Using Real World Evidence (RWE) to study vaccine effectiveness

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Sources:
Presentations by Jeff Roberts (OVRR/CBER/FDA), Hector S. Izurieta (OVRR/CBER/FDA), and Richard Forshee (OBE/CBER/FDA) at FDA's-sponsored Virtual Workshop: "Use of Real World Evidence to Support Effectiveness of Preventive Vaccines", Sept 17-18, 2020

Disclaimer

No conflicts of interest

The findings and conclusions in this presentation are those of the author and are not meant to represent the official positions of FDA or any other organization.

Real World Evidence (RWE) - background

21st Century Cures Act directs FDA to:

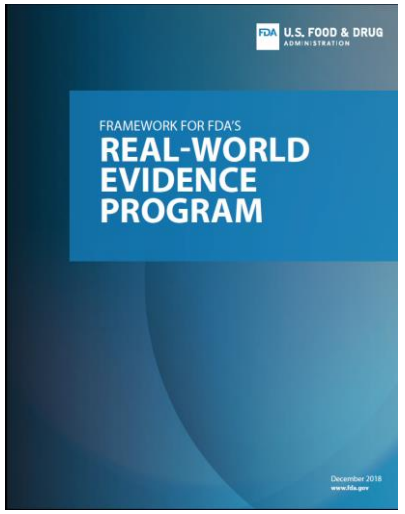
- evaluate the potential use of **RWE** for the following:
  - a) support approval of a new indication for a licensed drug or biologic
  - b) to support or satisfy post-approval study requirements

Real-World Evidence (**RWE)** is the *clinical* evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Real-World Data (**RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources*.

*Examples of RWD: *electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices.*

FDA's Framework for RWE



Safety

"FDA has a long history of using RWE to monitor and evaluate the safety of drug products after they are approved (postmarket)."

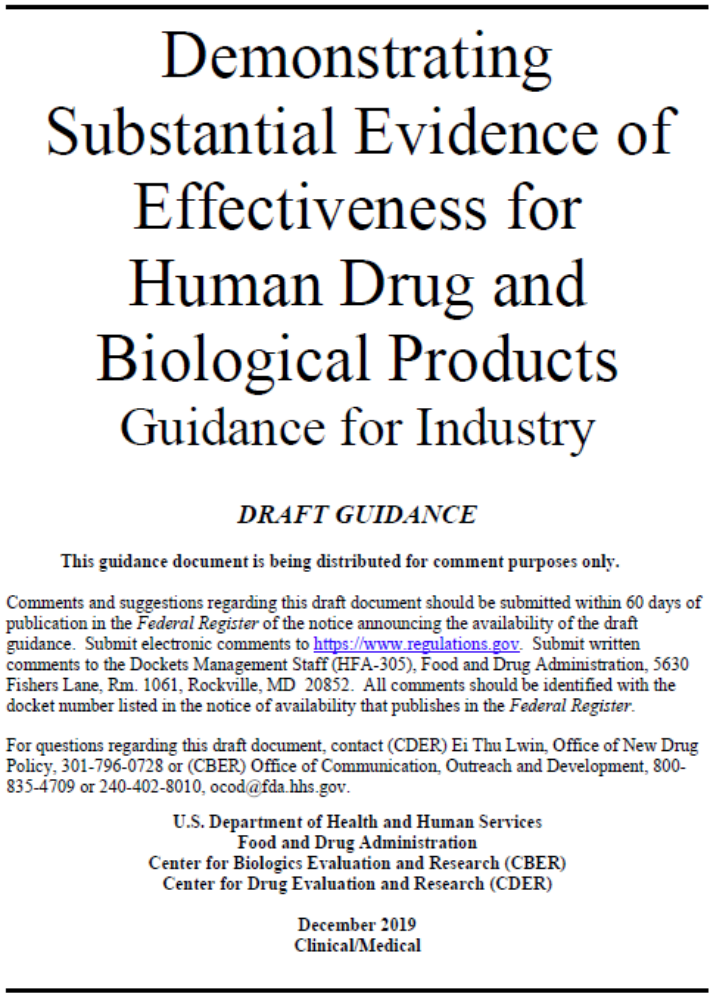
Effectiveness

"However, the use of RWE to support effectiveness determinations is much more limited."

https://www.fda.gov/media/120060/download

Evidentiary criteria for effectiveness

- "**substantial evidence**" – generally interpreted as calling for two adequate and well-controlled trials, each convincing on its own



Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ei Thu Lwin, Office of New Drug Policy, 301-796-0728 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010, ocod@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)

December 2019
Clinical/Medical

Reasons to consider observational RWE studies to support effectiveness of preventive vaccines

- **Emerging infectious diseases** (EID)
  - Traditional randomized controlled trials often difficult due to unpredictable epidemiology or declining rates of disease (e.g., zika virus)
  - EID vaccines may be licensed via Accelerated Approval, which would result in requirements to confirm clinical benefit postlicensure

- Randomized, controlled clinical **studies may be unethical/infeasible**

RWE to support effectiveness of preventive vaccines: critical components

In the context of new **indications**, new **claims of effectiveness**, or post-licensure requirements to **confirm clinical benefit** using RWE, the following are critical:

- **signed and dated study protocols** with pre-specified endpoints (to mitigate "data-mining")
- **description of study procedures** and study conduct, sufficient in detail to enable reproduction of the study findings
- protocol amendments and **information about protocol deviations**
- **statistical analysis plan** developed prior to conducting the analyses
- description of methods to reduce and **evaluate potential bias**
- **full clinical study reports**
- **product-specific data**
- **statistical program codes** used to generate the main analysis

RWE to support effectiveness of preventive vaccines: considerations for regulatory decision-making

Characteristics that increase confidence for regulatory decision-making:

- **size of the treatment effect**, i.e., observed high effectiveness as opposed to marginal effectiveness
- findings on endpoints also evaluated in RCTs, **consistent with the RCT results**; and/or other indicators of external validity
- **replication of findings**, e.g., availability of more than one independent study showing similar results
- **methodological rigor** in the design, conduct, and analysis of the study, including measures to reduce/evaluate potential bias; reliable and robust data sources (e.g., EHR, claims databases) that are **fit for purpose**
- FDA **pre-study agreement** on endpoints and analysis methods
- **registration** of the study, protocol, analysis and results on a publicly available website (to mitigate the effect of publication bias)
- availability of original **'locked' dataset(s)** to enable FDA analyses and verification

When to consult with FDA

- If the study objective is to produce product-specific absolute vaccine effectiveness data for regulatory purposes, and/or the investigators/manufacturer express intention to label the study.
  - Sponsors should meet FDA as early as possible in the planning process
  - FDA will provide feedback on elements that need to be revised/improved to increase the likelihood that the study will meet our standards for labeling.
- If the study has no labeling/licensing implications*:
  - If asked, FDA can still offer scientific/clinical advice to improve the studies (e.g. comparative effectiveness, studies demonstrating an effect like cocooning, herd immunity, ecological studies linking introduction of vaccines with epidemiologic trends, etc.

*This happens if the audience is primarily recommending bodies (e.g., American Academy of Pediatrics (AAP)), health systems deciding how to allocate resources, Health insurance companies, or National Immunization Technical Advisory Groups (NITAG) like the ACIP, etc (in such a case FDA is ultimately agnostic about study design, data sources, endpoints, etc).

Examples

Innovative approaches for using RWE in randomized trials

- **Clinical practice data** in randomized trials
  - Fluzone High Dose (HD) study in Finland*
    - 68,000 subjects individually randomized to Fluzone HD or standard dose influenza vaccine
    - all outcomes derived from electronic health records (EHR) in Finnish health care system

- RWD in **Decentralized Clinical Trials** (DCT)
  - Janssen case study: DCT design opportunities in COVID vaccine development

Reference: *ClinicalTrials.gov database #: NCT04137887

Observational approaches – study examples

- Zostavax long term effectiveness
  - BLA supplement approved in 2018 – study described in Section 14 of the package insert

- Fluzone High Dose relative effectiveness in the VA system*
  - Highlights one example of innovative approaches to controlling for bias and confounding in observational studies

References: *Young-Xu Y et al. Vaccine. 2019 Mar 7;37(11):1484-1490. doi: 10.1016/j.vaccine.2019.01.063. Epub 2019 Feb 8. PMID: 30745146

Our initial (2012-13 season) HD vs SD influenza comparative effectiveness results were published in Lancet Infect Dis, accompanied by a very positive editorial)

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.

Novel observational study designs with new influenza vaccines

In *The Lancet Infectious Diseases*, Hector Izurieta and colleagues[1] presented results of a cohort study in 929 730 older people (65 years and older) who received a high-dose influenza vaccine (high-dose Fluzone, Sanofi Pasteur, PA, USA, 60 µg per strain) and compared rates of influenza-related visits and hospital admissions with 1 615 545 older people who received a standard dose of the same vaccine (15 µg per strain). The high-dose vaccine seemed to be 22% more effective than the standard dose

symptoms of laboratory-confirmed influenza in the Netherlands.[3] Randomised placebo-controlled influenza vaccine trials in older people and other high-risk groups are usually thought to be unethical because many studies supporting the vaccine's benefit have already been done and immunisation is recommended worldwide.

Non-randomised (variations of) case-control or cohort vaccine effectiveness studies are suitable alternatives to randomised controlled trials. Such designs

Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty

Carlos A. DiazGranados[a,*], Andrew J. Dunning[a], Corwin A. Robertson[a], H. Keipp Talbot[b], Victoria Landolfi[a], David P. Greenberg[a,c]

[a] Sanofi Pasteur, 1 Discovery Drive, Swiftwater, PA 18370, United States
[b] Vanderbilt University Medical Center, A2200 MCN 1161 21st Ave S, Nashville, TN 37232, United States
[c] Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, United States

Background: A randomized trial demonstrated that a high-dose inactiv
was 24.2% more efficacious than a standard-dose vaccine (IIV-SD) against
illness in adults ≥65 years. To evaluate the consistency of IIV-HD benefits,
efficacy and immunogenicity by baseline characteristics of special intere
Methods: Double-blind, randomized, active-controlled, multicenter trial.
ized 1:1 to receive IIV-HD or IIV-SD and followed for 6–8 months postv
influenza. One third of participants were randomly selected to provide s
glutination inhibition antibody (HAI) titers. Efficacy (IIV-HD vs. IIV-SD
protocol-defined influenza-like illness (PD-ILI) and HAI geometric mean
SD) were evaluated by age, and number of high-risk comorbid and frailt
Results: Efficacy (95% confidence intervals) of IIV-HD relative to IIV-SD ag
ILI was 19.7% (0.4%; 35.4%) for participants 65–74 years, 32.4% (8.1%; 50.6%) for those ≥75 years, 22.1% (3.9%; 37.0%) for participants with ≥1 high-risk comorbidity, 23.6% (−3.2%; 43.6%) for those with ≥2 high-risk comorbidities, 27.5% (0.4%; 47.4%) for persons with 1 frailty condition, 23.9% (−9.0%; 47.2%) for those with 2 frailty conditions, and 16.0% (−16.3%; 39.4%) for those with ≥3 frailty conditions. There was no evidence of vaccine efficacy heterogeneity within age, comorbidity, and frailty strata (*P*-values 0.351, 0.875, and 0.838, respectively). HAI GMT ratios were significantly higher among IIV-HD recipients for all strains and across all subgroups.
Conclusions: Estimates of relative efficacy consistently favored IIV-HD over IIV-SD. There was no significant evidence that baseline age, comorbidity, or frailty modified the efficacy of IIV-HD relative to IIV-SD. IIV-HD significantly improved HAI responses for all strains and in all subgroups. IIV-HD is likely to provide benefits beyond IIV-SD for adults ≥65 years, irrespective of age and presence of comorbid or frailty conditions.

The Sanofi-sponsored randomized trial confirmed our findings. Referring to the comparison with our study, their paper said:

"These data derived from a randomized, controlled trial greatly reaffirm the results of a recently published large retrospective cohort study that reported similar estimates of vaccine effectiveness.17 "

Vaccine 33 (2015) 4565-4571

The Journal of Infectious Diseases
MAJOR ARTICLE

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]

[1]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Acumen LLC, Burlingame, California; [3]Centers for Medicare and Medicaid Services, Washington, District of Columbia; [4]Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland; [5]Battelle Memorial Institute, Atlanta, Georgia; and [6]Department of Health Sciences, Universidad Rey Juan Carlos, Madrid, Spain

(See the editorial commentary by Monto on pages 500–2.)

Background. Recipients of high-dose vs standard-dose influenza vaccines have fewer influenza illnesses. We evaluated the comparative effectiveness of high-dose vaccine in preventing postinfluenza deaths during 2012–2013 and 2013–2014, when influenza viruses and vaccines were similar.

Methods. We identified Medicare beneficiaries aged ≥65 years who received high-dose or standard-dose vaccines in community-located pharmacies offering both vaccines. The primary outcome was death in the 30 days following an inpatient or emergency department encounter listing an influenza *International of Classification of Diseases, Ninth Revision, Clinical Modification* code. Effectiveness was estimated by using multivariate Poisson regression models; effectiveness was allowed to vary by season.

Results. We studied 1 039 645 recipients of high-dose and 1 683 264 recipients of standard-dose vaccines during 2012–2013, and 1 908 176 high-dose and 1 877 327 standard-dose recipients during 2013–2014. Vaccinees were well-balanced for medical conditions and indicators of frail health. Rates of postinfluenza death were 0.028 and 0.038/10 000 person-weeks in high-dose and standard-dose recipients, respectively. Comparative effectiveness was 24.0% (95% confidence interval [CI], .6%–42%); there was evidence of variation by season ($P = .12$). In 2012–2013, high-dose was 36.4% (95% CI, 9.0%–56%) more effective in reducing mortality; in 2013–2014, it was 2.5% (95% CI, −47% to 35%).

Conclusions. High-dose vaccine was significantly more effective in preventing postinfluenza deaths in 2012–2013, when A(H3N2) circulation was common, but not in 2013–2014.

Keywords. influenza vaccines; influenza, human; comparative effectiveness; death.

Our two-season study (effectiveness against mortality), published in JID, accompanied also by an editorial, used the same methods as the lancet paper, finding results similar to those from a cluster randomized study (Gravenstein et al, Lancet 2017)

The Journal of Infectious Diseases
EDITORIAL

Moving Toward Improved Influenza Vaccines

Arnold S. Monto
Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor

In 1943, a placebo-controlled trial of inactivated influenza vaccine (IIV) produced in fertile eggs was carried out among members of the Army Specialized Training Program at the University of Michigan [1]. The vaccine was approxi-

[4]. This was based on the recognition that complications, including hospitalization and death, were more common in this population who actually had lower infection rates. Over a number of years, a variety of studies suggested that

they can ethically involve individuals of all ages. There has not been a consistent drop-off in VE at age 60 or 65 years; often there are also variations by age in other groups. Factors such as the virus type or subtype involved and prior year vaccina-

THE LANCET
Respiratory Medicine
Available online 20 July 2017
In Press, Corrected Proof

Articles

Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial

Prof Stefan Gravenstein MD[a,b,c,d,h], H Edward Davidson PharmD[a], Monica Taljaard PhD[f,g], Jessica Ogarek MS[c], Pedro Gozalo PhD[b,h], Lisa Han MPH[a], Prof Vincent Mor PhD[b,c,h]

Cited in the CDC ACIP recommendations for influenza vaccination, also used by the Canadian advisory committee for recommendation for individual level preference for HD vaccination

First RWE study to: (a) investigate RVE of cell-cultured vs. egg-based vaccines, and (b) compare the RVE of all main vaccines in a season: Positive CDC editorial

The Journal of Infectious Diseases

MAJOR ARTICLE

Relative Effectiveness of Cell-Cultured and Egg-Based Influenza Vaccines Among Elderly Persons in the United States, 2017–2018

Hector S. Izurieta,[1,4] Yoganand Chillarige,[2] Jeffrey Kelman,[3] Yuqin Wei,[2] Yun Lu,[1] Wenjie Xu,[2] Michael Lu,[2] Douglas Pratt,[1] Steve Chu,[3] Michael Wernecke,[2] Thomas MacCurdy,[2] and Richard Forshee[1]

[1]Center for Biologics Evaluation and Research Washington DC; [4]Department of Epidemiolog

Background. The low infl
be due to vaccine virus adaptat
Medicare beneficiaries.

Results presented at the June 2018 ACIP meeting.. Preliminary results presented in a congressional inquiry by FDA Commissioner, March , 2018

The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Comparing Influenza Vaccine Types: The Path Toward Improved Influenza Vaccine Strategies

Brendan Flannery and Alicia M. Fry

Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia

The 2017–2018 influenza season was a reminder that seasonal influenza can be associated with a large burden of severe disease and that adults aged ≥65 years are disproportionately affected; 660 000

A(H3N2)-predominant seasons, such as 2017–2018.

In this issue of *the Journal of Infectious Diseases*, Izurieta et al used data from Medicare beneficiaries aged ≥65 years

higher relative effectiveness of hig
as compared to standard-dose egg
vaccines, although results from ob
tional studies vary. An MF59-adju
egg-based vaccine is also licensed

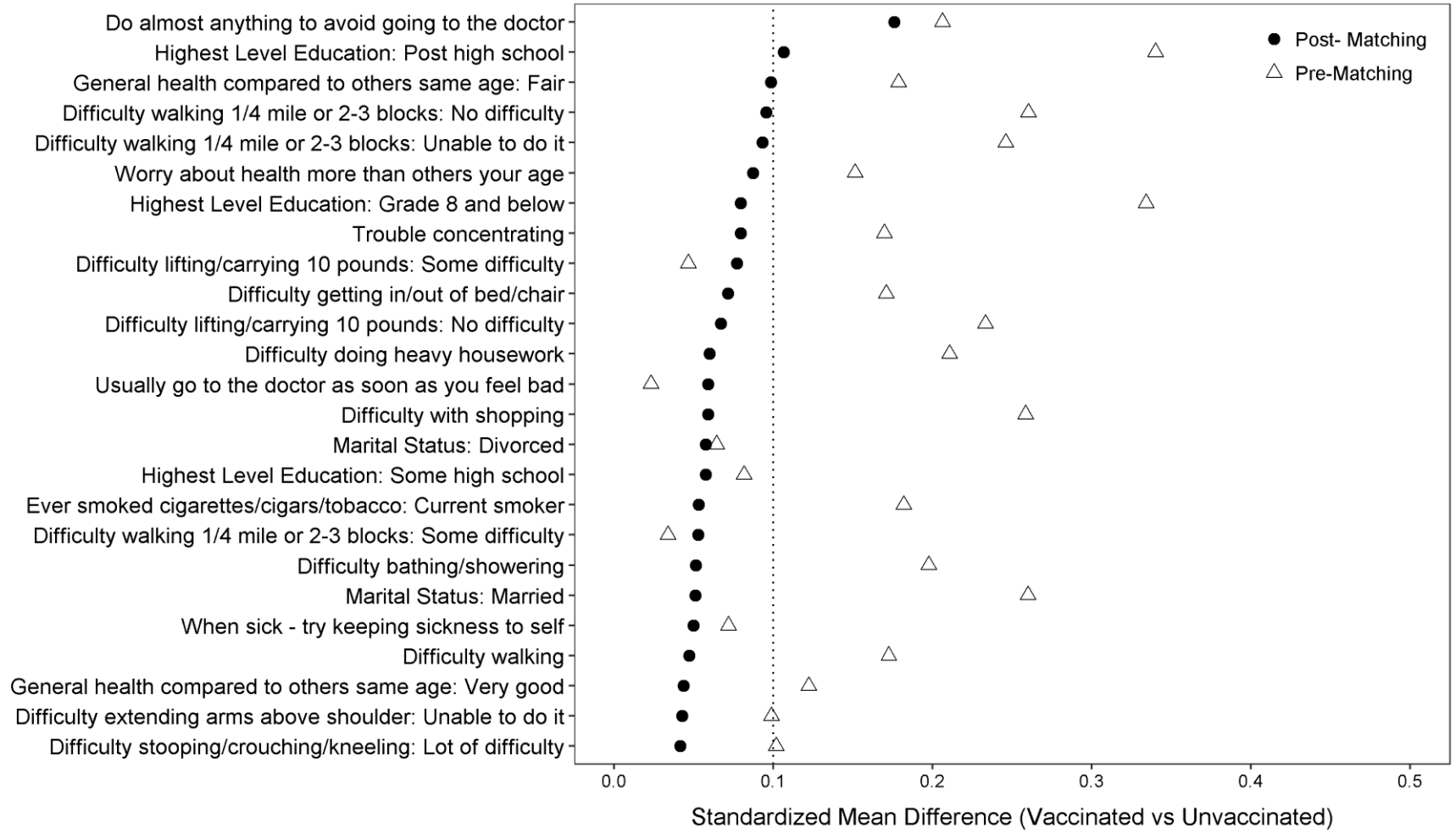
Other ongoing efforts

- Linking survey data to assess cohort balance
- Selecting falsification outcomes/negative endpoints suggestive of differences in heath seeking behavior
- Double negative controls
- Exploring use of natural experiment/instrumental variables
- Difference in difference approaches
- Quantitative bias analysis

Using the Medicare Current Beneficiary Survey (MCBS) to assess cohort balance

- Since 1991, CMS annually conducts MCBS
  - Continuous, multipurpose longitudinal survey of representative sample of Medicare population (about 15,000 Medicare beneficiaries)
- Survey provides comprehensive data on access to and satisfaction with health care services, daily living activities, medical conditions, health care expenditures, health insurance, and other health-related topics
- Linkable to Medicare data at beneficiary level

Medicare Current Beneficiary Survey (MCBS) to assess cohort balance

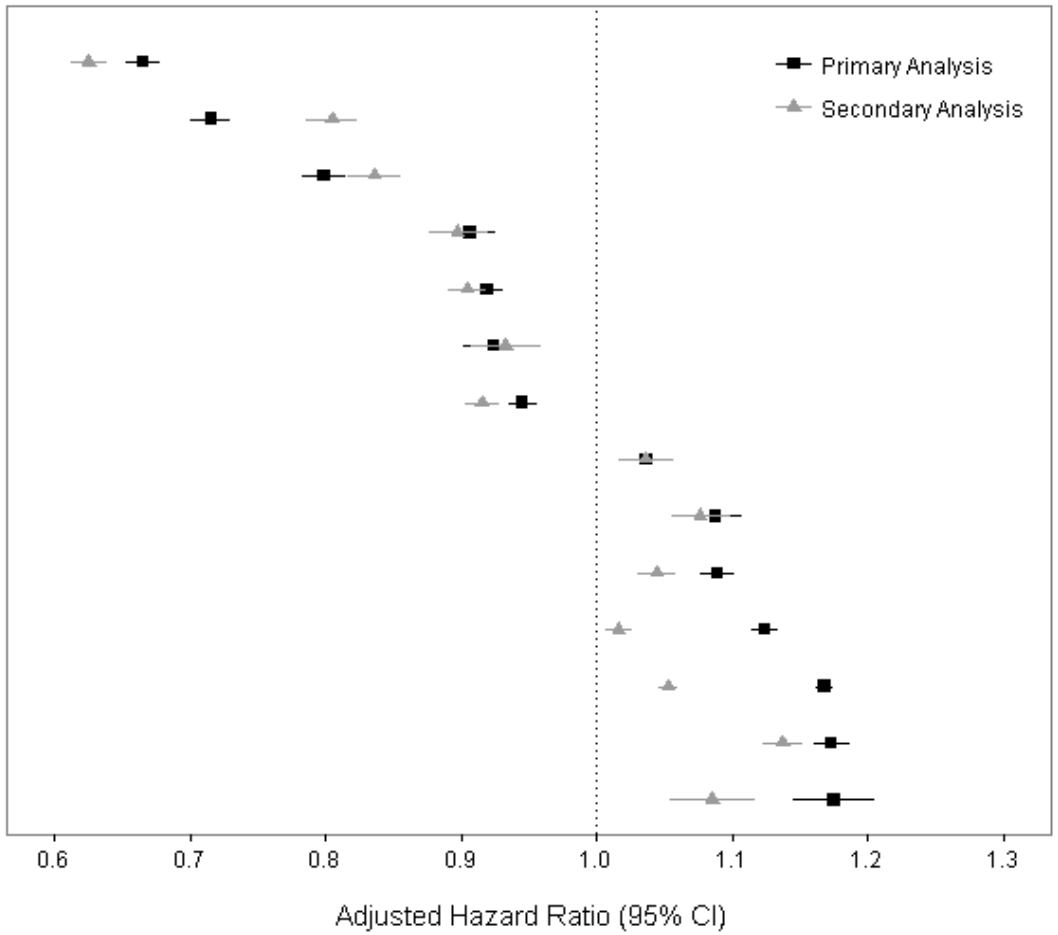


References: Izurieta et al, CID 2017; Izurieta et al, Pharmacoepidemiol Drug Saf. 2019

Using falsification outcomes to assess unmeasured confounding

Comparison of Adjusted Hazard Ratios of 13 Falsification Outcomes in Matched Populations

Outcome	Primary	Secondary
Outpatient Herpes Zoster*	0.67	0.63
Hip fracture	0.72	0.80
Thrombosis	0.80	0.84
Cholelithiasis and cholecystitis	0.91	0.90
Renal stone	0.92	0.90
Wrist fracture	0.92	0.93
Gout	0.95	0.92
Epistaxis	1.04	1.04
Wound of hand or finger	1.09	1.08
Ingrown nail	1.09	1.04
Hemorrhoids	1.12	1.02
Cataract	1.17	1.05
Eyelid disorder	1.17	1.14
Lipomas	1.17	1.09



Primary Analysis: This is the comparison between herpes zoster vaccinated and unvaccinated beneficiaries. Unvaccinated beneficiaries are the reference group.
Secondary Analysis: This is the comparison between herpes zoster vaccinees and pneumococcal vaccinees. Pneumococcal vaccinees are the reference group.

Reference: Izurieta et al, Pharmacoepidemiol Drug Saf. 2019

Assessing unmeasured confounding: Health-seeking behavior

Distribution of Health-Seeking Behavior Indicators across Five Cohorts after implementing IPTW

Covariate	Cohort					Pre-IPTW Max SMD	Post-IPTW Max SMD
	Product 1	Product 2	Product 3	Product 4	Product 5		
Health-Seeking Behavior Indicators							
Cataracts	8.8%	8.8%	8.9%	8.7%	8.8%	0.04	0.01
Eyelid Disorders	0.8%	0.8%	0.8%	0.8%	0.8%	0.02	0.01
Hemorrhoids	0.4%	0.4%	0.4%	0.4%	0.4%	0.01	0.00
Ingrown Nail	1.1%	1.1%	1.1%	1.1%	1.0%	0.03	0.01
Lipomas	0.2%	0.2%	0.2%	0.2%	0.2%	0.01	0.00
UTI	4.4%	4.4%	4.4%	4.5%	4.5%	0.04	0.01
Wound of Hand or Finger	0.3%	0.2%	0.3%	0.3%	0.2%	0.00	0.00

Abbreviations:

IPTW, inverse probability of treatment weighted; SMD, Standardized mean differences; UTI, urinary tract infection

Source: Izurieta et al, submitted manuscript

Cautionary notes about the role of observational approaches vs randomization

Weighing the Benefits and Risks of Proliferating Observational Treatment Assessments

Observational Cacophony, Randomized Harmony

Robert M. Califf, MD[1]; Adrian F. Hernandez, MD, MHS[2,3]; Martin Landray, MBChB[4]

» Author Affiliations | Article Information

JAMA. 2020;324(7):625-626. doi:10.1001/jama.2020.13319

"The growth of structured registries and electronic health record data have greatly expedited sophisticated comparisons of therapies provided in clinical practice settings (i.e., observational "real-world" evidence)."

The size/power of the datasets and the sometimes compelling results is…"t*urning the conclusion of "evidence from RCTs is needed" into a movement of "RCTs should cease."*

medRxiv

THE PREPRINT SERVER FOR HEALTH SCIENCES

Comments (15)

Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial.

Peter Horby, Marion Mafham, Louise Linsell, Jennifer L Bell, Natalie Staplin, Jonathan R Emberson, Martin Wiselka, Andrew Ustianowski, Einas Elmahi, Benjamin Prudon, Anthony Whitehouse, Timothy Felton, John Williams, Jakki Faccenda, Jonathan Underwood, J Kenneth Baillie, Lucy Chappell, Saul N Faust, Thomas Jaki, Katie Jeffery, Wei Shen Lim, Alan Montgomery, Kathryn Rowan, Joel Tarning, James A Watson, Nicholas J White, Edmund Juszczak, Richard Haynes, Martin J Landray

doi: https://doi.org/10.1101/2020.07.15.20151852

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

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- Richard Forshee, Acting Deputy Director, OBE/CBER/FDA