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Review

Integrated Approaches to Vaccine Safety Surveillance: Principles, Challenges, and Innovations

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Abstract:
Vaccine safety surveillance plays a pivotal role in ensuring public confidence and maintaining the integrity of immunization programs worldwide. With the rapid development and deployment of vaccines, particularly during global health emergencies, traditional surveillance methods alone are insufficient to address emerging challenges in detecting, evaluating, and managing adverse events following immunization (AEFI). This paper explores integrated approaches to vaccine safety surveillance, highlighting the principles that govern effective monitoring, the limitations of conventional systems, and the need for innovative strategies. It emphasizes the integration of epidemiological studies, pharmacovigilance systems, big data analytics, real-world evidence, artificial intelligence, and digital health tools to enhance early signal detection, causality assessment, and risk communication. Key challenges such as underreporting, data harmonization, ethical considerations, and public trust are critically analyzed. Furthermore, the paper discusses recent innovations including blockchain-enabled data security, machine learning algorithms for predictive modeling, and global collaborative platforms that strengthen vaccine safety monitoring. By adopting a multidimensional and technology-driven approach, stakeholders can build resilient surveillance systems that not only safeguard public health but also foster transparency, trust, and long-term sustainability of immunization programs.

Keywords: Vaccine safety surveillance; Adverse events following immunization (AEFI); Pharmacovigilance; Big data analytics; Artificial intelligence; Real-world evidence; Blockchain; Public trust; Global health; Immunization programs

Introduction:

Vaccination remains one of the most effective public health strategies for preventing infectious diseases and reducing morbidity and mortality worldwide. However, like all medical interventions, vaccines are associated with potential adverse events, which necessitates the implementation of robust surveillance systems to ensure vaccine safety post-licensure. Vaccine safety surveillance systems play a critical role in identifying, evaluating, and managing potential adverse events following immunization (AEFIs) to maintain public trust and inform policy decisions (1).

With increasing globalization and the rapid deployment of new vaccines—especially in response to emerging infectious diseases like COVID-19—information systems have become integral to vaccine pharmacovigilance. These systems facilitate the real-time collection, analysis, and sharing of data on vaccine-related adverse events, enabling timely risk assessment and decision-making by health authorities (2). Modern vaccine surveillance now relies heavily on digital

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health records, national immunization registries, passive and active reporting systems, and data integration tools powered by information technology.

The shift toward digitized vaccine safety surveillance has also opened avenues for advanced data analytics, machine learning, and artificial intelligence to enhance signal detection and prediction of rare or unexpected adverse events (3). Despite technological advancements, the success of these systems depends on the quality, completeness, and interoperability of data, as well as coordination among healthcare providers, regulatory agencies, and global stakeholders.

Why Vaccine Safety is Different

Vaccine safety differs from traditional drug safety in several important ways:

1. **Vaccines are preventive, not therapeutic** – Unlike most drugs used to treat existing conditions, vaccines are given to healthy individuals to prevent disease. This changes the risk-benefit threshold significantly; even rare adverse events can influence public perception and acceptance (4).
2. **Mass administration to large populations** – Vaccines are often administered to entire populations, including children, elderly, and immunocompromised individuals, which increases the chance of detecting rare adverse events due to broader exposure (2).
3. **Public trust is critical** – Vaccine programs depend heavily on public confidence. A single safety concern—whether confirmed or not—can lead to widespread vaccine hesitancy, reduced coverage, and resurgence of preventable diseases (5).
4. **Complex immunological responses** – Vaccines interact with the immune system, and adverse reactions may involve complex, sometimes delayed, immunological mechanisms that are harder to detect and study compared to conventional drugs (WHO, 2014).

Why Timely Surveillance is Needed

Timely detection of adverse events following immunization (AEFI) is critical for several reasons:

- **Early signal detection** helps identify unexpected or rare safety issues soon after vaccine deployment, allowing for rapid investigation and corrective action (1).
- **Timely data** enables health authorities to distinguish between true adverse reactions and coincidental medical events, thus maintaining scientific integrity and public trust (6).
- **Rapid communication** of safety findings is essential during emergency vaccine rollouts, such as during pandemics, where the balance of urgency and safety is especially delicate (7).
- **Global data sharing** supports consistent safety monitoring across countries, particularly with new vaccines introduced under emergency use authorization (EUA) (Brighton Collaboration, (8).

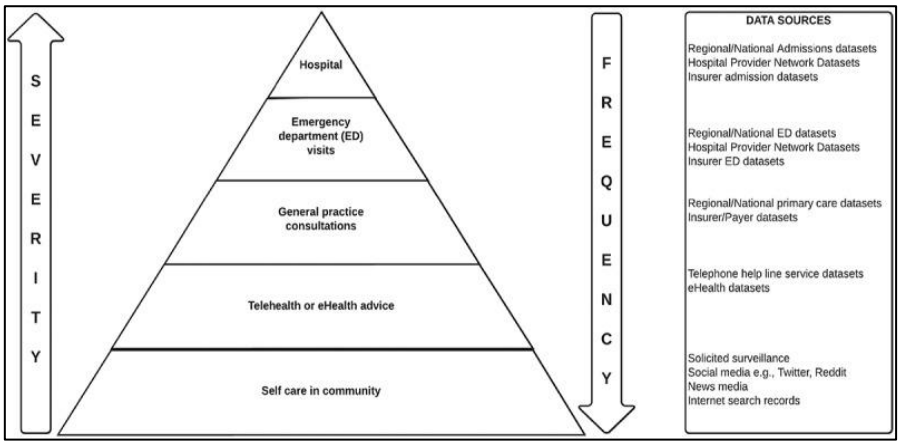

Fig.1. Potential vaccine safety data sources by severity of presentation. (9)

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Step	Goal	Method	Outcome
Signal Detection	Find potential safety concerns	Data mining, automated alerts	Potential signal flagged
Signal Validation	Confirm true and relevant signals	Clinical review, plausibility check	Signal prioritized or dismissed
Signal Investigation	Evaluate causality and risk impact	Epidemiology, expert review	Risk assessed, action decided

(10), (11).

Spurious reports

With vaccine hesitancy becoming a significant global health concern, the circulation of **spurious reports**—particularly on social media—regarding deaths or serious adverse events following vaccination has increased markedly (12). Even a **single unverified or misleading report** can rapidly erode public trust, fueling skepticism toward vaccines and undermining immunization efforts. Moreover, such reports can lead to **amplification through reposts or echo reporting**, potentially triggering **false safety signals** in surveillance systems that are designed to detect rare but true adverse events (14).

The rise of political polarization across various nations has coincided with a growing tendency for politicians—including those from mainstream parties—to express **anti-vaccine sentiments** publicly. These politically charged messages are often **disseminated through social media**, where they gain significant visibility and traction. Such platforms amplify these views rapidly, contributing to **misinformation ecosystems** that challenge public health messaging and erode trust in vaccination efforts (15,16,17).

Healthy recipients

Vaccination programs primarily target **healthy individuals**, which raises the **threshold for acceptable risk** and necessitates a more stringent demonstration of safety. This is especially true for **vulnerable subgroups** who are often excluded from pre-licensure clinical trials—such as pregnant women, immunocompromised individuals, those with chronic illnesses, and the frail elderly. Evidence suggests that **pregnant women exhibit more vaccine hesitancy** compared to when they are not pregnant, largely driven by concerns over safety for both themselves and their unborn children (18).

However, **routine pharmacovigilance systems are poorly equipped** to address these concerns. Many lack mechanisms to **systematically identify pregnancy status** or to **link maternal vaccination with neonatal outcomes**, making it difficult to conduct meaningful post-marketing surveillance in this group. Similarly, the immunocompromised and elderly with frailty are **not easily traceable** through existing databases, requiring **tailored studies and specialized registries** to assess vaccine safety outcomes with the necessary granularity. (19).

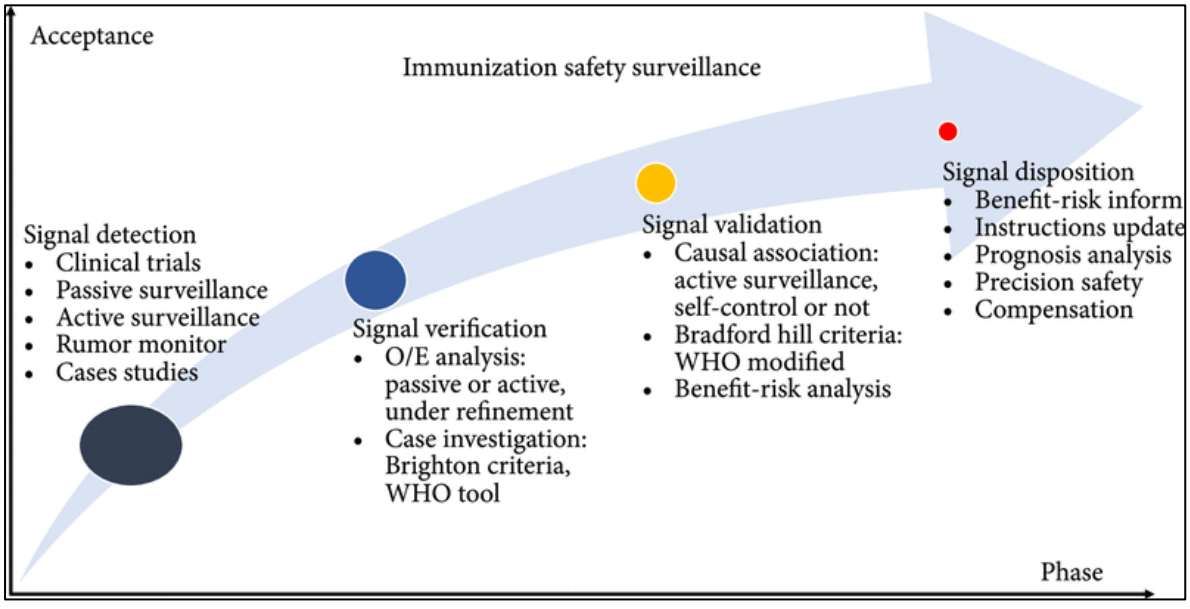

Fig.2. Framework for the immunization safety surveillance: the circle size indicates the number of safety signals or concerns. The more the unresolved vaccine safety concerns, the more likely vaccine hesitation or refusal would occur. The goal is to achieve maximum vaccine safety, in order to reduce phobias and increase acceptance in vaccination. WHO: World Health Organization; O/E: observed over expected. (59).

Spontaneous Surveillance and the Role of Background Rates in Vaccine Safety

Spontaneous (or passive) surveillance constitutes the foundation of vaccine pharmacovigilance in most countries and underlies international systems coordinated by organizations such as the WHO. These systems depend primarily on voluntary reporting of adverse events following immunization (AEFI) by healthcare providers, although in some jurisdictions, community members and patients may also contribute.

A major strength of passive surveillance lies in its broad population coverage, allowing potential adverse events to be captured across diverse demographics. However, under-reporting remains a persistent challenge, including for serious adverse events. While several countries have instituted mandatory reporting requirements for healthcare professionals, evidence suggesting this significantly improves reporting completeness is limited. Contributing factors to under-reporting are varied and often reflect local health system constraints or provider perceptions (20).

Some systems restrict reporting to licensed providers, yet emerging evidence indicates that patients and consumers are equally likely to report serious AEFI when given the opportunity. The expansion of online reporting tools has further increased accessibility, and several national programs now offer public-facing platforms where de-identified safety reports can be searched and reviewed (21,22).

At the international level, national regulatory authorities (NRAs) contribute to VigiBase, the global vaccine safety database maintained by the Uppsala Monitoring Centre in Sweden. This platform enables both national agencies and WHO to analyze aggregated global data. Nonetheless, VigiBase reflects biases from its largest contributors, such as the U.S. Vaccine Adverse Event Reporting System (VAERS) and Europe's EudraVigilance, potentially underrepresenting vaccines used primarily in low- and middle-income countries.

To address such disparities and enhance global vaccine safety monitoring, initiatives like the Global Vaccine Data Network (GVDN) have emerged. These collaborative networks aim to integrate and analyze data across both high- and low-resource settings. For instance, GVDN has been involved in large-scale COVID-19 vaccine safety studies supported by the U.S. CDC, focusing on adverse events of special interest (AESI) through data linkage efforts across diverse populations.

Importantly, not all AEFI are caused by vaccines. Some adverse health events occur coincidentally following immunization, and distinguishing these from genuine safety signals requires comparison with age- and sex-adjusted background incidence rates. These background rates are typically derived from hospital, outpatient, and emergency care records and serve as a baseline to evaluate whether observed event rates post-vaccination deviate from expected norms (24).

Spontaneous surveillance systems are fundamentally hypothesis-generating tools, and suspected safety signals identified through these means usually require validation through active surveillance or dedicated epidemiological studies. Over the past decade, spontaneous data analysis has been increasingly enhanced through automated statistical tools such as disproportionality analysis, Bayesian inference, and the Maximized Sequential Probability Ratio Test (MaxSPRT), which can expedite signal detection for predefined AEFI types. Additional refinements, like time-to-onset (TTO) analyses, provide complementary insights and help reduce false-positive signals (24).

The COVID-19 pandemic significantly increased the global volume of vaccine safety reports, placing immense pressure on pharmacovigilance systems. Upgrades in database infrastructure, real-time analytics, and visualization tools have been essential to prevent system overload and maintain analytical accuracy in an era of mass immunization.

Type of Surveillance System	Description	Primary Purpose	Strengths	Limitations	Examples
Passive (Spontaneous) Surveillance	Relies on unsolicited reports of adverse events from healthcare providers, patients, or manufacturers.	Signal detection	Broad population coverage; Low cost; Early detection of rare AEFI	Under-reporting; Reporting bias; No denominator data; Cannot confirm causality	VAERS (USA), VigiBase (WHO), EudraVigilance (EU)
Active Surveillance	Involves proactive follow-up of vaccine recipients to monitor AEFI.	Signal validation and risk quantification	Systematic data collection; More complete reporting; Enables incidence estimation	Expensive and resource-intensive; Limited coverage	Vaccine Safety Datalink (USA), AusVaxSafety (Australia)
Sentinel Surveillance	Surveillance in selected sites or cohorts to monitor AEFI trends and investigate signals.	Targeted monitoring	High data quality; Focus on priority populations	Limited generalizability; Not population-wide	PRISM (USA), EU-ADVANCE
Cohort Event Monitoring (CEM)	Prospective collection of data on pre-identified cohorts post-vaccination.	Risk assessment and causality	Captures common/rare AEFI; Suitable for LMICs	Requires high retention; Data complexity	CEM in Africa, Asia (WHO programs)
EHR-Linked Surveillance	Uses automated data from electronic records and claims.	Real-world monitoring and analysis	Real-time; Large datasets; Advanced analytics	Data access/privacy concerns; IT infrastructure dependent	VSD (USA), CPRD (UK), CNODES (Canada)
Social Media/Digital Surveillance	Uses digital tools to monitor vaccine discussions and self-reported AEFI.	Supplement traditional systems	Captures public perception; Timely detection	Data reliability issues; Clinical confirmation lacking	MedWatcher, Twitter, Google Trends
Enhanced Passive Surveillance (EPS)	Combines spontaneous reports with reminders or structured follow-up.	Improve detection	Better completeness; Increases volume	Still voluntary; Limited scalability	EU Influenza Campaigns

(26 to 35)

Table.1. Vaccine safety surveillance system types and attributes.

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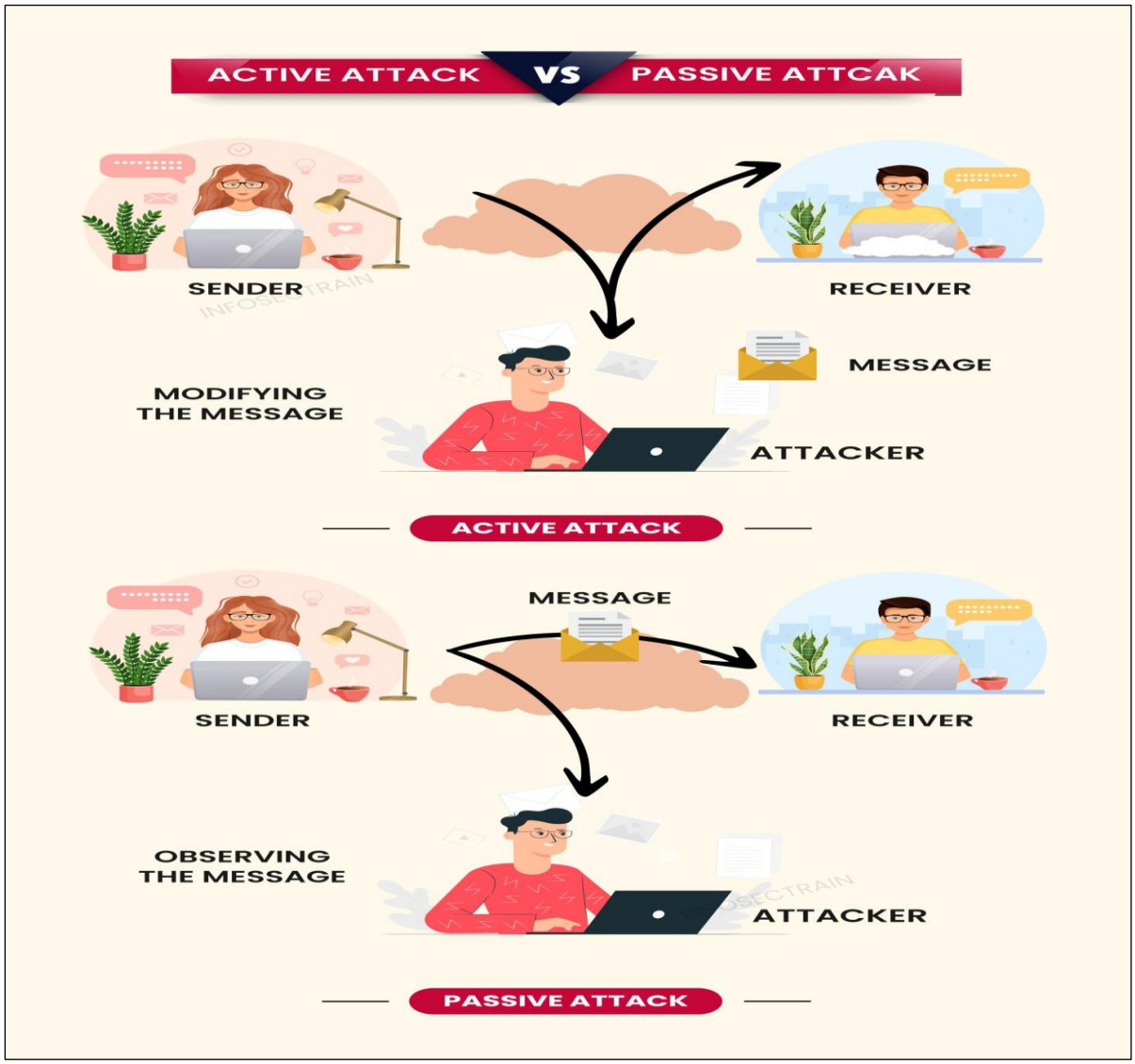

Fig.3. Differences between active attack and passive attack (60).

Syndromic Surveillance in Vaccine Safety Monitoring

Syndromic surveillance refers to the analysis of de-identified, near real-time data—such as clinical diagnosis codes or proxies—to detect anomalies or patterns in health events of interest, including vaccine-related adverse events. These systems have the capacity to scale widely and operate across diverse healthcare settings. A well-known example of syndromic surveillance is the tracking of influenza activity through internet-based search query trends, such as those from Google (36).

Recent advancements have demonstrated the applicability of similar methods for monitoring adverse events following immunization (AEFI). For instance, historical safety signal data related to influenza vaccines have been successfully analyzed using call center records and general practice consultations post-vaccination (37,38). Machine learning approaches are increasingly being applied to automate the monitoring of social media content to identify posts about AEFI and distinguish them from unrelated vaccine discourse (39,40). Additionally, media surveillance systems have been developed to flag and categorize news reports involving vaccine safety issues (41).

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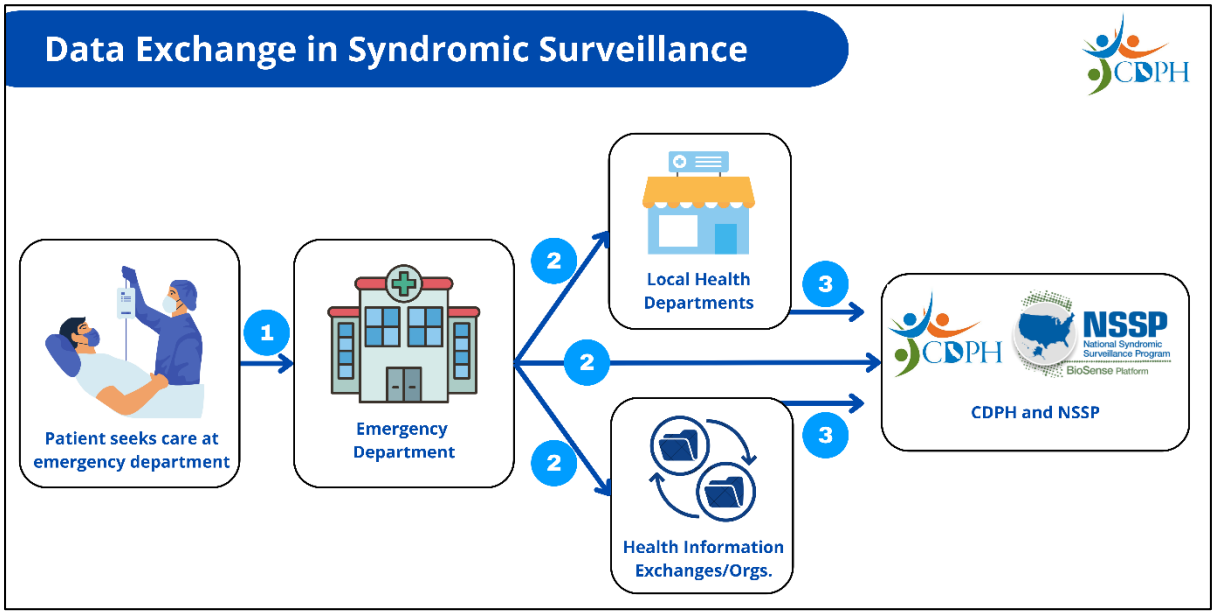

Fig.5. Here is a brief summary of the process of syndromic surveillance for California. (62).

These systems can potentially monitor a spectrum of healthcare engagement—from casual online searches to hospital admissions—enabling early detection of mild adverse events that may serve as precursors to more serious outcomes. For example, increases in reports of fever following pediatric immunizations could serve as an early warning for febrile seizure risks. Such capabilities align with the role of **solicited surveillance** in enhancing traditional pharmacovigilance systems.

Despite their wide reach, high sensitivity, and cost-effectiveness, syndromic surveillance systems may lack specificity. Therefore, their optimal use may be as a **complementary tool** for signal detection and characterization within broader vaccine safety surveillance networks.

Data Linkage in Vaccine Safety Surveillance

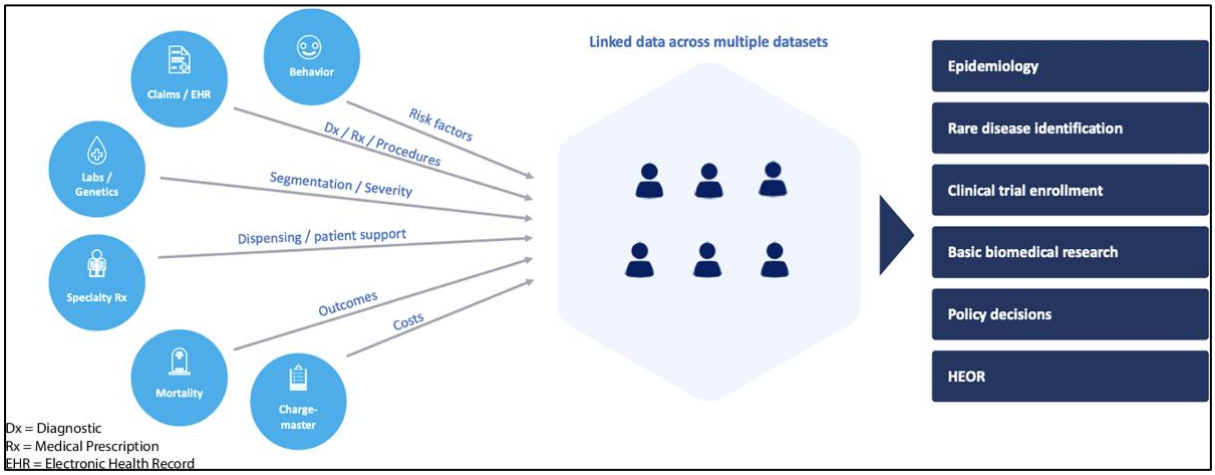

Fig. 4: Multiple types of Real-World Data (RWD) can be linked to facilitate diverse research and commercial activities. (61).

The integration of large, linked health data systems has transformed the way potential vaccine safety concerns—especially rare or unexpected adverse events following immunization (AEFI)—are detected and evaluated. These systems typically connect individual-level vaccination records (from immunization registries or provider databases) to various health outcome datasets, including hospitalizations, emergency visits, primary care consultations, and death records (42).

Through techniques such as rapid cycle analysis, these systems enable the continuous and near real-time assessment of predefined adverse events of special interest (AESI). The incorporation of both vaccinated and unvaccinated individuals in analyses supports multiple study designs, including the self-controlled case series (SCCS) approach, where each person serves as their own control during non-risk periods (44).

These linkage methods have been instrumental in identifying true increases in risk—such as Guillain-Barré syndrome following inactivated influenza vaccination—as well as in disproving suspected associations, like spontaneous abortion after flu vaccines (45,46). Distributed data models are often used in these networks, where all linkages are done locally, and only de-identified, aggregated data is shared centrally. This framework supports national initiatives like the U.S. Vaccine Safety Datalink (VSD) and international efforts like the Global COVID Vaccine Safety Study under the Global Vaccine Data Network (GVDN) (47).

However, a key limitation of these systems lies in their reliance on diagnostic classification codes—most commonly the ICD codes—to define clinical outcomes. The accuracy of these codes can vary significantly by country and health condition (48). In some situations, chart reviews and the use of standard case definitions are required to confirm whether a case truly meets criteria for an AESI, although this level of detail is more feasible in localized systems than at the national level (49).

Encouragingly, several LMICs such as Vietnam and Ecuador have successfully implemented vaccine safety data linkage studies, indicating the growing feasibility of this approach globally (5.,51). While privacy concerns are often cited in discussions around data linkage, public engagement efforts—including citizen juries and community consultations—have consistently shown support for such initiatives when they are used to enhance public health and vaccine safety (52).

Vaccine Safety Surveillance in Low-Resource Settings

The original Global Vaccine Safety Blueprint (GVSB 1.0), introduced in 2012, was designed to help low- and middle-income countries (LMICs) develop basic infrastructure for vaccine safety monitoring and progress toward more robust systems (53). The updated version, GVSB 2.0, builds on this foundation by incorporating a structured maturity model based on the WHO Global Benchmarking Tool, which provides a framework for assessing and improving regulatory capacities (54).

Despite these efforts, many LMICs still face significant gaps in safety surveillance capacity. This is particularly concerning as vaccines with limited post-marketing safety data are increasingly being introduced in these regions—often in response to emerging health threats such as Lassa fever and Nipah virus (55). The absence of established surveillance systems in such settings can hinder timely detection and management of potential safety signals.

To address these challenges, targeted strategies have been employed. One common approach involves strengthening surveillance infrastructure in sentinel health facilities—locations where adverse events following immunization (AEFI) are most likely to be reported. This model was successfully applied during the rollout of the meningococcal A conjugate vaccine in countries like Mali and Niger, leading to improved safety monitoring (56,57).

More recently, initiatives such as the COVID-19-SENT-[Africa-8] project exemplify regional efforts to build capacity for active safety surveillance. This project focuses on hospital-based monitoring of adverse events of special interest (AESIs) in selected African countries eligible under the COVAX Advance Market Commitment framework, helping ensure real-time data collection and safety assessment of COVID-19 vaccines 58).

Conclusion

The evolution of vaccine safety surveillance has been significantly enhanced by advancements in data systems and digital infrastructure. The global rollout of COVID-19 vaccines amidst the SARS-CoV-2 pandemic underscored both the value and the limitations of current pharmacovigilance strategies. While **spontaneous (passive) surveillance** continues to serve as the backbone of safety monitoring—especially for identifying rare or unforeseen adverse events—it is now complemented by web-based tools, public participation, and real-time data visualization technologies that have improved the sensitivity and responsiveness of signal detection.

Active surveillance systems, including large-scale data linkage and syndromic approaches, have

provided deeper insight into vaccine safety by leveraging real-world evidence. These systems have proven especially valuable in assessing both common and less frequent adverse events, offering a critical foundation for rapid signal validation, risk assessment, and policy action. Collaborative networks that span multiple countries and health systems are increasingly capable of detecting and confirming associations between vaccines and rare adverse events, supporting public health decision-making on a global scale.

In low- and middle-income countries, tailored strategies—such as sentinel site surveillance—have enabled targeted safety monitoring, even where broader infrastructure may be limited. The combination of traditional and innovative methods, when adapted to local contexts and supported by global cooperation, offers a pathway toward resilient, responsive, and equitable vaccine safety surveillance.

In conclusion, an integrated and multifaceted surveillance ecosystem is essential to uphold vaccine confidence, rapidly identify and investigate potential safety concerns, and ensure the long-term success of immunization programs worldwide.

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