Evaluating High-dimensional Surrogate Markers of Vaccine Response through Causal Mediation Analysis

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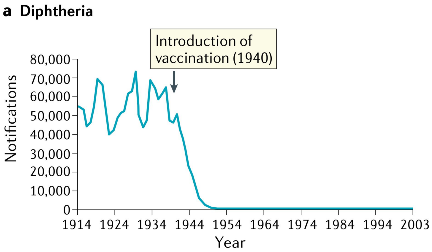
10/06/2024

Vaccination

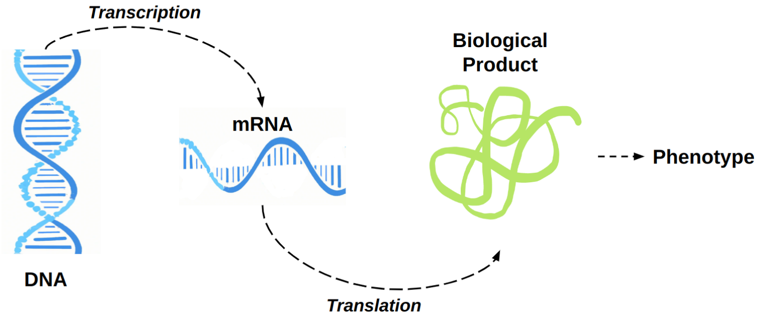
- Exploit immune system
- Most **cost-effective** measure in public health
  - **154 million** lives saved in last 50 years
  - **4-5 million** lives saved per year
- Historically developed empirically



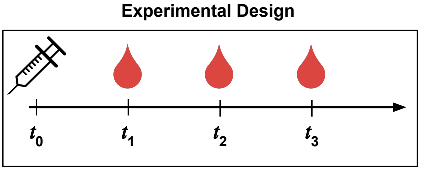
Pollard and Bijker, 2020

Transcriptomics

- **Gene expression**: Genes → Product



Transcriptomics in vaccinology



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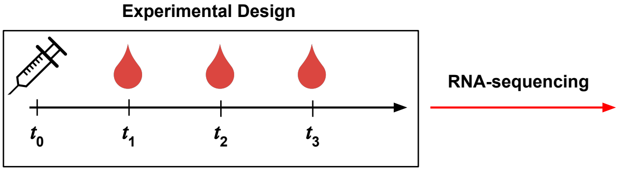


Count Matrix

Genes →

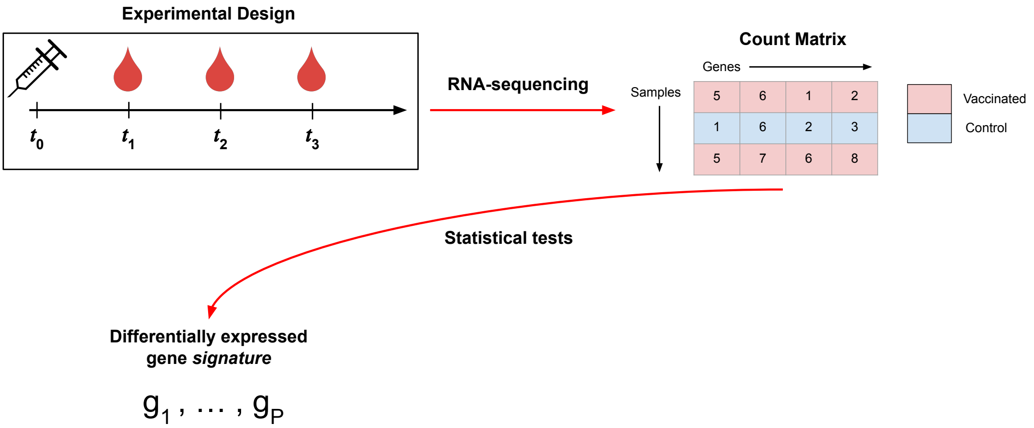
Samples ↓

5	6	1	2
1	6	2	3
5	7	6	8

Vaccinated

Control

Transcriptomics in vaccinology



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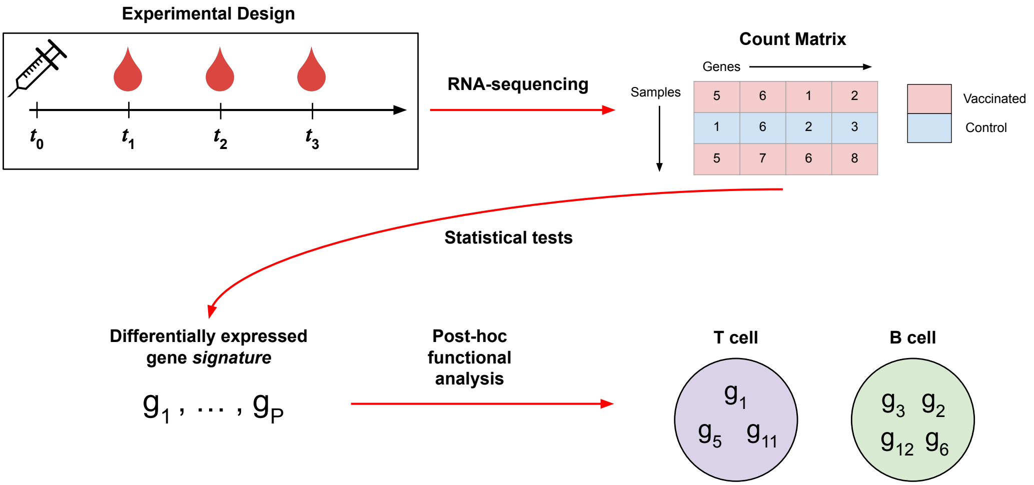

Why study gene expression?

Huge potential :

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✓ Holistic view of system

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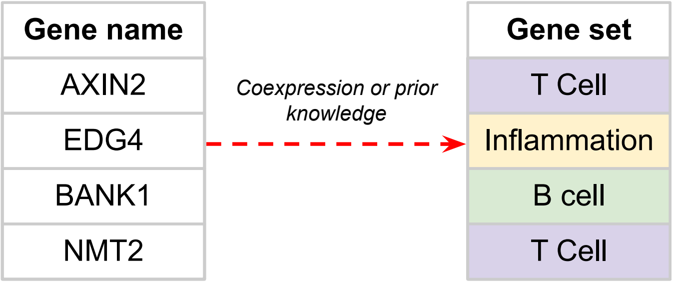
But challenges with high-dimensionality...

- ⚠ Interpretability
- ⚠ Sensitivity to investigator choices
- ⚠ Low signal-noise ratio

Gene Set Approaches

Investigate groups of biologically related genes



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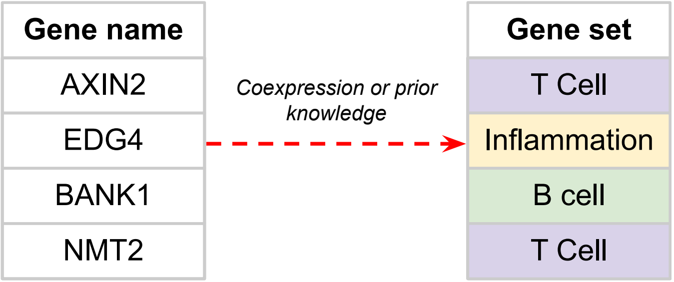

✓ Reduced dimensionality

Gene Set Approaches

Investigate groups of biologically related genes

Gene name	Gene set
AXIN2	T Cell
EDG4	Inflammation
BANK1	B cell
NMT2	T Cell

Coexpression or prior knowledge

✓ Reduced dimensionality

✓ Biological interpretability

Gene Set Approaches

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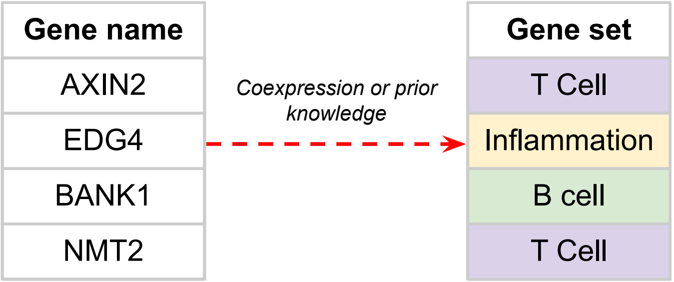
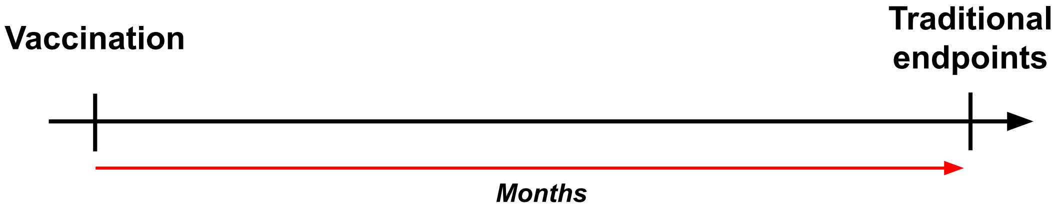
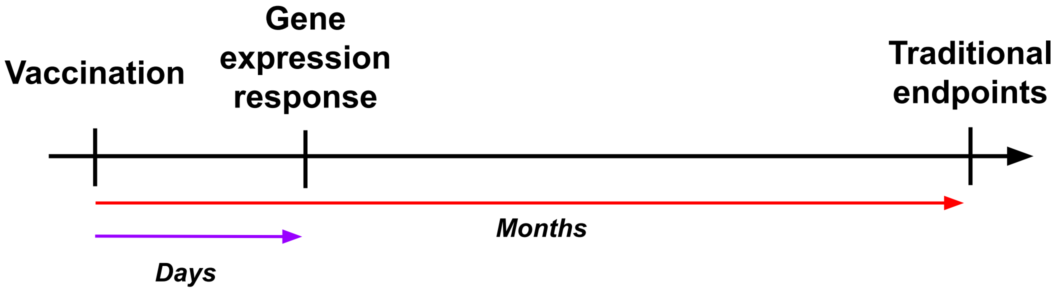


- ✓ Reduced dimensionality
- ✓ Biological interpretability
- ✓ Boost signal



Vaccination
Traditional endpoints
Months


Gene
expression
response
Vaccination
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Months
Days

Potential of an early gene expression surrogate

✓ Accelerating validation of candidate vaccines

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Difficulties in vaccine RCT context :

⚠ High-dimensional

⚠ Small sample size

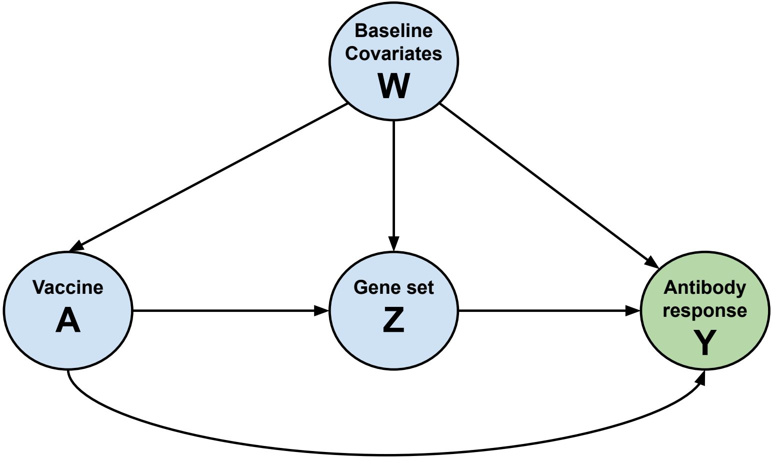
⚠ Complex data structures

Evaluating Gene Set Signals as Surrogates

Goal : Ranked list of gene sets by **proportion of treatment effect explained**

Gene Set	PTE
Z_1	R_1
Z_2	R_2
Z_3	R_3
....	....

where $R_1 > R_2 > R_3 > \ldots$


Baseline
Covariates
W
Vaccine
A
Gene set
Z
Antibody
response
Y

Potential outcomes framework

- Observed data consists of n i.i.d copies of $O = (W, A, Z, Y)$ where
  - W - baseline covariates (e.g. age, sex...)
  - $A \in \{0, 1\}$ - vaccine indicator
  - Z - m genes in the same biological pathway $(m > n)$
  - Y - antibody levels

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- $Z(a')$ - mediators had treatment been $A = a'$
- $Y(a, Z(a'))$ - response had treatment been $A = a$ and mediators under $A = a'$

Definition of effects

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Decompose total effect :

$$\underbrace{\mathbb{E}(Y(1) - Y(0))}_{\text{Total Effect}} = \underbrace{\mathbb{E}(Y(1, Z(0)) - Y(0, Z(0))}_{\text{Natural direct effect}} + \underbrace{\mathbb{E}(Y(1, Z(1)) - Y(1, Z(0))}_{\text{Natural indirect effect}}$$

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Define **proportion of treatment effect explained** as

$$R_S := \frac{NIE}{\text{Total Effect}} = 1 - \frac{NDE}{\text{Total Effect}}$$

Method 1 : G-computation

Goal : estimate $\Delta := \mathbb{E}\{Y(1) - Y(0)\}$

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Method 2 : Inverse probability weighting

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Not robust to sparsity

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✓ **Optimises bias-variance tradeoff for causal parameter of interest**

✓ **Doubly robust** - consistent if $\widehat{\mathbb{E}}\{Y|W,A\}$ or $\widehat{\mathbb{P}}(A=1|W)$ consistently estimated

G-Computation

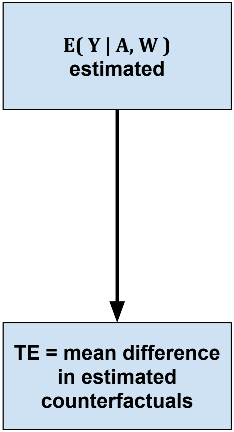
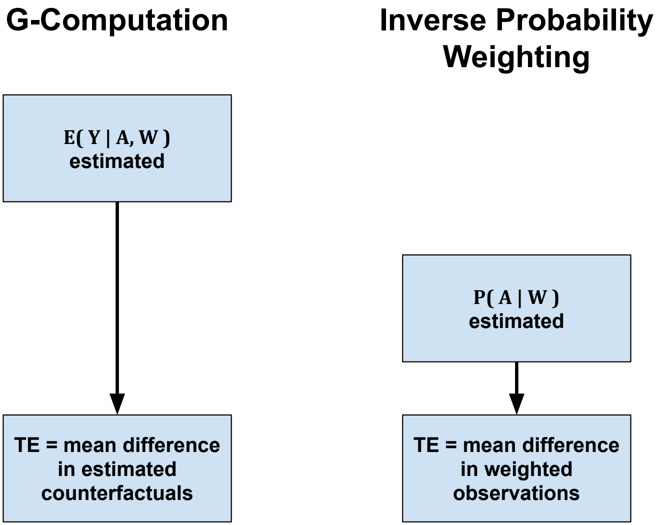


Figure adapted from Schuler and Rose, 2016



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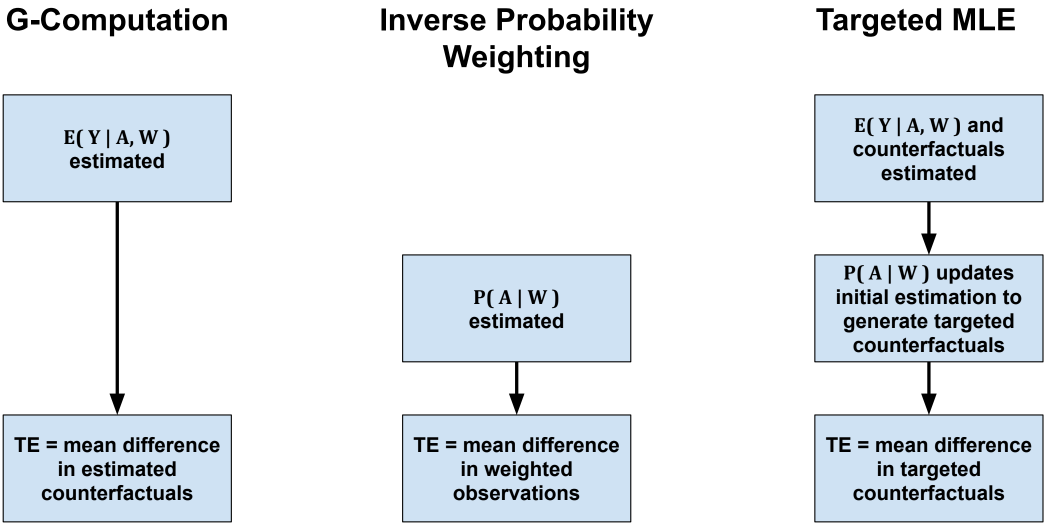

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$\Longrightarrow$ **Initial estimates** $\mathbb{E}\{\widehat{Y|W,A}\}$ and $\widehat{g_a} = \mathbb{P}(\widehat{A=a}|W)$

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3. Targeted potential outcomes $\Longrightarrow$

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Estimating the Natural Direct Effect

Goal : **estimate the natural direct effect** from n copies of $O = (W, A, Z, Y)$. Let

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Define NDE $= \underbrace{\mathbb{E}_W\{\mathbb{E}_Z[\underbrace{Q_Y(W, 1, Z) - Q_Y(W, 0, Z)}_{Q_{\text{diff}}}|A = 0, W]\}}_{\textit{Residual treatment effect} = \Delta_S}$

$\implies$ **two quantities to target** : Q_{diff} and Δ_S

$$\text{NDE} = \mathbb{E}_W\{\mathbb{E}_Z[Q_Y(W,1,Z) - Q_Y(W,0,Z)|A=0,W]\}$$

1. TMLE of Q_{Diff}

Initial estimates with super-learning :

E(Y | W, A, Z), P(Z | W, A), P(A | W)

↓

TMLE : E*(Y | W, A, Z)

↓

Estimate

Q_{Diff}* = E*(Y | W, 1, Z) - E*(Y | W, 0, Z)

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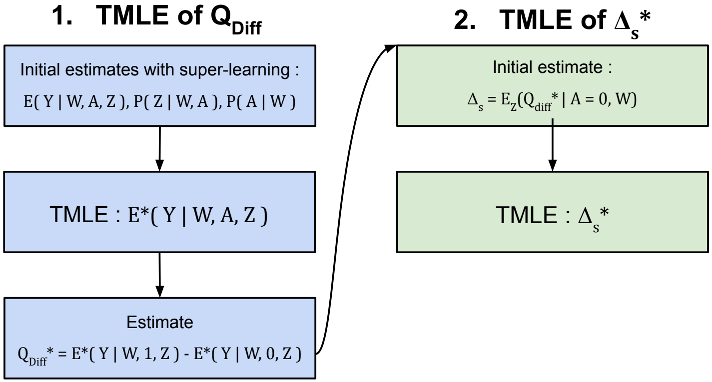

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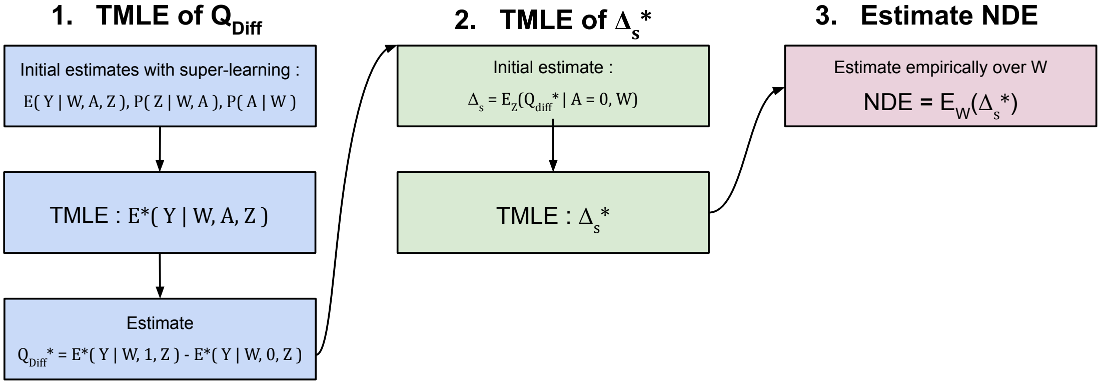

Identifiability conditions

Consistency

- $Y(a,m) = Y$ if $A = a$, $Z = m$
- $Z(a') = Z$ if $A = a'$
- $Y(a, Z(a')) = Y(a,m)$ if $Z = m$

Identifiability conditions

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Conditional independence

- $A \perp\!\!\!\perp Z(a')|W$
- $A \perp\!\!\!\perp Y(a,m)|W$
- $Z \perp\!\!\!\perp Y(a,m)|W, A = a$

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⚠ $Z(a') \perp\!\!\!\perp Y(a,m) | W$

Positivity

- $\mathbb{P}(A = 1 | W) \in (0,1)$
- $\mathbb{P}(Z = m | W, A = a) \in (0,1)$

Limitations of TMLE workflow

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Take-home messages

- Potential and challenges evaluating an early gene expression surrogate of vaccine response
- **Targeted learning to reduce bias** in causal estimands
- Methodological workflow for evaluating **PTE by gene sets** on vaccine response

Thank you for listening

References

Pollard, Andrew J. and Else M. Bijker (Dec. 2020). "A guide to vaccinology: from basic principles to new developments". In: *Nature Reviews Immunology* 21.2, pp. 83–100. ISSN: 1474-1741.

Schuler, Megan S. and Sherri Rose (Dec. 2016). "Targeted Maximum Likelihood Estimation for Causal Inference in Observational Studies". In: *American Journal of Epidemiology* 185.1, pp. 65–73. ISSN: 1476-6256.

Step 1 : TMLE of Q_{diff}

Define *auxiliary covariate*

$$H_Y(Q_Z, g) = \frac{\mathbb{1}(A=1)}{g(1|W)} \cdot \frac{Q_Z(W,0)}{Q_Z(W,1)} - \frac{\mathbb{1}(A=0)}{g(0|W)}$$

and *working parametric submodel*

$$Q_Y(\epsilon_1) = Q_Y + \epsilon_1 H_Y(Q_Z, g) \tag{1}$$

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4. Estimate $\widehat{Q_{\text{diff}}^*} = \widehat{Q_Y^*}(W, A=1, Z) - \widehat{Q_Y^*}(W, A=0, Z)$

Step 2 : TMLE of Δ_S

Define *auxiliary covariate*

$$H_Z(g) = \frac{1}{g(0|W)}$$

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$$\Delta_S(\epsilon_2) = \psi_Z + \epsilon_2 H_Z(g) \quad (2)$$

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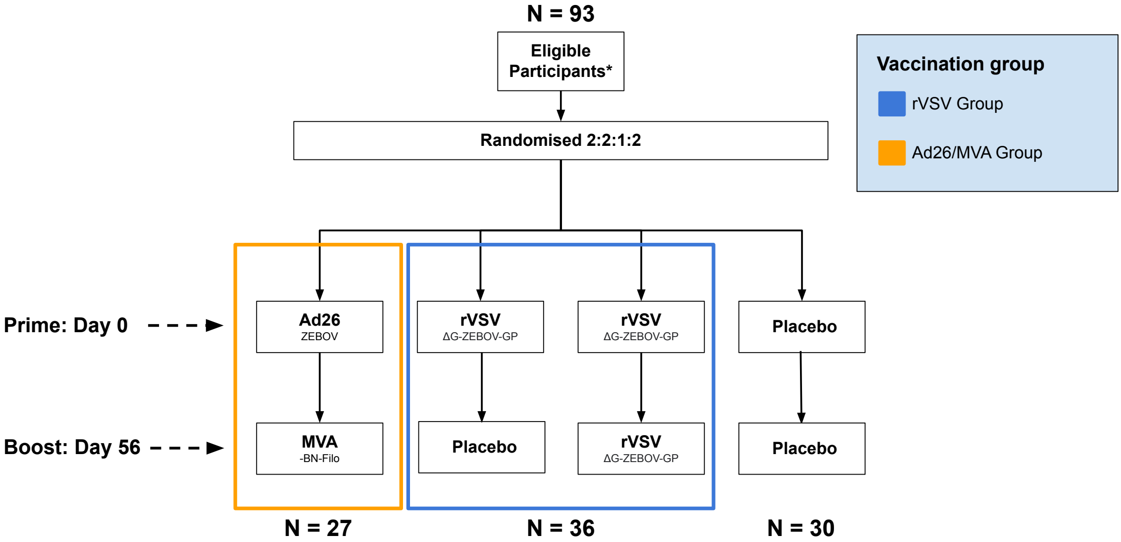
3. Plug in $\widehat{\epsilon_2^*}$ for targeted estimate $\widehat{\psi^*_Z(Q^*_Y)} = \psi_Z(\widehat{Q^*_Y}) + \widehat{\epsilon_2}^* H_Z(\widehat{g})$

Step 3 : Empirical estimate of Direct effect

$$\psi_{NDE} = \mathbb{E}_{Q_W}(\psi_Z(Q_Y))$$

$\Longrightarrow$ **Empirically average over covariates for NDE**

$$\widehat{\psi_{NDE}} = \frac{1}{n}\sum_{i=1}^{n} \widehat{\psi_Z^*(Q_Y^*)}(W_i)$$



N = 93
Eligible Participants*
Randomised 2:2:1:2
Vaccination group
rVSV Group
Ad26/MVA Group
Prime: Day 0
Boost: Day 56
Ad26
ZEBOV
MVA
-BN-Filo
rVSV
ΔG-ZEBOV-GP
Placebo
rVSV
ΔG-ZEBOV-GP
rVSV
ΔG-ZEBOV-GP
Placebo
Placebo
N = 27
N = 36
N = 30