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Main expertise:

Statistics/Modelling infectious diseases

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VERBINDT GEZONDHEID, WETENSCHAP EN SAMENLEVING

Estimating VE using eHR

Strenghts and Weaknesses

AIB - May 2026

.be

Early decision making

Early 18th century:

Anecdote, personal 'lived' experience

Quickly followed by data-driven analysis

James Jurin: An account of the success of inoculating the small-pox (1723-1727)

Daniel Bernoulli: An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation to prevent it (1760)

'I simply wish that, in a matter which so closely concerns the wellbeing of the human race, no decision shall be made without all the knowledge which a little analysis and calculation can provide'

Focus on **safety** analysis

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Early decision making

Critique on the work of Jurin & Bernoullie:

(D'Alembert, 1760, in todays terminology)

In addition to a more philosopical critique (societal vs individual perspective), a methodological critique:

-Data quality / Competing risks / Healthy vaccinee effect / Confounding / Selection

The introduction of vaccination (1796, Jenner):

Levels of evidence:

Does it work or doesn't it: *proof-of-concept immmunological demonstration (challenge)*

Trends in (cause-specific) mortality

These levels of evidence are challenged by the end of the 19th century

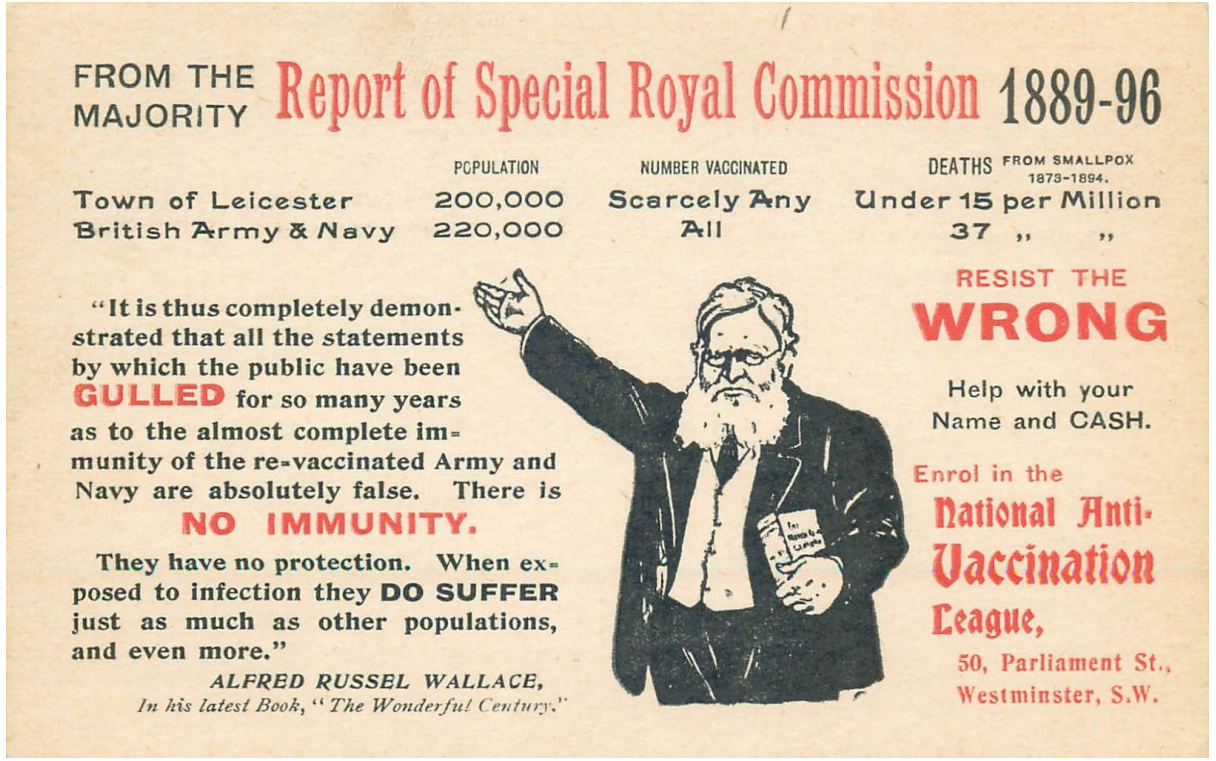
Early decision making

Arriving at VE:

*Outbreaks of smallpox at the end of the 19th century, despite mandatory vaccination

Trends in previous years were 'confounded' (by sanitation) (smallpox, cholera and typhoid)

⇒ Royal Commission on Vaccination (1889-1896)
- ⇒ Collecting all available data
  - ⇒ Prisons/military/hospitals
- ⇒ Lacking most of the statistical tools



A framework and its challenges

VE from observed data:

*The Boer War typhoid inoculation controversy (1900)

Wright introduced a vaccine, inoculated volunteers

Statistical analysis/data collection of its effectiveness was much debated

⇒ How to formally analyze observational vaccine data?

⇒ Pearson, Greenwood & Yule

- ⇒ 1915 paper
- ⇒ The statistics of anti-thyphoid and anti-cholera inoculations
- ⇒ Critical audit/Methodological proposal
  - ⇒ Contingency table logic **(1-RR)**
  - ⇒ Clearly grappling with observational data
    - ⇒ Dispersion!

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Solution: Randomization

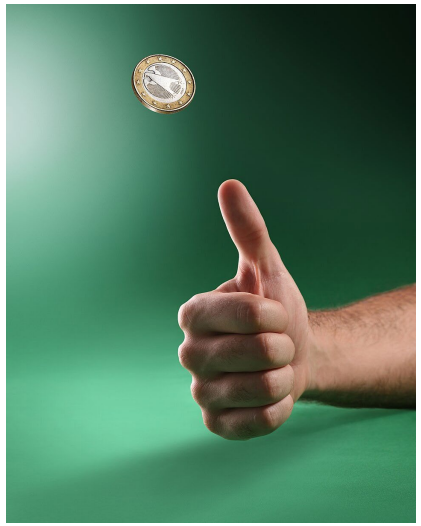
20th century evolution:

Confounding/selection hampers causal inference

*Design-based (alternative path) solutions:

⇒ Randomization (mid 20th century) => causal inference

- ⇒ Thalidomide (1961) => RCTs for pre-licensure efficacy/safety
- ⇒ Safety got institutionalized



⇒ Post-licensure a need remains:

- ⇒ Seasonal influenza: annual strain mismatch
- ⇒ COVID-19: variants, waning, hybrid immunity, immunocompromised

⇒ VE-estimation: still confounding, healthy vaccinee effect and heterogeneity!

Solution: Statistics

20th century statistics innovations:

*1918 influenza pandemic (*bacillus of influenza* vaccine)

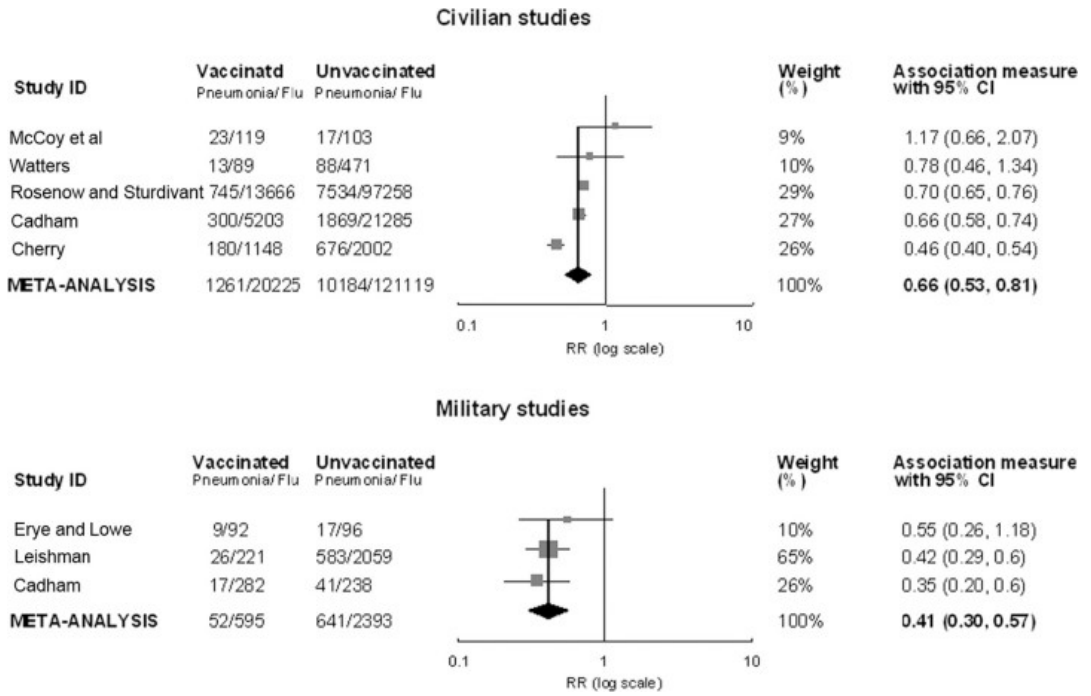
⇒ “No inferences can be drawn from a lower attack rate upon inoculated than upon uninoculated persons if the inoculations were carried out during the epidemic, without due allowance for variations of length of exposure.”

Data have been (re-)analyzed in 2010:

-Uncertainty: Risk ration with **confidence intervals** (1950)

-Heterogeneity: **Meta-analysis** (1970-80), I^2 (2003), **random-effect** models

-Presentation: Funnel plots (1984), trim-and-fill (2000)



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Solution: (More) Data

Stratification and adjusting:

*The statistics toolbox needs data

⇒ Regression adjustment

⇒ Propensity scoring

⇒ Random effects & meta-analysis for heterogeneity

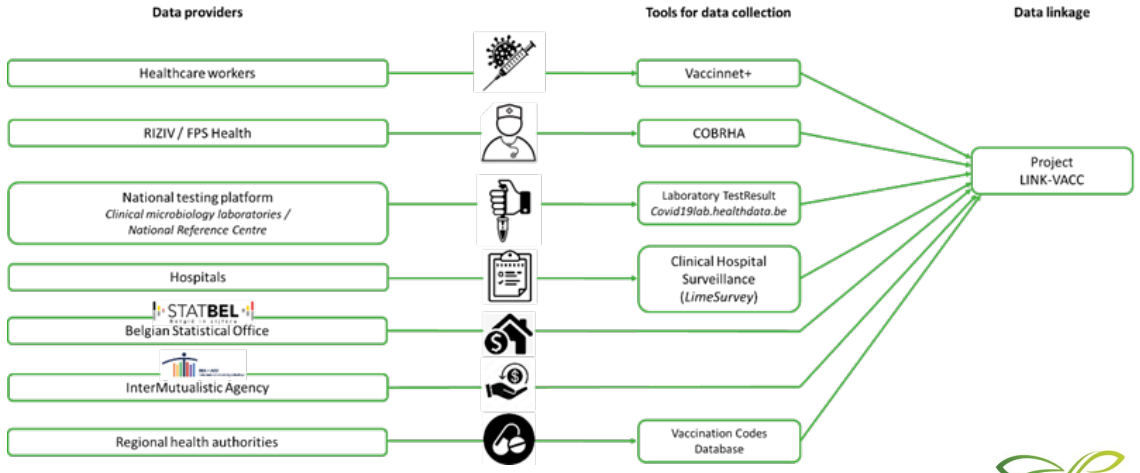
⇒ Time-to-even analysis

⇒ Kaplan-Meier and Cox PH, more precise and efficient method, but does not solve their core issue

*Samples of convenience (**EHR**)

⇒ EHR against unmeasured confounding?

⇒ A solid case for combining over epidemics/borders/settings/sources



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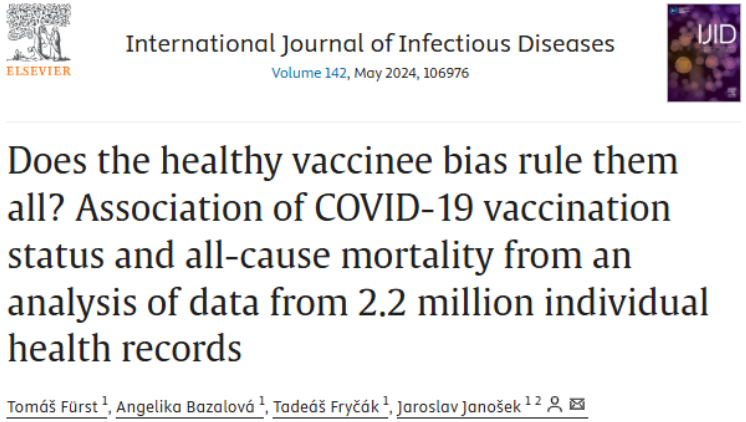
Solution: Design

Confounding/selection hampers causal inference

*Design-based (alternative path) solutions:


International Journal of Infectious Diseases
Volume 142, May 2024, 106976

Does the healthy vaccinee bias rule them all? Association of COVID-19 vaccination status and all-cause mortality from an analysis of data from 2.2 million individual health records

Tomáš Fürst [1], Angelika Bazalová [1], Tadeáš Fryčák [1], Jaroslav Janošek [1 2]

⇒ Test-negative design (early 2000), preceded by indirect cohort methods
- ⇒ Trades one bias (healthcare-seeking) for another (collider bias)
- ⇒ Strong assumptions

⇒ Self-controlled case series (1995)
- ⇒ Eliminates all time-fixed confounding by design
- ⇒ Requires rare-event assumptions and ‘temporal’ (eventually dissapearing effects)

⇒ ‘Natural experiments’ (regression discontinuity)
- ⇒ Find an artificial cut-off (vaccinees > 18y, compare 17y to 18y)

Solution: Diagnostics

⇒ Negative controls
  ⇒ Empirical measure for bias
  ⇒ Do not try to have comparable groups of vaccinees and non-vaccinees, but try to estimate the difference

⇒ Difference-in-differences
  ⇒ Similarly, try and correct for the ‘difference’ (between vaccinees and non-vaccinees)

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Solution: Institutionalize efforts

- ⇒ I-MOVE (Influenza – Monitoring Vaccine Effectiveness in Europe)
  - ⇒ 2007 -2022
  - ⇒ Voluntary, operational research project with funding rounds
- ⇒ Strenghtened Cooperaton against Vaccine Preventable Diseases
  - ⇒ 2018 Council recommendation
- ⇒ VEBIS (Vaccine Effectiveness Burden and Impact studies)
  - ⇒ 2021
  - ⇒ Absorved I-MOVE
  - ⇒ Epiconcept
- ⇒ ECDC reinforced mandate (European Parliament 10/2022) & EMA's reinforced mandate
  - ⇒ Vaccine Monitoring Platform (VMP)
  - ⇒ An umbrella for VEBIS

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VEBIS

⇒ Epiconcept reaches out to public health institutes
  ⇒ Lot 4 (EHR) Belgium joined in 2022
  ⇒ VE and the impact of COVID-19 vaccines through routine collected exposure and outcome data using health registries

Influenza and other respiratory viruses Open Access | ISRV International Society for Respiratory Viruses | Forward Series

ORIGINAL ARTICLE | Open Access

Monitoring COVID-19 vaccine effectiveness against COVID-19 hospitalisation and death using electronic health registries in ≥65 years old population in six European countries, October 2021 to November 2022

Irina Kislaya, Alexis Sentís, Jostein Starrfelt, Baltazar Nunes, Iván Martínez-Baz, Katrine Finderup Nielsen, Ala'a AlKerwi, Toon Braeye, Mario Fontán-Vela ... See all authors

First published: 28 November 2023 | https://doi.org/10.1111/irv.13195 | VIEW METRICS

⇒ Work separation
  ⇒ National: Data collection and analysis
  ⇒ Epiconcept: methods (code), meta-analysis, outputs

⇒ Benefit: Routine meta-analysis of *same-ish* estimates
  ⇒ Different data sources (eg Belgium has no data on unvaccinated/untested persons)
  ⇒ Different national models (eg confounder adjusting is country-specific)
  ⇒ National institutes simply do not have the power (man-power and statistical power) and incentive to achieve this regular reporting

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VEBIS

- ⇒ Novel methods/innovation
  - ⇒ Specific populations
    - ⇒ Immunocompromised
  - ⇒ Impact analysis
    - ⇒ Events averted
  - ⇒ TTE
    - ⇒ Counterfactual
    - ⇒ Alternative trajectories

Comparison of two methods for the estimation of COVID-19 vaccine effectiveness of the autumnal booster within the VEBIS-EHR network in 2022/23

Published online by Cambridge University Press: **17 March 2025**

Susana Monge, James Humphreys, Nathalie Nicolay, Toon Braeye, Izaak Van Evercooren, Christian Holm Hansen, Hanne-Dorthe Emborg, Massimo Fabiani, Chiara Sacco and Jesús Castilla ...Show all authors Show author details

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Evolution

Expanding Greenwood-Yule's framework to « more informative » metrics:

*Absolute numbers and counterfactual are very helpful for policy-makers

*High VE != « worth investing in » (low impact, many competing risks)

Counterfactual count: Absolute numbers

⇒ Impact analysis

- ⇒ Number of events averted = Coverage*Incidence*VE
- ⇒ Counterfactual count

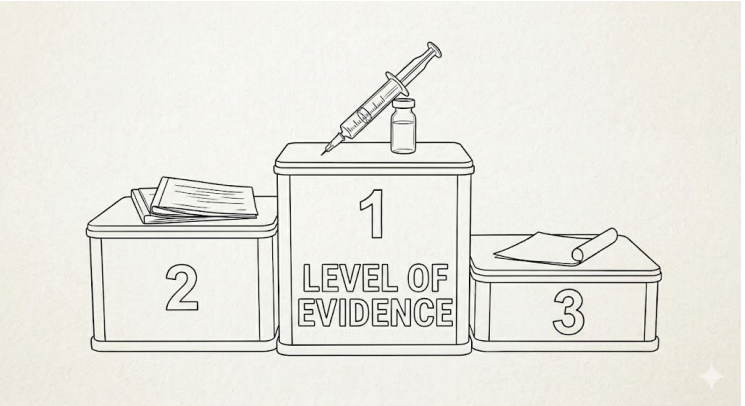
Counterfactual trajectories & Absolute numbers in person-time

⇒ Causal inference – Target Trail Emulation (TTE) / g-estimation / g-computation

⇒ Counterfactual trajectory

- ⇒ Life years saved
- ⇒ Vaccinees != non-vaccinees (if recorded)
- ⇒ Makes assumptions explicit
- ⇒ Handles competing risks

Conclusion



!High standards for vaccine recommandations!

History of mandates & injecting healthy persons & children

⇔ Cancer screening (opt-in)

⇔ Surgical procedures (clinical decision)

Greenwood-Yule's 1915 paper remains relevant

The toolbox expanded, but observed/routine collected data are vulnerable to biases

⇒ Negative control (quantify bias)

⇒ A continued push for data (confounder adjusting)

⇒ Counterfactuals (life-years gained & cost-benefit) speak to decision makers in ways that RR doesn't => active stakeholders

National and international incentives

Real-world effectiveness monitoring is essential to optimize protection, manage expectations, and maintain public trust — the cost of monitoring is trivial against the cost of a suboptimal schedule

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