Applying Target Trial Emulation in Vaccine Research: Methodological Insights and Regulatory Implications

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Background

- Target trial emulation (TTE) provides a rigorous causal inference framework for observational research by following RCT design principles using real-world data (RWD)
- TTE has been increasingly applied in vaccine effectiveness and safety evaluations, particularly during the COVID-19 pandemic
- Regulatory agencies, such as U.S. Food and Drug Administration (FDA) and The European Medicines Agency (EMA), emphasize data reliability, study design rigor, and transparent reporting for real-world evidence (RWE)
- No prior review has simultaneously examined adherence to core TTE principles alongside regulatory guidance in vaccine studies

Objectives

- Systematically review applications of TTE in vaccine research using RWD
- Evaluate adherence to the 7 core TTE design components and FDA regulatory expectations
- Identify methodological gaps and develop actionable guidance for future TTE vaccine studies

Methods

- Searched *PubMed, Embase, and Web of Science* using methodological search terms for TTE and causal inference from January 2021 to August 2025
- Included observational studies using RWD evaluating vaccine effectiveness or safety with comparative, causal inference-based designs (see Table 1)
- Two independent reviewers screened titles/abstracts and full texts; conflicts resolved by senior reviewer
- Extracted data including study metadata, data sources with QC/QA, and 7 core TTE components: eligibility, treatment strategies, assignment procedures, follow-up, outcomes, causal contrasts, and analysis plans
- Mapped FDA RWE guidance to TTE framework for joint assessment of each study

Table 1. Population, Intervention, Comparator, Outcome, Time, and Setting (PICOTS).

	Inclusion Criteria	Exclusion Criteria
Population(s)	No restriction on age, setting, or demographic characteristics. Includes general and special populations	Nonspecific (studies restricted to non-human populations will be excluded).
Interventions	Preventive vaccines for infectious diseases, including viral, bacterial, and parasitic infections (e.g., COVID-19, influenza, HPV, MMR).	Preventive monoclonal antibodies and therapeutic vaccines or immunotherapies for non-infectious conditions (e.g., cancer) will be excluded.
Comparisons	Studies must include a comparator group (e.g., vaccinated vs. unvaccinated or different vaccine regimens).	Single-arm studies without a comparator are excluded.
Outcomes	All clinical vaccine-related outcomes, both effectiveness and safety, will be included. This includes infection incidence, disease severity, hospitalization, ICU admission, mortality, long-term protection, and adverse events.	Studies reporting only immunological outcomes will be excluded unless those outcomes are linked to clinical endpoints.
Time	January 2021 to August 2025	Studies outside this timeframe.
Study Design	Observational studies using RWD. Includes cohort studies, case-control studies (e.g., test-negative design), registry-based studies. Must include comparative effectiveness or causal inference (e.g., TTE).	Non-comparative studies; non-observational designs (protocols, case reports)
Other	Full-text, peer-reviewed original research articles published in English, with no geographic restrictions.	Abstracts, preprints, editorials, commentaries, protocols, dissertations, and reviews.

Results

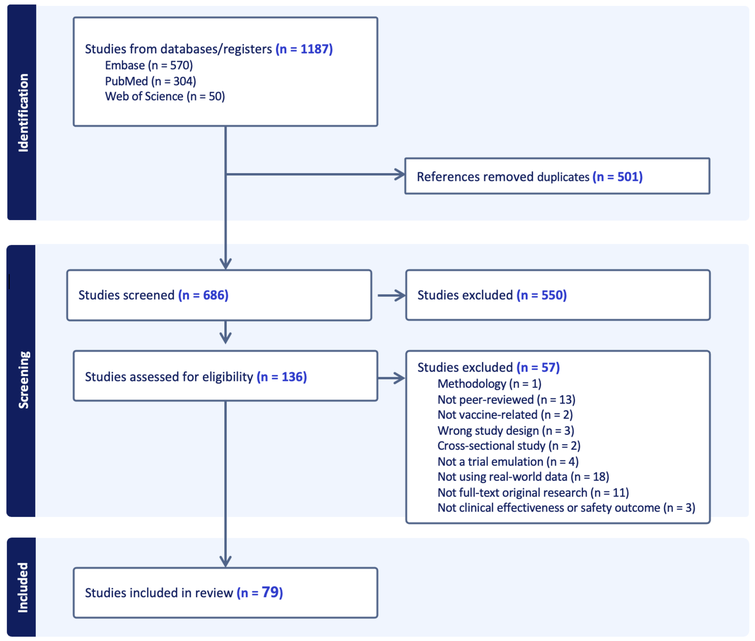

Figure 1. PRISMA flow diagram

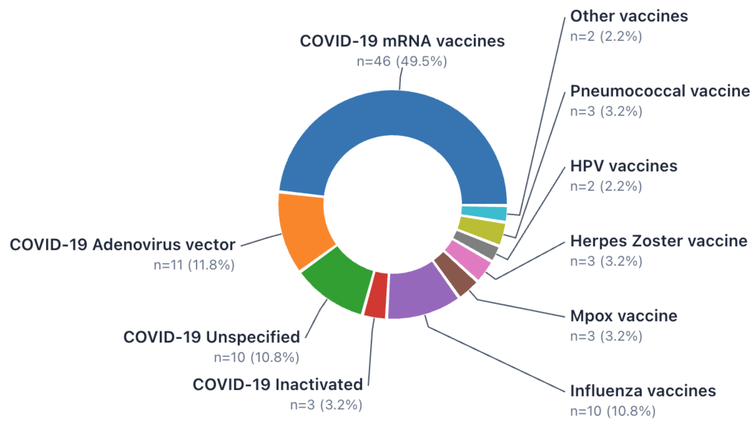

Figure 2. Distribution of vaccine types among included studies (N=79)

Key Study Characteristics

- 79 studies met inclusion criteria; COVID-19 most studied (75.3%), followed by influenza (10.8%)
- Geographically diverse: US (n=26), UK (n=6), Denmark (n=4), Canada (n=3), and 20+ other countries
- Multiple linked datasets (38.0%) and electronic health records (EHRs) (34.2%) were the most common data sources
- Propensity score (PS) matching (n=32), exact matching (n=26), and inverse probability of treatment weighting (IPTW) (n=19) were the most common treatment assignment methods
- Cox proportional hazards models were the most widely used analytical framework
- Three causal contrasts employed: per-protocol, as-treated, and intention-to-treat analyses

Table 2. Assessment of adherence to TTE reporting and regulatory guidelines (N=79)

Domain	Assessment Component	Clearly addressed n (%)	Partially / Not addressed n (%)
✓ STRONG ADHERENCE (≥90%)			
Treatment strategy	Comparator definition	79 (100%)	0/0 (0%)
Analysis plan	Primary metric	79 (100%)	0/0 (0%)
Treatment strategy	Exposure definition / identification	78 (98.7%)	0/1 (1.3%)
Time definition	Time period	77 (97.5%)	1/1 (2.5%)
Analysis plan	Primary models / causal contrast	77 (97.5%)	1/1 (2.5%)
Follow-up	Follow-up start / end	73 (92%)	4/2 (8%)
Assignment procedures	Mimicking randomization	73 (92.4%)	3/3 (7.6%)
⚠ MODERATE ADHERENCE (50–90%)			
Assignment procedures	Time-zero alignment strategy	70 (88.6%)	1/8 (11.4%)
Analysis plan	Subgroup analyses	70 (88.6%)	1/8 (11.4%)
Analysis plan	Sensitivity analyses	64 (81.0%)	2/13 (19.0%)
Treatment strategy	Index date illustration	61 (77.2%)	16/2 (22.8%)
Assignment procedures	Covariate balance check	57 (72.2%)	3/19 (27.8%)
Assignment procedures	Observation period	44 (55.7%)	1/34 (44.3%)
Data and reporting	Unmeasured bias as limitation	42 (53.2%)	1/36 (46.8%)
Analysis plan	Handle missing data	40 (50.6%)	13/26 (49.4%)
✕ LOW ADHERENCE (<50%)			
Data and reporting	Data sharing plan	36 (45.6%)	0/43 (54.4%)
Outcomes	Negative controls	26 (32.9%)	0/53 (67.1%)
TTE protocol	Protocol documentation	25 (31.6%)	54/0 (68.4%)
Eligibility criteria	Cohort ascertainment	25 (31.6%)	26/28 (68.4%)
Outcomes	Outcome validation	14 (17.7%)	14/51 (82.3%)
Outcomes	Competing risks	12 (15.2%)	0/67 (84.8%)
Treatment strategy	Exposure validation	4 (5.1%)	16/59 (94.9%)
Eligibility criteria	Cohort evaluation	4 (5.1%)	1/74 (94.9%)
Assignment procedures	Unmeasured bias assessment	2 (2.5%)	1/76 (97.5%)
Data and reporting	Data quality reports	5 (6.3%)	16/58 (93.7%)
Data and reporting	Quality assurance/control plan & data management	0 (0%)	0/79 (100%)

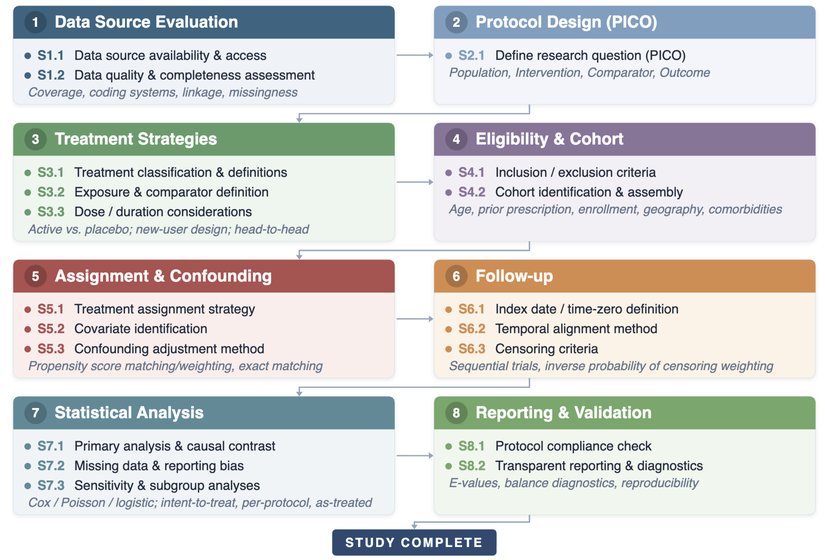

Figure 3. Proposed workflow of TTE protocol development

Summary of main findings

- TTE is widely adopted in vaccine research using RWD, but implementation varies substantially in rigor and transparency
- Strong conceptual adherence (comparators, exposure, eligibility), but critical operational gaps persist in cohort validation, outcome validation, and bias assessment
- Confounding control is commonly attempted (e.g., propensity scores), but rigorous bias diagnostics (e.g., negative controls, competing risks) are rarely applied
- Major deficiencies in data infrastructure: virtually no studies reported QA/QC or data quality assessment
- Using our proposed TTE decision checklist and design workflow to standardize future study designs can help better align with regulatory expectations

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Disclosures

- A. Eiden, W. Wang, K. Cassell, Y-L. Huang, Y-H. Kao, K. Mott, D. Wang, F. Li, and Y. Zheng are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA
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