Name: Alexander Domnich

Adult Immunization Board

Country: Italy

Affiliation: IRCCS Ospedale Policlinico San Martino

Function: Physician

Main expertise: Influenza epidemiology and prevention

Università degli Studi Firenze DSS Dipartimento di Scienze della Salute

University of Antwerp

Use of real-world data to complement experimental studies

Alexander Domnich, MD, PhD

Background

Continuum[1]

Randomization

Comparability between groups

Can it work?

Real-world evidence

(Comparative) effectiveness in the real world

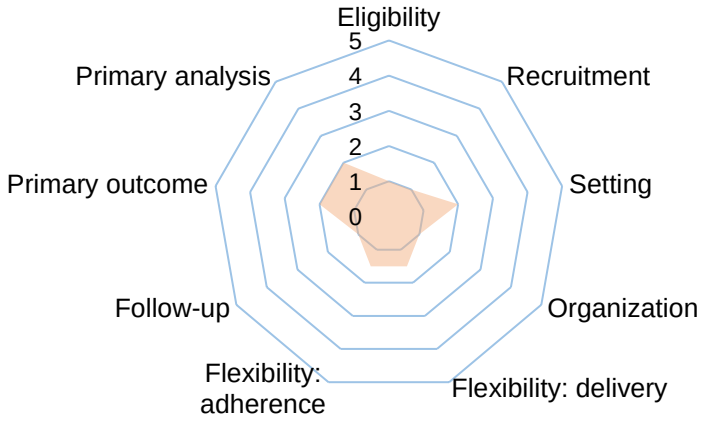
Does it work (help)?

Internal validity

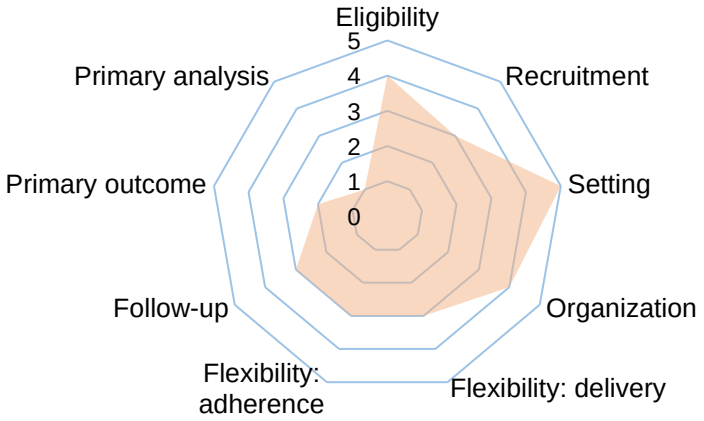
Bias

External validity

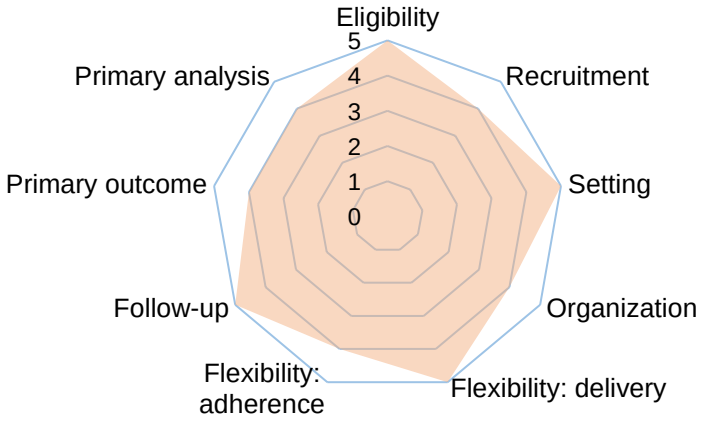
Explanatory clinical trials



Pragmatic randomized trial

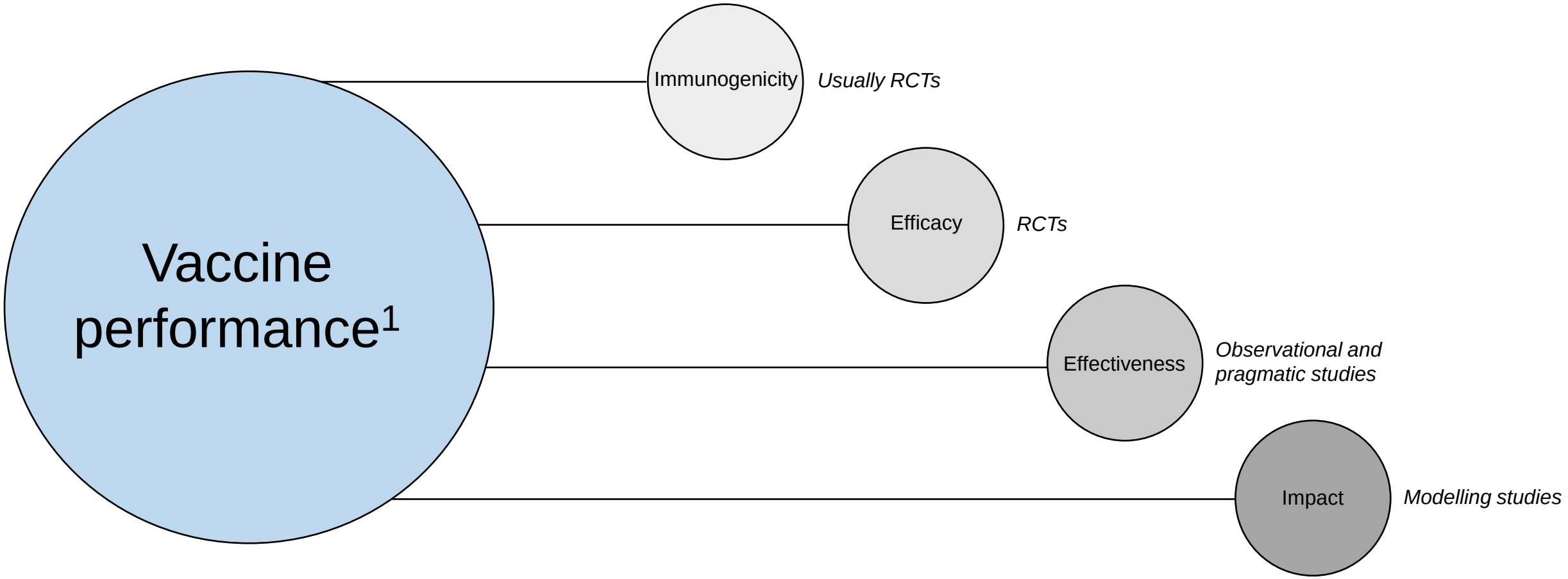


Retrospective observational study



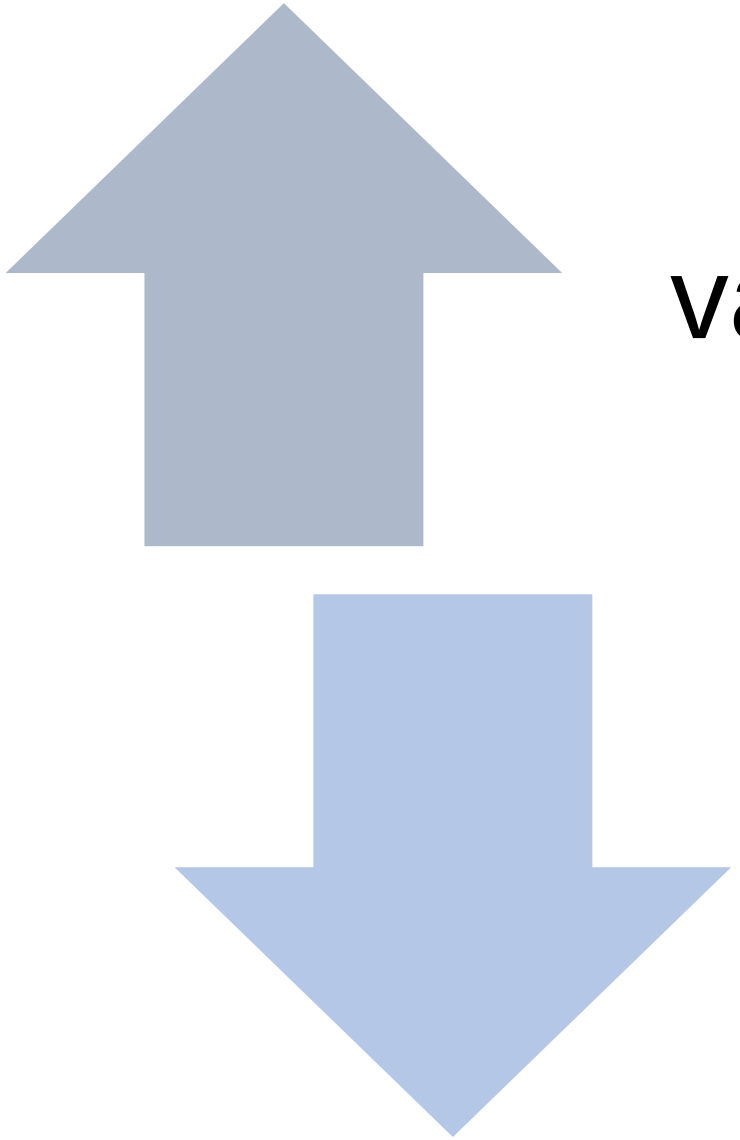
1. Jeong et al. Cardiovasc Prev Pharmacother. 2020;2(3):85-98.

Evaluation of vaccine performance



1. WHO. https://www.emro.who.int/images/stories/evidence-data/VE-studies-to-guide-immunization-policy.pdf

Bias and confounding in observational studies



Healthy vaccinee effect

Subjects who are in better health conditions are more likely to adhere to preventive measures like vaccination.
*It leads to an **overestimation** of vaccine effectiveness.*[1]

Confounding by indication

Subjects with underlying health conditions are more likely to be vaccinated (or to receive an “enhanced” vaccine formulation) than healthy study participants.
*It leads to an **underestimation** of vaccine effectiveness.*[1]

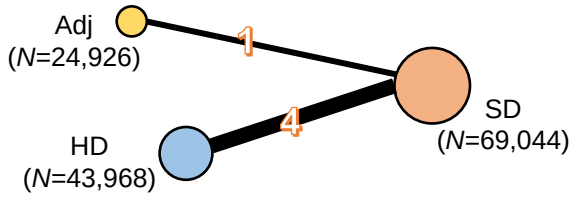
1. Remschmidt et al. BMC Infect Dis. 2015;15:429.

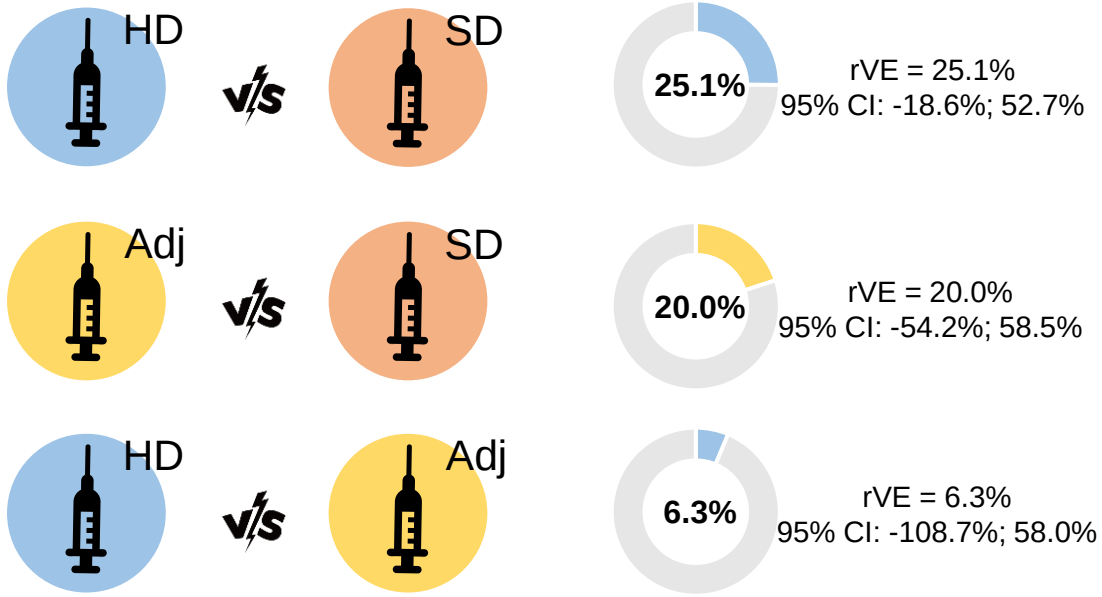
Treatment effects: randomized vs non-randomized studies

Network meta-analysis of randomized studies[1]

Outcome: Influenza (coded and/or confirmed)

Network:

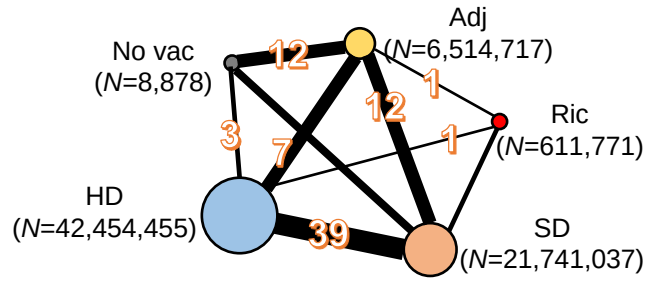


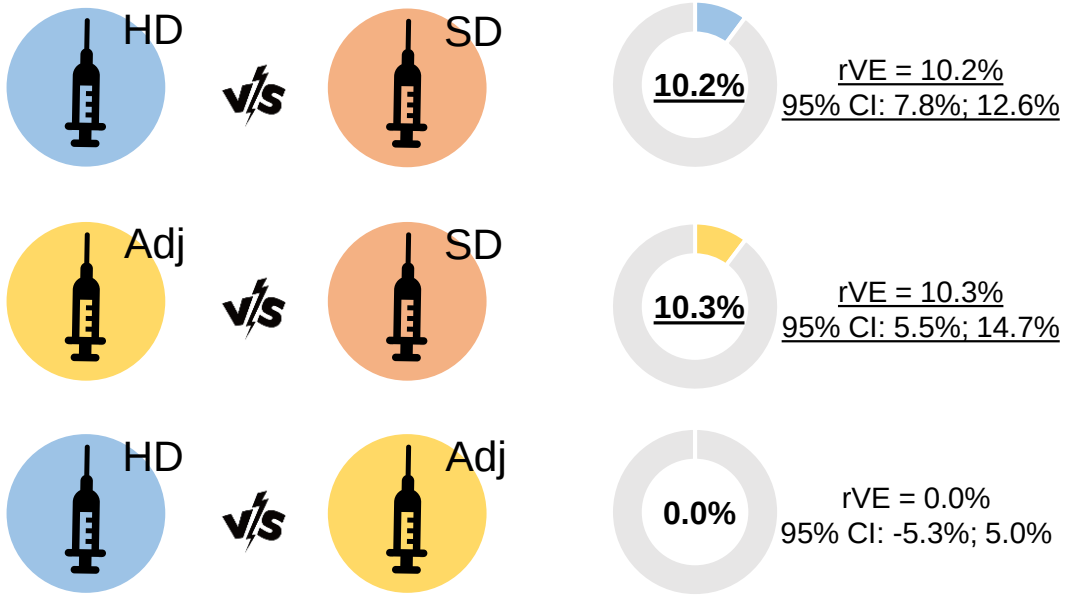


Network meta-analysis of observational studies[1]

Outcome: Influenza (coded and/or confirmed)

Network:





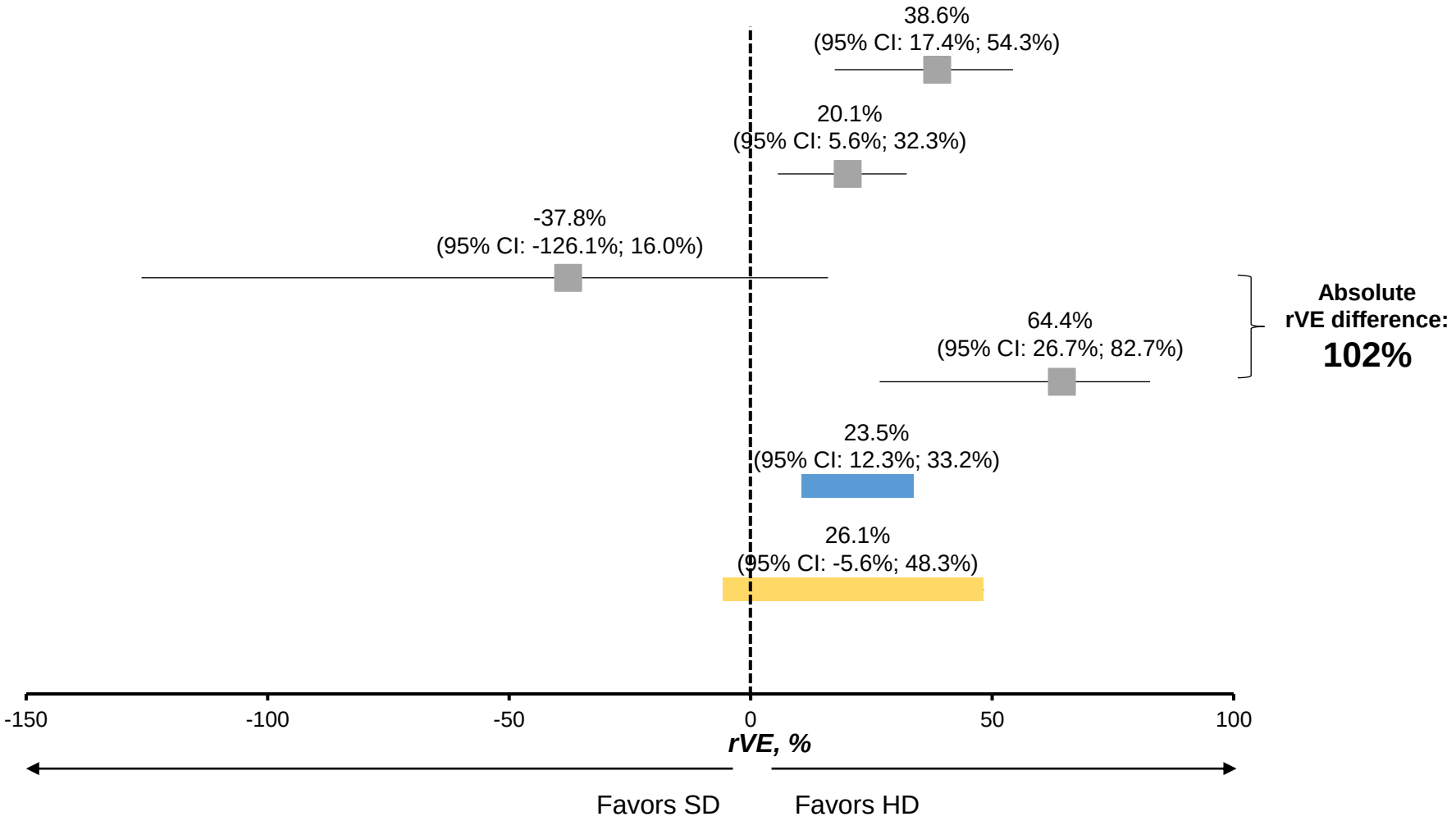
Statistically significant (P<.05) estimates are underlined

1. Ferdinands et al. J Am Geriatr Soc. 2024;72(12):3875-89.

Randomized studies and heterogeneity

Meta-analysis of randomized studies high-dose vs standard-dose influenza vaccines[1]

Outcome: Hospitalization for pneumonia and/or influenza



1. Skaarup et al. J Infect. 2024;89(1):106187; 2. DiazGranados et al. Vaccine. 2015;33(38):4988-93; 3. Gravenstein et al. Lancet Respir Med. 2017;5(9):738-46; 4. Vardeni et al. JAMA. 2021;325(1):39-49; 5. Johansen et al. NEJM Evid. 2023;2(2):EVIDoa2200206.

RCTs and representativity

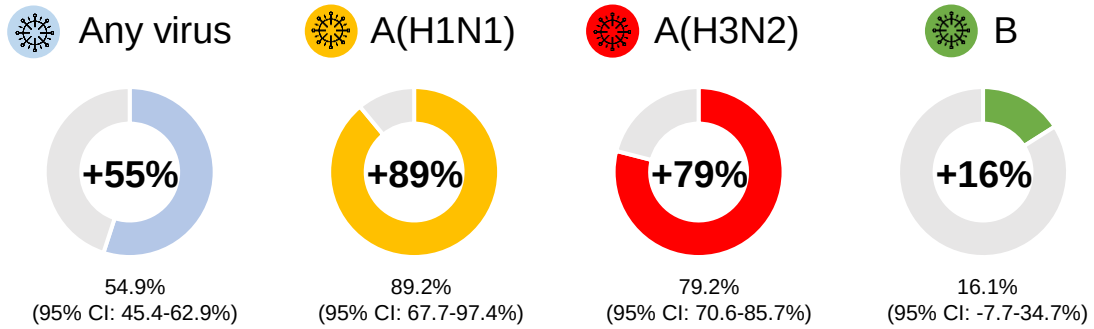
- There are no accepted criteria for a representative population for clinical trial enrolment;
- Major gaps in clinical trial participation during new drug evaluation include insufficient enrollment of:
  - Older adults aged 75 years and older, especially those older than 80 years
  - Those with multimorbidity (i.e., more than 3 chronic conditions)
  - Those receiving polypharmacy (i.e., three or more regular medications)
  - Those with a state of increased vulnerability across multiple health domains that leads to adverse health outcomes.[1]

1. Schwartz. Lancet Healthy Longev. 2023;4(7):e301-e303.

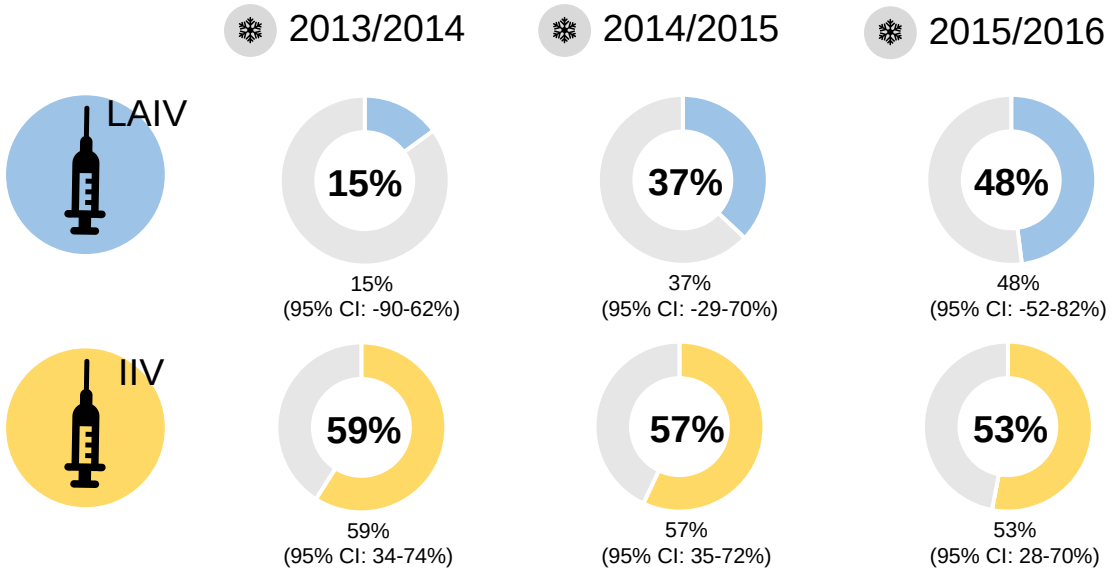
Pivotal role of observational studies (I)

- In June 2014, following review of evidence on the relative efficacy of LAIV compared with IIV for healthy children, ACIP recommended that when immediately available, LAIV should be used for healthy children aged 2 through 8 years who have no contraindications or precautions.[1]
- However, data from subsequent observational studies of LAIV and IIV vaccine effectiveness indicated that LAIV did not perform as well as expected based upon the observations in earlier randomized trials.[1]
- In the absence of data demonstrating consistent greater relative effectiveness of the current quadrivalent formulation of LAIV, preference for LAIV over IIV was no longer recommended.[1]

RCT data: Relative efficacy LAIV vs TIV (season 2004/2005)[2]



Observational data (TND): Absolute effectiveness of LAIV and IIV against influenza A[3]

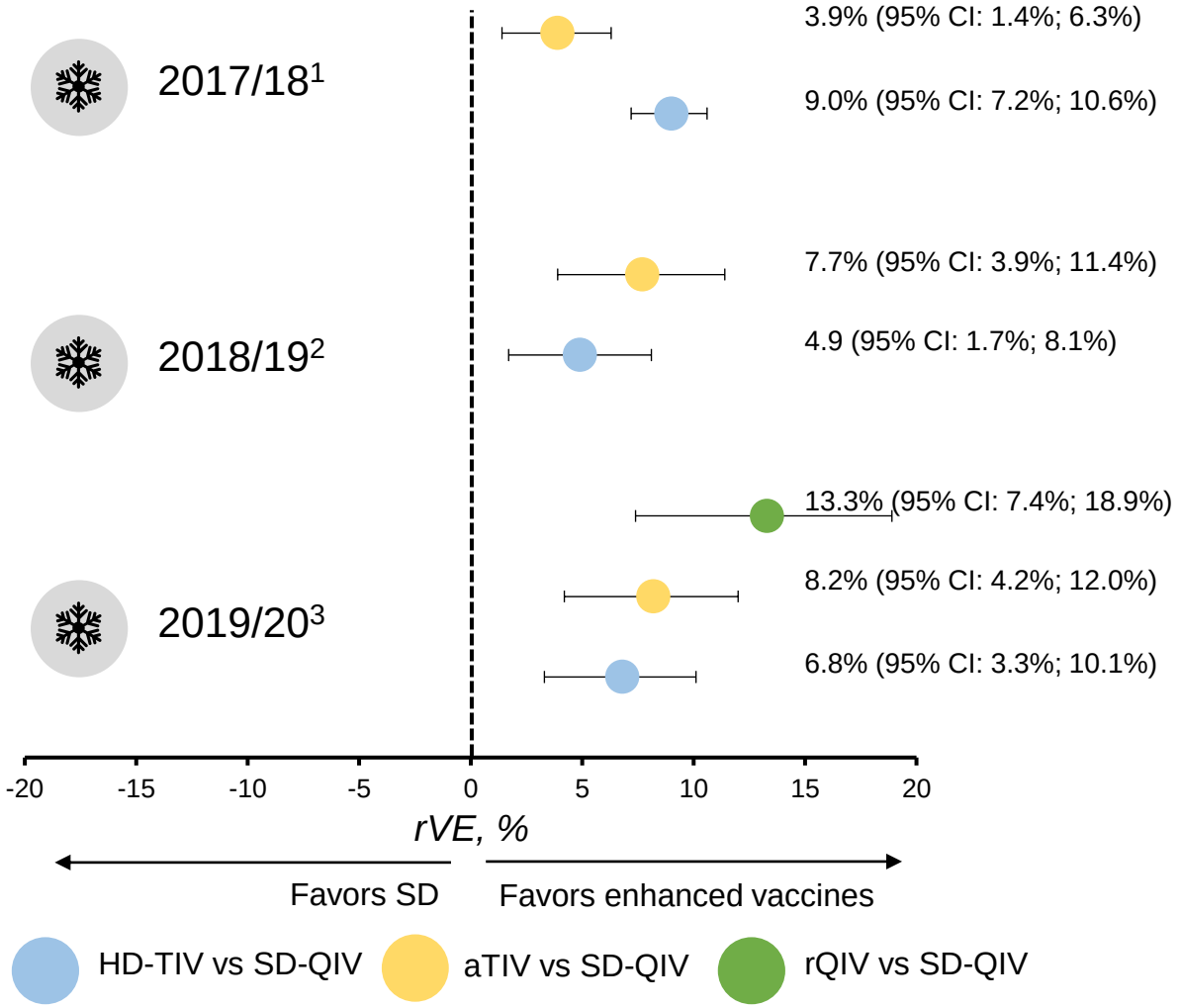


1. Grohskopf et al. MMWR Morb Mortal Wkly Rep. 2015;64(30):818-25; 2. Belshe et al. N Engl J Med. 2007;356(7):685-96; 3. Valdin et al. Vaccine. 2017;35(33):4088-93.

Pivotal role of observational studies (II)

- Background:
  - In 2014, one RCT[1] showed a significant relative vaccine efficacy of HD-TIV vs SD-TIV against lab-confirmed influenza in the adults aged ≥65 years (rVE: 24.2%; 95% CI: 9.7%; 36.5%)
  - In 2017, another RCT[2] showed a significant relative vaccine efficacy of rQIV vs SD-QIV against lab-confirmed influenza in adults aged ≥50 years (rVE: 30%; 95% CI: 10%; 47%)
  - Adjuvanted vaccine has no relative efficacy RCTs and it failed the primary endpoint in an absolute efficacy (i.e., versus non-active comparator) RCT in the elderly;[3]
- Despite this and until the 2021/2022 season, the US ACIP did not recommend preferentially any specific influenza vaccine for the elderly;[4]
- Large (~13 million) FDA-funded retrospective cohort studies conducted in three consecutive seasons (from 2017/2018 to 2019/2020) among Medicare beneficiaries aged ≥65 years showed a constant benefits of all three enhanced vaccines in preventing hospitalization for influenza. The effect size was plausible;[5-7]
- Starting from the 2022/2023 influenza season, the US ACIP has recommended[8] that adults aged ≥65 years should receive one of the following: high-dose, recombinant or adjuvanted vaccines (i.e., preference over standard-dose vaccines).

Relative effectiveness of the enhanced vs standard-dose influenza vaccines, by season



1. DiazGranados et al. N Engl J Med. 2014;371(7):635-45; 2. Dunkle et al. N Engl J Med. 2017;376(25):2427-36; 3. Beran et al. Lancet Infect Dis. 2021;21(7):1027-37; 4. Grohskopf et al. MMWR Recomm Rep. 2021;70(5):1-28; 5. Izurieta et al. J Infect Dis. 2019;220(8):1255-64; 6. Izurieta et al. J Infect Dis. 2020;222(2):278-87; 7. Izurieta et al. Clin Infect Dis. 2021;73(11):e4251-9; 8. Grohskopf et al. MMWR Recomm Rep. 2022;71(1):1–28.

Vaccine Monitoring Platform

The Vaccine Monitoring Platform (VMP) is a collaboration between the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) aiming to generate real-word evidence (RWE) on the safety, effectiveness and use of vaccines in the European Union (EU) and the European Economic Area (EEA).

Human | Vaccines

EMA and ECDC set up the research agenda based on categories of research topics which include:

Data gaps for authorized vaccines
Diseases for which post-authorization monitoring is a priority due to change in vaccine composition (e.g. flu and COVID-19)
Developing or re-purposing vaccines to support their use during a public health emergency
Preparedness for the evaluation of future vaccines (e.g. burden of a disease)
Post-authorization monitoring of vaccines to inform their benefit / risk profile[1]

1. EMA. https://www.ema.europa.eu/en/about-us/what-we-do/crisis-preparedness-management/vaccine-monitoring-platform

OPTIMAL framework

The EU OPTIMAL framework for RWE consists of 3 pillars: operational, technical, and methodological[1]

Objective

Appropriate use of valid RWE for regulatory purposes (e.g. safety, efficacy, benefit–risk monitoring)

Desired criteria

Evidence is:

- Derived from data source of demonstrated good quality
- Valid (internal and external validity)
- Consistent (across countries/data sources)
- Adequate (e.g., precision, adequate range of characteristics of population covered, dose and duration of treatment, length of follow-up)

Challenges

Operational:

- Feasibility (e.g., data access and cost, availability of relevant data needed, data protection, patients' consent, availability of hospital data source)
- Governance (e.g., data-sharing policy, transparency, policy towards funding source)
- Sustainability (sustained data collection and analysis)

Technical:

- Extent of data collected on clinical outcomes, exposure, and individuals
- Collection of adequate time elements
- Data completeness (missing data)
- Consistent use of appropriate terminologies and data formats
- Potential for data linkage
- Consistent, accurate, and timely data collection, recording, and management

Methodological:

- Variability in results from multi–data source studies.
- Understanding the data source environment
- Adequate data collection on potential confounders and effect modifiers
- Identifying the potential for selection bias and information bias
- Management of missing data
- Sound data analysis and interpretation

Solutions

Operational:

- Early and repeated consideration of the need for RWD during drug development
- Landscaping of potential data sources
- Long-term funding for data infrastructures
- Management of access in line with GDPR
- Data anonymization processes where required
- Data sharing agreements at study inception

Technical:

- Use of common data elements, data formats and terminologies, or mapping to international system
- Partial or full data mapping to CDM, including routine validation process
- Quality assurance and control procedures—indicators of data quality
- Internal or external data audit
- Benchmarking to external data source
- EMA qualification procedure for data source

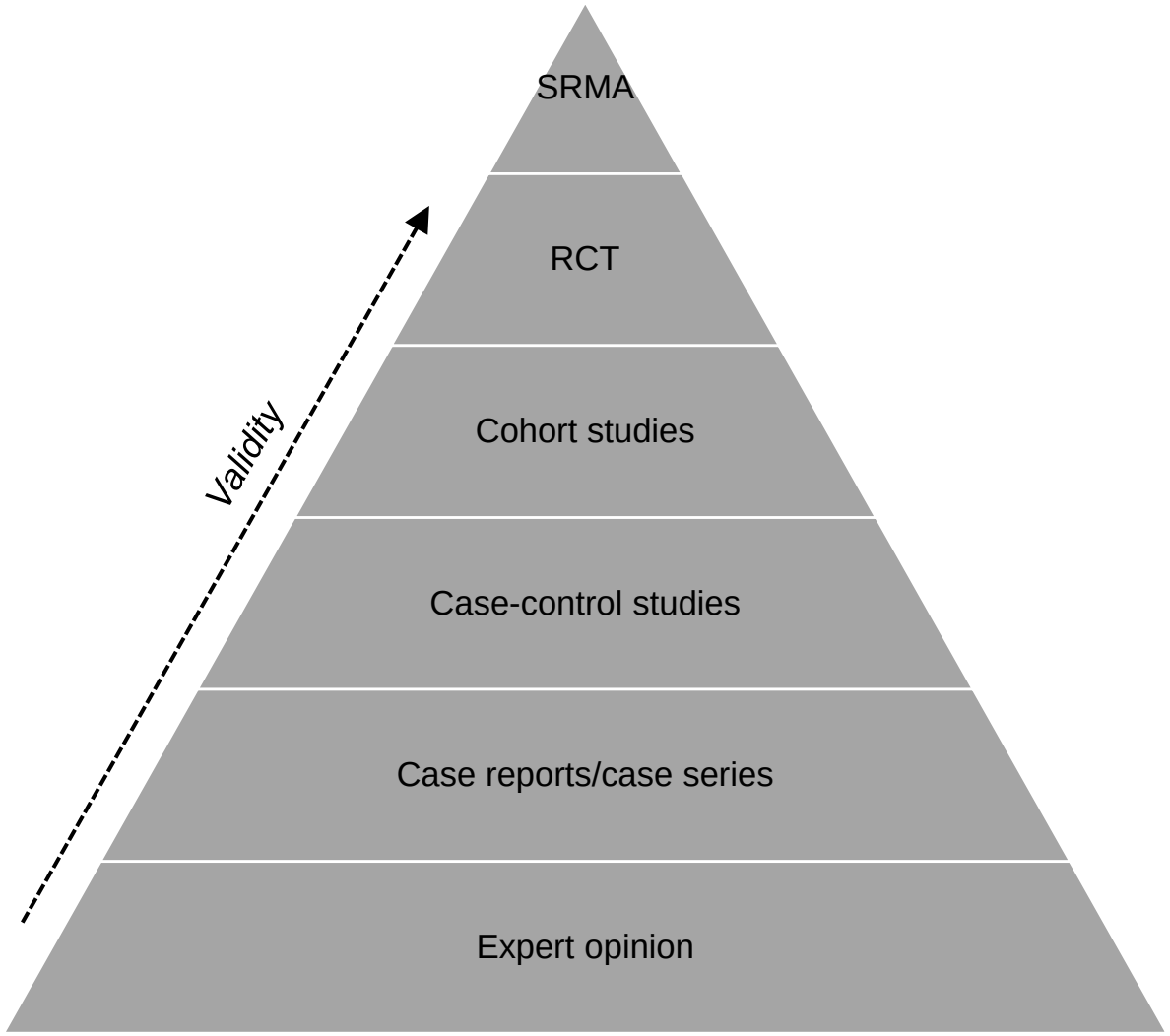
Methodological:

- Detailed description of study design and data collected in data sources
- Documentation of feasibility analyses
- Registration of study in public database, with study protocols and results
- Use of best methodological standards in statistics and epidemiology
- Use of EMA Scientific Advice procedures for study protocols

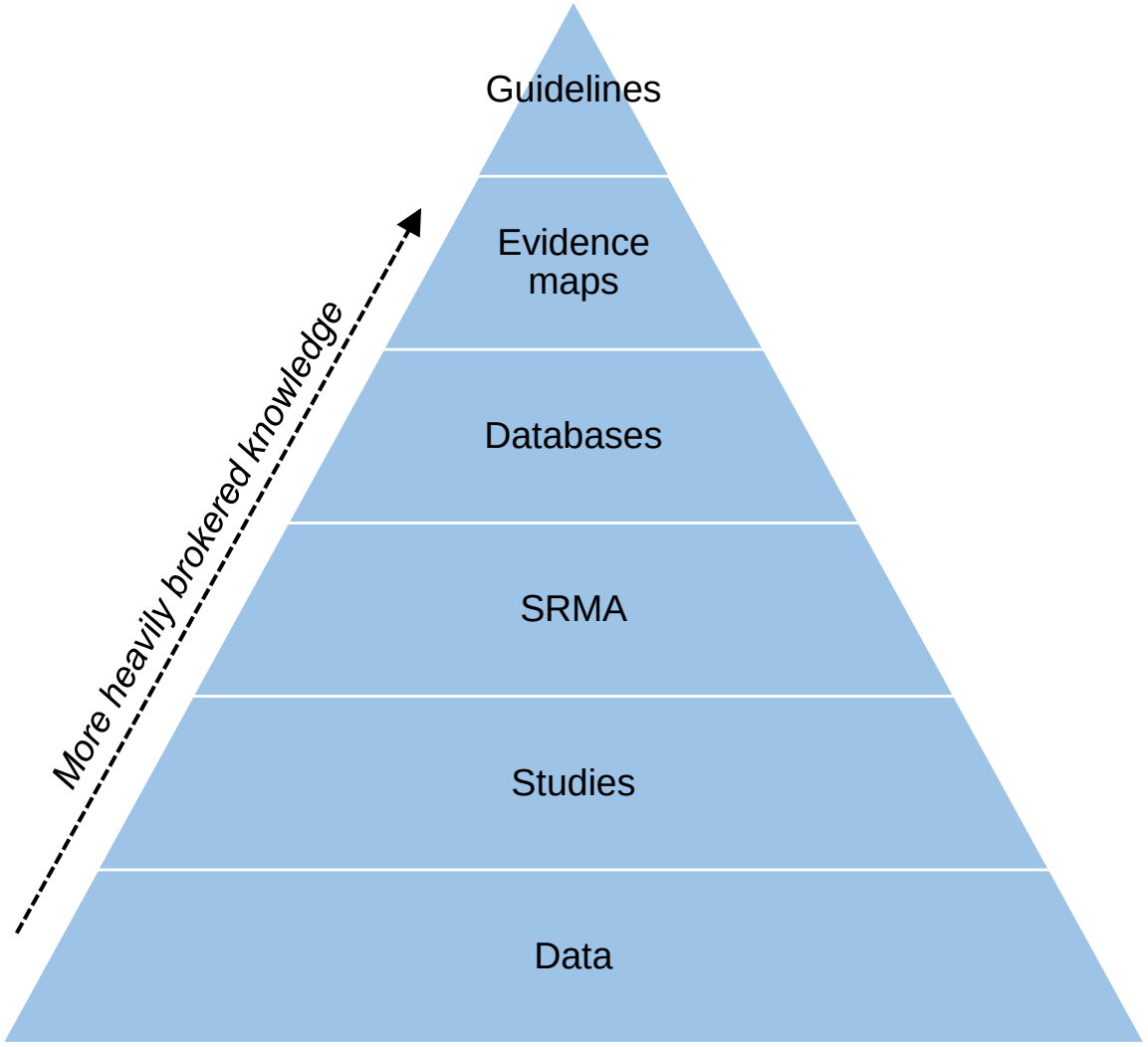
1. Cave et al. Clin Pharmacol Ther. 2019;106(1):36–39.

Evidence vs knowledge

Evidence-based pyramid



Knowledge brokering pyramid[1]



1. White. https://campbellcollaboration.org/blog/how-should-we-summarize-bodies-of-evidence-the-emerging-evidence-architecture-for-knowledge-brokering.html

Thank you

alexander.domnich@gmail.com