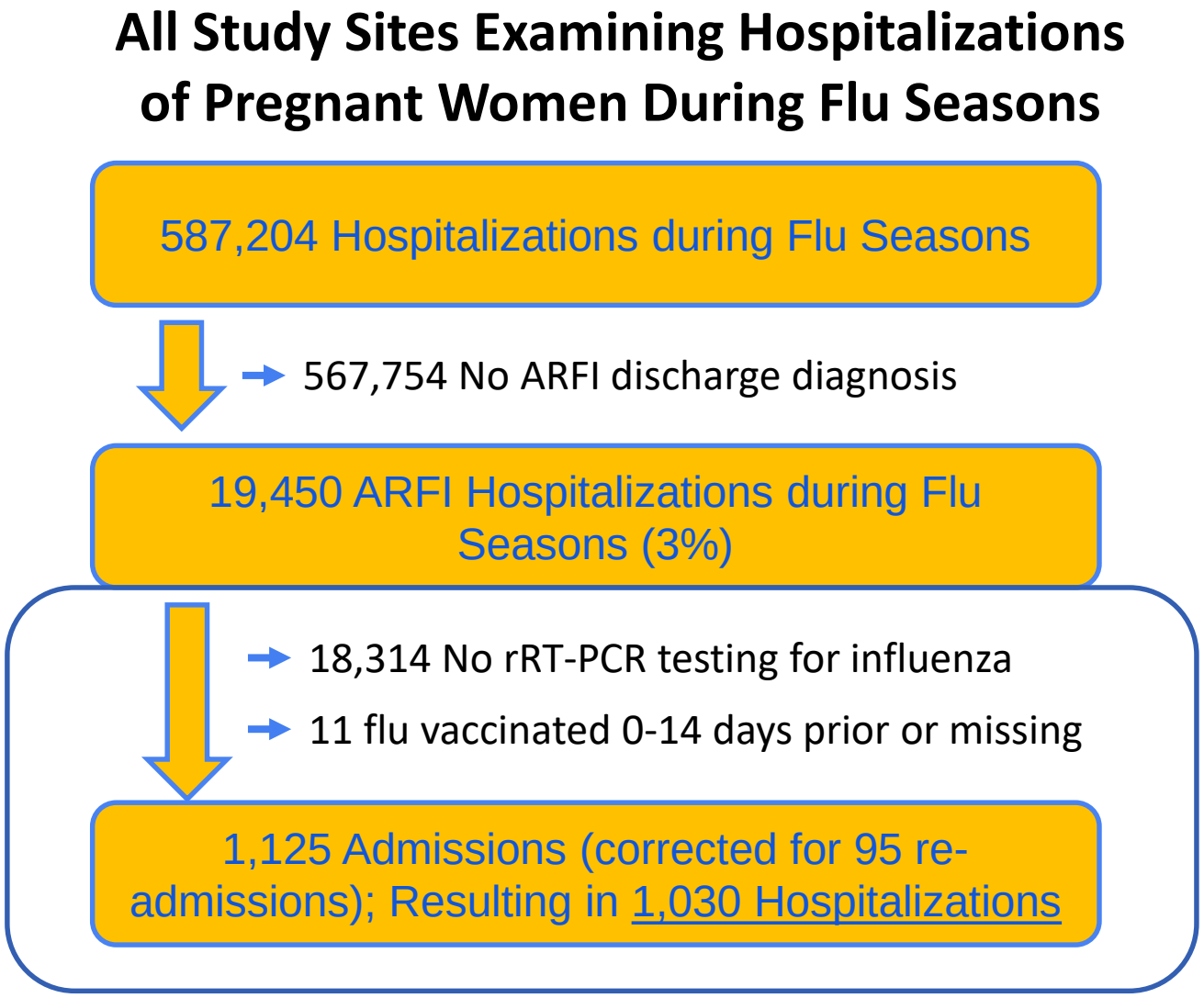
Clinical PCR Testing and Flu Positivity: ARFI Primary Discharge Diagnosis



Clinical PCR Testing and Flu Positivity: ARFI at Delivery

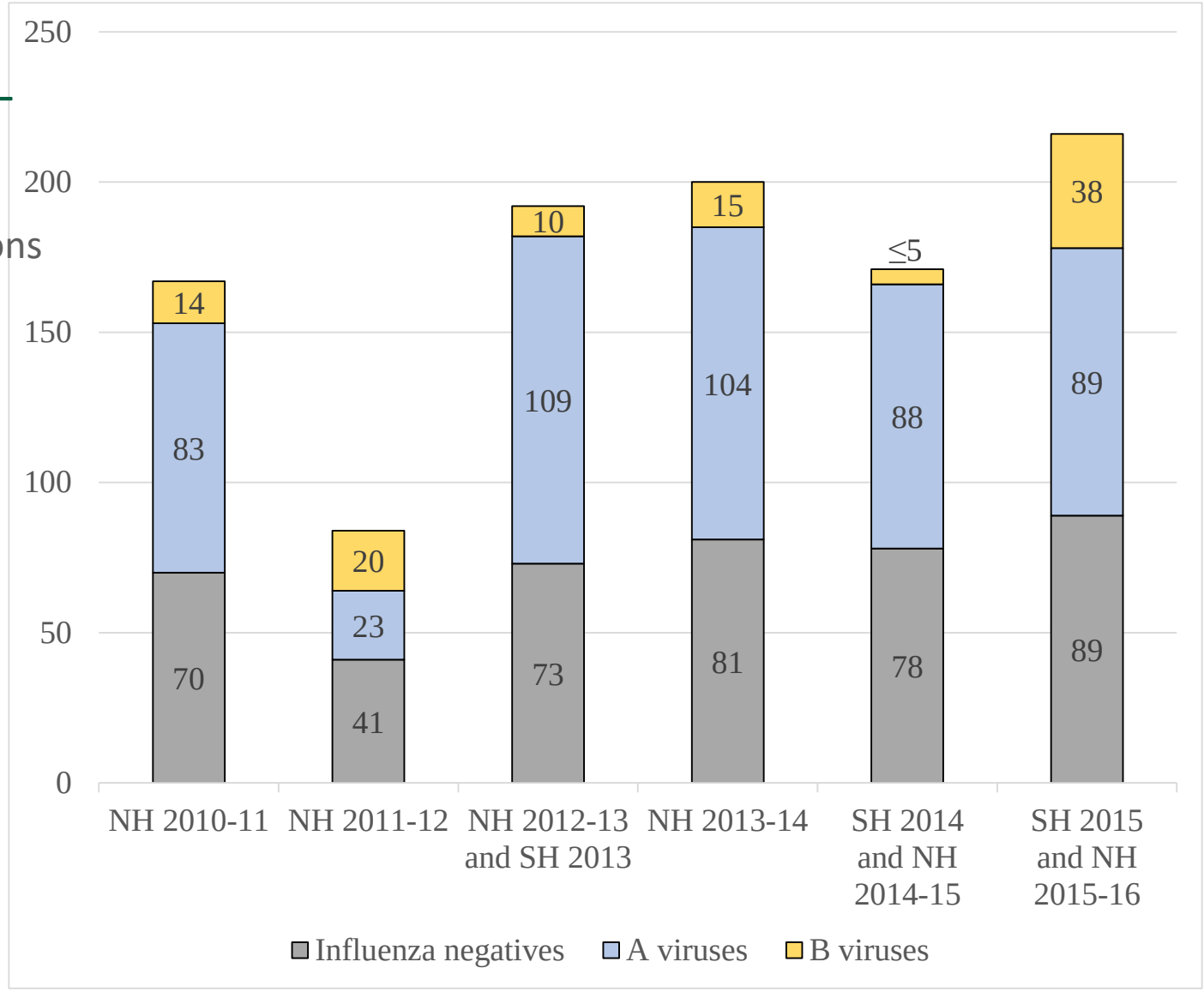


PREVENT's Analytic Sample: 1,030 PCR-tested ARFI Hospitalizations



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

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

		Influenza Positives			Influenza Negatives			Unadjusted IVE	Adjusted IVE
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)

- 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

DISCUSSION

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

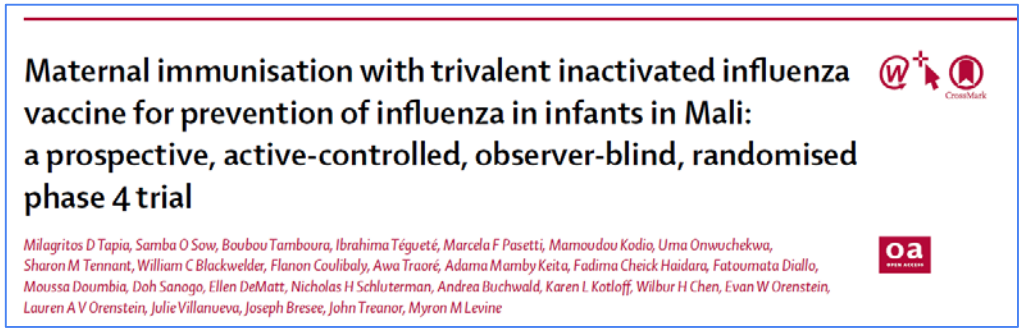
- **Across sites and seasons (2010-2016), influenza vaccines had the potential to prevent 40% (95% CI = 12-59%) of influenza-associated hospitalizations during pregnancy**
  - Likely a conservative estimate

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

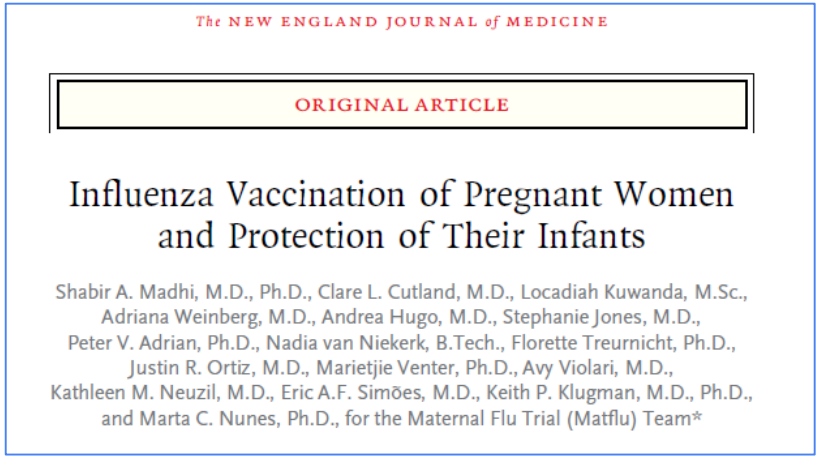
44% VE against symptomatic non-hospitalized PCR-influenza among pregnant women in a prospective TND study during 2010–11 and 2011–12 in the United States



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

Milagritos D Tapia, Samba O Sow, Boubou Tamboura, Ibrahima Tégueté, Marcela F Pasetti, Mamoudou Kodio, Uma Onwuchekwa, Sharon M Tennant, William C Blackwelder, Flanon Coulibaly, Awa Traoré, Adama Mamby Keita, Fadima Cheick Haidara, Fatoumata Diallo, Moussa Doumbia, Doh Sanogo, Ellen DeMatt, Nicholas H Schluterman, Andrea Buchwald, Karen L Kotloff, Wilbur H Chen, Evan W Orenstein, Lauren A V Orenstein, Julie Villanueva, Joseph Bresee, John Treanor, Myron M Levine

Lancet ID (2016)



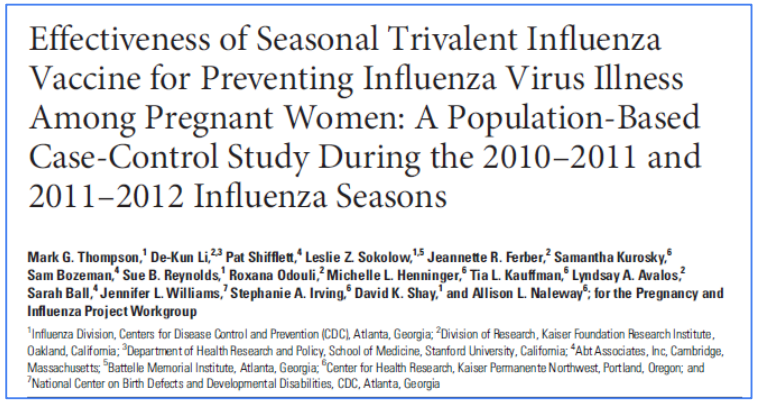
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Influenza Vaccination of Pregnant Women and Protection of Their Infants

Shabir A. Madhi, M.D., Ph.D., Clare L. Cutland, M.D., Locadiah Kuwanda, M.Sc., Adriana Weinberg, M.D., Andrea Hugo, M.D., Stephanie Jones, M.D., Peter V. Adrian, Ph.D., Nadia van Niekerk, B.Tech., Florette Treurnicht, Ph.D., Justin R. Ortiz, M.D., Marietjie Venter, Ph.D., Avy Violari, M.D., Kathleen M. Neuzil, M.D., Eric A.F. Simões, M.D., Keith P. Klugman, M.D., Ph.D., and Marta C. Nunes, Ph.D., for the Maternal Flu Trial (Matflu) Team*

NEJM (2014)



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

Mark G. Thompson,[1] De-Kun Li,[2,3] Pat Shifflett,[4] Leslie Z. Sokolow,[1,5] Jeannette R. Ferber,[2] Samantha Kurosky,[6] Sam Bozeman,[4] Sue B. Reynolds,[1] Roxana Odouli,[2] Michelle L. Henninger,[6] Tia L. Kauffman,[6] Lyndsay A. Avalos,[2] Sarah Ball,[4] Jennifer L. Williams,[7] Stephanie A. Irving,[6] David K. Shay,[1] and Allison L. Naleway[6]; for the Pregnancy and Influenza Project Workgroup

[1]Influenza Division, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia; [2]Division of Research, Kaiser Foundation Research Institute, Oakland, California; [3]Department of Health Research and Policy, School of Medicine, Stanford University, California; [4]Abt Associates, Inc, Cambridge, Massachusetts; [5]Battelle Memorial Institute, Atlanta, Georgia; [6]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon; and [7]National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, Georgia

CID (2014)

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

Acknowledgments

Influenza Division, US CDC
- Mark Thompson (PI)
- Eduardo Azziz-Baumgartner
- Fatimah Dawood
- Shikha Garg

Abt Associates
- Sarah Ball
- Brandy Wyant
- Laura Edwards
- Rebecca Fink
- Ryan Kling
- Omri Drucker
- Pat Shifflett

Curtin University
- Annette Regan

Kaiser Permanente Northwest
- Allison Naleway (Co-PI)
- Stephanie Irving
- Bradley Crane
- Matthew Slaughter

Kaiser Permanente Northern California
- Nicola Klein
- Edwin Lewis
- Sharareh Modaressi
- Kristin Goddard

Kaiser Permanente Washington
- Michael Jackson
- Hallie Phillips

WA Department of Health
- Paul Effler

Path West Laboratory Medicine WA
- Avram Levy

Institute for Clinical Evaluative Sciences
- Jeffrey Kwong
- Deshayne Fell
- Hannah Chung
- Sarah Buchan

Alberta Ministry of Health
- Kimberly Simmonds
- Lawrence Svenson

University of Calgary
- Stephanie Booth
- Margaret Russell

Alberta Health Services
- Steven Drews

Clalit Research Institute
- Becca Feldman
- Mark Katz
- Noah Barda