D2.4

Development of guidelines for the identification of vaccine status and brand in study participants

777363 - DRIVE

Development of robust and innovative vaccine effectiveness

WP2 –Study tools

Lead contributor	Gaël Dos Santos (15–GlaxoSmithkline [GSK])
	Gael.x.dos-santos@gsk.com
Other contributors	Harshana Liyanage (8–University of Surrey)
	Anke Stuurman (3–P95)
Reviewers	Miriam Levi (4–University of Florence)
	Hanna Nohynek, Ritva Syrjänen (6–THL)
	Jose Van Boxmeer, Mendel Haag (14–Seqirus)
	Simon de Lusignan (8–University of Surrey)
	Topi Turunen (1–FISABIO)
	Helene Bricout (12–Sanofi Pasteur)

Due date	31 October 2018
Delivery date	22 February 2019
Deliverable type	R
Dissemination level	PU

R: Document, report (excluding the periodic and final reports)
PU = Public, fully open, e.g., web
CO = Confidential, restricted under conditions set out in Model Grant Agreement
CI = Classified information as referred to in Commission Decision 2001/844/EC

Document History

Version	Date	Description
V0.1	26 Feb 2018	First Draft
	10 Mar 2018	Compiled Comments
V0.2	04 May 2018	Second Draft
	14 May 2018	Compiled Comments
V0.3	11 June 2018	Third Draft
	20 June 2018	Compiled Comments
V0.4	25 June 2018	SC Draft 1
	30 June 2018	Compiled Comments
V0.4	13 Nov 2018	Fourth Draft
	30 Nov 2018	Compiled Comments
V0.5	06 Feb 2019	SC Draft 2
V1.0	22 Feb 2019	Final version

Publishable Summary

Influenza viruses undergo constant, rapid evolution, and subsequently, seasonal influenza vaccines must be regularly reformulated. The benefits-risks profile of seasonal influenza vaccines must also be regularly monitored. Assessing vaccine effectiveness in this rapidly changing environment requires the ability to capture reliable information on the core elements of vaccination. Identification of vaccine details such as vaccine type, brand, and vaccination status at an individual level is crucial in measuring brand-specific vaccine effectiveness.

This document provides a comprehensive map of existing infrastructures used to collected relevant information on immunization (such as immunisation registries/immunisation information systems (IIS) and electronic healthcare databases) and highlights the core elements needed to evaluate brand-specific influenza vaccine effectiveness. Potential data sources are provided to identify vaccination status and brands using existing immunisation registries, Electronic Health Record (EHR) systems and healthcare databases. Moreover, we have provided an overview of existing registries/EHR systems which can help to inspire countries where computerized systems are not yet implemented or fully operational. The results of the review will be ultimately used in synergies with other work packages to define methodology guidelines for the identification of vaccine status of individual patients and brands used at a country or regional level.

A combination of reference documents was used to develop this document including vaccine registers from Europe and elsewhere, seasonal influenza vaccination in Europe, IIS in the European Union (EU) and the European Economic Area (EEA), national laws on electronic health records in the EU Member States, Initiative for patient registries, and the General Data Protection Regulation (GDPR).

Implementing IIS or healthcare databases is a massive endeavour and implies a substantial investment in terms of costs and human resources. Appropriate technological tools are necessary to ensure adherence to legal requirements. Recent GDPR legislation provides a framework detailing the expectations in term of data privacy and protection of data collected.

We observed important heterogeneity within EU/EEA member states in terms of infrastructures available to capture the vaccine-related information. Nevertheless, despite extensive published works on IIS and electronic heath records/databases, the specific information linked to seasonal influenza vaccine remains fragmented, and gaps still exist to better understand the completeness of records as well as the access rights associated with the use of such data. A targeted survey may be an effective approach to overcome those limitations and address some of the identified gaps.

List of Abbreviations

AEFi	Adverse events following immunisation
ASL	Local Health Authorities (Italy)
ASLCR	Azienda Sanitaria Locale della Provincia di Cremona (Italy)
ASHIP	Associations of Statutory Health Insurance Physicians
CEREES	Committee on health care data research (France)
CHIS	Child Health Information System
CNAMTS	Caisse Nationale d'Assurance Maladie des Travailleurs Salari (French National Health Insurance Agency for Wage Earners)
CNIL	National data protection agency (France)
CPP	Committee for the protection of persons involved in biomedical research (France)
CPRD	Clinical Practice Research Datalink
CRO	Contract Research Organisation
DIRAYA	Andalusian eHealth Strategy and System
DPA	Data protection authorities
DPOs	Data Protection Officers
DoB	Date of birth
DPO	Data protection officer
DRIVE	Development of robust and innovative vaccine effectiveness
EEA	European Economic Area
ECDC	European Centre for Disease Prevention and Control
EGB	Echantillon Généraliste de Bénéficiaires
EHR	Electronic Health Record
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
GIRS	Grampian Immunisation & Recall System
GP IT	General Practice Information Technology
GPs	General practitioners
GSK	GlaxoSmithkline
GVP	Good pharmacovigilance practices
HIV	Human immunodeficiency virus
HPV	Human papillomavirus

ICD-10 GM	German modification of the 10th International Classification of Diseases
ID	Identification number
IIS	Immunisation information systems
INDS	National institute for health care (France)
IPD	Invasive pneumococcal disease
IRs	Immunisation registries
ISS	Istituto Superiore di Sanità (Italian National Public Health Institute)
IT	Information Technology
IVE	Influenza vaccine effectiveness
LHU	Local Health Unit
MCC	Model Contract Clause
MHRA	Medicines and Healthcare Products Regulatory Agency
MOH	Ministry of Health
MSA	Mutualité Sociale Agricole
NACI	National Advisory Committee on Immunisation (Canada)
NFC	Near Field Communication
NG	National Government
NHS	National Health Service (subordinated to MoH)
NIHR	NHS National Institute for Health Research
NIP	National Immunisation Program
NIPH	National Institute of Public Health
NVR	National Vaccination Register
PASS-PAES	Post authorisation, safety or efficacy studies
PCV-7	Pneumococcal conjugate vaccine (Prevnar)
PediSurv	Paediatric Surveillance Network (Belgium)
RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre
RCP/IOD	Regional Coordination of Programmes/Purchase, Storage and Distribution
RSI	Régime Social des Indépendants
RVP	Rijksvaccinatieprogramma (Netherlands National Immunisation Program)
SGP	Sentinel network of General Practitioners (Belgium)
SHIs	Statutory health insurances (Germany)
SHS	School Health Services
SIDIAP	System for the Development of Research in Primary Care

SIRS	Scottish Immunisation Recall Service
SME	Subject matter expert
SNDS	National health care data system
SNIIRAM	Système National d'Informations Inter-Régimes de l'Assurance Maladie
SRL	Società Servizi Telematici (Italy)
SYSVAK	Norwegian national electronic immunisation registry
THIN	The Health Improvement Network
UK	United Kingdom
US CDC	United States Centers for Disease Control and Prevention
VIS	Vaccination Information Statement
VISI	Vaccine Identification Standards Initiative
VRVIS	Valencia Region Vaccine Information System
WHO	World Health Organisation
WIV-ISP	Belgian Institute of Public Health
WP	Work Package

Table of Contents

List of Tables

1. Background and Objectives

To measure brand-specific vaccine effectiveness, the identification of vaccine details such as vaccine type, brand, and vaccination status at an individual level is crucial.

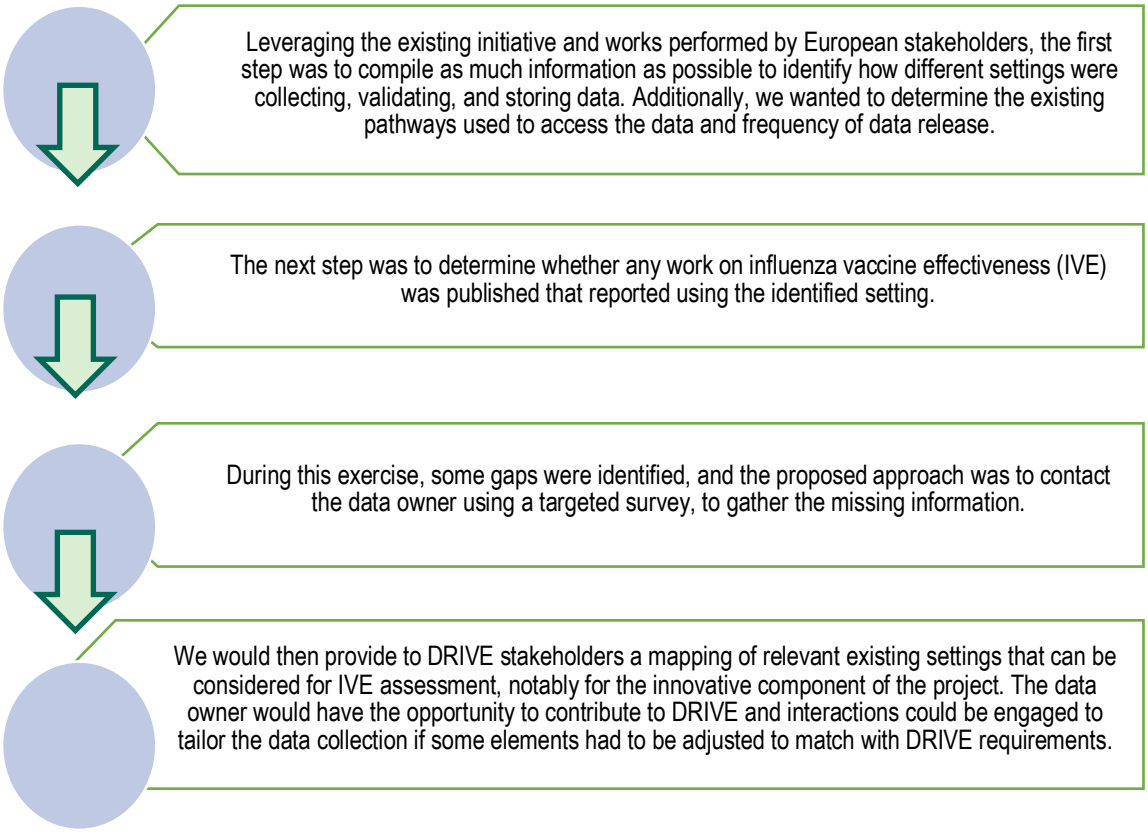
The overarching purpose of the Work Package (WP)2 Task 2.2 is to map the existing infrastructures used to collect relevant information on immunisation. This information is summarized at a country level, and pending the feasibility, at a more granular level.

This document provides additional inputs that could, in synergy with other WPs, ultimately help to define guidelines to identify vaccination status and brands using existing immunisation registries, EHR system or healthcare database, or to suggest an approach to follow in the absence of such infrastructure. An essential step is to map the existing infrastructures used to capture the relevant information among vaccinees in different settings.

We have provided an overview of existing registries/EHR system which can help to inspire countries where computerized systems are not yet implemented or fully operational. In addition, the different existing or in development tools for identification of brand, type, batch/lot number, expiry date and other characteristics of the administered vaccine will be identified and reviewed, such as the immunisation information systems, Vaccine Identification Standards Initiative (VISI) and the use barcodes or Near Field Communication (NFC) tags.

The results of the review are complementary to the Task 3.1 on the expected availability and use of influenza vaccine brand and will be used to define methodology guidelines for the identification of vaccine status of individual patients and brands used at a country or regional level. In order to inform the DRIVE stakeholders, this deliverable has been built using a stepwise approach as shown in Figure 1.

Figure 1 Steps to identify relevant setting that could be informative for DRIVE project



2. Core elements to collect for vaccine effectiveness assessment

2.1 Elements linked to the individual vaccination status:

- Vaccination status
- Date(s) of vaccination
- Number of doses (for “naïve” children)
- Details on vaccine used
  - Ideally: brand or batch/lot number
  - Alternatively: type (type alone may be sufficient if in the country only 1 vaccine per type is commercialised or if only 1 is licensed in the country of interest)
- Type of vaccine used in combination with the manufacturer information. The mapping of licensed influenza vaccines reported in WP3.1 (Task 3.1, D3.3) can thereafter help identify the vaccine brand used.

2.2 Elements linked to the administrative requirements

- Access to data (process, cost, timing)
- Frequency of database release for existing electronic system.

3. Sources of information

For this deliverable, a combination of reference documents (papers, reports) was used to develop this document.

- Vaccine registers – experiences from Europe and elsewhere [1]
- Seasonal influenza vaccination in Europe [2]
- Immunisation Information Systems – useful tools [3]
- Immunisation information systems in the EU and EEA (European Centre for Disease Prevention and Control [ECDC] technical report) [4]
- Overview of the national laws on electronic health records in the EU Member States [5]
- Initiative for patient registries [6]
- General Data Protection Regulation (GDPR) [7].

4. Existing infrastructures to capture vaccine relevant information

4.1 Immunisation Information Systems

The ECDC published the results of a survey conducted in EU/EEA countries which aimed to collect detailed information on existing IIS [4]. Seventeen countries provided information on the IIS. An overview of the IIS in these EU/EEA countries is shown in Table 1.

Definition of IIS (United States Centers for Disease and Prevention (US CDC)

An Immunisation registry or Immunisation information system (IIS) are confidential, population-based, computerized databases that record all immunisation doses administered by participating providers to persons residing within a given geopolitical area [8].

- At the *point of clinical care*, an IIS can provide consolidated immunisation histories for use by a vaccination provider in determining appropriate client vaccinations.
- At the *population level*, an IIS provides aggregate data on vaccinations for use in surveillance and program operations, and in guiding public health action with the goals of improving vaccination rates and reducing vaccine-preventable disease.

4.1.1 EU/EEA Countries with IIS in place

EU/EEA countries that provided information on their IIS currently in operation and an overview of the IIS is provided in Table 1.

Table 1 Overall Description of the IIS in 17 EU/EEA countries

Country	Name of the IIS	Year established	National (N)/ Subnational (S)	IIS gover-nance	Financial resources	Is there a legislation that governs the use of the IIS?	Population covered
Belgium (Flanders)	Vaccinnet	2005	S	RHA	RG	Yes [9]	Paediatric
Denmark	The Danish Vaccination Register	2013	N	NIPH	NG	Yes [10]	All age groups
Finland	The National Vaccination Registry	2011	N	NIPH	NG	No	All age groups
Germany	'KV-Impfsurveillance' [ASHIP vaccination monitoring]	2011	N	NIPH	NG	No	
Hungary	National Technical Information System, Immunisation and vaccine logistics subsystem*	2014 piloting	N	NIPH	NG	No	
Iceland	Central Immunisation Register	2007	N	NIPH	NG	Yes [11]	
Ireland	SIS	2011	N	MoH	NG	No	
Latvia	National e-health System	2016**	N	NHS	NG and EU funds	Yes [12]	
Malta	National Immunisation Electronic Database	2009	N	MoH and PHC	NG	No	
Netherlands	Praeventis	2005	N	NIPH	NG	No	<19 years
Norway	SYSVAK – Norwegian Immunisation Registry	1995	N	NIPH	NG	Yes [13,14]	Essentially Paediatric population
Portugal (mainland)	Vacinas	2016 piloting	S	NIPH and MoH	NG	NA	
Romania	National Electronic Registry of Immunisation	2011	N	NIPH and MoH	NG	Yes [15]	
Slovakia	National Health Information System	Unknown piloting	N	NHIC	NG and EU funds	Yes [16]	All age groups
Spain (Andalusia)	Módulo de vacunas DIRAYA	2016	S	RHA	RG	No	
Sweden	National Vaccination Registry	2013	N	NIPH	NIPH	Yes	All age groups
UK (England)	Child Health Information System	Late 1980s	S	RHA	NG	No	Paediatric

Reference: [4]
* OSZIR (Országos Szakmai Információs Rendszer) Védőoltási és oltóanyag logisztikai alrendszer (Hungary)
** IIS Pilot programme launched in 2017 (Latvia)
ASHIP= Associations of Statutory Health Insurance Physicians
SIS= School Immunisation System
DIRAYA= Andalusian eHealth Strategy and System
RHA= Regional Health Authority
NIPH= National Institute of Public Health
MoH= Ministry of Health
NHS= National Health Service (subordinated to MoH)
PHC= Primary Health Care
NHIC= National Health Information Centre
RG= Regional Government
NG= National Government

- Eight EU/EEA countries (Denmark, Finland, Iceland, Malta, the Netherlands, Norway, Romania and Ireland) have a national system currently operating that meets the US CDC definition of an IIS. In Finland the IIS includes more features than specified in the US CDC definition of an IIS.
- Two countries (Germany and Sweden) have national systems in place that do not fully meet the US CDC definition of an IIS. Their systems have no ability to consolidate immunisation histories for use at point of clinical care and only provide aggregated data on vaccinations at population level.
- Five countries have more than one subnational IIS: Austria (number not specified), Belgium (Flanders, covering parts of Brussels, and the Walloon region also covering parts of Brussels), Portugal (mainland and Madeira), Spain (Andalusia, Balearic Islands, Catalonia, Valencia region, Castilla-León, Galicia, Madrid region and Murcia region) and the United Kingdom (England, Northern Ireland, Scotland and Wales). For Belgium, Portugal, Spain and the United Kingdom, the survey describes the systems in operation in Flanders, mainland Portugal, Andalusia and England, respectively. The systems in Belgium, Portugal and Spain fulfil the criteria of the US CDC IIS definition. In the UK some of the subnational systems meet the US CDC definition of an IIS system while others do not. This information was not available for Austria as they completed the short version of the survey where this question was not included.
- Four countries (Greece, Hungary, Latvia and Slovakia) are piloting a national system. Latvia launched the pilot of its system in 2017.
  - France is piloting more than one subnational IIS.
  - Bulgaria is piloting one subnational IIS.
  - Among the countries piloting an IIS, whether at sub-national or national level, how the IIS was defined was only provided by Hungary and Latvia, as these two countries participated in the comprehensive survey. Both countries had an IIS fitting the US CDC IIS definition.

Additional characteristics of 16 of the 17 countries providing survey information are shown in Table 2. Note that information was not provided by Slovakia for this section of the survey.

Table 2 Characteristics of IIS

Country	Does the IIS record life-course vaccination data*?	Is each immunised individual recorded with a unique personal identifier?	How is the unique personal identifier generated?	Can vaccinations administered in the past be recorded?	Can Vaccinations administered in foreign countries be recorded?	How is vaccination data entered in the IIS?
Belgium (Flanders)	Yes	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list • Upload from electronic medical files by webservice
Denmark	Yes	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list
Finland	Yes	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list • Manually • Linking to product database
Germany	Yes	Yes	Specific for the IIS	No	No	• Selecting from list
Hungary	No	Yes	Specific for the IIS	Yes	Yes	• Manually • Linking to product database
Iceland	Yes	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list
Ireland	No	Yes	Specific for the IIS	Yes	No	• Selecting from list • Manually
Latvia	Yes	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list • Manually
Malta	Yes	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list
Netherlands	No	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list • Manually
Norway	Yes	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list
Portugal (mainland)	Yes	Yes	Uses number given for healthcare services	Yes	Yes	• Selecting from list • Manually
Romania	No	Yes	Specific for the IIS	Yes	Yes	• Selecting from list
Spain (Andalusia)	Yes	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list • Bar code reader
Sweden	No	Yes	Uses number given at birth or immigration	No	No	• Selecting from list
UK (England)	No	Yes	Uses number given at birth or immigration	Yes	Yes	• Selecting from list

Reference: [4]
*Life course refers to vaccination data provided at any age (i.e., over the course of a life-time of an individual).

4.1.2 EU/EEA Countries with no IIS

Among the countries that returned a survey response, six either had no IIS in operation or none being piloted (Croatia, Cyprus, Czech Republic, Estonia, Luxembourg and Slovenia).

4.1.3 Use of a personal ID

All 16 systems used a unique personal identifier for each immunised individual recorded in the IIS. In eleven countries (69%) the unique identifier used in the IIS is an identification number (ID) given to citizens at birth or immigration. For four countries (25%) the unique identifier is specific to the IIS. In Portugal (mainland) the IIS uses the unique identifier applicable for healthcare services.

4.1.4 Further comments from country respondents:

- Ireland: all local IIS use a system-generated patient identifier; however, the same identifiers are not used at national level. A national Individual Health Identifier project has commenced in Ireland and when implemented will be used in all the systems.
- Germany: administered vaccinations can be linked via a unique ID at the individual level so all vaccinations given at any point in time can be identified. However, this personal identifier cannot be used for re-identification of the individual outside the system.
- Denmark: asylum seekers are not assigned a unique identifier so it is not possible to register their vaccinations in the IIS.

4.1.5 Recording historical data

Fourteen country systems (88%) could record vaccinations that have been given in the past. This is not possible for the systems in Germany and Sweden.

4.2 Additional Information for Specific IIS

Vaccinnet (Belgium) [17]

Vaccinnet was built upon an existing infant vaccination database implemented in 1999 by Kind en Gezin, the Flemish organisation of well-baby clinics, which are public health service centres offering preventive health care for all children under the age of 3 years. Since September 2005, the School Health Services (SHS) record all newly administered vaccinations in Vaccinnet, and from early 2006, the system is accessible for all general practitioners (GPs) and pediatricians. Since the use of the register by these latter groups has increased over time, this electronic database could serve as an IIS.

The Danish Vaccination Register [18]

An overview of the Danish vaccination register is provided in Table 3.

Table 3 Overview of the Danish vaccination register

Danish Vaccine Register	
Registered vaccinations	All vaccinations including those given outside a national programme
Variables included	• Date of vaccination • Type of vaccine • Personal identifier of vaccinee • Personal identifier of vaccinator • Product name • Anatomical therapeutic chemical (ATC) code • Dosage • Batch number • Organisation of vaccinator
Registration	By healthcare personnel, real-time on date of vaccination and also through retrospective data-capture from existing administrative registries (in case of non-entry on vaccination date
Timeliness	Real-time registration
Mandatory reporting	Mandatory reporting of all given vaccines
Access	Healthcare personnel, citizens, and Statens Serum Institute
Accessibility	Either through a web-based system or by integration with an existing electronic patient record system
Informed consent from patient	No
Data retrieval and linkage allowed for surveillance or research	Yes
Other characteristics	An advanced Information Technology (IT) system with user interfaces that supports healthcare workers in decision making

The National Vaccination Registry (Finland) [19]

The National Vaccination Register (NVR) in Finland covers nationwide records of vaccinations administered in public primary health care since 2011 (and partially since 2009). All vaccinations registered in the NVR contain a record containing but not limited to the personal identity code, the administered vaccine, and the date of vaccination. Vaccinations are recorded in the patient information systems at batch number level. Vaccinations are identified in the first case on batch number level, with a system in place to do fuzzy matching, and further by brand name and vaccine. The vaccine lot number is the key component for recording and identifying vaccinations, because of its broad availability across patient information systems and its importance in vaccine safety monitoring. Vaccination records are accumulated and updated daily into the NVR, and their completeness is monitored monthly to assess deficiencies in data entry and data collection. Additionally, an alert system reports unexpected changes in data accumulation prompting the validation of observed changes in vaccination coverage.

Praeventis (Netherlands) [20**]**

All children under the age of 19 years eligible for the National Immunisation Program (NIP) are registered in the national immunisation register. For each newborn or immigrated child, a new NIP record with a unique client number is automatically created in Praeventis. Therefore, Praeventis includes a record for each child, irrespective of participation in the NIP. Praeventis is used as the national immunisation register but is also the database to facilitate other collective preventive programmes such as maternal screening for hepatitis B, syphilis, infection with human immunodeficiency virus (HIV), blood group and irregular antibodies, as well as neonatal screening for congenital diseases such as inborn errors of metabolism.

The execution of the NIP is coordinated operationally by the department Regional Coordination of Programmes/Purchase, Storage and Distribution (RCP/IOD). RCP/IOD is responsible for managing the registration process in both Præventis and Rijksvaccinatieprogramma (RVP) Online (i.e. NIP online).

Access to Præventis is only allowed to people who need to administer or register vaccinations and to the medical advisors and regional managers of the NIP. The data are saved on the level of the individual (i.e. they are not anonymous) but are only accessible at individual level for people who need to register vaccinations or assess the immunisation status of a particular child. All data requests made for the purposes of additional research through Præventis are assessed by a multidisciplinary team, specifically with regard to privacy aspects.

SYSVAK – Norwegian National Electronic Immunisation Registry (Norway) [21**]**

Norway has 15 national health registers, including the Norwegian immunisation register, SYSVAK. The national health registers have been established by national health authorities to safeguard nationwide commitments and are legally anchored in §8 of the Norwegian Law of Health Registers [22]. The original aim of SYSVAK was to register all vaccinations in the Childhood Immunisation Programme for the following purposes:

- To maintain an overview of the individual vaccination status of all vaccinees, ensuring that all children are offered adequate vaccination according to the schedule in the Childhood Immunisation Programme and to ensure a high vaccination coverage
- To monitor vaccination coverage for vaccine preventable diseases in the Norwegian population at national, county and municipality levels; and to form a reliable basis for research into the effectiveness and safety of the vaccines in the programme.

Since 2009, SYSVAK has expanded and currently the register includes besides information on all vaccinations in the Childhood Immunisation Programme, all human papillomavirus (HPV) vaccinations (including vaccinations given outside the Childhood Immunisation Programme to older girls, boys and adults), and vaccination against all other vaccine preventable diseases (influenza A(H1N1)pdm09, seasonal influenza, travel vaccines, etc.). Health professionals are obliged to notify all vaccinations in children and adults to SYSVAK.

SYSVAK influenza immunisation programme

In Norway, influenza vaccine is recommended to defined risk groups including elderly aged 65 years or older, through the influenza immunisation programme. The influenza vaccine, as well as other recommended vaccines, is provided both by GPs and through public and private health services [6]. Some vaccinations are also provided by hospitals. Influenza vaccines are not publicly reimbursed. SYSVAK supports reporting the following variables:

- personal identification number and name of vaccinee;
- specific code and name of each vaccine;
- batch number of the vaccine;
- date of vaccination for each dose;
- date of notification to SYSVAK for each dose; and

- name and location of vaccinating unit (health clinic, GP, etc).

Measuring the impact of a vaccine programme using SYSVAK data and data linkage

The fact that all registrations into SYSVAK are based on national personal identification numbers allows extensive linkage of information from different sources, both exposure data and outcome data. As an example, Pneumococcal conjugate vaccine (PCV-7, Prevnar) was licensed in Norway in 2001, and introduced into the Childhood Immunisation Programme in 2006. The vaccination coverage was monitored using data from SYSVAK, and quickly reached high levels. The effectiveness of the PCV-7 vaccination programme was assessed using:

- data on invasive pneumococcal disease (IPD) incidence obtained from the Norwegian Surveillance System for Communicable Diseases,
- pneumococcal serotype distribution obtained from the National Reference Laboratory for Pneumococci, NIPH, Oslo, and vaccination coverage and individual vaccination status from SYSVAK.

National Vaccination Registry (Sweden)

Sweden has national systems in place that do not fully meet the US CDC definition of an IIS. In particular, these systems have no ability to consolidate immunisation histories for use at point of clinical care and only provide aggregated data on vaccinations at population level. In Sweden, the objective of the national vaccination register is to improve monitoring of the national vaccination programmes and is not used by vaccination providers in determining appropriate client vaccinations at the point of clinical care.

Child Health Information System (CHIS) (England)

In the United Kingdom (UK), England, the CHIS data set holds a unique record for each child born in a defined geographical area up to the age of 18 years. Data from the CHIS are used for a variety of child health services, including immunisation services. The aim of the CHIS is to ensure that each child in England has an active care record, supporting delivery of, as a minimum, screening, immunisation and the healthy child programme services. The CHIS also supports the review of immunisation status at primary school entry and transition to secondary school through provision of immunisation status to the school nurse service. Most CHIS's will record HPV and school-based vaccinations from school nurses [23].

In the UK (England), availability of vaccination history at point of clinical care is variable. In primary care, it is dependent on the supplier of the General Practice Information Technology (GP IT) system and the local CHIS while in secondary care it is not available [3].

4.3 Identification of the Vaccine Administered

In eight countries (50%) the data that identified the vaccine were solely selected from a list of vaccines included in the IIS. In four countries (Ireland, Latvia, the Netherlands and Portugal [mainland]), the vaccine information was either selected from a list or entered manually. In Belgium, vaccination data was selected from a list and uploaded from electronic medical files by web service. In Finland, administered vaccines were recorded in the IIS either by selecting them from a list, entering them manually or linking to a product database. In Hungary, data were manually entered or linked to a product database. In Spain (Andalusia) vaccines were selected from a list and data could also be identified electronically with the help of a barcode reader.

Table 4 shows the minimal set of data variables required for a record to be considered valid in the IIS.

Table 4 Minimal set of data variables for a record to be valid in IIS

Country	ID	Name	DoB	Sex	Resi-dence	Vaccine Infor-mation	Batch	Expiry date	Date of Vac	Vac Pro-vider	Health-care Facility
Belgium	x					x	x		x	x	x
Denmark	x					x	x		x		
Finland	x					x	x		x		
Germany	x		x		x	x			x		
Hungary	x	x	x	x	x	x	x	x	x	x	x
Iceland	x	x	x	x	x	x			x	x	x
Ireland	x	x	x		x						
Latvia	x					x	x		x	x	x
Malta	x					x	x	x	x		
Netherlands	x	x	x			x			x		
Norway	x	x	x	x		x			x		x
Portugal (mainland)	x	x	x	x			x	x~	x	x*	x*
Romania	x	x	x		x	x	x	x	x		
Spain (Andalusia)	x					x	x	x		x	x
Sweden	x				x	x	x		x	x	
UK (England)	x	x	x	x	x	x	x		x	x	x

Reference: [4]
ID= (unique) identification number
DoB= Date of birth
Batch = batch number
* Automatic at log-in
~ Prefilled back-office
Belgium refers to Flanders, covering parts of Brussels, and the Walloon region also covering parts of Brussels.

All countries recorded a unique ID for the vaccine recipient, 14 countries (88%) recorded vaccine information (type and brand [Ireland and Portugal did not]) and 14 countries (88%) recorded date of vaccination as essential elements to make a record valid (Ireland and Spain did not). Additional information required by countries to ensure that a record is valid:

- Denmark: for vaccinations administered in the past, a batch number is not necessary.
- Germany: a valid vaccination claim code is required.
- Hungary: an insurance number is required.
- Ireland: the school and academic year needs to be recorded.
- Latvia: it is mandatory to record the volume of vaccine administered, route of administration of the vaccine, type of syringe used (e.g., pre-filled syringe) and who finances the vaccination (e.g., state budget).
- Malta: the dose number is recorded.
- Norway: the type of ID document used (from a list of 12 options) must be recorded.
- Other variables that are included, but their completion not mandatory, are:
  - Portugal (mainland): residence and vaccine information included but not part of minimal data;
  - Romania: place of birth, mother's name, healthcare provider name, recommended age of vaccination and adverse events following immunisation (AEFI).

4.4 Life-course vaccinations

Life-course vaccinations refers to vaccinations administered throughout a person's lifetime (i.e., administration at any age). The systems in 10 countries (63%) can record vaccinations provided at any age.

The national IIS in Ireland records only vaccinations included in the recommended school-based vaccination programme. Hungary, the Netherlands, Romania, Sweden and the United Kingdom (England) do not include vaccination data of persons over 18 years in their systems.

5. Time between vaccination and data entry

Time between vaccination and data entry among the 16 countries that provided this information in the survey is shown in Table 5.

Seven countries out of 15 (47%) responded that data are entered into the IIS at the time of vaccine administration (real-time). There was no information from Hungary for this question. In Belgium there is a one-day delay, and for Finland there is a lag of one week. In Germany it can take up to six months, Ireland up to one month and in the Netherlands, it can take up to two weeks.

Table 5 Time between vaccination and data entry

Country	What is the estimated time between vaccination and the information being entered into the IIS?
Belgium	Within 1 day
Denmark	Real-time
Finland	Within 1 week
Germany	6 months
Hungary	NA
Iceland	Real-time
Ireland	Within 1 month
Latvia	No defined period
Malta	Real-time
Netherlands	Within 2 weeks
Norway	Real-time
Portugal (mainland)	Real-time
Romania	No defined period
Spain (Andalusia)	Real-time
Sweden	Real-time
UK (England)	Varies from real-time to weeks

Reference: [4]
NA- no answer

The WP7 T2.1 & 2.2 and WP5 will have to define the acceptable timelines for data release to be able to use the data within a given season and communicate on a near real time manner the outcome generated.

6. Data validation

Validation processes provided by countries in the survey are shown in Table 6. Seven countries (44%) reported that data in the IIS were validated automatically only by the system through preset rules (or similar) with automatic quality control checks in place.

Table 6 Validation of IIS data

Country	How are the data captured in the IIS validated?
Belgium	Automatically
Denmark	Automatically
Finland	Automatically
Germany	Automatically, IIS management team
Hungary	Automatically
Iceland	IIS management team
Ireland	Local regional administrators
Latvia	Automatically
Malta	No checks, all data are considered valid
Netherlands	Automatically
Norway	Automatically
Portugal (mainland)	Automatically, IIS management team
Romania	Automatically for some data and manually by public health administration
Spain (Andalusia)	No checks, all data are considered valid
Sweden	Automatically for some variables. System has some validity checks
UK (England)	Local teams at entry level, national teams before reporting data

For the remaining nine countries:

- Germany: there is a combination of automatic data quality control and manual checks by the IIS management team at Robert Koch Institute. Data collected at Robert Koch Institute is pre-checked to some degree at the ASHIP level, however not directly for the IIS.
- Iceland: the IIS management team validate data.
- Ireland: validation of data is designated to local regional system administrators.
- Portugal (mainland): data are validated both automatically and by the IIS management team.
- Romania: there are monthly validations by the public health administration, but for some data there is automatic validation by the system through pre-set rules or similar.
- Sweden: the system has some validity checks (i.e. only valid batches, personal identifier, date of immunisation and selected vaccine).
- Spain (Andalusia) no one validates the data as all entries are considered valid.
- Malta: no one validates the data as all entries are considered valid.
- United Kingdom (England): there are several levels of validation: local teams validate when data are entered, and the national team carries out a quality assurance process when the data are submitted for publication of national statistics.

7. Access rights to the IIS

In each country with an IIS, various stakeholders (identified below) had a range of access rights to vaccination records in the IIS. Full access rights included the ability to create, read, write and delete information. Access for each type of stakeholder is summarised.

1.Vaccine recipients: Denmark, Iceland, Latvia and Norway allowed vaccine recipients to view their own records in the IIS. In Denmark recipients could enter their records in the system.

2.Public healthcare professionals providing vaccinations: Denmark, Hungary, Iceland, Latvia, Norway, Portugal (mainland), and Spain (Andalusia) allowed public healthcare providers (including doctors, nurses, vaccination services staff, school health services) to have full access to records in the IIS. Public healthcare providers could only enter and view data in Belgium, Malta, the Netherlands, Romania and Sweden. In Ireland, access rights for public healthcare professionals was limited to viewing only.

3.Private healthcare professionals providing vaccinations: Denmark, Hungary, Iceland, Latvia and Norway allowed full access to the IIS for private healthcare professionals. Belgium, Netherlands, Portugal (mainland), Romania and Sweden allowed private healthcare providers to enter and view records.

4.Vaccine recipients' first line healthcare providers (doctor, nurses, family pediatrician) even if they do not play a role in vaccination delivery: Denmark, Iceland, Latvia and Norway allowed full access to regular healthcare providers. There was no information from Hungary and the Netherlands for this question. In Belgium and Sweden, providers could enter and view records. In Portugal (mainland) and Spain (Andalusia) providers could only view records.

5.Other healthcare professionals even if they do not play a role in vaccination delivery: Iceland, Latvia and Norway gave full access to other healthcare professionals. There was no information provided by Hungary for this question. In Portugal (mainland) and Sweden, other healthcare professionals could only view records.

6.National public health institute (appointed staff): Denmark, Germany, Malta, Netherlands, Norway, Romania and Sweden provided full access to the IIS for national public health institute appointed staff. Finland, Hungary, Latvia and Portugal (mainland) allowed staff to only view records.

7.School immunisation programme (appointed staff): Hungary, Iceland, Ireland, and Norway allowed school immunisation programme staff full access. In Belgium and Malta staff could enter and view records and in Sweden staff were only able to view the records.

8.National health insurance organisation: None of the countries allowed full access. Only one country (Latvia) allowed the national health insurance organisation the ability to view records.

9.Private insurance organisation: No countries allowed private insurance organisations access to the IIS.

Other stakeholders identified by specific countries:

Belgium: changes could only be made by the medical managers of the system. Data from the IIS were available for consultation in a platform for visualizing medical data (Vitalink). These data could be viewed by vaccinees and other healthcare providers if allowed by the vaccinee. All vaccinators that had access to Vaccinnet could add AEFIs to a vaccination record, even if they were not the vaccinator.

Denmark: non-authorized healthcare professionals at regional level or in private nursing homes who handle a resident's medication had view-only rights.

Finland: data entry and queries were made within patient data systems by healthcare professionals.

The Netherlands: anonymous data could be viewed by researchers after permission was granted.

United Kingdom (England): only child health records department staff had full access. Specific public health staff at the local level had access to individual level data, whereas national level only had access to aggregated data.

8. IIS Websites

Countries were asked to add any additional information or links to references or websites to further describe the IIS in their country. Links to IIS websites are provided in Table 7.

Table 7 Website links or additional information provided by countries for further information on IIS

Country	Additional information or links to references or websites
Belgium	Cookbooks can be obtained for exchange of data from electronic medical files
Denmark	Danish Vaccination Register homepage: http://sundhedsdatastyrelsen.dk/vaccinationsregister Article on the Danish Vaccination Register: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20155
Finland	Finnish: Vaccination Register homepage: https://thl.fi/en/web/vaccination/vaccination-coverage/national-vaccination-register Article on establishing and maintaining the National Vaccination Register in Finland. https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2017.22.17.30520.
Germany	Articles on the German Immunisation Registry: http://europepmc.org/articles/PMC4185903 https://www.ncbi.nlm.nih.gov/pubmed/25131739 Bulletin of the World Health Organization on measles incidence reporting trends in Germany 2007-2011: http://www.who.int/bulletin/volumes/92/10/13-135145/en/
Malta	http://health.gov.mt/en/phc/pchyhi/Pages/PCYHIU.aspx
Netherlands	National institute for public health website: http://www.rivm.nl/ http://www.rivm.nl/en Article on the IIS in the Netherlands – Praeventis: http://www.eurosurveillance.org/images/dynamic/EE/V17N17/art20153.pdf
Norway	National institute for public health website: http://www.fhi.no/artikler/?id=52966 http://www.fhi.no/artikler/?id=90930 Article on the Norwegian immunisation registry - SYSVAK: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20147
Spain	http://formacion-tic.iavante.es/pluginfile.php/12678/mod_page/content/8/Guia%20rapida%20vacunas%205.0%20V.1.pdf
UK (England)	Child health information system service specification: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/05/chis-provider-servicespec.pdf National Health Service child health digital strategy: https://www.england.nhs.uk/digitaltechnology/info-revolution/digital-primary-care/child-health/

Reference: [4]

9. Additional IIS, Electronic health records and healthcare databases

Electronic Health Record Definition

An EHR is a digital version of a patient's paper chart. EHRs are real-time, patient-centered records that make information available instantly and securely to authorized users. While paper medical records contain the medical and treatment histories of patients, an EHR system is built to go beyond standard clinical data collected in a provider's office and can be inclusive of a broader view of a patient's care. EHRs can:

- Contain a patient's medical history, diagnoses, medications, treatment plans, details on immunisation records including for instance, dates, type of vaccine, number of doses, allergies, radiology images, and laboratory and test results
- Allow access to evidence-based tools that providers can use to make decisions about a patient's care
- Automate and streamline provider workflow.

One of the key features of an EHR is that health information can be created and managed by authorized providers in a digital format capable of being shared with other providers across more than one health care organization. EHRs are built to share information with other health care providers and organizations – such as laboratories, specialists, medical imaging facilities, pharmacies, emergency facilities, and school and workplace clinics – so they contain information from ***all clinicians involved in a patient's care***.

UNITED KINGDOM

Scottish Immunisation Recall Service (SIRS)

A primary aim of the SIRS is to ensure that children under the age of six years receive the appropriate immunisation according to the UK childhood immunisation schedule [24]. SIRS calls the children's parents/guardians when a scheduled vaccination is due and allows recording of immunisation data. SIRS began in 1987 and has been used by all National Health Service (NHS) boards since 2002 when it incorporated the Grampian Immunisation and Recall System (GIRS).

The two principal groups of users are health professionals (such as health visitors, GPs, practice nurses) and staff responsible for immunisation administration within an NHS Board. After an immunisation contact has taken place the immunisation details are keyed into the system by administrative staff. Data recorded on SIRS are used to monitor immunisation uptake rates at 12 months, 24 months, 5 years and 6 years and are published quarterly.

Potential uses of this database for vaccine safety and vaccine effectiveness studies are reported elsewhere [25].

Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC)

The RCGP RSC is a network of general practices, which extracts data from the computerised medical record systems of over 260 practices in England [26]. The network established a weekly returns service in 1967, which has enabled prompt surveillance of infectious diseases and identification of epidemics; with influenza surveillance as a key priority for the network [27]. The characteristics of the RCGP RSC practice network have been compared with population-level data to ascertain the representativeness of the sample [28]. However, since the most recent report in 2009, there have been substantial changes within the network, including the commissioning in 2015 of an entirely new data and analytics hub at the University of Surrey. Key changes were pseudonymisation as close to source as possible, using an NHS digital approve method that allows linkage to hospital, death and other data; extraction of data twice per week, and extraction of the complete coded record. Since 2017 the network has had a dashboard facility, which provides feedback to practices and is intended to be developed to allow the management of pragmatic trials [29].

In a recently published study, authors showed that the RCGP RSC network provides a representative sample of the population of England in terms of demographics and clinical outcomes. The RCGP RSC network, in addition to surveillance, could also be used for research into routine practice, and the interaction of infectious disease with long-term conditions [30]. The core areas of work of the network is flu vaccine surveillance and vaccine effectiveness, working in close collaboration with Public Health England. More recently the network has also undertaken passive surveillance of influenza vaccine [31]. RCGP RSC data are also used for studies of non-communicable disease [32, 33] and considered valid for health outcomes [34].

The Health Improvement Network (THIN) database

The THIN is an observational database of pseudonymized UK electronic primary healthcare records from general practices throughout the UK. Research studies for publication conducted using THIN data are approved by a nationally accredited ethics committee which has also approved the data collection scheme.

THIN covers over 3.7 million currently registered patients, and over 11 million patients in total [35] accounting for over 400 General Practices throughout the UK. These patients are representative of the UK population by age, sex, medical conditions, and death rates [36]. Records are constantly updated and can be followed over time Details of demographics and administrative data, symptoms and diagnoses, and prescription treatment are routinely recorded against date in separate files within individual patient records. Other health related information is detailed in the Additional Health Data File.

A recent feasibility assessment study reported that batch numbers or brand name can be identified for more than 90% of seasonal influenza vaccinations in THIN [37]. At the time of the analysis, the overall THIN database included approximately 5% of the population.

It may be possible to obtain further patient information via the Additional Information Service including:

- anonymized questionnaires completed by the patient or GP
- copies of patient-based correspondence
- a specified intervention (e.g., a laboratory test to confirm diagnosis)
- death certificates.

Strengths & Limitations of THIN database are summarized below [38].

Strengths

- Very large data set containing records of approximately 5% of UK population
- Broadly representative of the UK population
- Contains reliable information on brand data for influenza vaccination
- Allows all patients with a particular disease to be studied
- Can select control subjects from the same source population
- Is amenable to most epidemiological study designs (i.e. cohort, case-control, case-series)
- Can be used to study relatively rare exposures or outcomes
- A number of practices have been linked to Hospital Episode Statistics data [39].

Limitations

- Analysis requires an experienced data manager with access to appropriate computer software and hardware
- Even such a large data set may have power problems when exposure and outcomes are both rare.

- Situations where THIN data may not be appropriate include:
  - Non-compliance/adherence to medication prescriptions may be an issue for drug-related exposures. This may have an impact however, only if specific population are studied (e.g., immunocompromised, HIV patients, cancer patients)
  - Studies where data are primarily related to secondary care (e.g., cancer-care studies).
  - Studies looking at lab test results before computerization should be aware that only abnormal values may have been entered.

Clinical Practice Research Datalink (CPRD)

CPRD is a governmental, not-for-profit research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare Products Regulatory Agency (MHRA), a part of the Department of Health. The database contains anonymised primary care records for public health research for thirty years. Research using CPRD data has resulted in over 1,800 publications which have led to improvements in drug safety, best practice and clinical guidelines.

The CPRD provides three key services to academic, pharma/biotech/devices and contract research organisations (CRO) researchers both in the UK and globally, subject to legal arrangements and approvals:

- Interventional services [40] and IT systems for clinical trials, bio-sample collections and Patient Reported Outcomes
- Research services Full Pharmacoepidemiology, Pharmacoeconomics, Outcomes & risk benefit
- Observational data access to NHS and other health related data and linked data (suitably anonymised) [41]

Several uses of the CPRD in the seasonal influenza field have been reported [42, 43, 44].

GERMANY: GeParD (German Pharmacoepidemiological Research Database)

This database consists of claims data from four German statutory health insurances (SHIs) and includes more than 17 million insures covering all regions in Germany. It provides demographic information as well as information on hospital admissions, outpatient physician visits, and outpatient prescriptions. Hospital data include admission and discharge dates, information on in-hospital procedures and on four different types of hospital diagnoses: the main discharge diagnosis which codes the disease requiring the hospital stay, the admission diagnosis, which is a tentative diagnosis at hospital admission, diagnoses secondary to an admission or discharge diagnosis, and ancillary diagnoses (co-morbidities).

Outpatient data include diagnoses, diagnostic procedures and on-drug treatments. All diagnoses are coded according to the German modification of the 10th International Classification of Diseases (ICD-10 GM). More information is reported elsewhere [45].

France: Système National d'Informations Inter-Régimes de l'Assurance Maladie (SNIIRAM)

SNIIRAM is the main health care claims database, which now covers 98.8% of the French population with data collected from birth to death [46]. It includes information from the 3 main claims systems for salaried workers (Caisse Nationale d'Assurance Maladie des Travailleurs Salari *[French National Health Insurance Agency for Wage Earners*], CNAMTS) for independent workers (self-employed professionals, Régime Social des Indépendants [RSI]), and for farmers (Mutualité Sociale Agricole [MSA], which also includes the employees of the farmers' bank) and almost all the smaller systems. It was first set up in 2003 with just the data from the CNAMTS and has been growing since. It includes information on all health care expenses, including outpatient visits, dispensed medication, procedures, chronic conditions, as well as hospital admission diagnoses and procedures, and date of death, on an individual level.

The approach to accessing the national databases has been detailed elsewhere [47]. This access used to be reserved for non-profit organisations and essentially public research labs or administrative entities. Authorisation for access to SNIIRAM took from a few months up to 2 years. Access to the databases has changed drastically over the last year, as described in Law 2016-41. A flurry of decrees and other legal documents are still being produced and published. In brief, health care data are grouped in a national health care data system (SNDS), governed by a national institute for health care data (INDS). Access to individual healthcare data for research with public health intent is approved by the national data protection agency (CNIL) after advice from a specific committee on health care data research (CEREES) or the committee for the protection of persons involved in biomedical research (CPP), according to the study design. Data access can be requested by any legitimate entity, public or private, as long as the study objectives are in the interest of public health, and means are provided to ensure confidentiality, integrity, and traceability of data and its usage. Pharmaceutical companies and insurance companies cannot use the data to promote the sales of their drugs or limit the coverage of their clients, respectively. Research teams and study bureaus (CROs) need to comply with a charter (in preparation) that will include scientific proficiency, independence, and repeatability of studies. Protocols must be provided before the beginning of the study, and results made public at its end (with provisions for an embargo for justified industrial and intellectual property protection confidentiality). These conditions are very similar to those embodied in the European Network of Centres for Pharmacovigilance and Pharmacoepidemiology code of conduct and seal, and in the obligations of post authorisation, safety or efficacy studies (PASS‐PAES) studies at the European Medicines Agency (EMA, see www.encepp.eu).

Access for non-French nationals is described in the law (any person not based in Europe must have a representative in France), but the specifics of such access are still being worked out.

A number of processes are being developed to facilitate access, such as reference methodologies, single authorizations, or samples. There are 3 reference methodologies that have been developed for clinical research involving patients that exclude the use of the national claims data. Signed commitment to a methodology obviates the need for CNIL authorisation. Reference methodologies are being envisioned for pharmacoepidemiological studies involving the claims databases. Single authorisations concern similar studies with similar objectives, using the same categories of data for the same categories of final user. Once approved, as many studies as desired can be done without having to obtain individual authorizations for each study, though they need to be logged. The SNDS can develop samples (such as the Echantillon Généraliste de Bénéficiaires [EGB], the 1/97th random permanent representative sample of SNIIRAM) or aggregated data that can be used without having to obtain approval for individual studies. In all these cases, registries are kept of the different studies done using each simplified method. These should reduce access time to a few weeks.

At this time, access to the databases is free. This will persist for all studies developed to answer regulatory requests, but there is an ongoing process to evaluate the economic model of the use of the databases and possible charges for non-regulatory studies. The linkage of individual patients to their claims data, which was essentially impossible, is now possible using a relatively simple process, involving authorisation by the committee for protection of persons, and CNIL, and of course patient consent.

SPAIN: Valencia Region Vaccine Information System (VRVIS)

VRVIS is a population-based register that systematically records vaccine doses given at public and private vaccination points, including primary care centres, hospitals and residential facilities in the public sector and any private sector facility that applies for access. The sensitivity and specificity of VRVIS was estimated to be 90% and 99%, respectively. All registered residents of Valencia Region have a unique identification number that is linked to the VRVIS, inpatient and outpatient clinical records, and sociodemographic information.

Vaccine information is ascertained by recall in those patients whose vaccine administration is not registered in the system. Influenza vaccine effectiveness studies were conducted using this system [48].

ITALY

In Italy, several vaccines are actively offered to the population and administered free of charge by public vaccination services. The Italian Health System is decentralized, therefore a NIP providing a national strategy is issued by the Ministry of Health but implemented at regional level. On this basis, 21 Regional Immunisation Plans are then produced, one each, by 21 Regions/ Autonomous Provinces (herein called “Regions”). These Regions define the regional immunisation schemes leading unavoidably to heterogeneity in vaccine schedules and vaccination management across the country. In addition, the immunisation registries (IRs), used for the local management of the vaccination programmes, can be dissimilar from one Local Health Unit (LHU) to the other, even within the same Region.

Policymakers have been encouraging the implementation and the use of the electronic health records, including IRs, at local and regional level. In 2007, the Italian Ministry of Health, within the “MATTONI” (“Bricks”) Project, promoted and funded an inter-regional workgroup, whose primary aim was to define the minimum set of variables needed to compare data between Regions and to build up a national registry on immunisations; however, these variables have never been used for exchange or aggregation of data. Recommendation to implement IRs were also included in several national strategic documents, such as the National Plan for Measles and Congenital Rubella Elimination, the National Prevention Plan 2014- 2018 and the NIP 2017-2019. The objective is “to complete the transition from paper to electronic immunisation registries, to increase data sharing between and within regional and national levels and to guarantee interoperability among electronic vaccination registries and other population registries (such as infectious diseases surveillance databases, databases of adverse events following immunisations, civil registries, etc.)”.

Based on results from two surveys conducted by the Italian National Public Health Institute (Istituto Superiore di Sanità, (ISS) to map the distribution of IRs within Italy, in 2008, only nine Regions used IRs and, among those, only five used the same software in all LHUs. In the following years, IR use became more common in Italy. A second survey, conducted in 2011, showed that 15 Regions used an IR covering all the territory, however only eight out of them used the same software in all LHUs. Among the remaining 6 Regions, 5 were partially computerized (with a range of LHUs using an IR from 25% to 92%) and one Region did not use IR at all [49].

Recently a new survey has been conducted, and main results reported that 18/21 Italian Regions have fully implemented an IR [50]. Out of these, 11 used the same software for all LHUs. Two regions have partially implemented their IRs and one Region is not yet computerised. The decentralization of the Italian Health System is reflected also on the IRs characteristics and functionalities in terms of fragmented implementation of IRs and diversity in the software systems and data flows in place. Future efforts should not only aim not only to clarify the functionalities of Regional IRs, but should also aim to define how aggregation of data at national level can be optimised.

Notwithstanding, a computerized tool to monitor vaccination coverage at national level is still missing. For this reason, the Ministry of Health is currently designing a national IR that could aggregate data from different regional and local IR systems.

In parallel several GPs and pediatricians network have established electronic databases able to collect also vaccine histories of their served population. Some examples are reported below.

PEDIANET

PEDIANET - Società Servizi Telematici (SRL), Padua, Italy, is a network of approximately 400 family pediatricians who collect routine data and record in a centralized database, diagnosis, treatment and vaccination in children since 2003. The network has the ability of near to real time recording of vaccinations and capacity to contact the parents and children. The network has been the basis of published research on vaccine effects and safety. The PEDIANET database custodian is the SRL, a subject matter expert (SME) responsible for maintaining and querying the data for specific research purposes.

Azienda Sanitaria Locale della Provincia di Cremona (ASL CR)

The ASL CR holds a database of healthcare data in the northern Italian region of Lombardy that cover records of adults (18 – 65 years and 65+). The Italian National Health System (Servizio Sanitario Nazionale) is organized in Local Health Authorities (ASL) which are responsible for healthcare provision to the citizens in a given region, usually a province. The ASL CR provides healthcare services (prevention, treatment, nursing care, etc.) under universal access principles, to the population in the region of Cremona. In addition to providing healthcare, the ASL CR developed a research capacity to conduct epidemiology and intervention studies and have been part of international research projects both using integrated data linkage health records databases, as well as de novo data collection at point of care by activating a network of district health care centres and general practitioners in the region. At least one influenza vaccine effectiveness study has been conducted using this database [51].

BELGIUM

Paediatric Surveillance Network (PediSurv)

The PediSurv network consists of about 440 participating pediatricians and was set up in 2002 as part of the epidemiological surveillance of communicable diseases in Europe and in the framework of polio eradication and measles elimination [52]. PediSurv monitors the occurrence of vaccine preventable diseases such as measles, mumps and invasive pneumococcal disease. During the A(H1N1)2009 influenza pandemic, the monitoring activity of the PediSurv network was extended to include influenza surveillance [53].

Belgian Sentinel network of General Practitioners (SGP)

The Belgian Sentinel network of GPs is hosted by the Belgian Institute of Public Health (WIV-ISP). It was developed in 1979, drawing on experiences of the Weekly Returns Service of the Royal College of General Practitioners and the Dutch Sentinel Stations in the Netherlands.

The policy system has evolved towards a federal model composed of communities with specific cultural identities and different languages. The Dutch speaking community (northern part of Belgium) and the French speaking community (southern part of Belgium) have jurisdiction over matters that are linked to people rather than territory, such as health and social support insofar as they are not part of the social security system. The sentinel network is supported by the two concerned public health ministries, having set their own health priorities based on the health needs of their communities [54]. The GPs cover 1.75% of the total Belgian patient population.

The Academic Centre for General Practice from the KULeuven

The Academic Centre for General Practice from the KULeuven has a network of GPs and has built the INTEGO database, containing about 3 million diagnoses collected from GPs in Flanders. Since spring 2009, the registration network includes 55 GP practices spread across Flanders. They facilitate and conduct research.

Netherlands, NIVEL Primary Care Database

NIVEL Primary Care Database (NIVEL Zorgregistraties eerste lijn) uses routinely recorded data from health care providers to monitor health and utilisation of health services in a representative sample of the Dutch population [55].

These data have been used to monitor influenza vaccine coverage in the Netherlands [56] and to study vaccine effectiveness [57, 58].

Catalan Institute of Health, Information System for the Development of Research in Primary Care (SIDIAP)

SIDIAP is a primary care database containing patients' medical records covering 76% of the population of Catalonia (5.6 million) [59]. The SIDIAP includes data from the primary healthcare electronic medical records named e-CAP/ECAP on demographic information, appointment dates with doctors and nurses, clinical diagnoses, clinical variables, prescriptions written, referrals to specialists and hospitals, results from laboratory tests, vaccination and medication dispensed by pharmacies. Primary care data can be linked to hospital records

for a third of the population. Data on influenza vaccines administered in primary care are available; for each immunisation data are available on: code of vaccine, description of vaccine, dose number, date of immunisation, and UP where the immunisation is administered [60].

Public institutions can apply for data but private for-profit research institutions cannot [61]; however, studies can be outsourced to SIDIAP. More information on the application procedure can be found on the SIDIAP website [62].

10. Privacy and Confidentiality

Privacy and confidentiality rules associated with access to the electronic databases and use of the data are defined by the governance framework of the database owner. In addition, the recently updated European regulation on data protection defines new standards in the area, which are presented below.

General Data Protection Regulation (GDPR)

After four years of preparation and debate the General Data Protection Regulation GDPR was approved by the EU Parliament on 14 April 2016, with an enforcement date of 25 May 2018 - at which time organizations in non-compliance could face heavy fines. The EU GDPR replaced the Data Protection Directive 95/46/EC and was designed to harmonize data privacy laws across Europe, to protect and empower all EU citizens' data privacy and to reshape the way organizations across the region approach data privacy [63].

GDPR Key Changes

- Increased Territorial Scope (extra-territorial applicability)

Arguably the biggest change to the regulatory landscape of data privacy comes with the extended jurisdiction of the GDPR, as it applies to all companies processing the personal data of subjects (i.e., any person whose personal data is being collected, held or processed) residing in the EU, regardless of the company's location. Previously, territorial applicability of the directive was ambiguous and referred to data process 'in context of an establishment'. This topic has arisen in a number of high profile court cases. GDPR makes its applicability very clear - it will apply to the processing of personal data by controllers and processors in the EU, regardless of whether the processing takes place in the EU or not. The GDPR will also apply to the processing of personal data of data subjects in the EU by a controller or processor not established in the EU, where the activities relate to: offering goods or services to EU citizens (irrespective of whether payment is required) and monitoring behaviour that takes place within the EU. Non-EU businesses processing the data of EU citizens will also have to appoint a representative in the EU.

- Penalties

Under GDPR, organizations in breach of GDPR can be fined up to 4% of annual global turnover or €20 Million (whichever is greater). This is the maximum fine that can be imposed for the most serious infringements e.g., not having sufficient customer consent to process data or violating the core of Privacy by Design concepts. There is a tiered approach to fines e.g., a company can be fined 2% for not having their records in order (article 28), not notifying the supervising authority and data subject about a breach or not conducting impact assessment. It is important to note that these rules apply to both controllers and processors -- meaning 'clouds' will not be exempt from GDPR enforcement.

- Consent

The conditions for consent have been strengthened, and companies will no longer be able to use long illegible terms and conditions full of legalese, as the request for consent must be given in an intelligible and easily accessible form, with the purpose for data processing attached to that consent. Consent must be clear and distinguishable from other matters and provided in an intelligible and easily accessible form, using clear and plain language. It must be as easy to withdraw consent as it is to give it.

GDPR Key Changes that Affect Data Subject Rights

- Breach Notification

Under the GDPR, breach notification will become mandatory in all member states where a data breach is likely to "result in a risk for the rights and freedoms of individuals". This must be done within 72 hours of first having become aware of the breach. Data processors will also be required to notify their customers, the controllers, "without undue delay" after first becoming aware of a data breach.

- Right to Access

Part of the expanded rights of data subjects outlined by the GDPR is the right for data subjects to obtain from the data controller confirmation as to whether or not personal data concerning them is being processed, where and for what purpose. Further, the controller shall provide a copy of the personal data, free of charge, in an electronic format. This change is a dramatic shift to data transparency and empowerment of data subjects.

- Right to be Forgotten

Also known as Data Erasure, the right to be forgotten entitles the data subject to have the data controller erase his/her personal data, cease further dissemination of the data, and potentially have third parties halt processing of the data. The conditions for erasure, as outlined in article 17, include the data no longer being relevant to original purposes for processing, or a data subjects withdrawing consent. It should also be noted that this right requires controllers to compare the subjects' rights to "the public interest in the availability of the data" when considering such requests.

- Data Portability

GDPR introduces data portability - the right for a data subject to receive the personal data concerning them, which they have previously provided in a 'commonly use and machine-readable format' and have the right to transmit that data to another controller.

- Privacy by Design

Privacy by design as a concept has existed for years now, but it is only just becoming part of a legal requirement with the GDPR. At its core, privacy by design calls for the inclusion of data protection from the onset of the designing of systems, rather than an addition. More specifically - *'The controller shall implement appropriate technical and organisation measures in an effective way. In order to meet the requirements of this Regulation and protect the rights of data subjects'.* Article 23 calls for controllers to hold and process only the data absolutely necessary for the completion of its duties (data minimisation), as well as limiting the access to personal data to those needing to act out the processing.

Data Protection Officers (DPOs)

Currently, controllers are required to notify their data processing activities with local data protection authorities (DPAs), which, for multinationals, can be a bureaucratic nightmare with most Member States having different notification requirements. Under GDPR it will not be necessary to submit notifications / registrations to each local DPA of data processing activities, nor will it be a requirement to notify / obtain approval for transfers based on the Model Contract Clauses (MCCs). Instead, there will be internal record keeping requirements, as further explained below, and DPO appointment will be mandatory only for those controllers and processors whose core activities consist of processing operations which require regular and systematic monitoring of data subjects on a large scale or of special categories of data or data relating to criminal convictions and offences. Importantly, the DPO:

- Must be appointed based on professional qualities and, in particular, expert knowledge on data protection law and practices
- May be a staff member or an external service provider

- Contact details must be provided to the relevant DPA
- Must be provided with appropriate resources to carry out their tasks and maintain their expert knowledge
- Must report directly to the highest level of management
- Must not carry out any other tasks that could results in a conflict of interest.

11. Alternative methods to collect or capture vaccine/brand information

Alternative methods to collect or capture vaccine/brand information include the following:

- Mobile device application tools to track your immunisations on your smartphone and help to remind you to get vaccinated on time. Some initiatives already exist, such as in Canada [64]. The CANImmunize application can keep track of family vaccination records, provide appointment reminders, provide answers to vaccine/vaccination questions and even learn about disease outbreaks.
- Retrospective and prospective knowledge of market distribution (see detailed information in WP3 Task D3.1 and D3.2)

In a limited number of countries, such as Finland and Slovenia, generally only one seasonal influenza vaccine brand is centrally procured by the public health institute for use in a specific age group (D3.1, D3.3). In these cases, the vaccine brand received by those identified as vaccinated in a specific age group may be inferred.

- Barcodes

Barcode scanning technology enhances patient safety, reduces errors involving drug administration, and increases the timeliness and accuracy of medication-related documentation [65, 66, 67]. Since immunisation records may be missing or not well recorded/containing errors, possibly due to the small print used for lot number and expiry date on vaccine vials, the value of barcode scanning has been extended to vaccines in some countries. For instance, in 1999, Canada's National Advisory Committee on Immunisation (NACI) recommended placing barcodes on vaccine products to automate the recording of vaccine-related data in electronic systems [68].

A recent study compared barcode scanning with manual methods for entering vaccine data into electronic client immunisation records in public health settings concluded that the study demonstrated the benefits of barcode scanning of routine vaccines in two diverse public health settings. They showed that barcode scanning has good acceptability, and improvements in data quality were obvious, particularly when compared to the combination of typing in lot number and the use of drop-down menus for other data fields [69]. The barcode standards for vaccine products in Canada were identified and approved by the Automated Identification of Vaccine Products Advisory Task Group in 2009.

In the Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products (4 August 2016 EMA/168402/2014 Corr* [70]), EMA recommend that the traceability of medicinal products is fully integrated in different healthcare settings although infrastructures may vary across products and between countries, such as the infrastructure for electronic data recording and record linkage. For products supplied in a hospital setting, if record linkage does not exist, other methods need to be used to collect exposure information, such as routine barcode scanning at all points in the supply chain. National health authorities are encouraged to also work towards better integration and automation of prescription information.

- Vaccination card or Vaccination Information Statement (VIS)

Vaccination cards are often used as a tool to record children and adolescent vaccination. Vaccination cards may be either used by routine health care or are study-specific vaccination cards given to participants of a

clinical cohort study before the follow-up, to be filled by the vaccinator, and returned to the investigators. Several formats exist but usually the information collected encompass the generic abbreviation or the trade name for each vaccine received, to determine the vaccine type. Further details could be also required to know whether the vaccine injection was intramuscular or subcutaneous.

The date of vaccination (day/month/year) is also part of the critical information to be collected as well as the site/routine of administration where the vaccine was administered (e.g., right arm, left arm, right thigh, left thigh or intranasal). In addition, information on the vaccine lot/batch, and manufacturer is also reported. Examples of VIS templates are available online (e.g., US CDC Yellow Fever VIS [71] and World Health Organisation [WHO] International Certificate of vaccination or prophylaxis [72]).

- Records from pharmacies

In some European countries, public health agencies create incentive to encourage pharmacist to support the GPs to administer the influenza vaccination in order to maximise the possibility for patients to receive their vaccination during the peak of the vaccination period. This is a useful approach to reduce burden of work for GPs and preclude potential delay of vaccine administration. However, some studies reported limitation in the level of information that is collected by pharmacists that may limit the possibility to use records for research purposes [73]. Some studies reported some data integrity issues or suboptimal communication from pharmacist to GPs. For instance, the vaccine manufacturer or batch number is scarcely reported. In addition, information is rarely encoded using coding key data into computerised medical record systems, which can lead to inconsistency. This lack of a standardised approach may preclude the possibility to perform reliably vaccine safety (e.g., monitoring adverse events following immunisation) or vaccine effectiveness studies.

- Patient recall/Self-reporting

Self-reporting is also a way to collect information when no other standardised tool is available. Some studies compared the accuracy of self-reported vaccination compared to EHR or attempted to assess the reliability of self-reporting for influenza vaccines [74, 75]. Findings indicated that EMR and self-reporting do not always agree. Finding approaches to improve both EMR data capture and patient awareness would be beneficial. Although self-reporting is a useful way to collect vaccine status, it might be challenging to collect detailed information linked to the vaccine characteristics or the exact date of the receipt of the vaccine. Using self-reported information may thus lead to incomplete information and potential misclassification. To overcome potential pitfalls linked to self-reporting vaccination ascertainment by a healthcare professional can be a useful approach.

12. Discussion and Recommendations

Because influenza viruses undergo constant, rapid evolution, seasonal influenza vaccines must be regularly reformulated. Consequently, the benefits-risks profile of seasonal influenza vaccines must also be regularly monitored. Assessing vaccine effectiveness in this rapidly changing environment requires the ability to capture reliable information on the core elements of vaccination. We have presented the existing computerized infrastructures allowing standardized and accurate documentation of vaccine-related information.

However, implementing *de novo* IIS or healthcare databases is a massive endeavour and implies substantial investments, both financial and in terms of human resources, with appropriate technological tools to ensure that legal requirements and legislation are well respected. The recent GDPR legislation provides a framework detailing the expectations in term of data privacy and protection of data collected.

We have also proposed alternative solutions to apply when the computerized systems are not yet implemented or fully operational with the objective to flag pros and cons of each method.

Recommendations to appropriately leverage the available data include:

Use of an electronic database is the gold standard, but is costly, time consuming, and imposes some

governance rules to access the data, and time to release the data.

If no available alternative exists, such as vaccination cards or medical charts, records still need to be verified using a standardised approach to ensure the accuracy and completeness of records. Optimally chart review adjudication would be preferred.

To implement a vaccine effectiveness study based on electronic databases, the core elements to capture include:

- Vaccination status
- Date(s) of vaccination
- Number of doses (for “naïve” children)
- Details on vaccine used
  - Ideally: brand or batch/lot number
  - Alternatively: type (type alone may be sufficient if in the country only 1 vaccine per type is commercialised or if only 1 is licensed in the country of interest)
- Type of vaccine used in combination with the manufacturer information. The mapping of licensed influenza vaccines reported in WP3.1 (Task 3.1, D3.2) can thereafter help identify the vaccine brand used.

13. Conclusion

This report provides a comprehensive mapping of existing IIS and electronic databases and highlights the core elements to be considered in order to evaluate brand-specific influenza vaccine effectiveness. We observed important heterogeneity between EU/EEA member states in terms of infrastructures available to capture the vaccine related information. Nevertheless, despite extensive published works on IIS and electronic heath records/databases, the specific information linked to seasonal influenza vaccine remains scarcely reported and some gaps still exist to better understand the completeness of records as well as the access rights associated with the use of such data. A targeted survey may be an effective approach to overcome those limitations and address some of the identified gaps, and is currently under investigation.

14. References

1. Pebody R. Vaccine registers- experiences from Europe and elsewhere. Eurosurveillance. 2012;17(17). Available from : http://www.eurosurveillance.org/content/10.2807/ese.17.17.20159-en

2. European Centre for Disease Control and Prevention. Seasonal influenza vaccination in Europe – Vaccination recommendations and coverage rates for eight influenza seasons (2007–2008 to 2014–2015). Available from: https://ecdc.europa.eu/en/publications-data/seasonal-influenza-vaccination-europe-vaccination-recommendations-and-coverage-1

3. Derrough T, Olsson K, Gianfredi V, Simondon F, Heijbel H, Danielsson N, Kramarz P, Pastore-Celentano L. Immunisation Information Systems – useful tools for monitoring vaccination programmes in EU/EEA countries, 2016.Euro Surveill. 2017 Apr 27; 22(17): 30519. Available from:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5434883/

4. European Centre for Disease Control and Prevention. Immunisation information systems in the EU and EEA. Results of a survey on implementation and system characteristics. Stockholm: ECDC; 2017. Available from:https://ecdc.europa.eu/sites/portal/files/documents/immunisation-systems.pdf

5. European Commission. Overview of the national laws on electronic health records in the EU Member States. Available from:https://ec.europa.eu/health/ehealth/projects/nationallaws_electronichealthrecords_en Accessed 5 May 2018.

6. European Medicines Agency. Patient Registries. Available https://www.ema.europa.eu/en/human-regulatory/post-authorisation/patient-registries Accessed 06 Feb 2019

7. European Union General Data Protection Regulation. GDPR Key Changes. Available from: https://ec.europa.eu/commission/priorities/justice-and-fundamental-rights/data-protection/2018-reform-eu-data-protection-rules_en Accessed 06 Feb 2019

8. Centers for Disease Control and Prevention. Immunizatoin Information Systems (IIS). Available from: https://www.cdc.gov/vaccines/programs/iis/about.html

9. Flemish authority. Decree of 21 November 2003 concerning the preventive health policy. Ministerial Decree of 29 January 2015 to determine the vaccination scheme for Flanders, [internet]. Flanders2015 [2 December 2016]. Available from:http://www.etaamb.be/fr/arrete-ministeriel-du-29-janvier-2015_n2015035232.html.

10. Danish public legal information. Order on access and registration, etc. of pharmaceutical and vaccination information, [internet]. 2013 [2 December 2016]. Available from: https://www.retsinformation.dk/forms/R0710.aspx?id=163123#Kap1.

11. Icelandic parliament. Sóttvarnalög, [internet]. 2016 [2 December 2016]. Available from: http://www.althingi.is/lagas/nuna/1997019.html.

12. Republic of Latvia Cabinet. Regulations Regarding Unified Electrocnic Information System of the Health Sector [internet]. 2014 [2 December 2016]. Available from: http://vvc.gov.lv/export/sites/default/docs/LRTA/MK_Noteikumi/Cab._Reg._No._134_-_United_Electronic_Information_System_of_the_Health_Sector.pdf.

13. Norwegian Parliament. Regulations concerning the collection and processing of health data in national vaccination register (SYSVAK registry regulations) [internet]. 2016 [2 December 2016]. Available from:https://lovdata.no/dokument/SF/forskrift/2003-06-20-739?q=sysvak%20forskriften.

14. Norwegian Parliament. Law on health records and processing of health data (Health Register Act) [internet]. 2016 [2 December 2016]. Available from: https://lovdata.no/dokument/NL/lov/2014-06-20-43?q=helseregisterlov.

15. Romanian Parliament. Order of the Health Ministry 1234/03.08.2011 [internet]. 2011 [2 December 2016]. Available from:http://www.anm.ro/en/html/legislation_minister_orders.html.

16. Slovakia National Health Information Center. eHealth Programme [internet]. 2011 [2 December 2016]. Available from: http://www.ezdravotnictvo.sk/en/eHealth_Programme/Pages/default.aspx.

17. Vaccinnet: een bestelsysteem voor vaccins gekoppeld aan een vaccinatiedatabank Vlaams Infect Top, 2012:80(2) Available from: http://refhub.elsevier.com/S0264-410X(13)01562-4/sbref0050

18. Grove Krause T, Jakobsen S, Haarh M, Mølbak K. The Danish vaccination register. Euro Surveill. 2012 Apr 26;17(17): 20155.

19. Baum U, Sundman J, Jääskeläinen S, Nohynek H, Puumalainen T, Jokinen J. Establishing and maintaining the National Vaccination Register in Finland. Euro Surveill. 2017 Apr 27;22(17): 30520. doi: 10.2807/1560-7917.ES.2017.22.17.30520.

20. Van Lier A, Oomen P, de Hoogh P, Drijfhout I, Elsinghorst B, Kemmeren J, Conyn-van Spaendonck M, de Melker H. Præventis, the immunisation register of the Netherlands: a tool to evaluate the National Immunisation Programme. Euro Surveill. 2012;17(17): 20153. Available from : http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20153

21. Trogstad L, Ung G, Hagerup-Jenssen M, Cappelen I, Haugen IL, Feiring B. The Norwegian immunisation register – SYSVAK. Euro Surveill. 2012;17(16): 20147. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20147

22. Ministry of Health and Care Services. Om lov om helseregistre og behandling av helseopplysninger (helseregisterloven). [Law on health records and processing health information (Health Register Act)]. Oslo: Health and Care Services. Available from: https://www.regjeringen.no/no/tema/helse-og-omsorg/folkehelse/Act-of-18-May-2001-No-24-on-Personal-Health-Data-Filing-Systems-and-the-Processing-of-Personal-Health-Data-Personal-Health-Data-Filing-System-Act-/id224129/

23. Child Health Information Services (CHIS) Provider Service Specification. Available from:https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/05/chis-provider-service-spec.pdf

24. Information Services Division, NHS National Services Scotland. Immunisation: UK Childhood Immunisation Schedule. Available from:http://www.isdscotland.org/Health-Topics/Child-Health/Immunisation/schedule.asp

25. Simpson CR, Lone NI, Kavanagh K, Robertson C, McMenamin J, von Wissmann B, Vasileiou E, Butler C, Ritchie L, Gunson R, Schwarze J, Sheikh A. Evaluating the effectiveness, impact and safety of live attenuated and seasonal inactivated influenza vaccination: protocol for the Seasonal Influenza Vaccination Effectiveness II (SIVE II) study. BMJ Open 2017;7:e014200. doi:10.1136/bmjopen-2016-014200. Available from: http://bmjopen.bmj.com/content/bmjopen/7/2/e014200.full.pdf.

26. Royal College of General Practioners. Research and Surveillance Center. Available from: http://www.rcgp.org.uk/rsc.

27. de Lusignan S, Correa A, Smith GE, Yonova I, Pebody R, Ferreira F, Elliot AJ, Fleming D. RCGP Research and Surveillance Centre: 50 years' surveillance of influenza, infections, and respiratory conditions. Br J Gen Pract. 2017 Oct;67(663):440-441. doi: 10.3399/bjgp17X692645. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28963401.

28. Fleming DM, Miles J. The representativeness of sentinel practice networks. J Public Health (Oxf) 2010;32:90–6. Available from: https://academic.oup.com/jpubhealth/article/32/1/90/1551209.

29. Pathirannehelage S, Kumarapeli P, Byford R, Yonova I, Ferreira F, de Lusignan S. Uptake of a Dashboard Designed to Give Realtime Feedback to a Sentinel Network About Key Data Required for Influenza Vaccine Effectiveness Studies. Stud Health Technol Inform. 2018;247:161-165.

30. Correa A, Hinton W, McGovern A, van Vlymen J, Yonova I, Jones S, de Lusignan S. Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) sentinel network: a cohort profile. BMJ Open. 2016 Apr 20;6(4):e011092. doi: 10.1136/bmjopen-2016-011092. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27098827.

31. de Lusignan S, Dos Santos G, Correa A, Haguinet F, Yonova I, Lair F, Byford R, Ferreira F, Stuttard K, Chan T. Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: protocol of a pilot study in England. BMJ Open. 2017 May 17;7(5):e015469. doi: 10.1136/bmjopen-2016-015469. Available from: https://bmjopen.bmj.com/content/bmjopen/7/5/e015469.full.pdf.

32. Woodmansey C, McGovern AP, McCullough KA, Whyte MB, Munro NM, Correa AC, Gatenby PAC, Jones SA, de Lusignan S. Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c): A Retrospective Cohort Study. Diabetes Care. 2017 Nov;40(11):1486-1493. doi: 10.2337/dc17-0542. https://www.ncbi.nlm.nih.gov/pubmed/28860126.

33. Williams R, Alexander G, Armstrong I, Baker A, Bhala N, Camps-Walsh G, Cramp ME, de Lusignan S, Day N, Dhawan A, Dillon J, Drummond C, Dyson J, Foster G, Gilmore I, Hudson M, Kelly D, Langford A, McDougall N, Meier P, Moriarty K, Newsome P, O'Grady J, Pryke R, Rolfe L, Rice P, Rutter H, Sheron N, Taylor A, Thompson J, Thorburn D, Verne J, Wass J, Yeoman A. Disease burden and costs from excess alcohol consumption, obesity, and viral hepatitis: fourth report of the Lancet Standing Commission on Liver Disease in the UK. Lancet. 2018 Mar 17;391(10125):1097-1107. doi: 10.1016/S0140-6736(17)32866-0. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29198562.

34. Kumar S, de Lusignan S, McGovern A, Correa A, Hriskova M, Gatenby P, Jones S, Goldsmith D, Camm AJ. Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: a population based study from UK primary care. BMJ. 2018 Feb 14;360:k342. doi: 10.1136/bmj.k342. Available from: https://www.bmj.com/content/360/bmj.k342/related.

35. University College London .The Health Improvement Network (THIN) database. Available from: http://www.ucl.ac.uk/pcph/research/thin-database/database

36. Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. Pharmacoepidemiol Drug Saf 2009; 18: 76–83. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19065600.

37. Hall GC, Hill F. Descriptive investigation of the recording of influenza vaccination details on The Health Information Network database. Pharmacoepidem iol Drug Saf. 2014;23(6):595-600. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/pds.3515.

38. University College London. Primary Care and Population Health. THIN data: Strengths & Limitations. Available from: http://www.ucl.ac.uk/pcph/research/thin-database/database/pros-cons.

39. National information and technology partner to the health and care system in England (NHS digital). Hospital Episode Statistics (HES). Available from: https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics.

40. Clinical Practice Research Datalink (CPRD). Interventional Data. Department of Health. National Institute for Health Research, England. Available from: https://www.cprd.com/Interventional.

41. Clinical Practice Research Datalink (CPRD). Observational Data. Department of Health. National Institute for Health Research, England. Available from: https://www.cprd.com/ObservationalData.

42. Leite A, Thomas S, Andrews N. Implementing near real-time vaccine safety surveillance using the Clinical Practice Research Datalink (CPRD). Vaccine. 2017 Dec 14;35(49 Pt B):6885-6892. doi: 10.1016/j.vaccine.2017.09.022. Epub 2017 Oct 19. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29056424.

43. Fleming D, Taylor R, Haguinet F, Schuck-Paim C, Logie J, Webb D, Lustig R, Matias G. Influenza-attributable burden in United Kingdom primary care. Epidemiol Infect. 2016 Feb;144(3):537-47. doi: 10.1017/S0950268815001119. Epub 2015 Jul 13. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26168005.

44. Dos Santos G, Haguinet F, Cohet C, Webb D, Logie J, Ferreira G, Rosillon D, Shinde V. Risk of solid organ transplant rejection following vaccination with seasonal trivalent inactivated influenza vaccines in England: A self-controlled case-series. Vaccine. 2016 Jun 30;34(31):3598-606. doi: 10.1016/j.vaccine.2016.05.016. Epub 2016 May 20. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27216760.

45. Leibniz Institute for Prevention Research and Epidemiology – BIP. Available from: https://www.bips-institut.de/en/research/research-infrastructures/gepard.html

46. Moulis G, Lapeyre-Mestre M, Palmaro A, Pugnet G, Montastruc JL, Sailler L. French health insurance databases: what interest for medical research? Rev Med Interne. 2015;36(6):411-417. Available from: https://doi.org/10.1016/j.revmed.2014.11.009https://doi.org/10.1016/j.revmed.2014.11.009.

47. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, Moore N. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf. 2017 Aug;26(8):954-962. doi: 10.1002/pds.4233. Epub 2017 May 24. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28544284.

48. Mira-Iglesias Ainara, Valencia Hospital Network for the Study of Influenza and Respiratory Viruses Disease. Influenza vaccine effectiveness in preventing hospitalisation of individuals 60 years of age and over with laboratory-confirmed influenza, Valencia Region, Spain, influenza season 2016/17. Euro Surveill. 2018;23(8):17-00318. Available from: https://doi.org/10.2807/1560-7917.ES.2018.23.8.17-00318.

49. Alfonsi V, D'Ancona F, Rota MC, Giambi C, Ranghiasci A, Iannazzo S. Immunisation registers in Italy: a patchwork of computerisation. Euro Surveill 2012; 17(17). PubMed PMID: 22551498.Available from: https://www.eurosurveillance.org/content/10.2807/ese.17.17.20156-en.

50. D'Ancona F, Gianfredi V, Riccardo F, Iannazzo S.Immunisation Registries at regional level in Italy and the roadmap for a future Italian National Registry. Ann Ig. 2018 Mar-Apr;30(2):77-85. doi: 10.7416/ai.2018.2199. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29465145.

51. Manzoli L, Gabutti G, Siliquini R, Flacco ME, Villari P, Ricciardi W. Association between vaccination coverage decline and influenza incidence rise among Italian elderly. European Journal of Public Health. 26 March 2018. Available from: cky053, https://doi.org/10.1093/eurpub/cky053.

52. Paediatric Surveillance Network- Belgium. Available from: https://www.wiv-isp.be/Pedisurv/index.htm.

53. Hombrouck A, Sabbe M, Van Casteren V, Wuillaume F, Hue D, Reynders M, Gérard C, Brochier B, Van Eldere J, Van Ranst M, Thomas I. Viral aetiology of influenza-like illness in Belgium during the influenza A(H1N1)2009 pandemic. Eur J Clin Microbiol Infect Dis. 2012 Jun;31(6):999-1007. doi: 10.1007/s10096-011-1398-4. Epub 2011 Sep 8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21901635.

54. Boffin N, Bossuyt N, Vanthomme K, Van Casteren V. Readiness of the Belgian network of sentinel general

practitioners to deliver electronic health record data for surveillance purposes: results of survey study *BMC Family Practice* 2010, 11:50. Available from: https://bmcfampract.biomedcentral.com/track/pdf/10.1186/1471-2296-11-50

55. Netherlands Institute for Health Services Research. (NIVEL) Available from: https://www.nivel.nl/en/databases-and-panels.

56. Nationaal Programma Grieppreventie (NPG). Monitoring vaccinatiegraad. Available from: https://www.rivm.nl/Documenten_en_publicaties/Algemeen_Actueel/Uitgaven/Preventie_Ziekte_Zorg/Grieppri k/Monitoring_vaccinatiegraad_Nationaal_Programma_Grieppreventie_NPG.

57. Maryam Darvishian M, Dijkstra F, van Doorn E, Bijlsma M, Donker G, de Lange MM, Cadenau L, Hak E, Meijer A. Influenza Vaccine Effectiveness in the Netherlands from 2003/2004 through 2013/2014: The Importance of Circulating Influenza Virus Types and Subtypes. PLOS:January 9, 2017. Available from: https://doi.org/10.1371/journal.pone.0169528#sec002.

58. European Union Integrated Monitoring of Vaccines in Europe (I-MOVE+), Consortium of 26 partners (regional and national public health Institutes, SME, Universities frrom of 15 European Union / European Economic Area Member States. Available from: http://www.i-moveplus.eu/.

59. Catalan institute of health (National Health) Information system for research in primary care (SIDIAP) Available from: http://www.sidiap.org/index.php/en/component/content/article?id=33:base-de-dades.

60. Catalan institute of health (National Health) Information system for research in primary care (SIDIAP). Characteristics of the patient. Available from: http://www.sidiap.org/index.php/en/component/content/article?id=38:variables-disponibles.

61. Catalan institute of health (National Health) Information system for research in primary care (SIDIAP). Who can create data. Available from: http://www.sidiap.org/index.php/en/services/who-can-request-data.

62. Catalan institute of health (National Health) Information system for research in primary care (SIDIAP). Application procedure. Available from: http://www.sidiap.org/index.php/en/services/application-proccedure.

63. EU General Data Protection Regulation. Available from: https://www.eugdpr.org/.

64. Public Health Agency of Canada. A digital vaccination record for Canadians. Available from: https://www.canimmunize.ca/en/home.

65. Larrabee S, Brown MM. Recognizing the institutional benefits of bar-code point-of-care technology. Jt Comm J Qual Saf 2003;29(7):345–53. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12856556.

66. Morriss Jr FH, Abramowitz PW, Nelson SP, Milavetz G, Michael SL, Gordon SN, Pendergast JF, Cook EF. Effectiveness of a barcode medication administration system in reducing preventable adverse drug events in a neonatal intensive care unit: a prospective cohort study. J Pediatr 2009;154(3):363–8, 368. Available from: https://www.ncbi.nlm.nih.gov/pubmed/18823912.

67. Paoletti RD, Suess TM, Lesko MG, Feroli AA, Kennel JA, Mahler JM, Sauders T. Using bar-code technology and medication observation methodology for safer medication administration. Am J Health Syst Pharm 2007;64(5):536–43. Available from: https://www.ncbi.nlm.nih.gov/pubmed/17322168.

68. Public Health Agency of Canada. Canadian National Report on Immunisation, 2006. Can Commun Dis Rep 2006;32S3:1–44 (Ottawa, PHAC). Available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06pdf/32s3_e.pdf.

69. Pereira JA, Quach S, Hamid JS, Quan SD, Diniz AJ, Van Exan R, Malawski J, Finkelstein M, Samanani S,

Kwong JC; Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research Network (PCIRN) Program Delivery and Evaluation Group. The integration of barcode scanning technology into Canadian public health immunisation settings. Vaccine. 2014 May 13;32(23):2748-55. doi: 10.1016/j.vaccine.2013.11.015. Epub 2013 Nov 17. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24252700.

70. European Medicines Agency, Heads of Medicines Agencies. Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations II: Biological medicinal products. 4 August 2016 EMA/168402/2014 Corr. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211728.pdf

71. Centers for Disease Control and Prevention. Vaccine Information Statements (VISs) Yellow Fever VIS. 30 Mar 2011. Available from: https://www.cdc.gov/vaccines/hcp/vis/vis-statements/yf.html.

72. World Health Organisation. International Certificate of Vaccination or Prophylaxis. International Health Regulations 2005. Available from: http://www.who.int/ihr/IVC200_06_26.pdf?ua=1.

73. De Lusignan S, Hoghton M, Rafi I. Flu vaccination by pharmacists leads to suboptimal medical records. BMJ 2017;359:j5084 doi: 10.1136/bmj.j5084: 9 Nov 2017. Available from: https://www.bmj.com/content/359/bmj.j5084

74. Rolnick S,,Parker E, Nordin J, Hedblom B, Wei F,Kerby T, Jackson J, Crain A, Euler G. Self-report compared to electronic medical record across eight adult vaccines: Do results vary by demographic factors? Vaccine. 2013 Aug 20; 31(37): 3928–3935. 2013 Jun 24. doi: 10.1016/j.vaccine.2013.06.041 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4689428/.

75. Stupiansky N., Zimet G, Cummings T , Fortenberry JD, Shew M. J Adolesc Health. 2012 Jan; 50(1): 103–105. Accuracy of self-reported HPV vaccine receipt among adolescent girls and their mothers. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3245637/.