SANOFI PASTEUR

High-dose influenza vaccine

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Outline

High-dose influenza vaccine (HD)

- **Background**
  - Clinical development & registration milestones
  - Vaccine characteristics
- **Clinical data**
  - Two randomised controlled trials
  - Two large-scaled cohort studies by US CDC, FDA & CMS
- **Cost effectiveness**
- **Summary**

Abbreviations: CDC=Centers for Disease Control & Prevention; FDA=Food & Drug Administration; CMS=Center of Medicare & Medicaid Services;

Product characteristics

- **For 65+**
- **4x (60 mcg) of hemagglutinin in standard dose vaccine**
- **Single 0.5-mL dose; intramuscular**
- **Trivalent formulation**
  - Three strains: Influenza A/H3N2, A/H1N1 & one B lineage
  - Quadrivalent (incl. a second B lineage) under development

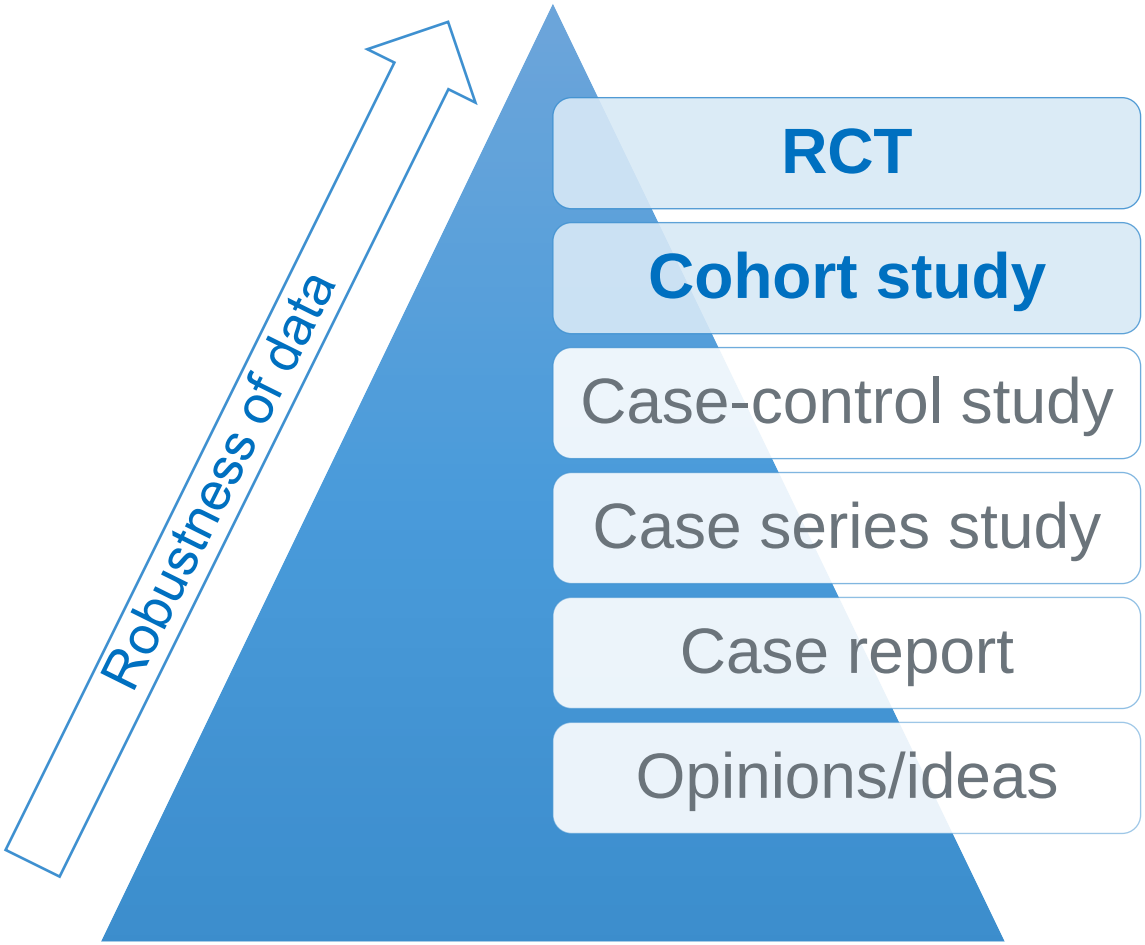
Reference: Fluzone High-Dose vaccine [Prescribing Information]. Swiftwater: Sanofi Pasteur Inc.; 2016.

HD in USA

- **Licensed in 2009 under FDA's Accelerated Approval Process to fill the unmet medical need**
  - Based on pre-licensure data on safety & enhanced immunogenicity compared to standard dose, trivalent influenza vaccine (SD TIV)
- **No safety concern identified from population use for 8 years**
  - ~70 million doses distributed since licensure
- **Extensively studied in USA/Canada**
  - 28 published studies
  - Most studies in 65+; some in younger persons with chronic medical conditions

Abbreviations: QIV=quadrivalent, inactivated influenza vaccine

Level of evidence of clinical studies



Available data on HD

This presentation only reports on evidence of highest levels

- **RCTs**
- **Large cohort studies (>2 million participants)**

Abbreviations: RCT=randomised controlled trial

Reference: Higgins et al. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0; Therapeutic Goods Administration (TGA). Evidence guidelines. 2014

Pivotal study (FIM12)

Post-licensure commitment study in 65+

- **Study endpoints**
  - Lab-confirmed influenza (primary)
  - Serious events possibly related to influenza

  …

- **Double-blinded RCT[1,2]**
  - 31,989 participants from 126 sites in USA & Canada
    - Mean age = 73
    - Two thirds had ≥1 chronic medical condition
  - 2011-12 & 2012-13 seasons*
  - 1:1 ratio for HD & SD TIV

- **Safety surveillance (6-8 months post vaccination)**
  - Serious adverse events (SAEs) leading to death, hospitalisation, and/or disability, regardless of causality

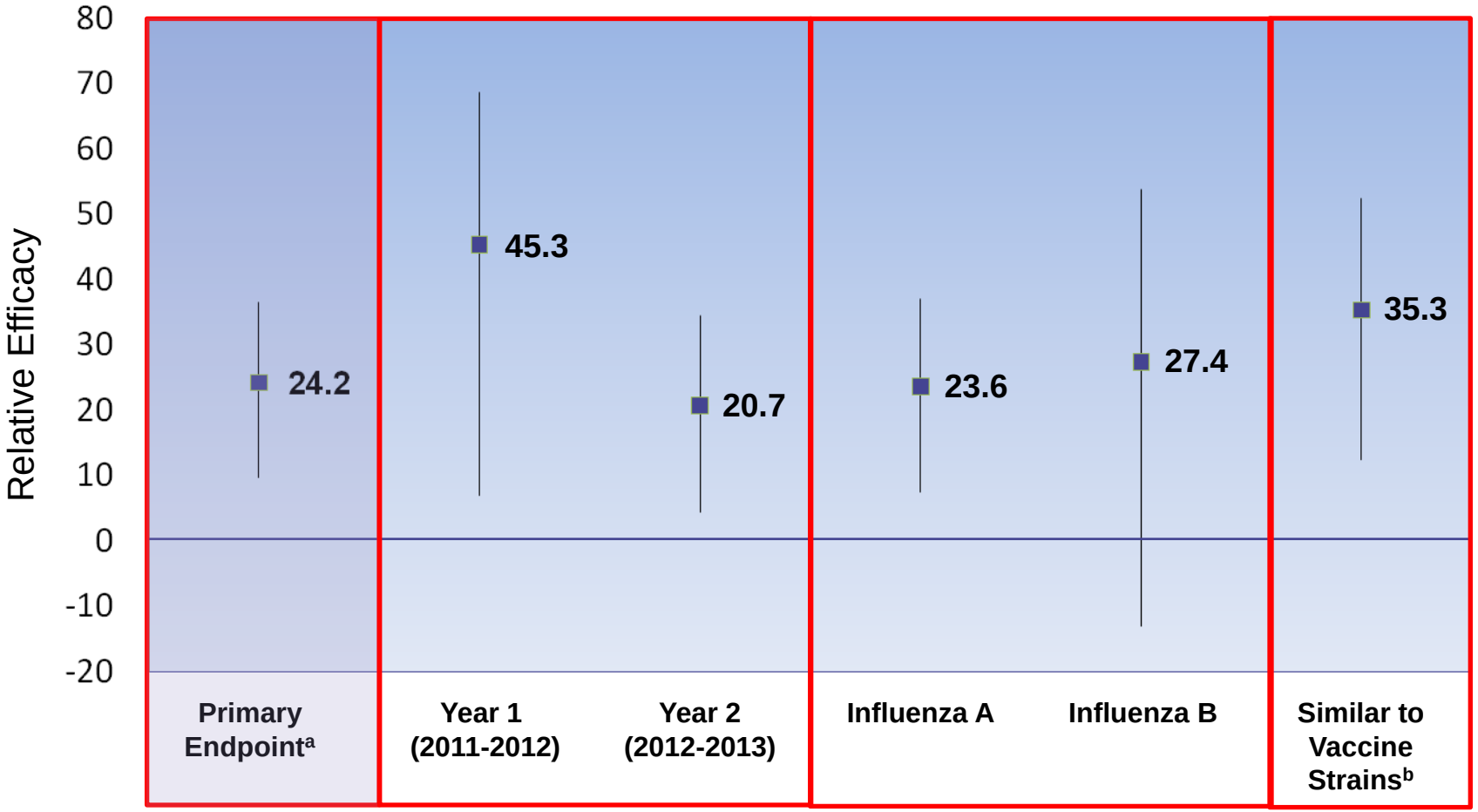
** A/H3N2 predominated in both seasons*

References:

1. DiazGranados et al. N Engl J Med 2014;371:635-45; 2. DiazGranados et al. Vaccine 2015;33:4988-93

Relative efficacy of HD to SD TIV

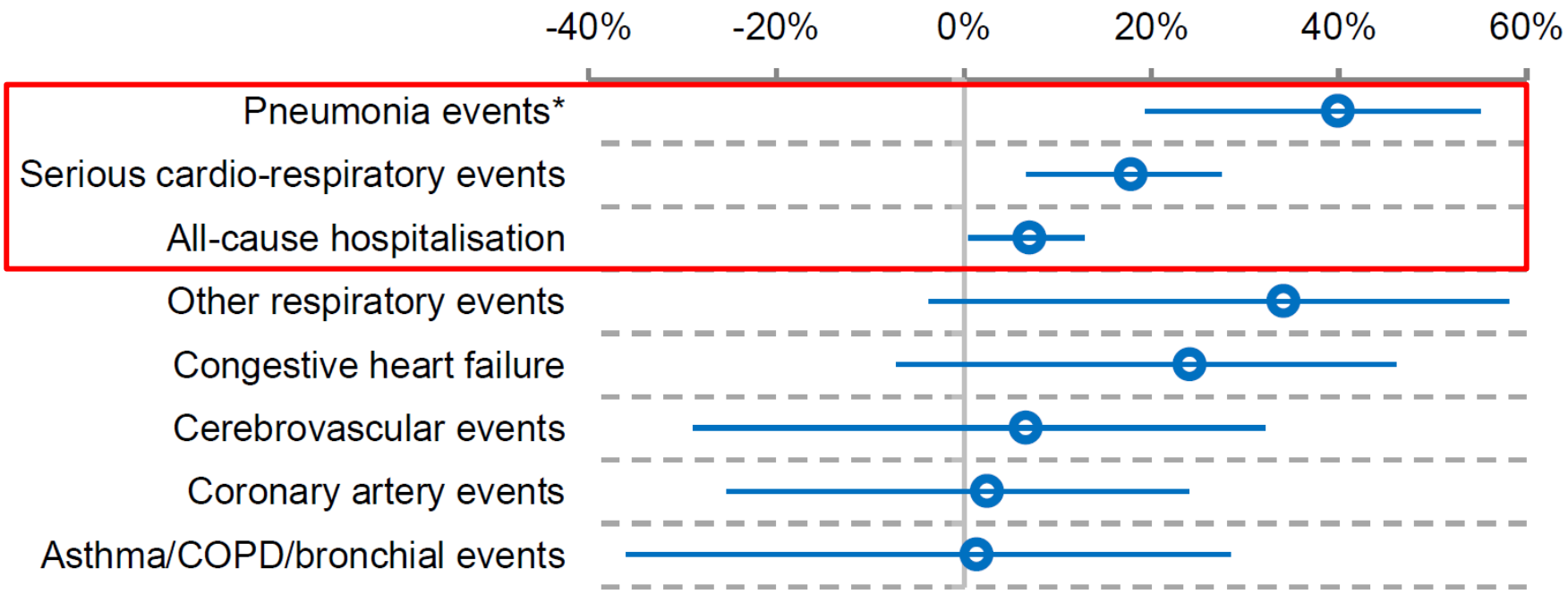
By study years, influenza types, & similarity to vaccine strains



[a] *Laboratory-confirmed influenza caused by any viral type or subtype (regardless of similarity) associated with a protocol-defined influenza-like illness.* [b] *Type A & B combined, similar to the vaccine strains by ferret antisera or genomic sequencing data.*

Relative effectiveness of HD to SD TIV

Secondary endpoint: serious events possibly related to influenza



** The % pneumococcal vaccination was similar in both study groups. Therefore, HD effect on pneumonia was not due to differences of pneumococcal vaccination between groups.*

Fewer SAEs observed in HD group than SD TIV group

Relative risk of SAE: 0.92 (95% CI 0.80-0.99)

	HD Vaccine (N=15,992)		SD TIV (N=15,991)	
(Number of participants)	n	%	n	%
SAE	1323	**8.27**	1442	**9.02**
Related SAE	3[b]	0.02	0	0.00
Adverse Event of Special Interest (AESI)	3[c]	0.02	6[d]	0.04
SAE leading to study discontinuation	99	0.62	103	0.64
Death (any cause)	83	0.52	84	0.53

Two large-scaled cohort studies in USA for 65+

Both were jointly conducted by US CDC, FDA & CMS

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Hector S Izurieta, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee, Thomas MaCurdy, Chris Worrall, Andrew E Howery, Jeffrey Kelman*

Summary

Background A high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria. We sought to establish whether high-dose inactivated influenza vaccine was more effective for prevention of influenza-related visits and hospital admissions in US Medicare beneficiaries than was standard-dose inactivated influenza vaccine.

Lancet Infect Dis 2015; 15: 293–300

Published Online February 9, 2015 http://dx.doi.org/10.1016/

The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries in Preventing Postinfluenza Deaths During 2012–2013 and 2013–2014

David K. Shay,[1] Yoganand Chillarige,[2] Jeffrey Kelman,[3] Richard A. Forshee,[4] Ivo M. Foppa,[1,5] Michael Wernecke,[2] Yun Lu,[4] Jill M. Ferdinands,[1] Arjun Iyengar,[2] Alicia M. Fry,[1] Chris Worrall,[3] and Hector S. Izurieta[4,6]

Two large-scaled cohort studies in USA for 65+

Both were jointly conducted by US CDC, FDA & CMS

	Izurieta et al. 2015	Shay et al. 2017
Study design	Retrospective cohort studies using administrative data (Medicare database in USA)	
Seasons*	2012-13	2012-13 & 2013-14
N of vaccinees (% HD)	2.5 million (37%)	6.1 million (42%)
Age	Mean age: 75-76	50-52% aged ≥65
% ≥1 medical condition	59-60%	62-65%
Endpoints	a. Probable influenza† b. Influenza hospitalisation	Post-influenza death‡

** A/H3N2 predominated 2012-13; A/H1N1 predominated in 2013-14*
† Defined by receipt of a rapid influenza test followed by dispensing of neuraminidase inhibitor oseltamivir
‡ Death within 30 days following an inpatient or emergency department encounter coded as influenza (ICD-9)
References: Izurieta et al. Lancet Infect Dis 2015;15:293-300; Shay et al. J Infect Dis 2017;215:510-7

Relative effectiveness demonstrated (HD vs SD TIV)

Magnitude consistent with FIM12

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Age	Mean age: 75-76	50-52% aged ≥65
% ≥1 medical condition	59-60%	62-65%
Endpoints	**a. Probable influenza† b. Influenza hospitalisation**	**Post-influenza death‡**
Relative effectiveness	**a. 22% (95% CI 15-29%) b. 22% (95% CI 16-27%)**	**24% (95% CI 0.6-42%)**

** A/H3N2 predominated 2012-13; A/H1N1 predominated in 2013-14*
† Defined by receipt of a rapid influenza test followed by dispensing of neuraminidase inhibitor oseltamivir
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Cost saving in USA (similar results for Canada)

Ad-hoc cost-effectiveness analyses using trial data of FIM12

Item/Outcome		HD	SD TIV	Difference
Study Vaccine		$31.8	$12.1	$19.8
Mean per-participant cost in FIM12	Hospitalisation	$1,320.5	$1,456.9	-$136.3
	Direct medical costs	$1,376.7	$1,492.6	**-$115.9**
	Direct & indirect costs	$1,506.5	$1,634.5	**-$128.0**

HD is a less costly & more effective alternative to SD TIV in USA, driven by a reduction in the number of hospital admissions

Reference: Chit et al. Lancet Infect Dis 2015; 15: 1459-66

Summary

High-dose influenza vaccine

- **Improved clinical protection demonstrated in robust studies**
  - Point estimates of relative benefits: 22% to 24%
- **Well-established safety profile**
- **Cost effective in US & Canadian settings**