

Can Rare Vaccine Adverse Effects Remain Undetected?

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Abstract

Rare adverse reactions may escape prelicensure trials even when those trials are appropriately designed. Detection power depends on how many people receive the product, event incidence, time at risk and clinical outcome definition. This paper uses the documented myocarditis signal following certain COVID-19 vaccines to explain why rigorous postauthorization surveillance is a normal part of vaccine medicine rather than a concession that all vaccine harms are hidden.

Very rare does not mean impossible to detect

Very rare adverse events may escape prelicensure trials without implying that an intervention is generally unsafe; the question is whether surveillance can detect a true signal promptly.

A trial enrolling thousands may identify common adverse events but have limited capacity to estimate an outcome occurring only a few times per hundred thousand doses. Passive reports can raise hypotheses but require verification; active linked-data systems and self-controlled case designs can help estimate associations. The analysis of myocarditis after particular mRNA products illustrates how age, sex and dose may substantially modify risk. The existence of a true rare adverse event does not establish all alleged events as causal.

Good signal evaluation specifies latency, case definition, background incidence, risk window and expected disease burden without vaccination. It also examines comparative infection risks and possible confounding by diagnostic intensity. Claims should report absolute as well as relative risks and note the difference between hospitalization, biomarker elevation, confirmed myocarditis and long-term outcomes.

Power, baseline incidence and active surveillance

This question turns on denominators and inference rather than dramatic anecdotes. Suppose an event occurs at a rate far below one in ten thousand exposed people; a licensing trial of several thousand participants may observe none even if the risk is real. The appropriate response is active surveillance and linkage of medical outcomes to accurately dated exposures. Yet the inverse mistake is equally serious: among millions of vaccinated people, many strokes, seizures and new diagnoses will occur afterward by coincidence. A postvaccination event is evidence of temporal order, not necessarily of causation. The methodological task is to estimate excess above expected background risk.

Rare adverse events are difficult to study because even relatively large preregistration trials can observe no events despite a genuine low-frequency risk. An event occurring once per hundred

thousand exposures, for instance, is unlikely to appear reliably in a trial enrolling only several thousand participants. The absence of events in such a trial therefore sets a limited upper bound, not a guarantee of impossibility. Postauthorization surveillance and large linked health records exist partly to address this issue.

At the same time, temporal coincidence becomes inevitable when millions of vaccinations occur. Neurological, autoimmune and cardiac diagnoses have background incidence unrelated to immunization. Detecting a rare signal requires an accurate denominator, well-defined risk window, comparison with an appropriate baseline and independent case validation. Stimulated reporting after publicity can inflate spontaneous reports even when underlying incidence does not change.

Detectability depends on background incidence, exposure prevalence, latency, diagnostic specificity and statistical power. Passive reports are useful for signal generation but lack denominators and are vulnerable to stimulated reporting. Linkage systems, self-controlled designs and independent case adjudication can test whether an apparent spike exceeds baseline. The provocative, useful claim is that population reassurance must be outcome-specific and accompanied by functioning detection systems rather than absolute declarations of zero risk.

From adverse-event report to verified signal

The proposed study should predefine both an outcome and a plausible risk interval, then use multiple designs when feasible: self-controlled series to adjust for time-invariant individual traits, and cohort comparisons to address population-level differences. Consistent evidence across systems is much stronger than a single uncontrolled cluster. Transparent uncertainty intervals are essential. The paper should treat a real confirmed rare risk as important while recognizing that unsubstantiated signals can distort decisions about preventing potentially severe infections.

Rare does not mean invisible forever. When an adverse event is sufficiently uncommon, a standard clinical trial can easily miss it. Large-scale linked records, spontaneous reporting and targeted studies after a signal arises can substantially improve detection. But the ability to detect a possible signal is not the same as demonstrating causation. The strongest conclusions arise when independent systems show similar relative timing, biological plausibility and an excess rate beyond expected background events.

Choosing an appropriate background. A neurologic diagnosis that typically appears within a particular age group may cluster around routine vaccine dates even if vaccination has no effect. Comparing events only after exposure exaggerates apparent temporal association. Better approaches estimate expected cases in comparable intervals and account for vaccination being postponed during illness or correlated with health-care use.

How to report uncertainty. A credible paper would show absolute excess events per specified number of doses, confidence intervals, strength of causal inference and which products or groups the estimate concerns. If a signal fails replication, that should be visible. If it is confirmed, risk communication should not conceal it. Balanced reporting also places any quantified harm alongside reduction in the target infection's consequences. Transparent surveillance is evidence of an attempt to detect harm, not proof that every reported coincidence is real.

Model detectable effect sizes under realistic event rates; compare active monitoring with passive reports using the same adverse-event definitions. Pre-register signal thresholds and follow-up adjudication, including checks for ascertainment changes. A hypothesized harm that fails repeatedly in adequately powered analyses should lose priority, even if individual temporally associated reports remain compelling narratives.

A robust investigation should identify a plausible risk window, adjudicate the clinical diagnosis and calculate absolute excess events with uncertainty intervals. The myocarditis experience shows how specific age and product patterns can emerge after deployment. A signal that disappears when ascertainment and background risk are controlled should not be retained as established harm.

The denominator is the difference between a signal and an incidence rate

A serious event reported after a vaccine can be medically important and worthy of investigation, but the report alone cannot show that the event occurred more often than it otherwise would have. The missing pieces are the number vaccinated, the age-specific background rate, the risk window and the completeness of event capture. Suppose an event naturally occurs in one of many thousands of people each year: some cases will follow vaccination by chance simply because vaccination is common. An elevated rate confined to a biologically plausible short window is more informative than a large number of undated reports. Active linkage datasets and self-controlled analyses can help test that pattern, although their own assumptions matter. For a very rare hazard, a credible null study should state what increase it had enough power to exclude. The scientific commitment should be symmetric: investigate reproducible excess risk promptly and avoid presenting absence of sufficient power as affirmative proof of damage.

A weak signal deserves study, not automatic attribution

When millions of people receive a medical intervention, some will experience serious illness soon afterward by coincidence. A surveillance system designed to detect rare harm must therefore distinguish reporting frequency from true excess incidence. Spontaneous reports are valuable for finding unusual patterns but cannot by themselves supply an accurate rate or establish the exposure as cause. Analytical studies should use appropriate background denominators, biologically plausible risk intervals and validated clinical outcomes. When feasible, separate data sources can reduce the chance that one system's reporting practice creates the whole signal. A confirmed rare event warrants clear communication and product-specific precautions; a signal that does not survive controlled investigation should be described accordingly. The question of detection limits is important, but it should make the methods more precise rather than imply that absence from an early trial is positive evidence of an unseen disorder.

The methodological danger runs in two directions. Uncritical dismissal of verified signals damages trust and delays risk mitigation; interpreting every temporally associated symptom as caused by vaccination generates misleading fear. Underreporting and stimulated reporting can coexist in passive systems. There is no fixed multiplication factor that converts all spontaneous reports into true incidence.

The paper concludes that scientific confidence should increase when monitoring detects and quantifies real harms. The value of a surveillance system lies in its ability to revise product-specific understanding, not in defending a prior narrative. Individual vaccine decisions belong in a context of actual risks and benefits rather than class-wide generalization.

Sources and research leads

1. [Patone et al. Risks of myocarditis, pericarditis, and arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection](#)

2. [Self-controlled case series design in vaccine safety: a systematic review](#)

- [CDC: Vaccine Safety Datalink active surveillance overview](#)

Editorial status: Third-pass conceptual research manuscript. The argument has been individually strengthened and shared boilerplate removed. Original reference leads were retained; a complete independent source-by-source scholarly verification has not been performed. No new clinical trial data are presented.