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Post-authorisation efficacy data in humans: Clinical perspective

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Outbreaks provide a unique opportunity to evaluate candidate vaccines by assessing their clinical efficacy, safety among populations at risk…

Valuable information can be obtained from randomized trials among high-risk people , if the goal of the trial is to determine if the vaccine has high true efficacy (as per TPPs):

Differences can be observed after relatively few cases: 15-20 events are plenty.

- After 20 cases, a 20% lower bound on efficacy is met with a point estimate of 70%
- With 20 cases, a vaccine with true efficacy of 85% has ~80% power to meet a 20% lower bound.
- For outbreak settings, this may be feasible even in a Phase 2b trial

If needed, to accumulate cases, trials can even continue across outbreaks

For example, for filovirus vaccines, Ervebo tells us that 90+% efficacy is feasible and that is a reasonable expectation for vaccine efficacy

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… what if the outbreak is rapidly controlled….?

We can not predict –a priori- what the size of an outbreak would be therefore there is value in planning for and attempt to conduct RCTs.

The sooner we start the trial, the sooner we would get the needed efficacy data

In parallel to any preparation for trials during outbreaks, a clinical development plan should aim to generate evidence to support market authorization using various regulatory pathways

If the animal rule is an option, then let's get the best animal data we can.

Regulators should be calling the shots and evaluating the animal data to decide if it is reasonable or ethical to approve (and deploy) the vaccine.

Unapproved candidate vaccines should not be distributed for "political" reasons.

CoP- a few observations

If ~20 events are needed in vaccine recipients to establish a CoP, with 1% attack rate, a vaccine with 85% efficacy requires 13,333 people in vaccinated group

Also need immunogenicity samples for all these participants

15-20 events (3,000-4,000 participants with 1% AR in 1:1 vaccine and placebo group combined) are usually enough to show efficacy of high efficacy vaccines

Perverse incentive: Finding a correlate works better if vaccines aren't highly immunogenic and don't work well

- More variability in response
- Ability to immunobridge from weak vaccine to better vaccine

Even then, it is generally much harder to find CoP than to study vaccine efficacy

Could we use observational trials to confirm efficacy in accelerated/animal rule/conditional approvals?

There is a regulatory requirement to confirm/study efficacy

RCTs are the gold standard, but it becomes very difficult to use placebo after a product is licensed; trials are ideally underway at the time of licensure (though this may not always be feasible)

There is substantial concern about bias in observational studies

Disease epidemiology is constantly evolving and “feasibility” of generating randomized evidence evolves too

Pragmatic trials have been offered by regulators as methods to confirm efficacy for COVID and chikungunya vaccines

Cohort studies: Vaccinees and non-vaccinees may differ

Retrospective cohort, 945K ≥65 y.o., 2007-2014, non-immunocompromised, not in assisted living study to investigate **live-attenuated Herpes Zoster vaccine** efficacy. Propensity score matching addressed age, sex, race, low-income subsidies

In primary analysis, efficacy against **community HZ was 33%, 74% against hospitalized HZ**

Study included 13 “falsification outcomes” to understand possible group differences

Vaccine appeared to be protective against hip fracture (28%) , and appeared to lead to cataracts, eyelid disorders, and lipomas…

Note very tight confidence intervals

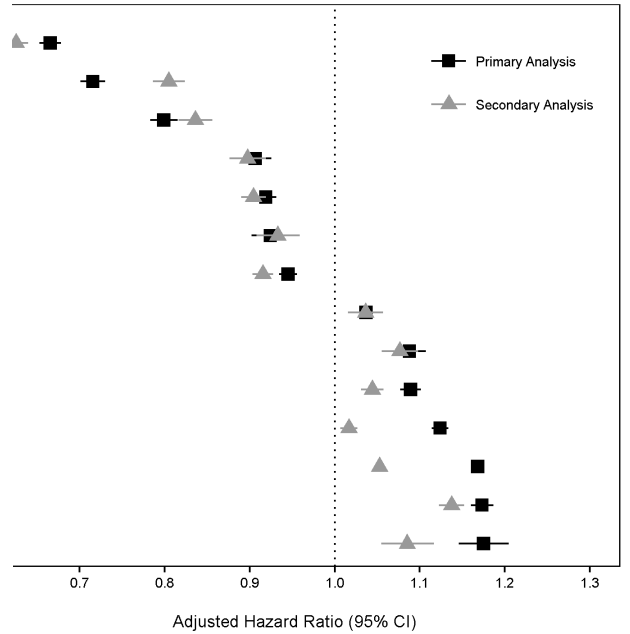
1° 2°

Comm HZ 0.67 0.63

Hip Fx 0.72 0.80

eFigure 3. Comparison of Adjusted Hazard Ratios of 13 Falsification Outcomes in the Matched Primary and Secondary Populations

Thrombosis	0.80	0.84
Cholelithiasis and cholecystitis	0.91	0.90
Renal stone	0.92	0.90
Wrist fracture	0.92	0.93
Gout	0.95	0.92
Epistaxis	1.04	1.04
Wound of hand or finger	1.09	1.08
Ingrown nail	1.09	1.04
Hemorrhoids	1.12	1.02
Cataracts	1.17	1.05
Eyelid Disord	1.17	1.14
Lipoma	1.17	1.09



Primary Analysis: This is the comparison between herpes zoster vaccinated and unvaccinated beneficiaries. Unvaccinated beneficiaries are the reference group.
Secondary Analysis: This is the comparison between herpes zoster vaccinees and pneumococcal vaccinees. Pneumococcal vaccinees are the reference group.
Similar to the primary and secondary analyses, the same set of demographic factors, socio-economic conditions, healthcare utilization characteristics, frailty characteristics, and functional immunocompromising chronic conditions were adjusted in each of the Falsification Outcome models.
Each Falsification Outcome model was run separately.
[a] The hazard ratio in the first 3 years of follow-up.

int

https://academic.oup.com/cid/article/64/6/785/3060361

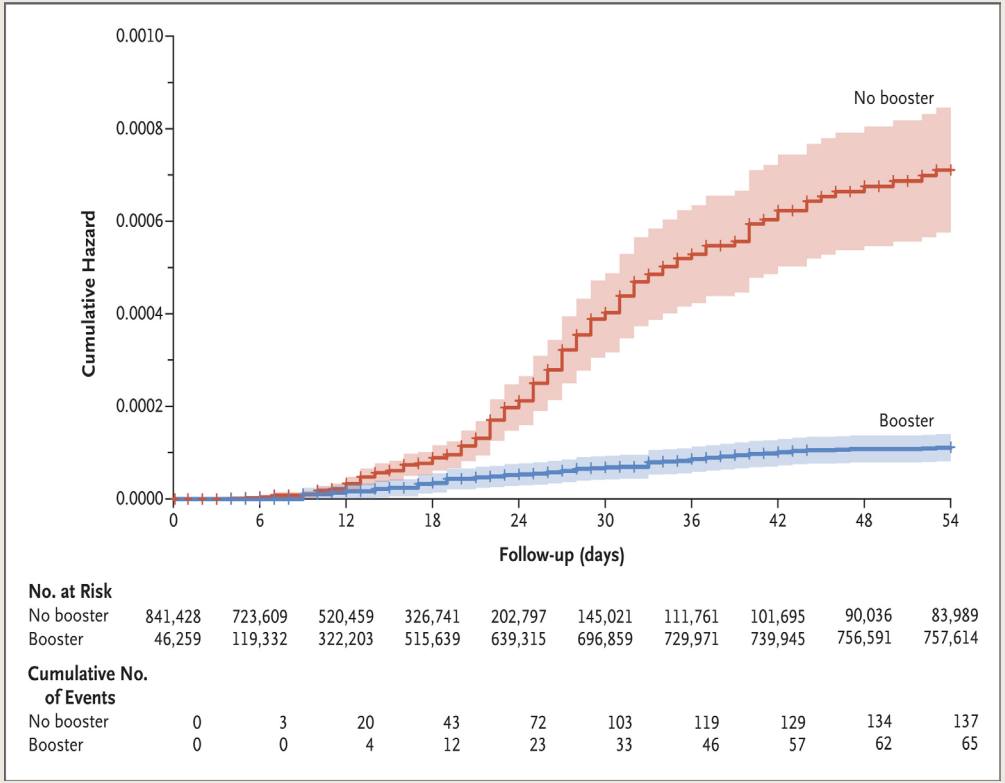
Take-home messages from Zostavax observational study

Falsification outcomes can provide critically important information about group differences, which might be sources of bias

Not all falsification outcomes are equal. Some would have detected no difference

Using pneumococcal vaccinees as the reference group reduced the potential bias without influencing HZ vaccine outcomes. Thus, this group difference, while detectable, turned out unlikely to be a major source of bias

COVID observational studies



No. at Risk										
No booster	841,428	723,609	520,459	326,741	202,797	145,021	111,761	101,695	90,036	83,989
Booster	46,259	119,332	322,203	515,639	639,315	696,859	729,971	739,945	756,591	757,614
Cumulative No. of Events										
No booster	0	3	20	43	72	103	119	129	134	137
Booster	0	0	4	12	23	33	46	57	62	65

Arbel, et al reported 90% reduction in mortality with COVID boosters in this retrospective cohort study

Criticized by Hoeg, Prasad because mortality NOT related to COVID was reduced by 94.8%, implying substantial healthy vaccinee bias

https://www.nejm.org/doi/full/10.1056/NEJMc2306683

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4314067

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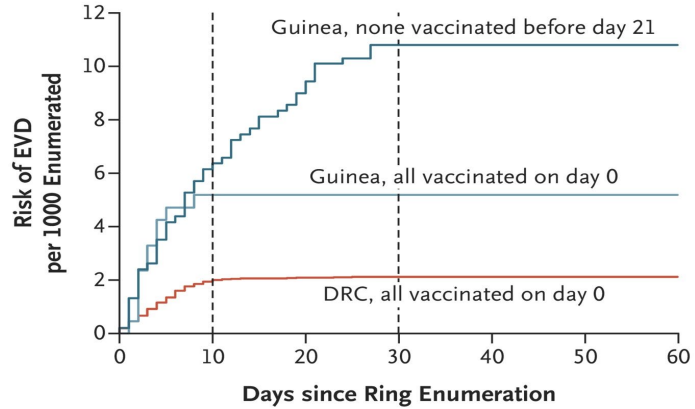
DRC Ebola vaccine observational study



No. Enumerated

Guinea, none before day 21	4,556
Guinea, all on day 0	2,119
DRC, all on day 0	194,399

No. with Onset of EVD (risk per 1000)	Days 0–9	Days 10–29	Day 30 or later
Guinea, none before day 21	28 (6.15)	21 (4.64)	0
Guinea, all on day 0	11 (5.19)	0	0
DRC, all on day 0	380 (1.95)	32 (0.16)	22 (0.11)

VSV-vectored Ebola vaccine was evaluated in ring vaccination of contacts, contacts of contacts (265,183 participants in 1853 rings)

Results after day 10 were very similar as compared with Guinea RCT comparing immediate vs. delayed vaccination

Both in Guinea and in the DRC, participants who were vaccinated on day 0 had a sudden decrease in EVD incidence around day 10, with low rates during days 10 to 29 that suggest substantial vaccine efficacy during this period.

Muyembe J-J et al. N Engl J Med2024;391:2327-2336

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DRC Ebola vaccine observational study

Table 2. EVD Onset in Vaccinated Contacts, According to Demographic and Clinical Characteristics and Interval after Vaccination.*

Characteristic	No. of Contacts Vaccinated	EVD Onset, According to Interval after Vaccination			10-Day Rate of EVD Onset
		Day 0–9	Day 10–29	Day ≥30	
		no. of contacts			*no. of contacts/ 1000 contacts*
Type of risk*					
High risk	47,904	316	20	8	6.6
Low risk	9,659	31	4	1	3.2
Age — yr					
<1†	290	1	0	0	3.4
1–9	10,595	25	4	1	2.4
10–17	9,663	27	0	1	2.8
18–49	31,118	235	10	7	7.6
≥50	5,897	59	10	0	10.0
Sex					
Male					
All ages	29,979	141	12	4	4.7
Age 14 to 49 yr†	6,324	49	4	1	7.7
Female		206	12	5	7.5
All ages	27,584				
Pregnant or lactating†	1,882	21	1	0	11.2
Age 14 to 49 yr†	4,488	69	2	0	15.4
Status of index case					
Vaccinated	7,540	26	0	0	3.4
Unvaccinated	50,023	321	24	9	6.4
Date of initiation of ring vaccination‡					
August 2018–March 2019	21,523	61	5	7	2.8
March 2019–June 2019	14,544	92	6	1	6.3
June 2019–September 2019	17,169	155	7	1	9.0
September 2019–January 2020	4,327	39	6	0	9.0

* High risk was defined as direct physical contact with an index case either before or after death.
† This category is restricted to contacts who were vaccinated after June 13, 2019, when infants and pregnant or lactating women became eligible.
‡ The dose of vaccine was 50 million plaque-forming units (PFUs) until June 13, 2019, when it was reduced to 25 million PFUs. The regulatory licensure calls for a dose of 20 million PFUs.

This also allows more refined look at the data in a larger number of participants

This gives further credibility to inferences about vaccine efficacy in pregnancy, by age group, etc.

Nonrandomized evidence from ring vaccination in eastern DRC reinforces the earlier randomized evidence from Guinea of vaccine efficacy against EVD onset 10 or more days after vaccination

Muyembe J-J et al. N Engl J Med2024;391:2327-2336

Non-randomized observational studies

There is always a risk of bias or mistaken conclusions

- Confounding; Healthy vaccinee bias; Misclassfication bias; Selection bias; Biases specific to test negative designs; Differential depletion of susceptibles; Waning immunity

Type I error is nearly impossible to control

Absence of randomization and potential for unmeasured biases mean that statistical significance does not guarantee a true association

Ways to reduce (but not eliminate) the risk:

- Prospective protocol
- Internal controls
- Falsification outcomes
- Require high efficacy
- Multiple studies or verify results of randomized trials
- Better matching of groups

https://www.who.int/news-room/events/detail/2023/09/14/default-calendar/improving-vaccine-effectiveness-studies--a-vital-step-before-the-next-pandemic

Better matching of groups

Test negative design case control study: by taking as controls people with symptoms similar enough to provoke testing, but negative test results, attempt to control for health-seeking behavior (didn't work very well for COVID)

Attempt to identify similar controls (e.g., in cohort studies)

Randomization

Pragmatic trials: Randomization during deployment

When FDA licensed the first COVID mRNA vaccines, reviewers suggested pragmatic trials of vaccine safety to gain confidence in the vaccines

Since (at least initially) demand greatly outstripped supply, it would have been ethical to randomize within risk groups between immediate vs. delayed vaccination

- (instead of allowing immunization managers to decide the order in which people get vaccinated, use randomization to decide it)

This could have allowed earlier and more confident detection of vaccine-associated adverse events

This same idea could be applied to collecting observational (real world) efficacy data

Pragmatic trials: practical considerations

POPULATION. All who were anyway eligible for deployment. These can be large studies

The enumeration/registration of those to be included (a given risk group) is defined in advance (e.g. in context where electronic vaccine registration is used).

RANDOMIZATION People who are in the registry or have signed up by a cutoff date receive randomized appointment times. All are randomized at the start.

Those randomized but not yet vaccinated serve as controls for those who were.

DELIVERY Vaccination occurs via normal deployment using regular vaccination teams in the order determined by the randomized vaccination appointments.

All available doses are used up!

ENDPOINTS All cases are detected independently by "routine surveillance and lab systems" using methods analogous to observational studies. Endpoints need to be severe enough to mitigate any bias from unblinded nature of study

INTERVAL Needs to be wide enough to allow comparisons in disease incidence between those vaccinated first and those vaccinated later. For multi dose vaccines, the delay would need to be lengthened by the time between vaccinations.

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Individually randomized pragmatic vaccine trials

DAN-RSV (NCT06684743)

- Individually randomized study of vaccine vs no vaccine in up to 130K adults during 2024/5 season
- All data collection via centralized health records & health registries
- Endpoint: hospitalizations

FLUNITY-HD (NCT06506812)

- Combines DANFLU-2 (NCT05517174) with GALFLU (NCT06141655) pragmatic studies (each randomizing high vs low dose flu vaccine in elderly adults) in total 466,320 participants
- Endpoint: severe clinical outcomes
- Showed 8.8% RVE vs hospitalization for flu or pneumonia

Finflu HD (NCT04137887)

- N>120,000 planned, 33K enrolled
- High vs low dose flu vaccine in elderly adults for cardiorespiratory hospitalization
- Showed point estimate of RVE 5.5% with overlapping confidence intervals

Conclusions

Observational studies can provide useful data, but there will always be some risk of bias.

Randomized pragmatic trials provide a less biased option to obtain reliable post-licensure safety and efficacy data

Regulators consider the totality of the evidence

Generation of evidence during outbreaks complements and does not replace other efforts to document vaccine efficacy and safety.

"Divide each difficulty into as many parts as is feasible and necessary to resolve it." — René Descartes

"If we did all the things we are capable of doing, we would literally astound ourselves." — Thomas Edison