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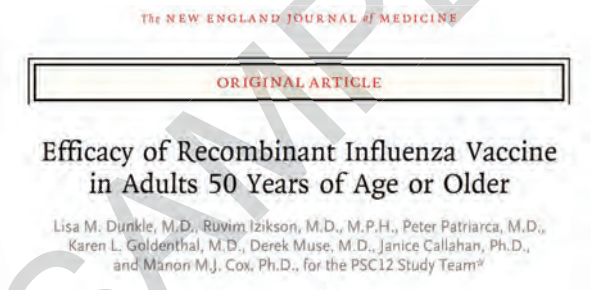
POWERPOINT PRESENTATIONS

Journal Club/Continuing Education #1

Recombinant Influenza Vaccine - 1 hour

Audience: Medical professionals

JOURNAL CLUB



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older

Lisa M. Dunkle, M.D., Ruvim Izikson, M.D., M.P.H., Peter Patriarca, M.D., Karen L. Goldenthal, M.D., Derek Muse, M.D., Janice Callahan, Ph.D., and Manon M.J. Cox, Ph.D., for the PSC12 Study Team*

DISCLOSURE

- No relationships with any commercial interests relevant to the content of this presentation

OBJECTIVES

- Describe the different variations and subtypes of influenza
- List available influenza vaccines
- Define Centers for Disease Control and Prevention (CDC)/Advisory Committee on Immunization Practices (ACIP) 2017-2018 recommendations for influenza vaccination
- Discuss the New England Journal of Medicine (NEJM) article *Efficacy of recombinant influenza vaccine in adults 50 years of age and older*

INFLUENZA (FLU)

- Global epidemic that infects millions of people and causes serious illness and death worldwide
- Results in hospitalization rate of 35.5 per 100,000 people
- Vaccination remains the primary and most effective strategy for prevention and control

Biomed Res Int. 2015;2015:1-11

INFLUENZA (FLU)

- 3 Types of Influenza Viruses
  - A, B, C
- Influenza A
  - Hemagglutinin (HA)
  - Neuraminidase (NA)
- Influenza B
  - Yamagata
  - Victoria
- Due to high mutation rate of the influenza virus, vaccine manufacturers must reformulate every year

Biomed Res Int. 2015;2015:1-11

INFLUENZA VACCINES

- Inactivated Influenza Vaccine (IIV)
  - Egg-based production (one vaccine dose/one-two eggs)
  - 6 months
- Recombinant Influenza Vaccine (RIV)
  - Cell-based production
  - Egg Free!
  - 6-8 weeks

Biomed Res Int. 2015;2015:1-11

TIME IS FLU!

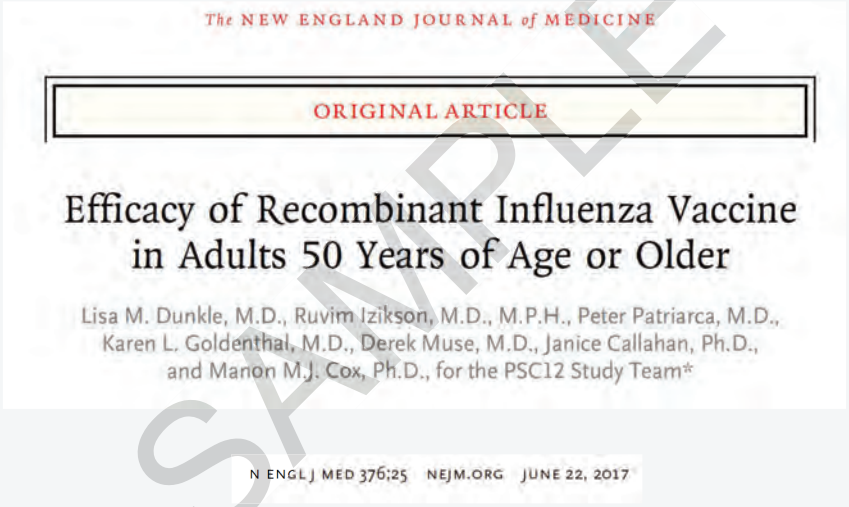
- Vaccine production huge challenge
- On average, 6 months to develop and supply vaccines for the start of flu season
- With egg-based production method this is possible, but what happens if something goes wrong?!
  - 2014-2015 Flu Season
    - Influenza A subtype H3N2 viruses were antigenically mismatched
      - Resulted in vaccine effectiveness of 27-36%

CDC. 2015

2017-2018 ACIP RECOMMENDATIONS

- ≥ 6 months of age
- Inactivated Influenza Vaccine (IIV)
  - Quadrivalent (IIV4) – Afluria, Fluarix, Fluzone
  - Trivalent (IIV3) – Afluria, Fluvirin
- Recombinant Influenza Vaccine (RIV)
  - Quadrivalent (RIV4) – Flublok
  - Trivalent (RIV3) – Flublok
- Live Attenuated Influenza Vaccine (LAIV)
  - Flumist—Not recommended

CDC. 2017



N Engl J Med. 2017;376:2427-2436

PURPOSE

- Compare quadrivalent, recombinant influenza (RIV4) with egg-grown quadrivalent, inactivated influenza vaccine (IIV4) to assess relative vaccine efficacy against reverse-transcriptase polymerase-chain-reaction (RT-PCR) confirmed influenza-like illness

N Engl J Med. 2017;376:2427-2436

ENDPOINTS

- Primary Endpoint
  - RT-PCR confirmed, protocol-defined, influenza-like illness caused by any influenza virus type or subtype that begins ≥14 days after vaccination
    - Modified intention-to-treat population (mITT)
      - All randomly assigned participants who received trial vaccine and provided follow-up efficacy data ≥14 days later
    - Modified per-protocol population (mPP)
      - All participants who received the trial vaccine and provided efficacy data ≥14 days later with no major protocol deviations
- Secondary Endpoint
  - Culture confirmed protocol-defined influenza-like illness that begins ≥14 days after vaccination
  - Culture confirmed influenza-like illness that begins ≥14 days after vaccination with fever (≥100˚F)
  - RT-PCR confirmed influenza-like illness that begins ≥14 days after vaccination caused by any influenza strain with fever (≥100˚F)

N Engl J Med. 2017;376:2427-2436

PROTOCOL-DEFINED INFLUENZA-LIKE ILLNESS

Respiratory Symptoms:

- Sore throat
- Cough
- Sputum production
- Wheezing
- Difficulty breathing

Systemic Symptoms:

- Fever (> 37.2 C)
- Chills
- Fatigue
- Headache
- Myalgia

≥1 symptom in each category

N Engl J Med. 2017;376:2427-2436

METHODS

- Study Design
  - Phase 3 – 4, randomized, double-blind, active-controlled trial
  - 40 outpatient centers across United States
  - October 22, 2014 through May 22, 2015
- 9003 patients randomized to receive
  - Recombinant Influenza Vaccine, Quadrivalent (RIV4)
    - Flublok (180µg) (N= 4474)
  - Inactivated Influenza Vaccine, Quadrivalent (IIV4)
    - Fluarix (60µg) (N= 4489)

N Engl J Med. 2017;376:2427-2436

METHODS

INCLUSION CRITERIA

- ≥50 years of age
- Living independently without clinically significant acute illness (medically stable)

EXCLUSION CRITERIA

- Contraindication to either study vaccine
- Received influenza vaccine within preceding 180 days
- Underlying disease or therapy rendering them immunocompromised

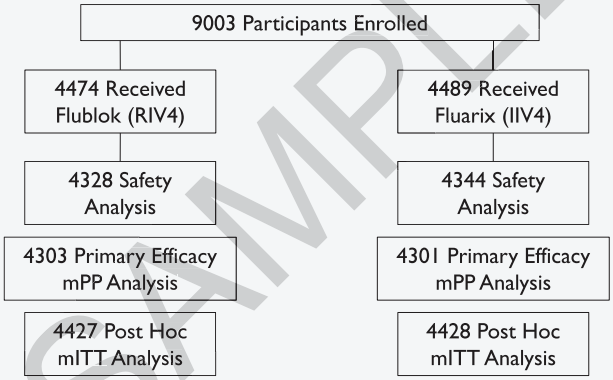
N Engl J Med. 2017;376:2427-2436

METHODS

- Efficacy Population
  - All randomized subjects who receive study vaccine and provide follow up for influenza-like illness ≥14 days after vaccination
- Safety Population
  - All randomized and vaccinated subjects who provide any safety data following administration of study vaccine
    - Solicited, unsolicited, serious and medically-attended

N Engl J Med. 2017;376:2427-2436

RANDOMIZATION



N Engl J Med. 2017;376:2427-2436

STATISTICAL ANALYSIS

- Powered at 80% to show noninferiority of relative vaccine efficacy
- Noninferiority concluded if lower bound of 95% confidence interval for relative vaccine efficacy > -20%
- Superiority of Flublok (RIV4) required lower bound of 95% confidence interval for relative vaccine efficacy >9%
- Hazard ratios
  - Cox proportional-hazards model
  - Log-rank test of significance

N Engl J Med. 2017;376:2427-2436

BASELINE CHARACTERISTICS

Characteristic	Flublok (RIV4) (N=4329)	Fluarix (IIV4) (N=4344)
Age	63	63
Male sex	41.5%	41.6%
Race/Ethnic Group	White – 80.1% Black – 17.9%	White – 80.4% Black – 17.3%
Coexisting Conditions		
Atherosclerotic CVD	30.5%	30.3%
Condition w/ Statin	27.6%	27.7%
Depression	18.2%	18.4%

No significant differences between the treatment groups

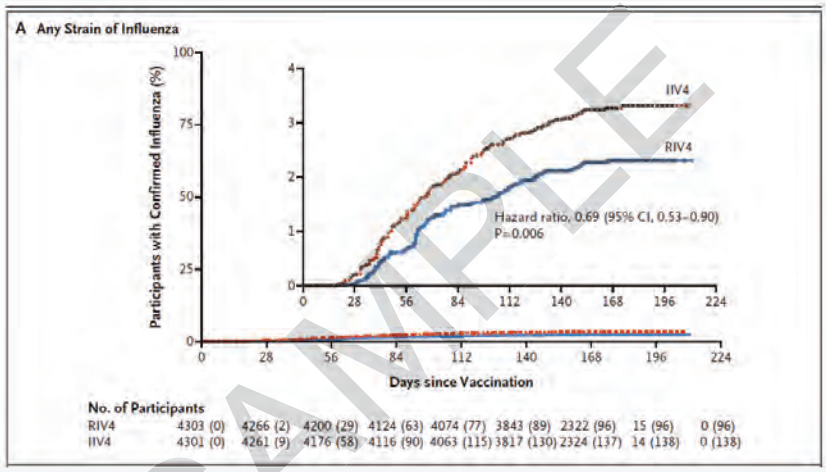
N Engl J Med. 2017;376:2427-2436

RESULTS: PRIMARY EFFICACY ENDPOINT

	Flublok (RIV4) Influenza Attack Rate	Fluarix (IIV4) Influenza Attack Rate	Number Needed to Treat (NNT)
Modified Per-Protocol (mPP)	2.2%	3.2%	100 (Flublok)
Modified Intention-To-Treat (mITT)	2.2%	3.1%	111 (Fluarix)

- Modified Per-Protocol (mPP):
  - Probability of influenza-like illness 30% lower with Flublok (RIV4) than Fluarix (IIV4) (95% CI 10-47; P=0.0006)
- Modified Intention-To-Treat (mITT):
  - Yielded same vaccine efficacy of 30%

N Engl J Med. 2017;376:2427-2436



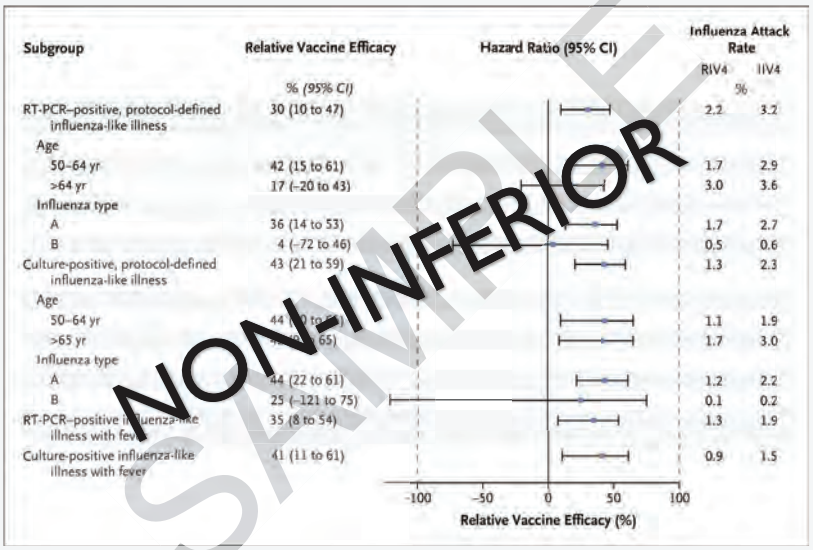
- Primary Endpoint:
  - RT-PCR confirmed, protocol-defined, influenza-like illness caused by any influenza virus type or subtype

N Engl J Med. 2017;376:2427-2436

RESULTS: SECONDARY ENDPOINT

- Culture confirmed protocol-defined influenza-like illness that begins ≥14 days after vaccination
- Culture confirmed influenza-like illness that begins ≥14 days after vaccination with fever (≥100˚F)
- RT-PCR confirmed influenza-like illness that begins ≥14 days after vaccination caused by any influenza strain with fever (≥100˚F)

N Engl J Med. 2017;376:2427-2436



N Engl J Med. 2017;376:2427-2436

RESULTS: SAFETY

Condition	Flublok (RIV4) (N=4328)	Fluarix (IIV4) (N=4344)
Unsolicited (Day 0-28)		
Cough	5.2% (226)	5.8% (253)
ILI	4.3% (186)	4.6% (199)
Oropharyngeal pain	4.1% (178)	4.1% (177)
Headache	3.3% (143)	3.3% (145)
Upper respiratory tract infection	3% (129)	3.6% (156)
Fatigue	2.4% (106)	2.3% (100)
Myalgia	2.2% (95)	1.8% (79)
Productive Cough	1.4% (59)	2.2% (97)

- Overall, safety profiles of vaccines were similar
- Solicited—incidence of injection site pain and tenderness slightly higher in Fluarix (IIV4)
- Serious and medically-attended events that occurred were not considered to be related to the vaccines

N Engl J Med. 2017;376:2427-2436

AUTHORS CONCLUSIONS

- Flublok (RIV4) compared with Fluarix (IIV4) improved protection against laboratory-confirmed influenza-like illness in adults 50 years or older

N Engl J Med. 2017;376:2427-2436

DISCUSSION

- Strengths
  - Randomized controlled
  - 80% power was achieved
  - Baseline characteristics were similar among both groups
- Limitations
  - Conducted during a single influenza season
  - Generalizability
  - No non-comparative efficacy data
  - Cost comparison
  - Industry funded

N Engl J Med. 2017;376:2427-2436

IMPACT ON CURRENT PRACTICE

- RIV4 is an effective vaccine produced using cell-based technology
  - Less susceptible to HA mutation which may reduce vaccine effectiveness
- Good alternative for patients with egg allergy
- Much quicker manufacturing process than that of egg-based IIV4 (~6-8 weeks)

WHICH OF THE FOLLOWING STATEMENTS IS TRUE REGARDING THE ACIP 2017-2018 VACCINATION RECOMMENDATIONS?

A. ACIP recommends vaccinating only those ≥18 years of age
B. Flumist, the live attenuated influenza vaccine (LAIV), is the vaccine of choice
C. Inactivated and recombinant influenza vaccines are both potential options when vaccinating
D. ACIP recommends vaccinating only those ≥8 months of age

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D. ACIP recommends vaccinating only those ≥8 months of age

REFERENCES

1. Milián E, Kamen AA. Current and emerging cell culture manufacturing technologies for influenza vaccines. Biomed Res Int. 2015;2015:504831.
2. Influenza (Flu). Centers for Disease Control and Prevention. https://www.cdc.gov/flu/news/2014-2015-flu-season-wrapup.htm. Published April 28, 2015. Accessed November 4, 2017.
3. Influenza (Flu). Centers for Disease Control and Prevention. https://www.cdc.gov/flu/professionals/acip/2017-18summary.htm. Published September 15, 2017. Accessed November 1, 2017.
4. Dunkle LM, Izikson R, Patriarca P, et al. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. N Engl J Med. 2017;376(25):2427-2436.

QUESTIONS?

Journal Club #2

Herpes Zoster: 1 hour

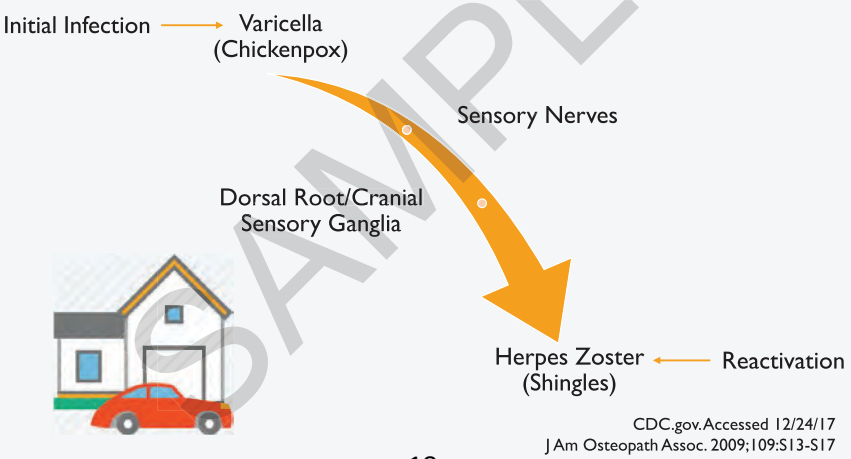
Audience: Pharmacists

HERPES ZOSTER (HZ) VACCINE

OBJECTIVES

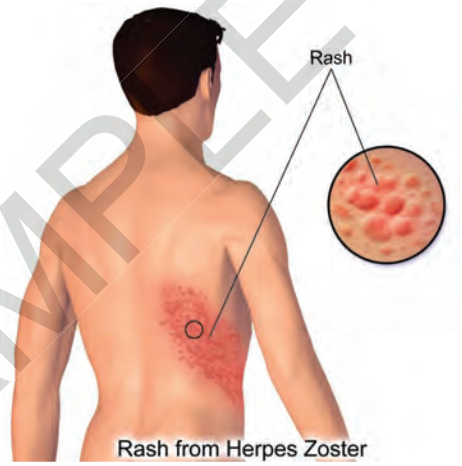
- Describe varicella zoster virus (VZV) and the clinical manifestations
- List the different types of herpes zoster (HZ) vaccines available
- Describe current CDC/ACIP recommendations for herpes zoster (HZ) vaccination
- Compare live attenuated Zostavax vaccine (ZVL) with the subunit vaccine candidate (HZ/su)
- Discuss *Immunogenicity and safety of the HZ/su adjuvanted herpes zoster subunit vaccine in adults previously vaccinated with a live attenuated herpes zoster vaccine*

VARICELLA ZOSTER VIRUS (VZV)



CDC.gov. Accessed 12/24/17
J Am Osteopath Assoc. 2009;109:S13-S17

HERPES ZOSTER (HZ)

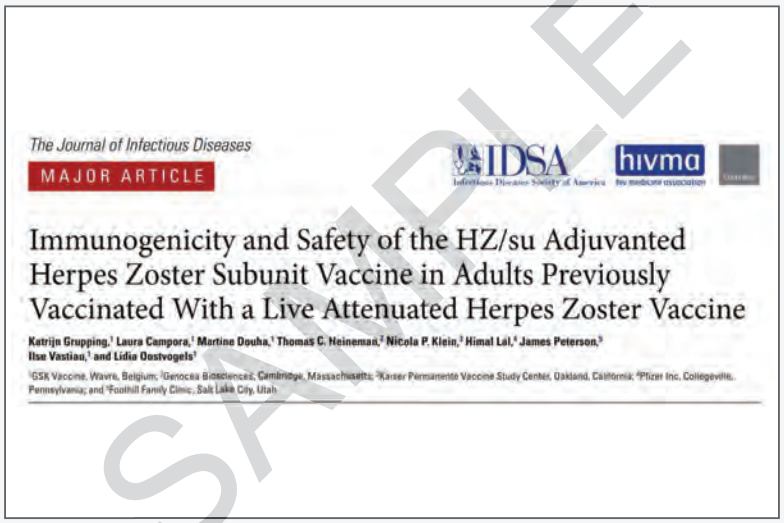


CDC.gov. Accessed 12/24/17
Wikimedia.org. Accessed: 1/5/18
Am J Infect Dis. 2017;216:1343-1351

ZOSTAVAX® Zoster Vaccine Live

- FDA indicated for prevention of herpes zoster in individuals ≥50 years
- CDC/ACIP recommendations for individuals ≥60 years
- Limitations of use
  - Immunosuppression/Immunodeficiency
  - Pregnancy
  - History of anaphylactic reactions to neomycin, gelatin, or other any component of the vaccine

CDC.gov. Accessed 12/24/17
Zostavax.com. Accessed 1/6/18
Dailymed.nlm.nih.gov. Accessed 1/6/18



Am J Infect Dis. 2017;216:1343-1351

PURPOSE

- Compare immunogenicity and assess reactogenicity and safety of HZ/su in adults ≥65 years who were vaccinated with ZVL ≥5 years before study start and group-matched ZVL – naïve adults

HZ/su – Shingrix
ZVL – Zostavax

Am J Infect Dis. 2017;216:1343-1351

OBJECTIVES

- Co-primary
  - Compare humoral immune response 1 month after dose 2 of HZ/su between the HZ-PreVac and HZ-NonVac groups
  - Evaluate reactogenicity and safety up to 1 month after dose 2 of HZ/su in both study groups
- Secondary
  - Assess humoral and cell-mediated immunity (CMI) responses to the HZ/su vaccine in both study groups at
    - Baseline (prevaccination)
    - 1 month post-dose 1
    - 1 month post-dose 2

Am J Infect Dis. 2017;216:1343-1351

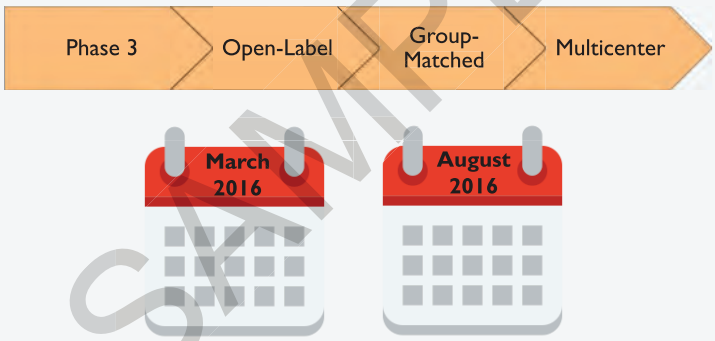
WHAT IS HZ/SU?

- HZ/su
  - Subunit vaccine
  - Contains recombinant VZV glycoprotein (gE)
  - Adjuvanted with AS01 adjuvant system

CDC.gov. Accessed 12/24/17
Shingrix.com. Accessed 12/28/17
Dailymed.nlm.nih.gov. Accessed 12/2817

METHODS

STUDY DESIGN



Am J Infect Dis. 2017;216:1343-1351

PARTICIPANTS

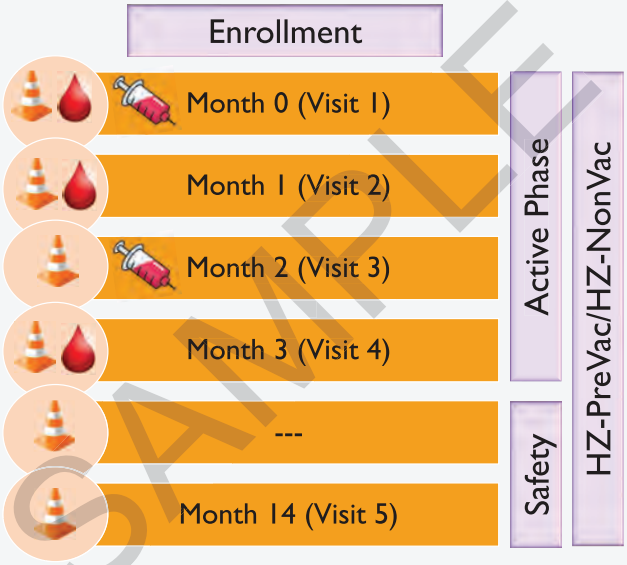
INCLUSION CRITERIA

- HZ-PreVac
  - ≥65 years previously vaccinated with ZVL ≥5 years prior to study start
- HZ-NonVac
  - Group-matched according to predefined variables
    - Age, sex, race, and medical condition

EXCLUSION CRITERIA

- Live vaccine within 30 days
- Investigational or nonregistered drug or vaccine within 30 days
- Immunosuppressants or other immune-modifying drugs for >14 consecutive days within 180 days
- Long-acting immune-modifying drugs within 180 days before first HZ/su vaccination
- History of herpes zoster
- Scheduled to receive herpes zoster vaccine
- Reaction or hypersensitivity to vaccine components

Am J Infect Dis. 2017;216:1343-1351



Adverse Effects: Solicited, Unsolicited, Serious, Potential Immune-mediated Diseases

Am J Infect Dis. 2017;216:1343-1351

STATISTICAL ANALYSES

CO-PRIMARY OBJECTIVES

1. Immunogenicity Data
   - Inferential analyses
     - ANOVA used on log transformed antibody concentration
     - Geometric mean concentrations (GMC) and GMC ratio
       - Adjusted means, difference of means, and 2-sided confidence intervals (CI)
2. Reactogenicity and Safety Data
   - Descriptive analyses

Am J Infect Dis. 2017;216:1343-1351

CO-PRIMARY OBJECTIVES

Noninferiority of humoral response was demonstrated if upper limit of 2-sided CI of adjusted GMC ratio of HZ-NonVac/HZ-PreVac at 1 month post-dose 2 (active phase) was <1.5

Powered at 99% to show noninferiority in humoral immunogenicity

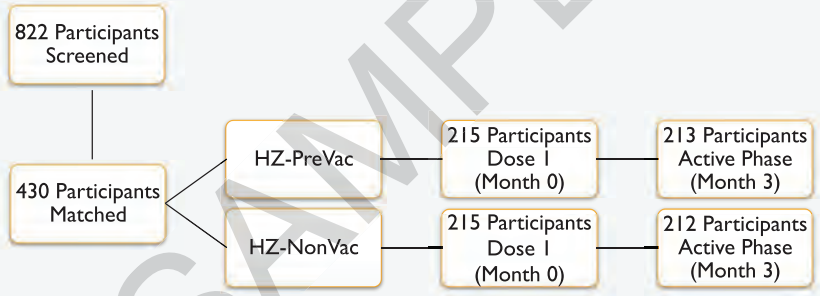
SECONDARY OBJECTIVES

1. Immunogenicity Data
   - Descriptive analyses
     - Humoral Immunity
       - 95% CI for GMCs was obtained for each group separately
         - 95% CI of mean log-transformed concentrations obtained
         - 95% CI for GMCs was calculated by anti-log transformation of previously calculated 95% CI for mean log-transformed concentrations
     - Cell-mediated Immunity
       - Frequency of gE-specific $CD4^{2+}$ T cells was calculated as the difference between the frequency of $CD4^{2+}$ stimulated in vitro with gE antigen and those stimulated with culture alone

Am J Infect Dis. 2017;216:1343-1351

RESULTS

PARTICIPANTS



Am J Infect Dis. 2017;216:1343-1351

BASELINE CHARACTERISTICS

Characteristic	Total (N=430)	HZ-NonVac (n=215)	HZ-PreVac (n=215)
Age (SD)	70.9 (4.6)	70.8 (4.6)	71.1 (4.5)
Sex No. (%)			
Female	220 (51.2)	111 (51.6)	109 (50.7)
Male	210 (48.8)	104 (48.4)	106 (49.3)
White/European No. (%)	430 (100)	215 (100)	215 (100)

Am J Infect Dis. 2017;216:1343-1351

PRIMARY OBJECTIVE: IMMUNOGENICITY

Adjusted Mean Concentrations (GMC) and Adjusted GMC Ratio of Anti-Glycoprotein E Antibody Concentrations

Group	Value	No.	Adj GMC	95% Confidence Interval	
				Lower Limit	Upper Limit
HZ-PreVac	---	204	48589.4	42649.4	55356.6
HZ-NonVac	---	204	50522.9	44347.4	57558.4
GMC Ratio (HZ-NonVac/HZ-PreVac)	1.04	---	---	0.92	1.17

Primary objective of noninferiority was met!
GMC ratio of HZ-NonVac group/HZ-PreVac group <1.5

Am J Infect Dis. 2017;216:1343-1351

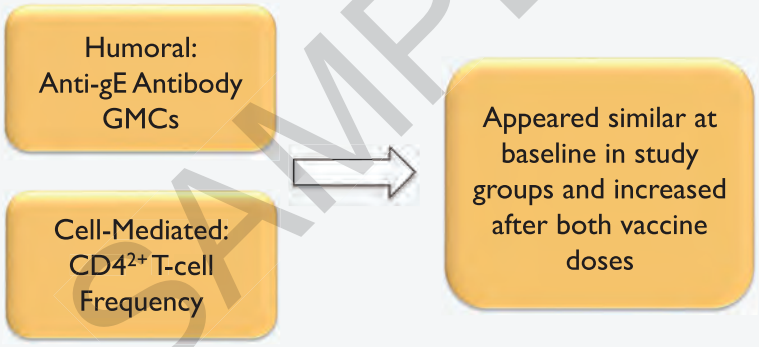
PRIMARY OBJECTIVE: REACTOGENICITY AND SAFETY

Adverse Event	HZ-NonVac (n=214) No. (%)	HZ-PreVac (n=215) No. (%)
Solicited – Days 0-6 postvaccination		
Participants reporting local reaction	Pain, ≤3 days	
Participants reporting systemic reaction	Fatigue, ≤2 days	
Unsolicited – Days 0-29 postvaccination		
Participants reporting any AE	52 (24.2%)	78 (36.3%)
Related by investigator	12 (5.6%)	13 (6%)
Serious (SAE) – 1st vaccination to 30 days post 2nd vaccination		
Participants reporting any AE	None related to vaccine	
pIMDs		
Total reported	0	0

Percentage of participants reporting adverse effects were comparable among groups

Am J Infect Dis. 2017;216:1343-1351

SECONDARY OBJECTIVE: HUMORAL AND CELL-MEDIATED RESPONSES



Am J Infect Dis. 2017;216:1343-1351

AUTHORS CONCLUSIONS

- Humoral immune response to HZ/su 1 month post-dose 2 was noninferior in adults >65 years who were vaccinated with live attenuated zoster vaccine (Zostavax) >5 years ago compared to those who never received this vaccine
- HZ/su was well-tolerated in both study groups, and no safety concerns were identified from vaccine dose 1 up to 1 month post-dose 2

Am J Infect Dis. 2017;216:1343-1351

DISCUSSION

+	−
- Multi-center - Baseline characteristics were similar between groups - 99% power was achieved	- Matching resulted in groups that were of white ancestry - United States only

Am J Infect Dis. 2017;216:1343-1351

SHINGRIX
(ZOSTER VACCINE RECOMBINANT, ADJUVANTED)

- FDA indicated for prevention of herpes zoster in ≥50 years
- ACIP voted that Shingrix is recommended:
  - ≥50 years to prevent shingles and complications
  - Adults who previously received Zostavax to prevent shingles and related complications
  - Preferred vaccine for preventing shingles and related complications

CDC.gov.Accessed 12/28/17
Shingrix.com.Accessed 12/28/17
Dailymed.nlm.nih.gov.Accessed 12/2817

SHINGRIX VS ZOSTAVAX

Shingrix	Zostavax
Non-live	Live attenuated
Two dose series (2-6 months apart)	One dose series
Intramuscular	Subcutaneous
Vaccine Efficacy >90%	Vaccine Efficacy 70%

CDC. gov.Accessed 12/24/17
Am J Infect Dis. 2017;216:1343-1351
Dailymed.nlm.nih.gov.Accessed 12/2817

IMPACT ON CURRENT PRACTICE

Patient Education!

Shingrix.com. Accessed 12/28/17
Am J Infect Dis. 2017;216:1343-1351

PATIENT EDUCATION

- S – SHARE the reasons why the vaccine is right for the patient
- H – HIGHLIGHT the positive experiences
- A – ADDRESS patient questions
- R – REMIND patients that vaccines protect them and their loved ones
- E – EXPLAIN the potential costs of getting herpes zoster

CDC.gov. Accessed 1/6/18

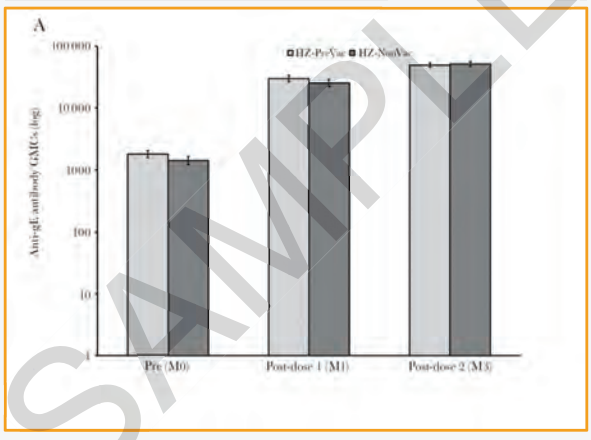
REFERENCES

1. Oxman MN. Herpes zoster pathogenesis and cell-mediated immunity and immunosenescence. J Am Osteopath Assoc. 2009;109(6 Suppl 2):S13-7.
2. Vaccines and Preventable Diseases. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/vpd/shingles/public/index.html. Published December 5, 2017. Accessed December 24, 2017.
3. Main Page. Wikimedia Commons. https://commons.wikimedia.org/wiki/. Accessed January 6, 2018.
4. Grupping K, Campora L, Douha M, et al. Immunogenicity and Safety of the HZ/su Adjuvanted Herpes Zoster Subunit Vaccine in Adults Previously Vaccinated with a Live-Attenuated Herpes Zoster Vaccine. J Infect Dis. 2017.
5. DailyMed - ZOSTAVAX- zoster vaccine live injection, powder, lyophilized, for suspension STERILE DILUENT- sterile water injection. U.S. National Library of Medicine. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=30a0464e-e012-4c16-bc05-88f07e412203. Accessed January 6, 2018.
6. Are you a health care professional? Shingles Vaccine | Official Web Site. https://www.zostavax.com/. Accessed January 6, 2018.
7. Be one of the first to get information about SHINGRIX. Homepage | SHINGRIX. https://www.shingrix.com/. Accessed December 28, 2017.
8. DailyMed - SHINGRIX- gE recombinant varicella zoster virus (vzv) glycoprotein e. U.S. National Library of Medicine. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0280849d-5c78-4a9d-8941-4eab429f6bd8. Accessed December 28, 2017.
9. Vaccines and Preventable Diseases. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/vpd/shingles/hcp/index.html. Published December 5, 2017. Accessed December 28, 2017.

QUESTIONS?!

EXTRA SLIDES

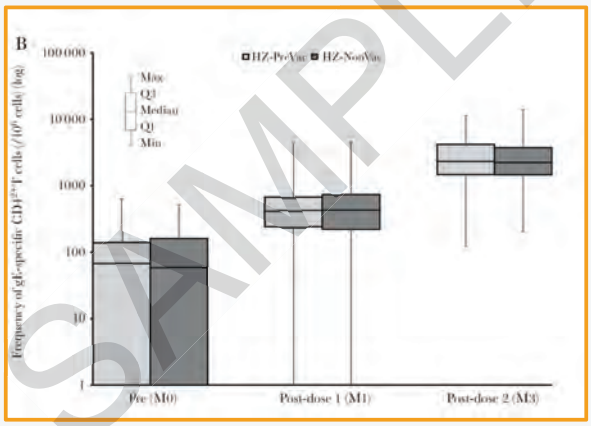
IMMUNOGENICITY



Primary objective met!
GMC ratio of HZ-NonVac group/HZ-PreVac group <1.5

Am J Infect Dis. 2017;216:1343-1351

IMMUNOGENICITY



Am J Infect Dis. 2017;216:1343-1351

IMMUNOGENICITY

Humoral Immunity (Anti-gE Antibodies)				
Group	**Timing**	**N**	**GMC**	**95% CI**
HZ-PreVac	Month 0	204	1784.3	1,572.9-2,024.1
	Month 1	204	29959.0	26,633.6-33,699.6
	Month 3	204	49327.2	45,388.2-53,608.1
HZ-NonVac	Month 0	202	1408.5	1,203.3-1,648.8
	Month 1	202	25233.7	22,072.3-28,848.0
	Month 3	204	51618.5	47,224.8-56,420.9

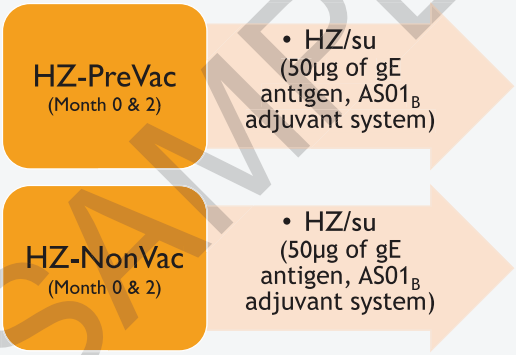
Primary objective met!
GMC ratio of HZ-NonVac group/HZ-PreVac group <1.5

IMMUNOGENICITY

Cell-Mediated Immunity (Frequency of $CD4^{2+}$)					
Group	**Timing**	**N**	**Q1**	**Median**	**Q3**
HZ-PreVac	Month 0	152	1.0	67.4	138.2
	Month 1	177	240.6	425.1	673.0
	Month 3	170	1,464.5	2,312.1	4,148.3
HZ-NonVac	Month 0	140	1.0	58.1	160.3
	Month 1	170	219.7	426.8	733.4
	Month 3	177	1,448.6	2,214.2	3,734.5

N=number of participants with available results; $CD4^{2+}$ CD4 T cells expressing at least two activation markers among CD40 ligand, interleukin-2, tumor necrosis factor-alpha, interferon-gamma; Q1, Q3, first and third quartiles

STUDY VACCINES



Am J Infect Dis. 2017;216:1343-1351

HERPES ZOSTER (HZ)

- Vesicular dermatomal rash lasting several weeks
- 1 out of every 3 people will get shingles in their lifetime
  - 50% of cases occur in ≥60 years
- High risk
  - Immunocompromised and age
- Most common complication
  - Postherpetic neuralgia (PHN)

CDC. 2017

ASSESSMENT

- Immunogenicity
  - Blood samples collected at baseline, and at 1 month post first and second vaccine doses
- Reactogenicity and Safety
  - Solicited – recorded 7 days after each vaccination
    - Local or systemic
  - Unsolicited – recorded 30 days after each vaccination
    - Any adverse effect not recorded as a solicited
  - Serious and potentially immune-mediated diseases – entire duration of study

Am J Infect Dis. 2017;216:1343-1351

IMPACT ON CURRENT PRACTICE

- Zostavax provides a moderate level of protection that declines over time
- HZ/su has been shown to be highly effective
- HZ/su induced a strong immune response irrespective of prior vaccination
- Attractive option for vaccination and revaccination
- PATIENT EDUCATION!

Am J Infect Dis. 2017;216:1343-1351

Journal Club #3

Recombinant Influenza Vaccine: 1 hour

Audience: Physicians & pharmacists

RECOMBINANT INFLUENZA VACCINE

OBJECTIVES

- Describe the different types and subtypes of influenza
- List the different types of influenza vaccines available
- Compare recombinant influenza vaccine (RIV4) with inactivated influenza vaccine (IIV4)
- Describe CDC/ACIP 2017-2018 recommendations for influenza vaccination
- Discuss how *Efficacy of recombinant influenza vaccine in adults 50 years of age and older* can impact clinical practice

PATIENT CASE

AB - 59 year old female, current smoker

- Past Medical History (PMH)
  - Obesity
  - GERD
  - Hyperlipidemia
  - Hypertension
  - Irritable Bowl Syndrome (IBS)
- Medications
  - Aspirin 81mg 1 PO Daily
  - Atorvastatin 10mg 1 PO Daily
  - HCTZ 25mg 1 PO Daily
  - Lisinopril 10mg 1 PO Daily
  - Ranitidine 150mg 1 PO Daily

Allergies: NKDA
Vaccination History: Tdap (2015), MMR & Meningitis (up to date)

What vaccines is this patient eligible for?!

IMMUNIZATIONS CAN BE FUN!

AB'S IMMUNIZATIONS

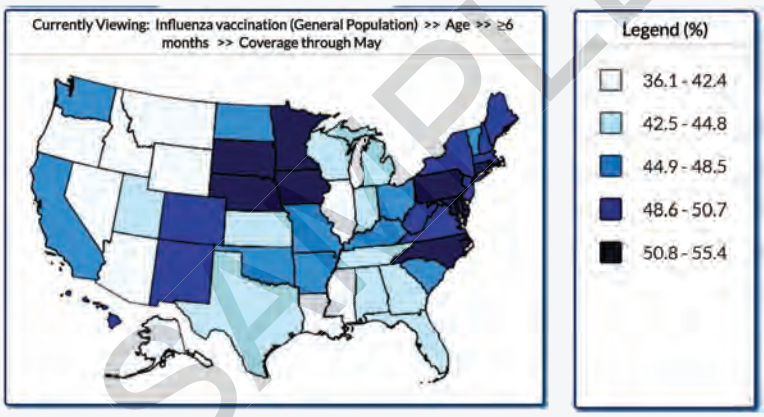
- Influenza
- Pneumovax (PPSV23)
- Prevnar 13 (PCV13)
- Tetanus/Diptheria/ Pertussis (Td/Tdap)
- Measles/Mumps/Rubella (MMR)
- Varicella (VAR)
- Human Papillomavirus (HPV)
- Hepatitis A/B (Hep A/Hep B)
- Meningococcal (MenACWY or MPSV4)
- *Haemophilus influenzae* type b (Hib)
- Herpes Zoster (HZV)

INFLUENZA (FLU)

- Global epidemic that infects millions of people and causes serious illness and death worldwide
- Results in hospitalization rate of 35.5 per 100,000 people
- Vaccination remains the primary and most effective strategy for prevention and control

Biomed Res Int. 2015;2015:1-11

2016-2017 VACCINATION RATES



Average 46.8%

CDC. 2016-2017

INFLUENZA (FLU)

- 3 Types of Influenza Viruses
  - A, B, C
- Influenza A
  - Hemagglutinin (HA)
  - Neuraminidase (NA)
- Influenza B
  - Yamagata
  - Victoria
- Due to high mutation rate of the influenza virus, vaccine manufacturers must reformulate every year

Biomed Res Int. 2015;2015:1-11

INFLUENZA VACCINES

- Inactivated Influenza Vaccine (IIV)
  - Egg-based production (one vaccine dose/one-two eggs)
  - 6 months
- Recombinant Influenza Vaccine (RIV)
  - Cell-based production
  - Egg Free!
  - 6-8 weeks

Biomed Res Int. 2015;2015:1-11

TIME IS FLU!

- Vaccine production huge challenge
- On average 6 months to develop and supply vaccines for the start of flu season
- With egg-based production method this is possible, but what happens if something goes wrong?!
  - 2014-2015 Flu Season
    - Influenza A subtype H3N2 viruses were antigenically mismatched
      - Resulted in vaccine effectiveness of 27-36%

CDC. 2015

2017-2018 ACIP RECOMMENDATIONS

- ≥ 6 months of age
  - Emphasis on high-risk groups, contacts, and caregivers
- Inactivated Influenza Vaccine (IIV)
  - Quadrivalent (IIV4) – Afluria, Fluarix, Fluzone
  - Trivalent (IIV3) – Afluria, Fluvirin
- Recombinant Influenza Vaccine (RIV)
  - Quadrivalent (RIV4) – Flublok
  - Trivalent (RIV3) – Flublok
- Live Attenuated Influenza Vaccine (LAIV)
  - Flumist—Not recommended

CDC. 2015

WHO IS CONSIDERED HIGH-RISK?

- Children 5-59 months
- Adults aged ≥50 years
- Chronic pulmonary, cardiovascular, renal, hepatic, neurologic, hematologic or metabolic disorders
- Immunocompromised
- Pregnant
- American Indians/Alaska Natives
- BMI ≥40 years
- Caregivers and contacts of those at risk

CDC. 2015

PATIENT CASE

AB, 59 year old female, current smoker

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  - Obesity
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  - Hypertension
  - Irritable Bowl Syndrome (IBS)
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  - Ranitidine 150mg 1 PO Daily

Allergies: NKDA
Vaccination History: Tdap (2015), MMR & Meningitis (up to date)

Is our patient high-risk?

PICO QUESTION

- In older adults, is one influenza vaccine more efficacious than another at decreasing incidence of the flu?

SEARCH STRATEGY

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older

Lisa M. Dunkle, M.D., Ruvim Izikson, M.D., M.P.H., Peter Patriarca, M.D., Karen L. Goldenthal, M.D., Derek Muse, M.D., Janice Callahan, Ph.D., and Manon M.J. Cox, Ph.D., for the PSC12 Study Team*

N ENGL J MED 376;25 NEJM.ORG JUNE 22, 2017

N Engl J Med. 2017;376:2427-2436

PURPOSE

- Compare quadrivalent, recombinant influenza (RIV4) with egg-grown quadrivalent, inactivated influenza vaccine (IIV4) to assess relative vaccine efficacy against reverse-transcriptase polymerase-chain-reaction (RT-PCR) confirmed influenza-like illness

N Engl J Med. 2017;376:2427-2436

SAMPLE

ENDPOINTS

- Primary Endpoint
  - RT-PCR confirmed, protocol-defined, influenza-like illness caused by any influenza virus type or subtype that begins ≥14 days after vaccination
    - Modified intention-to-treat population (mITT)
      - All randomly assigned participants who received trial vaccine and provided follow-up efficacy data ≥14 days
    - Modified per-protocol population (mPP)
      - All participants who received trial vaccine and provided efficacy data ≥ 14 days later with no major protocol deviations
- Secondary Endpoint
  - Culture confirmed protocol-defined influenza-like illness that begins ≥14 days after vaccination
  - Culture confirmed influenza-like illness that begins ≥14 days after vaccination with fever (≥100°F)
  - RT-PCR confirmed influenza-like illness that begins ≥14 days after vaccination caused by any influenza strain with fever (≥100°F)

N Engl J Med. 2017;376:2427-2436

SAMPLE

PROTOCOL-DEFINED INFLUENZA-LIKE-ILLNESS

Respiratory Symptoms:

- Sore throat
- Cough
- Sputum production
- Wheezing
- Difficulty breathing

Systemic Symptoms:

- Fever (>98.9 F°)
- Chills
- Fatigue
- Headache
- Myalgia

≥1 symptom in each category

N Engl J Med. 2017;376:2427-2436

METHODS

- Study Design
  - Phase 3 – 4, randomized, double-blind, active-controlled trial
  - 40 outpatient centers across United States
  - October 22, 2014 through May 22, 2015
- 9003 patients randomized to receive:
  - Recombinant Influenza Vaccine, Quadrivalent (RIV4)
    - Flublok (180µg) (N= 4474)
  - Inactivated Influenza Vaccine, Quadrivalent (IIV4)
    - Fluarix (60µg) (N= 4489)

N Engl J Med. 2017;376:2427-2436

METHODS

INCLUSION CRITERIA

- ≥50 years of age
- Living independently without clinically significant acute illness (medically stable)

EXCLUSION CRITERIA

- Contraindication to either study vaccine
- Received influenza vaccine within preceding 180 days
- Underlying disease or therapy rendering them immunocompromised

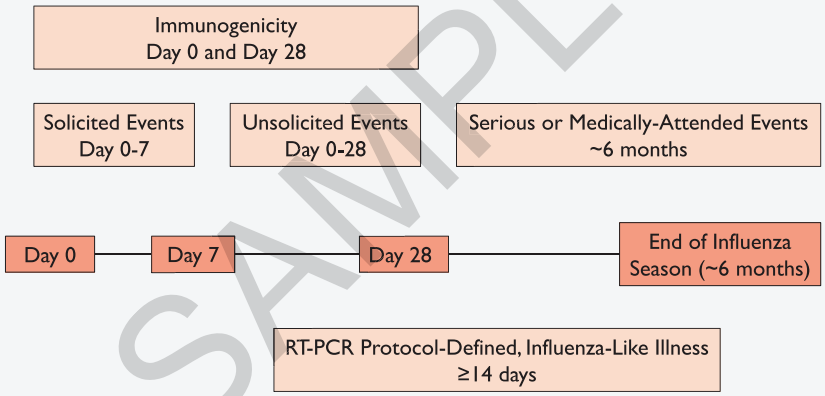
N Engl J Med. 2017;376:2427-2436

METHODS

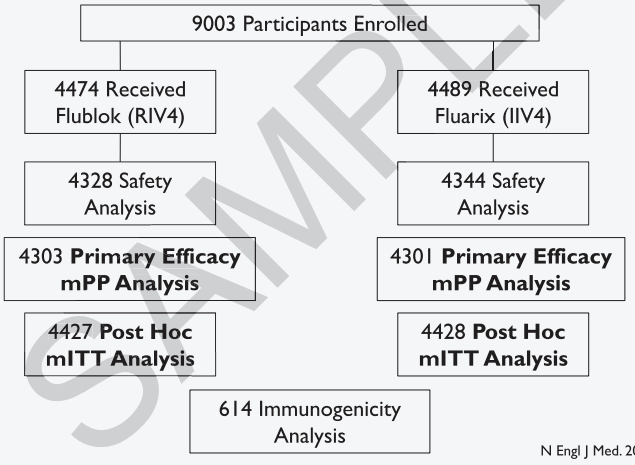
- Efficacy Population
  - All randomized subjects who receive study vaccine and provide follow up for influenza-like illness ≥14 days after vaccination
- Safety Population
  - All randomized and vaccinated subjects who provide any safety data following administration of study vaccine
    - Solicited, unsolicited, serious and medically-attended
- Immunogenicity Population
  - All randomized subjects at pre-selected study sites who receive vaccination and provide serum samples on Day 0 and Day 28

N Engl J Med. 2017;376:2427-2436

METHODS



RANDOMIZATION



N Engl J Med. 2017;376:2427-2436

STATISTICAL ANALYSIS

- Powered at 80% to show noninferiority of relative vaccine efficacy
- Noninferiority concluded if lower bound of 95% confidence interval for relative vaccine efficacy > -20%
- Superiority of Flublok (RIV4) required lower bound of 95% confidence interval for relative vaccine efficacy >9%
- Hazard ratios
  - Cox proportional-hazards model
  - Log-rank test of significance

N Engl J Med. 2017;376:2427-2436

PER-PROTOCOL

INTENTION TO TREAT

PER-PROTOCOL VS INTENTION TO TREAT

- Per-protocol
  - Includes only patients who completed the treatment originally allocated
  - If done alone, leads to bias
- Intention to treat
  - Once randomized, always analyzed!
  - Comparison of the treatment groups that includes all patients as originally allocated after randomization
  - Noninferiority trials—both are recommended

CMAJ.2011;183(6):696

BASELINE CHARACTERISTICS

Characteristic	Flublok (RIV4) (N=4329)	Fluarix (IIV4) (N=4344)
Age	63	63
Male sex	41.5%	41.6%
Race/Ethnic Group	White – 80.1% Black – 17.9%	White – 80.4% Black – 17.3%
Coexisting Conditions		
Atherosclerotic CVD	30.5%	30.3%
Condition w/ Statin	27.6%	27.7%
Depression	18.2%	18.4%

No significant differences between the treatment groups

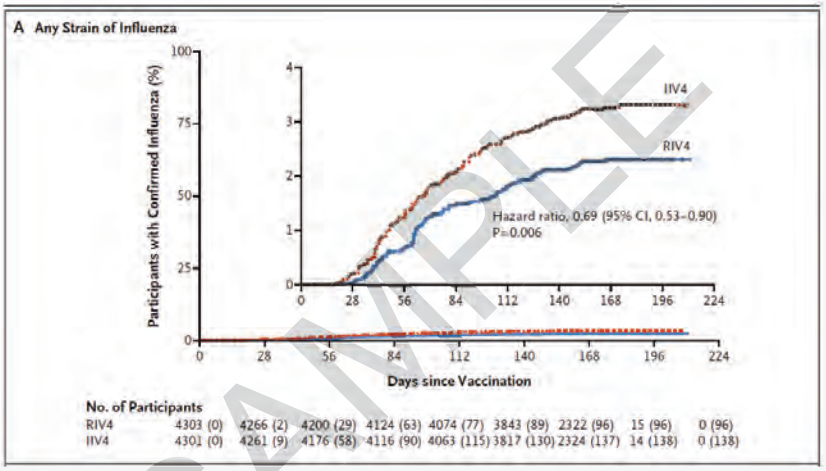
N Engl J Med. 2017;376:2427-2436

RESULTS: PRIMARY EFFICACY ENDPOINT

	Flublok (RIV4) Influenza Attack Rate	Fluarix (IIV4) Influenza Attack Rate	Number Needed to Treat (NNT)
Modified Per-Protocol (mPP)	2.2%	3.2%	100 (Flublok)
Modified Intention-To-Treat (mITT)	2.2%	3.1%	111 (Fluarix)

- Modified Per-Protocol (mPP):
  - Probability of influenza-like illness 30% lower with Flublok (RIV4) than Fluarix (IIV4) (95% CI 10-47; P=0.006)
- Modified Intention-To-Treat (mITT):
  - Yielded same vaccine efficacy of 30%

N Engl J Med. 2017;376:2427-2436



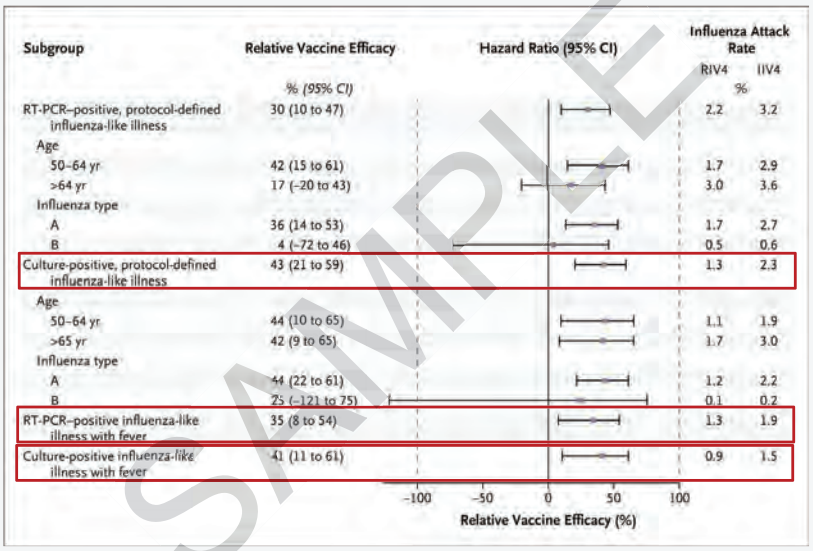
- Primary Endpoint:
  - RT-PCR confirmed, protocol-defined, influenza-like illness caused by any influenza virus type or subtype

N Engl J Med. 2017;376:2427-2436

RESULTS: SECONDARY ENDPOINT

- Culture confirmed protocol-defined influenza-like illness that begins ≥14 days after vaccination
- Culture confirmed influenza-like illness that begins ≥14 days after vaccination with fever (≥100˚F)
- RT-PCR confirmed influenza-like illness that begins ≥14 days after vaccination caused by any influenza strain with fever (≥100˚F)

N Engl J Med. 2017;376:2427-2436



N Engl J Med. 2017;376:2427-2436

RESULTS: SAFETY

- Overall, safety profiles of vaccines were similar
- Solicited—incidence of injection site pain and tenderness slightly higher in Fluarix (IIV4)
- Serious and medically-attended events that occurred were not considered to be related to the vaccines
- Immunogenicity—high antibody responses to A/H3N2 in Flublok (RIV4)

RESULTS: SAFETY

Condition	Flublok (RIV4) (N=4328)	Fluarix (IIV4) (N=4344)
Unsolicited (Day 0-28)		
Cough	5.2% (226)	5.8% (253)
ILI	4.3% (186)	4.6% (199)
Oropharyngeal pain	4.1% (178)	4.1% (177)
Headache	3.3% (143)	3.3% (145)
Upper respiratory tract infection	3% (129)	3.6% (156)
Fatigue	2.4% (106)	2.3% (100)
Myalgia	2.2% (95)	1.8% (79)
Productive Cough	1.4% (59)	2.2% (97)

N Engl J Med. 2017;376:2427-2436

AUTHORS CONCLUSIONS

- Flublok (RIV4) compared with Fluarix (IIV4) improved protection against laboratory-confirmed influenza-like illness in adults 50 years or older

N Engl J Med. 2017;376:2427-2436

DISCUSSION

- Strengths
  - Randomized controlled
  - 80% power was achieved
  - Baseline characteristics were similar among both groups
- Limitations
  - Conducted during a single influenza season
  - Generalizability
  - Cost comparison
  - Industry funded

N Engl J Med. 2017;376:2427-2436

IMPACT ON CURRENT PRACTICE

- RIV4 is an effective vaccine produced using cell-based technology
- Good alternative for patients with egg allergy
- Much quicker manufacturing process than that of egg-based IIV4 (~6-8 weeks)

What Can We Do To Improve Vaccination Rates?

IMPROVING VACCINATION RATES

- **S** – SHARE the reasons why influenza vaccine is right for the patient
- **H** – HIGHLIGHT the positive experiences
- **A** – ADDRESS patient questions
- **R** – REMIND patients that influenza vaccines protect them and their loved ones
- **E** – EXPLAIN the potential costs of getting the flu

CDC. 2017

REFERENCES

1. Milián E, Kamen AA. Current and emerging cell culture manufacturing technologies for influenza vaccines. Biomed Res Int. 2015;2015:504831.
2. Influenza (Flu). Centers for Disease Control and Prevention. https://www.cdc.gov/flu/news/2014-2015-flu-season-wrapup.htm. Published April 28, 2015. Accessed November 4, 2017.
3. Influenza (Flu). Centers for Disease Control and Prevention. https://www.cdc.gov/flu/professionals/acip/2017-18summary.htm. Published September 15, 2017. Accessed November 1, 2017.
4. Dunkle LM, Izikson R, Patriarca P, et al. Efficacy of Recombinant Influenza Vaccine in Adults 50 Years of Age or Older. N Engl J Med. 2017;376(25):2427-2436.
5. Shah PB. Intention-to-treat and per-protocol analysis. CMAJ. 2011;183(6):696.

QUESTIONS?