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D5.8 Tailored, timely seasonal summaries of VE results for different stakeholder/clients in layer 1 and 2

DRIVE 116134-2
DEVELOPMENT OF ROBUST AND INNOVATIVE VACCINE EFFECTIVENESS

[WP5 – Communications]

Lead contributor	Riia Järvenpää (6 – THL)
	riia.jarvenpaa@thl.fi
Other contributors	Hanna Nohynek, Suvi Hyökki (6 – THL)
	Sharon McHale (14 – Seqirus)
	Topi Turunen (1 – FISABIO)

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[1] **Use one of the following codes:**
R: Document, report (excluding the periodic and final reports)
DEM: Demonstrator, pilot, prototype, plan designs
DEC: Websites, patents filing, press & media actions, videos, etc.
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PU = Public, fully open, e.g. web;
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CI = Classified, information as referred to in Commission Decision 2001/844/EC.

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Document History

Version	Date	Description
V0.1	17 Nov 2018	First Draft
V0.2	8 Nov 2018	Comments
V0.3	13 Dec 2017	Draft
V1.0	31 Dec 2018	Final Version

Introduction

The first influenza season of the DRIVE project in 2017/18 was considered a pilot. The project's main objective in this season was to establish and test the new platform using a limited number of sites.

The results of the pilot season are described in a full report and two summaries that were published on the DRIVE website (under Results, 2017/18 season) on 17 December 2018.

Publication of the results, an overview

The full report (WP7 deliverable D7.4) is a detailed document describing the study platform and the pilot year's methodology and results. Before publication on 17 Dec 2018, the report had been circulated to European Medicines Agency, European influenza experts (through the European Centre for Disease Control and Prevention) and IMI.

Two summaries prepared by WP5 of DRIVE outline the key findings of D7.4:

- The "layer 1 summary") is a scientific text intended for public health and regulatory professionals: the primary target group of DRIVE as laid out in D5.4 Communications plan. The layer 1 summary includes the key findings and graphs.
- The "layer 2 summary" is a plain language summary intended for healthcare practitioners, media and society at large, the secondary target group of DRIVE. The layer 2 summary focuses on how and why brand-specific influenza vaccine effectiveness studies are conducted.

A news item was also published on the DRIVE website and LinkedIn, and tweets were used to increase awareness of the results. The summaries are also delivered to stakeholders via newsletter.

Conclusion

The results of DRIVE's pilot season were disseminated to various stakeholders in three different formats taking into account the needs of different stakeholder groups.

Annexes

1. Layer 1 summary:
   As a PDF https://www.drive-eu.org/wp-content/uploads/2018/12/DRIVE_report-summary_layer-1.pdf
   As a web article: https://www.drive-eu.org/index.php/2018/12/30/results-of-the-pilot-season-2017-18-executive-summary/
2. Layer 2 summary:
   As a PDF https://www.drive-eu.org/wp-content/uploads/2018/12/DRIVE_report-summary_layer-2.pdf
   As a web article: https://www.drive-eu.org/index.php/2018/12/30/lay-summary-for-media-and-the-general-public-brand-specific-influenza-vaccine-effectiveness-setting-up-studies-in-europe-season-2017-2018/

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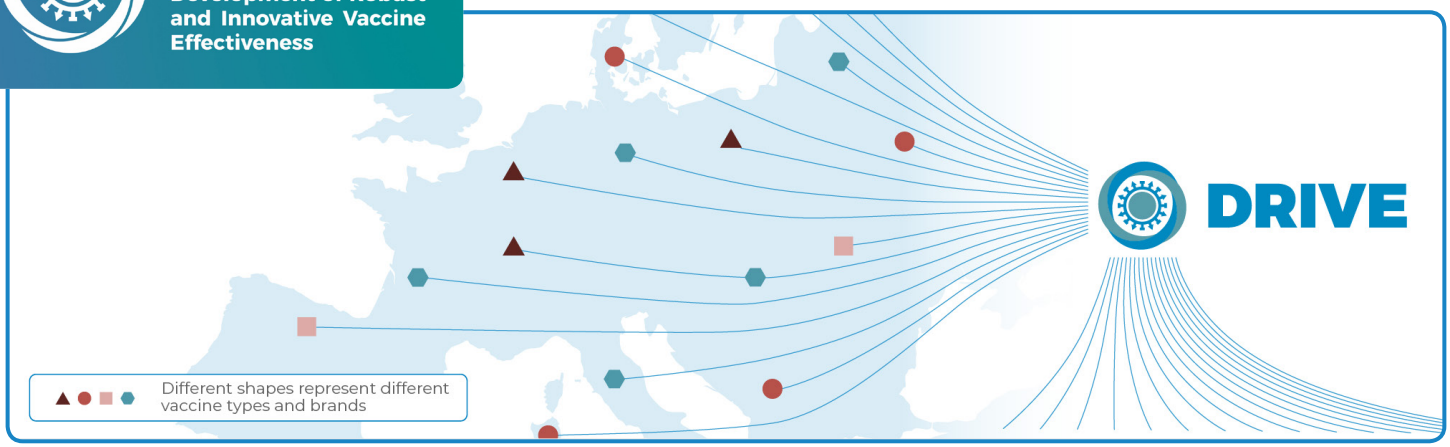
DRIVE
Development of Robust and Innovative Vaccine Effectiveness



ESTABLISHING BRAND-SPECIFIC INFLUENZA VACCINE EFFECTIVENESS STUDIES IN EUROPE, 2017/18 SEASON

Anke Stuurman, Margarita Riera, Kaatje Bollaerts, Maria Alexandridou, Topi Turunen, Caterina Rizzo, Hanna Nohynek, Ulrike Baum, Ritva Syrjänen, Uy Hoang, Miriam Levi & the DRIVE Consortium.

Table of contents

DISCLAIMER: The results presented here arise from a pilot season whose main objective was to build the DRIVE study platform for estimating brand-specific IVE in Europe. They are based on a limited number of sites using partially differing study protocols. 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.

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.

http://www.imi.europa.eu

innovative medicines initiative

efpia

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/EEA	European Union/European Economic Area
FISABIO	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana
GP	General Practitioner
GSK	GlaxoSmithKline
ILI	Influenza-like illness
IMI	Innovative Medicines Initiative
IRD	Institut de recherche pour le développement
ISC	Independent Scientific Committee
ISS	Istituto Superiore di Sanitá / Italian Public Health Agency
IVE	Influenza Vaccine Effectiveness
LCI	Laboratory-Confirmed Influenza
RT- PCR	Reverse Transcriptase - Polymerase Chain Reaction
SP	Sanofi Pasteur
THL	Terveyden ja hyvinvoinnin laitos / National Institute for Health and Welfare, Finland
TND	Test-negative design
QCAC	Quality Control and Audit Committee
OR	Odds Ratio
SARI	Severe Acute Respiratory Infection
VAHNSI	Valencia Hospital Network for the study of influenza

Introduction

This report presents an executive summary of how the European DRIVE research platform for brand-specific influenza vaccine effectiveness estimates was tested during the 2017/18 influenza season. DRIVE (Development of Robust and Innovative Vaccine Effectiveness) is a public-private partnership that aims to answer the new European regulatory requirements for influenza vaccines by providing brand-specific influenza vaccine effectiveness data annually. The results of the DRIVE collaboration will serve the regulators, healthcare professionals as well as the society at large. A detailed description of the season and the various pilot vaccine effectiveness analyses conducted by DRIVE is provided in the DRIVE deliverable 7.4: First seasonal final report of conducted studies.

Background

A NEED FOR BRAND-SPECIFIC INFLUENZA VACCINE EFFECTIVENESS ESTIMATES

Influenza is a major public health problem. Vaccines are the cornerstone of preventing influenza illness, but their effectiveness can vary from year to year and across recipient groups.

While influenza vaccine effectiveness is being evaluated annually in many EU member states, the results are generally not specific or robust enough to gain a thorough understanding of influenza vaccine effectiveness by type and brand.

There is an increasing number of different types of influenza vaccines available, which differ in composition and manufacturing process. The efficacy of these vaccines has been established in clinical studies, which form the basis of their licensure, however, vaccine performance in real word settings can vary between different groups within given populations and from season to season due to a number of factors.

The main aim of DRIVE is not to study differences in IVE between different brands, but rather understand further how individual vaccines perform in the context of annual recommendations. Thus, DRIVE is part of an ongoing effort to monitor the benefit and risk of influenza vaccines from a regulatory perspective. DRIVE can help demonstrate the value of influenza vaccination, but also to potentially identify vaccines with consistent suboptimal responses for some subgroups of the population or support signal detection.

The European Medicines Agency (EMA) has issued a new guideline that came into force in 2017[1]. It requests influenza vaccine effectiveness (IVE) evaluation for all influenza vaccine brands used in Europe each season. Responding to these regulatory requirements is the responsibility of the marketing authorization holders. However, brand and particularly type-specific IVE estimates are also of public health importance. Since many European public health institutions have extensive experience of IVE studies, EMA has encouraged the industry and public health institutes to work together to address these regulatory and public health needs.

Hence, a new public-private partnership named DRIVE (Development of Robust and Innovative Vaccine Effectiveness) was launched by the Innovative Medicines Initiative (IMI) in July 2017 to establish a sustainable platform for brand-specific IVE studies in the European Union.

THE DRIVE MODEL

In DRIVE, data from several independently operating national or regional study sites located in different parts of Europe are analysed jointly with the aim of obtaining sufficient geographical coverage and sample size for brand-specific IVE estimates (fig. 1).

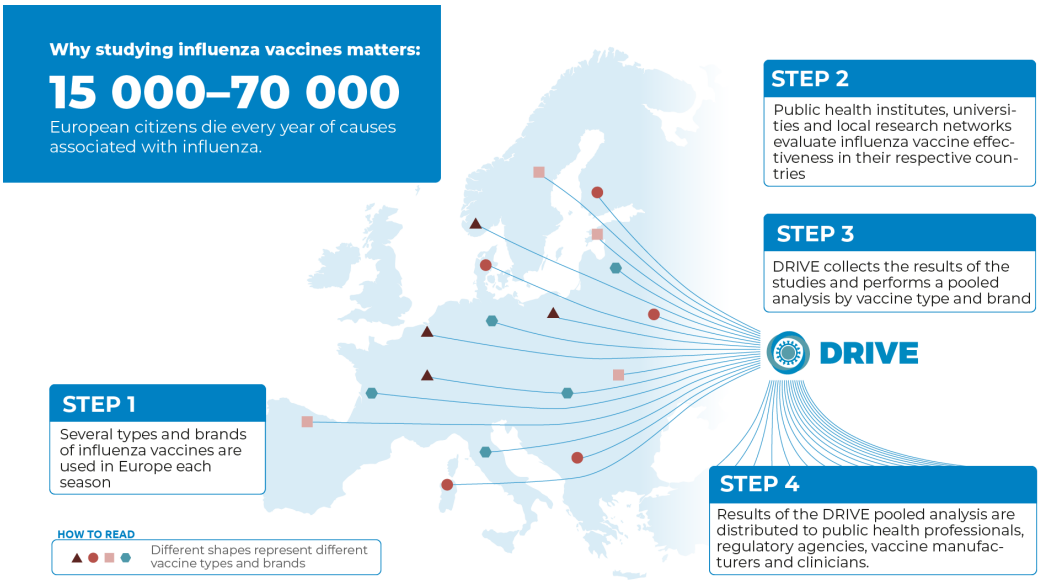


Figure 1. DRIVE collects the results of several European IVE studies and performs a pooled analysis by vaccine brand.

[1] https://www.ema.europa.eu/documents/scientific-guideline/influenza-vaccines-non-clinical-clinical-module_en.pdf

As understanding the effectiveness of influenza vaccines is a priority for both those in charge of public health and vaccine manufacturers, DRIVE operates under a public-private partnership. The studies themselves are conducted independently by public partners, without involvement of vaccine manufacturers. In the interest of scientific independence, rigour and transparency an Independent Scientific Committee (ISC) of external experts oversees the studies and the resulting scientific outputs of DRIVE. Once written by the public partners, the vaccine manufacturers review the scientific outputs through a transparent and traceable written process, however the ISC ultimately decides upon the inclusion of the vaccine manufacturers' comments.

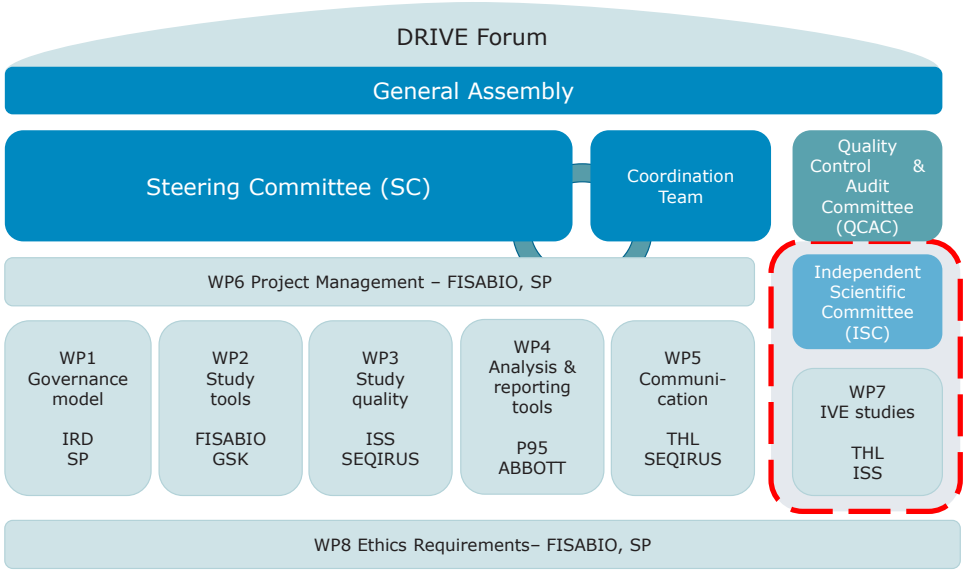


Figure 2. DRIVE is governed by a Steering Committee and ultimately, a General Assembly. Work Package 7, responsible for the studies, operates independently from vaccine manufacturers. The other Work Packages, co-led by public and private partners, perform supporting tasks such as quality assurance, communications and mapping where the different brands are used.

INFLUENZA SEASON 2017/18 IN EUROPE

Based on the WHO recommendations on strains to include in seasonal influenza vaccines, the vaccines used in the Northern hemisphere in the 2017/18 season contained the following strains:

- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus (B/Victoria lineage)
- B/Phuket/3073/2013-like virus (B/Yamagata lineage; only in quadrivalent vaccines).

https://www.who.int/influenza/vaccines/virus/recommendations/2017_18_north/en/

Based on the surveillance data generated by ECDC with the contributions of the Member States, influenza viruses circulated at high levels between weeks 51/2017 and 13/2018[2]. The majority were influenza B viruses of the B/Yamagata lineage, which was not included in the trivalent influenza vaccines. Different patterns of dominant virus types and A subtypes were observed between the European countries. Country-specific descriptions of the epidemic are included in pilot year report.

[2] ECDC Surveillance Report. Annual Epidemiological Report for 2017 Seasonal influenza, 2017–2018, available at: https://ecdc.europa.eu/sites/portal/files/documents/seasonal-influenza-annual-epidemiological-report-2017.pdf. Accessed 4.12.18.

Methods

The first year of DRIVE was dedicated to establishing and testing the IVE research platform through a pilot study. The study was not designed to generate robust IVE estimates but rather to refine the methodology for future studies to ensure DRIVE can meet its intended aim.

OVERVIEW OF STUDY SITES

Five study sites from four countries (Austria, Finland, Italy & Spain) contributed data to the DRIVE pilot study. Study sites used their own protocols for data collection, as the influenza season started only a few months after the launch of the DRIVE project. Inclusion and exclusion criteria were harmonized where possible at the time of data analysis. 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, laboratory tests performed, and variables available to adjust for confounding. An overview of the most important study site characteristics is given in Figure 3.

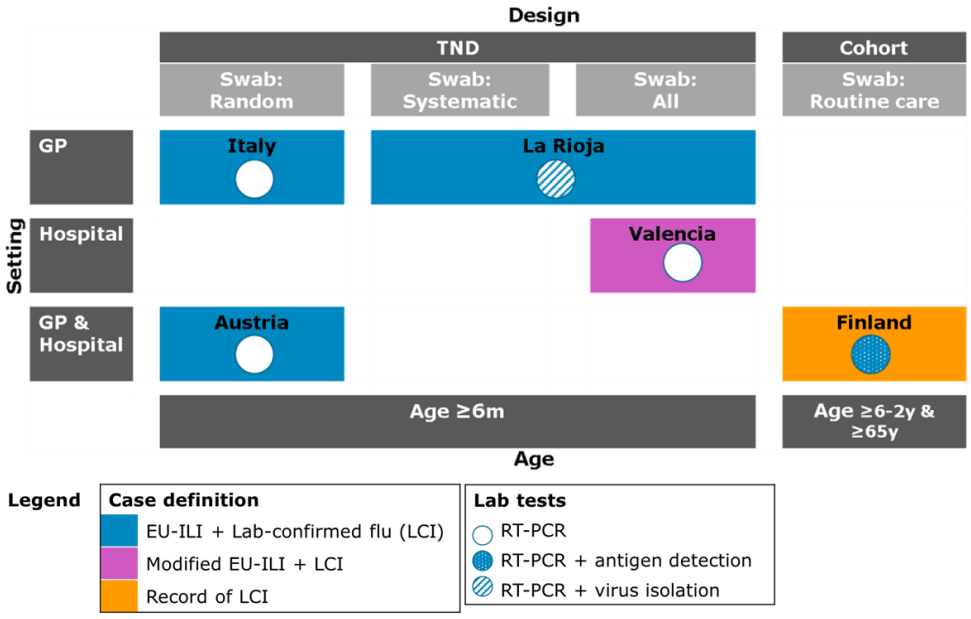


Figure 3. Characteristics of study sites included in the pilot, 2017/2018. In La Rioja, the first 2 ILI patients aged <65 years each week who provided informed consent were swabbed; whereas all ILI patients aged ≥65 years who provided informed consent were swabbed.

POOLED ANALYSIS

Influenza VE brand 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, a random effects meta-analysis of odds ratio estimates (TND studies) or log-transformed relative risk estimates (cohort study) of IVE was conducted. IVE was adjusted for confounders including sex, age group, hospitalizations in the previous 12 months (except for Austria), influenza vaccination in the previous season and the presence of at least one chronic condition but only if retained from the model build. More information on the study design and statistical methods can be found in Pilot year report (DRIVE deliverable D7.4) and its annexes (available at www.drive-eu.org). All analyses were performed centrally at the DRIVE server.

Results

ASSEMBLY OF THE DRIVE RESEARCH PLATFORM

A separate work package (WP7) consisting of non-industry organizations was set up to carry out the studies, whose results are evaluated by an Independent Scientific Committee (ISC). Harmonized study protocols for TND and cohort studies (D7.1 & D7.2) were developed during the 2017/18 season 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) which will also be implemented in the 2018-19 season. The ISC was assembled in January 2018.

INFLUENZA VACCINE EFFECTIVENESS ESTIMATES

Overall, data were collected on 2,573 cases and 2,426 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 the 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 the DRIVE analyses of IVE by any vaccine, vaccine type and brand (all anonymized due to the pilot nature of the first year) are shown in forest plots and meta-analyses in figures 4–8. IVE by influenza virus type and subtype is shown in figure 9. Due to limited sample size, brand-specific pooled analyses were only performed for two brands. In addition, IVE was estimated for two brands included in the Finnish cohort study.

Discussion

The influenza season of 2017/18 was considered a pilot for the DRIVE consortium to test the feasibility of its research platform for brand-specific IVE studies. A separate work package consisting of non-industry organizations was set up to design and carry out the studies, whose results were evaluated by an Independent Scientific Committee. The multi-country study included one register-based cohort study and four test-negative design studies. Influenza VE estimates were calculated using a two-stage pooling approach.

This pilot study comes with limitations. Due to lack of generic protocols, there were methodological differences between the study sites. Some differences in effectiveness estimates may also be due to variability in study populations or influenza epidemiology. While a total of 11 brands were covered by the studies, the sample size only allowed IVE estimates for four of them. Because of limited statistical power, limited ability to stratify by age and study setting and differences between studies, the type- and brand-specific estimates are not directly comparable with each other. For these reasons, **the results of this pilot year cannot be used to inform medical or regulatory decision-making on any influenza vaccine brand per se.**

Conclusion

The DRIVE platform was successfully established during the influenza season 2017/18. Brand information was captured successfully and comprehensively by all but one site. Even with the limitations described above, the results demonstrated the general feasibility of evaluating brand-specific IVE in a multicenter setting. In the 2018/19 season, the number of study sites included in the platform will more than double, data collection will be harmonized through generic protocols, and analysis will be stratified by study setting and age group. This is intended to overcome some of the main limitations identified during the 2017/2018 pilot seasons and is anticipated to further increase the possibility to generate robust pooled IVE estimates for more brands in the future.

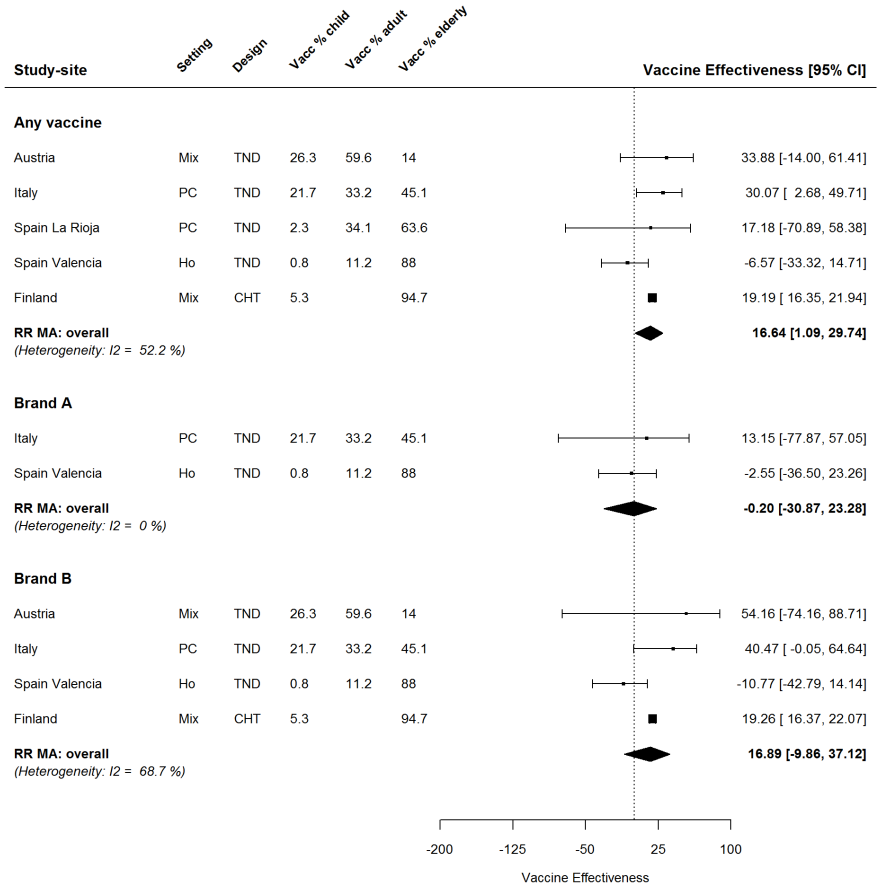


Figure 4. Overall IVE by any vaccine and vaccine brand, adjusted estimates, 2017/18.

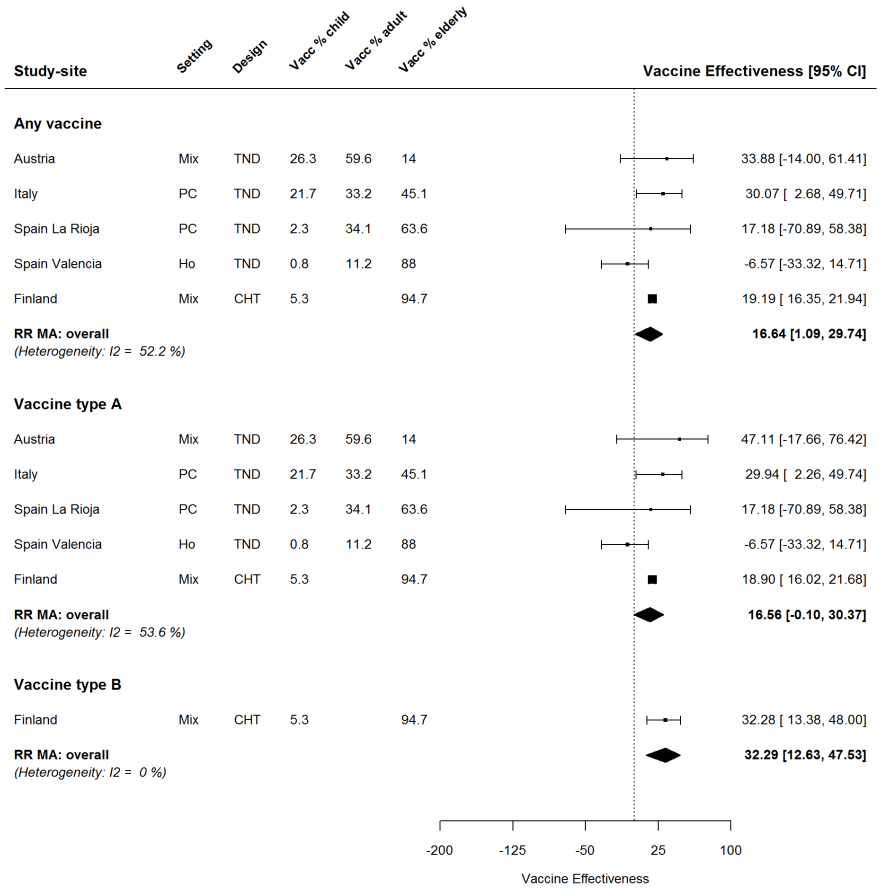


Figure 5. Overall IVE by vaccine antigen (live attenuated vs. inactivated), adjusted estimates, 2017/18. In Finland, LAIV was only offered to children aged 24-35 months

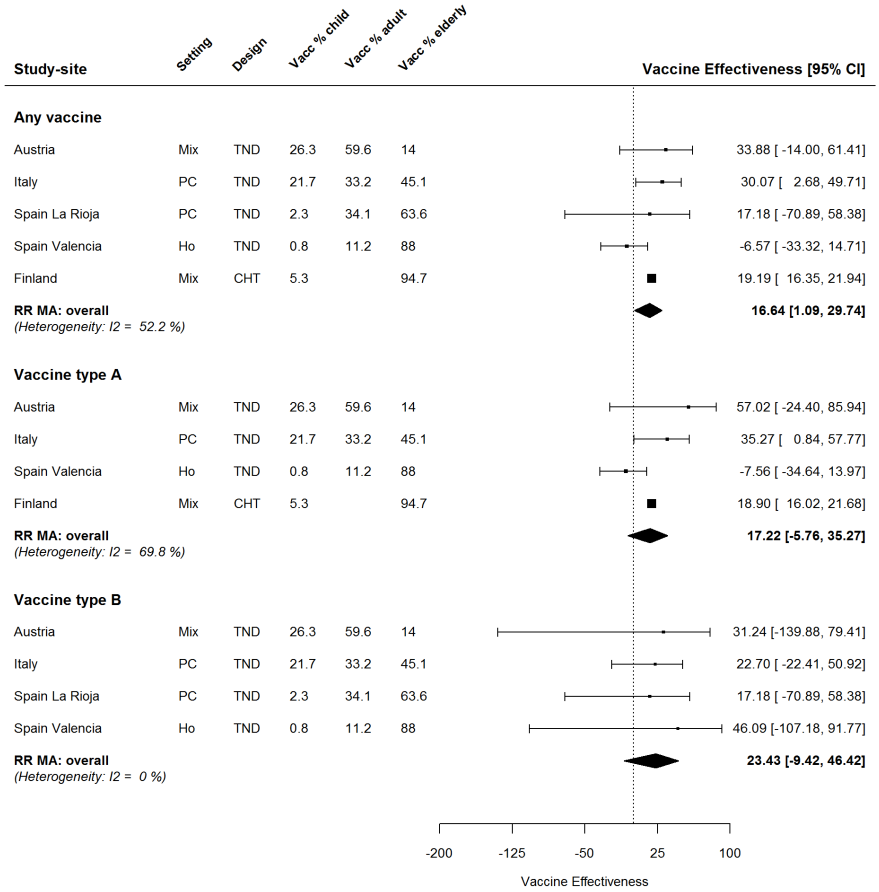


Figure 6. Overall IVE by vaccine antigen (subunit vs. split virion), adjusted estimates, 2017/18

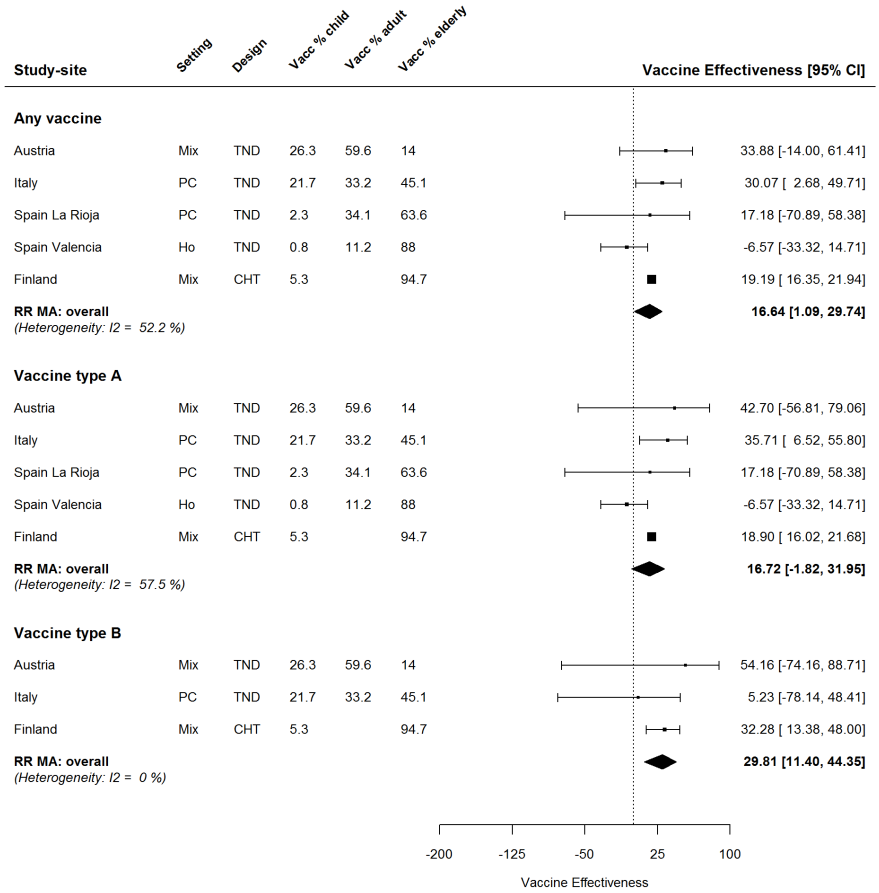


Figure 7. Overall IVE by vaccine valency, adjusted estimates, 2017/18

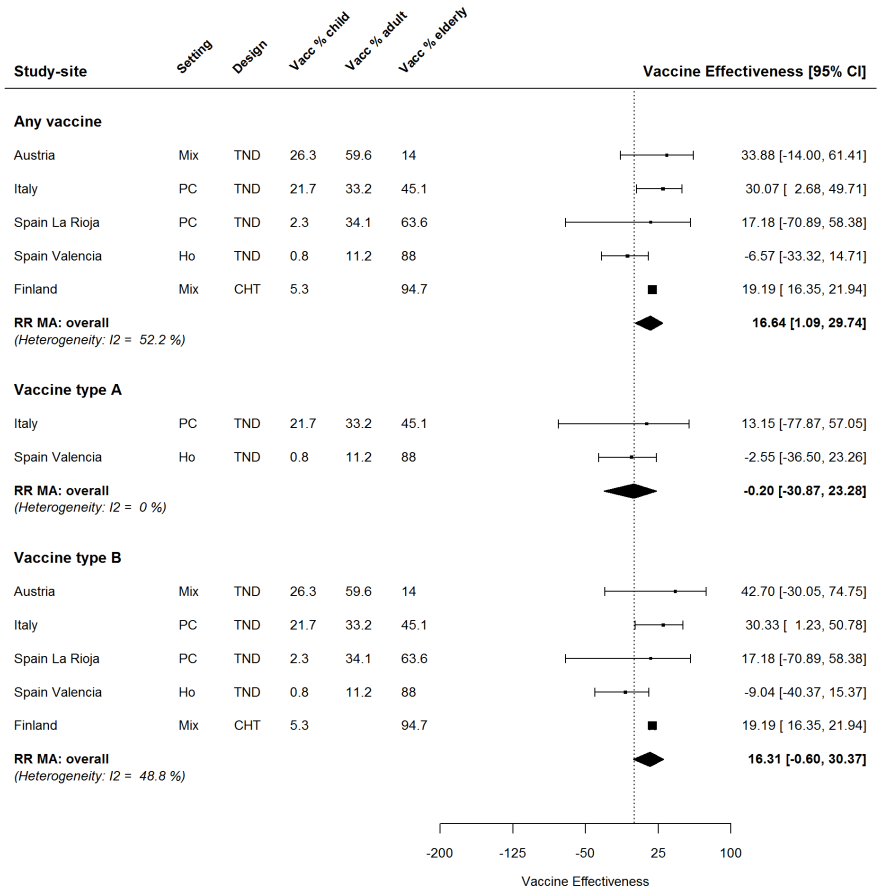


Figure 8. Overall IVE by vaccine type (adjuvanted vs. non-adjuvanted), adjusted estimates, 2017/18

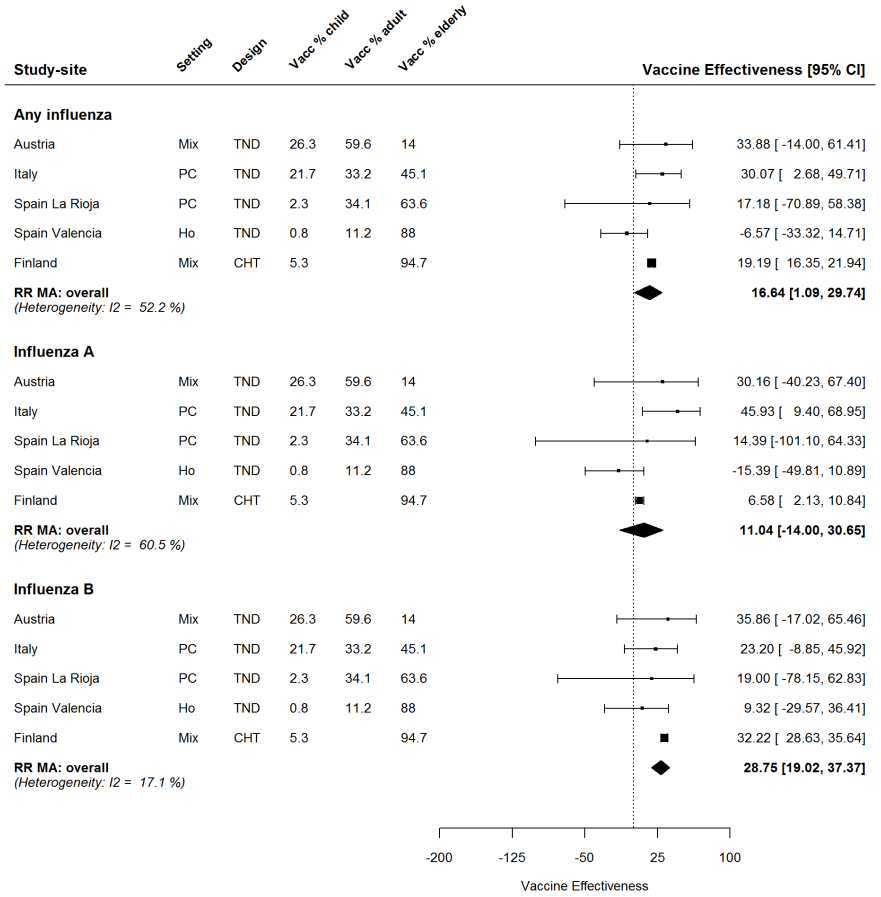


Figure 9. Overall IVE for any vaccine, by influenza type, adjusted estimates, 2017/18

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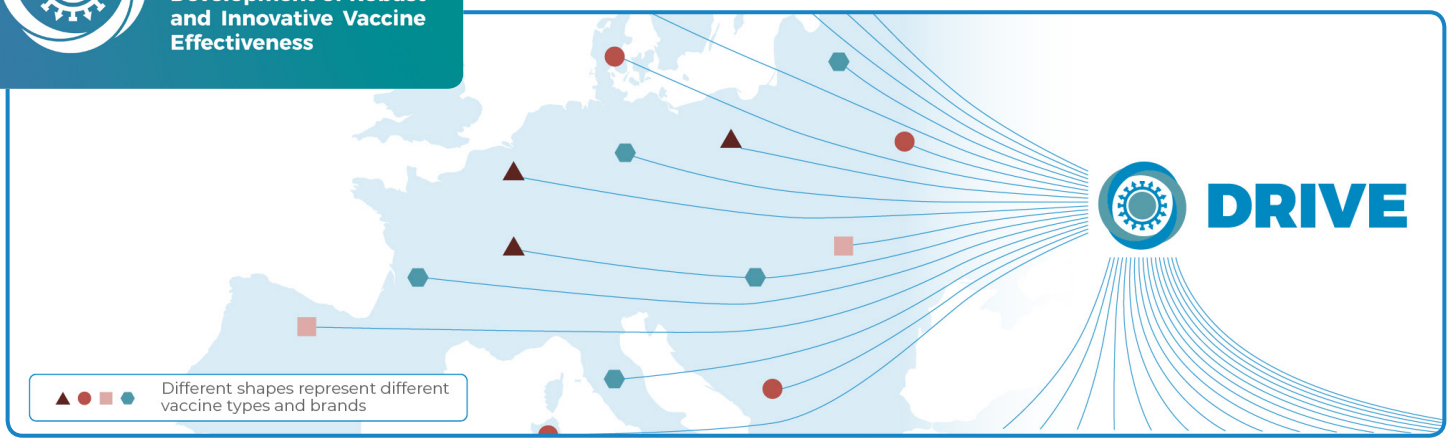

BRAND-SPECIFIC INFLUENZA VACCINE EFFECTIVENESS:

Setting up studies in Europe, season 2017-2018

Data brief

Seasonal influenza (flu) is an infectious disease with a major impact on European citizens because of its high incidence rate and severity. Although vaccination is the best way to protect against influenza, several factors affect how well vaccines will work in a given influenza season. Europe-wide research is needed to understand how different influenza vaccines perform each influenza season.

The DRIVE consortium has built a research platform for studying brand-specific influenza vaccine performance, known as "vaccine effectiveness" during its pilot years 2017–2018. As more study sites join the DRIVE network, DRIVE can expect to answer the regulatory and public health need of better understanding influenza vaccine effectiveness.

Why?

WHY EU-WIDE RESEARCH ON BRAND-SPECIFIC INFLUENZA VACCINE EFFECTIVENESS IS NEEDED

Several types and brands of influenza vaccines are used in Europe each season. Some vaccines contain inactivated viruses or parts of viruses and are given as injections. Another type of vaccine contains live but weakened viruses and is given as nasal spray. Influenza vaccines are also made using different manufacturing processes. Some are produced in eggs, others in cells. Some vaccines contain adjuvants that aim to promote a better immune response. Vaccine type and brand availability differs by country, but also by region or even at the clinic level and this may change each season, depending on by whom, how and when influenza vaccines are procured.

Influenza viruses are continuously changing. The World Health Organization conducts year-round surveillance of flu viruses globally and recommends the strains to be included in influenza vaccines each season. The aim is to protect people against the viruses anticipated to circulate predominately in the upcoming season.

If a change in the structure of an influenza virus is detected after the vaccine production has started – either in the circulating viruses or in the vaccine virus during production – there is no time to change the vaccine composition. This can result in a so-called mismatch which lowers the effectiveness of the vaccine – as may have happened during the 2017/18 season.

Considering the complexity of accurately evaluating the performance of each brand of influenza vaccine each year, a large amount of data is needed in a real-world setting.

How?

HOW DOES DRIVE STUDY BRAND-SPECIFIC INFLUENZA VACCINE EFFECTIVENESS?

Influenza vaccine effectiveness studies assess how well flu vaccines perform by comparing the incidence of the disease in those who have been vaccinated against those who have not received the vaccine.

European public health institutes, universities, and local research networks evaluate influenza vaccine effectiveness on a yearly basis. The studies are often conducted in primary care or among hospitalized patients and some make use of large databases that are gathered during routine healthcare practices.

However, in most European countries only a few different vaccine brands are used, or different brands are available but the use of each may be limited. This means the data from one or even a few countries is not enough to gain extensive insight on brand-specific effectiveness. Therefore, DRIVE collects the results of independently conducted studies from several European countries and analysises them together to reach as broad a coverage of vaccine brands as possible.

As understanding the effectiveness of vaccines is a priority for both public health officials and vaccine manufacturers, DRIVE operates as a public-private partnership. The studies themselves are conducted by public partners without the involvement of vaccine manufacturers and are reviewed by an independent scientific committee. The DRIVE consortium also includes one non-government organization to represent the patients' voice.

In order to make sure that relevant information regarding influenza vaccine performance are available to European citizens, the European Medicines Agency (EMA) has issued a guideline that requests effectiveness evaluation for all brands used in the EU. Results of the DRIVE analysis are distributed also to public health professionals, regulatory agencies, vaccine manufacturers and clinicians.

WHY STUDYING INFLUENZA VACCINES MATTERS

According to the European Centre for Disease Prevention and Control (ECDC), seasonal influenza causes 4–50 million symptomatic cases in Europe each year, and 15 000–70 000 European citizens die every year of causes associated with influenza. The yearly economic and healthcare burden of influenza is substantial.

Links:

- The scientific summary
- The report
- The consortium members

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.

http://www.imi.europa.eu

CONTACT

Professor Javier Díez-Domingo
DRIVE Coordinator -
Spanish Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO).

info@drive-eu.org
www.drive-eu.org

twitter.com/drive_eu · linkedin.com/drive-project

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