Logistic regression-based approach to assess heterogeneity in vaccine efficacy using immunogenicity measurements in phase 3 clinical trials

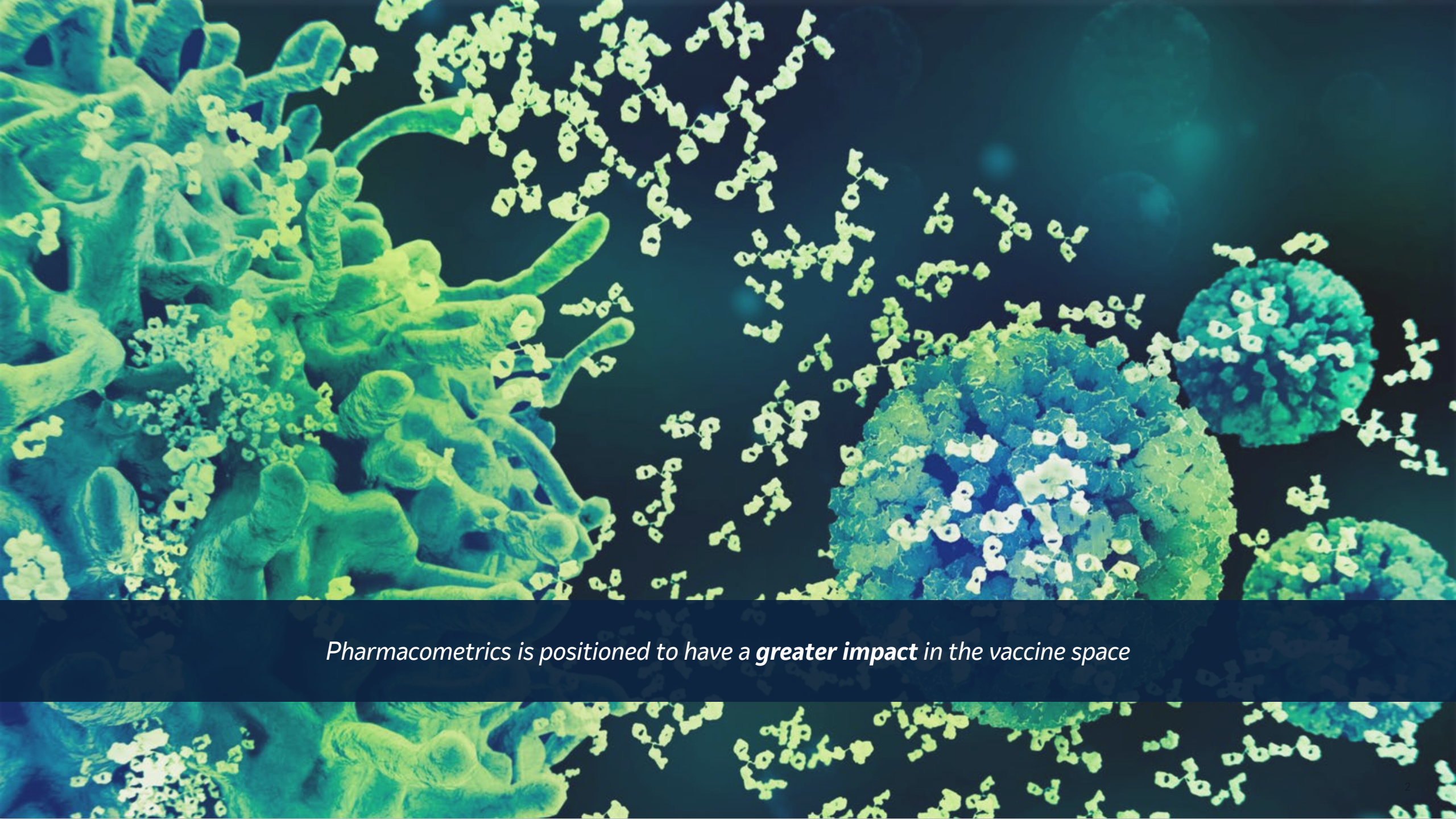
Julie Dudášová[1,2], Zdeněk Valenta[3], Andreea Măgălie[4], Jeffrey R. Sachs[4]

[1] Quantitative Pharmacology and Pharmacometrics, MSD Czech Republic, Prague, Czech Republic
[2] First Faculty of Medicine, Charles University, Prague, Czech Republic
[3] Statistical Modelling, Institute of Computer Science of the Czech Academy of Sciences, Prague, Czech Republic
[4] Quantitative Pharmacology and Pharmacometrics, Merck & Co., Inc., Rahway, NJ, USA

The Lewis Sheiner Student Session

PAGE 2024, Rome, Italy

June 27, 2024



*Pharmacometrics is positioned to have a **greater impact** in the vaccine space*

Outline

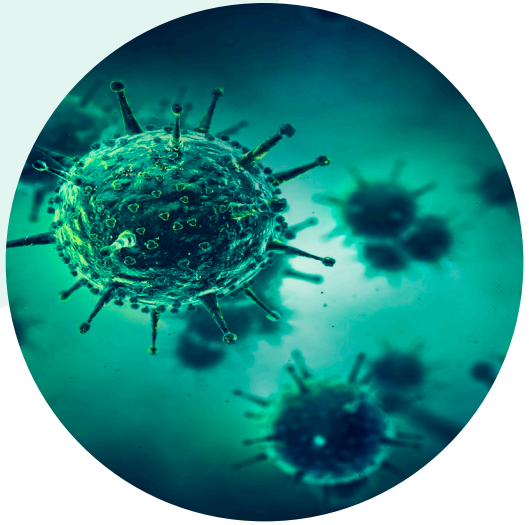
Motivation: Heterogeneity in vaccine efficacy, trial size & time

Background: Predictive biomarkers in vaccine development

Methods, Real vaccine example, Simulations:
Framework for immunogenicity-based estimation of efficacy in subgroups

Conclusions: Impact in vaccine development and future work

Are some demographic groups less protected than others?



Assessing covariate effects on vaccine efficacy (VE) in phase 3 is challenging

Phase 3 trials are typically designed for overall VE assessment

Covariate effects on VE are often evaluated in effectiveness studies

Assessing covariate effects on vaccine efficacy (VE) in phase 3 is challenging

Phase 3 trials are typically designed for overall VE assessment

Phase 3 randomized clinical trial of Vaxzevria for COVID-19 prevention (**~30 thousand** participants) did not reveal significant age effect on efficacy

Efficacy End Point	AZD1222	Placebo	Vaccine Efficacy
	no. of events/total no. (%)		*% (95% or 97.5% CI)*
Primary: symptomatic Covid-19			
Overall	73/17,662 (0.4)	130/8550 (1.5)	74.0 (65.3 to 80.5)
Age			
≥18 to 64 yr	68/13,966 (0.5)	116/6738 (1.7)	72.8 (63.4 to 79.9)
≥65 yr	5/3696 (0.1)	14/1812 (0.8)	83.5 (54.2 to 94.1)

Covariate effects on VE are often evaluated in effectiveness studies

Falsey AR et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. *The New England Journal of Medicine* **385**, 2348-2360 (2021).

Assessing covariate effects on vaccine efficacy (VE) in phase 3 is challenging

Phase 3 trials are typically designed for overall VE assessment

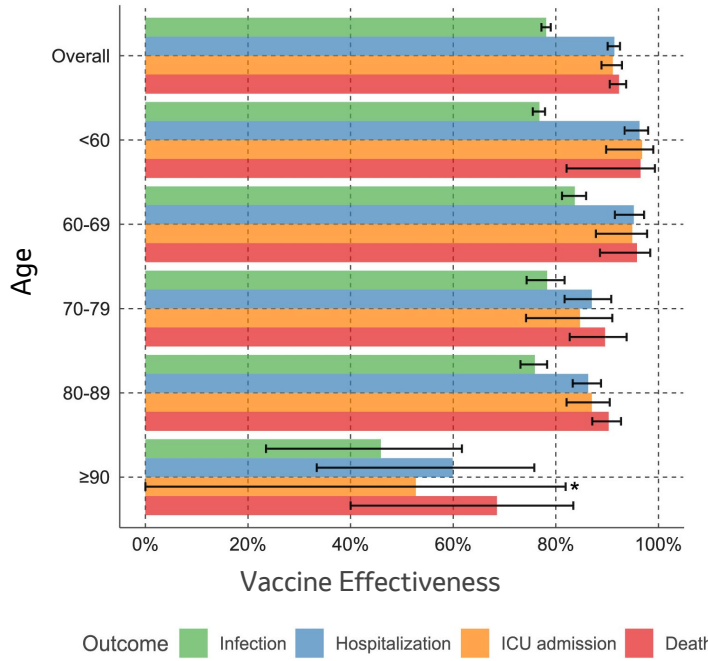
Phase 3 randomized clinical trial of Vaxzevria for COVID-19 prevention (**~30 thousand** participants) did not reveal significant age effect on efficacy

Efficacy End Point	AZD1222	Placebo	Vaccine Efficacy
	no. of events/total no. (%)		*% (95% or 97.5% CI)*
Primary: symptomatic Covid-19			
Overall	73/17,662 (0.4)	130/8550 (1.5)	74.0 (65.3 to 80.5)
Age			
≥18 to 64 yr	68/13,966 (0.5)	116/6738 (1.7)	72.8 (63.4 to 79.9)
≥65 yr	5/3696 (0.1)	14/1812 (0.8)	83.5 (54.2 to 94.1)

Falsey AR et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. *The New England Journal of Medicine* **385**, 2348-2360 (2021).

Covariate effects on VE are often evaluated in effectiveness studies

Retrospective study of **>75 million** Brazilian vaccinees showed significant age effect on effectiveness of Vaxzevria



Cerqueira-Silva T et al. Influence of age on the effectiveness and duration of protection of Vaxzevria and CoronaVac vaccines: A population-based study. *The Lancet Regional Health – Americas* **6**, 1001544 (2022).

Assessing covariate effects on vaccine efficacy (VE) in phase 3 is challenging

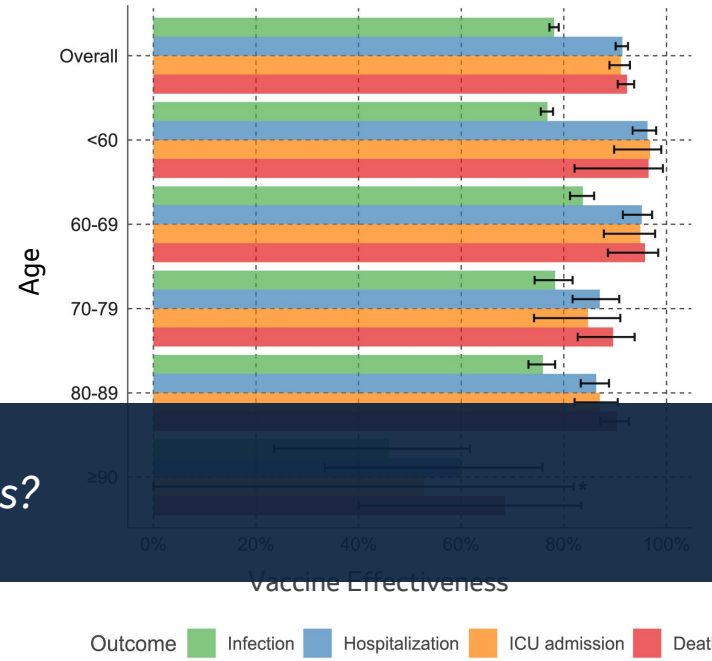
Phase 3 trials are typically designed for overall VE assessment

Phase 3 randomized clinical trial of Vaxzevria for COVID-19 prevention (**~30 thousand** participants) did not reveal significant age effect on efficacy

Efficacy End Point	AZD1222	Placebo	Vaccine Efficacy
	no. of events/total no. (%)		*% (95% or 97.5% CI)*
Primary: symptomatic Covid-19			
Overall	73/17,662 (0.4)	130/8550 (1.5)	74.0 (65.3 to 80.5)
Age			
≥18 to 64 yr	68/13,966 (0.5)	116/6738 (1.7)	72.8 (63.4 to 79.9)
≥65 yr	5/3696 (0.1)	14/1812 (0.8)	83.5 (54.2 to 94.1)

Covariate effects on VE are often evaluated in effectiveness studies

Retrospective study of **>75 million** Brazilian vaccinees showed significant age effect on effectiveness of Vaxzevria



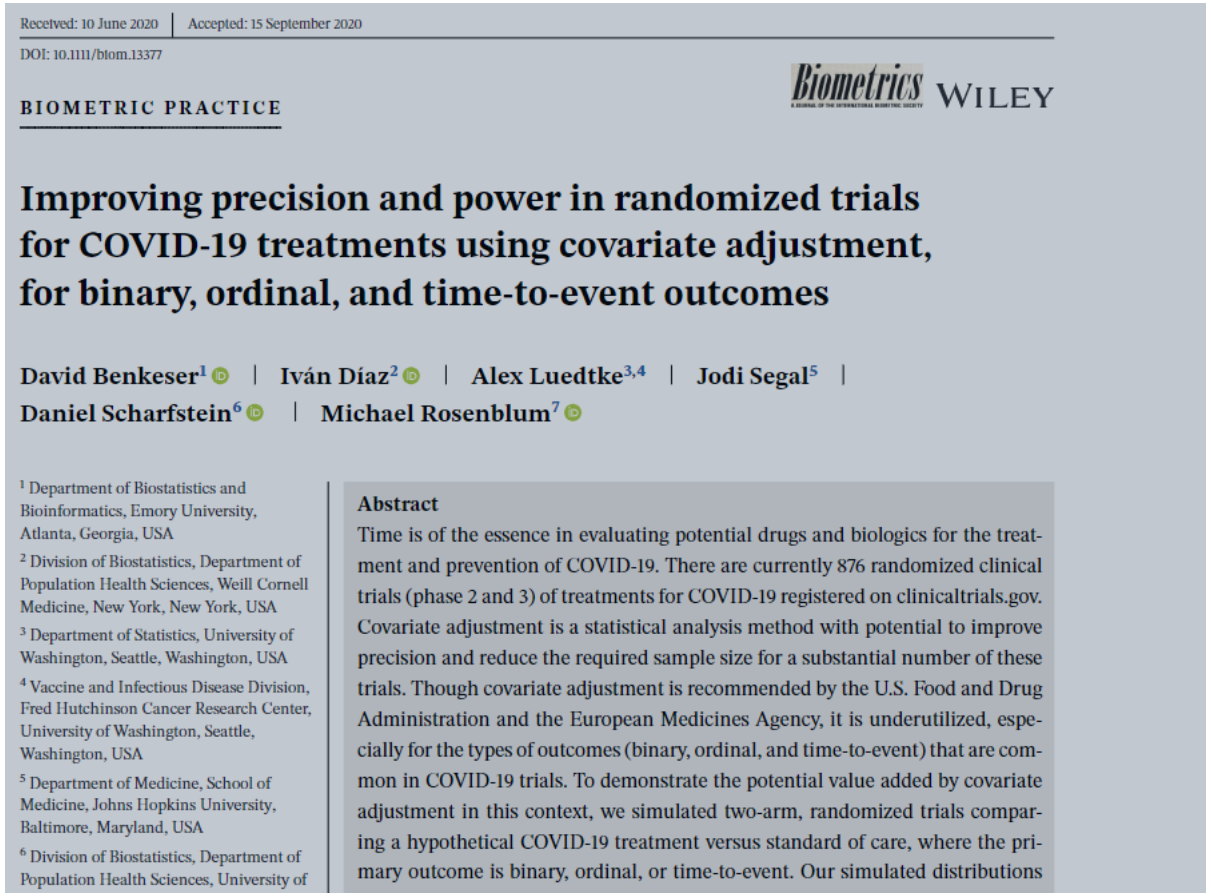
Could we have anticipated this?

Falsey AR et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. *The New England Journal of Medicine* **385**, 2348-2360 (2021).

Cerqueira-Silva T et al. Influence of age on the effectiveness and duration of protection of Vaxzevria and CoronaVac vaccines: A population-based study. *The Lancet Regional Health – Americas* **6**, 1001544 (2022).

Precision of efficacy can be increased by using additional information

2020: Benkeser et al.'s article "Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes"



Received: 10 June 2020 | Accepted: 15 September 2020
DOI: 10.1111/biom.13377

Biometrics WILEY

BIOMETRIC PRACTICE

Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes

David Benkeser[1] | Iván Díaz[2] | Alex Luedtke[3,4] | Jodi Segal[5] | Daniel Scharfstein[6] | Michael Rosenblum[7]

[1] Department of Biostatistics and Bioinformatics, Emory University, Atlanta, Georgia, USA
[2] Division of Biostatistics, Department of Population Health Sciences, Weill Cornell Medicine, New York, New York, USA
[3] Department of Statistics, University of Washington, Seattle, Washington, USA
[4] Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington, USA
[5] Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA
[6] Division of Biostatistics, Department of Population Health Sciences, University of

Abstract

Time is of the essence in evaluating potential drugs and biologics for the treatment and prevention of COVID-19. There are currently 876 randomized clinical trials (phase 2 and 3) of treatments for COVID-19 registered on clinicaltrials.gov. Covariate adjustment is a statistical analysis method with potential to improve precision and reduce the required sample size for a substantial number of these trials. Though covariate adjustment is recommended by the U.S. Food and Drug Administration and the European Medicines Agency, it is underutilized, especially for the types of outcomes (binary, ordinal, and time-to-event) that are common in COVID-19 trials. To demonstrate the potential value added by covariate adjustment in this context, we simulated two-arm, randomized trials comparing a hypothetical COVID-19 treatment versus standard of care, where the primary outcome is binary, ordinal, or time-to-event. Our simulated distributions

Benkeser D et al. Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes. *Biometrics* **77**, 1139-1508 (2021).

2023: FDA Guidance "Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products"

FDA U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot

Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products
Final Guidance

What is recommended in the guidance?

A final guidance has been issued providing recommendations on adjusting for covariates in randomized clinical trials to improve statistical power and the precision of treatment effect estimates.

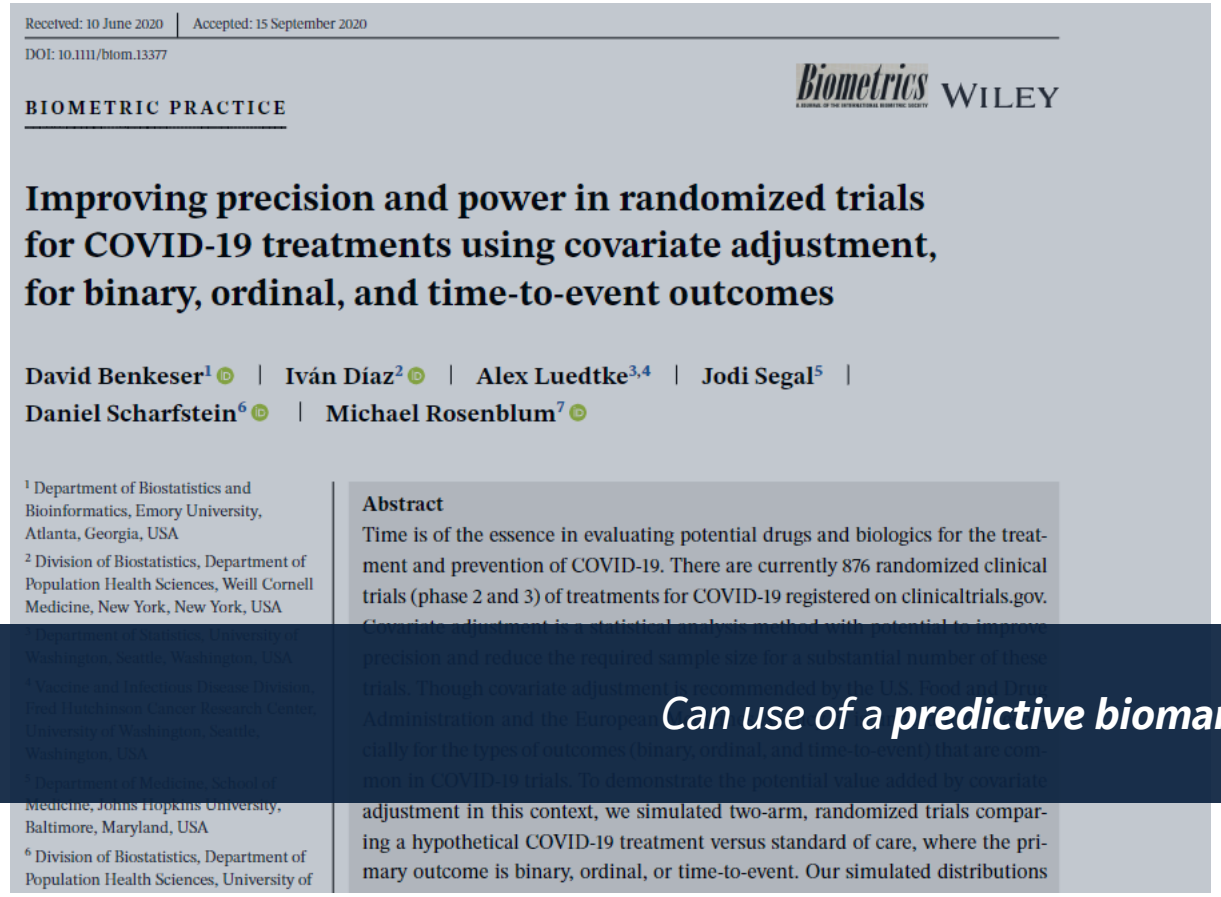
What is covariate adjustment?

Covariate adjustment refers to the use of information measured on a subject before the time of randomization (e.g., demographic factors, disease characteristics) for estimating and testing treatment effects between randomized groups.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adjusting-covariates-randomized-clinical-trials-drugs-and-biological-products

Precision of efficacy can be increased by using additional information

2020: Benkeser et al.'s article "Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes"



Received: 10 June 2020 | Accepted: 15 September 2020
DOI: 10.1111/biom.13377

BIOMETRIC PRACTICE

Biometrics WILEY

Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes

David Benkeser[1] | Iván Díaz[2] | Alex Luedtke[3,4] | Jodi Segal[5] | Daniel Scharfstein[6] | Michael Rosenblum[7]

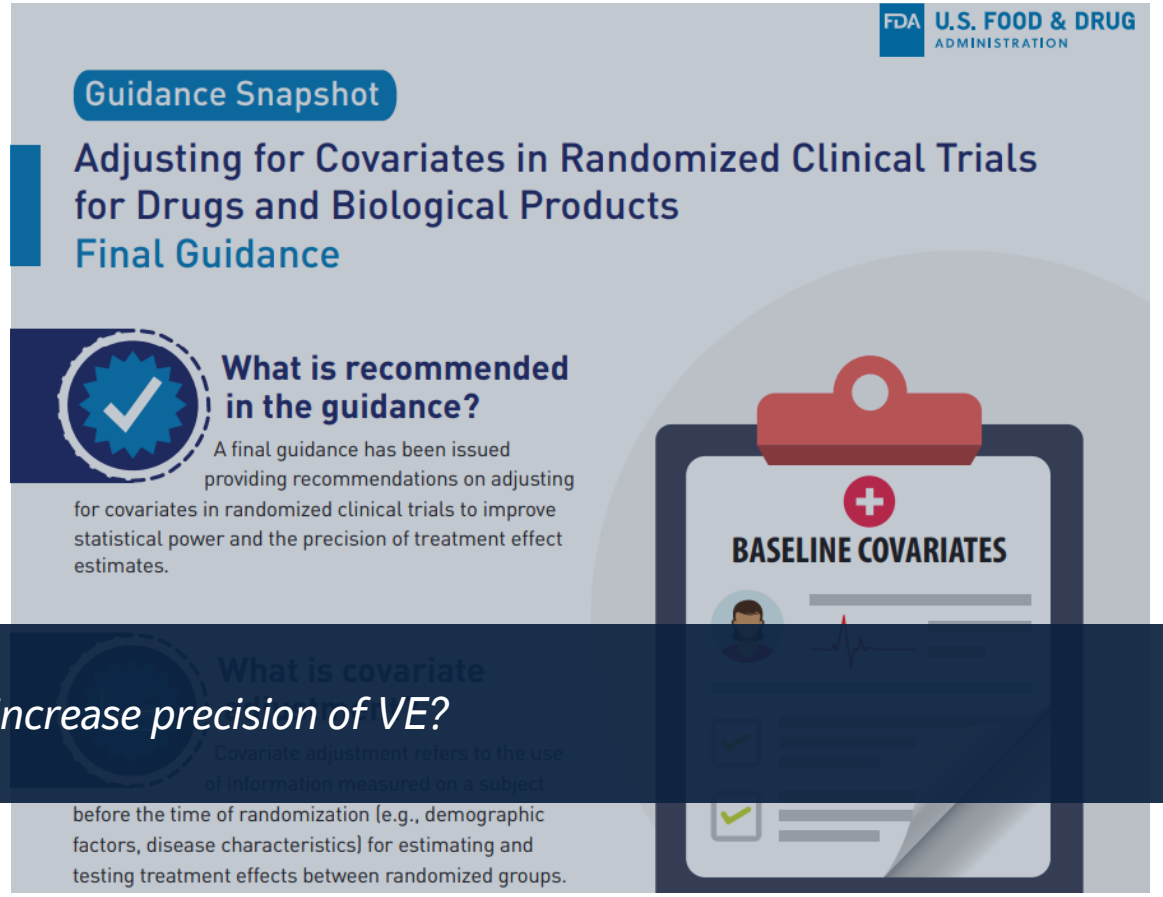
[1] Department of Biostatistics and Bioinformatics, Emory University, Atlanta, Georgia, USA
[2] Division of Biostatistics, Department of Population Health Sciences, Weill Cornell Medicine, New York, New York, USA
[3] Department of Statistics, University of Washington, Seattle, Washington, USA
[4] Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, Washington, USA
[5] Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland, USA
[6] Division of Biostatistics, Department of Population Health Sciences, University of

Abstract

Time is of the essence in evaluating potential drugs and biologics for the treatment and prevention of COVID-19. There are currently 876 randomized clinical trials (phase 2 and 3) of treatments for COVID-19 registered on clinicaltrials.gov. Covariate adjustment is a statistical analysis method with potential to improve precision and reduce the required sample size for a substantial number of these trials. Though covariate adjustment is recommended by the U.S. Food and Drug Administration and the European [illegible] especially for the types of outcomes (binary, ordinal, and time-to-event) that are common in COVID-19 trials. To demonstrate the potential value added by covariate adjustment in this context, we simulated two-arm, randomized trials comparing a hypothetical COVID-19 treatment versus standard of care, where the primary outcome is binary, ordinal, or time-to-event. Our simulated distributions

Benkeser D et al. Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes. *Biometrics* **77**, 1139-1508 (2021).

2023: FDA Guidance "Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products"



FDA U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot

Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products
Final Guidance

What is recommended in the guidance?

A final guidance has been issued providing recommendations on adjusting for covariates in randomized clinical trials to improve statistical power and the precision of treatment effect estimates.

What is covariate

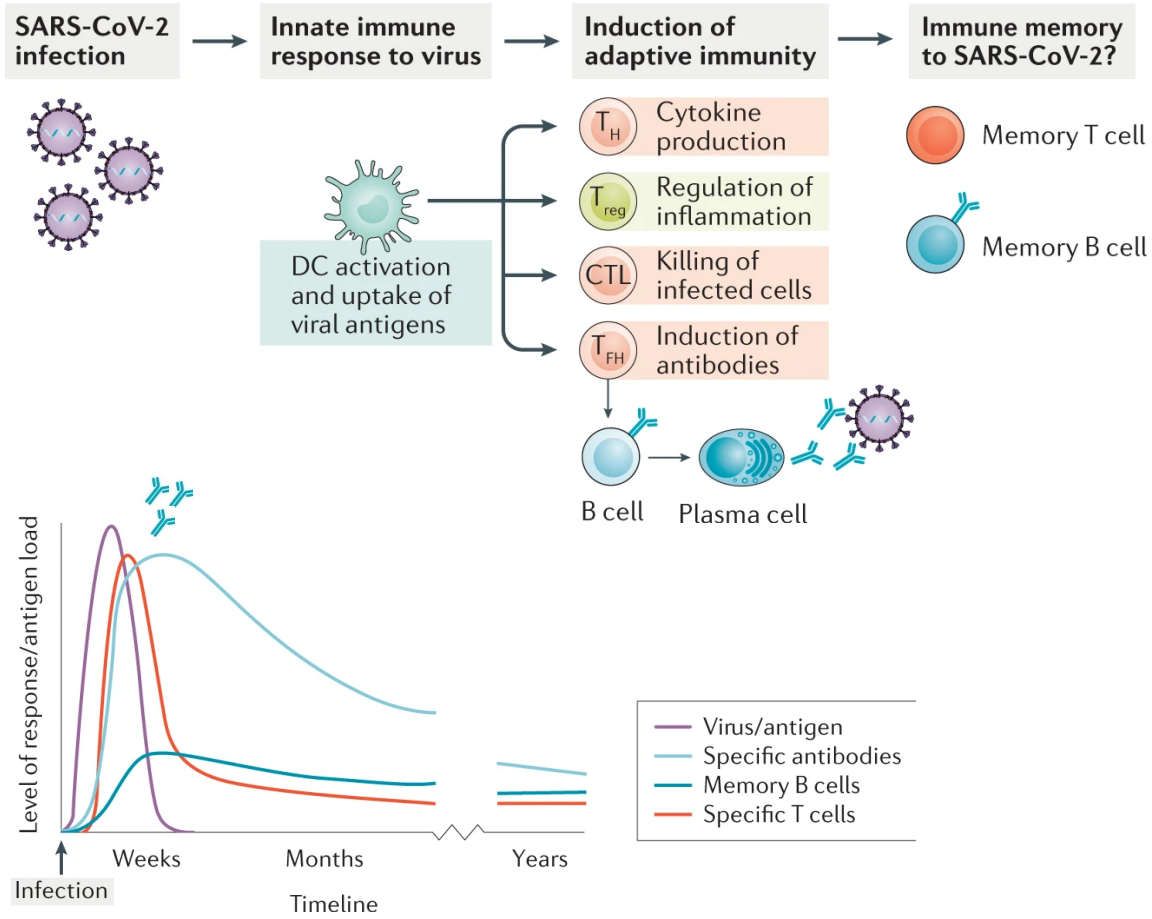
Covariate adjustment refers to the use of information measured on a subject before the time of randomization (e.g., demographic factors, disease characteristics) for estimating and testing treatment effects between randomized groups.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adjusting-covariates-randomized-clinical-trials-drugs-and-biological-products

*Can use of a **predictive biomarker** increase precision of VE?*

Biomarkers in vaccine development

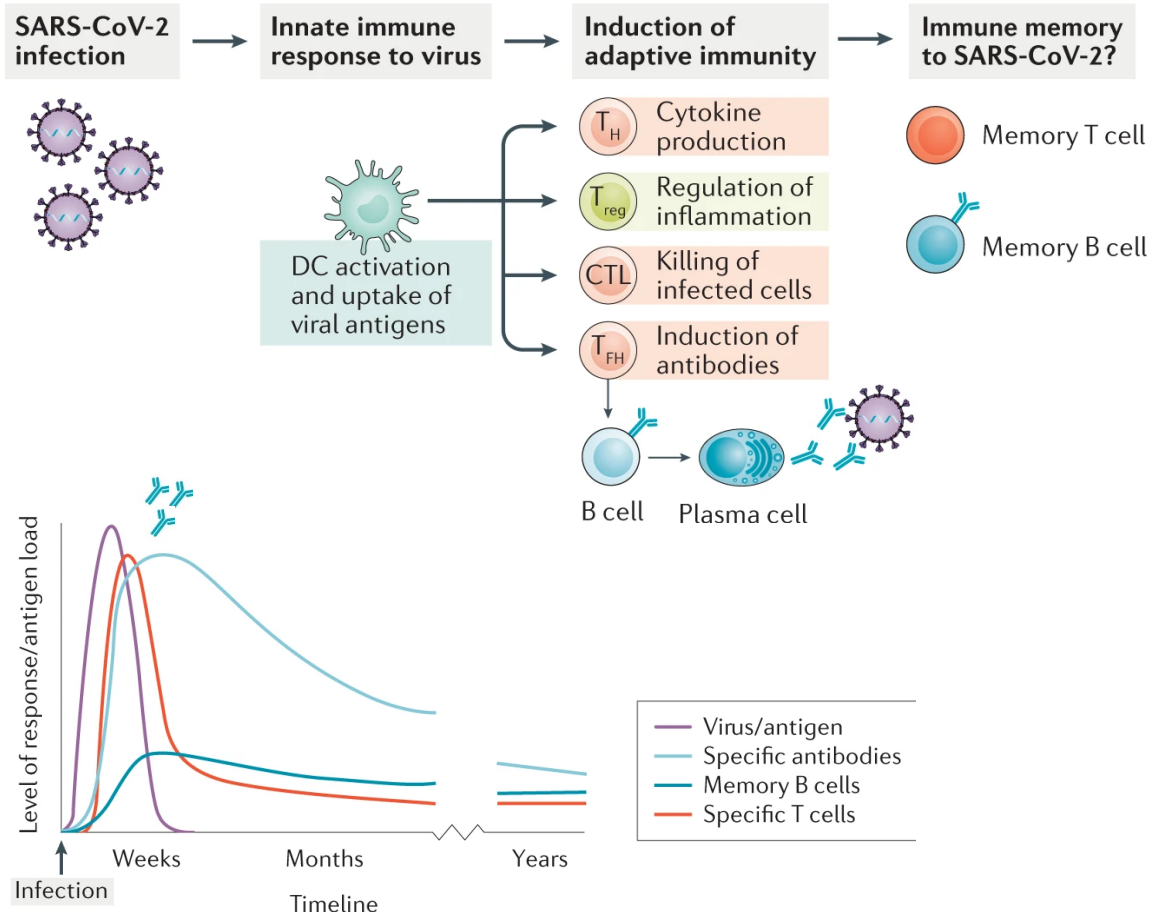
Immunogenicity: immune responses (antibodies, T cells) induced by vaccination



Cox RJ, Brokstad KA. Not just antibodies: B cells and T cells mediate immunity to COVID-19. *Nature Reviews Immunology* **20**, 581-582 (2020).

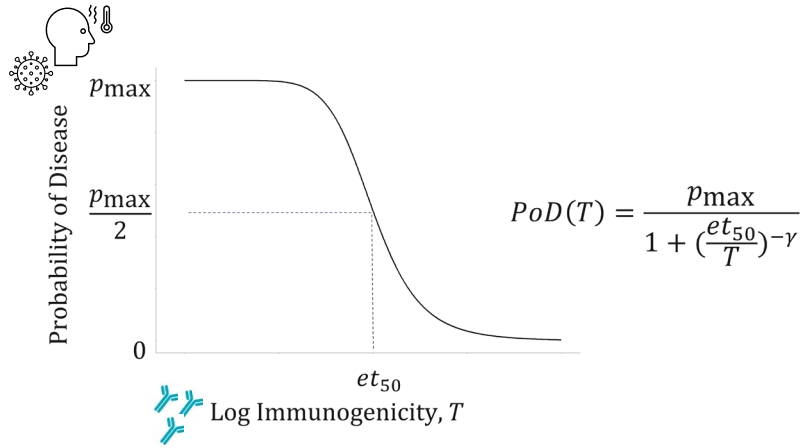
Biomarkers in vaccine development

Immunogenicity: immune responses (antibodies, T cells) induced by vaccination



Cox RJ, Brokstad KA. Not just antibodies: B cells and T cells mediate immunity to COVID-19. *Nature Reviews Immunology* **20**, 581-582 (2020).

Correlate of protection (CoP): an immune marker that correlates with and may be biologically responsible for vaccine-induced protection



Plotkin SA, Gilbert PB. Correlates of protection. Plotkin's Vaccines. 7th ed., 35-40 (Elsevier, 2017).

Dudasova J et al. A method to estimate probability of disease and vaccine efficacy from clinical trial immunogenicity data. *npj Vaccines* **6**, 133 (2021).

Methods: Modeling probability of disease (PoD) with phase 3 data

Step 1: Is immunogenicity biomarker a CoP?
(Multiple logistic regression)

Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

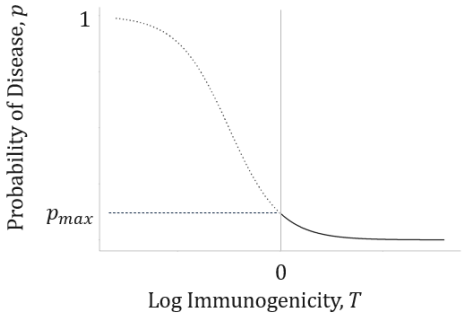
Step 3: Qualification of the model

Methods: Modeling probability of disease (PoD) with phase 3 data

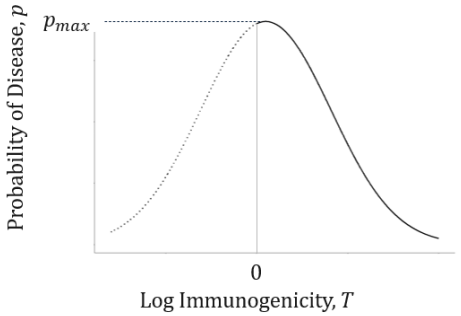
Step 1: Is immunogenicity biomarker a CoP? (Multiple logistic regression)

- Linear or non-linear effect of immunogenicity titer, T

$$y = \ln\frac{p}{1-p} = \beta_0 + \beta_1 T$$



$$y = \beta_0 + \beta_1 T + \beta_2 T^2$$



Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

Step 3: Qualification of the model

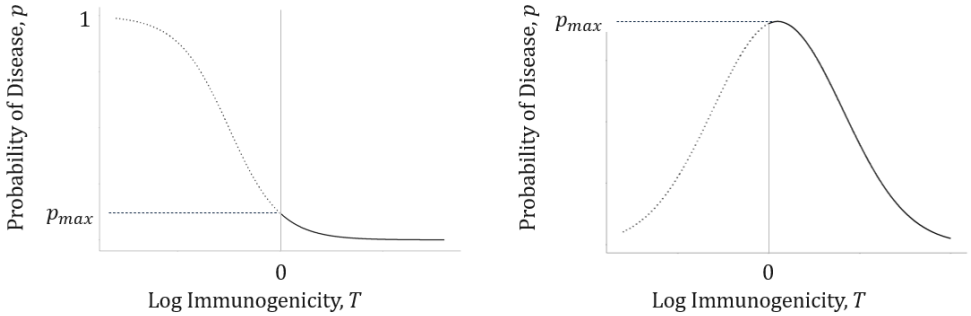
Dudasova J et al. Elucidating vaccine efficacy using a correlate of protection, demographics, and logistic regression. *BMC Medical Research Methodology* **24**, 101 (2024).

Methods: Modeling probability of disease (PoD) with phase 3 data

Step 1: Is immunogenicity biomarker a CoP? (Multiple logistic regression)

- Linear or non-linear effect of immunogenicity titer, T

$$y = \ln\frac{p}{1-p} = \beta_0 + \beta_1 T \qquad y = \beta_0 + \beta_1 T + \beta_2 T^2$$



- Effect of baseline covariates, e.g., A

$$y = \beta_0 + \beta_1 T + \beta_2 A \qquad y = \beta_0 + \beta_1 T + \beta_2 A + \beta_{1,2} A \cdot T$$

Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

Step 3: Qualification of the model

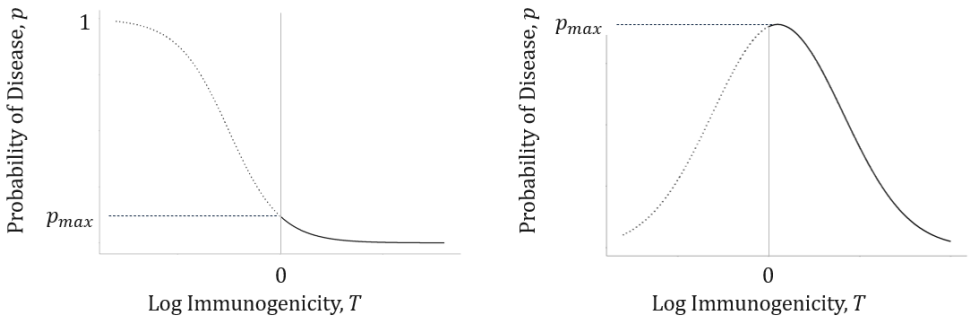
Dudasova J et al. Elucidating vaccine efficacy using a correlate of protection, demographics, and logistic regression. *BMC Medical Research Methodology* **24**, 101 (2024).

Methods: Modeling probability of disease (PoD) with phase 3 data

Step 1: Is immunogenicity biomarker a CoP? (Multiple logistic regression)

- Linear or non-linear effect of immunogenicity titer, T

$$y = \ln\frac{p}{1-p} = \beta_0 + \beta_1 T \qquad y = \beta_0 + \beta_1 T + \beta_2 T^2$$



- Effect of baseline covariates, e.g., A

$$y = \beta_0 + \beta_1 T + \beta_2 A \qquad y = \beta_0 + \beta_1 T + \beta_2 A + \beta_{1,2} A \cdot T$$

- Prentice criterion 4 for a CoP: conditional independence of vaccination status, V

$$y = \beta_0 + \beta_1 T + \beta_2 A + \beta_3 V$$

Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

Step 3: Qualification of the model

Dudasova J et al. Elucidating vaccine efficacy using a correlate of protection, demographics, and logistic regression. *BMC Medical Research Methodology* **24**, 101 (2024).

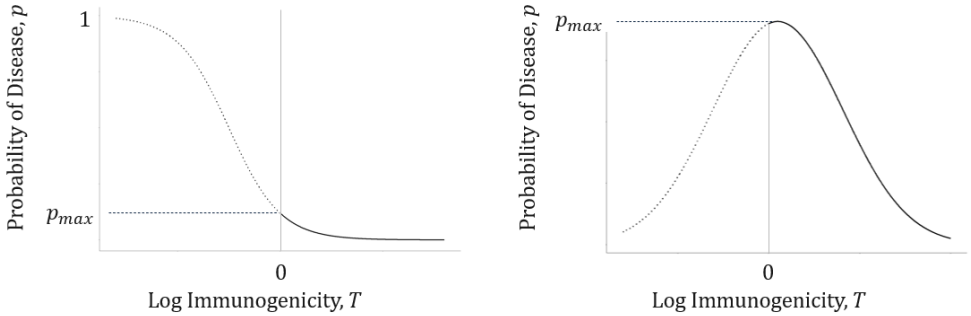
Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in Medicine* **8**, 431-440 (1989).

Methods: Modeling probability of disease (PoD) with phase 3 data

Step 1: Is immunogenicity biomarker a CoP? (Multiple logistic regression)

- Linear or non-linear effect of immunogenicity titer, T

$$y = \ln\frac{p}{1-p} = \beta_0 + \beta_1 T \qquad y = \beta_0 + \beta_1 T + \beta_2 T^2$$



- Effect of baseline covariates, e.g., A

$$y = \beta_0 + \beta_1 T + \beta_2 A \qquad y = \beta_0 + \beta_1 T + \beta_2 A + \beta_{1,2} A \cdot T$$

- Prentice criterion 4 for a CoP: conditional independence of vaccination status, V

$$y = \beta_0 + \beta_1 T + \beta_2 A + \beta_3 V$$

Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

- Use the best-fitting PoD model from Step 1

$$\mathrm{VE} = 1 - \mathrm{RR} = 1 - \frac{p^{\mathrm{vaccinated}}}{p^{\mathrm{control}}},$$

$$p^{\mathrm{vaccinated}} = \frac{1}{N} \cdot \sum_{i=1}^{N} \frac{1}{1 + e^{-y_i^{\mathrm{vaccinated}}}}$$

$$p^{\mathrm{control}} = \frac{1}{M} \cdot \sum_{j=1}^{M} \frac{1}{1 + e^{-y_j^{\mathrm{control}}}}$$

Calculate 95% confidence interval accounting for:

- the uncertainty regarding the PoD curve parameters (by parametric resampling of the posterior distribution for parameters)
- the variability in the observed data (by bootstrapping)

Step 3: Qualification of the model

Dudasova J et al. Elucidating vaccine efficacy using a correlate of protection, demographics, and logistic regression. *BMC Medical Research Methodology* **24**, 101 (2024).

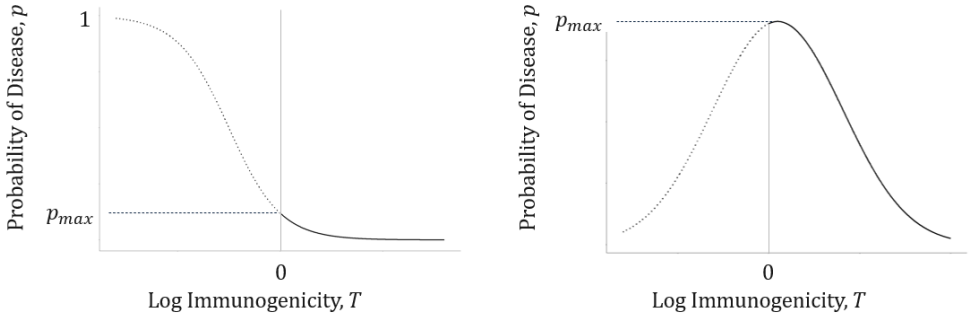
Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in Medicine* **8**, 431-440 (1989).

Methods: Modeling probability of disease (PoD) with phase 3 data

Step 1: Is immunogenicity biomarker a CoP? (Multiple logistic regression)

- Linear or non-linear effect of immunogenicity titer, T

$$y = \ln\frac{p}{1-p} = \beta_0 + \beta_1 T \qquad y = \beta_0 + \beta_1 T + \beta_2 T^2$$



- Effect of baseline covariates, e.g., A

$$y = \beta_0 + \beta_1 T + \beta_2 A \qquad y = \beta_0 + \beta_1 T + \beta_2 A + \beta_{1,2} A \cdot T$$

- Prentice criterion 4 for a CoP: conditional independence of vaccination status, V

$$y = \beta_0 + \beta_1 T + \beta_2 A + \beta_3 V$$

Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

- Use the best-fitting PoD model from Step 1

$$\mathrm{VE} = 1 - \mathrm{RR} = 1 - \frac{p^{\mathrm{vaccinated}}}{p^{\mathrm{control}}},$$

$$p^{\mathrm{vaccinated}} = \frac{1}{N} \cdot \sum_{i=1}^{N} \frac{1}{1 + e^{-y_i^{\mathrm{vaccinated}}}}$$

$$p^{\mathrm{control}} = \frac{1}{M} \cdot \sum_{j=1}^{M} \frac{1}{1 + e^{-y_j^{\mathrm{control}}}}$$

Calculate 95% confidence interval accounting for:
- the uncertainty regarding the PoD curve parameters (by parametric resampling of the posterior distribution for parameters)
- the variability in the observed data (by bootstrapping)

Step 3: Qualification of the model

- Evaluate degree of consistency between VE estimated in Step 2 and case-count VE
- Use an independent dataset when possible

Dudasova J et al. Elucidating vaccine efficacy using a correlate of protection, demographics, and logistic regression. *BMC Medical Research Methodology* **24**, 101 (2024).

Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Statistics in Medicine* **8**, 431-440 (1989).

Case-study: Immune correlates assessment and immunogenicity-based VE for Zoster Vaccine (Zostavax)

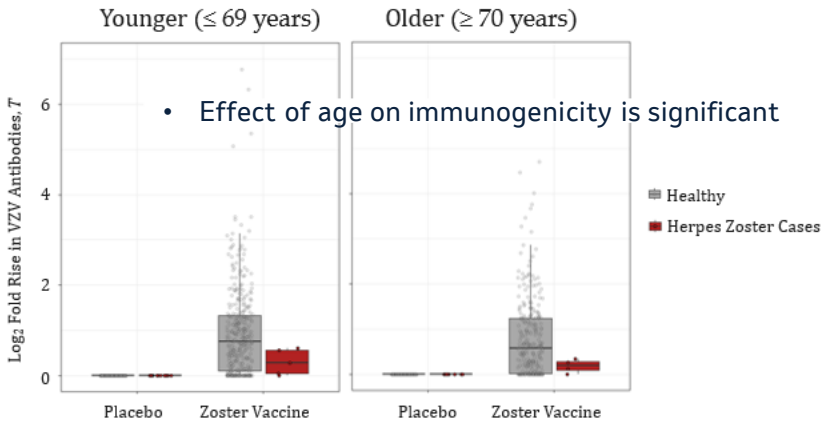
Step 1: Is immunogenicity biomarker a CoP? (Multiple logistic regression)

Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

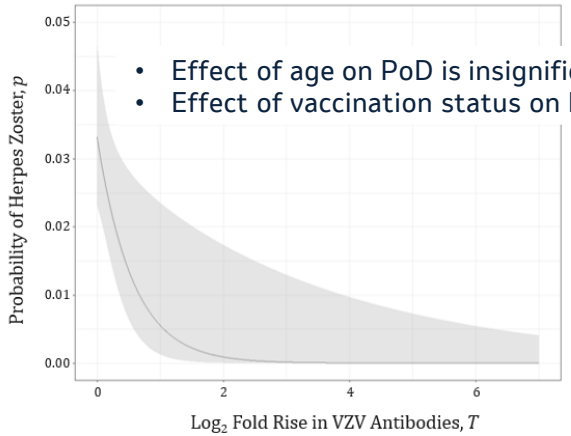
Step 3: Qualification of the model

Case-study: Immune correlates assessment and immunogenicity-based VE for Zoster Vaccine (Zostavax)

Step 1: Is immunogenicity biomarker a CoP? (Multiple logistic regression)



- Effect of age on immunogenicity is significant



- Effect of age on PoD is insignificant
- Effect of vaccination status on PoD is insignificant

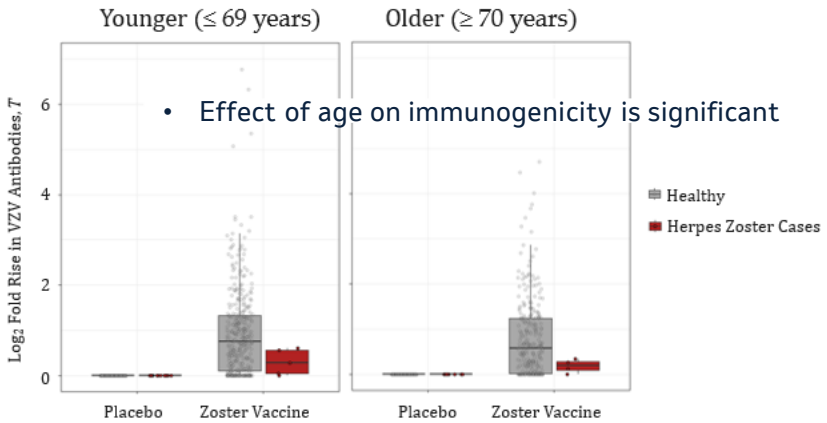
Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

Step 3: Qualification of the model

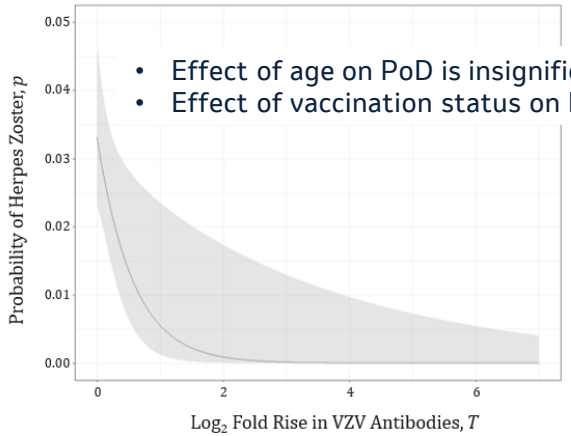
PoD = Probability of Disease

Case-study: Immune correlates assessment and immunogenicity-based VE for Zoster Vaccine (Zostavax)

Step 1: Is immunogenicity biomarker a CoP? (Multiple logistic regression)



- Effect of age on immunogenicity is significant



- Effect of age on PoD is insignificant
- Effect of vaccination status on PoD is insignificant

Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

1,326 participants of the immunogenicity substudy to the phase 3 Shingles Prevention Study (SPS), 32 cases:

Age group	**Control**		**Vaccinated**		**Vaccine Efficacy, % (95% CI)**	
	Person-years at risk	Cases	Person-years at risk	Cases	Case-count-based estimation	**Immunogenicity-based estimation**
Younger (≤ 69 years)	1,059	12	983	5	55 (-27 to 84)	**58 (24 to 68)**
Older (≥ 70 years)	654	11	728	4	67 (-2 to 90)	**52 (18 to 63)**

Levin MJ et al. Varicella-zoster virus–specific immune responses in elderly recipients of a herpes zoster vaccine. *The Journal of Infectious Diseases* **197**, 825-835 (2008).

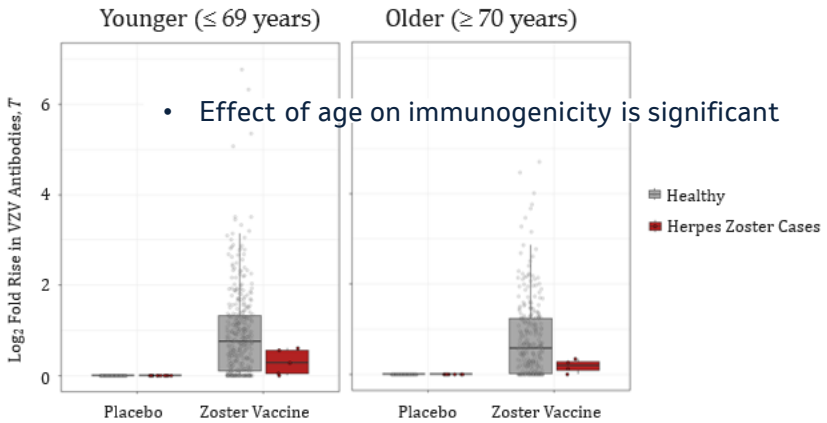
Oxman MN et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *The New England Journal of Medicine* **352**, 2271-2284 (2005).

Step 3: Qualification of the model

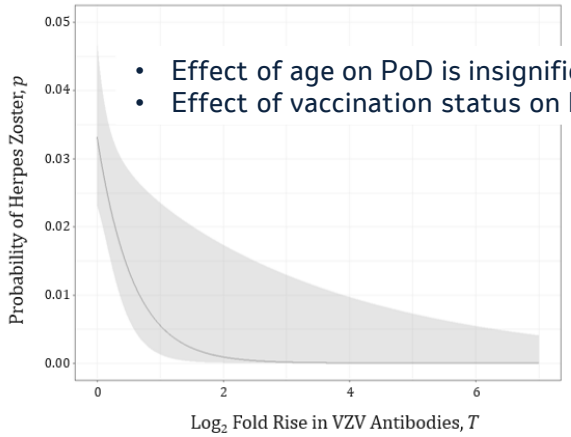
PoD = Probability of Disease

Case-study: Immune correlates assessment and immunogenicity-based VE for Zoster Vaccine (Zostavax)

Step 1: Is immunogenicity biomarker a CoP? (Multiple logistic regression)



- Effect of age on immunogenicity is significant



- Effect of age on PoD is insignificant
- Effect of vaccination status on PoD is insignificant

PoD = Probability of Disease

Step 2: Estimate VE in covariate-defined subgroups using the immunogenicity marker

1,326 participants of the immunogenicity substudy to the phase 3 Shingles Prevention Study (SPS), 32 cases:

Age group	Control		Vaccinated		Vaccine Efficacy, % (95% CI)	
	Person-years at risk	Cases	Person-years at risk	Cases	Case-count-based estimation	**Immunogenicity-based estimation**
Younger (≤ 69 years)	1,059	12	983	5	55 (-27 to 84)	**58 (24 to 68)**
Older (≥ 70 years)	654	11	728	4	67 (-2 to 90)	**52 (18 to 63)**

Levin MJ et al. Varicella-zoster virus–specific immune responses in elderly recipients of a herpes zoster vaccine. *The Journal of Infectious Diseases* **197**, 825-835 (2008).

Oxman MN et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *The New England Journal of Medicine* **352**, 2271-2284 (2005).

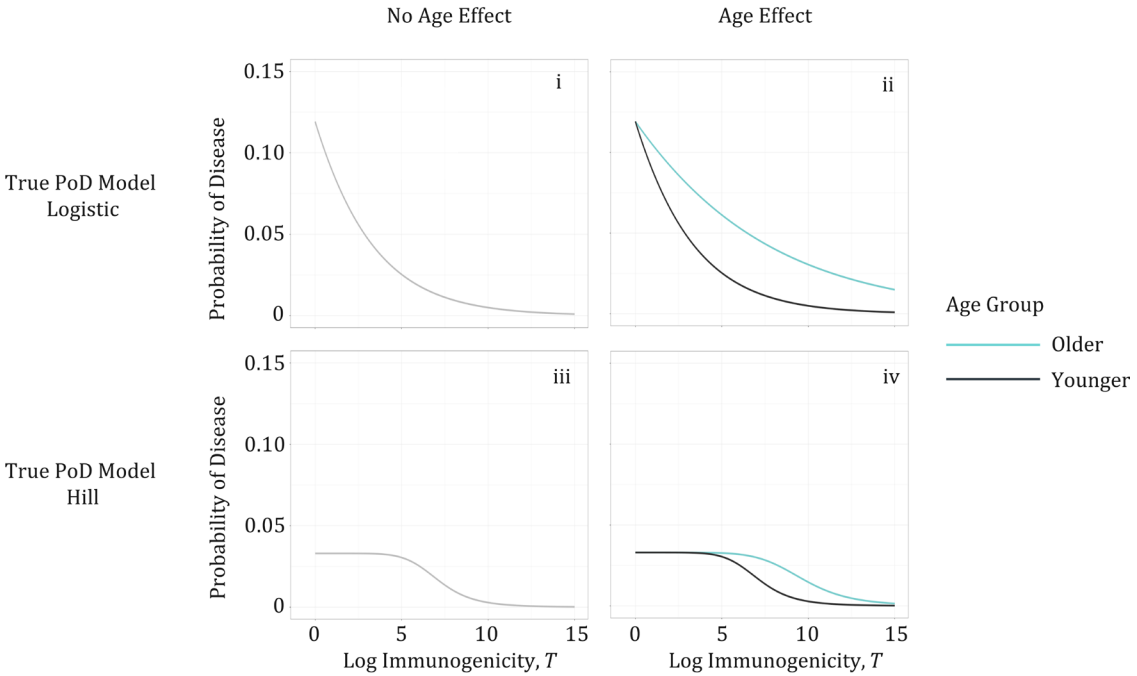
Step 3: Qualification of the model

38,546 participants of the phase 3 SPS, 957 cases:

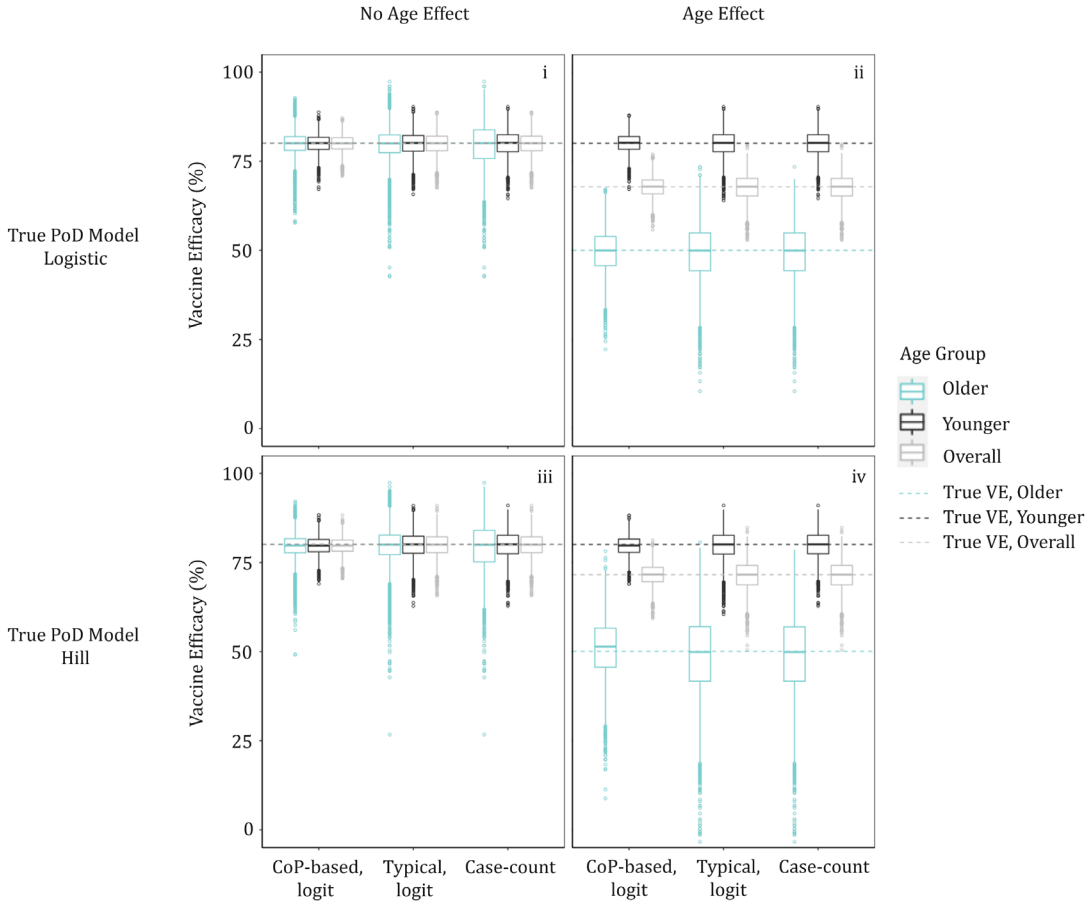
Age group	Vaccine Efficacy, % (95% CI), Case-count-based estimation
Younger (≤ 69 years)	**64 (56 to 71)**
Older (≥ 70 years)	**38 (25 to 48)**

Simulated vaccine phase 3 trials: Immunogenicity-based VE estimated by logistic regression is **accurate and precise**, when immunogenicity fully mediates the protection

Definition of simulation scenarios i, ii, iii, iv by shapes of the true PoD curve

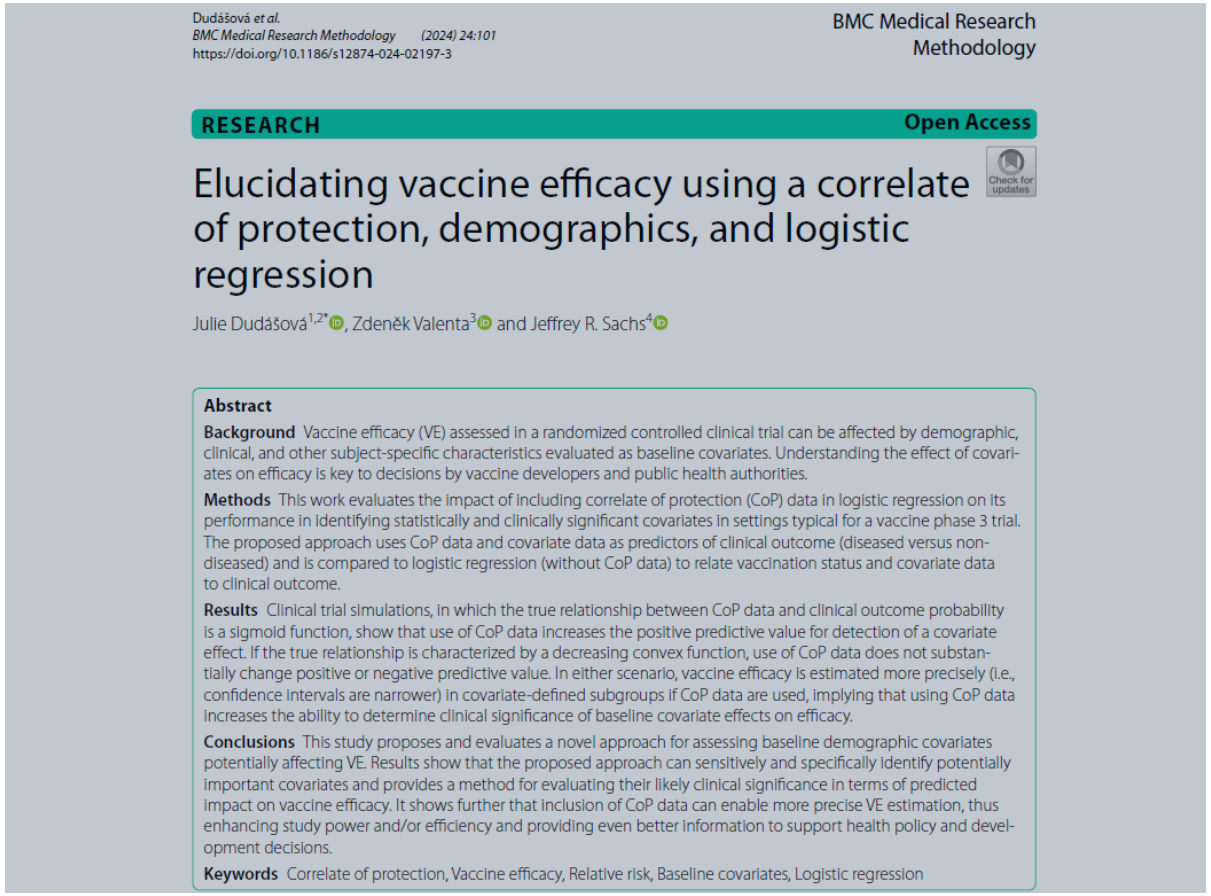


VE point estimates by immunogenicity-based logistic regression are generally closer to the "truth" (lower variance)



Additional resources

2024: Dudasova et al.'s article "Elucidating vaccine efficacy using a correlate of protection, demographics, and logistic regression"



Dudášová et al.
BMC Medical Research Methodology (2024) 24:101
https://doi.org/10.1186/s12874-024-02197-3

BMC Medical Research Methodology

RESEARCH Open Access

Elucidating vaccine efficacy using a correlate of protection, demographics, and logistic regression

Julie Dudášová[1,2*], Zdeněk Valenta[3] and Jeffrey R. Sachs[4]

Abstract

Background Vaccine efficacy (VE) assessed in a randomized controlled clinical trial can be affected by demographic, clinical, and other subject-specific characteristics evaluated as baseline covariates. Understanding the effect of covariates on efficacy is key to decisions by vaccine developers and public health authorities.

Methods This work evaluates the impact of including correlate of protection (CoP) data in logistic regression on its performance in identifying statistically and clinically significant covariates in settings typical for a vaccine phase 3 trial. The proposed approach uses CoP data and covariate data as predictors of clinical outcome (diseased versus non-diseased) and is compared to logistic regression (without CoP data) to relate vaccination status and covariate data to clinical outcome.

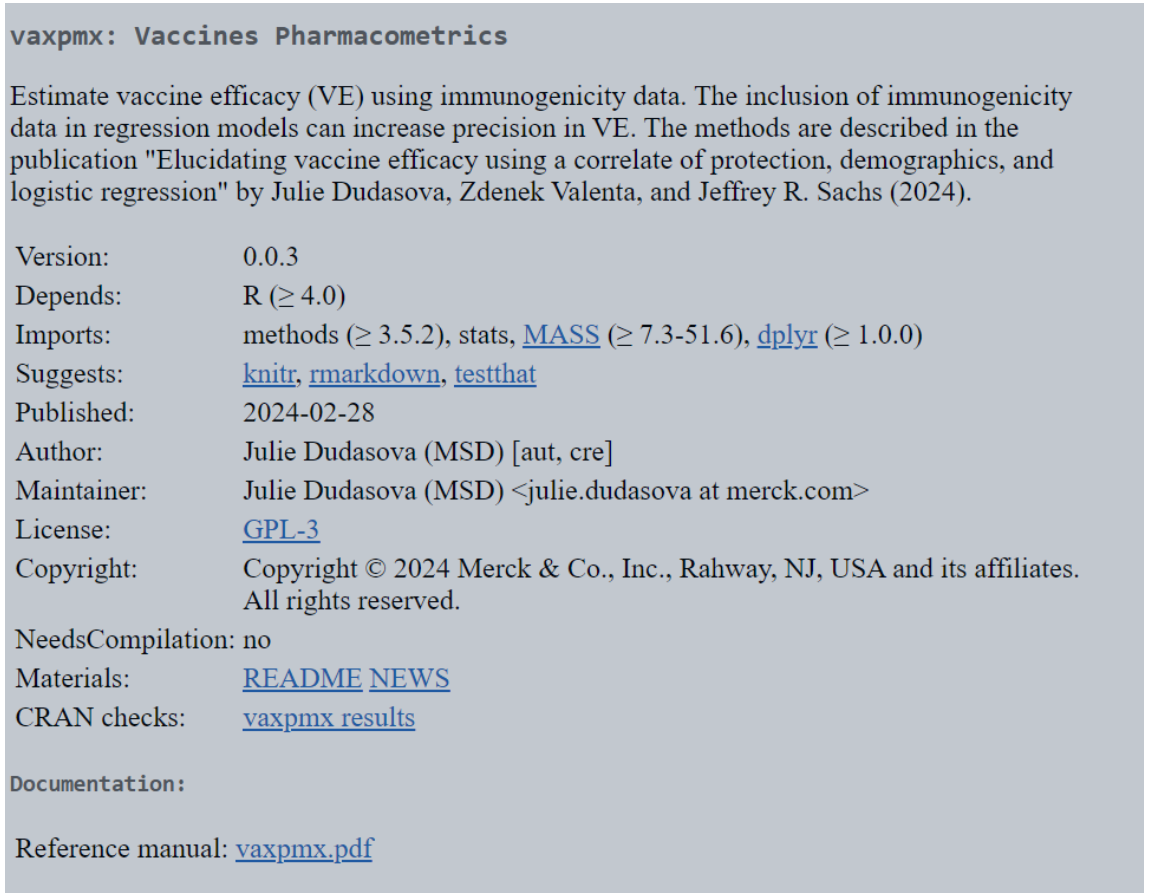
Results Clinical trial simulations, in which the true relationship between CoP data and clinical outcome probability is a sigmoid function, show that use of CoP data increases the positive predictive value for detection of a covariate effect. If the true relationship is characterized by a decreasing convex function, use of CoP data does not substantially change positive or negative predictive value. In either scenario, vaccine efficacy is estimated more precisely (i.e., confidence intervals are narrower) in covariate-defined subgroups if CoP data are used, implying that using CoP data increases the ability to determine clinical significance of baseline covariate effects on efficacy.

Conclusions This study proposes and evaluates a novel approach for assessing baseline demographic covariates potentially affecting VE. Results show that the proposed approach can sensitively and specifically identify potentially important covariates and provides a method for evaluating their likely clinical significance in terms of predicted impact on vaccine efficacy. It shows further that inclusion of CoP data can enable more precise VE estimation, thus enhancing study power and/or efficiency and providing even better information to support health policy and development decisions.

Keywords Correlate of protection, Vaccine efficacy, Relative risk, Baseline covariates, Logistic regression

Dudasova J et al. Elucidating vaccine efficacy using a correlate of protection, demographics, and logistic regression. *BMC Medical Research Methodology* **24**, 101 (2024).

2024: R package *vaxpmx* available at CRAN



vaxpmx: Vaccines Pharmacometrics

Estimate vaccine efficacy (VE) using immunogenicity data. The inclusion of immunogenicity data in regression models can increase precision in VE. The methods are described in the publication "Elucidating vaccine efficacy using a correlate of protection, demographics, and logistic regression" by Julie Dudasova, Zdenek Valenta, and Jeffrey R. Sachs (2024).

Version:	0.0.3
Depends:	R (≥ 4.0)
Imports:	methods (≥ 3.5.2), stats, MASS (≥ 7.3-51.6), dplyr (≥ 1.0.0)
Suggests:	knitr, rmarkdown, testthat
Published:	2024-02-28
Author:	Julie Dudasova (MSD) [aut, cre]
Maintainer:	Julie Dudasova (MSD) <julie.dudasova at merck.com>
License:	GPL-3
Copyright:	Copyright © 2024 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.
NeedsCompilation:	no
Materials:	README NEWS
CRAN checks:	vaxpmx results

Documentation:

Reference manual: vaxpmx.pdf

https://cran.r-project.org/web/packages/vaxpmx/index.html

Conclusions

Summary of learnings:

- Use of immunogenicity data can increase precision in estimating vaccine efficacy
  - Key especially in analyses of data from smaller trials (e.g., phase 2b studies), or in subgroup analyses in phase 3 trials
  - Illustrated with a real vaccine example
  - Demonstrated via a simulation study
  - Implemented in the *vaxpmx* R package

Impact:

- Understanding heterogeneity in efficacy sooner enables better-informed decisions by:
  - vaccines developers (e.g., go/no-go decisions, reformulation strategies, booster strategies)
  - public health authorities (e.g., decisions based on risk-benefit profile, vaccine recommendations, modifications to immunization schedules)

Future work:

- Predicting durability of efficacy using time-dependent immunogenicity

Let's impact the vaccine space with modeling and simulation together…

Acknowledgements

Institute of Computer Science of the Czech Academy of Sciences

Zdeněk Valenta

MSD

Jeff Sachs
Andreea Măgălie
Alex Becker
Ferdous Gheyas
Brian Maas
Bhargava Kandala
Jeff Perley
Maurice Ahsman
Chihiro Hasegawa
Pavel Fišer
Ryan Vargo
Matt Rizk
Tjerk Bueters
Larissa Wenning
Julie Stone
Beth-Ann Coller
Germán Áñez
Luis Castagnini
Paula Annunziato

Trial participants and their families

julie.dudasova@merck.com