

Full Title: Suitability of databases in the Asia-Pacific for collaborative monitoring of vaccine safety.

Short Running Title: Suitability of Multi-Country VacSafety in Asia-Pacific

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Key points:

- The capability for vaccine safety and effectiveness monitoring has become increasingly important as evidenced by COVID-19, with multiple vaccines in development and specific vaccines potentially utilized in regions of high need.
- Available data sources and their capabilities for use in vaccine safety surveillance is not well documented in the Asia-Pacific region.
- Nineteen countries in the Asia-Pacific region were approached with 11 healthcare databases containing vaccine-specific information identified from 8 countries (Australia, China, Hong Kong, Republic of Korea, Malaysia, New Zealand, Thailand and Taiwan).
- Capture of vaccine exposure information including, recording of individual vaccines, coding systems and vaccine characteristics is a key source of variability across data sources and will be a limitation in developing a cross-national post-licensure surveillance system for vaccines in the Asia-Pacific region and globally. Outcome information for investigating adverse events or to inform effectiveness of immunization was integrated with vaccination data in seven databases while requiring data linkage for remaining databases.
- Accessibility and timeliness in access to data will be a particular barrier to creating a responsive vaccine safety surveillance system across Asia-Pacific. A Common Data Model will be critical in developing an Asian-Pacific distributed network for investigating vaccine safety.

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Abstract

Introduction: Information regarding availability of electronic healthcare databases in the Asia-Pacific region is critical for planning vaccine safety assessments particularly, as COVID-19 vaccines are introduced. This study aimed to identify data sources in the region, potentially suitable for vaccine safety surveillance.

Methods: Nineteen countries targeted for database reporting were identified using published country lists and review articles. Surveillance capacity was assessed using two surveys: a 9-item introductory survey and a 51-item full survey. Survey questions related to database characteristics, covariate and health outcome variables, vaccine exposure characteristics, access and governance, and dataset linkage capability. Other questions collated research/regulatory applications of the data and local publications detailing database use for research.

Results: Eleven databases containing vaccine-specific information were identified across 8 countries. Databases were largely national in coverage (8/11, 73%), encompassed all ages (9/11, 82%) with population size from 1.4 to 52 million persons. Vaccine exposure information varied particularly for standardized vaccine codes (5/11, 46%), brand (7/11, 64%) and manufacturer (5/11, 46%). Outcome data were integrated with vaccine data in 6 (55%) databases and available via linkage in 5 (46%) databases. Data approval processes varied impacting on timeliness of data access.

Conclusions: Variation in vaccine data availability, complexities in data access including, governance and data release approval procedures, together with requirement for data linkage for outcome information, all contribute to the challenges in building a distributed network for vaccine safety assessment in the Asia-Pacific and globally. Common data models may help expedite vaccine safety research across the region.

Introduction

While the knowledge base regarding robust sources of secondary data and capabilities for vaccine safety surveillance in the US and Europe continues to expand, less is known about available data sources in the Asia-Pacific region. Capability for vaccine safety monitoring has become increasingly important as evidenced by the occurrence of COVID-19, with new vaccines being developed locally and specific vaccines potentially utilized in regions of high need.^{1,2} To date, studies of vaccine safety or effectiveness in the Asia-Pacific region have been limited to single-country databases³⁻¹⁰, however individual countries in the region have contributed to multi-country studies as part of larger global consortia.^{3,4,11-13}

Globally, there are a number of well-established systems for generating real-world evidence for the safety and effectiveness of vaccines. In the United States (US), the Vaccine Safety Datalink (VSD) established by the Centers for Disease Control and Prevention, and the Food and Drug Administration's (FDA) Post-licensure Rapid Immunization Safety Monitoring (PRISM)¹⁴ are well-established systems used to evaluate multiple vaccine products across a distributed network using a common data model (CDM) approach.^{15,16} National databases and registries in other countries have also been used for vaccine evaluation.¹⁷⁻¹⁹ In recent years, initiatives for assessing vaccine safety, combining data from multiple databases in Europe and Canada have also been implemented.^{12,20-22} However, similar coordinated efforts using multiple databases across the Asia-Pacific region are lacking.

Opportunities to conduct vaccine safety research on emergent issues of existing vaccines and for novel and recently-licensed vaccines are paramount. A functional post-licensure surveillance system for vaccines anywhere, including the Asia-Pacific region, requires in-depth knowledge of what data are recorded on vaccine exposure, medical outcomes, potential covariates, data reliability and validity. Additionally, to ensure responsive post-licensure vaccine surveillance, it remains critical to determine which datasets have exposure and outcome data available in a single source and, where data are not available in a single source, whether there exists the ability to link different datasets to obtain outcome

information.²³ The experience in other regions that have developed multi-database vaccine surveillance systems suggests that key strength of databases for this purpose lies in their ability to record vaccination data linked with inpatient and/or outpatient safety outcomes.^{24,25}

The aim of this paper was to identify potential national data sources (EHR, claims, vaccine registries) in the Asia-Pacific region and their suitability for contributing to a distributed network for monitoring vaccine safety.

Methods

This paper responds to a call for manuscripts from the International Society of Pharmacoepidemiology (ISPE). A working group was convened which included a diverse group of 15 volunteers from private and public sectors and including representation from two ISPE special interest groups (SIGs): Vaccines and Asian Pharmacoepidemiology Network (AsPEN), many of whom live or conduct research in the Asia-Pacific region.

Selection of countries and survey participants

A list of countries in the Asia-Pacific region targeted for this research was established from the following resources: United Nations geoscheme²⁶, Asia-Pacific Economic Cooperation (APEC)²⁷, Association of Southeast Asian Nations (ASEAN)²⁸ & Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET).²⁹ Selected review articles³⁰⁻³⁶ were also consulted to further identify databases in the Asia-Pacific region with potential for population surveillance of vaccines. Based on the working group's prior database knowledge, research experience in specific countries, and association with locations in the region, 19 countries located in the Asia-West Pacific region were identified (Appendix A). Survey contacts for each country were identified using three strategies. First, contacts were provided by working group members. Second, a snowball approach was employed where respondents to the initial survey could nominate a preferential contact for survey participation. Third, a flyer advertising the study was enclosed in participant packs attending the ISPE 11th Asian Conference on Pharmacoepidemiology held in Xi'an, China (October 2018).

Survey development, administration & questions

Survey questions were developed from previously implemented regional and international surveys seeking to identify data sources for pharmacoepidemiological research and further refined by the working group. Surveys included items developed for the Asian Pharmacoepidemiology Network (AsPEN) initiative³³, for former European public-private projects such as the Innovative Medicines Initiative (IMI) Accelerated Development of Vaccine Benefit-Risk Collaboration in Europe (ADVANCE) project³⁷, database fingerprinting from the European Medical Information Framework (EMIF)³⁸, the Global Research in Pediatrics (GRIP) survey on electronic health care databases³⁹, the Global Vaccine Safety Datalink (GVSD) initiative and other published sources.^{8,32,40,41}

Survey administration (using the Survey Monkey platform) commenced in June 2018 and involved a two-stage process comprising an initial brief nine-item introductory survey followed by a longer 51-item 'full' survey. The introductory survey served two functions: to collate preliminary information on available data sources in a country for conducting vaccine safety research and, to identify a preferential contact for completion of a longer survey. The introductory survey also included questions on source of funding (government, insurance, self) for child and adult vaccines within the country. The second more comprehensive survey comprised nine sections and was completed by either introductory survey respondents self-identifying as a suitable contact for completing the longer survey or referring an alternative contact. A description of the nine survey sections and question items appear in Appendix B.

Frequency of survey responses were summarized as proportions with analysis conducted using SAS 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Survey response

Thirty-seven individuals representing academic researchers, medicine/vaccine regulatory and other government agencies from 19 countries were approached for survey participation (Figure 1). Twenty

individuals (54%) representing 11 (58%) countries responded to the introductory survey. One respondent from Japan completed the introductory survey, but not the full survey as immunization records were not available in reimbursement-based databases.^{42,43} An introductory survey response from Singapore was unable to identify an appropriate contact for full survey completion. A Philippines respondent completed the full survey. However, the database described was the World Health Organization (WHO) Vigiflow containing spontaneous reports of immunization adverse events rather than EHR, administrative claims or immunization registry data. A full survey response from Vietnam, also excluded from analysis, similarly described a spontaneous adverse reports database. No response at all was received from Bangladesh, Brunei Darussalam, Cambodia, India, Indonesia, Laos or Papua New Guinea (n=7). Full surveys were completed for eight countries on 11 databases (Australia, China, Hong Kong, Republic of Korea, Malaysia, New Zealand, Thailand and Taiwan). Two databases were described each for the Republic of Korea, Taiwan and Thailand.

[Insert Figure 1 here]

Database characteristics

The majority of the 11 data sources contained national (complete population) coverage data (8/11, 73%), information relating to all ages (9/11, 82%) with population size from 1.4 to 52 million individuals and data collation spanning 10 years or more (Table 1). Source records covered a range of primary (general practitioner, community clinic) to secondary/ tertiary (hospital inpatient/outpatient) settings or immunization registries. Australia, Korea, New Zealand and Taiwan maintain an immunization registry and require external data linkage to obtain health outcome information.

[Insert Table 1 here]

Demographic and covariate data

Age and gender were recorded across all databases while only four data sources captured ethnicity (Table 2). Medication treatment was recorded in 7/11 (64%) databases while information on weight, height and socioeconomic status was available in nearly half of the databases (5/11, 46%).

Educational levels and lifestyle variables (smoking, alcohol, diet and physical activity) were rarely recorded.

Vaccination data

Details on vaccine exposure differed across data sources, however nearly all databases recorded date of vaccination (Table 3). A country-specific vaccine code was available for 8/11 (73%) databases. New Zealand and one Thailand database instead used only the WHO standard Anatomical Therapeutic Chemical (ATC) classification system code. Vaccine ATC codes were recorded in (5/11, 45%) databases. Variability across data sources was identified for brand, dose, route and body site of injection, however most databases recorded the vaccination setting e.g. inpatient/outpatient/primary care. The specific vaccines recorded in data sources varied (Table 4). Tetanus vaccination was recorded by all but Hong Kong and Korean (National Health Insurance) (9/11, 82%) databases. Administration of vaccines such as diphtheria, measles, mumps, pertussis, pneumococcal, poliomyelitis, rubella, and BCG were recorded in 8/11 (73%) data sources. Tropical vaccines such as typhoid, yellow fever and dengue were only recorded in the Chinese and Korean databases.

[Insert Tables 2, 3 & 4 here]

Potential for linkage of vaccine exposure information to health outcomes

Integrated vaccine exposure and diagnosis outcome information was available for 6/11 (55%) databases, with Thailand (2) and Taiwan's national claims database able to be further linked to other external data sources, unlike databases in China, Hong Kong and Malaysia having no external linkage ability. For five (45%) databases (Australia, Korea (2), New Zealand, Taiwan's immunization registry data), external data linkage was needed to achieve access to person-level vaccine and outcome data (Table 5). For the databases requiring external data linkage, only Australia required probabilistic linkage methods to join datasets. Procedural and laboratory results either within, or via linked external sources, were available for 9/11 (82%) and 7/11 (64%) databases, respectively. In seven (64%) databases, linkage of mother-child information could be performed. Appendix C lists selected vaccine

safety or effectiveness studies reported by survey respondents for countries (Australia^{5,6,44-46}, China, New Zealand^{9,47,48}, Taiwan^{10,49-57}) linking vaccine exposure and outcome data.

Data governance

Australian, Chinese and Taiwanese databases required the most extensive range of approvals (Table 6). In contrast, the Hong Kong Clinical Data Analysis and Reporting System required a single ethics committee approval while approval to access Malaysia QUEST 3+ data was limited to data governance committee approval. Ethics and data governance committee approvals were the most frequently described approvals needed for 10/11 (91%) and 9/11 (82%) of databases, respectively. Data access charges were reported for over half of 11 data sources including, Australia, Korea, New Zealand, Thailand and Taiwan. Of nine databases providing information on time to data release, 4/9 databases (44%) reported time-frames of 2 months or less. Four databases (36%) stated time-frames of between 3 and 6 months. Data release in Australia was estimated to be one to two years.

[Insert Tables 5 & 6 here]

Discussion

Significant variation was found for the 11 databases identified for 8 countries in the Asia-Pacific. Key areas of heterogeneity included scope of vaccine information time to data access approval, number of approval requirements for data release, and population coverage. Critically, only six databases contained integrated outcome and vaccine exposure data while a further five required external data linkage to combine these data. Together the heterogeneity and non-integrated vaccine-outcome information present challenges for creating a coordinated distributed surveillance network for vaccine safety across the Asia-Pacific.

An important requirement of a post-market surveillance system for vaccines is availability of detailed vaccine exposure data. Substantial variation in capture of vaccine exposure information was identified across countries. While all databases recorded vaccine administration date, the type and coding of

individual vaccines varied. For example, only influenza vaccine was uniformly recorded across (almost all) countries. The Expanded Program on Immunization (EPI)⁵⁸, recommends a minimum vaccine requirement to protect against six diseases: tuberculosis (BCG), diphtheria, tetanus, pertussis (DTP vaccine), measles and poliomyelitis, (with more recent recommendations⁵⁹ also including hepatitis B, *Haemophilus influenzae* type b, pneumococcal conjugate rotavirus and human papilloma virus vaccines), with capture of these vaccines expected in all countries. However, we identified inconsistent recording of EPI vaccines within databases, possibly due to differing reimbursement/payment arrangements for vaccines across health care systems. The Hong Kong CDARS database for example, recorded only two vaccines and no EPI vaccines. Vaccination in Hong Kong including, the childhood vaccination programme is mainly provided by the Department of Health in Hong Kong. These childhood vaccines are not within the service area of the Hospital Authority (the host of CDARS) and so most routine vaccines are not captured in the CDARS database. Vaccine information maintained by the Department of Health is not currently available to researchers. Additionally, we found other non-EPI vaccines were also variably captured across databases, likely due to local disease epidemiology, licensure status or insurance/out-of-pocket payments. For example, cholera, and tick-borne encephalitis vaccine data were only routinely recorded in Korea and China while typhoid and yellow fever vaccine data were captured in Korea, China and Malaysia. Information on batch, brand, dose and manufacturer information was consistently recorded in only four countries (Australia, China, Korea, and Malaysia). This will be a particular issue as different strains, formulations and manufacturing processes may have important impact on vaccine safety. Additionally, while the majority of databases employed standard WHO ATC codes for vaccine identification, half of the survey countries applied their own country-specific coding indicating a map to standardized vaccine codes will be required prior to undertaking cross-country studies.

In this survey, it was identified that integrated vaccine and outcome data were available for six databases (five countries) with external data linkage a possibility for the remaining five survey databases (four countries: Australia, Korea, New Zealand and Taiwan). Where data linkage was

required, a national unique identifier was available in all countries except Australia. The use of separate databases may arise from differing funding arrangements for vaccines (compared with medicines), particularly where governments are responsible for ensuring high coverage such for childhood vaccines. For example, in Australia, Korea, New Zealand and Taiwan all maintain vaccine registries that require linkage to external datasets to capture outcome data. While the advantage of vaccine registries is their more detailed data capture of and vaccine-specific information such as components of multivalent vaccines, administration route, injection site and vaccine brand, the requirement for linkage to other data sources to obtain outcome information such as hospitalization for adverse events, can impact on timeliness of these data when generating evidence of vaccine safety. Our survey also identified that information on potential confounders are rarely captured in immunization registries with linkage to external databases required to obtain this information. Whilst data linkage is feasible in many countries, access to these data may be restricted, presenting a particular barrier to creating a responsive vaccine safety surveillance system across Asia-Pacific. For example, in Korea, KCDC vaccine registration data can only be used internally by KCDC, and in other cases can only be accessed by researchers directly funded by KCDC, or at the request of KCDC-related government body. Additionally, while the linkage between KCDC registry data and nationwide Health Insurance Database is feasible, privacy protection laws are a strong regulatory hurdle to linking the two databases. Time to data release varied across data sources from <1 month to 3-6 months, with access to Australian data exceeding one year. The number of approvals required for data release however, was not necessarily reflective of time to data release. Access to Taiwan databases for example, required three approval processes with expedient data release.

Another challenge to undertaking cross-national studies across the Asia-Pacific is variability in the scope of population coverage identified in the databases. Korea and New Zealand have full population coverage in their registries while Australia has only recently introduced collection of adult immunizations (since 2016) with an initial focus on Government subsidized vaccines. Taiwan only mandates recording of childhood EPI vaccines and while immunization data are available in the national claims database, only selected vaccines are included.

Despite the disparities across Asia-Pacific data sources, a number of multinational initiatives^{60,61,62} have demonstrated that the identified challenges can be overcome. Increasingly, large-scale distributed analyses to support post-licensure surveillance of medicines and vaccines have been facilitated through the use of Common Data Models (CDMs).^{62,63} A CDM is designed to standardize the format, both structure and coding systems, of observational data. The advantage of a CDM is by transforming data into a similar format, combined analyses can be undertaken across several databases using standardized analytic code. While some existing CDMs contain structures relevant for vaccine studies, a key step in CDM translation is the process of mapping terminology codes from domestic vaccine codes to common terminology systems. Lai *et al.*⁶⁴ recently reported recently reported the successful conversion to the OMOP⁶⁵ CDM for many of the Asian databases identified in this study. However, the biggest challenge was the mapping of drug codes and coding of combination products due to differences in coding systems across countries and differences in health care systems. Mapping of vaccine codes will present similar challenges due to some vaccines being unique to particular areas or constituent vaccine components such as adjuvants differing despite having the same antigen composition. While standardization of vaccine coding will help facilitate cross-country analyses, funding for this conversion and ongoing maintenance will be required. Another limiting factor for developing a comprehensive distributed network for vaccine safety across the Asia-Pacific region is the diversity of languages, cultures and health care systems. The experience of AsPEN has shown these challenges can be addressed with a formalized governance structure, and in fact can help when investigating potentially heterogeneous effects of treatment due to genetic and ethnic differences.^{66,67} Networks such as VAESCO⁶⁸ and the current ADVANCE³⁷ initiative developed in the European region, are also examples of successful multi-country vaccine networks. Elements contributing to the success of these initiatives include, stable core funding (with contributions from regulatory agencies) to support coordination and work plans. Common research and data management protocols with member country input for interpretation of local data together with, a distributed data approach with a common data model to address governance and ethics issues are also important elements for successful studies.^{37,69} As well as easier geographical access⁷⁰, cross-national studies involving countries across the Asia-Pacific are important for providing the necessary population

numbers for investigation of vaccine safety issues but also, for generating data generalizable to other Asian-Pacific countries, given the mix of ethnicities and socioeconomic diversity across the region, rather than relying on information from Western nations. Participation in these networks further provides opportunities for strengthening vaccine safety monitoring and increasing the capacity of individual countries to engage in active surveillance of vaccines.⁷⁰ Despite the disparities observed across Asia-Pacific data sources, a number of other multinational initiatives^{60,61,62} have also demonstrated that the identified challenges can be overcome.

The strength of our study was the consolidated reporting of potential data sources in the Asia-Pacific, including, the breadth and depth of data available for undertaking vaccine surveillance. To our knowledge, no such detailed vaccine information exists for the region. This information will be useful for investigators and regulators seeking to undertake cross-national vaccine utilization and safety studies, particularly for vaccines with more localized supply protecting against endemic disease such as yellow fever and Japanese encephalitis. Limitations of our study include our purposive selection of countries for survey participation, low response rate and database number reported given the range of Asian-Pacific countries. Collectively, these limitations contribute to incomplete reporting of available databases for possible vaccine surveillance. Some of the largest countries in the region, Indonesia and India did not participate, while only a single regional database was reported for China – despite reporting of other regional data sources which may be available for possible surveillance.³⁰ While non-participation may have arisen due to limited or lack of suitable databases for surveillance, it may also reflect the differing maturity in the ability of individual country's to electronically capture and contribute the necessary vaccine exposure and outcome identification needed for surveillance purposes. We were also largely reliant on potential English-speaking participants identified through existing ISPE networks to be involved in survey participation. While survey participants were asked to nominate additional individuals who could assist with the identification and/or reporting of country databases for vaccine surveillance, responses to subsequent survey invitations were frequently not successful. A more comprehensive literature review supplemented by communication with primary authors of other database publications could be undertaken in future studies to identify other potential data sources for vaccine surveillance.

Our study has highlighted the clear challenges facing the research community in ensuring a responsive post-market surveillance program for existing vaccines as well as those being developed for COVID-19. In the COVID-19 era, a coordinated approach will be critical for conducting post-licensure COVID-19 vaccine safety studies. Multiple vaccines are in development for COVID-19 with country access to vaccines enabled either through COVAX⁷¹ or by independently pursuing contracts with vaccine manufacturers. Given the vast number of vaccines in development with expedited timelines to address the pandemic, head-to-head trials of vaccine candidates have not occurred. Multi-country studies may therefore provide the only opportunity to conduct comparative assessments, and provide insights into vaccine safety and effectiveness. Development of a coordinated distributed research network for vaccine safety assessment in the Asia-Pacific will help to facilitate access to larger datasets cumulatively covering an estimated 170 million individuals, helping to identify rare vaccine safety concerns that may go unnoticed in smaller datasets. Importantly, evidence generated from cross-country studies will have additional value in strengthening vaccination policy in resource-poor countries in the region with limited or no ability to conduct routine safety assessment of vaccines. Furthermore participation in vaccine safety projects will provide opportunities for pharmacovigilance and pharmacoepidemiology training and capacity building in low-to-middle income countries.⁷²

Conclusion

The COVID-19 pandemic has highlighted the need for an established Asia-Pacific database network to provide population-level evidence of effectiveness and safety of newly-developed vaccines. In this study, we provided an overview of electronic databases currently available across the Asia-Pacific region with potential to be utilized for assessing safety and effectiveness of vaccines. Substantial variation was identified in the availability and extent of detail of vaccine data including, coding systems and vaccine administration details. Key challenges for building a distributed network to assess vaccine safety across the Asia-Pacific will be access to data and reliance on data linkage to obtain outcome information. Learnings from implementation of existing vaccine networks, including PRISM and Vac4EU and DARWIN⁷³, will be critical in developing a distributed network.

Implementation of a CDM approach may help to address these issues and facilitate a coordinated system for vaccine safety and effectiveness in the Asia-Pacific region.

Accepted Article

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ETHICS STATEMENT

The authors state that no ethical approval was needed.

CONFLICT OF INTEREST STATEMENT

AK is employed by Sanofi Pasteur and holds company shares.

CC at time of manuscript development was employed by, and holds shares in the GlaxoSmithKline group of companies.

JS and KH are employed by Pfizer Inc.

TK is employed by Astellas Pharma Inc.

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Table 1: Database characteristics

Country Database	Coverage	Source Records	Year Database Start	Overall Size of the Database	Age Groups	Vaccine + Outcome (internal)	Vaccine + Outcome (linkage)
AUSTRALIA: Australian Immunisation Registry	National	Immunisation registry only	1996 Child 2016 Adult	Not stated (estimated 45m)	0-7 years + older age groups	✘	✓✓
CHINA: Yinzhou Electronic Health Record	Regional	Source records from all settings: Outpatient EMR, Community/ambulatory; , Inpatient EMR / hospital, Adverse event reporting system	2008	1.6m	All ages	✓	-
HONG KONG: Clinical Data Analysis and Reporting System	National	Outpatient electronic medical record (EMR), community/ambulatory; Inpatient EMR/hospital	1993	11m (est. 7.4 m active population)	All ages	✓	-
KOREA: Immunization registry system	National	Immunisation registry only	2002	51.7m	All ages	✘	✓✓
KOREA: National Health Insurance Database linked with health screening data	National	Health care reimbursement claims	2002	51.7m	All ages	✘	✓✓
MALAYSIA: QUEST 3+	National	Outpatient EMR, community/ambulatory; Inpatient EMR/hospital; Adverse event reporting system	2000	Not stated	All ages	✓	-
NEW ZEALAND: National Immunisation Register	National	Immunisation registry only	2006	1.7m	All ages	✘	✓✓
THAILAND: Hospital Information	Regional	Outpatient EMR, community/ambulatory; Inpatient EMR/hospital	2003	Not stated	All ages	✓	-
THAILAND: Hospital Information Management professional	Regional	Source records from all settings	2004	1.4m	All ages	✓	-
TAIWAN: National Health Insurance Databases	National	Health care reimbursement claims	1998	27.2m	All ages	✓	-
TAIWAN: National Immunization Information System	National	Immunisation registry only	1995	4.8m	0-5 years	✘	✓✓

Explanation of symbols: '✓' signifies both vaccine exposure and outcome data e.g. diagnoses are contained within the same database; '✓✓' signifies that outcome data (from different data sources) are available for linkage with the vaccine exposure data using a deterministic or probabilistic linkage process to match individuals across databases; '✘' signifies only vaccine exposure data (but no outcome data) are available within the named database; '-' signifies no linkage is required for outcome data.

Table 2: Availability of demographic, covariate and other variables

Country Database	Gender	DOB	Ethnicity	Education	SES*	Weight	Height	Medication	Smoking	Alcohol	Diet	Physical activity
AUSTRALIA: Australian Immunisation Registry	✓	✓	✓	✗	✓	✗	✗	✗	✗	✗	✗	✗
CHINA: Yinzhou Electronic Health Record	✓	✓	✗	✗	✓	✓	✓	✓	✗	✗	✗	✗
HONG KONG: Clinical Data Analysis and Reporting System	✓	✓	✗	✗	✓	✗	✗	✓	✗	✗	✗	✗
KOREA: Immunization registry system	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
KOREA: National Health Insurance Database linked with health screening data	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	✓
MALAYSIA: QUEST 3+	✓	✓	✓	✗	✗	✓	✓	✓	✗	✗	✗	✗
NEW ZEALAND: National Immunisation Register	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗
THAILAND: Hospital Information	✓	✓	✗	✗	✗	✓	✓	✓	✓	✓	✗	✗
THAILAND: Hospital Information Management professional	✓	✓	✗	✗	✗	✓	✓	✓	✓	✗	✗	✗
TAIWAN: National Health Insurance Databases	✓	✓	✓	✗	✓	✗	✗	✓	✗	✗	✗	✗
TAIWAN: National Immunization Information System	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
	11/11 (100)	11/11 (100)	4/11 (36)	1/11 (9)	5/11 (46)	5/11 (46)	5/11 (46)	7/11 (64)	3/11 (22)	2/11 (18)	0/12 (0)	1/11 (9)

*SES = Socio-economic status

Table 3: Availability of vaccination/vaccine variables

Country Database	Date Vaccination	Batch No.	Vaccine ATC Code	Country-specific Vaccine Code	Brand	Dose	Manufacturer	Route	Body Site	Setting
AUSTRALIA: Australian Immunisation Registry	✓	✓	✗	✓	✓	✓	✓	✗	✗	✗
CHINA: Yinzhou Electronic Health Record	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓
HONG KONG: Clinical Data Analysis and Reporting System	✓	✗	✗	✓	✗	✓	✗	✓	✗	✓
KOREA: Immunization registry system	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
KOREA: National Health Insurance Database linked with health screening data*	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
MALAYSIA: QUEST 3+	✗	✓	✓	✓	✓	✓	✓	✓	✗	✗
NEW ZEALAND: National Immunisation Register	✓	✓	✓	✗	✓	✓	✗	✓	✓	✓
THAILAND: Hospital Information	✓	✗	✓	✓	✗	✓	✗	✓	✗	✓
THAILAND: Hospital Information Management professional	✓	✗	✓	✗	✗	✗	✗	✓	✗	✓
TAIWAN: National Health Insurance Databases	✓	✗	✗	✓	✓	✗	✓	✗	✗	✓
TAIWAN: National Immunization Information System	✓	✗	✗	✓	✗	✓	✗	✗	✗	✗
	9/11 (82)	5/11 (46)	5/11 (46)	8/11 (73)	6/11 (55)	8/11 (73)	5/11 (46)	7/11 (64)	3/11 (27)	7/11 (64)

* Health insurance database itself does not have any information regarding the use of vaccines. When two databases are linked there may be information on vaccines.

Table 4: Database availability of specific vaccine types

Country Database	Diphtheria	H.Influenzae	Hepatitis A	Hepatitis B	Influenza	Measles	Meningococcal	Mumps	Pertussis	Pneumococcal	Poliomylitis	Rotavirus	Rubella	Tetanus	BCG	Cholera	HPV	Japanese Encephalitis	Rabies	Tick-born Encephalitis	Typhoid	Varicella	Yellow Fever	Dengue	Other
AUSTRALIA: Australian Immunisation Registry	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	×	×	×	✓	×	×	HZ, QF
CHINA: Yinzhou Electronic Health Record	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×
HONG KONG: Clinical Data Analysis and Reporting System	×	×	×	×	✓	×	×	×	×	✓	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
KOREA: Immunization registry system	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	HV
KOREA: National Health Insurance Database linked with health screening data	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	HV
MALAYSIA: QUEST 3+	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	✓	✓	×	×
NEW ZEALAND: National Immunisation Register	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	×	×	×	×	✓	×	×	×
THAILAND: Hospital Information	✓	✓	×	✓	✓	✓	×	✓	✓	×	✓	×	✓	✓	✓	×	✓	✓	✓	×	×	×	×	×	×
THAILAND: Hospital Information Management professional	✓	×	×	✓	✓	✓	×	✓	✓	×	✓	×	✓	✓	✓	×	✓	✓	✓	×	×	×	×	×	×
TAIWAN: National Health Insurance Databases	×	×	×	×	✓	×	×	×	×	✓	×	×	×	✓	×	×	×	×	✓	×	×	×	×	×	×
TAIWAN: National Immunization Information System	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓	×	×	✓	×	×	×	✓	×	×	×
	8/11 (73)	7/11 (64)	5/11 (46)	8/11 (73)	10/11 (91)	8/11 (73)	5/11 (46)	8/11 (73)	8/11 (73)	8/11 (73)	8/11 (73)	6/11 (55)	8/11 (73)	9/11 (82)	8/11 (73)	2/11 (18)	7/11 (64)	6/11 (55)	6/11 (55)	2/11 (18)	3/11 (27)	6/11 (55)	3/11 (27)	2/11 (18)	3/11 (27)

Abbreviations: BCG = Bacille Calmette-Guerin (tuberculosis vaccine), HPV = Human papilloma virus, HV = Hantaan virus, HZ= Herpes zoster, QF=Q-fever.

Table 5: Database availability of standard identifier, linkage capacity with external datasets and capture of outcome data.

Country Database	Standard identifier*	Data linkage	Diagnosis†	Procedures	Laboratory Results	Mother-child linkage
AUSTRALIA: Australian Immunisation Registry	✗	✓	External linkage only	External linkage only	✗	✗
CHINA: Yinzhou Electronic Health Record	✗	✗	✓	✓	✓	✓
HONG KONG: Clinical Data Analysis and Reporting System	✓	✗	✓	✓	✓	✓
KOREA: Immunization registry system	✓	External linkage only	External linkage only	External linkage only	✗	✗
KOREA: National Health Insurance Database linked with health screening data	✓	External linkage only	External linkage only	External linkage only	✗	✗
MALAYSIA: QUEST 3+	✗	✗	✓	✗	✗	✗
NEW ZEALAND: National Immunisation Register	✓	✓	External linkage only	External linkage only	External linkage only	✓
THAILAND: Hospital Information	✓	✓	✓	✓	✓	✓
THAILAND: Hospital Information Management professional	✓	✓	✓	✓	✓	✓
TAIWAN: National Health Insurance Databases	✓	✓	✓	✓	External linkage only	✓
TAIWAN: National Immunization Information System	✓	✓	External linkage only	External linkage only	External linkage only	✓
	8/11 (73)	6/11 (55)	6/11 (55)	5/11 (46)	4/11 (36)	7/11 (64)

*Standard identifier = national unique identifier.

†Diagnosis (outcome) = refers to health condition or disease diagnosis information being recorded within a named database. Diagnosis outcomes may be sourced from hospital inpatient/emergency department databases and/or primary care databases.

‘External linkage only’ signifies vaccine exposure data can be externally linked to another data source containing diagnosis, procedures or laboratory data. Linkage of two or more datasets is conducted using a standard identifier or where no standard identifier exists, by probabilistic linkage methods (as for the Australian dataset).

Table 6: Database access documentation and approval requirements.

Country Database	Publicly available policy on data access	Publicly available procedures document	Approval: Data Governance Committee	Approval: Institutional Committee	Approval: National data protection agency	Approval: Regional data protection agency	Approval: Ethics committee	Other approval	Data access charges	Time to data release
AUSTRALIA: Australian Immunisation Registry	✗	✗	✓	✓	✗	✗	✓	✓ ^a	✓	1-2 years
CHINA: Yinzhou Electronic Health Record	✓	✓	✓	✓	✓	✗	✓	✓ ^b	✗	3-6 months
HONG KONG: Clinical Data Analysis and Reporting System	✓	✗	✗	✗	✗	✗	✓	✗	✗	1-2 months
KOREA: Immunization registry system	✗	✗	✓	✓	✗	✗	✓	✗ ^c	✗	N/A ^d
KOREA: National Health Insurance Database linked with health screening data	✓	✓	✓	✓	✗	✗	✓	✓	✓	3 months
MALAYSIA: QUEST 3+	✓	✗	✓	✗	✗	✗	✗	✗	✗	Not stated
NEW ZEALAND: National Immunisation Register	✓	✓	✓	✗	✗	✗	✓	✓ ^e	✓	<1 month
THAILAND: Hospital Information	✓	✗	✓	✗	✗	✗	✓	✗	✓	3-6 months
THAILAND: Hospital Information Management professional	✗	✗	✗	✗	✗	✗	✓	✓ ^f	✗	3-6 months
TAIWAN: National Health Insurance Databases	✓	✓	✓	✓	✗	✗	✓	✗	✓	1-2 months
TAIWAN: National Immunization Information System	✓	✓	✓	✓	✗	✗	✓	✗	✓	1-2 months
	8/11 (73)	5/11 (46)	9/11 (82)	6/11 (55)	1/11 (9)	0/11 (0)	10/11 (91)	5/11 (46)	6/11 (55)	

Explanation of symbols: ‘✓’ signifies either that (i) The information is available (as in a publically-available policy or procedures document) or (ii) Approval is necessary from the nominated Committee or Agency or, (iii) A cost is involved in accessing the data. Conversely, a ‘✗’ signifies either no information document is available or, approval is not necessary or no cost is applied in seeking to access the data.

^a Australian Government Immunisation Branch (department with policy responsibility for use and disclosure of immunisation registry data)

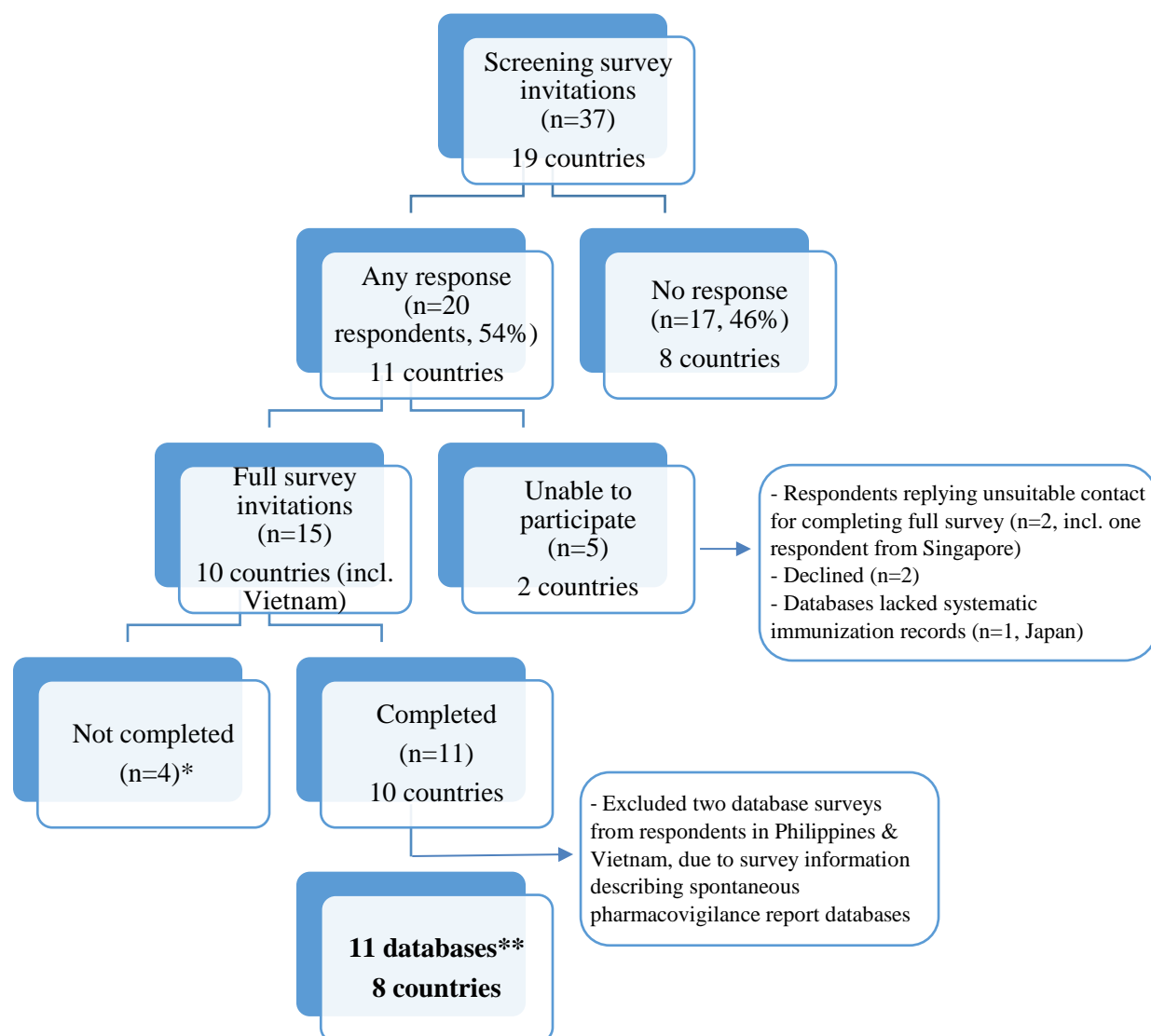
^b Data can only be accessed by academic institutions via a secure server.

^c KCDC immunization registry database is not publically available. It is provided in link with National Health Insurance Service (NHIS) database at the request of researcher, funded by KCDC.

^d KCDC immunization registry database is not provided to external users.

^e Ministry of Health approval required.

^f Approval from hospital director required.

Figure 1: Survey distribution and response rate**FIGURE 1 EXPLANATION**

- ▶ Note for some countries, multiple individuals were invited to participate in the screening (or full) survey. Consequently, the number of countries associated with survey non-response/non-completion exceeds the number of countries providing completed survey information.
- ▶ **Eleven countries completing a screening database survey:** Australia, China, Hong Kong, Japan, Republic of Korea, Malaysia, New Zealand, Philippines, Singapore, Thailand, Taiwan.
- ▶ **Ten countries completed full database survey:** Australia, China, Hong Kong, Republic of Korea (2 databases), Malaysia, New Zealand, Philippines, Thailand (2 databases), Taiwan (2 databases), Vietnam.
- ▶ **Eight countries did not respond to the screening survey (and so no participant could be confirmed for completion of full survey):** Bangladesh, Brunei Darussalam, Cambodia, India, Indonesia, Laos, Papua New Guinea, Vietnam. However, a third round contact identified for Vietnam was sent a full survey invitation without first receiving the screening survey.
- ▶ **No response to full survey:** Singapore.
- ▶ Note a minimum of three attempts were made to contact survey participants not responding to screening or full survey invitations.

*'Not completed' signifies a full survey was sent to an individual but not returned. Non-returns included both,

- a) non-responses from additional country participants invited to complete a full survey,
- b) no full survey response received from an invited country e.g. Singapore

**Two surveys were completed for Republic of Korea (2 databases), Taiwan (2 databases) & Thailand (2 databases).