Work package number [9]	WP7	Lead beneficiary [10]	6 - THL
Work package title	Influenza Vaccine Effectiveness Pilot Studies		
Start month	1	End month	60

Objectives

To develop protocols and carry out pilot studies for determining type/brand-specific seasonal influenza vaccine effectiveness in Europe, that meets regulatory requirements. Assess the potential of DRIVE platform in performing these studies with scientific independence from EFPIA, as required by ECDC/PHIs.

Description of work and role of partners

WP7 - Influenza Vaccine Effectiveness Pilot Studies [Months: 1-60]
THL, FISABIO, IRD, P95, UNIFI, SYNAPSE , ISS, SURREY, UCBL
This work package will be co-led by THL and ISS.

Within this WP, pilot studies to address the IVE by vaccine brand/type will be conducted. The (core and locally adapted) protocols will ensure that the results can meet the regulatory requirements. Important efforts will be devoted to collect data for possible confounders. A major challenge will be to carry out the studies in different countries or regions so that the effectiveness for the different vaccine brands will be available for regulatory requirements. To achieve this aim, the electronic study support application (developed in WP2) will support future study tenders and potentially study data collection. Capacity building will be an important component of this WP for new sites. Results will be combined using deliverables and data management infrastructure of WP4 to produce an interim and a final pooled statistical analysis. Feasibility and quality parameters/criteria delivered by WP3 will be collected from the sites through WP7.

Task 7.1: Development of updated innovative study protocols for determining type/brand-specific influenza vaccine effectiveness
Partners involved: FISABIO, P95 UNIFI, THL, ISS, SURREY, UCBL (M1-60)

We will develop study protocols to assess influenza vaccine effectiveness (IVE) by vaccine brand or type that can fulfil regulatory requirements. This activity will build on the scientific tools produced since 2008 under the leadership of ECDC. Feedback from the regulators will be incorporated in the protocol and documented. This task is subdivided into five subtasks:

T. 7.1.1: Development of a protocol for field-based influenza VE studies (ISS, UNIFI, SURREY, UCBL) (M1-60). The protocol for field-based VE studies will be deliverable 7.1.
Protocol for field-based observational studies will allow to implement prospective, multicentre, hospital/primary care setting based, influenza surveillance study assessing vaccine effectiveness using a case-control test negative design among patients hospitalized or seeking care with conditions related to influenza. The severity or other relevant conditions of influenza is likely to be assess during the clinical examination as it may influence the effectiveness of influenza vaccine.
Specifically, for the field-based based studies, inclusion and exclusion criteria will have to be defined with the intent to identify the conditions (patients presenting with Influenza Like Illness EU case definition or broader conditions related to influenza) that would trigger the swab testing for influenza. Moreover, criteria for random sampling of patients with Influenza-like Illness, Acute respiratory Infection, Severe acute respiratory Infection, Acute Respiratory Distress Syndrome, presenting to health care will be considered to avoid selection bias.

T. 7.1.2: Development of a protocol for population-based database VE studies (THL, UNIFI, SURREY) (M1-60). Influenza vaccine effectiveness can be estimated using good quality register-based databases that in addition to possible exposure data, capture the routine diagnostic test results, ICD-codes of hospitalization and of outpatient visits as well as underlying conditions and treatments.
In case vaccine register data is not available, different approaches (GP records, personal vaccination card information, etc.) will be included in the protocol to capture sufficiently detailed information on vaccination, as the type or brand of the vaccine used, which is important for DRIVE, has not been usually collected in studies published so far. The protocol for population-based database VE studies will be part of deliverable 7.2. Definitions of the cohort to be studied and the follow-up periods will also be part of the protocol. Vaccine effectiveness varies considerably depending on the population considered; therefore, different cohorts will be strictly defined and followed. Specifically, for studying influenza vaccine effectiveness in pregnant women, not only for prevention of the disease in them but also in their children record linkage between the mother vaccine status and the child will be a major challenge, especially in registries

where mother and child are not linked. These situations can be overcome by using other registries, e.g. the neonatal register or birth registers metabolic screening where both mothers and children are identified.
For both task 7.1.1 and 7.1.2 other key variables such as timing of the vaccination, previous influenza vaccinations, co-vaccination (e.g., pneumococcal vaccination), etc. will be collected when possible. The population of interest will be defined, with the intent to account for all age groups (Paediatric, adults and elderly) and taking into account specific conditions (patients with underlying conditions or co-morbidity) and target population of different vaccine programs. Relevant confounders and background or intrinsic variables affecting influenza (identified in Task 2.1) will be included in the protocol.

T. 7.1.3: Development of process descriptions and generic protocols (when feasible) for novel approaches (P95, FISABIO, IRD THL, ISS, UCBL) (M1-60). In addition to the two approaches described above (field-based and population-based studies), the consortium wishes to explore the potential use of novel data sources to assess influenza VE. As an example, networks that rely on participatory epidemiology to monitor the spread of seasonal influenza have already piloted the use of their systems to assess VE . Similarly, simplification of influenza tests could lead to bed-side testing or even self-sampling. Integrating these trends into existing data collection could lead to more cost-efficient VE monitoring. Such innovative approaches will need to be validated against current gold standards. Processes on how such new sources of data can be used and validated, as well as the associated generic protocols will be developed as part of this task. These processes and protocols will be tested and modified accordingly based on the feedback from proof-of-concept novel studies outlined in WP3. A report on feasible and innovative approaches will be part of deliverable 7.3.

Task 7.2: Conduct of pilot observational studies
Partners involved: ISS, FISABIO, P95, SYNAPSE, UNIFI, SURREY (M1-60)

Protocols developed in task 7.1-7.4 will be locally adapted to sites and tested. The start and end of the studies will be based on the start and defined end of the influenza season.
We will conduct pilot studies for protocols and data sources identified and in particular:
• 7.2.1. Field based (hospital and outpatient care) studies. (ISS, FISABIO, UNIFI, SURREY)
• 7.2 2. Population-based register observational studies. (THL, FISABIO, SURREY)
• 7.2.3. Novel approaches studies. (ISS, FISABIO, P95, UNIFI, THL, SURREY)
Protocols developed in task 7.1 will be adapted for local implementation at the different study sites. During the first season, we will pilot study protocols and standard procedures focussing on alignment on execution on the national and local level of the protocols aligning timelines, sampling, and variable collection in the clinical sites of the PHIs partners of the consortium. Then after the first season we will refine protocols and standard procedures and we will scale up the activities according to the defined objectives of the Project Expansion of the number of sites and sample sizes per site will be facilitated by incorporating additional operational efficiencies (such as electronic data capturing) and ensuring sites are selected based on the appropriate criteria to support success as identified from WP3 task 3. 3.
As part of this task we will pilot deliverables of WP2 (electronic study tools, guidelines, etc.), collect data and provide input to the feasibility and quality assessment (WP3). The final annual interim and final seasonal reports of conducted studies will be deliverables 7.4, 7.6, 7.7,7.8 and 7.9.
The Timeline of the implementation of the studies considering dependences between different WP involved (WP 2-3-4-7) is provided in Figure 7.
See Figure 7 in Annex I of the DoA. Timeline for implementation of the studies.

Task 7.3: Conduct of a feasibility study for influenza virus characterization, molecular epidemiology studies related to influenza related disease in vaccinated and unvaccinated subjects
Partners involved: UCBL, FISABIO, SYNAPSE, (M24-48).

The integration of virological data into influenza VE studies is an important issue; particularly when low vaccine effectiveness against a specific clade is suspected or several clades are circulating (vaccine effectiveness against a specific clade could differ from VE estimated against the subtype or lineage). Currently, selection of cases to be further genetically analysed is done according to the objectives of surveillance and therefore biased to the more severe cases and to vaccine failures.
This task will focus on including in IVE pilot studies data collection from haemaglutinin/neuraminidase and whole-genome influenza virus sequencing for molecular epidemiology and characterization of strains identified in vaccinated and non-vaccinated (control) individuals.
In order to measure the influenza vaccine effectiveness against a specific clade in a pooled analysis to identify key influenza virus genotypic evolutions that could affect vaccine performances. These investigations will enable studying vaccine effectiveness in relation to strain drifts across the season, duration and breadth of protection and informing on the timing of the strain selection and provide targets for new vaccine development. The report on feasibility study for

influenza virus characterization, molecular epidemiology studies related to influenza related disease in vaccinated and unvaccinated subjects will be described in deliverable 7.5.

Task 7.4: Perform the mid seasonal interim and final pooled data analysis that will feed the annual interim and final seasonal reports.
Partners involved: P95, FISABIO, UNIFI, ISS, THL, UCBL (M8-60).

Study-specific statistical analysis plan (SAP) will be developed for locally as well as centrally conducted analyses according to standards defined in task 4.2. Study-specific reports will be based on the template reports developed in WP4. Depending on the start of the season, the study-specific interim reports are expected to be available within a 1,5 month from the study start for register based studies and 2,5 months for field based studies. Results will be communicated in timely manner through WP5 (D7.5).
It is expected that these reports will gradually evolve from a synthesis of locally conducted analyses to a more comprehensive centrally coordinated pan-European pooled analysis (for individual data) or meta-analysis (for aggregated data) for each brand. Similarly, it is expected that analyses will originally be conducted per source of data (Active health-care provider, Population-based register studies, Novel approaches) and later through the development of methods to integrate such different sources into single reports. As an example, nested case-control data could be extracted from cohort studies that could then be pooled with the test-negative case-control studies. Beyond the above we will examine the possibility of applying alternative analytical methods such as the case-cohort methods to assess their potential to combine the different data sources without the restriction of having nested test-negative case-control data in the cohort designs.

Participation per Partner

Partner number and short name	WP7 effort
1 - FISABIO	9.00
2 - IRD	7.70
3 - P95	12.00
4 - UNIFI	9.00
5 - SYNAPSE	5.80
6 - THL	9.00
7 - ISS	12.00
8 - SURREY	7.00
10 - UCBL	13.00
Total	84.50

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D7.1	Updated and developed protocol for type- and brand- specific IVES	7 - ISS	Report	Public	3
D7.2	Updated protocol for type- and brand- specific influenza vaccine effectiveness studies	6 - THL	Report	Public	3

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
	(population-based database studies)				
D7.3	Report on feasible novel and innovative approaches for measuring influenza VE	3 - P95	Report	Public	12
D7.4	First seasonal final report of conducted studies	3 - P95	Report	Public	12
D7.5	Report on feasibility study for influenza virus characterization, molecular epidemiology studies related to influenza related disease in vaccinated and unvaccinated subjects	10 - UCBL	Report	Public	22
D7.6	Second seasonal final report of conducted studies	3 - P95	Report	Public	22
D7.7	Third seasonal final report of conducted studies	3 - P95	Report	Public	34
D7.8	Fourth seasonal final report of conducted studies	3 - P95	Report	Public	46
D7.9	Fifth seasonal final report of conducted studies	3 - P95	Report	Public	58

Description of deliverables

D7.1. Updated and developed protocol for type- and brand- specific influenza vaccine effectiveness studies (field-based studies) (M3, updates on M11, M23, M35);
D7.2. Updated protocol for type- and brand- specific influenza vaccine effectiveness studies (population-based database studies) (M3, updates on M11, M23, M35);
D7.3. Report on feasible novel and innovative approaches for measuring influenza VE (M12, periodic updates);
D7.4. First seasonal final report of conducted studies (M12);
D7.5. Report on feasibility study for influenza virus characterization, molecular epidemiology studies related to influenza related disease in vaccinated and unvaccinated subjects (M22 updates if needed);
D7.6. Second seasonal final report of conductes studies (M22);
D7.7. Third seasonal final report of conducted studies (M34);
D7.8. Fourth seasonal final report of conducted studies (M46);
D7.9. Fifth seasonal final report of conducted studies (M58).

D7.1 : Updated and developed protocol for type- and brand- specific IVES [3]

This report will have periodic updates on M11, M23 and M35

D7.2 : Updated protocol for type- and brand- specific influenza vaccine effectiveness studies (population-based database studies) [3]

This deliverable will have periodic updates on M11, M23 and M35.

D7.3 : Report on feasible novel and innovative approaches for measuring influenza VE [12]

This deliverable will have periodic updates

D7.4 : First seasonal final report of conducted studies [12]

Final report on the analysis of the seasonal results to be produced annually

D7.5 : Report on feasibility study for influenza virus characterization, molecular epidemiology studies related to influenza related disease in vaccinated and unvaccinated subjects [22]

Report on feasibility study for influenza virus characterization, molecular epidemiology studies related to influenza related disease in vaccinated and unvaccinated subjects

D7.6 : Second seasonal final report of conducted studies [22]

Final report on the analysis of the seasonal results to be produced annually

D7.7 : Third seasonal final report of conducted studies [34]

Final report on the analysis of the seasonal results to be produced annually

D7.8 : Fourth seasonal final report of conducted studies [46]

Final report on the analysis of the seasonal results to be produced annually

D7.9 : Fifth seasonal final report of conducted studies [58]

Final report on the analysis of the seasonal results to be produced annually

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS21	Meeting with all stakeholders for the consultation process to meet the regulatory needs	6 - THL	6	Milestone co-led by THL and ISS. It will be verified through the meeting report.
MS22	Study protocols accepted by the Independent Scientific Committee	7 - ISS	3	Milestone co-led by THL and ISS. Deliverable 7.1 Submitted.
MS23	POC recruitment started	7 - ISS	9	Milestone co-led by THL and ISS. First study subject recruited.
MS24	First seasonal final report on conducted studies completed	3 - P95	12	Milestone co-led by THL and ISS. Deliverable 7.4. submitted.
MS25	Second seasonal final report on conducted studies completed	3 - P95	22	Milestone co-led by THL and ISS. Deliverable 7.6 submitted.
MS26	Third seasonal final report on conducted studies completed	3 - P95	34	Milestone co-led by THL and ISS. Deliverable 7.7 submitted.
MS27	Fourth seasonal final report on conducted studies completed	3 - P95	46	Milestone co-led by THL and ISS. Deliverable 7.8 submitted.
MS28	Fifth seasonal final report on conducted studies completed	3 - P95	58	Milestone co-led by THL and ISS. Deliverable 7.9 submitted.