



Differential depletion of susceptibles

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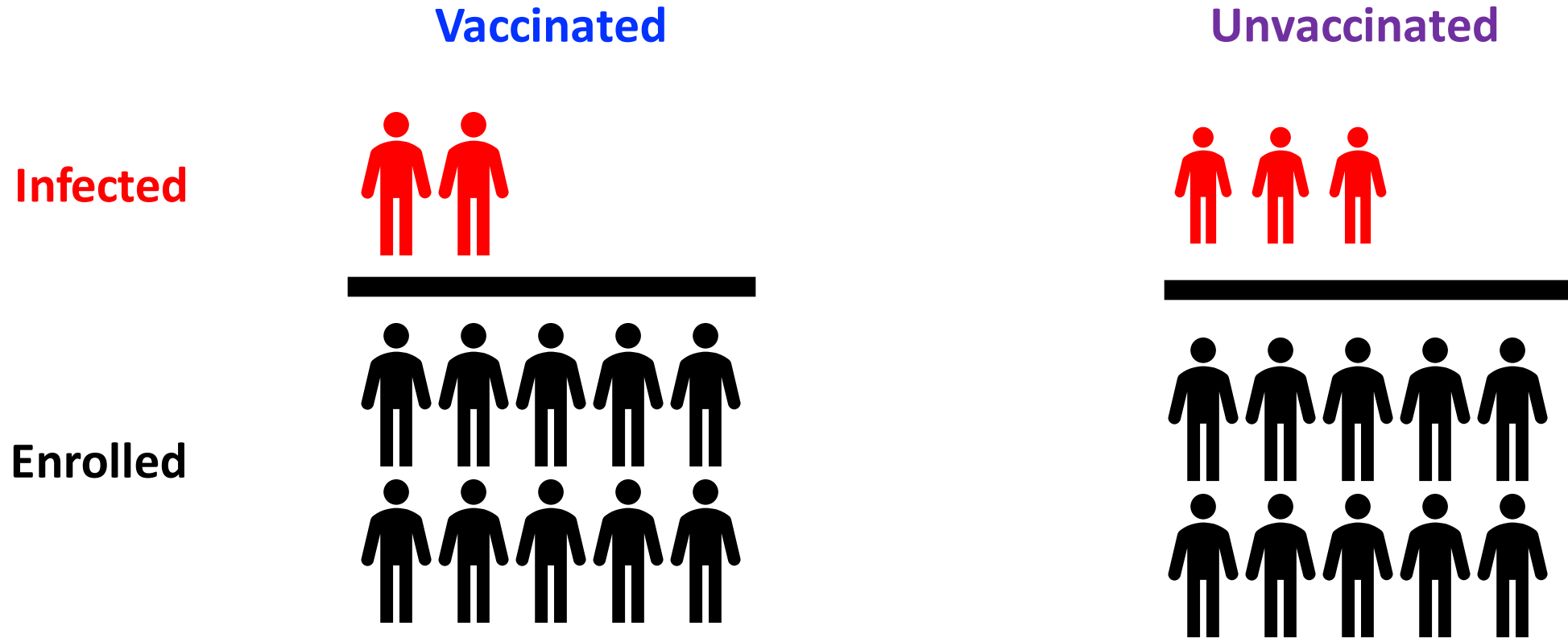
September 14, 2023

Differential depletion of susceptibles

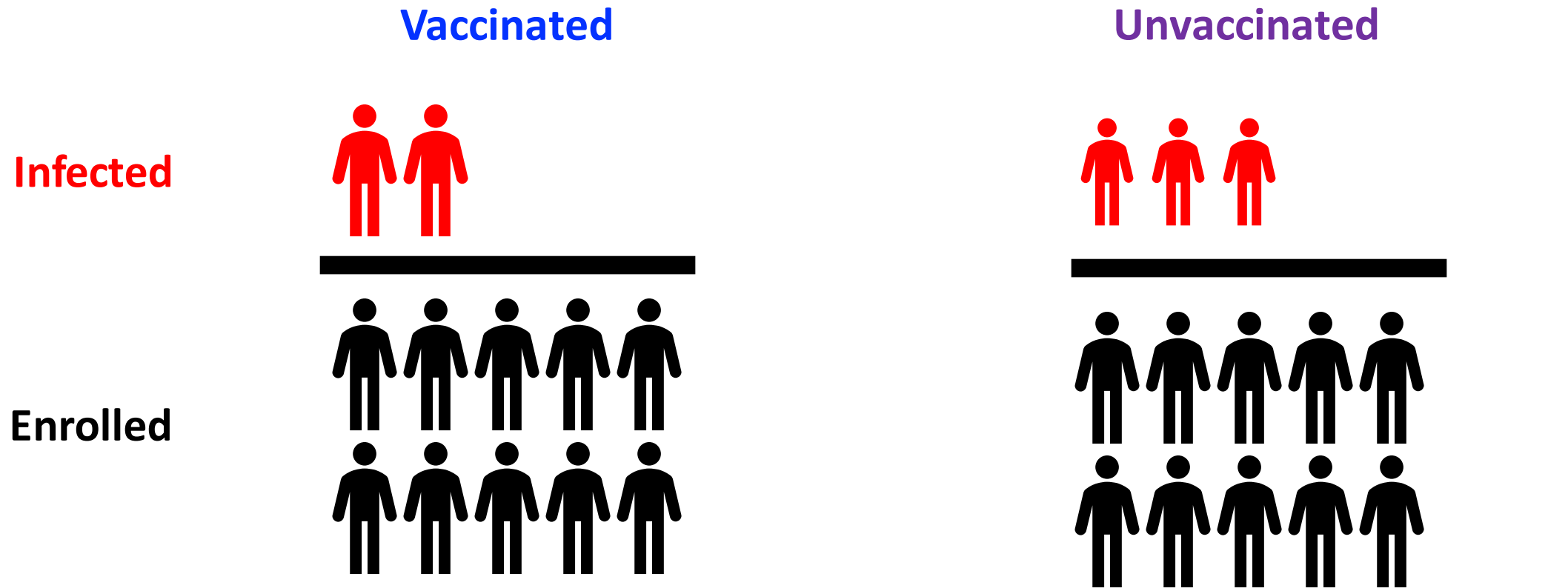
- Estimates of vaccine effectiveness (VE) over time are subject to bias from differential depletion of susceptibles between vaccinated and unvaccinated.
- Bias occurs when individuals who are no longer at risk of infection due to protection from past infection are included in the analysis.
- Assuming $VE > 0$, these individuals are more likely to be unvaccinated than vaccinated (*differential* depletion by vaccine status).
- Over time, more previously-infected and unvaccinated individuals who are at low/no risk of infection are included in the analysis, biasing VE estimates downward (spurious waning).
- Can also occur due to heterogeneous risk in the population.

Example: true VE = 60%

Biased VE



Biased VE



$$\text{Estimated VE} = 1 - \frac{2/10}{3/10} = 33\%$$

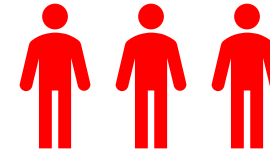
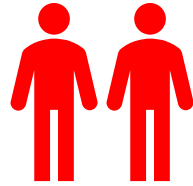
$$\text{True VE} = 60\%$$

Unbiased VE

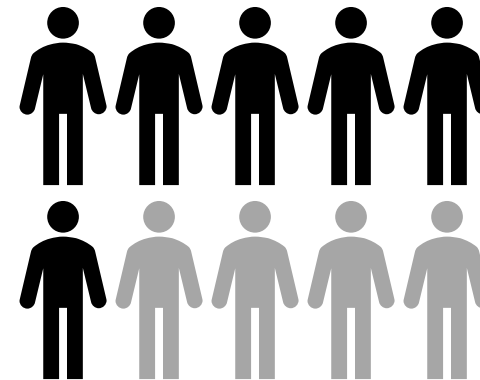
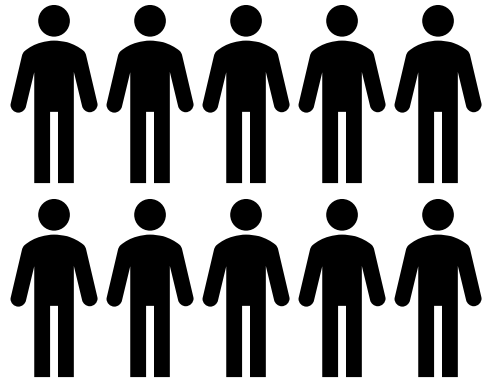
Vaccinated

Unvaccinated

Infected

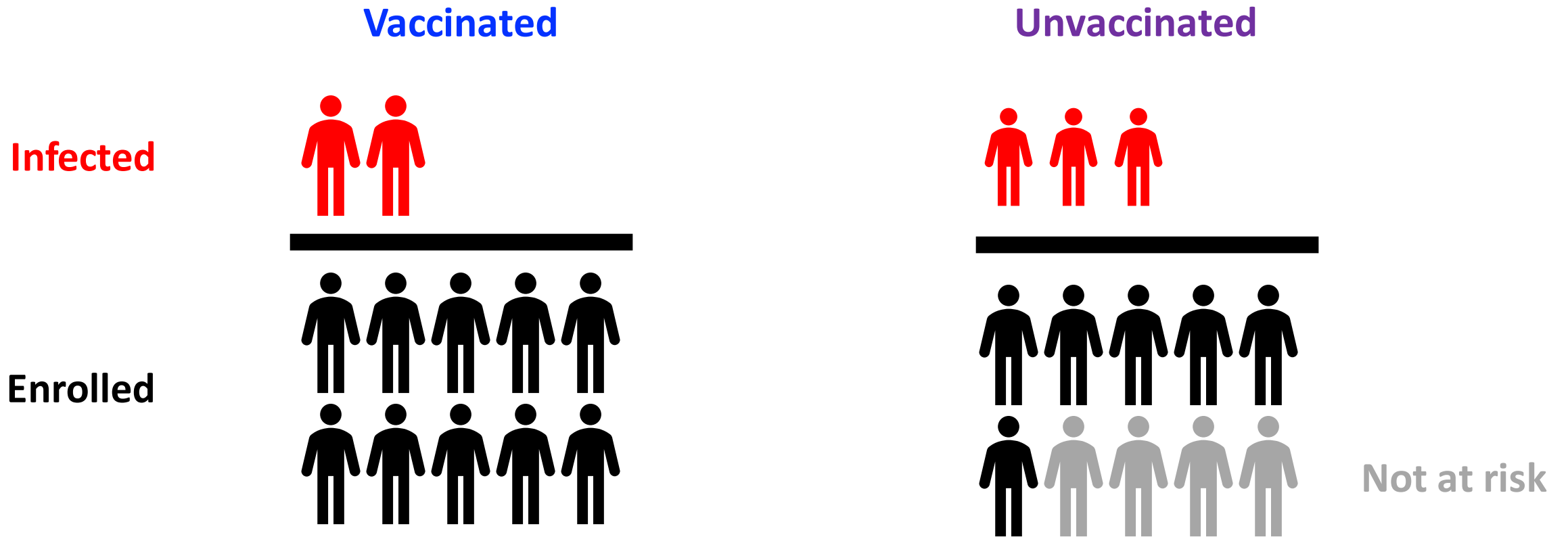


Enrolled



Not at risk

Unbiased VE



$$\text{Estimated VE} = 1 - \frac{2/10}{3/6} = 60\%$$

True VE = 60%

Challenges with examples

- True waning and spurious waning due to differential depletion of susceptibles can occur at the same time
 - Disentangling these different effects can be hard
- Defining susceptibles
 - Reinfection – people with prior infection become susceptible again

Example: SARS-CoV-2

- Waning began to be observed a few months after vaccine introduction
 - Question: could this be driven by bias?
- Simulations
 - Larger bias when initial VE is lower
 - Larger bias in test-negative design than cohort studies
- Given the high initial VE, these findings suggested the waning was not all due to bias

JOURNAL ARTICLE

Identifying and Alleviating Bias Due to Differential Depletion of Susceptible People in Postmarketing Evaluations of COVID-19 Vaccines FREE

Rebecca Kahn ✉, Stephanie J Schrag, Jennifer R Verani, Marc Lipsitch

American Journal of Epidemiology, Volume 191, Issue 5, May 2022, Pages 800–811, <https://doi.org/10.1093/aje/kwac015>

Published: 27 January 2022 [Article history](#)

JOURNAL ARTICLE

Waning of 2-Dose BNT162b2 and mRNA-1273 Vaccine Effectiveness Against Symptomatic SARS-CoV-2 Infection Accounting for Depletion-of-Susceptibles Bias Open Access

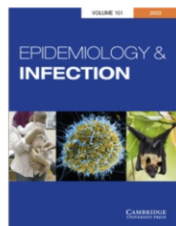
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American Journal of Epidemiology, Volume 192, Issue 6, June 2023, Pages 895–907, <https://doi.org/10.1093/aje/kwad017>

Published: 24 January 2023 [Article history](#)

Example: Influenza

- When differential depletion of susceptibles is a concern:
 - 1) after periods of high incidence during which some were already vaccinated and others weren't AND
 - 2a) when immunizing events are often not observable (i.e. very mild infections that are not identified) OR
 - 2b) there is high heterogeneity in exposure or susceptibility to infection that is not adjusted for in the analysis



Depletion-of-susceptibles bias in influenza vaccine waning studies: how to ensure robust results

Published online by Cambridge University Press: 27 November 2019

M. Lipsitch , E. Goldstein, G. T. Ray and B. Fireman

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Thank you!