D7.4 Setting up brand-specific influenza vaccine effectiveness studies in Europe – results of the pilot season 2017/18

777363 – DRIVE

Development of Robust and Innovative Vaccine Effectiveness

WP7 – Influenza vaccine effectiveness pilot study

Date: 16 November 2018

Pilot season 2017-2018

DISCLAIMER

The results presented here are based on a limited number of sites using partially differing study protocols. They arise from a pilot season whose main objective was to build the DRIVE study platform for estimating brand-specific IVE in Europe. Due to the pilot nature of the study, the brands have been anonymized. The results should not be used to inform medical or regulatory decision-making.

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V1.0	16 Nov 2018	Brand and type anonymization

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List of abbreviations and acronyms

CI	Confidence interval
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
ECDC	European Centre for Disease Prevention and Control
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
FISABIO	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana
GP	General Practitioner
ILI	Influenza-like illness
IMI	Innovative Medicines Initiative
InfluNet	Italian National Influenza Surveillance System
ICU	Intensive Care Unit
ISC	Independent Scientific Committee
ISS	Istituto Superiore di Sanitá / Italian Public Health Agency
IVE	Influenza Vaccine Effectiveness
LAIV	Live attenuated influenza vaccine
MAH	Marketing authorization holder
MD	Medical doctor
MUW	Medizinische Universitat Wien / Medical University Vienna
REML	Restricted maximum likelihood
RENAVE	Spanish National Epidemiological Surveillance Network
OPBG	Ospedale Pediatrico Bambino Gesu
OR	Odds Ratio
PMO	Project Management Office
QIV	Quadirvalent influenza vaccine
RE	Random effects
RR	Relative risk
RT- PCR	Reverse Transcriptase - Polymerase Chain Reaction
SAP	Statistical Analysis Plan
SARI	Severe Acute Respiratory Infection
SC	Steering committee
SOP	Standard Operating Procedures
TC	Teleconference
THL	Terveyden ja hyvinvoinnin laitos / Finnish Public Health Agency
TIV	Trivalent influenza vaccine
TND	Test-negative design
VAHNSI	Valencia Hospital Network for the study of influenza
VE	Vaccine effectiveness
WP	Work package
WPL	Work package leaders

National institutions/organizations providing data

Table 1. Institutions providing data

Country	Location	Type of Study	Participant Institution/s	Contact person
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Spain	Valencia	TND	FISABIO	Javier Díez Domingo
Italy	Rome	TND	ISS	Caterina Rizzo
Spain	La Rioja	TND	Rioja Salud	Eva Martinez Ochoa
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Seqirus: Seqirus R&D

Executive Summary

Background

The DRIVE consortium (Development of Robust and Innovative Vaccine Effectiveness) has been established to answer the updated European regulatory requirements which include annual brand-specific influenza vaccine effectiveness (IVE) estimates. This report presents the achievements and results of the pilot study 2017/2018.

Objectives

The overarching objective of this pilot study was to test the different operational aspects of the project including the IT infrastructure, the DRIVE governance for conducting IVE studies and streamlining key processes such as data collection, statistical analyses and dissemination of study results.

Methods

A multi-country study was conducted comprising one register-based cohort study in Finland and four test-negative design (TND) studies from Austria, Italy, and two regions in Spain. For this pilot study, study sites used their own protocols for data collection as the influenza data collection for the season 2017/18 started only a few months after the launch of the DRIVE project. In- and exclusion criteria were harmonized where possible at the time of data analysis.

Influenza VE estimates were calculated using a two-stage pooling approach. In a first step crude and confounder adjusted site-specific IVE estimates were calculated. In a second step, the site-specific IVE estimates were pooled using random-effects meta-analysis. All analyses were done centrally at the DRIVE server.

Results

The DRIVE research platform was assembled. A separate work package (WP7) consisting of non-industry organizations was set up to carry out the studies, whose results are to be evaluated by an Independent Scientific Committee (ISC). Harmonized study protocols for TND and cohort studies (D7.1 & D7.2) were developed and will be implemented in the 2018/19 season. A framework for data analysis (D4.1), a data management plan (D4.2), a report template (D4.3) and a generic Statistical Analysis Plan (SAP) (D4.4) were written during the first year of the DRIVE project. P95 provided the IT infrastructure needed to share, access and analyse data and has built an Electronic Study Support Application (D2.3). The ISC was assembled in January 2018.

Overall data was collected on 2573 cases and 2426 controls in the TND studies and 241,394 person-years for vaccinated subjects and 288,655 person-years for non-vaccinated subjects in the register-based cohort study. Information on vaccine brand used was successfully collected at all sites, except Austria where vaccine brand was unknown for 55% of vaccinated subjects. IVE estimates by vaccine type, vaccine brand and overall as well as by host-related covariates, type of influenza outcomes and study characteristics were calculated in accordance to the SAP. The results of this pilot year were produced to test different operational aspects of the DRIVE project and should not be used to inform medical or regulatory decision-making as the sample size was insufficient to obtain brand-specific IVE estimates within comparable age groups and healthcare settings to allow a proper interpretation of the results.

Discussion

The experience from the pilot study was overall positive, but several improvements need to be made. For the pilot study, much time was spent on data cleaning and some aspects of the data collection

remained unclear. The engagement of the study sites and harmonization of the data collection is a priority for the 2018/2019 season. To this end, study sites visits will be organized, communication channels established, support teams will be set up and the functionalities of the Electronic Study Support Application (ESSA) will be expanded to allow data upload by the study sites, data monitoring and data management throughout the influenza season. Some changes to the generic study protocols, minimum data requirements and the SAPs will be required as well.

The DRIVE platform has been successfully built and will be expanded in the 2018/2019 season, during which harmonized protocols will be implemented and the number of sites contributing data will be at least doubled. The tools and processes that will be used for the 2018/2019 influenza season will build upon the experiences and lessons learned from this pilot season.

Lay Summary

Nowadays, there are several different types and brands of vaccines against influenza (“flu”), a common and sometimes severe respiratory infection. The DRIVE project (Development of Robust and Innovative Vaccine Effectiveness) has been established to evaluate the effectiveness of the various flu vaccines. In doing so, the project attempts to answer the updated requirements set to vaccine manufacturers by the European Medicines Agency.

This report presents the achievements and results of the first annual study in 2017–2018. The overarching objective of this year was to test the DRIVE governance model and the infrastructure, tools and procedures developed during the first year of the DRIVE project.

Five study sites from four countries (Austria, Finland, Italy, and Spain) participated in this first pilot study. This time, the study sites used their own procedures for data collection, though the aim is to harmonize these in the future. Data from the five studies were analyzed together in two steps: first obtaining a site-specific effectiveness estimate and then pooling these together in a meta-analysis.

Although DRIVE is a public-private partnership which includes partners from both public sector and vaccine manufacturers, all studies were done in a separate working group consisting of organizations other than manufacturers. The results are also evaluated by an Independent Scientific Committee (ISC) which first convened in January 2018.

Information on vaccine brand used was successfully collected at most sites. It was possible to calculate effectiveness for four different brands, although these results are preliminary and should not yet be used to inform medical or regulatory decision-making.

Other accomplishments of the first year of the project include the writing of harmonized study protocols that will be implemented in the 2018/19 season, a framework for data analysis, a data management plan, a report template and a generic statistical analysis plan. P95 provided the IT infrastructure needed to share, access and analyse data, has developed several analysis scripts and has built an Electronic Study Support Application.

Milestones

Table 2. Dates important milestones in the cohort and TND studies were met in the pilot year 2017/2018

	Start of data collection/ surveillance period	End of data collection	Data cleaning and database available for analysis	Results pooled analysis available
MUW, Austria	Week 41 2017	Week 15 2018	July 3, 2018	July 24, 2018
THL, Finland	Week 40 2017	Week 20 2018	June 11, 2018	
ISS, Italy	Week 47 2017	Week 17 2018	June 18, 2018	
Rioja Salud, Spain	Week 46 2017	Week 20 2018	June 11, 2018	
FISABIO, Spain	Week 36 2017 (Flu circulation 2017-45)	Week 26 2018 (Flu circulation 2018-20)	June 11, 2018	

1 Background

Influenza is a major public health problem and vaccines are the cornerstone for preventing influenza. Vaccine effectiveness (VE) can vary every season due to differences in e.g. circulating strains, level of match between these circulating strains and the vaccine strains, the influenza vaccination coverage in the population and prior exposure to the antigen. Knowledge on VE by vaccine type and brand is still limited.

The new Guideline on Influenza Vaccines (non-clinical and clinical model) from the European Medicines Agency (EMA) requests influenza vaccine effectiveness (IVE) evaluation for all individual influenza vaccine brands used in the European Union (EU) [1]. Marketing Authorization Holders (MAHs) are requested to respond to the regulatory requirements. This information is also of public health importance, and since many European public health institutions have extensive experience in conducting IVE studies, EMA encourages the MAHs to liaise with public health institutions.

In this context, a new public-private partnership (PPP) named DRIVE (Development of Robust and Innovative Vaccine Effectiveness) was launched by the Innovative Medicines Initiative (IMI) in 2017. DRIVE aims to establish a sustainable platform for brand-specific IVE studies in the EU.

For the DRIVE consortium, the influenza season 2017/18 was considered a pilot season. The overarching objective of this pilot study was to test the different operational aspects of the project including the IT infrastructure, the DRIVE governance for conducting IVE studies and streamlining key processes such as data collection, statistical analyses and dissemination of study results.

2 Study objectives

2.1 Overarching objective

The overarching and primordial objective of this pilot study was to test the different operational aspects of the project including the IT infrastructure, the DRIVE governance for conducting IVE studies and streamlining key processes such as data collection, statistical analyses and dissemination of study results.

The objectives in accordance with the Statistical Analysis Plan are given below.

2.2 Primary objectives

To estimate seasonal IVE against any medically attended (primary care/hospital) laboratory-confirmed influenza case,

- **by vaccine brand**
- **by influenza vaccine type**: by vaccine antigen (live attenuated, inactivated, subunit, split virion), by valency (number of vaccine virus strains) and by adjuvant (adjuvanted vs. non-adjuvanted)
- **by any influenza vaccine**

2.3 Secondary objectives

To estimate seasonal overall IVE by any influenza vaccine, stratified by **host-related covariates**:

- age group (6 months – 14 years, 15 – 64 years and 65+ years)
- presence of at least one chronic condition (yes or no, see also Section 9.8.2)
- vaccination status in previous season (yes or no)

To estimate seasonal IVE by any influenza vaccine, stratified by **type of influenza outcome**:

- laboratory-confirmed influenza A, overall and by subtype (A(H1N1)pdm09, A(H3N2))
- laboratory-confirmed influenza B, overall and by lineage (B/Victoria, B/Yamagata)

To estimate seasonal overall IVE by any influenza vaccine, stratified by **study characteristics**:

- healthcare setting (primary care, hospital, mixed)

2.4 Exploratory objectives

2.4.1 Comparing pooling approaches: 1-stage vs 2-stage pooling

There are two commonly used statistical approaches for pooling data from different study sites: a one-stage or a two-stage pooling approach. The two-stage approach refers to the classical meta-analytical approach. In this approach, the patient-level or minimally aggregated data from each study are analyzed separately in order to obtain the effect estimates of interest (here IVE and corresponding confidence intervals, CIs). Then, in the second step, the effect estimates are combined by an appropriate meta-analysis model to obtain the meta-analytical (pooled) estimate. The one-stage pooling approach analyses all the combined patient-level or minimally aggregated data from the different data sources in a single step.

To objective of this analysis is to compare the one-stage and two-stage pooling approaches using

data from all participating test-negative design (TND) case-control studies (e.g. Austria, Italy and two regions from Spain). For this exploratory objective, we estimated seasonal overall IVE by any influenza vaccine.

2.4.2 Time since vaccination

To explore waning of the vaccine effect by estimating seasonal overall IVE by any influenza vaccine by time since vaccination using the combined TND data.

3 Methods

3.1 Study design

A multi-country study was conducted comprising one register-based cohort study in Finland and four TND case-control studies from Austria, Italy, and two regions in Spain. A third site from Spain, from the Canarias region, had to be excluded from the analysis due to data quality issues.

Influenza VE estimates were calculated through two-stage pooling. In a first step, site-specific IVE estimates were calculated. These site-specific estimates were centrally calculated, either from individual-level data (all TND studies) or from aggregated format (Finnish cohort study). In this pilot year, study sites used their own protocols for data collection as the influenza data collection for the season 2017/18 started at few months after the launch of the DRIVE project. The data analysis was identical across study sites that used the same study design, though the operationalization of some variables could not be harmonized (see Appendix 9.1). In a second step, the site-specific IVE estimates were pooled using random-effects meta-analysis.

3.2 Description of the influenza surveillance systems

MUW, Austria

Influenza virus activity in Austria is monitored within the frame of the Austrian Influenza Sentinel Network, by the Diagnostic Influenza Network Austria (DINÖ), a group of sentinel physicians throughout Austria, who collect clinical nasopharyngeal swab samples, as well as epidemiological information. Within this sentinel network, nasopharyngeal swabs are collected from patients with acute influenza infections (fulfilling ILI case definition) in Austria from calendar week 40 of one year to week 16 of the following year. Sentinel physicians are encouraged to collects swabs from +- 5 patients per week. Physicians decide themselves from which patients to take swabs. Specimens are sent to the Centre of Virology at the Medical University of Vienna (National Reference Laboratory) and investigated for the presence of influenza viruses. Influenza virus positive nasopharyngeal swab samples are further analysed to identify the type, subtype or lineage and strain. In addition to the sentinel physicians, swabs from routine clinical practice are also analysed at the Centre of Virology.

THL, Finland

During the 2017-2018 influenza season, THL, the National Institute for Health and Welfare, Finland, performed a population-based study which made use of secondary data from existing health care databases. The study was part of the national routine practice for assessing IVE by using data derived from the National Vaccination Register (all vaccinations administered in public primary health care) and the National Infectious Diseases Register (all positive influenza findings from all laboratories) complemented with data from other routine administrative registers.

ISS, Italy

In Italy the IVE study has been based on a sample of sentinel general practitioners (GPs) under the national influenza surveillance system (InfluNet) that includes the epidemiological and virological influenza surveillance systems. The system aims to monitor the incidence of ILI, define the extent of the seasonal epidemics, and collect information on circulating strains. For virological surveillance, nasopharyngeal swab are collected from a sample of ILI cases by GPs between week 46 and week 10 of each season. Specimens are tested at the regional Reference Laboratories distributed in 15 different Italian regions. Results are collected and reported using web-based electronic case report forms to the National Influenza Centre.

In Italy, in 2013 there were approximately 45,000 GPs and 8,000 pediatricians (data from the National Bureau of Statistics). InfluNet was implemented nationwide in season 1999-2000. InfluNet is based on voluntary participation of an average of 900 (range 648-1100) general practitioners (including paediatricians) per year, covering 2% of the national population distributed in all Italian regions for each age group (2% is also requested at regional level). The system aims to monitor the incidence of influenza-like illness (ILI), defining the extent, the timing and severity of seasonal epidemics. GPs are asked to report ILI cases (according to ILI EU case definition) weekly (from week 42 to week 17) using standardized forms. Specific information regarding age (0-14, 15-64, >64 years) and influenza vaccine status are also collected.

Rioja Salud, Spain

La Rioja's influenza sentinel surveillance network is part of the cycEVA study carried out within the framework of the Influenza Surveillance System in Spain. The cycEVA study is the Spanish component of IMOVE.

FISABIO, Spain

Since 2011, FISABIO has conducted a hospital-based TND study applying an active annual surveillance scheme in the Valencia Hospital Network for the Study of Influenza (VAHNSI) to monitor influenza virus epidemiology and its impact in different age and risk groups. For the 2017-2018 influenza season FISABIO enlarged the time window of the VAHNSI study from 1st of September to 30th of June (4 months longer than currently) to capture, in the period 1st September to 30th June (10 consecutive months) admissions with laboratory confirmed (RT-PCR), respiratory syncytial virus and their seasonality with confidence.

3.3 Overview study site characteristics

Apart from study design, the studies differed with respect to healthcare setting, catchment area, swabbing strategy of influenza-like illness (ILI) cases, ILI case definitions, age groups, and laboratory tests performed. An overview of the most important study site characteristics is given in Figure 1.

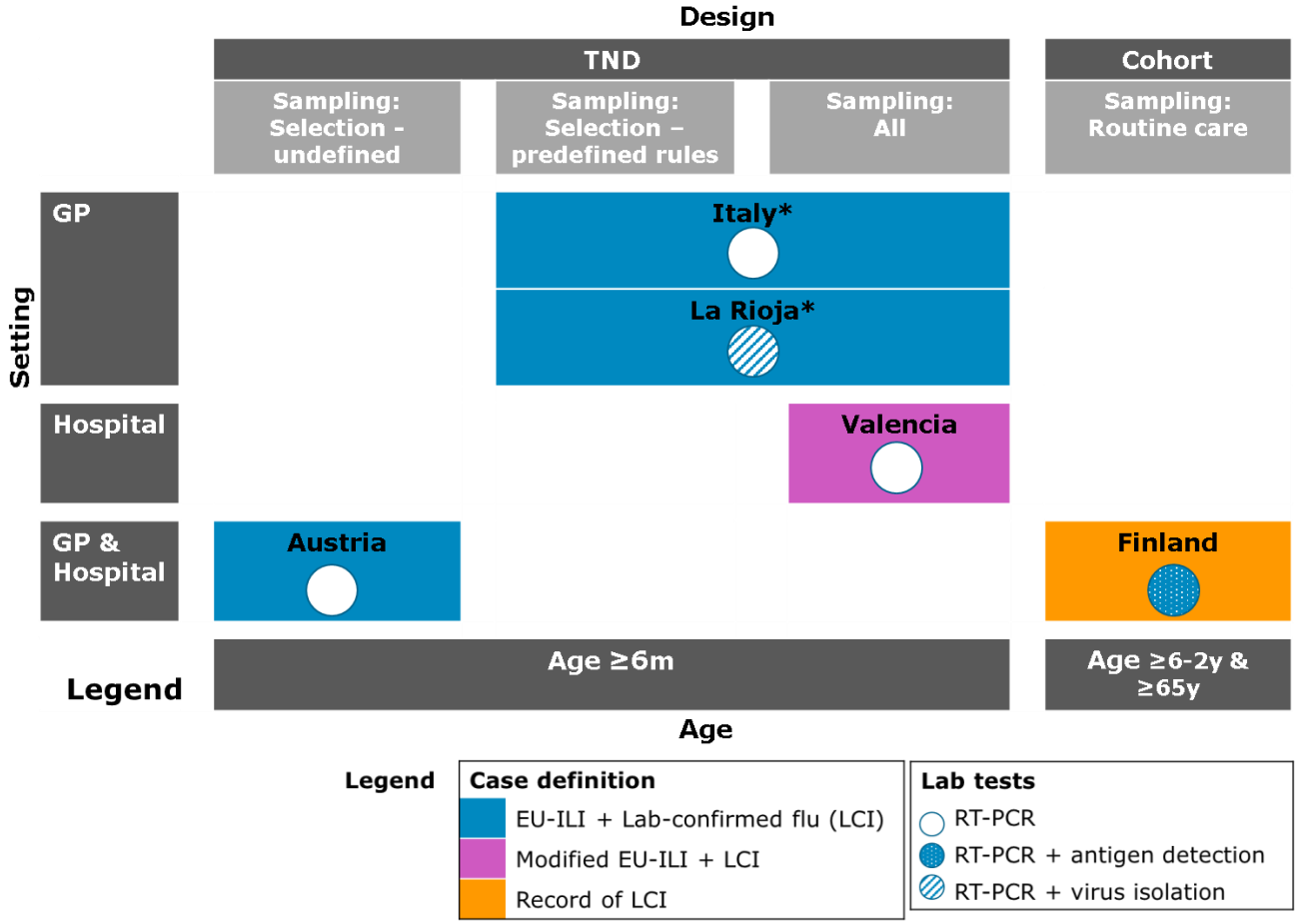


*Figure 1. Characteristics of study sites included in the pilot, 2017/2018. *Sampling strategy depends on age*

3.4 Catchment population and sampling strategy

The catchment population of the included sites and the sampling strategies to enroll subjects into the study (incl. taking a swab) are summarized in Table 3.

Table 3. Catchment population and sampling strategy, 2017/18 season

Site	Catchment population	Sampling strategy	Description of sampling strategy
MUW, Austria	Catchment population of sentinel physicians • ca. 1% of Austrian physicians)	Selection (undefined)	Physicians choose which subjects* to enrol without predefined rules
THL, Finland	Individuals registered to the Finnish Information System as permanent resident of Finnish municipalities, aged 6 to 35 months (N=135,173) or 65 years and older (N=1,190,924)	Routine care±	Swabbing takes place at discretion of physician as part of routine care.
ISS, Italy	Catchment population of sentinel physicians • Ca. Ca. 900 out of 53,000 GPs and paediatricians, • Covering 2% of the population in each region and at national level.	<65y: Selection (predefined rules)	The first 2 subjects* <65y per week on predefined days are enrolled
		≥65y: All	All subjects* ≥65y are enrolled
Rioja Salud, Spain	Catchment population of sentinel physicians • 26 out of 246 GPs in La Rioja (10.6%), including 20 GPs (one for each health zone), 5 primary care paediatricians and one GP in an elderly home • Covering ca. 29,800 people, i.e. 8% of the La Rioja region population, representative by age, sex and degree of urbanization	<65y: Selection (predefined rules)	The first 2 subjects* <65y per week are enrolled
		≥65y: All	All subjects* ≥65y are enrolled
FISABIO, Spain	Residents in one of the four hospitals' catchment areas • Ttotal source population of 1 105 570, or 22% of Valencia region's population	All	All subjects* are enrolled

± *Routine care: swabbing of subjects takes places at discretion of physician as part of routine clinical care.*
**Subjects fulfilling the inclusion criteria*

3.5 Study period

For the TND studies, the analysis was restricted to the period during which influenza was circulating. Therefore, the study period was defined as starting from the 1st week of 2 consecutive weeks with at least 1 influenza detection each (calculated from date of symptom onset when available) and ending at 2 consecutive weeks with no influenza detections (2 weeks of no case are included in the data) (Figure 2).

For the register-based cohort study, the study period was defined as starting from the early stage of the epidemic until the end of the study (Figure 2).

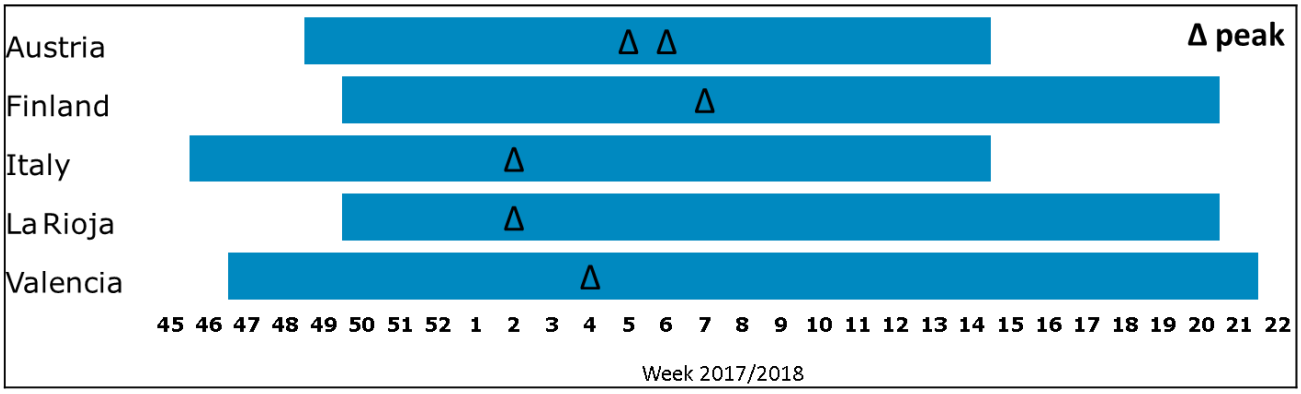


Figure 2. Study periods at the sites included in the pilot, 2017/2018.

3.6 Data sources

Data sources used at each site are listed in Table 4. Primary data collection via interviews and/or medical and laboratory records was performed for all TND studies. In Finland, all data comes from national registers.

Table 4. Data sources for baseline clinical data, for verification of immunization status and for assessment of outcomes, 2017/18 season

Site	Source for baseline clinical data	Source for verification of immunization status	Source for assessment of outcomes
TND			
MUW, Austria	Interview and medical records	Medical records	Primary data collection, Laboratory results
ISS, Italy	Interview and medical records	Medical records	Regional reference laboratories identified by the National Influenza Centre based at ISS
Rioja Salud, Spain	Interview and medical records	Medical records	Medical records
FISABIO, Spain	Interview and medical records	Interview and/or vaccine registry	Centralized laboratory
Cohort			
THL, Finland	Population Information System, Care Register for Health Care, Register for Primary Health Care visits	National Vaccination Register	National Infectious Diseases Register

3.7 Outcome

For the TND studies, the outcome of interest was laboratory-confirmed influenza in a subject presenting with ILI (see Statistical Analysis Plan (SAP), Appendices 9.2 and 9.3 for more details). The respiratory sample needed to be taken within 7 days after ILI onset for subjects to be included in the primary analysis.

In the Finnish register-based cohort study, the outcome of interest was laboratory-confirmed influenza irrespective of the clinical presentation.

3.7.1 Case definitions

Case definitions used at site level are presented in Table 5, for more details refer to the site-specific study protocols (Appendices 9.4 – 9.7).

Austria, Italy and Spain-La Rioja used the EU-ILI case definition, while Spain-Valencia used a modified EU-ILI case definition for those aged 5 years and above. In this modified EU-ILI case definition, "sudden onset" was not required for subjects aged 5 years and older. In addition, in Spain-Valencia, all children <5 years hospitalized for any acute reason with symptom onset <8 days before admission were systematically swabbed.

Finland used only laboratory confirmation without clinical definition.

Table 5. Site-specific case definitions

Site	Case definition
TND	
MUW, Austria	EU-ILI case definition + Laboratory confirmed influenza
ISS, Italy	EU-ILI case definition + Laboratory-confirmed influenza
Rioja Salud, Spain	EU-ILI case definition + Laboratory-confirmed influenza
FISABIO, Spain	≥5 years: Modified EU-ILI Case definition[1] + Hospitalization with laboratory-confirmed influenza <5 years: Hospitalization for any acute reason (not only ILI) with symptoms beginning <8 days before admission + laboratory-confirmed influenza
Cohort	
THL, Finland	Record of laboratory confirmed influenza in National Infectious Diseases Register

Information on laboratory confirmation of influenza is presented in Table 6.

Table 6. Methods for laboratory confirmation of influenza and availability of information on influenza type, subtype or lineage and strain, 2017/18 season

Site	Laboratory assays for detection of influenza	Type available	Subtype/ lineage available	Strain available
MUW, Austria	Realtime RT-PCR	Yes	Yes	Yes, for a subset
THL, Finland	RT-PCR, antigen detection	Yes	No*	No*
ISS, Italy	RT-PCR	Yes	Yes	Yes
Rioja Salud, Spain	RT-PCR, virus isolation	Yes	Yes	Yes
FISABIO, Spain	RT-PCR	Yes	Yes	Yes

** Subtype/strain not available at individual level. However, subtype/strain data is available from sentinel surveillance.*

3.7.2 Case definition verification

ILI case definition could be verified based on symptoms for Spain Valencia and Spain La Rioja.

[1] Subjects that complied with EU-ILI case definition were included even if "sudden onset" was absent, if all other criteria from the case definition were met.

3.8 Inclusion and Exclusion criteria

3.8.1 Individual TND studies

Inclusion and exclusion criteria from the generic TND protocol (D7.1) are listed here. These were applied to the extent possible to the data sets received from the sites before calculating site-specific IVE estimates. As in this pilot year data was collected using pre-existing protocols (Appendices 9.4-9.7) and not the generic protocols, not all in- and exclusion criteria could be harmonized and major differences between sites are presented in Table 7.

Inclusion criteria

For TND studies, ILI patients meeting the case definition were eligible if they accepted to participate and did not fulfil any of the exclusion criteria listed below.

Exclusion criteria

An ILI patient was not enrolled in the study if she or he:

- Was less than 6 months of age at the time of recruitment
- Had a contraindication for influenza vaccine
- Was unwilling to participate
- Was unable to communicate and give consent (the consent may also be given by her/his legal representative, or by specific consent procedures, acceptable according to the local ethical review process)
- Was institutionalised at the time of symptoms onset (lives in a residence for people who require continual nursing care and have difficulty with the required activities of daily living)
- Had a respiratory specimen taken ≥ 8 days after ILI onset
- Tested positive for any influenza virus in the current season before the onset of symptoms leading to the current primary care visit/hospitalisation
- Was not a resident in the health catchment area
- Had a damaged specimen
- Presented outside of the study period (i.e. when influenza was not circulating)

Note: a patient could be selected several times as long as he/she did not have a previous laboratory confirmed influenza for the current season

3.8.2 Individual cohort study

Inclusion criteria

- Children aged 0.5 – 2 years in week 40 2017
- Elderly aged 65 years and above in week 40 2017
- Individuals in these age groups resident in the catchment area throughout the influenza season (i.e. individuals registered to the Finnish Population Information System as permanent residents of Finnish municipalities completely covered by the National Vaccination Register)

Exclusion criteria

- Subjects not resident in catchment area
- Subjects with incomplete vaccination records for the season studied (2017-2018) and for previous seasons (2014-2015, 2015-2016 and 2016-2017)

Table 7. Site-specific exclusion criteria

	TND				Cohort
	MUW, Austria	**ISS, Italy**	**Rioja Salud, Spain**	**FISABIO, Spain**	**THL, Finland**
Exclusion criteria from the generic protocols:					
Age	<6 months	<6 months	<6 months	<6 months	<6 months, 3-64 years
Cannot communicate	No	No	Yes	Yes	No
Contraindication to influenza vaccine	No	Yes	Yes	Yes	No
Institutionalization	Yes	Yes	Yes	Yes	No
Not a resident in the catchment area	Yes	No	Yes (must have been resident at least previous 6 months)	-	Yes*
Tested positive for any influenza before onset of symptoms leading to current visit/hospitalization	Yes	Yes	Yes	Yes (only among those ≥65 years)	No, but individual follow-up is censored after first positive influenza test during study period
Additional site-specific exclusion criteria					
Egg allergy	No	No	Yes	No	No
Remained in hospital for <24 hours	No	No	Yes	No	No
Received antiviral treatment prior to swabbing	No	No	No	Yes (only among those ≥65 years)	No
Subjects vaccinated against seasonal influenza 2017/18 before week 40/17	No	No	No	No	Yes

*For Finland exclusion criteria were: a) Subjects resident outside the catchment area in 2016/17, or b) Children aged 2 years resident outside the catchment area in 2015/16.

3.8.3 Pooled analyses

All site-level estimates were included in the pooled analysis.

3.9 Exposure (vaccination)

3.9.1 Vaccinee definition

For all objectives, the following exposure definitions were used.

Scenario A: An individual aged ≥9 years, or a child aged <9 years who had been fully vaccinated before the current season (at least two injectable doses or one live attenuated influenza vaccine (LAIV) dose) was considered as

- **vaccinated** with the influenza vaccine(s) of interest when > 14 days have elapsed since the record of influenza vaccination during the season;
- **partially vaccinated** during the first 14 days after the record of vaccination;
- **unvaccinated** until the vaccination record during the season, if any;
- **unknown** if information on date of influenza vaccination is missing.

Scenario B: A child aged < 9 years who had not been fully vaccinated (see above) before the current season was considered as

1. **vaccinated** with the influenza vaccine(s) of interest when >14 days have elapsed since
   the second record of injectable vaccination during the current season
   OR
   the first record of LAIV vaccination during the current season;
2. **partially vaccinated** during the first 14 days after
   the first record of injectable vaccination until >14 days after the second record of vaccination during the current season
   OR
   the first record of LAIV vaccination during the current season
3. **unvaccinated** until the first vaccination record during the season, if any;
4. **unknown** if information on date of influenza vaccination is missing.

Note 1: If no information on exposure in previous season was available in the dataset, the exposure definition 'scenario A' was used for all subjects.

Note 2: The partially vaccinated subjects were excluded from the primary analyses; their significance was assessed through sensitivity analyses (Section 3.11.5).

Note 3: The exposure assessment was done once for each study subject at the time of symptom onset for case-control studies, while vaccination status for subjects within a cohort study were treated as time-varying.

3.9.2 Target group for vaccination

Target groups for vaccination at the study site level are heterogeneous (Table 8). Austria was the only site with a general recommendation for vaccination for the whole population, while the other sites recommend vaccination in the elderly and high-risk groups only. Finland also recommends vaccination for children 6 to 35 months of age.

Table 8. Target groups for vaccination for each study site, 2017/18 season

Site	Target groups for vaccination
Austria	General vaccine recommendation
Finland	Children 6 to 35m
	36m – 64y with underlying medical conditions
	Pregnancy
	Social care workers, healthcare workers, Pharmacy personnel
	Military conscripts
	Elderly 65+ y
	Contacts of persons at high risk
Italy	Elderly 65+ y
	6m – 64y with underlying conditions
	Pregnancy
	Individuals in long-term care facilities
	Healthcare workers
	Contacts of persons at high risk
	Essential public service workers
	Workers in direct contact with poultry and swine
Spain: La Rioja region	Elderly 60+ y
	6m – 64y with underlying conditions
	Pregnancy
	Individuals in long-term care facilities
	Healthcare workers
	Household members of persons at high risk
	Essential public service workers
	Workers in direct contact with poultry and swine
Spain: Valencia region	Elderly 65+ y
	6m – 64y with underlying conditions
	Pregnancy
	Healthcare workers
	Household members of persons at high risk
	Essential public service workers
	Workers in direct contact with poultry and swine

Vaccine types used or recommended differ across the countries and sites. Table 9 presents the vaccine type and brand used in each site for each target group.

Table 9. Recommendations of specific vaccine types by country, 2017/2018 season

	Vaccine target group	Preferred vaccine type listed in recommendations	Alternative vaccine type
Austria[2]	Children 6months – 2 years	Inactivated TIV	-
	Children 2-3 years	Quadrivalent LAIV	Inactivated TIV
	Children 3-18 years (primary vaccination)	Quadrivalent LAIV (for children ≤8 years)	Inactivated QIV (for children ≤9 years) Inactivated TIV (for children ≤8 years)
	Children 3-18 (repeated vaccination)	Quadrivalent LAIV Inactivated QIV	Inactivated TIV
	Adults (18-60y)	Inactivated QIV Inactivated TIV	-
	Adults 60/65 years	Adjuvanted or intradermal vaccine	Inactivated QIV Inactivated TIV
	HCW and persons with contact with persons at risk	Inactivated QIV	Inactivated TIV
	Persons at risk	Inactivated QIV Adjuvanted or intradermal vaccine	Inactivated TIV
Finland	Children	No preferential recommendation, both quadrivalent LAIV or inactivated TIV available	-
	Other	No preferential recommendation but only inactivated TIV was available	-
Italy	At risk 6 months – 64 years	Inactivated QIV Inactivated TIV	
	Adults 65 years and above	Inactivated QIV Inactivated TIV MF59 adjuvanted	
Spain – La Rioja region [3]	All	Recommendations are based on inactivated TIV.	
Spain – Valencia region [4]	Institutionalized persons aged 65 years and above; and persons aged 75 years and above [5]	Adjuvanted vaccine	
	All others	Inactivated trivalent vaccine	

HCW: healthcare workers; LAIV: live attenuated influenza vaccine; QIV: quadrivalent influenza vaccine; TIV: trivalent influenza vaccine

[2] Arrouas M, Tiefengraber D, Nationales Impfgremium. Österreichischer Impfplan 2017. Empfohlene Auswahl der Impfstoffart gegen die saisonale Influenza für unterschiedliche Alters- und Personengruppen. Vienna: Bundesministerium für Arbeit, Soziales, Gesundheit und Konsumentenschutz; 2017 [cited 2017 September]. Available from: https://www.bmgf.gv.at/home/Impfplan.

[3] Gobierno de La Rioja and Rioja Salud. VACUNACIÓN FRENTE A LA GRIPE ESTACIONAL VACUNACIÓN FRENTE A LA GRIPE ESTACIONAL CAMPAÑA 2017 CAMPAÑA 2017-2018 2017 [cited 2017 September 4]. Available from: https://www.riojasalud.es/f/rs/docs/PROTOCOLO%20CAMPA%C3%91A%20ANTIGRIPAL%202017-2018.pdf.

[4] Generalitat Valenciana. Vacunacion antigripal estacional 2017 2017 [cited 2017 September 4]. Available from: http://www.sp.san.gva.es/DgspPortal/docs/Protocolo_gripe_2017-18.pdf.

[5] In practice the adjuvanted vaccine was widely used in those 65 years and above (personal communication, Javier Diez-Domingo)

3.10 Risk groups, confounding factors and effect modifiers, other variables

The following covariates were used: age group, sex, presence of at least one chronic condition, number of hospitalizations in previous 12 months, vaccination status in previous season.

3.10.1 Age groups

Age was categorized into the age groups 6 months to 14 years, 15-64 years and ≥65 years for all sites except for Finland. For Finland the age categories were 6 months to 2 years and ≥65 years (Table 10).

Table 10. Description of age groups per site included the pooled analysis

Site	Pooled analysis age group: 6m-14y	Pooled analysis age group: 15y-64y	Pooled analysis age group: ≥65y
MUW, Austria	6m-14y	15y-64y	≥65y
THL, Finland	6m-2y	Not available	≥65y
ISS, Italy	6m-14y	15y-64y	≥65y
Rioja Salud, Spain	6m-14y	15y-64y	≥65y
FISABIO, Spain	6m-14y	15y-64y	≥65y

3.10.2 Chronic conditions

The presence of at least one chronic condition was categorized as yes/no. There were differences on how chronic conditions were identified and categorized in each site. The differences are summarized below in Table 11. Roughly, the chronic conditions considered were cardiovascular diseases, diabetes mellitus, other chronic endocrine and metabolic diseases, chronic pulmonary, renal and liver diseases, immunodeficiency and organ transplant, cancer, dementia, rheumatological disease, chronic neurological or neuromuscular diseases, and anemia. However, differences in chronic conditions captured between the sites exists. The full list of chronic conditions considered at each site can be found in the SAP (Appendix 9.2).

The main differences between the sites was whether they in- or excluded obesity, as well as pregnancy. For Italy, since information on pregnancy was collected separately, a new variable was created where pregnancy was also included as a chronic condition to harmonize its definition of chronic conditions with that of the other sites.

Table 11. Description of chronic conditions included in the variable 'chronic disease' per site

Chronic condition	THL, Finland	ISS, Italy	FISABIO, Spain	Rioja Salud, Spain	MUW, Austria
Cardiovascular diseases	Yes	Yes	Yes	Yes	Yes
Diabetes mellitus	Yes	Yes	Yes	Yes	Yes
Autoimmune	No	No	Yes	No	Yes
Other chronic endocrine and metabolic diseases	Yes	Yes	Yes	Yes	No
Chronic pulmonary diseases	Yes	Yes	Yes (asthma, bronchitis)	Yes	Yes
Chronic renal diseases	Yes	Yes	Yes	Yes	Yes
Chronic liver diseases	Yes	Yes	Yes	Yes	Yes
Immunodeficiency and organ transplant	Yes	Yes	Yes	Yes	Yes
Cancer	Yes	Yes	Yes	Yes	Yes
Dementia	Yes	Yes	Yes	Yes	Yes
Stroke	Yes	Yes	No	No?	Yes
Rheumatologic disease	Yes	Yes	Yes	No	Yes
Chronic neurological or neuromuscular disease	Yes	No	Yes (neuromuscular)	Yes	Yes
Anaemia	Yes	Yes	Yes	Yes	Yes
Perinatal or congenital risk factor	Yes	No	No	No	No
Obesity	No	Yes, if serious concomitant diseases	Yes (BMI)	Yes	No
Pregnancy	No	No	Yes	Yes	Yes

3.10.3 Number of hospitalizations in previous 12 months

Site-level analyses were adjusted for the number of hospitalizations in the previous 12 months (0, 1-5 and >5) except for Austria, for which no information on this covariate was available (Table 12). La Rioja had no subjects with more than 5 hospitalizations.

Table 12. Description of number of hospitalizations in previous 12 months per site

Site	Nr of hospitalizations in previous 12 months
MUW, Austria	Not available
THL, Finland	0, 1-5, >5
ISS, Italy	0, 1-5, >5
Rioja Salud, Spain	0, 1-5
FISABIO, Spain	0, 1-5, >5

3.10.4 Vaccination in the previous season

Influenza vaccination in the previous season was categorized as yes/no. This information was available for all sites.

3.11 Data quality, management and verification procedures

Please refer to the sites-specific protocols for local procedures of data cleaning and transformation. All sites uploaded their data to the central server as per the procedures described in D4.2 (Data management plan). The data management report for data cleaning and transformation procedures conducted centrally for the pooled analysis can be found in Appendix 9.1.

3.12 Sample size considerations

Simulation-based sample size calculations for the random effects meta-analysis of IVE were performed. Sample size calculations for random effects meta-analysis are very challenging as they depend on many factors, including vaccination coverage, the influenza attack rate, the number of studies to pool, the sample sizes and designs of the individual studies as well as the between-study variance. For details please refer to the Annex 3 of the SAP (Appendix 9.2).

3.13 Statistical methods

Statistical methods are described in detail in the SAP (Appendices 9.2 and 9.3).

3.13.1 Descriptive analysis

For the combined individual-level TND data an attrition diagram was created, giving an overview of the number of excluded cases (per exclusion criterion) and number of discarded cases (for reasons of missing or incomplete information). An analogous attrition diagram was created for the cohort study of Finland.
For the combined individual-level TND data, the characteristics of the laboratory-confirmed influenza cases and test-negative controls were described by covariates, influenza vaccination status and study sites. Similar information was provided for the study population of the cohort study from Finland.

3.13.2 Step 1: Site-specific estimates

Logistic regression was used to analyze the data collected using TND case-control studies. Poisson regression was used for the cohort study. Both crude and confounder-adjusted IVE estimates and their 95% CIs were obtained. The potential confounders considered for adjustment include sex, age group, number of hospitalizations in the previous 12 months, influenza vaccination in the previous season and presence of at least one chronic condition. For each site separately, model building was performed using backwards model selection.

Additional stratified analysis were obtained by type of influenza outcome, by age group, presence of at least one chronic condition, influenza vaccination in the previous season and healthcare setting. The variable used to stratify on was excluded from the covariate adjustment, when applicable.

3.13.3 Step 2: Meta-analysis

We applied standard meta-analysis using random effects inverse variance weighted averages with a moment estimate of the between-study variances based on the log-transformed relative risk (RR) estimates (for the cohort study) and odds ratio (OR) estimates (for case-control studies). Restricted maximum likelihood (REML) was used to obtain the pooled (meta-analyzed) risk estimate (and 95% CIs). The pooled estimate (and 95% CIs) was then back-transformed to obtain the pooled IVE estimate (and 95% CIs), expressed in %.

For every meta-analysis performed, the potential impact of outliers and influential estimates on the pooled estimate was evaluated. An indication for the heterogeneity among estimates from different study sites was obtained by calculating the I^2- statistic.

3.13.4 Exploratory analyses

One-stage and 2-stage pooling were compared using data from all study sites that used the TND case-control design. We used data from all study sites that used the TND design for data collection, being Austria, Italy and two Spanish regions (Valencia and la Rioja). The confounders commonly present in all databases were age-group, sex and presence of chronic conditions. We then estimated crude IVE against all influenza types, influenza type A and influenza type B as well as IVE adjusted for age, sex and presence of at least one chronic condition. The crude and the adjusted VE were obtained using 1-stage and 2-stage pooling approaches. In the 1-stage pooling approach, the individual-level data were first combined across study sites and subsequently jointly analysed. As 1-stage pooling approaches, we used logistic regression treating study site as a fixed main effect and mixed effects logistic regression models treating study site as random intercept and treating study site as random intercept plus random vaccination effect. The first two models assume the IVE is the same across study sites and differences in study-sites are related to differences in influenza attack rates among the unexposed. The model with random intercepts plus random slopes allows for differences in IVE across different study sites. As 2-stage pooling approaches, we used fixed effects and random effects meta-analysis using exactly the same data as used for the 1-stage pooling approaches. The fixed effects meta-analysis model assumes that all differences in site-specific estimates are due to random error whereas the random effects meta-analysis model assumes that these differences are partially due to other sources (e.g. differences in populations, data collection).

To explore waning of the vaccine effect, generalized additive models (GAMs) were used modelling the confounder-adjusted IVE as a smooth function of time since vaccination, avoiding the need to create time categories. Bootstrap sampling was used to obtain the 95% CIs. For this exploratory analysis, we modelled VE against influenza AH1N1 as the highest VE estimates were observed for this strain. For comparison, we also estimated crude and confounder adjusted IVE by time since vaccination as a categorical variable (<=1, 2-3, 4-4, >4 months). The confounders adjusted for were study-site, age groups, presence of at least 1 chronic condition and influenza vaccination in previous season.

3.13.5 Sensitivity analyses

The following sensitivity analyses were conducted for the primary analysis:

- Inclusion of partially and potentially vaccinated subjects in the vaccinated group, and in the unvaccinated group
- Exclusion of ILI/severe acute respiratory infection (SARI) patients if the respiratory specimen was taken ≥ 4 days after ILI onset

No sensitivity analysis for outlying and influential estimates was conducted, since none were identified.

3.13.6 Deviations from the SAP

The definition in the site-specific SAP for TND studies (Appendix 9.3) for the study period was: “The seasonal assessment will start when the influenza virus circulation begins (first of two consecutive weeks when influenza viruses are detected at the national/study site level) in the country/region and will finish at the end of the influenza season (first of two consecutive weeks when no influenza viruses are detected)”. In the site-specific analysis, the end of the influenza season was set at the second week of the first two consecutive weeks when no influenza viruses are detected.

The exploratory objective on the waning of the vaccine effect is performed based on VE against AH1N1 because the highest VE was observed for this strain.

4 Ethics approval/informed consent

The approval process at the different sites are described below. Please refer to D3.4 for informed consent documentation.

MUW, Austria

In Austria the ethics committee approval to perform IVE studies is required for the duration of one year (for each season an amendment is needed). The feedback received from the ethics committee on the protocol used in the last influenza season was received approximately two months after submitting the required documentation and was positive. The ethics committee is based at the Medical University of Vienna and composed of clinicians, psychologists, lay persons, pharmacologists, GPs, paediatricians, microbiologists, biostatisticians, pharmacists, experts in legal and insurance matters or a coroner, experts in bioethics, representatives of patient associations. Informed consent was not required, as data were fully anonymized. The study was performed according to the Declaration of Helsinki and its Amendments and the research protocol is approved by the ethics committee of the Medical University of Vienna.

THL, Finland

In Finland, since the population-based study conducted made use of secondary data from routine databases, the ethics evaluation was not mandatory. However, the investigators requested an evaluation from an institutional ethics review group, mainly composed of clinicians and experts in legal and insurance matters or coroners (the composition of the institutional ethical work group varies). Clearance was provided by the institutional ethics committee within about four weeks. In addition, an approval was needed from all register controllers of the used registers. Collection of informed consent from the study subjects is not required in this kind of pure register-based study.

ISS, Italy

As for Italy, since the influenza virological surveillance is under the framework of the Influnet surveillance system, the swabs were taken according to national guidelines that fall under routine activities of the GPs, therefore informed consent was not needed to collect specimens. The ethics committee approval was required only to collect the minimum data set needed to fulfil the I-MOVE protocol requests. The protocol was submitted in June 2017 to the National and local (hospital) Ethical Committee and approval was received after approximately four weeks after the submission of the documentation to the national ethical committee. The national ethical committee is based at the ISS and composed of the following professional figures: clinicians, pharmacologist, paediatrician, biostatistician, pharmacist, expert in legal and insurance matters/coroner and an expert in bioethics.

Rioja Salud, Spain

The study is set within the framework of the Spanish Sentinel System of Influenza Surveillance and is included in the surveillance activities of the National Epidemiological Surveillance Network (RENAVE), so it did not need the approval of an ethics committee. However, verbal consent was obtained from all patients prior to data collection and participants had the right to refuse participation in the study. Participants in the study were provided with general information about the study and informed about the use of the data.

FISABIO, Spain

The annual studies that have been conducted in the Valencia region, Spain, were approved seven years ago. In order for the study to be performed, the study protocol had to be accepted by the Ministry of Health and by the National Ethics Committee. It took approximately six weeks to receive the approval after the submission of the documentation to the ethics committee. The National Ethics Committee is composed by clinicians, lay persons, pharmacologists, GPs, paediatricians, pharmacists, lawyer and epidemiologists.

5 Results

5.1 Assembly of the DRIVE research platform

Since 2017/18 was the first influenza season of the DRIVE consortium, the research platform had to be built and developed. The principles of the platform were laid out in the DRIVE Document of Action. A separate work package (WP7) consisting of non-industry organizations would carry out the studies, whose results would be evaluated by an Independent Scientific Committee (ISC). The industry partners of DRIVE would also review the outputs and provide written comments which the ISC would then accept or reject (Figure 3).

Figure 3. Review process of WP7 deliverables (Source: DRIVE D1.2 Governance Standard Operation Procedures).(WP = work package, SC = steering committee, PMO = project management office)

Due to the limited time from the launch of DRIVE in July 2017 to the beginning of the influenza season, it was decided to use existing site-level study protocols for 2017/18. Nevertheless, harmonized study protocols for TND and cohort studies (D7.1 & D7.2) were developed alongside the first year's studies. A framework for data analysis (D4.1), a data management plan (D4.2), a report template (D4.3) and a generic SAP (D4.4) were developed during the season 2017/18. P95 provided the IT infrastructure needed to share, access and analyse data, complemented with an Electronic Study Support Application (D2.3). The ISC was assembled in January 2018.

From the start of the DRIVE project it was known that DRIVE partners from Italy, Finland and Spain (Valencia) would contribute data to the pilot study (influenza season 2017/ 2018). For the purposes

of this pilot study, a few additional collaborators were sought among European public health institutes; this led to MUW Austria and Spain (La Rioja and Canarias regions) contributing data to the pilot study.

5.2 Influenza vaccines and epidemiology in Europe, 2017/2018

The 2017/2018 Northern hemisphere trivalent vaccines contained the following strains:

- A/Michigan/45/2015 (H1N1)pdm09
- A/Hong Kong/4801/2014 (H3N2)
- B/Brisbane/60/2008 (B/Victoria lineage).

Quadrivalent vaccines contained additionally:

- B/Phuket/3073/2013-like virus (B/Yamagata lineage).

According to ECDC [2] and Flu News Europe [3], influenza viruses circulated at high levels between weeks 52/2017 and 12/2018. The majority of the detected influenza viruses were of type B, and B/Yamagata lineage viruses greatly outnumbered those of the B/Victoria lineage. Different patterns of dominant influenza virus types and A subtypes were observed between the European countries. The majority of severe cases were due to influenza type B virus infection and occurred mostly in persons older than 15 years of age. In laboratory-confirmed influenza cases in Intensive Care Units (ICU), numbers of influenza type A infections were slightly higher than type B infections.

The A(H1N1) and B/Yamagata vaccine components for this season were well matched with the circulating strains. However, there was a partial mismatch between circulating A(H3N2) and B/Victoria strains and the corresponding vaccine component. 42% of circulating A(H3N2) viruses were from subclade 3C.2a1 while 45% of circulating B/Victoria viruses were from a subclade of clade 1A antigenically different from the vaccine component.

Influenza epidemiology reported in the regions where the sites are located are described below. Strain circulation is summarized in Figure 4.

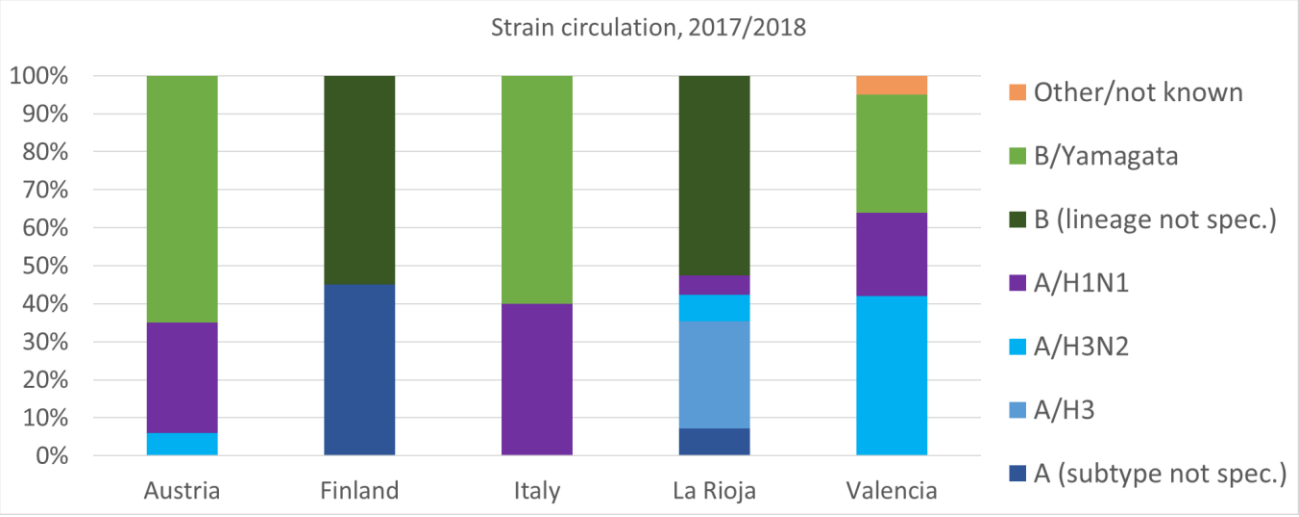


Figure 4. Strains circulating in the areas where the sites included in the pilot are located, 2017/2018

Austria

In Austria, the epidemic period was from 2/2018 to 14/2018, reaching its peak in weeks 5 and 6/2018.

This influenza season was dominated by influenza B/Yamagata viruses (65%), with an observed co-circulation of Influenza A(H1N1)pdm09 (29%) and A(H3N2) (6%).

Finland

In Finland, the epidemic period was from week 52/2017 to week 14/2018. Influenza activity reached high levels in nearly the entire country.

Severe infections occurred most often in people over 65 years of age, and majority of these were A(H3N2).

Overall, 17,017 influenza A cases 20,965 influenza B cases were reported to the National Infectious Diseases Register held by THL. Between November 2017 and mid-February 2018 twice as many influenza B as influenza A was detected. Starting from mid-March, influenza A surpassed influenza B in detections. Most viruses belonged to B/Yamagata lineage and A(H3N2) subtype but there were occasional detections of B/Victoria and A(H1N1)pdm09.

Italy

In Italy, the epidemic period was from week 49/2017 to week 11/2018, reaching its peak in the week 2/2018. The national sentinel surveillance system (InfluNet) reported the highest ILI incidence rate since the seasons 2009/2010 and 2014/2015, peaking at 14.7 cases per 1000 population (ca. 20,000 cases reported by sentinel practitioners in one week).

The highest incidence rate was reported in younger age groups (0-4 and 5-14). The excess mortality reported in the elderly (≥65 years old) for all causes was low during this season in comparison with the previous one. A total of 764 severe cases of confirmed influenza in patients admitted to intensive care, with 173 deaths were reported.

The 2017-18 season in Italy was characterized by a co-circulation of influenza viruses type A/H1N1pdm09 (40%) and B (60%) in particular Yamagata lineage (99.6% of characterized B strains) while a very low circulation of A/H3N2, accounting for less than 1% of total influenza virus detections.

Spain

In Spain, nationwide, information is collected on severe cases of influenza by the Institute of Health Carlos III. 95 hospitals contribute data: in total, they represent 51% of total population of Spain. The majority of cases were registered in the 65+ (66%) years old age group followed by age group 45-64 (20%) years. 88% of patients with available information had risk factors for complications of influenza. 73% of patients with severe infection developed pneumonia, 1,281 cases were admitted to the ICU and 991 died. A total of 5,977 severe cases were reported in 2017/18: 55% influenza B and 45% influenza A. Of influenza A, 63% were A(H3N2) and 37% A(H1N1)pdm09. Of the patients belonging to target groups for vaccination, more than 50% had not received the seasonal influenza vaccine.

In the Valencia region, the epidemic period was from week 45/2017 to week 20/2018, reaching its peak in the week 04/2018.

The season was characterized by co-circulation of influenza A(H1N1)pdm09, A(H3N2) and B/Yamagata-lineage; Influenza A(H3N2) and B/Yamagata appeared first and influenza A(H1N1)pdm09 arrived in the second half of the season. Laboratory-confirmed influenza detections

in hospitalized patients in Valencia were most often from influenza A(H3N2) (42%), followed by B/Yamagata (31%) and A(H1N1)pdm09 (22%).

In the La Rioja region, the epidemic period was from week 51/2017 to week 13/2018, reaching its peak in the week 2/2018. During the peak week, the maximum incidence was 533 ILI cases per 100,000 population.

Both influenza A and B viruses circulated during the season. Influenza B accounted for 53% of the detections. Influenza A accounted for 47% of detections. Among all influenza A, 60% were A(H3), 14.7% A(H3N2), 11% A(H1N1)pdm09 and 15% A not subtyped.

5.3 Descriptive analyses

Baseline characteristics of cases and controls from TND studies are shown in Table 13 and exposed and unexposed subjects from the cohort study are shown in Table 14.

La Rioja was a small study site, with fewer than 300 cases and controls. On the other hand, the Finnish register used in the study covers the entire country's population (in the selected age group) and is therefore very large.

The cases and controls enrolled in Valencia, the only hospital-based TND study site, tended to be older, with chronic conditions and hospitalization in the past year, and were also more frequently vaccinated in the previous season (Appendix 9.8).

Table 13. Characteristics of laboratory confirmed cases, overall and by influenza type, and test negative-controls, 2017/2018

Characteristic		Cases N (%)			Controls N (%)	Cases ALL/Controls ratio
		Influenza all*	Influenza A	Influenza B		
Age group						
	0-14 y	1085 (38%)	432 (40%)	654 (37%)	635 (25%)	0.59
	15-64 y	1254 (44%)	387 (36%)	871 (49%)	982 (37%)	0.78
	65 + y	516 (18%)	267 (25%)	249 (14%)	1003 (38%)	1.94
Sex						
	Female	1399 (49%)	537 (49%)	863 (49%)	1189 (45%)	0.85
	Male	1456 (51%)	549 (51%)	911 (51%)	1431 (55%)	0.98
Any chronic condition						
	Yes	1000 (35%)	451 (41%)	550 (31%)	1434 (55%)	1.43
	No	1836 (64%)	629 (58%)	1211 (68%)	1174 (45%)	0.64
	Unknown	19 (1%)	6 (1%)	13 (1%)	12 (0%)	0.63
Influenza vaccination status in previous season						
	Vaccinated	433 (15%)	224 (21%)	211 (12%)	808 (31%)	1.87
	Unvaccinated	2376 (83%)	847 (78%)	1532 (86%)	1769 (68%)	0.74
	Unknown	46 (2%)	15 (1%)	31 (2%)	43 (2%)	0.93
Number of hospitalizations in the previous 12 months						
	0	1711 (60%)	628 (58%)	1088 (61%)	1560 (60%)	0.91
	1-5	151 (5%)	93 (9%)	58 (3%)	450 (17%)	2.98
	>5	2 (0%)	0 (0%)	1 (0%)	9 (0%)	4.50
	Unknown	991 (35%)	364 (34%)	627 (35%)	601 (23%)	0.61
Influenza vaccination status in current season						
	Vaccinated					
	Brand A	28 (6%)	12 (5%)	16 (7%)	16 (2%)	0.57
	Brand B	19 (4%)	3 (1%)	16 (7%)	21 (3%)	1.11
	Brand C	124 (28%)	70 (31%)	54 (25%)	289 (35%)	2.33
	Brand D	1 (0%)	0 (0%)	1 (0%)	3 (0%)	3.00
	Brand E	16 (4%)	3 (1%)	13 (6%)	13 (2%)	0.81
	Brand F	1 (0%)	0 (0%)	1 (0%)	0 (0%)	0
	Brand G	188 (43%)	114 (51%)	74 (34%)	424 (52%)	2.26
	Brand H	16 (4%)	4 (2%)	12 (5%)	21 (3%)	1.31
	Brand I	11 (3%)	3 (1%)	8 (4%)	9 (1%)	0.82
	Brand J	16 (4%)	6 (3%)	10 (5%)	11 (1%)	0.69
	Unknown	20 (4%)	8 (4%)	12 (5%)	15 (2%)	0.75
	Unvaccinated	2415	863	1555	1798	0.74
Study-site						
	MUW, Austria	756 (26%)	263 (24%)	493 (28%)	442 (17%)	0.58
	ISS, Italy	1464 (51%)	446 (41%)	1023 (58%)	905 (34%)	0.62
	FISABIO, Spain	436 (15%)	298 (27%)	138 (8%)	1181 (45%)	2.71
	Rioja Salud, Spain	199 (7%)	79 (7%)	120 (7%)	92 (4%)	0.46
Total		2855	1086	1774	2620	0.92

*influenza all includes influenza A, influenza B and influenza undefined. Co-infections are only counted once.

Table 14. Characteristics of vaccinated and unvaccinated cases, cohort study, Finland, 2017/2018

		Vaccinated (n)				Unvaccinated (n)			
		All	A	B	Person years	All	A	B	Person years
Age group									
	6m – 2y	223	134	94	12733	664	317	355	32431
	65+ y	5485	3239	2285	228661	6945	3547	3462	256224
Sex									
	Female	3064	1779	1311	134992	4304	2188	2157	160370
	Male	2644	1594	1068	106402	3305	1676	1660	128285
Any chronic condition									
	Yes	5121	3043	2117	179296	6001	3111	2947	170952
	No	587	330	262	62098	1608	753	870	117703
Influenza vaccination status in previous season									
	Vaccinated	4441	2682	1791	4441	1385	776	624	40034
	Unvaccinated	1267	691	588	47698	6224	3088	3193	248620
Vaccine received									
	Brand A	138	78	60	5222				
	Brand B	65	58	10	4532				
	Brand C	5450	3205	2285	229266				
Number of hospitalizations in previous 12 months									
	0	3743	2252	1519	201409	5183	2592	2636	247597
	1-5	1902	1087	830	39420	2341	1228	1140	40381
	>5	63	34	30	565	85	44	41	677

The attrition diagram for the combined individual-level TND data for the exploratory objective is shown in Figure 5. Site-specific attrition diagrams are presented in Appendix 9.8.

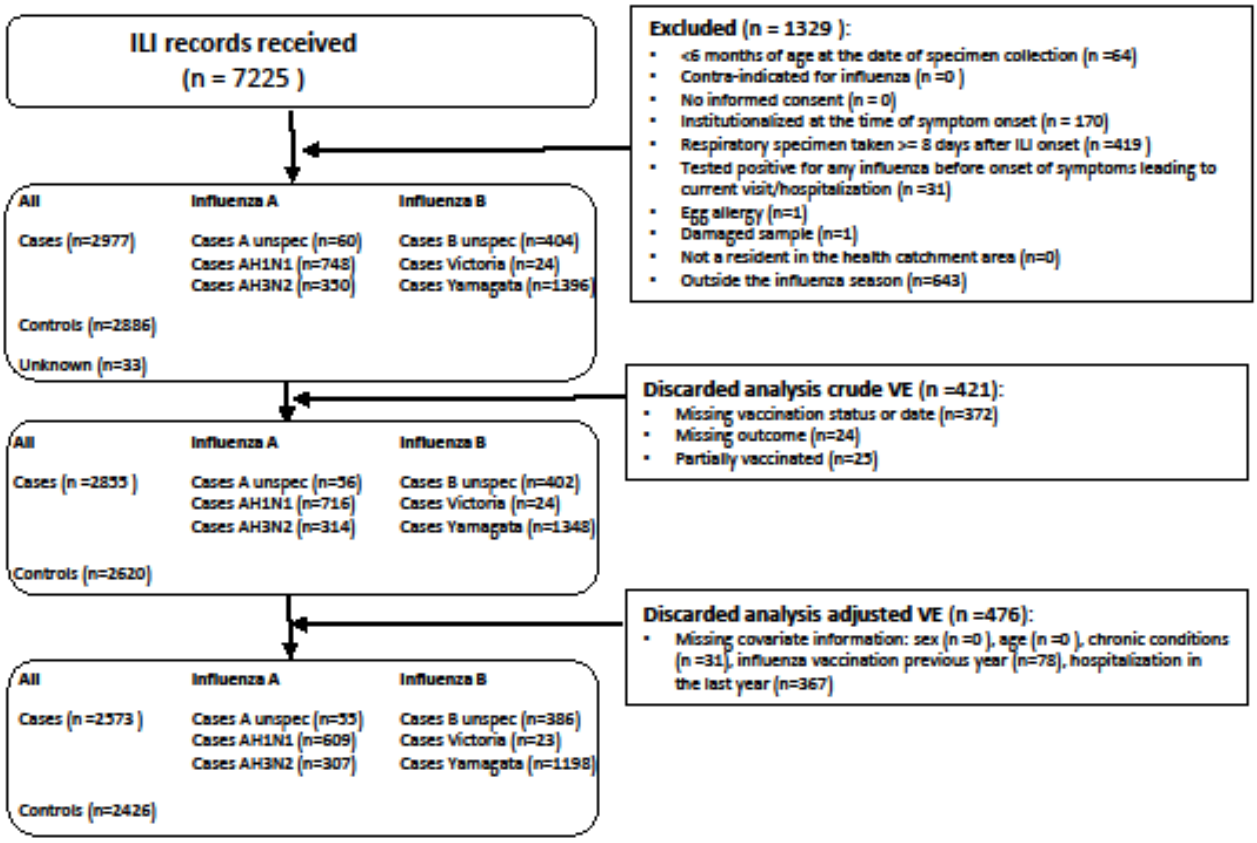


Figure 5. Attrition diagram for the combined individual-level TND data

Availability of influenza vaccine types and brands is shown in Table 15 and Figure 6. Austria and Italy had the higher diversity of vaccines brands, with 7 or 8 brands used in each, whereas 1 or 2 brands accounted for the majority of vaccines used in Finland, Italy and La Rioja. Austria and Italy had the higher diversity of vaccine brands with 7 vaccine brands in use each. Live attenuated vaccines were only used in children aged 2 to 23 months in Finland.

Table 15. Availability of influenza vaccine types for each study site, 2017/18 season

		Vaccine type available		
	Valency	Inactivated, Live attenuated	Sub-unit, Split virion	Adjuvants
MUW, Austria	Trivalent Quadrivalent	Inactivated	Sub-unit Split virion	Non-adjuvanted Adjuvanted
THL, Finland	Trivalent Quadrivalent	Inactivated Live attenuated	Sub-unit	Non-adjuvanted
ISS, Italy	Trivalent Quadrivalent	Inactivated	Sub-unit Split virion	Non-adjuvanted Adjuvanted
Rioja Salud, Spain	Trivalent	Inactivated Inactivated	Split virion Subunit	Non-adjuvanted Adjuvanted
FISABIO, Spain	Trivalent	Inactivated	Sub-unit	Non-adjuvanted Adjuvanted

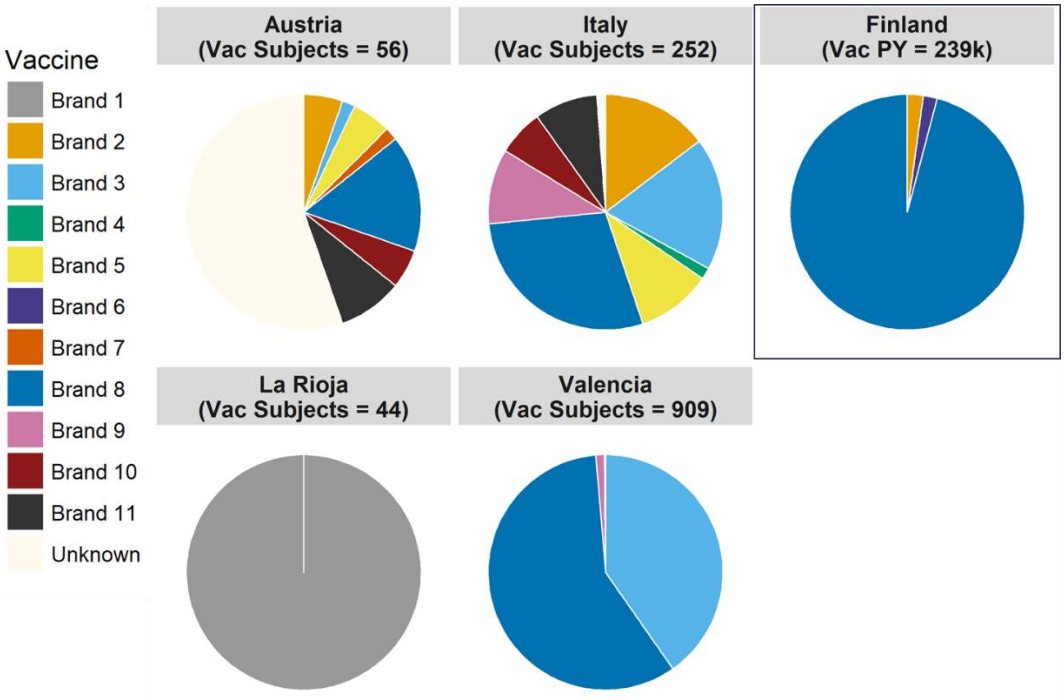


Figure 6. Overview of influenza vaccines used at sites included in the pilot, 2017/2018.

5.4 Results of primary objectives

The site-specific adjusted IVE estimates (and 95% CIs) complemented with the meta-analyzed adjusted IVE estimates (and 95% CIs) are presented using forest plots in Figures 9-20. Crude site-specific IVE estimates and crude meta-analyzed estimates are presented in Appendix 9.8.

5.4.1 Considerations for results interpretation

Differences in study characteristics and circulating strains

The small number of studies included in the meta-analysis in the pilot year limited the number of possible brand-specific estimates and stratifications (e.g. by both brand and age, or brand and setting). The complexity of interpreting pooled brand-specific IVE estimates is illustrated for brand B in Figure 7. It shows the interplay of several important characteristics such as healthcare settings capturing influenza cases of different levels of severity, age, and varying patterns of influenza circulation across Europe affecting the match between the circulating vs. the vaccine strain. These heterogeneous characteristics exist against a backdrop of different vaccine recommendations across the sites, both in terms of groups targeted for vaccination and vaccine type recommended for use.

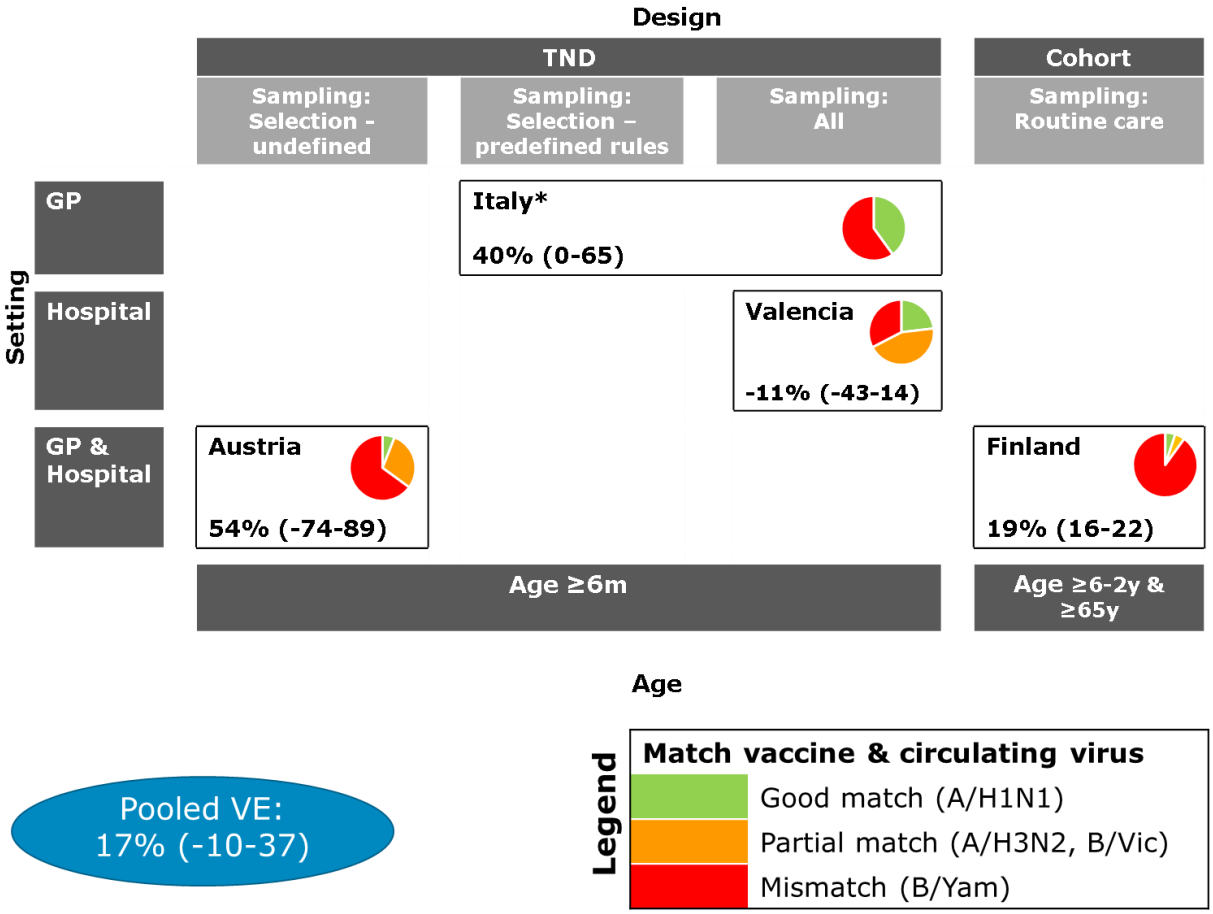


Figure 7. Complexity of interpreting pooled brand-specific IVE for brand B. **Sampling strategy depends on age*

Differences in covariate adjustment

The covariates that were considered for adjustment were age group, sex, presence of chronic conditions, number of hospitalizations in previous 12 months (except for Austria), and vaccination status in previous season. The covariates adjusted for in the final model for each site-specific estimate are presented in Figure 8.

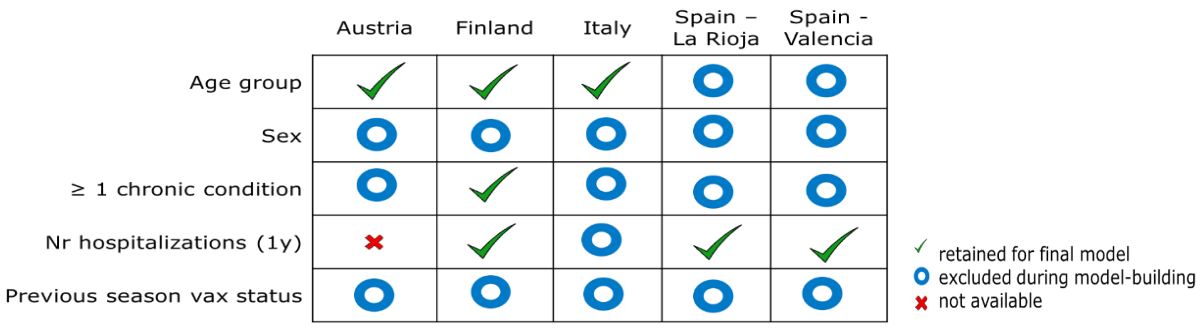


Figure 8. Covariates adjusted for in final site-specific models, 2017/2018

5.4.2 IVE by any vaccine and by vaccine brand

The forest plot and pooled adjusted estimates of overall IVE for any vaccine and by vaccine brand are shown in Figure 9. Due to small numbers, brand-specific pooled analyses were only performed for two brands, the remaining brands were combined as 'other'.

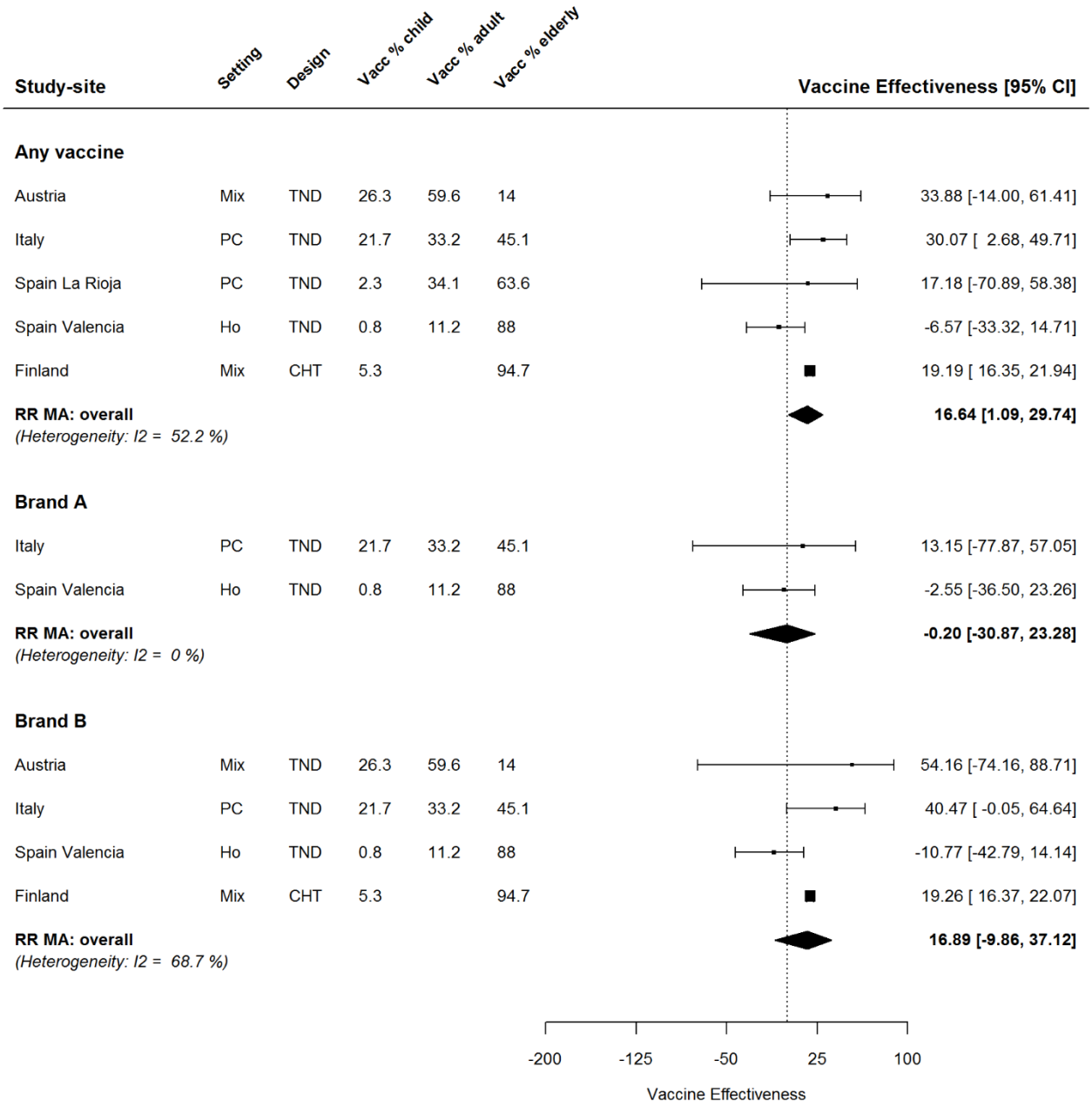


Figure 9. Forest plot and meta-analyses of overall influenza vaccine effectiveness by any vaccine and vaccine brand, adjusted estimates, 2017/2018

5.4.3 IVE by vaccine antigen (live attenuated, inactivated)

The forest plot and pooled adjusted IVE estimates of inactivated and live attenuated vaccine are shown in Figure 10. Note that whilst LAIV vaccine is only indicated for children, the estimates were not stratified by age, nor restricted by age groups. This warrants caution when interpreting the results.

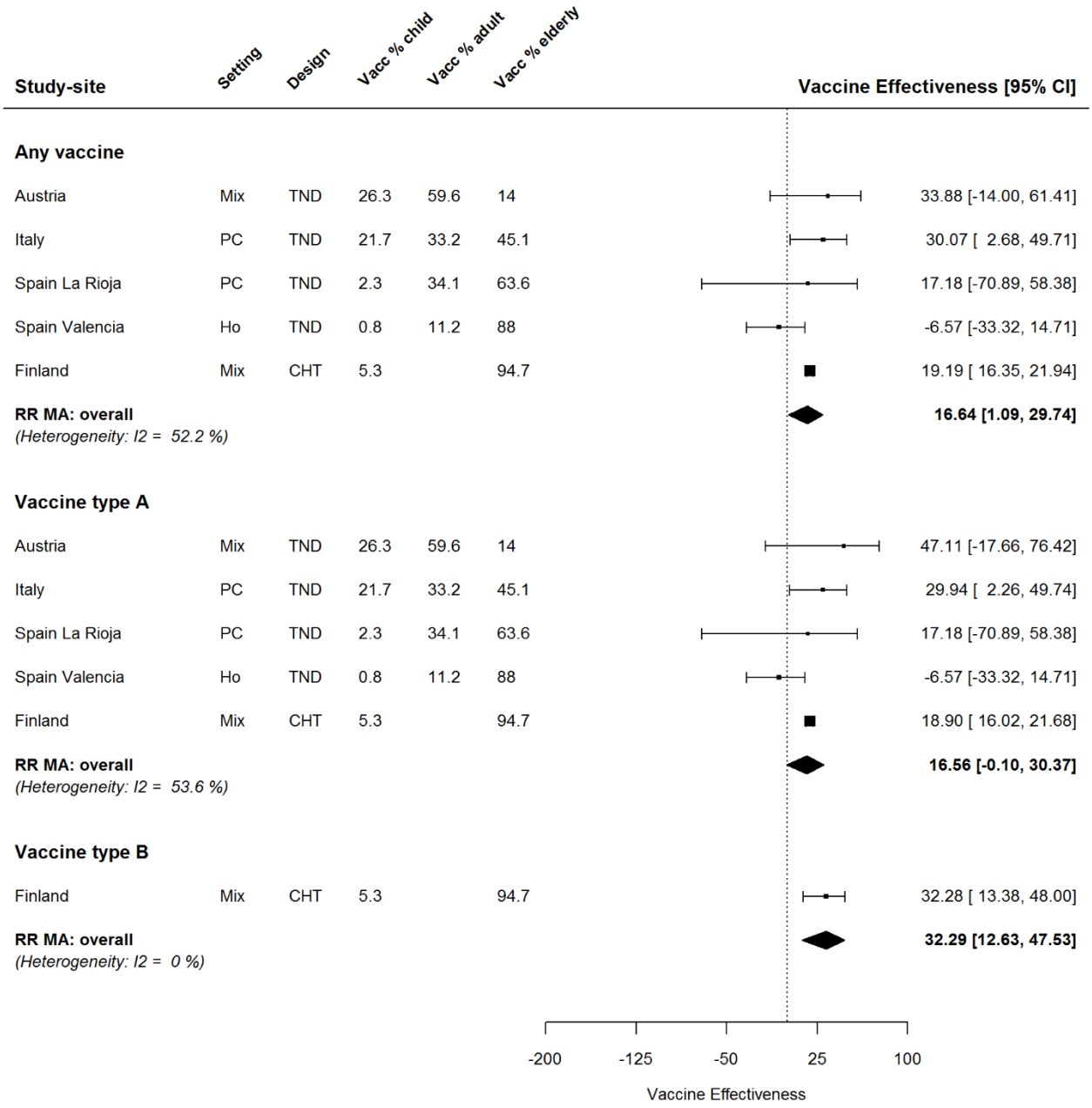


Figure 10. Forest plot and meta-analyses of overall influenza vaccine effectiveness by vaccine antigen (live attenuated, inactivated), adjusted estimates, 2017/2018

5.4.4 IVE by vaccine antigen (subunit, split virion)

The forest plot and pooled adjusted IVE estimates of subunit and split-virion vaccines are shown in Figure 11.

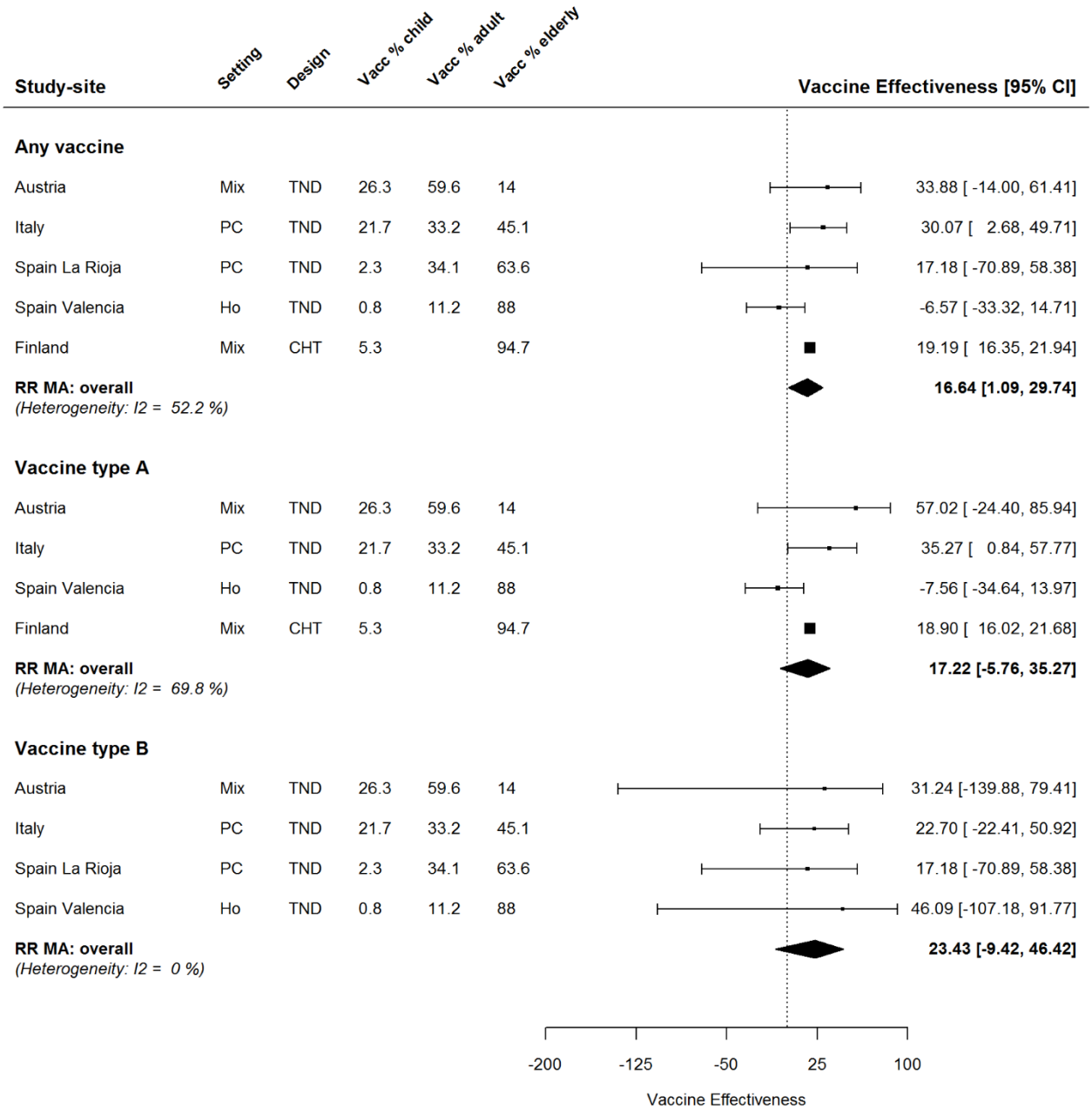


Figure 11. Forest plot and meta-analyses of overall influenza vaccine effectiveness by vaccine antigen (subunit, split virion), adjusted estimates, 2017/2018

5.4.5 IVE by vaccine valency

The forest plot and pooled adjusted IVE estimates of trivalent and quadrivalent vaccines are shown in Figure 12.

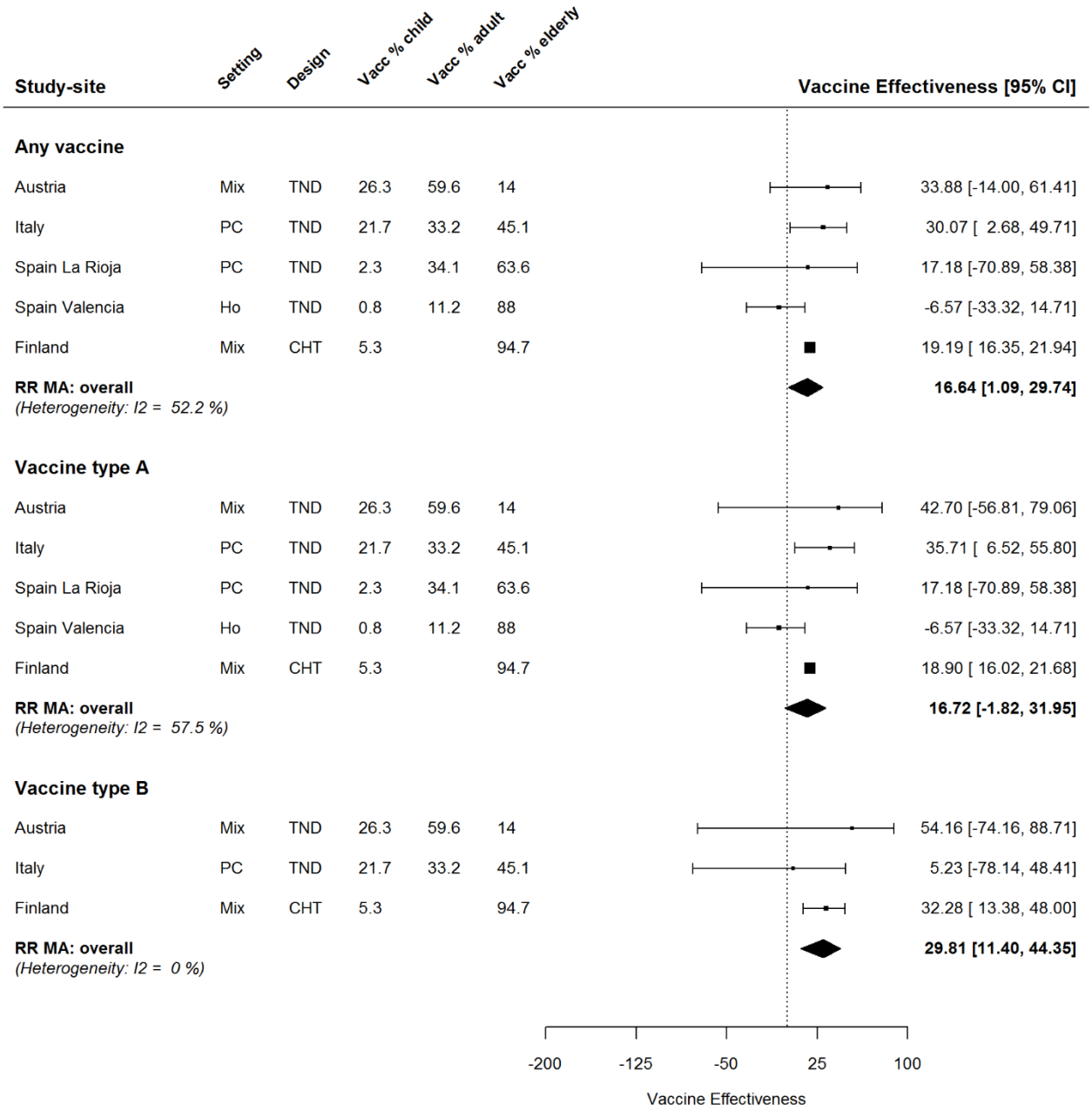


Figure 12. Forest plot and meta-analyses of overall influenza vaccine effectiveness by valency, adjusted estimates, 2017/2018

5.4.6 IVE by vaccine type (adjuvanted, non-adjuvanted)

The forest plot and pooled adjusted IVE estimates of adjuvanted and non-adjuvanted vaccines are shown in Figure 13.

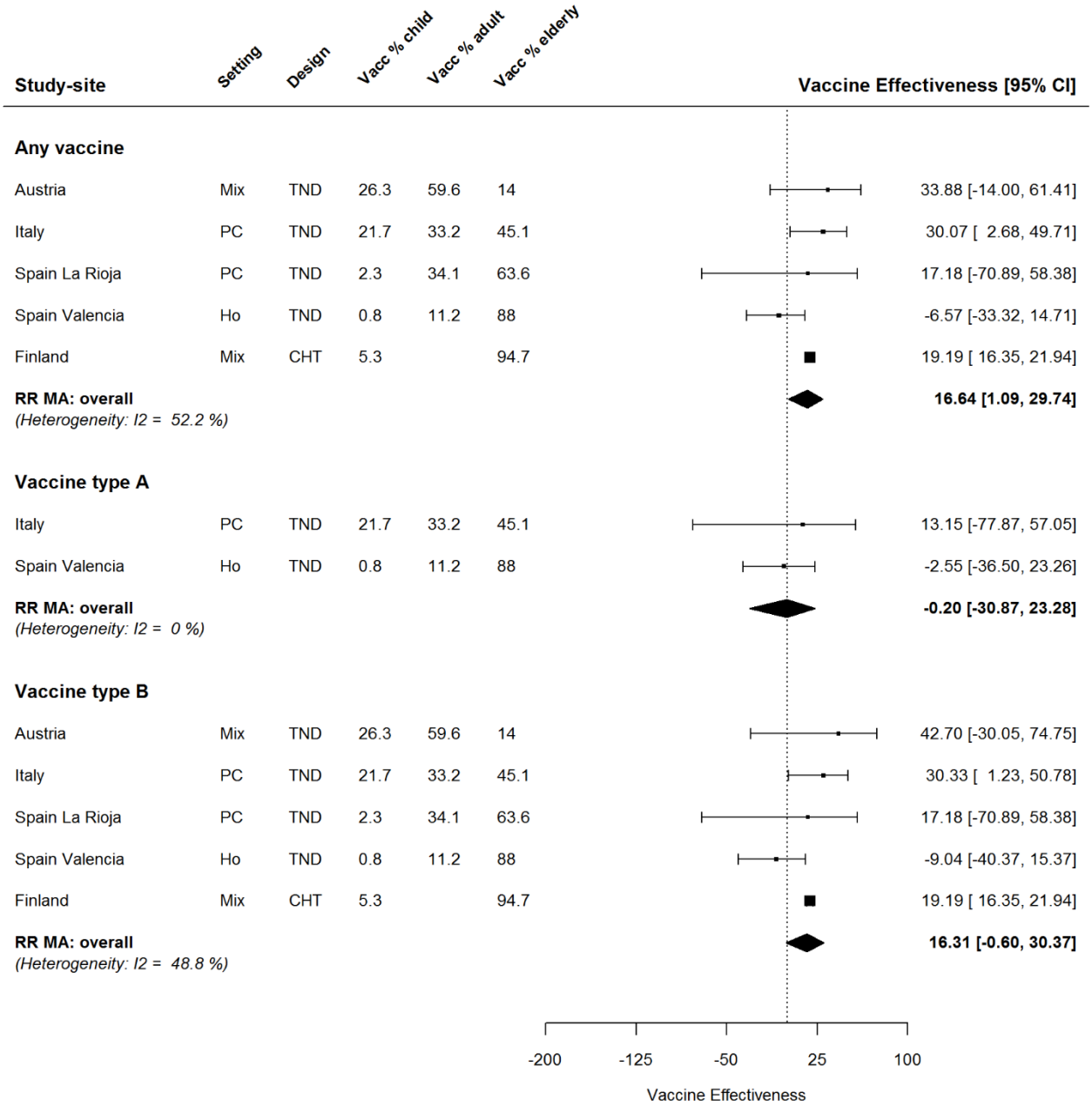


Figure 13. Forest plot and meta-analyses of overall influenza vaccine effectiveness by vaccine type (adjuvanted, non-adjuvanted), adjusted estimates, 2017/2018

5.5 Results of secondary objectives

The site-specific IVE estimates (and 95% CIs) complemented with the meta-analyzed IVE estimates (and 95% CIs) are presented using forest plots in Figures 7-11.

5.5.1 IVE by age group

The forest plot and pooled adjusted IVE estimates by age group are shown in Figure 14.

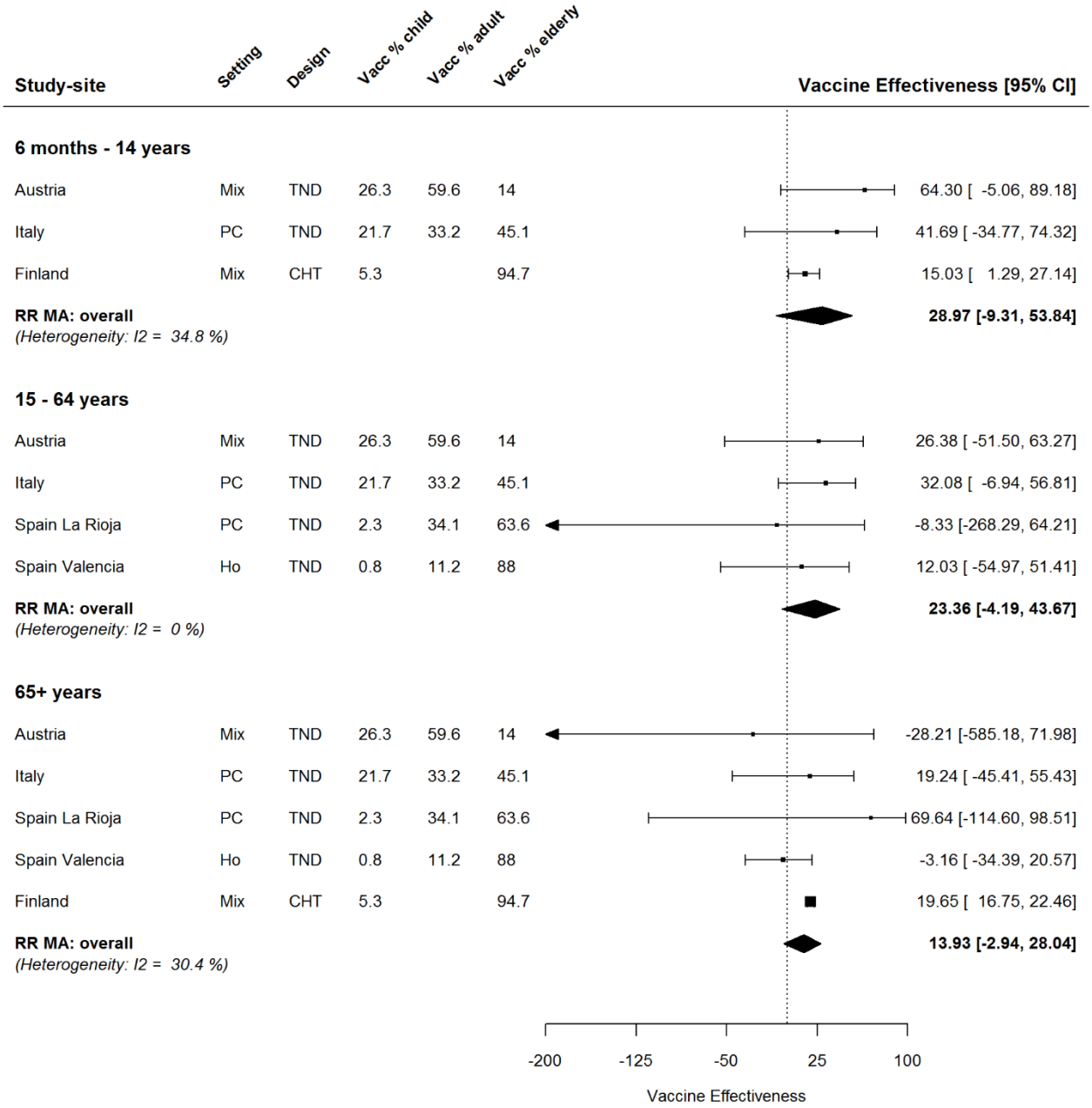


Figure 14. Forest plot and meta-analyses of overall influenza vaccine effectiveness by any vaccine, by age groups, adjusted estimates, 2017/2018

5.5.2 IVE by presence of at least one chronic condition

The forest plot and pooled adjusted IVE estimates by presence of at least one chronic condition or pregnancy are shown in Figure 15.

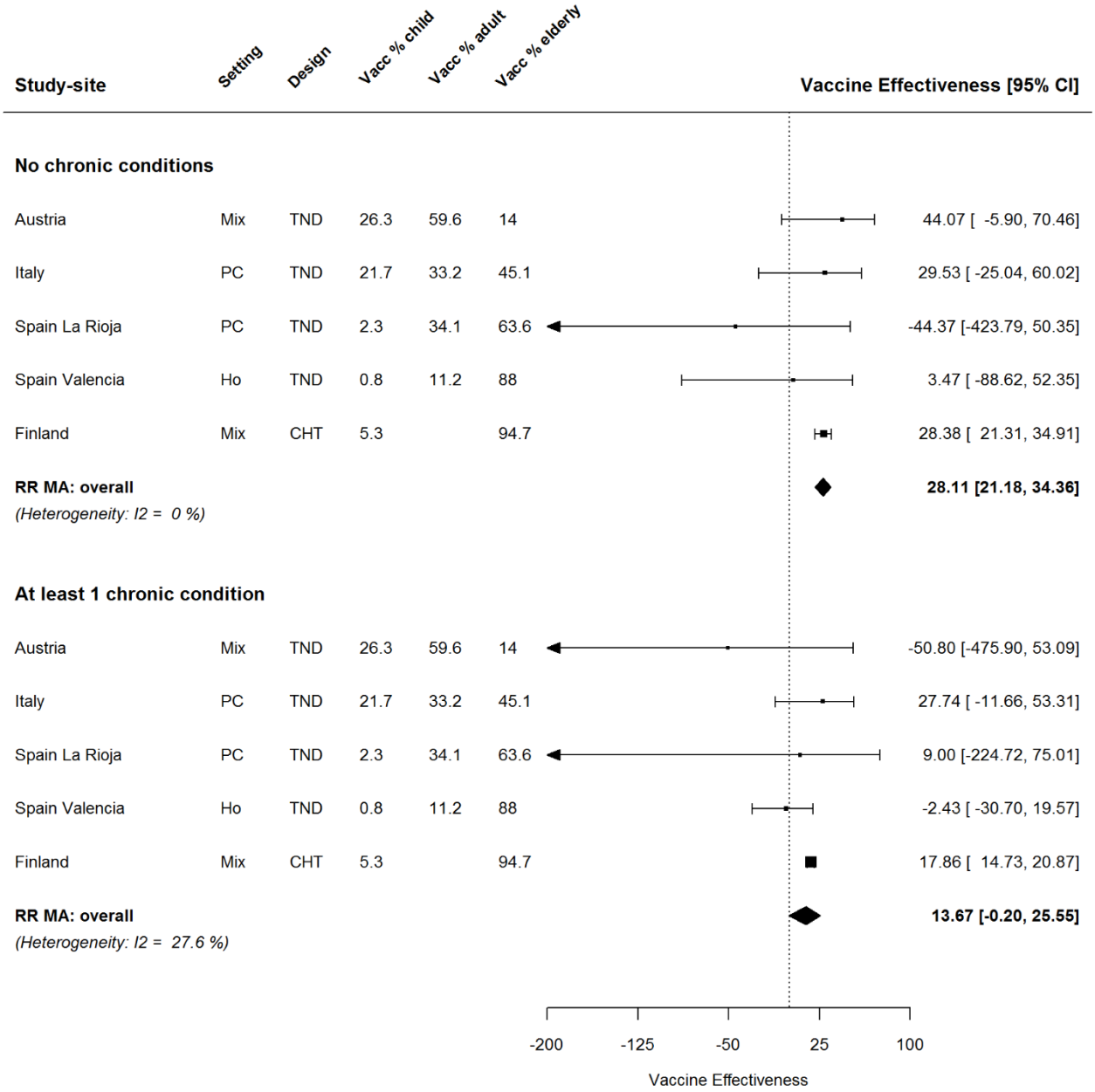


Figure 15. Forest plot and meta-analyses of overall influenza vaccine effectiveness by any vaccine, by absence or presence of at least one chronic condition or pregnancy, adjusted estimates, 2017/2018

5.5.3 IVE by previous influenza vaccination status

The forest plot and pooled adjusted IVE estimates by vaccination status in the previous season are shown in Figure 16.

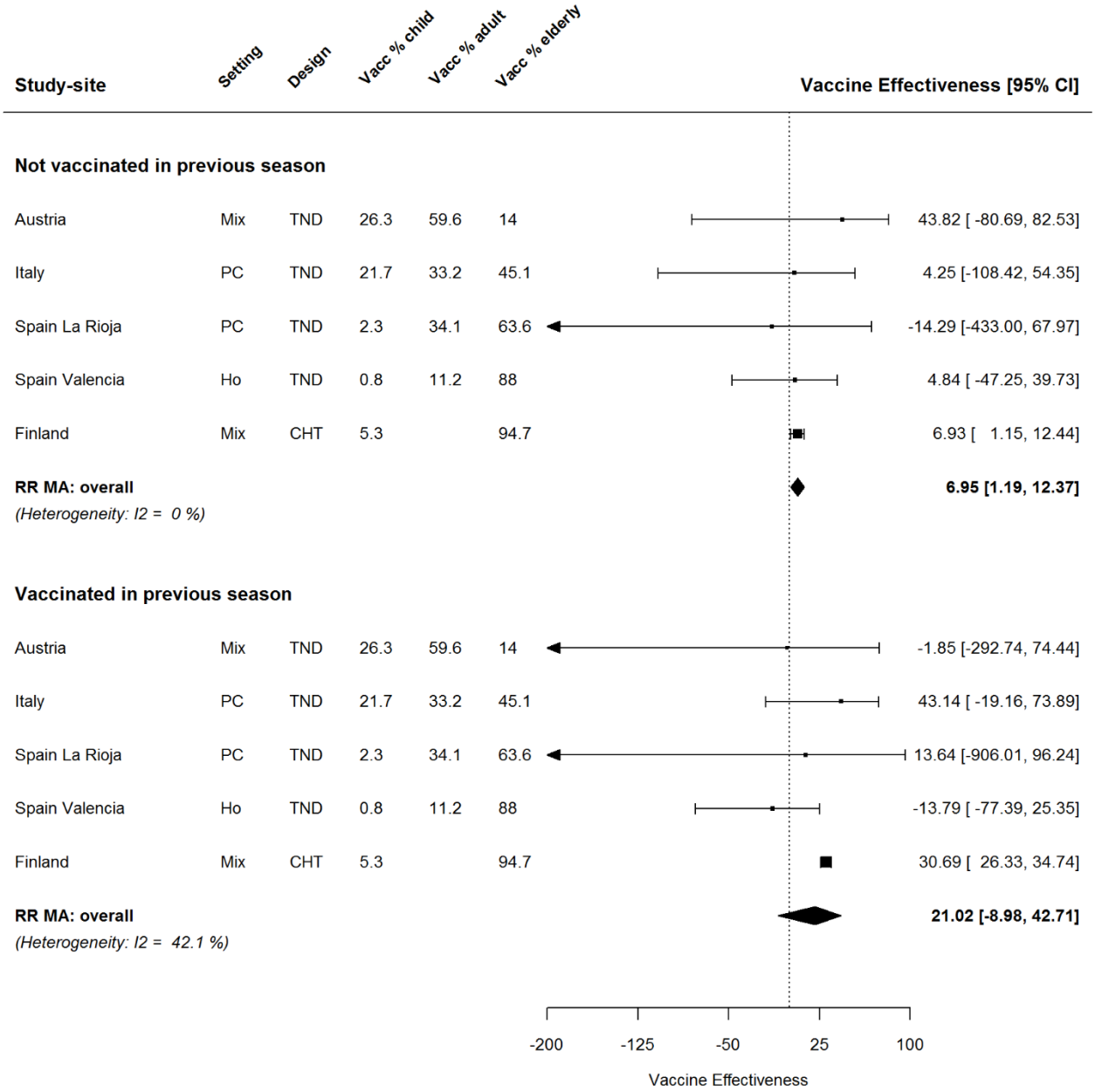


Figure 16. Forest plot and meta-analyses of overall influenza vaccine effectiveness by any vaccine, by previous influenza vaccination status, adjusted estimates, 2017/2018

5.5.4 IVE by influenza type and subtype

The forest plot and pooled adjusted IVE estimates by influenza type, by influenza A subtypes and by influenza B lineages are shown in Figures 17-19.

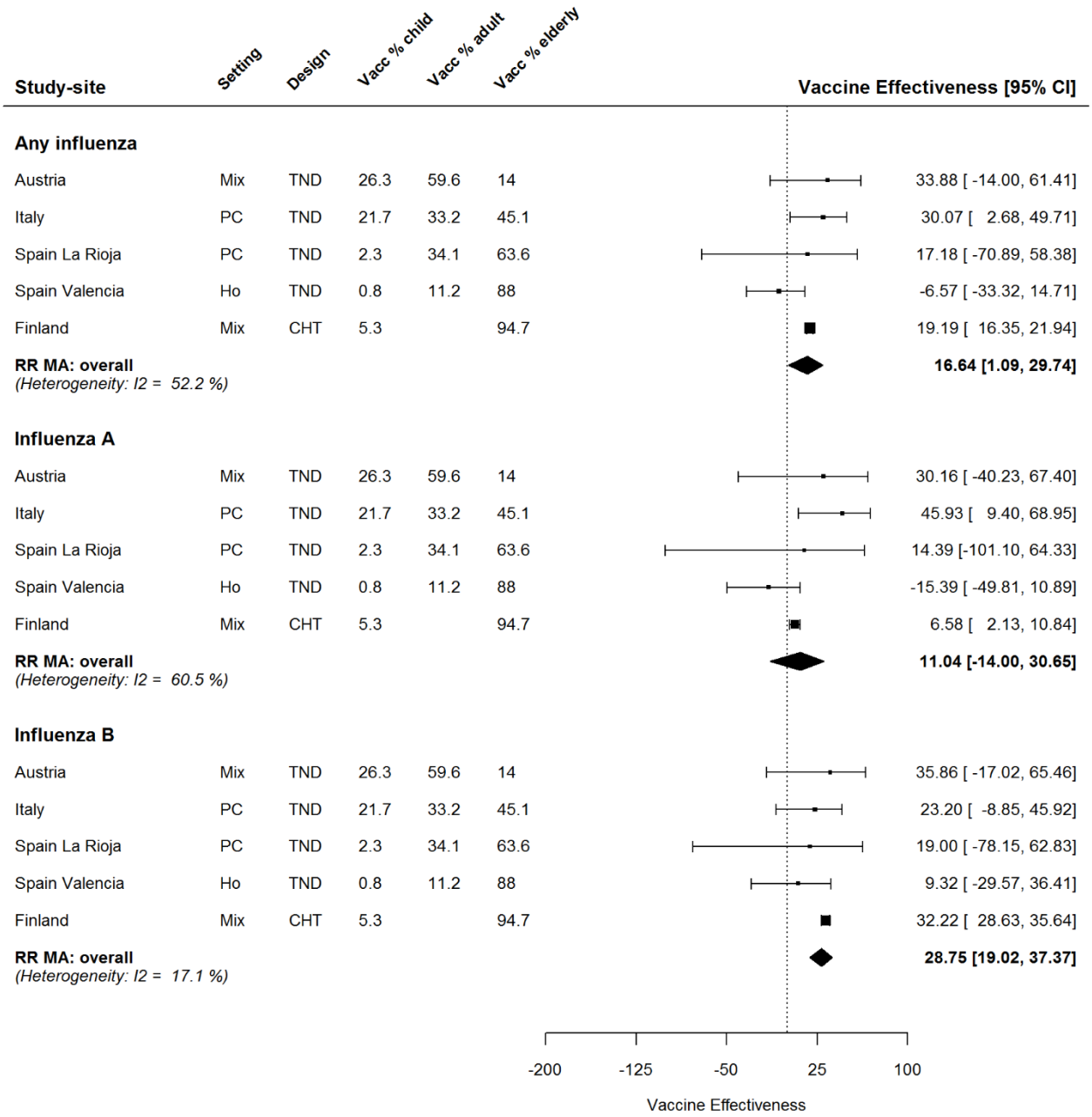


Figure 17. Forest plot and meta-analyses of overall influenza vaccine effectiveness for any vaccine, by influenza type, adjusted estimates, 2017/2018

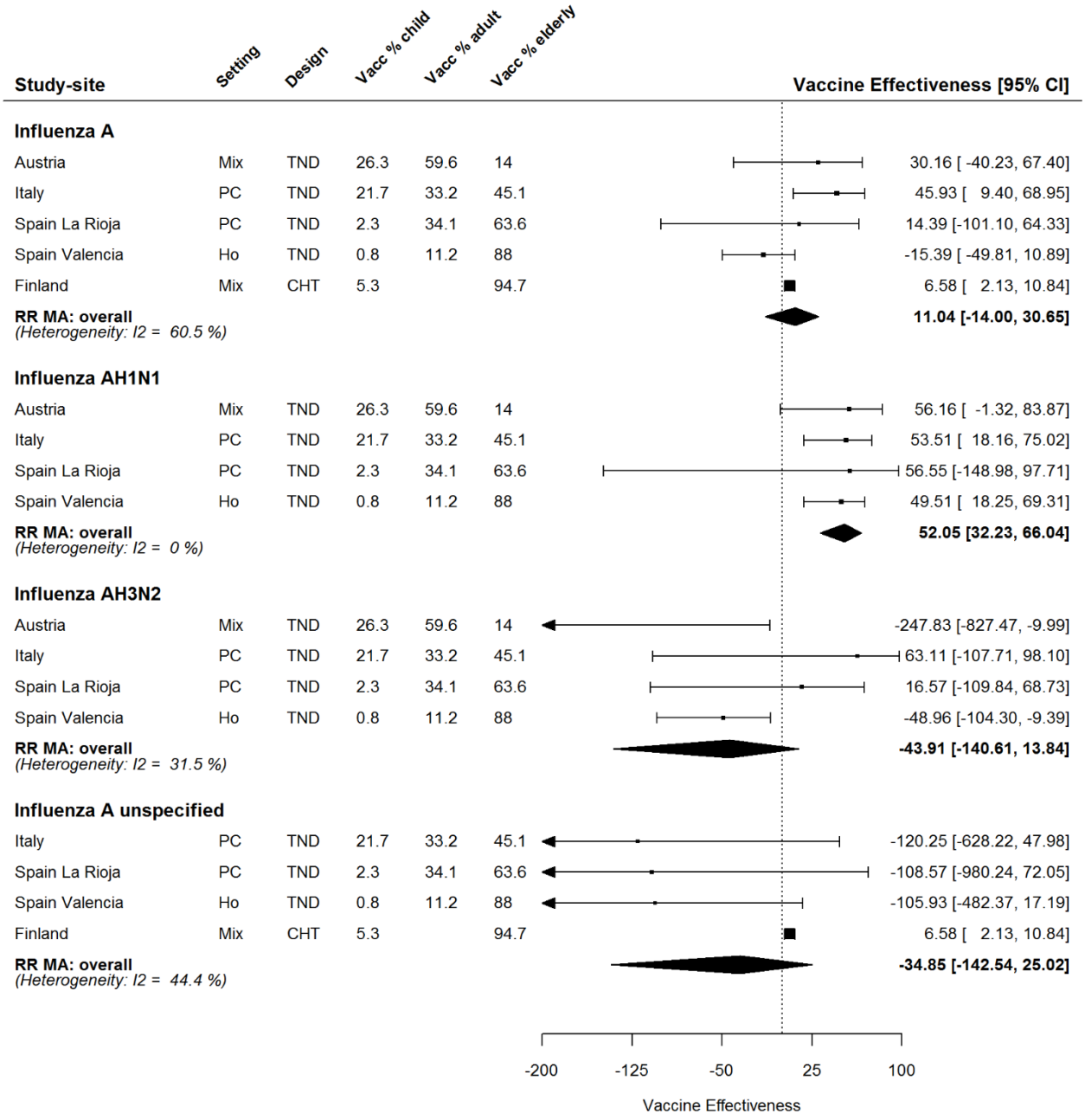


Figure 18. Forest plot and meta-analyses of overall influenza vaccine effectiveness for any vaccine, by influenza A subtypes, adjusted estimates, 2017/2018

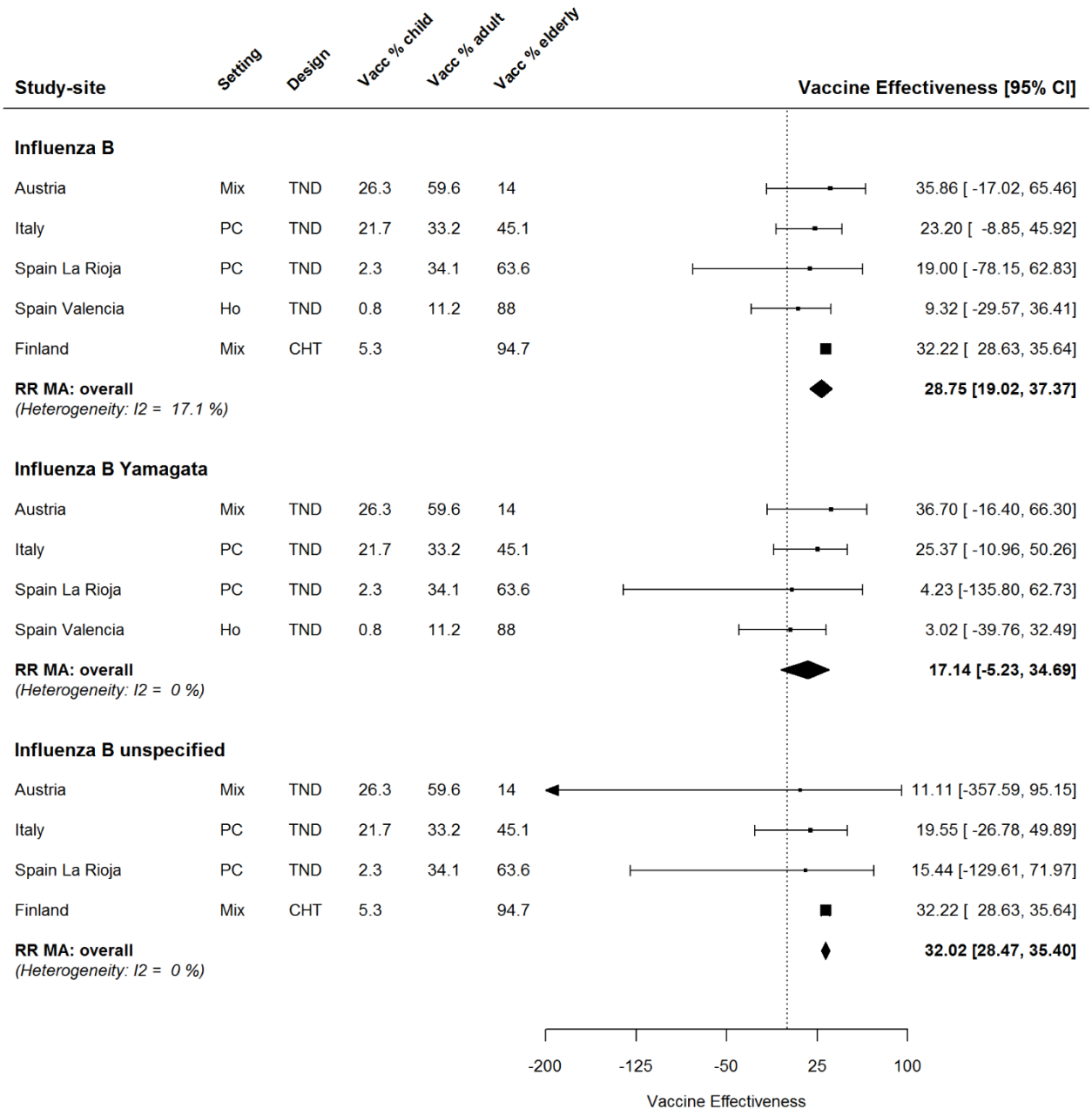


Figure 19. Forest plot and meta-analyses of overall influenza vaccine effectiveness for any vaccine, by influenza B lineages, adjusted estimates, 2017/2018

5.5.5 IVE by healthcare setting

The forest plot and pooled adjusted IVE estimates by health care setting are shown in Figure 20.

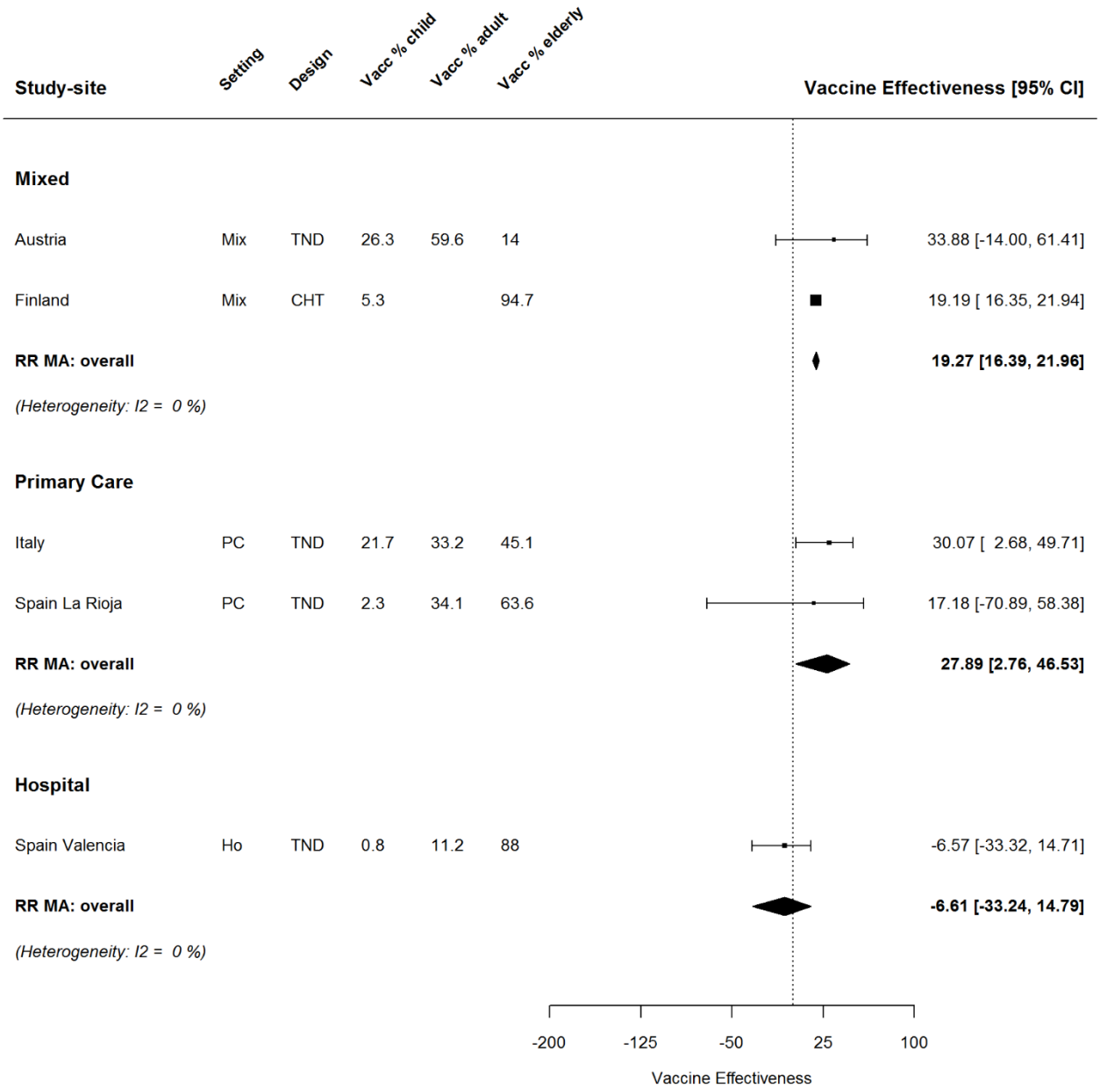
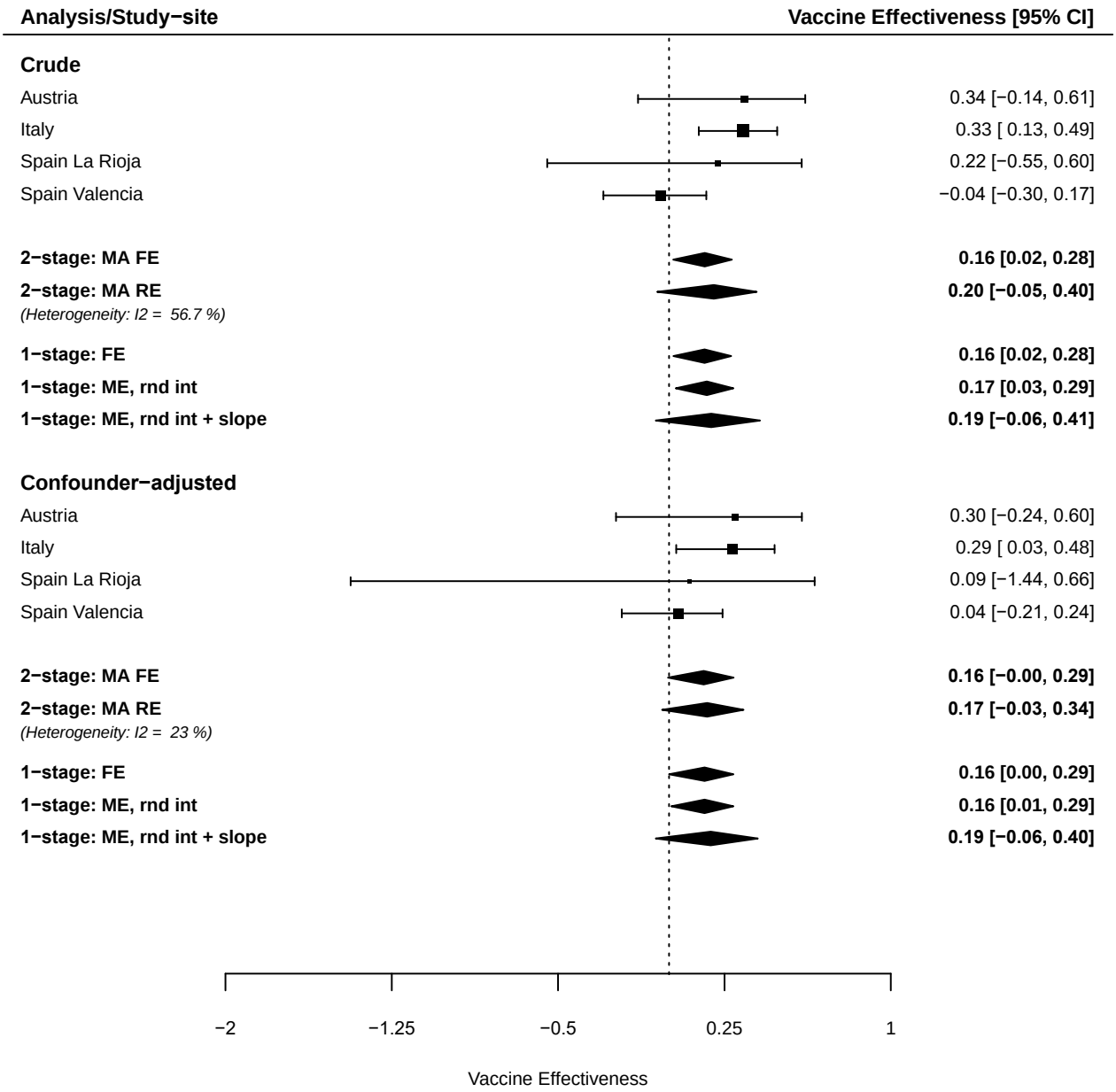


Figure 20. Forest plot and meta-analyses of overall influenza vaccine effectiveness by any vaccine, by healthcare setting, adjusted estimates, 2017/2018

5.6 Exploratory objectives

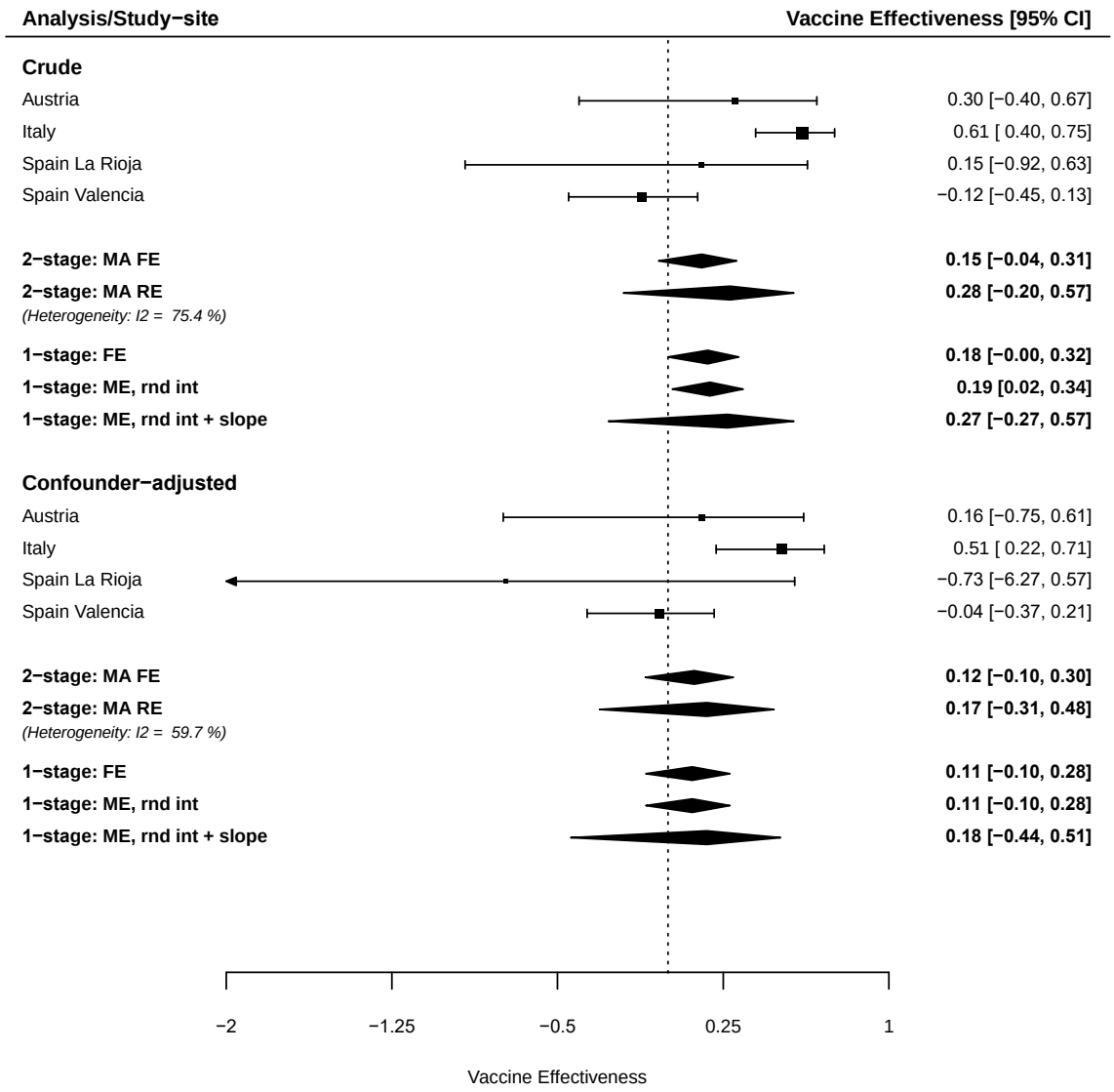
5.6.1 Comparison of 1-stage and 2-stage pooling approaches

The results of the comparison of pooling approaches were in line with expectations based on statistical theory, with identical to very similar results in main effect and 95% CIs for all models assuming the same IVE across study sites, being the fixed effects meta-analysis model and the 1-stage fixed effects model and the 1-stage random intercept model (Figures 21, 22, 23). Also both models allowing for differences in study-site specific IVE estimates beyond random error, yield similar results. In case of between-study heterogeneity, the models assuming a constant IVE across study sites obtain narrower CIs compared to studies allowing for differences in site-specific IVE estimates beyond random error. The study-site specific IVE estimates against influenza type B do not show heterogeneity (I^2 = 0%), and consequently all models provide similar results.



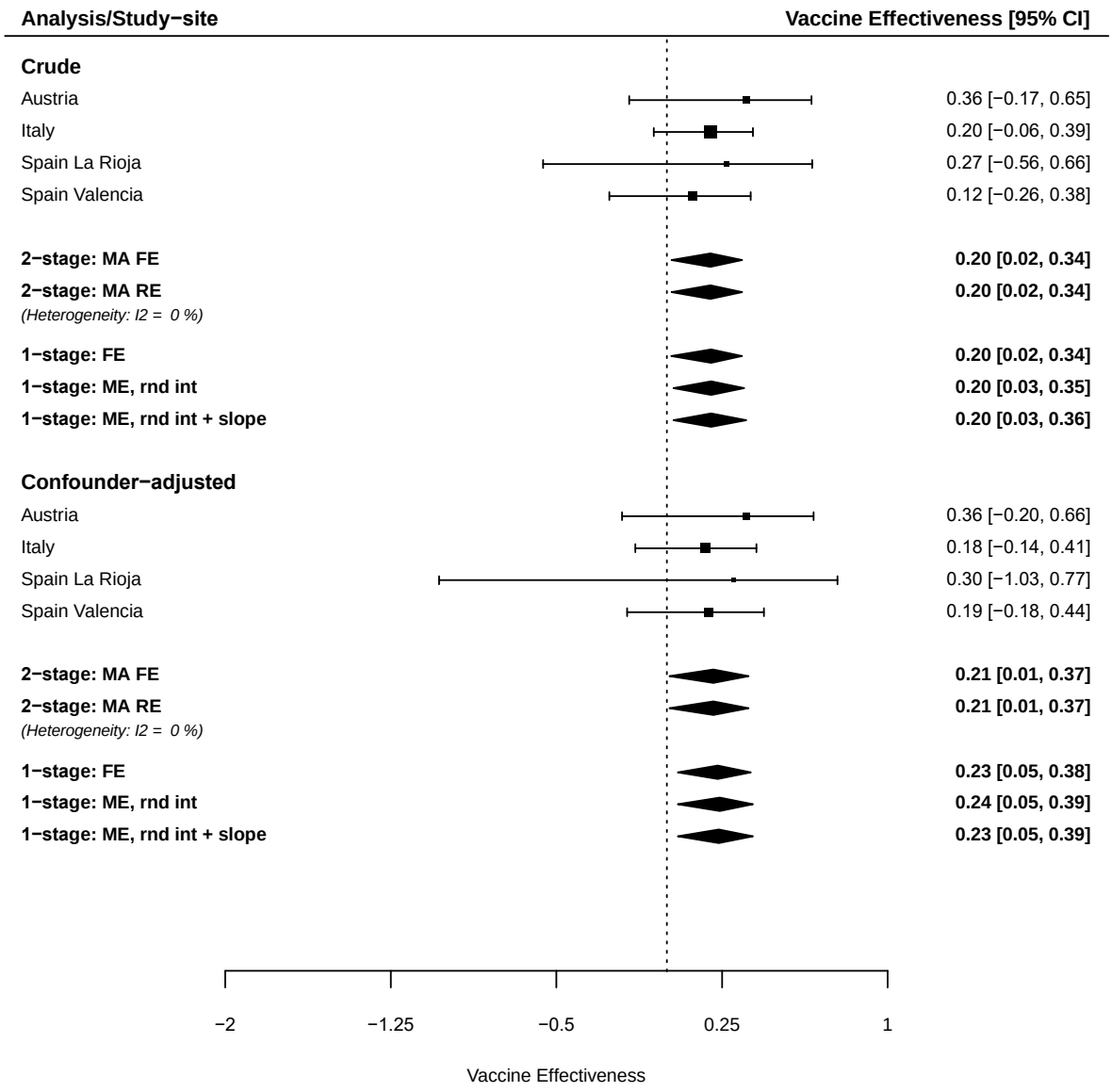
NB: MA: meta-analysis; FE: fixed effects; ME: mixed effects: rnd int: random intercept

Figure 21. Overall influenza vaccine effectiveness by any vaccine: methods comparison 1-stage versus 2-stage pooling



NB: MA: meta-analysis; FE: fixed effects; ME: mixed effects: rnd int: random intercept

Figure 22. Influenza A vaccine effectiveness by any vaccine: methods comparison 1-stage versus 2-stage pooling



NB: MA: meta-analysis; FE: fixed effects; ME: mixed effects: rnd int: random intercept

Figure 23. Influenza B vaccine effectiveness by any vaccine: methods comparison 1-stage versus 2-stage pooling

5.6.2 Time since vaccination

The IVE against AH1N1 was high within the first month after vaccination, and dropped afterwards before reaching higher levels again at 4 months after vaccination (Table 16, Figure 24). The results are unexpected and should be interpreted cautiously as the CIs are wide and time since vaccination co-varies with other time-varying factors (e.g. changes in the influenza virus, other circulating viruses and pathogens). The generalized additive models are an interesting statistical approach as they allow a non-parametric exploration of the effect of time since vaccination and do not require a-priori categorization of the time since vaccination. Further research is required to disentangle factors that might impact the changing IVE over time.

Table 16. Influenza vaccine effectiveness against AH1N1, crude and adjusted estimates

Time since vaccination	Crude		Adjusted	
	est	95%CI	est	95%CI
<=1 mo	85.5	75.1-92.4	69.5	39.2-85.7
2-3 mo	76.3	59.5-87.3	52.9	8.04-77.3
3-4 mo	59.1	35.6-75.4	5.6	-75.3-50.7
>4 mo	91.2	84.3-95.7	6904	37.3-86.3

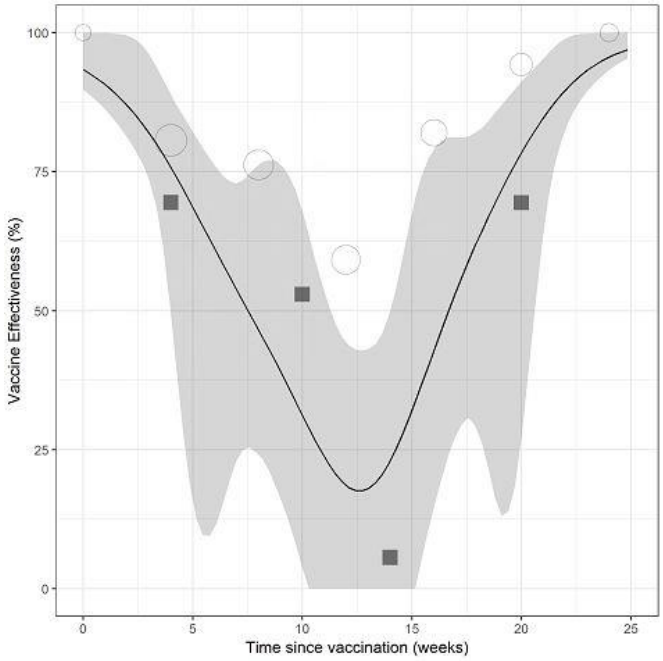


Figure 24. Influenza AH1N1 vaccine effectiveness by time since vaccination

5.7 Sensitivity analysis of primary objective

Full results of the sensitivity analyses are presented in Appendix 9.8. No change in IVE was observed when those who were partially vaccinated were considered vaccinated (1a) or unvaccinated (1b) instead of excluded (main analysis). Excluding patients with swab date >4 days after ILI/SARI onset date increased the point estimates of brand-specific IVE estimates and the IVE estimate for adjuvanted vaccine. No large changes were observed in other point estimates.

6 Discussion

Objectives of the pilot study

The focus of the 2017/18 influenza season for the DRIVE consortium was testing the different operational aspects of the project including the IT infrastructure, the DRIVE governance for conducting IVE studies and streamlining key processes such as data collection, statistical analyses and dissemination of study results.

Achievements of this pilot year

The DRIVE study governance allowed public institutions to contribute data while maintaining their scientific independence. This means that all Work Package 7 activities, which include study protocol development and conduct, data analysis and results reporting are firewalled from EFPIA partners.

In this pilot year, the research platform included data from three partners of the DRIVE consortium and two additional study sites. Generic TND and cohort study protocols were developed and used to inform the SAP on data pooling for this pilot year. As the generic protocols were not ready at the start of the 2017/18 influenza season, they could not be used to steer the data collection of this year. The generic protocols and the SAP for pooling data were reviewed by the ISC.

An IT infrastructure was developed for data sharing, access and analysis. Four sites (all TND studies) shared individual-level data while one site (Finnish cohort study) shared aggregated data. Site-specific IVE estimates were obtained and pooled using random effects meta-analysis. This study report was written by the public partners of DRIVE and reviewed by the DRIVE ISC.

The DRIVE platform has been successfully built and will be expanded in the 2018/2019 season, during which harmonized protocols will be implemented and the number of study sites contributing data will be at least double.

Experiences and next steps: generic protocols

The generic protocols, including minimum data requirements, were developed to inform the protocols at study-site level. It is noted that important heterogeneity will still exist even after the implementation of generic protocols, due to inherent differences between the study sites.

Adherence to minimum data requirements

Adherence to the minimum data requirements and the pre-defined data formats is important to have complete information, to avoid misinterpretation of the shared data and to allow for common statistical analysis, using standardized analysis scripts. In 2017/2018, a substantial amount of time was spent on data cleaning. Next seasons, sites will be encouraged to adhere to the minimum data requirements. To this end, the functionalities of the Electronic Study Support Application (ESSA) will be expanded to allow the sites to perform data cleaning throughout the season. This will enable flagging of potential issues (e.g. non-compliance with minimum data requirements) at an early stage and eventually speed up the analyses once the datasets are received. The inconsistencies found in the pilot season data will help to build the checks for the data cleaning process.

Revisions to minimum data requirements

The minimum data requirements used during the pilot season did not allow to easily report co-infection, this will be revised for the coming season. Furthermore, one site (Austria) initially only reported age in years, and this was not sufficient to apply one of the exclusion criteria (children aged <6 months). The need to provide (information to calculate) age in months for children under the age

of 1 year will also be incorporated in the next version.

Chronic conditions

The conditions included in the covariate “at least one chronic condition” varied across the sites as pre-existing protocols were used. In future seasons, generic protocols will be used and therefore the definition of this covariate will be more harmonized. However, it was felt that even the harmonized list of conditions may be subject to interpretation. For this reason, a working group was set up to provide the sites with more guidance on how to define each of the chronic conditions of interest.

ILI case definition verification

For one site, the ILI case definition could not be verified as information on symptoms was missing. Ideally, ILI case definition verification should take place; the feasibility of collecting information on symptoms will be assessed during the study-site visits.

Experiences and next steps: DRIVE server

A secure IT infrastructure was developed for data sharing, access and analysis. The DRIVE Research Server is a highly secure environment and network, with strict rules for data access. The access to the server is governed by a two-factor authentication process using the DUO Mobile suite. The infrastructure is in accordance to the new General Data Protection Regulation (GDPR) guidelines on storing personal identifier data in a processor role, as well as storing anonymized data. The DRIVE Research Server architecture is based on a Windows Server 2012 running on a virtual server. The DRIVE Research Server was found to be very user-friendly with no time- and location-related access restrictions.

Experiences and next steps: data analysis

All the analyses were performed centrally at the DRIVE server. Centralized data analysis is both time- and human resource efficient and facilitates a common statistical analysis across study sites as analysis scripts can be re-used. Additional analyses and quality checks can be easily performed when having data centrally available. For this pilot year, the data management and cleaning was cumbersome. The expanded Electronic Study Support Application will encourage the adherence to the minimum data requirements. The SAP for the season 2018/2019 will be modified based on the experiences from this pilot study. Additional stratified analyses will likely be possible when additional study sites will contribute data.

Confounder adjustment and model building

Five covariates were considered to calculate confounder-adjusted IVE estimates: age, sex, presence of at least one chronic condition, number of hospitalizations in previous 12 months and influenza vaccination status in the previous season. For each site-specific analysis, confounders were selected through model-building, starting from the full model including all potential confounders listed above and subsequently dropping the least significant ones till only significant terms remained. This resulted in important confounders – such as age – not being included in the final model of some of the sites and that the confounders included in the final models varied across sites. In future analyses, full or partial common confounder adjustment will be considered. Partial common confounder adjustment would require pre-specification of biologically important confounders to be forced into the final model. The model building was done based on the F-statistic, requiring complete cases. Model selection based on e.g. AIC/BIC criteria would not have suffered from this shortcoming.

1-stage vs 2-stage pooling approaches

The IVE estimates obtained using 1-stage versus 2-stage pooling methods yielded comparable results, as expected based on statistical theory. The 2-stage pooling approach is the only approach that allows to easily combine data collected using different study designs. In addition, the 2-stage pooling approach is very transparent regarding the within- and between-study heterogeneity. The major advantage of the 1-stage pooling approach is its modelling flexibility (e.g. using splines to model waning vaccine protection). Both 1-stage and 2-stage pooling approaches can be used to obtain IVE estimates that allow for between-study heterogeneity apart from chance (i.e. random effects meta-analysis in case of 2-stage pooling and mixed effects regression models with random intercept and random vaccination effect estimates by study site in case of 1-stage pooling). For future analysis, we recommend to use a statistical model that allows for between-study heterogeneity in IVE estimates as the assumption that all variation in IVE estimates between study sites is explained by chance only is unrealistic. There are many differences between the study sites that might result in differences in IVE estimates, including e.g. differences in strain circulations, vaccination recommendations and previous exposure to the influenza virus and other influenza vaccines. Furthermore, a random effects model will boil down to a fixed effects model in case of absence of between-study heterogeneity. For future studies, the between-study heterogeneity will be minimized to the extent possible (and within reasonable limits of time and costs) through study harmonization as this will result in increased precision (as also shown by the sample size calculations). Understanding the remaining heterogeneity would aid results interpretation.

Target groups of vaccination

For this pilot year, no analyses were done by target groups for vaccination as this information was not commonly available (apart from age groups). For next season, we will try to collect more information on target groups. In addition, a survey will be developed to better understand whether for some sites (especially for sites using multiple brands), certain vaccine brands are preferentially used for certain (risk) populations.

Heterogeneity across study sites

Characteristics of the studies that generated the IVE estimates are heterogeneous. Whilst the implementation of generic protocols in future seasons should result in better alignment across study sites, much of this heterogeneity stems from inherent differences between the sites and will continue to exist.

One way of addressing heterogeneity is through multi-stratified analyses. In this pilot year, due to limited expected sample size, only single-stratified analyses were foreseen in the SAP. Consequently, results were pooled across ages groups, healthcare settings, influenza subtypes/lineages etc. and therefore this year's results should be interpreted with caution.

Random effects meta-analysis was performed; this model assumes that differences in site-specific estimates are partially due to sources other than random error, such as differences in population, data collection etc. If sufficient studies are included, meta-analysis can be complemented with meta-regression to better characterize the impact of different sources of heterogeneity on the IVE.

Enrolling more sites and being selective in the choice of study sites (i.e. choosing to enrol sites with more similar characteristics) will be important to achieve sufficient sample size for multi-stratified analyses and meta-regression.

Experiences and next steps: brand-specific information

Information on vaccine brands was successfully retrieved for almost all vaccinated subjects in Finland, Spain and Italy. Only in Austria the vaccine brand was unknown for 55% of vaccinated subjects.

Overall, 11 vaccine brands were included in the data, yet pooled IVE estimates could be calculated only for 2 that together accounted for >85% of vaccines in the TND studies. We could additionally estimate IVE for 2 brands based on the Finnish cohort data. This illustrates that large sample sizes and a large geographical coverage are needed to obtain brand-specific IVE estimates. At some sites, a high diversity of brands was observed, whereas at other sites only 1 or 2 brands accounted for most vaccinations. For optimal study design, sites with a high diversity of brands should be preferentially included. However, sufficient sample size is also a requirement and both aspects should be balanced.

Experiences and next steps: study site engagement

Special attention will need to be paid to site engagement at all stages of the study to ensure overall data quality. In addition, a collaborative relationship would enable more timely input on site-specific questions that need to be answered when performing the analyses, interpreting the results and at the report-writing stage. To stimulate site engagement and support capacity building especially of new sites, site visits will take place prior to the start of data collection for the 2018/2019 season, communication channels will be established (e.g. regular telephone conferences, newsletter), and the Electronic Study Support Application will be further developed. Common understanding of the minimum dataset should be established in advance. For instance, in 2017/18, a dataset from a potential new site had to be discarded because it only contained information on cases (and not controls).

Experiences and next steps: ISC review process

Work Package 7 deliverables are developed by the public partners and reviewed by the ISC and EFPIA. The ISC decides on integration of EFPIA comments or justifies non-integration. This year, ISC and EFPIA review occurred in parallel, however an update to the process has been proposed. First, deliverables are to be reviewed by the ISC and revised by WP7. Only then will the deliverable be sent to EFPIA for review, with mediation from the ISC. The feedback loops from WP7 to the ISC and from the ISC and WP7 to EFPIA will need to be improved, so that all parties are aware of how their comments were dealt with.

Experiences and next steps: report template and writing

A report template was developed and used as basis for this report. Adaptations were made where necessary, for example to avoid overlap between the different sections and to accommodate all analyses done. More detailed guidance should be provided to the sites when asking for input, such as when asking for a description of the site and the catchment population (section 9.2), or for influenza epidemiology in their region (section 11.2), to enable better standardization of the information presented on each site.

The review process of the report within WP7 and the participating sites should be streamlined to enable faster and more efficient completion of the report.

The initial draft of this report focused on the results obtained from the pooled analyses. However, upon reflection and input from the ISC, this was considered inappropriate due to the limitations of this year's analyses (notably limited sample size and limited stratifications). Therefore, it was deemed more appropriate to focus the report on the achievements of the DRIVE pilot year as a whole, where the data pooling was carried out in the context of system testing.

Experiences and next steps: recruiting new study sites

For future seasons, it will be important to incorporate more sites to increase sample size and to allow for more precise IVE estimates and further stratified analysis, as well as to increase the sample size per brand to be able to meet regulatory requirements.

The number of sites participating to the 2018/2019 season will be more than doubled. These will include the five sites that participated in 2017/2018 and amongst others, the Helsinki University Central Hospital (Finland), Kapodistrian University of Athens (Greece), Bambino Gesù Children's Hospital (Italy), CIRI-IT (Italy), National Institute for Infectious Diseases (Romania), Vall d'Hebron University Hospital (Spain), and the University of Surrey (UK). At some of these sites, the DRIVE generic protocols will be implemented and will therefore have harmonized study procedures, criteria and definitions; other sites will implement novel approaches.

Conclusion

The main purpose of the first pilot season of the DRIVE consortium was to build and test the DRIVE platform for estimating brand-specific IVE in Europe. We successfully built this platform that allows estimating brand-specific IVE across different study sites, including the development of IT-infrastructure, study tools and processes as well as a governance model for the conduct of IVE studies. Five sites provided data that was included in the pooled analyses. Information on brand-specific vaccine exposure was successfully retrieved for most sites. The tools and processes that will be used for the 2018/2019 influenza season (with double the number of participating study sites), will build upon the experiences and lessons learned from this pilot season.

7 References

[1] Committee for Medicinal Products for Human Use. Guideline on Influenza Vaccines - Non-clinical and Clinical Module. EMA/CHMP/BWP/310834/2012. London: Eur Med Agency; 2016.
[2] ECDC. Weekly influenza update, week 20, May 2018. Stockholm: ECDC; 2018.
[3] Flu News Europe. 2017/18 season overview Stockholm: ECDC; 2018.

8 Other information

8.1 Funding

The DRIVE project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777363. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

8.2 Dissemination

This report will be made publicly available following submission to IMI. It is expected that these results will be submitted to a peer-reviewed journal and at least one conference. The dissemination plan will be developed in WP5.

9 Appendix list