



Population-Level Surveillance of Breakthrough Infections Post-Immunization

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Abstract

Breakthrough infections -- documented infections occurring after completion of a vaccination course -- moved from a vaccinology footnote to a central object of population-level surveillance during the COVID-19 pandemic, as hundreds of millions of people were vaccinated within months of one another against a still-evolving pathogen under near-real-time case counting. This article synthesizes the methodological literature that grew out of that experience: the migration from randomized efficacy trials to test-negative case-control surveillance networks, the role of scheduled-testing cohorts such as SIREN in capturing infections that never reach a testing site, and the genomic and wastewater systems needed to distinguish waning immunity from variant-driven immune escape. We trace the well-replicated finding that vaccine effectiveness against infection declines substantially within months of vaccination while effectiveness against severe disease is better preserved, the immunological correlate-of-protection work that anticipated this pattern, and the emerging evidence that hybrid immunity from vaccination plus prior infection is more durable than either exposure alone. We close by examining unresolved surveillance problems -- denominator uncertainty, calendar-time confounding, ascertainment drift from home testing, and the gap between individual-level and population-level inference -- that remain open regardless of any single pathogen's biology.

Keywords: breakthrough infection; vaccine effectiveness; population surveillance; waning immunity; hybrid immunity

1. Introduction

By the time the first cohorts of fully immunized people were large enough to study, "breakthrough infection" had already stopped being a theoretical edge case and become a routine epidemiological event. A breakthrough infection — most simply, a documented infection occurring in a person who has completed a recommended vaccination course — is not itself evidence that a vaccine has failed; nearly every vaccine ever fielded, from measles to influenza to pertussis, produces some rate of post-immunization infection, because no vaccine drives sterilizing immunity to zero risk in every recipient. What changed with SARS-CoV-2 was scale and visibility: hundreds of millions of people were vaccinated within months of each other, against a virus still actively evolving and against a backdrop of near-real-time public case counting, so breakthrough infections that would once have been an obscure vaccinology footnote became a matter of nightly news coverage and, more usefully, a rich natural experiment in population-level surveillance methodology.

This article synthesizes that methodology. It is not a clinical review of breakthrough infection pathophysiology, nor a policy brief on booster schedules; it is a synthesis of how population-level surveillance systems have been built, validated, and used to answer three linked questions that recur across every vaccine-preventable disease program: how much protection does a vaccine actually confer once fielded outside a trial, does that protection decay over time or in the presence of a new pathogen variant, and how do surveillance systems distinguish a genuine erosion of vaccine effectiveness (VE) from artifacts of who gets tested, who gets counted, and who was vaccinated first. The literature that has accumulated around COVID-19 breakthrough infection surveillance is unusually large and unusually well-instrumented compared to prior vaccine programs, in part because genomic sequencing, electronic health record linkage, and wastewater monitoring all matured and became affordable at almost exactly the moment they were needed [1,2]. That convergence is itself worth examining, because the surveillance architecture assembled for COVID-19 — cohort studies of defined populations, test-negative case-control networks embedded in health systems, genomic surveillance of circulating lineages, and population-scale registry linkage — is now a template other vaccine programs will draw on.

The sections that follow move from foundations to open problems. We first define breakthrough infection carefully, since sloppy definitions are one of the most common sources of disagreement across studies. We then trace the methodological lineage from randomized controlled trials through the test-negative design that now underpins most operational VE surveillance. A section on correlates of protection connects individual immunology to population outcomes. Two sections examine, respectively, the well-documented waning of vaccine effectiveness over time and the concrete surveillance architectures — cohort, test-negative, and genomic — that detected and quantified that waning. A further section addresses the genomic dimension: how variant emergence is tracked and linked to breakthrough case clusters. We then turn to hybrid immunity, the increasingly dominant immune landscape in populations with both vaccination and prior infection. A concluding section on open challenges argues that the hardest unsolved problems in this literature are not virological but statistical and infrastructural: case ascertainment bias, denominator uncertainty, and the difficulty of separating individual-level vaccine effects from population-level transmission dynamics.

2. Defining and Classifying Breakthrough Infections

A breakthrough infection requires, at minimum, three things to be well specified before it can be compared across studies: a case definition (symptomatic infection, any documented infection, hospitalization, or death), a vaccination status definition (which product, how many doses, and how much time must have elapsed since the last dose to count as "fully vaccinated"), and a testing or ascertainment window. Early in the COVID-19 vaccination campaign, health authorities in the United States and United Kingdom converged on broadly similar operational definitions — infection detected fourteen days or more after completion of the primary series — but these definitions shifted repeatedly as booster doses, new variants, and new products (viral vector, mRNA, protein subunit) were introduced, and comparing "breakthrough rate" figures across studies that used different windows or different primary-series definitions is a common source of confusion in secondary literature.

The clearest early empirical demonstration of how much granularity matters came from a prospective cohort of

vaccinated healthcare workers at a large Israeli medical center, who were followed with regular RT-PCR testing regardless of symptoms. Among 1,497 fully vaccinated staff with available testing data, 39 breakthrough infections were documented — a small but non-trivial fraction — and the study's design allowed the investigators to show that these breakthrough cases were not evenly distributed: peri-infection neutralizing antibody titers were significantly lower in the 39 breakthrough cases than in matched uninfected controls, roughly 85% of sequenced breakthrough infections were the then-circulating Alpha variant, and 74% of infected individuals had a high viral load at some point during infection even though only 59% tested positive on a concurrent rapid antigen test — with no secondary transmission documented among their contacts [3]. That single study illustrates why "breakthrough infection" as a category conceals enormous heterogeneity: an infection captured only because of scheduled asymptomatic surveillance testing is a fundamentally different signal than one captured because a person sought care for a hospitalizable illness, and both are legitimate but non-interchangeable outcomes for a surveillance system to track.

This heterogeneity motivates the now-standard practice of reporting vaccine effectiveness against a hierarchy of outcomes — infection (with or without symptoms), symptomatic disease, emergency department or urgent care presentation, hospitalization, and death — rather than a single number. Effectiveness against the mildest end of that hierarchy is the most sensitive to waning immunity and immune escape, while effectiveness against the most severe end tends to be better preserved, a pattern that recurs across nearly every study discussed below and that has direct implications for how surveillance systems should be designed: a system optimized to detect any breakthrough infection needs different sampling and testing infrastructure than one optimized to detect breakthrough hospitalizations.

3. Methodological Foundations: From Clinical Trials to Test-Negative Surveillance

Randomized, placebo-controlled trials remain the gold standard for establishing that a vaccine works at all, and the pivotal trials of the two mRNA vaccines used against COVID-19 are foundational to everything that follows. The BNT162b2 (Pfizer-BioNTech) trial reported by Polack and colleagues demonstrated high efficacy

against symptomatic, confirmed COVID-19 in a randomized population followed for a median of two months post-second-dose [4], and the parallel trial of mRNA-1273 (Moderna) reported similarly high efficacy under equivalent randomized conditions [5]. These trials answered the essential first question — can this vaccine reduce disease risk under controlled, blinded conditions — but by design they could not answer the questions population-level surveillance exists to address: how does effectiveness hold up over many months, against variants that had not yet emerged when the trial was conducted, in older and more comorbid populations who were underrepresented in trial enrollment, and under real-world conditions where testing behavior, exposure risk, and prior infection status vary enormously and are not randomized away.

Filling that gap required a different study design, and the workhorse of postmarketing vaccine effectiveness surveillance — for COVID-19 as for influenza before it — is the test-negative design (TND). The logic is straightforward: rather than trying to enroll a representative cohort and follow it prospectively, a TND study enrolls people who present for testing with an acute respiratory illness (or, for asymptomatic surveillance systems, simply present for routine testing) and compares vaccination status between those who test positive for the pathogen of interest ("cases") and those who test negative ("test-negative controls"). Because both groups were symptomatic enough, or otherwise motivated enough, to seek testing, the design implicitly controls for much of the healthcare-seeking-behavior bias that plagues simpler observational comparisons. De Serres and colleagues formalized the validity, accuracy, and precision of this approach relative to randomized trials using influenza vaccine data, establishing the methodological case that made the TND the default choice for national VE surveillance systems well before COVID-19 existed [6].

That prior investment paid off immediately once COVID-19 vaccines were deployed. The UK's national surveillance system used a test-negative case-control design embedded in routine PCR testing data to produce some of the earliest, largest real-world estimates of VE against the Delta variant, reporting effectiveness that varied meaningfully by vaccine product and by number of doses and that was noticeably lower against symptomatic disease with the AstraZeneca vector

vaccine than with BNT162b2 after a single dose, though the gap narrowed substantially after the second dose [7]. In the United States, the CDC-coordinated VISION Network assembled electronic health record and immunization registry data from multiple large integrated health systems across ten states specifically to run TND analyses of VE against emergency department, urgent care, and hospitalization outcomes in near-real time, an infrastructure investment that let investigators report interim estimates within weeks of a new variant's emergence rather than the many months a purpose-built cohort study would require [8,9]. The IVY Network took a complementary hospital-based TND approach focused specifically on severe, hospitalized disease among immunocompetent adults, directly comparing effectiveness across the three vaccine products then authorized in the US and finding effectiveness against hospitalization of 93% (95% CI 91–95%) for mRNA-1273, 88% (95% CI 85–91%) for BNT162b2, and 71% (95% CI 56–81%) for the Ad26.COV2.S viral vector vaccine, a product-level difference large enough to shape both clinical guidance and subsequent booster policy [10].

Cohort designs did not disappear; they specialized. Where TND surveillance is efficient for tracking effectiveness against outcomes that reliably bring people to a testing site, prospective cohorts with scheduled regardless-of-symptoms testing remain the only design that can estimate effectiveness against infection overall, including asymptomatic and mildly symptomatic cases that would never generate a test-seeking visit. The UK's SIREN study exemplifies this approach: a multicentre prospective cohort of healthcare workers tested on a fixed schedule (rather than only when symptomatic), which allowed the investigators to estimate VE against any PCR-confirmed infection — not just symptomatic, care-seeking infection — and to separately quantify how much protection was contributed by prior natural infection versus vaccination versus both together [11,12]. That distinction between what a TND surveillance system can and cannot see, versus what a scheduled-testing cohort can see, is one of the more consequential methodological lessons of the whole literature: no single design captures the full outcome hierarchy, and robust population-level VE estimation increasingly means triangulating results from more than one design in parallel.

4. Correlates of Protection and the Immunological Basis of Breakthrough Risk

Surveillance systems tell us that breakthrough infections happen and roughly how often; immunological correlate-of-protection research tells us why some vaccinated individuals are protected and others are not, and it provides the quantitative bridge that lets surveillance data be interpreted mechanistically rather than purely descriptively. Khoury and colleagues assembled neutralizing antibody titer and efficacy data across seven vaccine platforms and used a mathematical model to show that neutralization level, expressed relative to the mean titer in convalescent individuals, was highly predictive of protection from symptomatic infection across those very different vaccine technologies, and that the model could be used to predict the decline in efficacy expected as neutralizing titers wane after vaccination [13]. This work gave the field something it previously lacked: a quantitative, cross-platform framework for anticipating where and when breakthrough infections would begin to rise, months before the confirmatory surveillance data arrived. Earle and colleagues independently assembled evidence across multiple vaccine efficacy trials to make a parallel case that binding and neutralizing antibody levels function as a reasonably reliable protective correlate for COVID-19 vaccines specifically, a finding with direct regulatory relevance because immunobridging on the basis of antibody titers, rather than waiting for new large efficacy trials, became the basis for authorizing variant-adapted booster formulations [14].

The individual-level story these correlate-of-protection studies tell — titers decline after vaccination on a predictable biological timescale, and infection risk rises as titers fall below some threshold — maps directly onto what population surveillance subsequently observed: breakthrough infections cluster in individuals with lower or more distant vaccination, in older or immunocompromised people whose peak antibody response was lower to begin with, and around the arrival of new variants whose surface protein has drifted far enough from the vaccine strain to reduce neutralization even at a fixed titer. This convergence between immunological modeling and empirical surveillance is one of the more genuinely satisfying arcs in the pandemic-era literature, because it means population-level breakthrough infection curves are not

just an epidemiological curiosity to be tracked passively; they are, in principle, forecastable from serological data collected well before the case counts themselves rise.

5. Waning Effectiveness and the Case for Continuous Surveillance

If breakthrough infection rates were constant over time, a single well-designed VE study per vaccine product would largely suffice. They are not. The single most consistent finding across the post-authorization COVID-19 literature is that vaccine effectiveness against infection — and, to a lesser but still real degree, against severe disease — declines with time since vaccination, independent of any change in the circulating variant. Tartof and colleagues followed 3.4 million members of a large integrated US health system for six months after BNT162b2 vaccination and found that effectiveness against SARS-CoV-2 infection was 73% overall but fell substantially over the follow-up window, from 88% in the first month after full vaccination to 47% at five months or more, while effectiveness against COVID-19-associated hospitalization was much better preserved, remaining around 90% throughout, and the authors argued the pattern was better explained by waning immunity with time than by any change attributable to the Delta variant specifically, since the decline in effectiveness against infection was seen even restricting analysis to variant-specific subsets of the data [15]. Qatar's national testing registry data, similarly, showed BNT162b2 protection against infection waning steadily after the second dose, with effectiveness dropping toward the range where population transmission is only modestly suppressed by vaccination alone even as protection against severe outcomes fared better [16].

Because these were two of many such studies conducted independently in different populations, health systems, and testing regimes, the natural next question was whether waning was a real, generalizable biological and epidemiological phenomenon or an artifact particular to any one dataset's confounding structure — the calendar-time confounding problem, in which people vaccinated earliest (and therefore with the most elapsed time by any given follow-up point) also tended to be the highest-priority, highest-exposure-risk groups such as healthcare workers and the elderly, which could spuriously produce an apparent decline in effectiveness with time since vaccination even if biological protection

were constant. Feikin and colleagues addressed this directly with a systematic review and meta-regression across seventy-eight studies from eighteen countries, modeling vaccine effectiveness as a function of time since the primary series for both infection and severe disease outcomes across multiple products, and found a consistent pattern: effectiveness against symptomatic infection declined by roughly 20 to 30 percentage points across the six months following primary vaccination for most product and variant combinations examined, while effectiveness against severe disease declined more modestly and from a higher baseline, a pattern robust enough across so many independently conducted studies that a purely confounding-driven explanation became increasingly implausible [17]. This meta-regression is arguably the single most important piece of surveillance-synthesis literature produced during the pandemic, because it converted dozens of individually noisy, differently designed national surveillance estimates into a single quantitative waning curve that could be used directly for booster-timing policy.

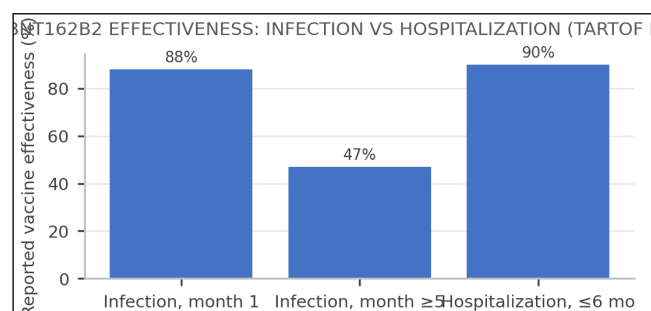


Figure 1: BNT162b2 vaccine effectiveness against SARS-CoV-2 infection at 1 month versus 5 or more months after the second dose, compared with effectiveness against COVID-19-associated hospitalization over the same 6-month follow-up, as reported in a 3.4-million-member cohort study -- the empirical basis for continuous, rather than one-time, population-level breakthrough infection surveillance [15].

Figure 1 illustrates this waning pattern using the reported effectiveness figures from the Tartof cohort discussed above [15]: effectiveness against infection falls by more than 40 percentage points between the first month after vaccination and the fifth month onward, while effectiveness against hospitalization is far better preserved across the same follow-up window — the empirical basis for the now widely repeated public health message that vaccines "hold up better against severe disease than against infection."

The practical surveillance implication of waning is that a single cross-sectional VE estimate is close to

meaningless without a time-since-vaccination axis attached to it, and that any population-level surveillance system intended to inform booster policy has to be built for continuous, longitudinal re-estimation rather than a one-time confirmatory study. This is a genuinely different design requirement than the trial-era mindset of "does the vaccine work," and it is the main reason the test-negative, registry-linked surveillance networks described in the next section were built to update their estimates on a rolling, often monthly, basis rather than issue a single final report.

6. Surveillance Architectures: Cohorts, Test-Negative Networks, and Genomic Systems

Turning waning-immunity concerns and correlate-of-protection theory into operational, near-real-time population surveillance required purpose-built infrastructure, and the resulting systems differ substantially in design, in what outcomes they can see, and in how quickly they can produce an estimate after a new variant or a new booster rollout begins. **Table 1** summarizes six representative examples spanning cohort, test-negative, genomic, and ecological approaches, together with a key quantitative or qualitative finding each contributed to the literature.

Table 1: Representative population-level breakthrough infection surveillance architectures, the design each uses, and a key reported finding, illustrating the division of labor between hospital-based test-negative networks, scheduled-testing cohorts, genomic/wastewater surveillance, and ecological population-level analysis. [10,3,15,8,1,18].

Surveillance approach	Study / Source	Design and population	Key reported finding
Hospital-based test-negative network	Self et al., IVY Network [10]	Test-negative case-control, 21 US hospitals, 3,689 immunocompetent adults	VE against hospitalization: 93% mRNA-1273, 88% BNT162b2, 71% Ad26.COV2.S
Scheduled-testing occupational cohort	Bergwerk et al. [3]	Prospective cohort, Israeli hospital healthcare workers, n=1,497 fully vaccinated	39 breakthrough infections (2.6%); 85% Alpha variant; no secondary transmission documented
Large integrated-health-system cohort	Tartof et al. [15]	Retrospective cohort, Kaiser Permanente Southern California, 3.4 million members	VE vs infection waned 88% (month 1) to 47% (month >=5); VE vs hospitalization ~90% throughout
Multistate test-negative registry network	Grannis et al., VISION Network [8]	Test-negative case-control, ED/urgent care/hospital encounters, 9 US states	Near-real-time VE monitoring framework used to track effectiveness during Delta predominance

Surveillance approach	Study / Source	Design and population	Key reported finding
Genomic wastewater surveillance	Karthikeyan et al. [1]	Environmental sequencing of municipal wastewater, San Diego County	Detected cryptic SARS-CoV-2 lineages in wastewater days to weeks before matching clinical sequences
Ecological population-level analysis	Subramanian and Kumar [18]	Cross-country/cross-county ecological analysis, 68 countries and 2,947 US counties	No significant association found between vaccination coverage and case growth at this level of aggregation

What the table makes visible is a genuine division of labor rather than redundancy. Hospital-embedded test-negative networks such as IVY and VISION are fast and well suited to comparing effectiveness across products and variants for severe outcomes, because hospitalized patients are reliably tested and captured in electronic health records, but they structurally cannot see the large majority of infections that never escalate to a hospital encounter [10,8,9]. Scheduled-testing cohorts like SIREN and the Israeli healthcare-worker cohort can see that larger denominator of mild and asymptomatic infection precisely because they test on a fixed schedule independent of symptoms, at the cost of being far more expensive to run at scale and generally restricted to occupational cohorts such as healthcare workers rather than the general population [11,3]. Genomic wastewater surveillance adds a population-level, individual-consent-free layer that can flag the presence of a new or divergent lineage in a community's viral load before any single breakthrough case is diagnosed and sequenced, as demonstrated when environmental sequencing in San Diego detected cryptic SARS-CoV-2 lineages circulating in the community days to weeks before matching clinical sequences were identified [1]. And large ecological analyses spanning many countries or counties serve a different but important function: they are a check on whether population-level correlations between vaccination coverage and case trends hold up as cleanly as individual-level VE studies would predict, and an instructive 2021 analysis across 68 countries and nearly 3,000 US counties found no statistically significant association between vaccination coverage and COVID-19 case growth at that level of aggregation, a genuinely uncomfortable finding that its authors and subsequent commentators attributed primarily to well-known limitations of ecological-level inference — confounding by testing intensity,

non-pharmaceutical interventions, and prior-infection prevalence that individual-level studies are specifically designed to control for and ecological studies are not [18]. That contrast is itself a methodological lesson worth stating plainly: population-level correlation and individual-level vaccine effectiveness are not interchangeable evidence, and a surveillance program that reports only one of the two risks either overstating precision (ecological data presented as if causal) or understating real-world population impact (individual VE estimates that ignore transmission-level externalities). A complementary US-wide modeling analysis of the public health impact of the vaccination campaign, using individual-level effectiveness estimates propagated through a transmission model rather than raw ecological correlation, estimated the number of infections, hospitalizations, and deaths averted at the national level, illustrating one way to reconcile the two levels of evidence rather than treating them as competing claims [19].

7. Variant Escape and the Genomic Dimension of Breakthrough Surveillance

None of the surveillance architectures described above would be interpretable without a parallel genomic surveillance layer tracking which viral lineages are actually causing the breakthrough infections being counted, because "vaccine effectiveness declined" and "a more immune-evasive variant became dominant" are observationally similar signals that can only be disentangled by linking case data to sequencing data. The foundational infrastructure step here was establishing a shared, stable nomenclature for SARS-CoV-2 lineages in the first place; Rambaut and colleagues proposed the dynamic Pango lineage-naming system specifically to give genomic epidemiologists a consistent way to track, name, and compare emerging lineages across countries and sequencing efforts, a seemingly modest bookkeeping contribution that turned out to be a prerequisite for nearly every subsequent variant-specific breakthrough analysis, since without a shared naming convention, studies from different countries could not be meaningfully compared or pooled [2].

With that naming infrastructure in place, breakthrough surveillance studies were able to attribute rising infection rates to specific, named variants rather than treating "waning" and "immune escape" as an

undifferentiated blur. The Massachusetts outbreak investigation following a series of large July 2021 public gatherings in Barnstable County is one of the clearest illustrations: among 469 identified COVID-19 cases linked to the gatherings, 74% occurred in fully vaccinated people, genomic sequencing confirmed the Delta variant as the dominant circulating lineage, and cycle-threshold values in specimens from vaccinated and unvaccinated cases were similar, indicating that vaccinated people with Delta breakthrough infections could carry viral loads comparable to unvaccinated cases — a finding with direct implications for whether vaccinated people needed to be considered in transmission-control measures during a variant surge, and one that would have been uninterpretable without simultaneous case counting and sequencing [20]. Direct viral-culture studies reinforced the cycle-threshold observation with a more mechanistic measure: peak viral RNA concentrations were similar between vaccinated and unvaccinated persons infected with Delta, and while the rate of decline in viral RNA and the probability of culturing live virus fell faster in vaccinated individuals, the shedding overlap was large enough to explain why vaccinated people could still transmit, particularly early in infection [21]. As Omicron and its sublineages displaced Delta, this same sequencing-linked surveillance approach was applied again, with US test-negative studies reporting a further decline in VE against symptomatic infection with Omicron relative to Delta, alongside preserved though attenuated protection against severe disease, particularly after a booster dose restored substantial protection that had waned with the primary series alone [22,23].

A recurring methodological point across this genomic-linked literature deserves emphasis: attributing a change in population-level breakthrough rates to "the variant" requires either individual-specimen sequencing linked to the case record, as in the Barnstable County investigation, or population-representative sequencing surveillance of the kind wastewater systems now provide, as opposed to simply noting that a new variant became dominant nationally around the same calendar time that breakthrough rates rose. The latter, purely temporal correlation is vulnerable to exactly the same calendar-time confounding that complicated early waning-immunity studies, since variant replacement and elapsed time since vaccination are themselves

correlated in most real-world rollouts.

8. Hybrid Immunity and the Reinfection Landscape

As the pandemic progressed, an increasing share of any population carried both vaccine-induced and infection-induced immunity, and the resulting "hybrid immunity" turned out to be a distinct and generally more durable immune state than either exposure alone, which has substantial implications for how breakthrough and reinfection surveillance should be designed and interpreted going forward. Nordström and colleagues used Sweden's linked national registries to conduct a retrospective, total-population cohort study comparing the risk of reinfection and COVID-19 hospitalization among people with natural infection alone, vaccination alone, and both combined, and found that the combination of prior infection and vaccination was associated with a markedly and durably lower risk of both reinfection and hospitalization than either exposure alone, with meaningful protection still detectable many months out — a total-population registry design large and long enough to resolve a question that smaller cohort studies could not answer with adequate statistical power [24]. The SIREN cohort of UK healthcare workers reached a broadly consistent conclusion using prospective, scheduled testing rather than registry linkage: prior infection combined with vaccination provided greater and more durable protection against subsequent infection than vaccination without a prior infection history, reinforcing the registry-based finding with a methodologically distinct study design [12].

This convergence of hybrid-immunity findings across registry and cohort designs has a direct surveillance consequence that is easy to overlook: any VE estimate that does not stratify by, or at minimum adjust for, prior infection history is implicitly averaging over an increasingly heterogeneous population whose "vaccinated" label conceals two immunologically distinct groups. As population-level seroprevalence of prior infection rose over the course of the pandemic — a rise that serosurveillance and, later, wastewater-based community prevalence estimates helped quantify even where testing-based case counts undercounted true infection incidence — failing to account for hybrid immunity risked attributing to "vaccine effectiveness" a protective effect that was substantially a joint product of

vaccination and undocumented prior infection. This is one of the more subtle sources of estimate heterogeneity across the studies discussed in this article, and later-generation surveillance systems increasingly built serological or self-reported prior-infection status directly into their case-control matching to address it.

9. Open Challenges in Population-Level Surveillance

Several problems in this literature remain genuinely unresolved rather than merely underexplored. The first is denominator uncertainty: nearly every VE study, whether cohort or test-negative, depends on an accurate count of who was vaccinated, when, and with which product, drawn from immunization registries that are known to have variable completeness, particularly for doses administered outside the health system generating the study's case data, and a systematically undercounted vaccinated denominator will bias VE estimates in ways that are difficult to detect from within a single dataset. The second is the calendar-time confounding problem discussed above in the context of waning immunity, which meta-regression approaches like Feikin and colleagues' can partially address across many pooled studies but cannot fully eliminate within any single site [17]. The third, illustrated starkly by the ecological analysis discussed earlier, is the gap between individual-level and population-level inference: a surveillance program that only ever reports individual VE, however well estimated, cannot by itself answer whether a vaccination campaign measurably slowed community transmission, and a program that only reports population-level case-count correlations cannot control for the confounders that make such correlations unreliable [18].

A fourth, less frequently discussed problem is what might be called ascertainment drift: as home antigen testing became widely available later in the pandemic, an increasing share of infections — vaccinated and unvaccinated alike — went entirely uncaptured by the PCR-based testing infrastructure that most of the surveillance systems described in this article were built around, and there is no fully satisfactory way to know whether this uncaptured share differs systematically by vaccination status, which would bias VE estimates in an unpredictable direction depending on whether vaccinated or unvaccinated people were more or less likely to test at home rather than seek a registered test.

Fifth, and perhaps most consequential for the future of this field, is the question of generalizability across pathogens: the infrastructure built for COVID-19 — national genomic sequencing capacity, registry-linked test-negative networks, wastewater surveillance — is a substantial public investment that took years to mature, and whether that infrastructure will be sustained and repurposed for influenza, RSV, or the next novel pathogen, rather than allowed to atrophy once acute pandemic funding ends, remains an open policy question rather than a scientific one. Katzourakis, writing during the transition from pandemic to endemic framing of COVID-19, cautioned specifically against the assumption that an endemic pathogen with a well-characterized vaccine no longer merits continuous population-level surveillance, arguing that endemicity describes a transmission pattern rather than a level of harm, and that the surveillance infrastructure this article has described remains necessary precisely because breakthrough infection and reinfection dynamics continue to evolve even after a pathogen stops making headlines [25].

10. Conclusion

Population-level surveillance of breakthrough infections after immunization matured, across the years surveyed in this synthesis, from a set of ad hoc observational reports into a genuinely rigorous, multi-method discipline combining randomized trial foundations, test-negative case-control networks, scheduled-testing cohorts, genomic lineage tracking, and registry-scale hybrid-immunity analysis. The consistent findings across this now-substantial literature are that vaccine effectiveness against infection wanes measurably within months of vaccination while effectiveness against severe disease is better preserved, that variant emergence and time-since-vaccination are both real and separable contributors to that waning when genomic data are linked to case surveillance, and that hybrid immunity from combined vaccination and prior infection is more durable than either exposure alone. What remains unresolved is less about any single pathogen's biology and more about surveillance infrastructure and inference: denominator accuracy, ascertainment bias as home testing displaces registered testing, the gap between individual and population-level evidence, and whether the substantial investment made in COVID-19-era surveillance systems will be sustained as a general-purpose capability for the vaccine-preventable

disease programs that come after it.

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Conflict of Interest

The authors declare that they have no competing interests relevant to the content of this article.

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Ethical Approval

Not applicable. As a synthesis of previously published literature, this work did not involve human participants, animal subjects, or the collection of primary clinical data.

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