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Establishing an Active Vaccine Safety Surveillance System Using Large Scale Databases in Korea: Lessons and Scalable Insights for Global Application

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ABSTRACT

Vaccines are highly effective, but rare or delayed adverse events following immunization (AEFIs) require post-licensure surveillance beyond clinical trials. Korea lacks a comprehensive, active, database-based framework, yet key assets exist: nationwide claims databases (National Health Insurance Service/Health Insurance Review and Assessment Service), the national immunization registry (Korea Disease Control and Prevention Agency's Immunization Registry Information System) for National Immunization Program (NIP) and non-NIP vaccines, and increasingly standardized hospital electronic health records. We propose a federated, code to data architecture with data linkages between these data. Implementation should adopt a common data model (CDM), standardized case definitions, latency accounting, and transparent public reporting under strong privacy governance. Major challenges include multi step administrative approvals for data linkage, incomplete capture of adult non-NIP vaccinations, heterogeneous hospital data structures, and strict data protection constraints. Strategic priorities are to streamline statutory and administrative processes for public health use, mandate or enable claims-based capture of adult vaccinations, enhance CDM based interoperability, and develop secure hubs for aggregated outputs. With these measures, Korea will be well positioned to establish a scalable active surveillance system capable of detecting rare AEFIs, supporting transparent and evidence-based communication, and ensuring equitable injury compensation grounded in domestic data.

Keywords: Vaccines; Safety; Adverse Effects; Database; Surveillance; Korea

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BACKGROUND

Vaccination is one of the most effective public health interventions for preventing infectious diseases and has dramatically reduced infection-related morbidity and mortality worldwide.[1] Although vaccines are generally considered safe and effective, adverse events can occur after immunization; these are collectively referred to as adverse events following immunization (AEFI). Some AEFIs are coincidental and unrelated to the vaccine exposure, but certain events including anaphylaxis, arthralgia, encephalitis and febrile seizures have shown causal or temporal associations with specific vaccines.[2]

During vaccine development, safety is evaluated in relatively small and controlled populations compared with real-world settings. Early-phase trials typically enroll hundreds of participants, and phase III studies usually include several thousand.[3] Consequently, very rare adverse events (1 per 100,000 or less) may be difficult to detect prior to licensure. Moreover, clinical trial participants often exclude individuals with complex comorbidities, and the follow-up period is limited; thus, adverse outcomes that manifest only in certain subgroups or after prolonged latency may remain unrecognized until widespread use. Without structured post-licensure surveillance, such delayed or rare AEFIs may be under-recognized or ignored. For these reasons, many countries operate post-licensure vaccine safety surveillance systems designed to rapidly detect safety signals, assess causality, and provide timely evidence to guide public communication and immunization policy.

Public attention to vaccine safety intensified during the coronavirus disease 2019 (COVID-19) pandemic. Novel adverse events, including vaccine-induced immune thrombotic thrombocytopenia with adenovirus-vectored vaccines and myocarditis linked to mRNA vaccines, were not detected during clinical trials but were later identified through post-licensure surveillance.[4,5] These findings highlight the effectiveness of vaccine safety monitoring systems; paradoxically, however, they also heightened public concern and anxiety regarding newly developed vaccines. Moreover, the introduction of novel vaccine platforms, the accelerated phase of clinical development, and the use of emergency use authorizations by the U.S. Food and Drug Administration (FDA) collectively contributed to increased vaccine hesitancy, ultimately elevating the risk of infection at the population level.[6] Unlike therapeutic drugs that may carry an acceptable level of risk, vaccines must meet far stricter safety standards because they are administered to healthy individuals. For this reason, establishing a vaccine safety surveillance system based on large-scale, population-level databases is crucial. In contrast to several high-income countries that operate institutionalized, nationwide systems, South Korea currently lacks a comprehensive, active, and database-driven framework.

To ensure preparedness for the introduction of new vaccines and potential future pandemics, the establishment of a robust national vaccine safety surveillance system is imperative. This review explores database-driven models of vaccine safety monitoring implemented in advanced countries and examines the current status, limitations and future directions of vaccine safety-related data assets and registry infrastructures in South Korea.

TYPES OF VACCINE SAFETY SURVEILLANCE

Vaccine safety surveillance system is a type of pharmacovigilance system, which can be divided into passive and active surveillances. Passive surveillance aggregates spontaneous

Table 1. Characteristics of active vaccine safety surveillance systems in the United States, Canada and Europe

Region/System	Agency	Network and data architecture	No. of covered population (approximate)	Data collection and analysis
USA/VSD	CDC Immunization Safety Office	EHR integration using CDM; linkage to insurance claim data and immunization registries (if applicable)	EHR data ~15 million from 13 sites	Weekly RCA using MaxSPRT; SCRI, PS matching for analysis
USA/BEST	FDA/CBER (Sentinel Initiative)	Linkage of insurance claim data with immunization information system; expanded to CMS and EHR	Claim-based data > 400 million including commercial insurance and CMS	Sequential quarterly monitoring with claim-lag adjustment; protocolized studies
Canada/IMPACT	PHAC and Canadian Pediatric Society	Pediatric hospital EHR collected by active chart review	~90% of tertiary pediatric bed capacity in nationwide	Continuous monitoring of AEFI with standardized validation
EU/VAC4EU	EMA/ECDC and VAC4EU consortium	Mixed sources (including EHR, claim data, immunization registries and other healthcare datasets) from federated pan-Europe network	> 150–180 million	Localized data extraction according to ConcePTION CDM by DAP; data pooling and meta-analysis

VSD = Vaccine Safety Datalink, CDC = Centers for Disease Control and Prevention, EHR = electric health record, RCA = rapid-cycle monitoring, MaxSPRT = Maximum Sequential Probability Ratio Test, SCRI = self-controlled risk interval, PS = propensity score, BEST = Biologics Effectiveness and Safety, FDA = Food and Drug Administration, CBER = Center for Biologics Evaluation and Research, CMS = Centers for Medicare & Medicaid Services, IMPACT = The Canadian Immunization Monitoring Program Active, PHAC = Public Health Agency of Canada, AEFI = adverse events following immunization, EU = European Union, VAC4EU = Vaccine Monitoring Collaboration for Europe, EMA = European Medicines Agency, ECDC = European Centre for Disease Prevention and Control, CDM = common data model, DAP = data access providers.

reports of suspected adverse events from healthcare providers, patients, and vaccine manufacturers, and is used to generate safety signals from accumulated data.[7] This includes the U.S. Vaccine Adverse Event Reporting System (VAERS) and the European Medicines Agency's (EMA) EudraVigilance database. Passive systems enable broad, low-cost data collection across large populations, but rely on voluntary reporting and are therefore subject to underreporting, selection biases, stimulated reporting, variable data quality, and the frequent absence of appropriate comparators.[8] Despite these limitations, passive surveillance remains essential for hypothesis generation and for flagging potential associations between vaccine and adverse events which warrant formal evaluation in active systems.

To overcome the limitations of passive systems, many countries operate active vaccine safety surveillance. Active surveillance collects data directly from defined populations or data sources (e.g., electronic health records (EHR), administrative claims, immunization registries) rather than relying on spontaneous reports.[9] In developed countries, large, computerized health-information databases are commonly leveraged, allowing efficient case ascertainment and statistical evaluation of rare AEFIs using prespecified algorithms and designs. This approach can reduce time and cost while providing adequate statistical power for uncommon outcomes. However, data latency can hinder real-time monitoring, and there's a risk of data security for individual privacy during data extraction and analysis. Representative database-driven active surveillance systems are described in the following sections and **Table 1**.

MAJOR DATABASE-DRIVEN ACTIVE VACCINE SAFETY SURVEILLANCE SYSTEMS IN DEVELOPED COUNTRIES

UNITED STATES – VACCINE SAFETY DATALINK AND BIOLOGICS EFFECTIVENESS AND SAFETY PROGRAM

Passive reporting through the U.S. VAERS alone is insufficient to fully characterize vaccine risks. To complement VAERS, the U.S. Centers of Disease Control and Prevention (CDC) established the Vaccine Safety Datalink (VSD) in 1990 as a large, population-based, active surveillance network linking data from integrated health care systems.[10] VSD currently includes 13 participating member sites and covers more than 8 million enrollees (2.7% of

the U.S. population, in 2010), providing adequate power to evaluate rare AEFIs.[11,12] During the first decade, VSD used centralized data processing, but since 2001 has adopted a common data model (CDM) and a distributed data network to enhance privacy and reproducibility. Under this model, individual-level data remain at each site; standardized programs are executed locally, and only aggregated outputs are shared with the CDC, with dynamic files updated on a regular cadence. Beginning in the mid-2000s, VSD implemented rapid cycle analysis with weekly sequential monitoring, enabling near real time signal detection during vaccination campaigns.[13] This infrastructure proved particularly valuable during the 2009 H1N1 influenza pandemic, when VSD supported timely safety assessments across prespecified AEFIs.[14]

The Post-licensure Rapid Immunization Safety Monitoring (PRISM) program originated during the 2009 H1N1 pandemic as an FDA initiative to enable active post-authorization safety surveillance of H1N1 influenza vaccines to complement CDC's VSD.[15] The initial H1N1 PRISM network linked administrative claims from four national U.S. health insurers with immunization information systems from nine jurisdictions, yielding a distributed database of roughly 38 million individuals. Within a CDM, FDA/its coordinating center authored standardized analytic programs that were posted to a secure portal; data partners executed these programs locally and returned only aggregate results for central pooling.[16] Following the pandemic, PRISM was continued under the Sentinel Initiative (Mini-Sentinel) as a vaccine-focused capability, combining three multiple insurer claims databases with eight state immunization registries to achieve coverage larger than VSD for specific questions. Because claims data are not native electronic medical records and are subject to processing lags, Mini-Sentinel/PRISM files were typically refreshed on a quarterly cadence, in contrast to VSD's weekly dynamic files used for near real time monitoring. When needed, targeted medical record review could be performed to validate outcomes. Vaccines under monitoring and health outcomes of interest were specified a priori by expert panels, with outcome definitions based on ICD code algorithms and validation procedures.[17]

PRISM's functions have since been integrated into FDA/the Center for Biologics Evaluation and Research (CBER)'s Biologics Effectiveness and Safety (BEST) program, which expands data sources beyond commercial claims to include large-scale EHR data and Centers for Medicare & Medicaid (CMS) data, enabling multi-source, privacy-preserving, distributed analyses with more frequent and timely sequential monitoring.[18] During the COVID-19 vaccination program, CBER used BEST and linked CMS data to conduct near real time surveillance for prespecified AEFIs.[19,20]

CANADA – CANADIAN IMMUNIZATION MONITORING PROGRAM, ACTIVE AND RELATED DATA NETWORKS

Canada's pediatric active vaccine safety surveillance began in the early 1990s with Immunization Monitoring Program, ACTive (IMPACT), a hospital-based sentinel network run by the Canadian Pediatric Society in collaboration with the Public Health Agency of Canada (PHAC).[21] IMPACT functions as the active surveillance component within Canada's national system, Canadian Adverse Events Following Immunization Surveillance System. As of the mid-to-late 2010s, 12 tertiary pediatric hospitals participated, covering roughly 90% of Canadian tertiary pediatric beds.[22] At each site, trained nurses identify and validate suspected serious AEFIs, and report standardized case data to PHAC.

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For large-scale, population-based pharmacoepidemiology, Canada also operates Canadian Network for Observational Drug Effect Studies (CNODES), a distributed research network established in 2011 under the Canadian Institutes of Health Research-funded Drug Safety and Effectiveness Network.[23] CNODES conducts common-protocol analyses across multiple provincial administrative databases (e.g., physician billing, hospital discharge abstracts, pharmacy claims) with linkages to registries such as vital statistics; the availability of immunization and laboratory data varies by province.[24] Some CNODES projects have incorporated external data sources (e.g., the UK Clinical Practice Research Datalink and the U.S. MarketScan) to enable cross-jurisdictional comparisons. While CNODES is not itself a dedicated vaccine surveillance registry, it provides the infrastructure to perform rigorous, multi-province observational studies using a privacy-preserving, distributed model conceptually similar to other international networks.

EUROPE – VACCINE MONITORING COLLABORATION FOR EUROPE

Since the European Union comprises multiple countries with heterogeneous health systems and data infrastructures, substantial effort has focused on harmonizing and linking vaccine-related data across jurisdictions. Recognizing the need for active vaccine safety assessment, the European Centre for Disease Prevention and Control (ECDC) in 2008 convened the Vaccine Adverse Event Surveillance and Communication (VAESCO) consortium, linking healthcare databases from eight countries to enable coordinated post-licensure studies.[25,26] Case definitions were supplied by the Brighton Collaboration, and findings were reported to the EMA. During the 2009 H1N1 pandemic, VAESCO supported monitoring of Guillain-Barré syndrome and other AEFIs, but the initiative ended after several years due to funding constraints.[27] Subsequently, the Innovative Medicines Initiative (IMI) funded the Accelerated Development of Vaccine benefit-risk Collaboration in Europe (ADVANCE) project, a large public-private partnership (including National Regulatory Agency, ECDC, EMA, and industry) that developed a code of conduct and governance framework for vaccine benefit-risk studies.[28,29] Building on the deliverables of the ADVANCE project, Vaccine Monitoring Collaboration for Europe (VAC4EU) was launched in 2019 to operationalize multi-country, database-based studies across a network of expert partners. VAC4EU provides access to a broad set of data environments (e.g., hospital and primary-care EHRs, administrative claims, disease registries, prospective cohorts) across multiple European countries, with study-specific selection of data sources.[30]

Analytically, VAC4EU employs a federated code to data workflow. Upon receiving a study protocol and corresponding extraction specifications, participating Data Access Providers transform their source data into the IMI-ConcePTION CDM through a study-directed ETL process. They then apply standardized case definitions (e.g., via the open CodeMapper tool), and execute common modular programs locally.[31,32] Only aggregated, de-identified outputs are uploaded to a secure hub for pooling and meta-analysis.[33] This approach which performs study specific CDM transformations rather than permanently converting entire local databases, differs operationally from several U.S. networks. At the same time, it maintains data privacy and allows rapid and reproducible analyses across multiple countries.

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CURRENT STATUS OF VACCINE SAFETY SURVEILLANCE IN KOREA

Korea currently lacks a comprehensive, database-driven active vaccine safety surveillance system for both National Immunization Program (NIP) and non-NIP vaccines. Instead, passive reporting systems operated by the Korea Disease Control and Prevention Agency (KDCA) and the National Institute of Food and Drug Safety Evaluation (NIFDS) under the Ministry of Food and Drug Safety (MFDS) collect suspected AEFIs. Certain adverse events are designated as notifiable under the Enforcement Rule of the Infectious Disease Control and Prevention Act, providing the legal basis for case reporting by vaccine. In 2011, the MFDS and KDCA strengthened their cooperative system for managing adverse reactions to vaccines and made it a principle that the KDCA would respond to domestic reports, and the MFDS would respond to international signals.

Reports to KDCA may be submitted by healthcare professionals or the public via web-based or paper forms to local public health centers; entries are integrated into the Disease and Health Integrated Management System (https://is.kdca.go.kr), and causality assessment may support compensation when applicable. Reports to MFDS/NIFDS can be filed through the Drug Safety Information System (https://nedrug.mfds.go.kr), which aggregates both domestic and international cases; while the public can submit reports, most entries are typically generated by pharmaceutical companies and healthcare institutions as part of pharmacovigilance (including PMS and clinical studies).[34]

At present, there is no routine, privacy-preserving linkage or integration across these databases, limiting system-level analytics and timely public reporting. Active or quasi-active assessments conducted in Korea to date have largely been post-marketing observational studies using the national immunization registry or hospital data, and ad hoc linkage projects undertaken during the COVID-19 pandemic by major data holders.[35-38] Consequently, findings are often disseminated as study-specific reports or journal articles rather than as regular national summaries, making it difficult for clinicians and the public to appreciate the overall epidemiology of AEFIs in Korea. For accurate risk communication and fair injury compensation, Korea requires domestically generated evidence that reflects its specific vaccines, immunization schedules, and population structure. Accordingly, there is an urgent need to establish a structured, proactive, large-scale database surveillance system, with standardized analytics, transparent public reporting, and sustained education and outreach.

CHARACTERISTICS AND CURRENT STATUS OF VACCINE-RELEVANT DATABASES IN KOREA

Korea maintains one of the largest public medical big data resources among high income countries, consisting of nationwide health insurance claims collected under a single payer system that covers nearly the entire population of about 50 million people. These claims records include fee for service procedures, surgeries, diagnostic and therapeutic services, outpatient and inpatient visits, prescriptions, discharge diagnoses, and deaths.[39] Two closely related institutions manage these data: the National Health Insurance Service (NHIS) and the Health Insurance Review and Assessment Service (HIRA). While both contain claims information, NHIS further includes death records, health screening results, and socioeconomic variables not fully available in HIRA.[39] Since amendments to

personal-information legislation in 2020, controlled research access has expanded, and NHIS provides multiple research-ready datasets (e.g., sample cohorts, health-screening cohorts, and customized extracts) with linkage and data import/export services.[40,41]

However, the NHIS or HIRA claim data does not contain complete vaccine exposure data and thus cannot support active vaccine safety surveillance without linkage to an immunization registry. For NIP vaccines, doses administered at public health centers and private clinics have been captured electronically since the early 2000s in KDCA's Immunization Registry Information System (IRIS), enabling routine national coverage reporting.[42] Unfortunately, for most adult, non-NIP vaccines (e.g., herpes zoster), capture relies on voluntary report, so population-level denominators are incomplete. Operational heterogeneity between public health information system and clinic-level input system, periodic recoding after the introduction of new vaccines, and digitization errors can introduce misclassification; nonetheless, the KDCA registry remains Korea's most comprehensive, curated source for vaccine exposure and is the natural linkage partner for claims-based surveillance.[43]

Hospital EHRs provide an additional, clinically rich source of data for assessing AEFI. They capture vaccination details when administered on site, along with comprehensive clinical information such as laboratory results, imaging findings, and clinical notes. Since data models and warehouses vary across institutions, interoperability requires CDM and standardized vocabularies. Recent pharmacovigilance research have applied CDMs within hospital systems, providing a pathway to extend similar methods to vaccine safety.[36,44] Key barriers include the fact that many vaccinations are delivered in small outpatient clinics rather than large hospitals, and that multi-institutional linkage must address privacy, governance, and secure federation to mitigate re-identification risk.

PROPOSAL FOR ESTABLISHING ACTIVE, DATABASE-DRIVEN VACCINE SAFETY SURVEILLANCE SYSTEM IN KOREA

We propose a federated data architecture that integrates existing data resources to support active vaccine safety surveillance (**Fig. 1**). First, linkage of the NHIS claims data with the KDCA's IRIS would provide population-scale vaccine exposure and AEFI outcome ascertainment. NHIS can supply diagnoses, hospitalizations, emergency visits, and mortality, whereas IRIS provides vaccination records; privacy-preserving linkage would rely on pseudonymization and secure, coded identifiers. The principal strengths of this approach are its very large population denominators and nationwide follow-up. However, key limitations include incomplete capture of non-NIP adult vaccines in the IRIS system, inherent data latency in administrative claims (typically several months and occasionally up to a year) and the absence of near real time data updates.

Second, a hospital network component could support more timely monitoring, which is conceptually similar to the U.S. VSD. Participating hospitals would execute common analytics locally on EHR data (vaccination when administered on site, clinical outcomes, laboratory results), while outcome confirmation could be strengthened by linking aggregated results to NHIS for cross-institutional follow-up. Since many vaccinations in Korea are delivered in small outpatient clinics, adequate capture of vaccine exposures remains a challenge. Moreover,

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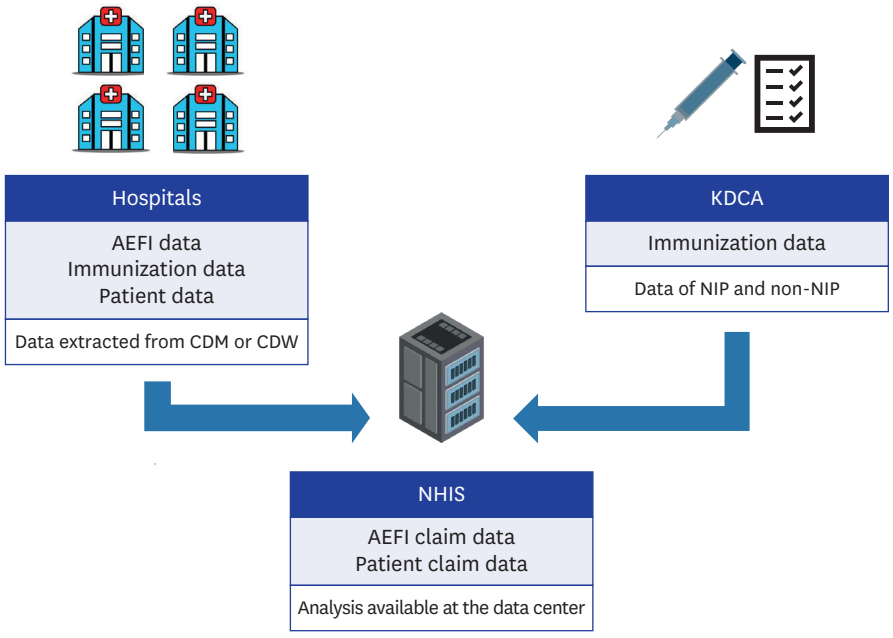


Fig. 1. Overview of data integration of each agency and individual health care centers. NHIS not only provides the claim data of national health insurance but also serves as a data integration agency, enabling analysis of combined data.
AEFI = adverse events following immunization, CDM = common data model, CDW = clinical data warehouse, KDCA = Korea Disease Control and Prevention Agency, NIP = National Immunization Program, NHIS = National Health Insurance Service.

adopting a CDM and a distributed data model is essential to harmonize heterogeneous hospital data and to enable 'code to data' analyses. To protect privacy, queries should be dispatched to each node, with only de-identified, aggregated outputs returned to a secure coordinating hub for pooling.

LIMITATIONS AND OUTLOOK

At present, substantial barriers hinder the establishment of an active AEFI surveillance system through data linkage. Foremost are the complex administrative and regulatory steps required for data integration (**Fig. 2**), including approval by institutional review boards, review of pseudonymization processes by Korea Internet & Security Agency, evaluation by designated data integration agencies, and separate permissions for data export, import and analysis. These sequential steps often require six months or longer, reflecting essential safeguards against privacy breaches but limiting the timeliness required for effective surveillance. While strict protection of personal information is indispensable, overly restrictive or redundant data access controls should be reconsidered. Striking an appropriate balance between privacy protection and data utility is crucial to ensure that vaccine safety surveillance systems remain both ethically sound and analytically responsive. To achieve this balance in practice, statutory provisions specifically designed for public health surveillance, along with streamlined administrative workflows enacted by the National Assembly and implemented by executive agencies, will be essential to enable near real time monitoring.

Strengthening source data is equally important. KDCA's IRIS currently relies on voluntary capture for most non-NIP adult vaccinations; making reporting mandatory would improve

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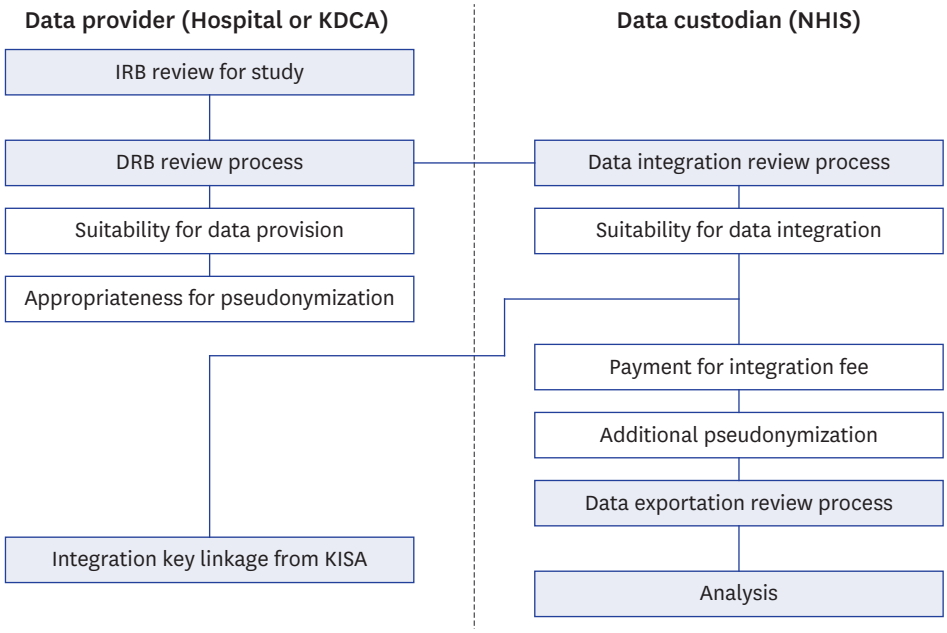


Fig. 2. Data integration request and process for the combined analysis of immunization data and individual vaccine adverse event data. The data provider must obtain approval from IRB and DRB for data provision and pseudonymization. Then the data provider should undergo the data integration review at the data custodian. When approved, the data provider creates integration keys and provides them to the data custodian. After payment of the integration fee and approval of data exportation review, analysis can be performed on the analysis server.
KDCA = Korean Disease Control and Prevention Agency, NHIS = National Health Insurance Service, IRB = Institutional Review Board, DRB = Institutional Healthcare Data Review Board, KISA = Korea Internet & Security Agency.

completeness of data, including vaccinations delivered in small clinics and public health centers that are otherwise difficult to link. Alternatively (or in parallel), incorporating vaccination events into the NHIS claims data by introducing a reimbursement code for the act of vaccination or vaccine products would allow claim-based ascertainment of vaccine exposure. This would enable large-scale effectiveness and safety analyses using NHIS data alone, while preserving flexibility for registry linkages.

For hospital data, harmonization is critical. Large hospitals should continue adopting a CDM to standardize EHR data structures and terminologies. If needed, a vaccine-focused CDM module, which is similar to Europe, could be deployed for AEFI surveillance. Privacy protection should be ensured through a federated code to data framework, in which common analytic programs are executed locally and only deidentified aggregate results are securely shared.

CONCLUSION

Establishing an active, database-driven vaccine safety surveillance system in Korea is both necessary and achievable. The country already possesses core data resources of sufficient scale and quality to support robust monitoring. With coordinated action by the executive agencies and National Assembly to streamline data-linkage governance, and with sustained participation from hospitals and the public, Korea will be well positioned to establish an active surveillance platform comparable to those in other high-income settings. Such a system would enable timely detection and evaluation of rare and delayed AEFIs, mitigate unwarranted public concern through transparent, evidence-based risk communication, and ensure equitable injury compensation grounded in domestically generated data.

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