

# D7.2 Core protocol for type/brand - specific influenza vaccine effectiveness studies (population-based database cohort studies)

## DRIVE 116134-2 DEVELOPMENT OF ROBUST AND INNOVATIVE VACCINE EFFECTIVENESS

### [WP7 – Influenza Vaccine Effectiveness Pilot Studies]

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## Document History

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V0.9	27 Apr 2018	Semifinal version
V1.0	4 Jun 2018	Final version approved by Independent Scientific Committee
V1.1	5 Dec 2018	Updated codebook / minimum dataset requirement

## List of abbreviations

DRIVE	Development of Robust and Innovative Vaccine Effectiveness
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ENCePP	European Network of Centres for Pharmacoepidemiology & Pharmacovigilance
EU	European Union
GEP	Good Epidemiological Practice
GP	General Practitioner
ICD	International Classification of Diseases
IMI	Innovative Medicines Initiative
ILI	Influenza-like illness
IVE	Influenza vaccine effectiveness
LCI	Laboratory-confirmed influenza
MAH	Marketing Authorization Holder
RT-PCR	Real Time Polymerase Chain Reaction
SARI	Severe Acute Respiratory Infection
VC	Vaccination coverage
VE	Vaccine effectiveness
WHO	World Health Organization

## Preface

The IMI project DRIVE aims to create a European platform for studying brand-specific influenza vaccine effectiveness (IVE) and to develop a governance model for scientifically robust, independent and transparent implementation of IVE studies in a public-private partnership.

In DRIVE, data collected by several independently operating national or regional study sites according to protocols harmonised with a core protocol and procedures developed in DRIVE will be analysed jointly to obtain sufficient geographical coverage and sample size for brand-specific IVE estimates. DRIVE recognizes the value of current study networks and strives to include secondary data from existing studies and initiatives. This is expected to foster European cooperation and maximize the sustainability of the pooled IVE studies.

The main objective of the 2017/18 pilot season is to test the different operational aspects of the DRIVE project, including governance, data collection, statistical analyses and dissemination of study results. Consequently, the number of study sites for this season is limited with limited possibility to study the full range of vaccine brands used across Europe.

This generic protocol is intended to be adapted to the local procedures at each individual study site from season 2018/19 onwards. Its aim is to achieve maximum harmonization between the different sites while respecting their different backgrounds. Experience from the pilot studies, together with the completion of other, interconnected DRIVE tasks, will inform the subsequent versions of the protocol.

## Background

Influenza is a major public health burden. It is responsible for an estimated 50 million disease episodes and 15,000 to 70,000 deaths in the EU/EEA each year, although with considerable variation from season to season [2] and by methodology used [3]. Complications including deaths are more common in the elderly and in children younger than one year of age [4]. Vaccination is considered as the most effective means for preventing influenza and its complications [5] and the World Health Organization has set a vaccination coverage target of at least 75% in the elderly population and among risk groups [6].

Due to frequent genetic and antigenic changes in influenza viruses, the seasonal vaccine is regularly reformulated (almost annually) to match with the characteristics of the viruses circulating, and annual vaccination is recommended. Observed IVE varies year-to-year due to a variety of reasons including mismatch between the vaccine virus strains and the circulating strains, waning immunity and possible interference from previous vaccinations [6, 7]. In the last two decades, controversies have sprung around the effectiveness of influenza vaccines [8]. While past IVE estimation efforts have led to significant achievements using generic protocols, standard methodologies and laboratory confirmation, several questions about IVE remain open.

In its new guideline on influenza vaccines, the European Medicines Agency (EMA) [9] requires that observational IVE studies be conducted in the EU/EEA as part of the post-licensure commitments of the vaccine manufacturers. Specifically, manufacturers are requested to replace the annual clinical immunogenicity trials (with no clear correlates of protection) with product-specific vaccine effectiveness data. To reach this goal, manufacturers are encouraged to liaise with organisations/institutions/public health authorities. The studies are expected to be conducted in line with Good Epidemiological Practice (GEP) guidelines and with European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP) guidelines.

To establish sustainable collaboration between vaccine manufacturers and the collaborating organisations and study sites, the studies should fulfil both the needs of manufacturers to fulfil the requirements of EMA and the needs of other organisations to have scientific independence in their research and to target outcomes that are relevant from the public health of view. Also non-specific outcomes are relevant, since only a minor part of the total disease burden is recognised by laboratory confirmed disease. However, the total vaccine-preventable disease burden and severity and the cost-effectiveness of vaccination are highly relevant for public health and the decision makers and stakeholders for implementation of vaccination programmes. Because the hidden disease burden is large, even low VE against non-specific disease may indicate larger amount of disease prevented than high VE against specific disease and a 'vaccine probe' can be used to indirectly measure the total [10, 11].

This document presents the generic DRIVE protocol for population-based cohort studies. The focus is on secondary use of data from existing national or local electronic databases or health registers and/or surveillance systems. These are usually established for medical and social administrative and/or research purposes. The contents and structures of databases are based on the primary data collection, which cannot be influenced by the researches. Thus, the databases may differ considerably across study sites.

While the data from each of the study sites can be analysed separately, pooling them into one analysis will provide a sample size big enough to answer study questions with a reasonable precision. For optimising the homogeneity of data provided by the study sites for pooled analysis, guidelines for harmonisation of the study methods between study sites will be provided, with instructions and/or alternatives for defining the variables. The guidelines will be updated annually before the start of the study period, according to experience of the collaboration, to availability of

data in participating study sites, and perhaps to predicted features of the upcoming epidemic. The guidelines for harmonisation also forms the basis for documenting of potential systematic or other major deviations from the guidelines, and interpreting the results accordingly. It is, however, not realistic to provide the guidelines before detailed analysis of the characteristics and structure of data are available at the participating study sites.

The protocol builds on the European Centre for Disease Prevention and Control (ECDC) Protocol for cohort database studies to measure pandemic and seasonal influenza vaccine effectiveness in the European Union and European Economic Area Member States [12] and the WHO guide to the design and interpretation of observational studies [13]. It will be updated according to the pilot conducted in the participating EU member states. The details of each site-specific study will be provided in the study annexes (e.g. ethical committee clearance, data collection strategy).

## Objectives

The study is conducted as part of the DRIVE collaboration project. Therefore, the study may not alone be powered to give precise estimates for the objectives.

### Primary objective

To measure seasonal IVE against medically attended laboratory-confirmed influenza, by vaccine brand, then by vaccine type (e.g. by antigen preparation strategy, number of virus strains, adjuvant; see section *Exposure*), then by overall influenza vaccination.

### Secondary objectives

To estimate IVE (brand-specific, type specific and total, if possible) against laboratory-confirmed influenza by:

- age group (children, young adults and elderly; the age groups will be further defined in the generic and/or study specific SAP)
- influenza virus type (A, B) and/or subtype (A/H1N1, A/H3N2) and lineage (B/Victoria, B/Yamagata)
- severity/level of health care required (primary health care, hospitalisation)
- risk groups / target groups for vaccination, e.g.
  - pregnant women
  - healthcare workers
  - any chronic condition (see Annex 1)
  - specific chronic conditions (see Annex 1)
- time since vaccination
- time window in the epidemic season (early, middle, end)( see section Study period)

- previous influenza vaccinations (one or preferably more previous seasons)

To estimate IVE (brand-specific, type specific and total, if possible) against non-specific outcomes with public health relevance, e.g.

- suspected or diagnosed influenza requiring medical attention (primary care and/or hospitalisation)
- respiratory infection, pneumonia or other respiratory conditions requiring hospitalisation, intensive unit care, or leading to death other non-specific outcomes such as cardiovascular events or deterioration of chronic conditions

To estimate brand-specific, type specific or total IVE against laboratory confirmed influenza and/or unspecific outcomes across several seasons, considering the local circulation of the strains and clades detected by the virus surveillance systems, if possible

The details of the analyses will be described in the generic and study specific SAPs, updated annually according to the characteristics and structure of data available at the participating study sites

## Methods

### Study design

In each participating study site, a cohort study using secondary data from existing databases or health care registers (see section *Cohort of interest*). To reach appropriate sample size for assessing brand-specific VE, the data from individual studies will be pooled.

### Study setting

The population-based study setting is defined by each study site, based on the available data.

- *Each study site to describe the source population and definition of the study cohort Each study site to specify the target groups for which influenza vaccination is recommended, which vaccines are used in the database catchment area, and how the choice of vaccine brand happens*

### Study period

The study follow-up will start before the seasonal influenza vaccine is available and before the influenza virus circulation begins in the country/region, to ensure that all vaccinations and all outcomes in the defined cohort are captured. If only aggregated data will be collected that does not allow the shortening of the study subjects' follow-up as part of the statistical analysis, the follow-up may be restricted to the time the vaccine first becomes available or the virus circulation starts, whichever occurs first. The study period will finish at the end of the influenza season.

- *Each study site to specify the study period: the definition of the beginning and end of the study period*
- *Each study site to specify the early, middle and end of the influenza epidemic at the study site according to the information provided by the local influenza surveillance system.*

For the pooled analysis, a harmonised minimum period will be defined (e.g. from week 40 till week 20), but if needed, it will be extended to fully cover the vaccination campaign and the epidemic in each study site. Definition of shorter time periods (e.g. early, middle and end season) will be developed to take into account differences in influenza activity over time and probable development of immunity in unvaccinated population through encounters with the circulating viruses

For addressing the secondary objective of estimating influenza vaccine effectiveness over several seasons, multiple study periods will be combined. If possible, the information from the local surveillance systems of major circulating strains in the study regions will be considered in the analysis. The details of the analysis will be described in the generic and/or study specific SAPs.

## Study population and follow-up

### Cohort of interest

The study cohort will be the whole catchment population of a health care services providing the relevant information for the analyses, characterised e.g. by place of residence or other administrative definition. The databases may also be characterised by or restricted to e.g. age, or medical, physiological or occupational conditions (e.g. pregnancy, health care workers, other risk/target groups).

The cohort should be restricted to and include all individuals eligible for the defined exposure (e.g. children at least 6 months of age in the beginning of the follow-up), for which data of the exposure (i.e. influenza vaccination status including brand information), the defined outcome(s), and at least the defined minimum, preferably the most important set of potential confounders and effect modifiers can be retrieved reliably enough (See sections Exposure, Outcome, and Confounders and effect modifiers and Potential biases).

Restricting the cohort with any exclusion criteria based on potential individual confounders or effect modifiers is not advisable, since this includes a risk of selecting the population also by other, unknown underlying factors. Instead, individual analyses may be restricted to defined subpopulations, or stratified or sensitivity analyses may be conducted.

For an analysis adjusted by chronic conditions, the cohort should be defined according to the availability of either historic diagnostic data or e.g. data on recent medications used to treat chronic conditions or permanent reimbursement status for such medications. The harmonisation of the data used for adjusted analyses will be performed between study sites after evaluating the characteristics and structure of the databases available and their potential validation information.

### The follow-up

The study cohort is defined at a fixed time point at the start of the study period. The study subjects will be prospectively followed in time for having a record for vaccination and for occurrence of the defined outcome event. The subjects will leave the follow-up at dynamic time points, either at occurrence of the defined outcome, or e.g. death, but latest at the end of the study period (see



section 'Individual follow-up'). If the data sources are available without remarkable delay, the study cohort may be defined and followed concurrently [14], which may allow providing the VE estimate almost in real-time. If there is delay in availability of the data sources or resources, the same cohort and follow-up can be constructed afterwards, in which case the follow-up is named non-concurrently. The data (the cohort population, vaccination, occurrence of the outcome and confounders/effect modifiers) are derived from pre-existing registers and databases, which ideally can be linked on individual bases by a unique identifier, or as aggregates allowing estimation of VE (see section Sources of information)

- *Each study site to specify and describe the study population, the cohort of interest and the follow-up.*

## Outcome

### Specific outcome: laboratory-confirmed influenza

The specific outcome, laboratory-confirmed influenza (LCI), will be detected through one of the following laboratory tests, according to the practices of sites providing the primary data into the database(s) used in the study: reverse transcription-polymerase chain reaction, viral culture, and immunofluorescence or rapid influenza diagnostic tests based on antigen detection, the positive or all results of which are transferred to the database used in the study. Each positive test result is to be classified by influenza type (A and B) and preferably also subtype (A/H1N1, A/H3N2) and lineage (B/Victoria, and B/Yamagata).

Usually the sampling will be driven by the local medical practices and/or the decision by the clinician. It may also be possible that sampling has followed a pre-defined protocol, if the cohort database is primarily established for study purposes.

The occurrence of an event may be dated to the date the symptom onset, if this information is available, which probably rarely is the case in studies based on registers collected in the routine health care. Otherwise, the occurrence of the outcome event is to be dated to the date the respiratory sample was taken, or the date of consultation/hospitalization with influenza sampling, or according to other definition of a disease episode, provided in the generic and/or study specific SAP, or in the guidelines for harmonisation of the study methods between study sites (Annex 1). For pooled analysis, the outcome definitions will be harmonised between the study sites, if possible, after evaluation of the practices relevant to each study site.

- *Each study site to describe the way to determine the date of occurrence of specific events.*

### Non-specific outcomes

The non-specific outcomes may include suspected or diagnosed influenza (requiring medical attention, either primary care or hospitalisation), respiratory infection, pneumonia or other respiratory conditions requiring hospitalisation or leading to death, and/or other relevant non-specific outcomes potentially related to influenza infection, as recommended by EMA [9] and as agreed within the consortium based on available data.

The identification of cases is based on diagnostic information available in the database. In studies based on routine health care registers, the diagnostic codes are based on the choice of the treating clinician and the routine local diagnostic coding systems (e.g. ICD, ICPC, OPC, Medcode, Read

codes). For pooled analysis, the diagnostic codes will be harmonised between different coding systems using pre-existing diagnosis transmission systems or developing new ones within DRIVE, after evaluation of the practices relevant to each study site. Examples of definitions can be found in [13] and [15]. The interchangeable diagnosis codes will be provided as part of the guidelines for harmonisation of the study methods between study sites (Annex 1).

- *Each study site to define the non-specific outcome(s) and the methods for detecting them in the databases*

The occurrence of an event is dated to the date of the symptom onset if this information is available, which probably rarely is the case in studies based on registers collected in the routine health care. Otherwise, the occurrence of an event is to be dated to the date of the consultation/hospitalization with the defined outcome event, or the date of the first visit of the defined disease episode (see section *Disease episode*). For pooled analysis, the non-specific outcomes will be harmonised between the study sites, after evaluation of the practices relevant to each study site.

- *Each study site to describe the way to determine the date of occurrence of non-specific events.*

If the individual has a record of laboratory confirmed influenza with a type or subtype/lineage other than the one of interest (defined outcome for the analysis) during the study period, she/he will be right-censored at this time point (see section Individual follow-up). For analyses of non-specific outcomes, the generic and/or study specific SAP will define whether the first or all relevant events/episodes will be regarded as outcomes of interest.

## Exposure (vaccination)

### The exposures of interest

The most important objective of the study as part of DRIVE is to assess the brand-specific VE. However, assessing a precise VE for all brands may not be possible, because the sample size depends of the distribution of vaccine brands used in the attachment are of the databases (and at DRIVE level also the season-specific participants). Assessing the VE by vaccine type is part of the primary objective of the study, because it gives more information than the total VE for any influenza vaccination only.

The vaccine type specific VE may be assessed e.g.

- by strategy used for influenza antigen preparation (live attenuated, inactivated, subunit, split virion),
- by number of vaccine virus strains contained in the different vaccines available (trivalent, tetravalent)
- by adjuvant (adjuvanted, non-adjuvanted)
- by vaccine dose (one dose, two doses; 0,25 ml, 0,5 ml)
- by manufacturing process (egg-based, cell-based)

The vaccine types selected to primary and potential sensitivity analyses will be specified in the generic and/or study specific SAPs.

### Vaccination status ascertainment

The exposure of interest is vaccination with any seasonal influenza vaccine in the season under investigation (index season). For vaccination status ascertainment, it is crucial to know about the date of vaccine administration and the type/brand of the vaccine. .

The sources of information for the vaccination status may include:

- vaccination registry
- health care visit/hospitalisation register with relevant information of the vaccinations
- relevant insurance company register or prescription register showing evidence of pharmacy delivery or reimbursement of influenza vaccine

➤ *Each study site to describe the precise way of vaccination status ascertainment.*

### Definition of vaccination status

An individual aged  $\geq 9$  years, or a child aged  $< 9$  who has been fully vaccinated (has received at least two injectable doses or one LAIV dose) during the previous influenza seasons will be considered as

- **vaccinated** with the influenza vaccine of interest (defined exposure) if  $>14$  days have elapsed since the first record of influenza vaccination during the season (see section *Vaccination status ascertainment*)
- **partially vaccinated** during the first 14 days after the first record of vaccination (defined exposure) during the season
- **unvaccinated** until the first vaccination record during the season

A child aged  $< 9$  years who has not been fully vaccinated (see above) during the previous influenza seasons will be considered as

- **vaccinated** with the influenza vaccine of interest if  $>14$  days have elapsed since the second record of injectable vaccination or the first record of LAIV vaccination during the current season (see section *Vaccination status ascertainment*)
- **partially vaccinated**
  - during the first 14 days after the second record of injectable vaccination or the first record of LAIV vaccination during the current season
  - after the first record of injectable vaccination until  $>14$  days have elapsed since the second record of vaccination during the current season
- **unvaccinated** until the first vaccination record during the season

If vaccination cannot be assessed as a time-dependent event, and for the description of demographics and baseline characteristics, the vaccination status (yes/no) will be assessed at the end of the individual follow-up.

If the individual has a record of vaccination with a type or brand other than the one of interest (defined exposure) during the study period, she/he will be right-censored at this time point (see section *Individual follow-up*).

## Potential confounders and effect modifiers

The following list presents known and potential confounders and effect modifiers in population-based IVE studies using secondary data from pre-existing databases (please also refer to DRIVE deliverable 4.1: Framework for analysis of influenza vaccine effectiveness studies).

The minimum set for a pooled analysis is marked with an asterisk (\*). If available, also as many as possible of the other determinants will be harmonised between the study sites for pooled analysis. according to the guidelines for harmonisation of the study methods between study sites, developed according to availability of data (Annex 1).

- Age\*
- Sex\*
- Number of healthcare visits 12 months prior to the study period describing a study subject's healthcare seeking behaviour
- For children: Adherence to the local childhood vaccination programme
- Chronic underlying conditions like chronic pulmonary disease, cardiovascular disease, metabolic disorders, renal disease, treatment-induced immunosuppression and disease-induced immunosuppression, medically attended obesity etc.
- For children: Perinatal and congenital risk factors (e.g. birth weight and/or maturity at birth, perinatal factors, inborn errors of metabolism, relevant malformations and congenital syndromes)
- Number of hospitalisations 12 months prior to the study period to be used as proxy for the severity of the chronic conditions
- Pregnancy
- Influenza vaccination in previous influenza seasons; preferably more than one season,
- Pneumococcal vaccination
- Institutionalization, nursing home residence
- Contraindication to influenza vaccination
- Use of influenza antivirals
- Use of statins
- Socio-economic status or applicable proxy
- Smoking behaviour or parental smoking behaviour (for subjects ≤18 years)
- For children: Number of siblings

➤ *Each study site to describe the factors included in the study & how these are identified.*

The list will be updated based on results of DRIVE D2.2: Systematic review of the sources of confounding, bias and strategies to manage their impact in influenza vaccine effectiveness studies, due June 2018.

## Sources of information

The studies will utilize secondary data from existing population-based national, local or cohort based databases, health and social registers and/or surveillance systems by combining the information with an individual identification number, or relevant aggregation. Examples of source databases:

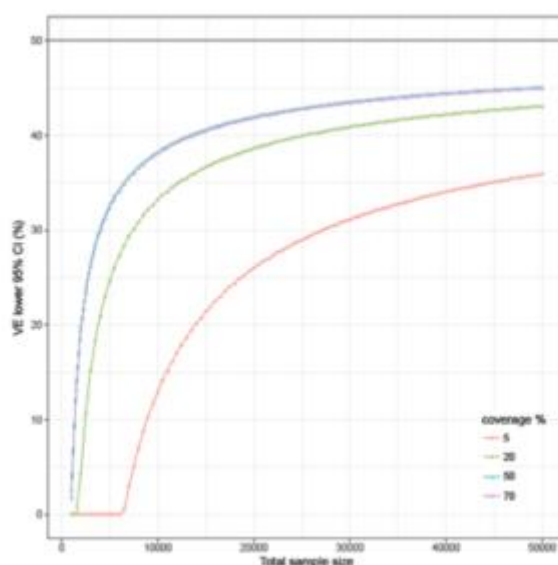
- Population and demographic registers
  - Registers of catchment of medical care or assurance
  - Registers of vaccinations
  - Registers of GP/primary health care visits and diagnoses
  - Registers of outpatient and inpatient visits and diagnoses in secondary health care
  - Registers for reimbursement (medicines, vaccines, medical treatments/measures for outcome or chronic diseases)
  - Registers for prescriptions and those showing evidence of pharmacy delivery (medicines, vaccines)
  - Registers for diagnostic microbiological test results
  - Causes of death registers
  - Medical birth registers (timing of pregnancy, perinatal and congenital problems)
  - Cancer registers
  - Registers for congenital malformations
  - Registers of housing, nursing and other social services
  - Registers established for study purposes
- *Each study site to describe the databases (contents, origin) that will be used in the study for assessing information of the exposure, defined outcomes and data of potential confounders and effect modifiers will be derived from (see sections Outcome, Exposure, and Potential confounders and effect modifiers).*

## Sample size considerations

This section gives sample size considerations and formulates recommendations. These recommendations are meant to support the design of the cohort studies on IVE. Obtaining a minimum sample size is not a requirement for study participation. Details on the sample size calculations based on the minimal detectable VE as well as precision are given in Annex 3.

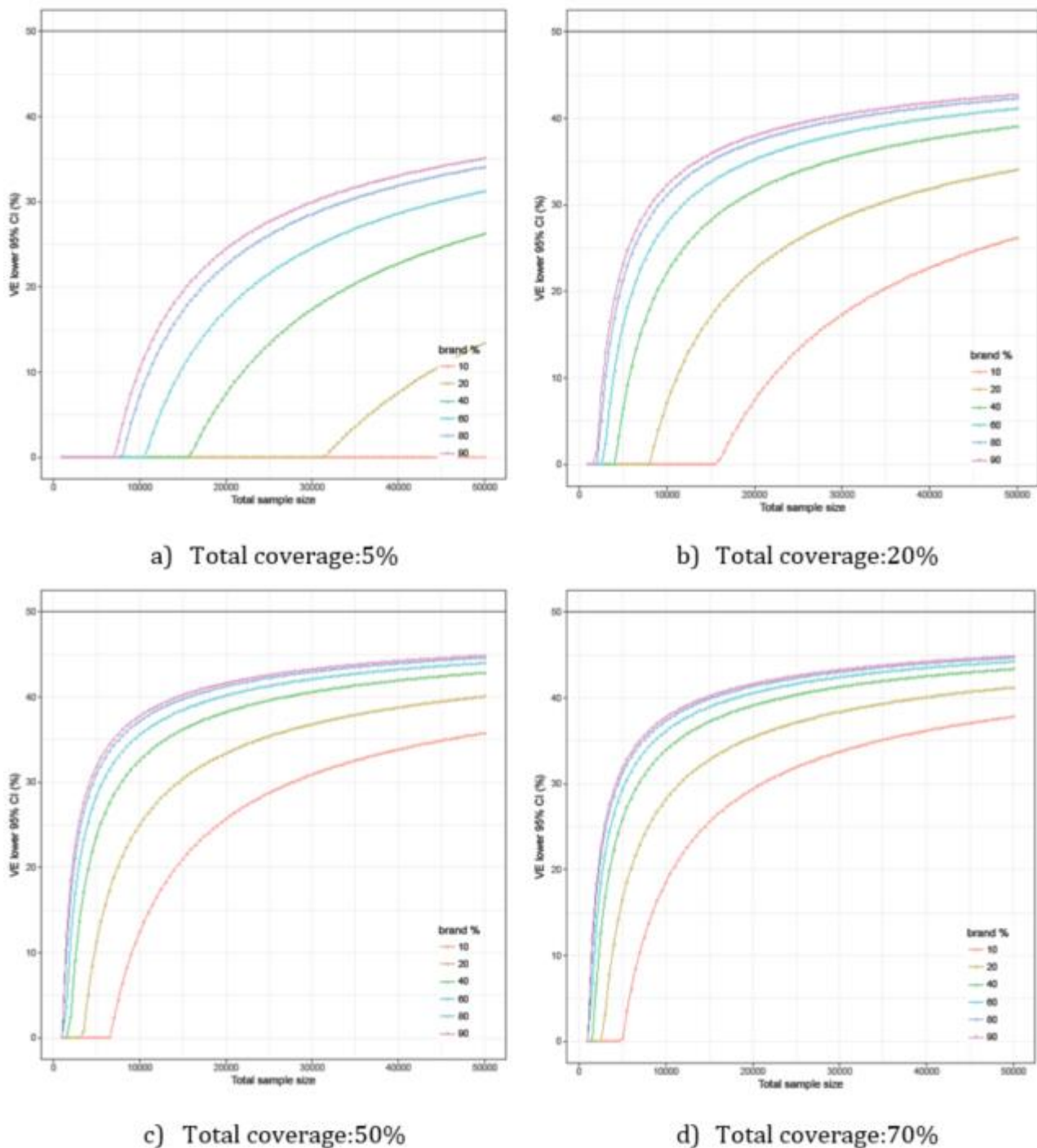
DRIVE recommends cohort studies based on 5000 subjects or more. However, studies with smaller sample sizes might still contribute to the power of the pooled analyses, provided that the study site is able to optimally harmonise its protocol with the other study sites to minimize the between-study heterogeneity. In case VE estimates with unacceptable large CIs are obtained, it might be considered to only report these estimates as DRIVE deliverables but to not publish them.

Figure 1 presents the precision of the overall VE for total sample sizes (cohort sizes) varying from 1,000 to 50,000 subjects, when assuming a true VE of 50%, an influenza attack rate in the unvaccinated of 5% and a total vaccination coverage of 5%, 20%, 50% and 70%. The calculations are based on an anticipated true VE of 50% as this is a conservative choice, requiring larger sample sizes compared to assuming lower/higher VE values. A cohort study based on 5000 subjects will result in 95% CIs of the overall VE with a lower limit larger than 25% given a true VE of 50% and an influenza attack rate of 5%, for coverages of >20%.



**Figure 1.** Precision of the overall VE expressed as the lower limit of the 95% CI, assuming a true VE of 50% (indicated with the black horizontal line), an attack rate in the unvaccinated of 5% and a total vaccination coverage of 5%, 20%, 50% and 70%.

Figure 2 presents the precision of the brand-specific VE for total sample sizes (cohort sizes) varying from 1,000 to 50,000 subjects for the same parameter settings as above and additionally assuming the brand of interest accounts for 10%, 20%, 40%, 60%, 80% and 90% of the total vaccination coverage. A cohort study based on 5000 subjects will result in 95% CIs of the brand-specific VE with a lower limit larger than 25% given a true VE of 50% and an influenza attack rate of 5%, for brands covering 40% to 90% of the influenza vaccines when the overall vaccination coverage is 50% or more.



**Figure 2.** Precision of the overall VE expressed as the lower limit of the 95% CI, assuming a true VE of 50% (indicated with the black horizontal line), an attack rate in the unvaccinated of 5%, a total vaccination coverage of 5%, 20%, 50% and 70% and that the brand of interest accounts for 10%, 20%, 40%, 60%, 80% and 90% of the total vaccination coverage.



## Data management

Each study site is responsible for the data collection, data validation, and data management of their individual study. DRIVE has developed a generic data management plan (task 4.2.1) and set up the necessary infrastructure for data collection and analysis of the pooled data (task 4.2.2).

- *Each study site to specify how data are collected and validated.*
- *Each study site to specify procedures of data management.*
- *Each study site to specify the data checking and cleaning process*

## Statistical analysis

This section describes the main principles for the study site specific analysis. Details on the site-specific analyses will be provided in the site-specific Statistical Analysis Plans (SAPs). The statistical analyses are attempted to be harmonised between the study sites, to optimise the numbers of variables to be used in the adjustment and the heterogeneity/homogeneity between the study sites. A generic Statistical Analysis Plan (SAP) including information on the two-stage pooling of data from several study sites is provided in the DRIVE D4.4: “*Generic statistical analysis plan; combining information on influenza vaccine effectiveness across study sites.*” In addition, guidelines for harmonisation of the study variables between study sites will be provided as Annex 1 of this protocol. Based on the D4.4, season-specific SAPs for pooling data across study sites will be written, after analysing the characteristics and structure of the databases of the participating study sites. The season-specific SAP is expected to be modified each season to reflect the specificities of the season’s influenza epidemic as well as changes in participating study sites and data availability.

### Individual follow-up

The follow-up of an individual belonging to the defined study cohort starts at a fixed time point at the start of the study period, and the follow-up continues until the first occurrence of the defined outcome, until another event leading to right-censoring as defined below, or until the end of the study period, whichever comes first.

Study subjects are right-censored, i.e. their individual follow-up ends, after the first occurrence of the outcome defined for the analysis in question. Other reasons for right-censoring have to be defined according to data availability and harmonised between the study sites: death, moving out of from the cohort catchment area, administration of an influenza vaccine of a type or brand other than the exposure defined for the analysis, having and influenza infection caused by an influenza virus type/subtype/lineage other than the one defined as the outcome for the analysis.

Thus, each study subject may contribute to the follow-up time (person time) as unvaccinated, as partly vaccinated and as vaccinated, according to the definitions in section Exposure, Definition of vaccination status.

### Disease episode

Repeated influenza infections during a season are extremely rare, and the first influenza infection affects the probability of the second one. Thus, for specific outcomes, only the first record is considered. However, in addition to the date of the laboratory test for positive influenza finding, the outcome date may be defined as a few days before the test as a proxy for the symptom onset, e.g. for sensitivity analysis.



Instead, there may be repeated visits because of reasons compatible with the non-specific outcomes, e.g. primary care visits before hospitalisation. Outcome-specific definitions for a disease episode will be needed to define the vaccination status at the time of the onset of the disease episode and to indicate which outcome measures are considered to belong to the same disease episode. Outcome-specific definitions for a disease episode are included in the generic and/or site-specific statistical analysis plan (SAP).

### **Demographics and baseline characteristics**

The baseline characteristics of the study cohort will be described and tabulated by exposure status at the end of the individual follow-up. The association between the baseline characteristics and the exposure status will be investigated using the Fisher's exact test (in case of nominal variables for the baseline characteristics), Mann-Whitney test (in case of ordinal or non-normal continuous variables) or Student's t-test (in case of normal variables). The description of the baseline characteristics will be stratified by the vaccination status at the end of the follow-up and by most important outcome(s) (e.g. laboratory confirmed influenza cases versus others). The proportion of positive influenza tests of all obtained tests will be described, if available.

### **Measure of effect**

The crude (or unadjusted) brand-specific IVE will be estimated as

$$VE = (1 - RR) \times 100\%,$$

where RR denotes the relative risk (ratio of probabilities) or rate ratio (ratio of incidence or hazard rates) of the outcome n for vaccinated individuals versus unvaccinated individuals. The 95% confidence intervals will be calculated as well.

The analysis must be conducted for each exposure and outcome of interest separately. Confounder-adjusted brand-specific, type specific or overall IVE estimates will be obtained from multivariable regression models, regressing the health outcomes of interest on exposure status, age, sex and the confounders of interest. In case of effect modifiers, an interaction term between exposure and the effect modifier will be included in the regression model or stratified regression analyses will be performed.

Depending on the type of data available, the analytical method(s) will be described in the generic and/or study-specific SAPs before the start of the study period. For the outcome of interest, irrespective of its type, multivariable logistic regression will be used, if only the number of events as vaccinated and unvaccinated by number of subjects vaccinated and unvaccinated at the end of the follow-up is known. If the number of events by person time and vaccination status can be assessed, Poisson regression will be used. In case of time-to-event data, Cox regression (proportional hazards) will be used.

### **Missing data**

The cohort should be defined so that the missing data is minimised: the cohort should cover all subjects targeted, especially for the vaccination, and only those subjects. Especially the outcome should be caught non-differentially, i.e. similarly for vaccinated and unvaccinated (see section Study population and follow-up; Cohort of interest). Missing data for events occurring during the follow-up is not available, since 'no record' means by definition 'no event' (unless also the negative outcome

information, e.g. negative influenza tests are available, when a nested case control analysis could be performed).

Missing data may be present, if historical data for background factors at start of the follow-up is not available, e.g. if the subject has moved into the attachment area of the database recently, or it is incomplete, e.g. only part of the databases used in defining the different background factors are available. This sub-cohort may be excluded from the adjusted analyses.

Multiple imputation methods are rarely used to correct for missing data in cohort studies, but it may be applied for categorical background factors at start of the follow-up, assuming that the missingness does not depend on unobserved variables. A sensitivity analysis may be carried out comparing the IVE estimates based on the multiple imputation approach with the IVE estimates based on a restricted subpopulation with full background data available.

### Addressing confounding & bias

Observational influenza vaccine effectiveness studies are prone to several sources of confounding and other types of bias. Please also refer to section *Potential confounders and effect modifiers* and DRIVE D2.2: Systematic review of the sources of confounding, bias and strategies to manage their impact in influenza vaccine effectiveness studies.

- *Negative confounding* refers to biases that reflect the fact that high risk groups (people more likely to develop severe complications) will be more likely to be vaccinated and therefore reduce VE. If negative confounding is present, the VE will be underestimated. Adjustment for potential negative confounding factors documented in the study (e.g. presence of chronic diseases) will minimise negative confounding.
- *Positive confounding* refers to biases that reflect a 'healthy vaccine effect'. People with a healthy lifestyle will be more likely to accept vaccination, thus leading to an increase of measured VE. Or, similarly, people being in a state of "extreme frailty" will not be offered vaccination. If positive confounding is present, VE will be overestimated.

Thus, methods should be developed to recognise, and if possible, to model both the frailty (e.g. number and severity of underlying conditions) and the healthcare seeking behaviour adequately and to balance possible differences between the vaccinated and the unvaccinated in the study cohort e.g. by applying the propensity score methodology. Propensity score is the probability of being vaccinated given the baseline information. It is estimated as a unique value for each study subject and used in the VE model to adjust for baseline differences between the non-vaccinated and vaccinated, e.g. in quintiles (please, refer also DRIVE D7.3).

As the data are collected from databases or registers, outcome or exposure misclassification (information bias) might occur. It is common among such data sources that only the presence of a disease (positive laboratory test result) or an administered vaccination is recorded but not its absence. Consequently, all study subjects without a respective record are considered healthy or unvaccinated. If the chance of being identified and recorded during a healthcare visit as an influenza case depends on the study subject's vaccination status, this leads to differential misclassification of the outcome. In some small and administratively uniform cohorts, it may be possible to be reduced by implementing strict criteria for taking respiratory samples and other diagnostic procedures in the population. However, if databases are based on established routine health care practises and if the population is very large, it is more difficult to control this bias.

Additionally, if vaccinations are given by various providers, they all should be covered by the available data sources to avoid an underestimation of the vaccination coverage.

Due to the population-based cohort design, the risk of upfront selection bias at recruitment is minimised, although not removed. However, the data source defining the study cohort must not depend on the influenza vaccination data source, and ideally a cohort should be defined, where all individuals have equal chance to be detected with the exposure and outcome events. Restricting the study cohort to a specific subpopulation does not add selection bias but reduces the generalisability of the findings.

The available databases may compromise these ideal requirements. During the DRIVE collaboration process, the potential confounders and biases as well as strategies to reduce their impact in VE studies will be identified by a systematic literature review (DRIVE D2.2), and the protocol may be updated accordingly.

## Sensitivity analyses

When appropriate, sensitivity analyses may be conducted to test different outcome definitions, different exposure definitions or exclude a subset of the data (e.g. different outcome onset and disease episode definitions, different definitions for non-specific outcomes, different influenza testing methods, VE against matched and non-matched vaccine strains, VE for one and two doses of injectable vaccines and for 0.25 ml or 0.5 ml doses in children, 'potential vaccination' status).

For interpretation of the results, the potential differences between levels of influenza circulation (e.g. attack rates in unvaccinated) and in the distributions of the molecular (sub)classes of the circulating strains across subpopulations in large cohorts should be described, and if relevant, used as stratification factors in sensitivity analyses.

The most important sensitivity analyses to be used in pooled analysis will be described in the generic and/or study-specific SAPs, but sensitivity analyses may also be planned after the data has raised additional questions.

## Adverse events reporting

This is a non-interventional epidemiological study for assessing the effectiveness of routine influenza vaccination, using secondary data from existing databases. No data of adverse events will be collected or reported.

## Ethical evaluation and other relevant approvals

Each study site will comply with the relevant international, national and regional regulations and ethics requirements. Special attention will be paid to data protection. Where applicable, the local processes of ethical evaluation and relevant approvals to use the databases and obtaining informed consent, if applicable, will be adhered to.

- *If an informed consent is needed, the following information should be specified: Who is responsible for the study, aim of the study, nature of processed data, purposes of processing, purpose of the use of the data, recipients of possible data transfers, rights of data subject & consequences of not accepting the informed consent.*

DRIVE will collect copies of the appropriate approvals from each site and submit them to IMI. If no formal approvals or ethical review is required and not available, a statement signed by the responsible investigator of the study site with rationale of this must be provided.

- *Each study site to describe the processes of ethical evaluation and approvals needed, compliance with the relevant legislation and guidelines and principles of data protection.*
- *Each study site to provide a copy of the ethical approval, or a statement on why this is not needed.*

## Dissemination of results

The study site will remain the owner of the data and may disseminate the study results according to their local practices. The data will also be submitted to DRIVE WP7 for common European pooled and/or meta-analyses. EFPIA members do not have access to this data. DRIVE will disseminate the results of its analyses according to its Communications plan (DRIVE D5.4).

## Study reports

Each study site will write a report at the end of the season and submit it to DRIVE WP7. DRIVE WP7 will write a final report presenting the results of the pooled analysis.

Both study site- and consortium level reports are to follow the template provided by DRIVE D4.3: Report templates.

## Publications

Study sites may publish their own data independently from DRIVE. If DRIVE funds were used to collect the data, this should be acknowledged in the publications.

Authorship of joint DRIVE publications follows the rules of International Committee of Medical Journal Editors (ICMJE).

## Logistical aspects

### Study sites

A study site is any entity that administers and conducts the individual studies according to the regulations and ethical codes of EU and the country and institutions involved. The study site collects the data and provides it to DRIVE as a whole. EFPIA members do not have access to this data. Study sites may be local, regional or national; examples include GP and hospital networks having access to databases from established population based cohorts, influenza surveillance schemes and public health institutes utilizing routine health care, social service and demographic databases.

## Study leader

In each study site, a study leader (principal investigator) will coordinate and be responsible for the study at the study site level and act as focal point towards DRIVE. The WP7 of DRIVE is in charge of the pooled and/or meta-analysis across several study sites.

- *Each study site to introduce the study leader and the study team with brief CVs and Declarations of Interest.*

## Standard operating procedures and quality issues

Standard operating procedures (SOPs) developed and harmonised in DRIVE should be adapted to the individual studies and used by investigators during all the steps of the study for identification of study subjects, data collection, laboratory methods, data entry, monitoring, etc. as provided in DRIVE. Guidelines of definitions for the study variables will be included in the guidelines for harmonisation of the methods between the study sites (Annex 1).

Potential systematic or major deviations from the SOP and generic SAP should be described for further development of the methodology and for interpretation of the results. DRIVE WP 2 and WP 3 will further evaluate the quality of the studies and develop guidelines and methods for improving the quality.

- *Each study site to adapt DRIVE study SOPs and guidelines to be used by the study team and provide a summary of systematic or other major deviations from them to WP7, to be stored*

## Training

- *Each study site to describe the trainings to be organised*

## Changes to the protocol

After further evaluation of the characteristics of the data available in the study sites, the protocol will be further developed to define the minimum data set to provide crude VE estimates and datasets to provide adjusted VE estimates. The aim of DRIVE is to develop methods and receive sufficient data to reach the highest possible accuracy in controlling for confounding and other bias. However, also less optimal datasets may be valuable in improving the precision of the VE estimates and in analysing the nature and impact of bias in observational study designs.

## Archiving

Each study site will archive the data used for the analyses, the description of the data (metadata), the study-specific protocol including the analysis plan(s), a description of major deviations from the generic or study-specific protocols, SAP and SOPs, the ethical and other relevant approvals according to EU level and local regulations, however at least for 5 years.

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## Annex 1: The dataset

Annex 1 defines the data elements to be used for estimating brand-specific VE in a population-based cohort study using secondary data from pre-existing databases. The minimum dataset initially needed for creating the individual based analysis dataset is marked with an asterisk(\*), but preferably the most important covariates to adjust for will be included. According to these data elements, the analysis database will be developed to include the defined outcome events by person months vaccinated, (partially vaccinated) and unvaccinated, considering the events leading to right-censoring, and the covariates needed for adjustment or stratification.

The database may also be structured as aggregated data, initially based on these data elements. The data provided to DRIVE may comprise individual level data or aggregated data including the elements needed for one-stage or two-stage pooled analysis.

The 'column 'Description' provides guidelines for harmonisation of the variables. This Annex 1 also forms the basis for reporting the deviations from the guidelines, to allow discussion on the interpretation of the results and further development of the guidelines.

See also section 'Missing data', page 18.

**DRIVE – The dataset for estimating VE in a population-based cohort study using secondary data from pre-existing databases.** The minimum individual data set initially needed is marked with an asterisk(\*)

Variable	Description	Additional info	Format	Values and coding	Example
idcountry*	Country code defined in ISO 3166-1 alpha-2		2 letters text		FI
idcohort*	Cohort name		Text		THL
region*	Region name		Text		Whole country
dataset*	Data set name		text		Elderly
setting*	Outcome identified from outpatients, inpatients or both		Numeric (categorical)	1=Outpatients 2=Inpatients 3= Both	3
id*	Participant identification number		Unique integer		12345678
aggregate	Aggregate name (if data is delivered as aggregates of variables)		Text		Age 60 y, females, propensity score 4
sex*	Sex		Numeric (Binary)	0=Female 1=Male	0
dob or ageyears*	Date of birth or age in years at the start of the follow-up for individuals		dd/mm/yyyy or Numeric	Date (or age) between the date of birth (or age) of the	1/1/1960 (58)

	aged $\geq 1$ year		(categorical)	oldest and youngest study subject	
dob or agemonths*	Date of birth or age in months at the start of the follow-up for individuals aged < 1 year		dd/mm/yyyy or Numeric (categorical)	Date (or age) between the date of birth (or age) of the oldest and youngest study subject	1/1/2018 (11)
startdate*	Date of the start of the study period		dd/mm/yyyy	Date within the study period	1/10/2018
enddate*	Date of the end of the study period <sup>a</sup>		dd/mm/yyyy	Date within the study period	19/5/2019
middledate	Date separating the early and the middle epidemic season	According to national routine definition, or e.g. the date by which 1/3 of the influenza cases in the cohort have been occurred	dd/mm/yyyy	Date within the study period	31/1/2019
latedate	Date separating the middle and the end epidemic season	According to national routine definition, or e.g. the date by which 1/3 of the influenza cases in the cohort have been occurred	dd/mm/yyyy	Date within the study period	30/3/2019
death(*) <sup>a</sup>	Died during the follow-up		Numeric (Binary)	0=No 1=Yes	1
deathdate(*) <sup>a</sup>	Date of death <sup>a</sup>		dd/mm/yyyy	Date within the study period or missing <sup>a</sup>	6/3/2019
moved(*) <sup>a</sup>	Moved out of the cohort catchment area during the follow-up		Numeric (Binary)	0=No 1=Yes	1
movedate(*) <sup>a</sup>	date of moving out of the catchment area of the cohort <sup>a</sup>		dd/mm/yyyy	Date within the study period or missing <sup>a</sup>	6/3/2019
infl*	Any positive influenza test during the follow-up		Numeric (Binary)	0=No 1=Yes	1
infldate*	Date of positive influenza test <sup>b</sup>		dd/mm/yyyy	Date within the study period or missing	15/1/2019
inflA*	Any positive influenza A test during the follow-up		Numeric (Binary)	0=No 1=Yes	1



inflAdate*	Date of positive influenza A test <sup>b</sup>		dd/mm/yyyy	Date within the study period or missing	15/1/2019
inflH1N1	Any positive influenza A(H1N1) test during the follow-up		Numeric (Binary)	0=No 1=Yes	1
inflH1N1date	Date of positive influenza A(H1N1) test <sup>b</sup>		dd/mm/yyyy	Date within the study period or missing	15/1/2019
inflH3N2	Any positive influenza A(H3N2) test during the follow-up		Numeric (Binary)	0=No 1=Yes	1
inflH3N2date	Date of positive influenza A(H3N2) test <sup>b</sup>		dd/mm/yyyy	Date within the study period or missing	15/1/2019
inflB*	Any positive influenza B test during the follow-up		Numeric (Binary)	0=No 1=Yes	1
inflBdate*	Date of positive influenza B test <sup>b</sup>		dd/mm/yyyy	Date within the study period or missing	15/1/2019
inflYamagata	Any positive influenza B/Yamagata test during the follow-up		Numeric (Binary)	0=No 1=Yes	1
inflYamagatadate	Date of positive influenza B/Yamagata test <sup>b</sup>		dd/mm/yyyy	Date within the study period or missing	15/1/2019
inflVictoria	Any positive influenza B/Victoria test during the follow-up		Numeric (Binary)	0=No 1=Yes	1
inflVictoriadate	Date of positive influenza B/Victoria test <sup>b</sup>		dd/mm/yyyy	Date within the study period or missing	15/1/2019
outcomeX	Occurrence of outcome X		Numeric (Binary)	0=No 1=Yes	1
outcomeXdate	Date of defined time of outcome		dd/mm/yyyy	Date within the study period or	15/1/2019

	X <sup>c</sup>			missing	
Inflvac*	Vaccination at least once with any influenza vaccine during the follow-up		Numeric (Binary)	0=No 1=Yes	1
inflvacdate*	First date of any influenza vaccination <sup>d</sup>		dd/mm/yyyy	Date within the study period or missing	1/11/2018
Inflvac2 <sup>(*e)</sup>	Vaccinated twice with any influenza vaccine during the follow-up <sup>e</sup>		Numeric (Binary)	0=No 1=Yes	1
Inflvacdate2 <sup>(*e)</sup>	Second date of any influenza vaccination <sup>e</sup>		dd/mm/yyyy	Date within the study period or missing	1/11/2018
brandX*	Vaccination at least once with brand X during the follow-up		Numeric (Binary)	0=No 1=Yes	1
brandXdate1*	First date of the influenza vaccination brand X <sup>d</sup>		dd/mm/yyyy	Date within the study period or missing	31/11/2018
brandX2 <sup>(*e)</sup>	Vaccinated twice with brand X during the follow-up <sup>e</sup>		Numeric (Binary)	0=No 1=Yes	1
BrandXdate2 <sup>(*e)</sup>	Second date of the influenza vaccination brand X <sup>e</sup>		dd/mm/yyyy	Date within the study period or missing	1/11/2018
vactypeX*	Vaccination at least once with type X vaccine during the follow-up		Numeric (Binary)	0=No 1=Yes	1
vactypeXdate1*	First date of the influenza vaccination type X <sup>d</sup>		dd/mm/yyyy	Date within the study period or missing	30/12/2017
VactypeX2 <sup>(*e)</sup>	Vaccinated twice with type X during the follow-up <sup>e</sup>		Numeric (Binary)	0=No 1=Yes	1
VactypeXdate2 <sup>(*e)</sup>	Second date of the influenza vaccination brand X <sup>e</sup>		dd/mm/yyyy	Date within the study period or missing	1/11/2018
seasvacn1	Received influenza		Numeric (Categorical)	0=No 1=Yes, full	1

	vaccination in previous season (season n – 1)			vaccination 2=Yes, partial vaccination <sup>f</sup>	
seasvacn2	Received influenza vaccination in season n – 2		Numeric (Categorical)	0=No 1=Yes, full vaccination 2=Yes, partial vaccination <sup>f</sup>	1
prevpneumovac	Received pneumococcal vaccine before the start of the study period		Numeric (Categorical)	0=No 1=Yes	0
pneumovacdate	Date of pneumococcal vaccination		dd/mm/yyyy	Date before the start of the study period within the time for which retrospective data is available, or missing	1/11/2018
liverdis	Chronic liver disease diagnosed before the start of the study period within the time for which retrospective data is available	Any of the following dg codes (ICD-10): B18, K70-74, K75.0-75.1, K75.3-75.9, K76-77 INCLUDING: Alcoholic liver disease, Toxic liver disease, Hepatic failure, Chronic hepatitis (viral & other), Fibrosis and cirrhosis of liver, Other inflammatory liver diseases, Other diseases of liver EXCLUDING: Clinically insignificant liver cysts, liver cancer	Numeric (Categorical)	0=No 1=Yes	0
diabetes	Diabetes diagnosed before the start of the study period within the time for which retrospective data is available	Any of the following dg codes (ICD-10): E10-E14, O24 INCLUDING: Any form of diabetes, including sequelae & DM in pregnancy	Numeric (Categorical)	0=No 1=Yes	0
heartdis	Heart or cardiovascular disease diagnosed before the start of the	Any of the following dg codes (ICD-10): A52.0, B37.6, I01-02, I05-09, I11.0, I13.0, I13.2, I20-	Numeric (Categorical)	0=No 1=Yes	1

	study period within the time for which retrospective data is available	<p>25, I26-28, I30-43, I44-46, I48, I49.0, I49.5, I50-52, I70-71, Q20-Q28.</p> <p>INCLUDING: all conditions of heart &amp; large vessels that are chronic or likely to have chronic sequelae. Cardiovascular syphilis, endo-, myo- and pericarditis, rheumatic fever, chronic rheumatic heart diseases, congenital malformations, hypertensive (renal) diseases with heart failure, ischaemic heart diseases, diseases of pulmonary circulation, atherosclerosis, cardiomyopathies, most conduction disorders, heart failure, aortic aneurysms &amp; dissection, other heart diseases and their complications.</p> <p>EXCLUDING: uncomplicated hypertension, previous uncomplicated pulmonary embolism (with no lasting cardiac insufficiency), paroxysmal tachycardias, most cases of premature depolarization.</p>			
cancer	Cancer diagnosed before the start of the study period within the time for which retrospective data is available	<p>Any of the following dg codes (ICD-10):C00-97 (except for C44.01, C44.11, C44.21, C44.31, C44.41, C44.51, C44.61, C44.71, C44.81, C44.91 and C51.04, C51.14, C51.24, C51.84), depending of the database: D37-48, Z85, Z92.3, Z92.6.</p>	Numeric (Categorical)	0=No 1=Yes	0

		<p>INCLUDING: All malignant neoplasms (both solid and haematologic) with potential to metastasize, either in treatment, active followup, or &lt;5 years post curative treatment.</p> <p>EXCLUDING: Benign &amp; in situ neoplasms. Basal cell carcinomas. Any cancer previously treated with curative intent &amp; in complete remission for ≥5 years.</p>			
immuno	Immuno-deficiency or organ transplant diagnosed before the start of the study period within the time for which retrospective data is available	<p>Any of the following dg codes (ICD-10): B20-B24, D80–84, D89, Z94.</p> <p>INCLUDING: HIV infections, immunodeficiencies &amp; organ transplants. Or iatrogenic: systemic treatment with any of the following: corticosteroid (≥20 mg prednisolone daily or equivalent), ciclosporin, tacrolimus, mycophenolate, methotrexate, azathioprine, TNF-α blockers and other biological or cytostatic drugs with immunosuppressive effect (Yes= during the whole study period; Potentially = ≥2 weeks during the study period or within 3 months before the start of the influenza virus circulation).</p> <p>EXCLUDING: Disorders of the immune system which do not lead to immunosuppression</p>	Numeric (Categorical)	0=No 1=Yes 2= Potentially	0

		(e.g. some autoimmune conditions).			
lungdis	Lung disease diagnosed before the start of the study period within the time for which retrospective data is available	Any of the following dg codes (ICD-10): A15-16, A19, A31.0, B33.4, E84.0, J40-47, J60-70, J80-84, J85-86, J90-91, J92.9, J93-94, J95-99 INCLUDING: TB (pulmonary, miliary but not that of other systems), atypical mycobacteria, cystic fibrosis, asthma, COPD, bronchiectasis and other chronic sequelae of infections, chronic lung diseases due to external agents, interstitial lung diseases, pleural diseases, respiratory failure. EXCLUDING: acute respiratory infections, lung cancer, diseases of pulmonary circulation, pleural plaques without asbestos, previous uncomplicated pneumothorax.	Numeric (Categorical)	0=No 1=Yes	1
anemia	Anemia diagnosed before the start of the study period within the time for which retrospective data is available	Any of the following dg codes (ICD-10): D50-D64 diagnosed before the start of the study period EXCLUDING: coagulopathies, uncomplicated hypersplenism, hepato/splenomegaly	Numeric (Categorical)	0=No 1=Yes	0
rendisease	Renal disease diagnosed before the start of the study period within the time for which retrospective data is available	Any of the following dg codes: (ICD-10): I12-13, M10.30, N00-19, N20.0, N25-27, N28.0, N28.9, Q63.9, Z90.5 EXCLUDING: Clinically nonsignificant kidney cysts, renal cancer	Numeric (Categorical)	0=No 1=Yes	0
dement	Dementia	Any of the following dg	Numeric	0=No	0

	diagnosed before the start of the study period within the time for which retrospective data is available	codes (ICD-10): F00-03, F05.1, G30-31. EXCLUDING delirium w/o underlying dementia, hydrocephalus.	(Categorical)	1=Yes	
stroke	History of stroke before the start of the study period within the time for which retrospective data is available	Any of the following dg codes (ICD-10): I61-64, I67.8, I69, G93.1 INCLUDING: both ischaemic and haemorrhagic strokes and anoxic brain damage. Also counting previous episodes and clear ischaemic findings seen in cranial imaging (even if fully recovered / no symptoms).	Numeric (Categorical)	0=No 1=Yes	0
rheumat	Rheumatologic diseases diagnosed before the start of the study period within the time for which retrospective data is available	Any of the following dg codes ICD-10: M05–09, M13, M30–36, M45. INCLUDING rheumatoid diseases with presumed autoimmune origin and primarily musculoskeletal presentation. EXCLUDING: arthrosis, gout, scoliosis, infectious conditions etc.	Numeric (Categorical)	0=No 1=Yes	0
childrisk	Any perinatal or congenital risk factor in children	B20-24, C00-97, D55-D89, E10-14, E65-68, E84, F71-73, F79.1, G31, G40-41, G70-73, G80-83, I34-37, I42, I50, J35, J40-47, L20, M02-07, M13, M30-36, N0-19, P07 (or birth weight < 2500 g or gestational age < 37 weeks), P27, Q00-07, Q20-39, Q89.00, Q90, Z94.0-94.6	Numeric (Categorical)	0=No 1=Yes	0
obesity	Obesity diagnosed before the start of the study period within the time for which retrospective data is available	BMI ≥30 or the dg codes (ICD-10): E66, E68 EXCLUDING: local adiposity and "other hyperalimen-tation" (=vitamin overdoses etc.)	Numeric (Categorical)	0=No 1=Yes	0

chronic1	At least one chronic disease	Including: the diseases mentioned above Excluding: pregnancy	Numeric (Binary)	0=No 1=Yes	1
chronic5	At least 5 chronic diseases	Including: the diseases mentioned above Excluding: pregnancy	Numeric (Binary)	0=No 1=Yes	1
pregnancy	Pregnancy at start of the study period	Any trimester at the start of the study period	Numeric (Categorical)	0=No 1=Yes	0
nhosp	Number of hospitalisations 12 months prior to the start of the study period	Any overnight stay in hospital or administrative information. (One disease episode counts as one hospitalization even if a patient is moved from one unit to another)	Numeric	≥0	2
nphcvisit	Number of outpatient primary health care visits to physician 12 months prior to the start of the study period	Any outpatient consultation to GP/specialist in a primary health care setting. Not counting follow-up visits for the same cause	Numeric	≥0	5
adherence	Adherence in the childhood vaccination program (in children) at the start of the study period	Proportion of received vaccine doses of those scheduled by the National Vaccination Programme by age	Numeric (Categorical)	0=No (0%) 1=Low (>0% and <50%) 2= Moderate (≥50% and <100%) 3= Complete (100%)	3
siblings	In children, at birth: Number of siblings living in the household		Numeric	≥0 or	2
propensity score	Quintiles of the probability to be vaccinated according to background factors		Numeric	1-5	4
hcw	Health care worker at the start of the study period		Numeric (Categorical)	0=No 1=Yes	1
bmi	Body Mass Index		Numeric	10 to 55 or	22.4
smoking	Smoking status at the start of the follow-up For children: maternal smoking during pregnancy after 1. trimester		Numeric (Categorical)	0=Non-smoker 1=Ex-smoker 2=Smoker	0



functstatus	Patient has contract to regular home care or difficulty in at least one category of daily living <sup>a</sup> at the start of the study period	Difficulty = needs help from others, or administrative information	Numeric (Categorical)	0=No 1=Yes	0
inst	Institutionalized at the start of the study period	Living in a residence or nursing home (any such institution where nurse present 24/7); administrative information	Numeric (Categorical)	0=No 1=Yes	0
contra	Contraindication for influenza vaccination at the start of the study period	Based on locally used criteria ICD-10: (e.g. T88.6#J07BB)	Numeric (Categorical)	0=No 1=Yes	0
sosstatus	Socio-economic status or applicable proxy at the start of the study period		Numeric (Categorical)	1=low 2=medium 3= high	2
antiviral	Antiviral use against influenza virus during the follow-up	Yes= during the whole study period; Potentially = during part of the study period	Numeric (Categorical)	0=No 1=Yes 2= Potentially	1
statin	Statin use during the follow-up	Yes= during the whole study period; Potentially = during part of the study period	Numeric (Categorical)	0=No 1=Yes 2=Potentially	1

<sup>a</sup>date of an event leading to right-censoring/end of follow-up of the analysis. If the cohort has been defined as individuals staying in the cohort during the whole follow-up, these are not obligatory.

<sup>b</sup>one of these dates is the analysis-specific outcome date and the others are dates for events leading to right-censoring.

<sup>c</sup>refers either to non-specific outcomes (e.g. visit, hospitalisation, start of a disease episode) or onset defined as proxy for start of the specific outcome disease. Outcome dates will be defined for all outcomes used.

<sup>d</sup>one of these dates is the analysis-specific exposure date and the others are analysis-specific dates for events leading to right-censoring. There must be as many exposure dates as there are vaccine brands/types available in the database

<sup>e</sup>for children aged <9 years who have not been fully vaccinated before the current season (i.e. received at least two doses of injectable vaccine or one dose of LAIV).

<sup>f</sup>one dose of injectable vaccine in children aged <9 years who had not been fully vaccinated (see<sup>e</sup>) before the season in question (season n-1 or season n-2)

<sup>g</sup>bathing, dressing, eating, going to the toilet, stairs, walk, wheelchair user

## **Annex 2: Study specific Statistical Analysis Plan (SAP)**

- *Each study site to provide a study specific analysis plan to describe the methods to be used in the study*

## **Annex 3: Sample size considerations for cohort studies**

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This document provides sample size estimations for estimating overall and brand-specific influenza vaccine effectiveness (VE) using the cohort design. The minimal detectable VE as well as precision estimates are provided for various parameter settings and recommendations are formulated.

## Minimal detectable vaccine effectiveness

The minimal detectable VE is the smallest VE that can be detected as significantly greater than zero in a given study using hypothesis testing. The minimal detectable VE for a cohort study is estimated as

$$VE_{MD} = 1 - RR_{MD(RR < 1)}, \quad (1)$$

where  $RR_{MD(RR < 1)}$  is the minimal detectable relative risk (RR) if  $RR < 1$ , or

$$RR_{MD(RR < 1)} \cong \frac{1}{2a} \left( b - \sqrt{b^2 - 4ac} \right), \quad (2)$$

where

$$a = Y + \pi Z; \quad b = 2Y + Z; \quad c = Y - r(1 - \pi)Z,$$

in which

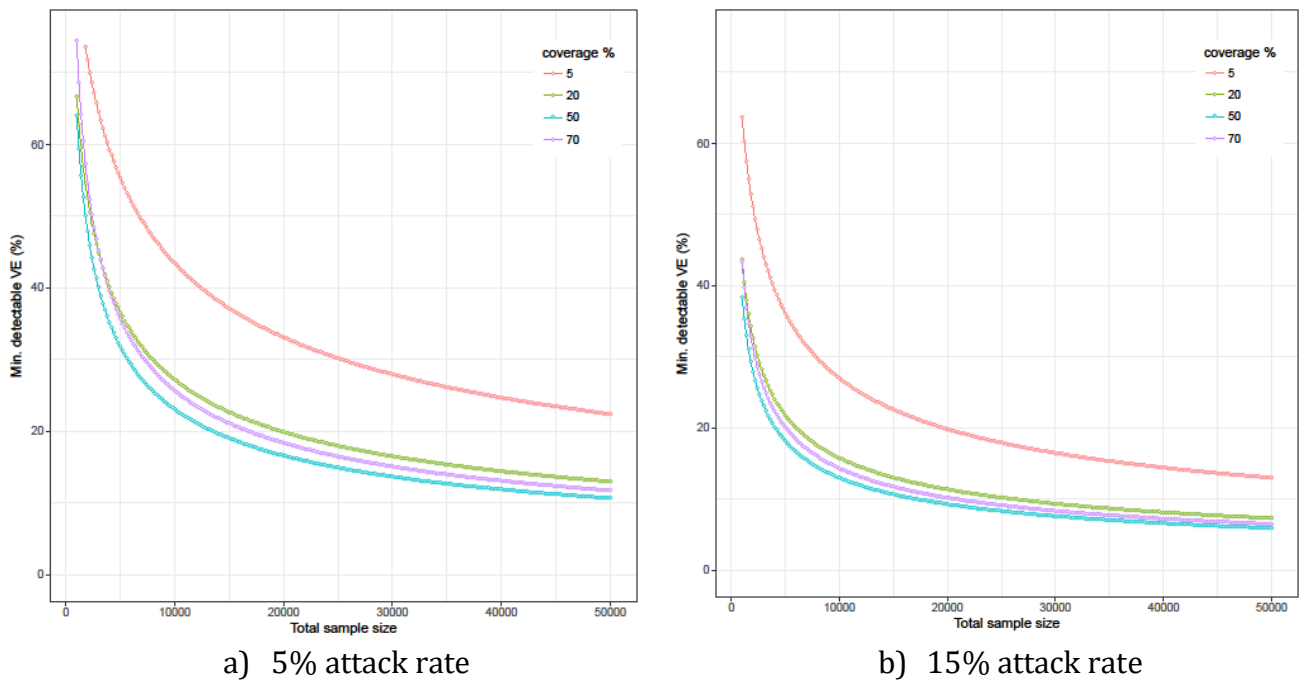
$$Y = rN\pi^2; \quad Z = (r + 1)\pi \left( \frac{z_\alpha}{2} + z_\beta \right)^2$$

for attack rate in the unexposed  $\pi$ , exposed to unexposed ratio  $r$  with  $r = \gamma/(1 - \gamma)$  with coverage  $\gamma$ , total sample size  $N$ , and where  $z_\alpha$  and  $z_\beta$  are the standard normal z-score for the type I and type II error rates (Woodward 2013).

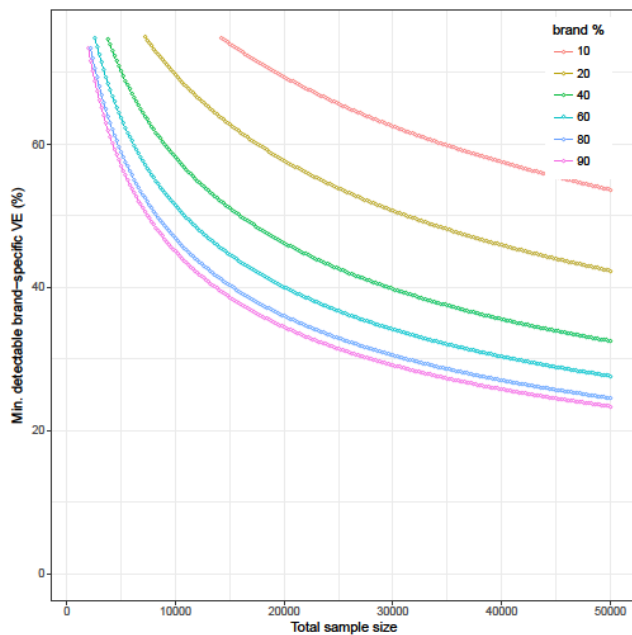
We calculated the minimal detectable overall VE (1) with 80% power ( $1 - \beta$ ) and a two-sided 95% confidence coefficient ( $1 - \alpha/2$ ) for cohort studies with the total number of subjects varying from 1000 to 50000, while assuming overall vaccination coverages of 5%, 20%, 50% and 70% and an attack rate of 5% and 15% in the unvaccinated.

We additionally calculated the minimal detectable brand-specific VE, where subjects are considered exposed when they were vaccinated with the brand of interest and unexposed when they were unvaccinated during the study's follow-up. This means that the same comparator group of unexposed subjects is used for the different brand-specific estimates. The minimal detectable brand-specific VE is calculated for the same settings above, additionally assuming that the brand of interest accounts for 10%, 20%, 40%, 60%, 80% and 90% of the overall vaccination coverage.

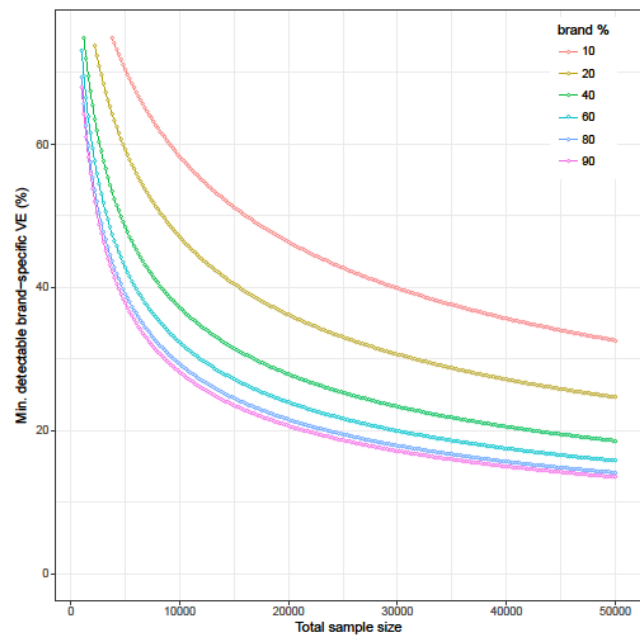
The results for the minimal detectable overall VE are given in Figure 1. These figures represent the minimal detectable VE by total sample size. The results for the minimal detectable brand-specific VE for 5% and 15% attack rates in the unvaccinated are given in Figure 2 and Figure 3, respectively.



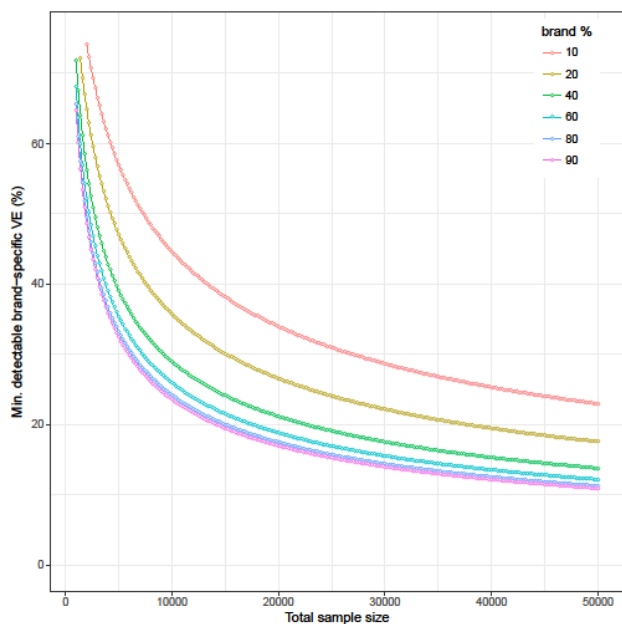
**Figure 1.** Minimal detectable overall VE for a cohort study assuming vaccination coverage of 5%, 20%, 50% and 70%, and 5% and 15% attack rate in the unvaccinated, by total sample size.



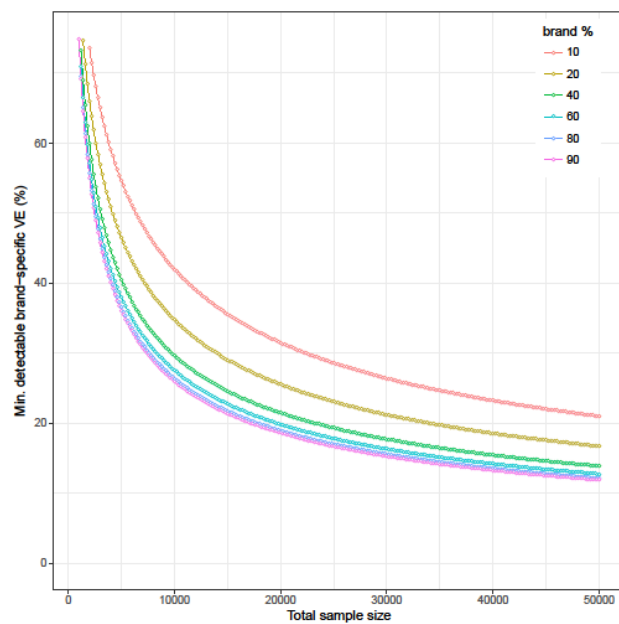
a) 5% overall coverage



b) 20% overall coverage

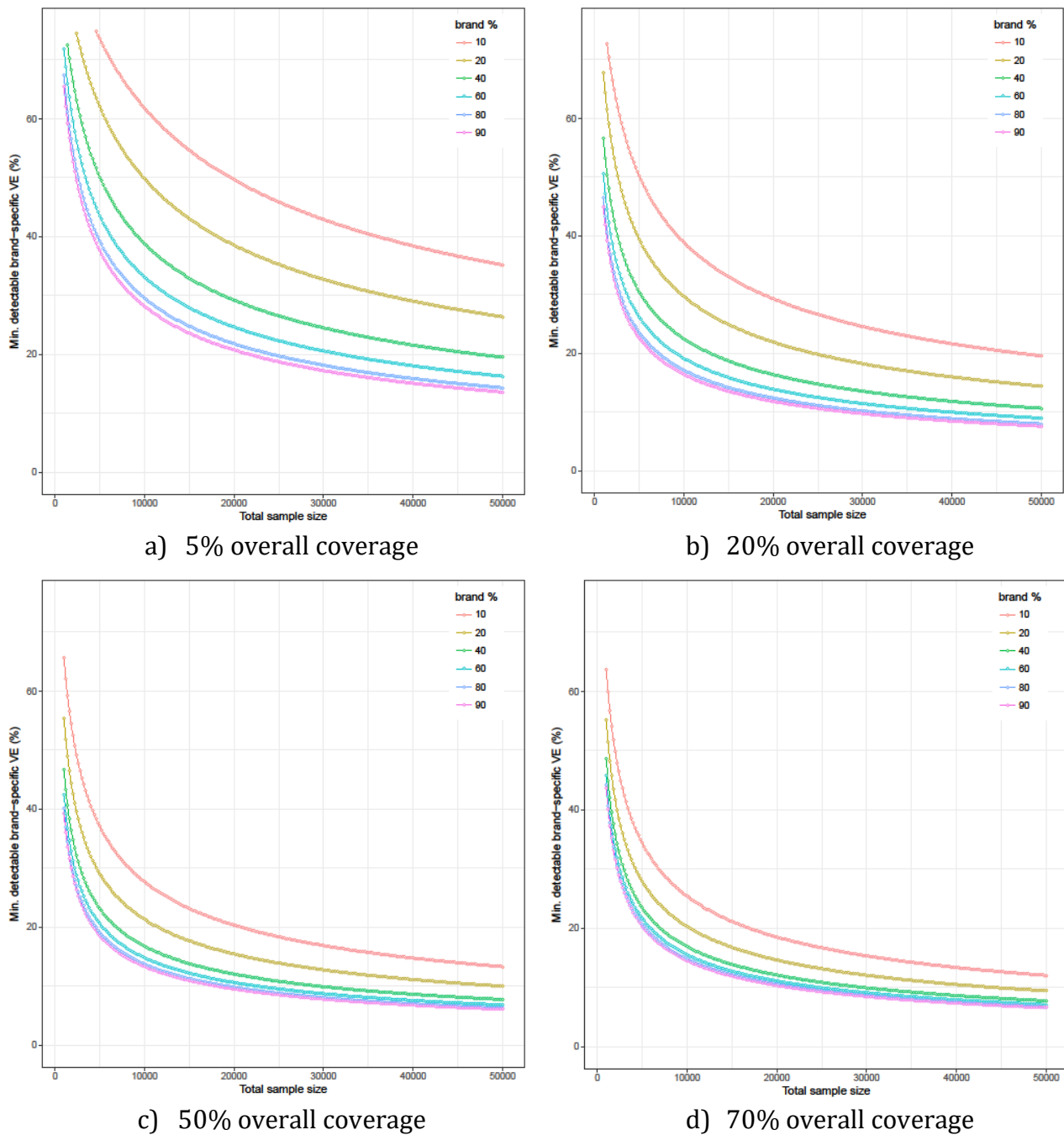


c) 50% overall coverage



d) 70% overall coverage

**Figure 2.** Minimal detectable brand-specific VE for a cohort study assuming 5%, 20%, 50% and 70% overall vaccination coverage with the brand of interest covering 10%, 20%, 40%, 60%, 80% and 90% of the overall coverage and 5% attack rate in the unvaccinated, by total sample size.



**Figure 3.** Minimal detectable brand-specific VE for a cohort study assuming 5%, 20%, 50% and 70% overall vaccination coverage with the brand of interest covering 10%, 20%, 40%, 60%, 80% and 90% of the overall coverage and 15% attack rate in the unvaccinated, by total sample size.

## Precision

The precision refers to the level of sampling error. The standard error and consequently the width of confidence intervals (CI) are measures of precision. As the VE CI are asymmetric, we express precision as the lower limit of the two-sided CI of the anticipated true VE, expressed in %.

For a cohort study, the precision can be derived starting from the anticipated true VE, the confidence coefficient  $(1 - \alpha/2)$ , the total sample size  $N$ , the attack rate  $AR$  in the unvaccinated and the overall vaccination coverage  $\gamma$ .

Then, from the lower limit of the CI for VE based on cohort studies, or

$$VE_{LL\ CI} = 1 - \exp \left[ \log(RR) + Z_{\alpha/2} \sqrt{\frac{1}{A_1} - \frac{1}{N_1} + \frac{1}{A_0} - \frac{1}{N_0}} \right], \quad (3)$$

where  $RR = 1 - VE$ ,  $Z_{\alpha/2}$  is the standard normal z-score,  $A_1$  and  $A_0$  are the number of exposed and unexposed cases and where  $N_1$  and  $N_0$  are the number of exposed and unexposed subjects, it follows that the precision is determined for given values  $A_1$ ,  $A_0$ ,  $N_1$  and  $N_0$ .

The values for  $A_1$ ,  $A_0$ ,  $N_1$  and  $N_0$  can be derived from the sample size  $N$ , the attack rate  $AR$  and the overall vaccination coverage  $\gamma$ , or

$$A_1 = N * \gamma * AR * (1 - VE)$$

$$A_0 = N * (1 - \gamma) * AR$$

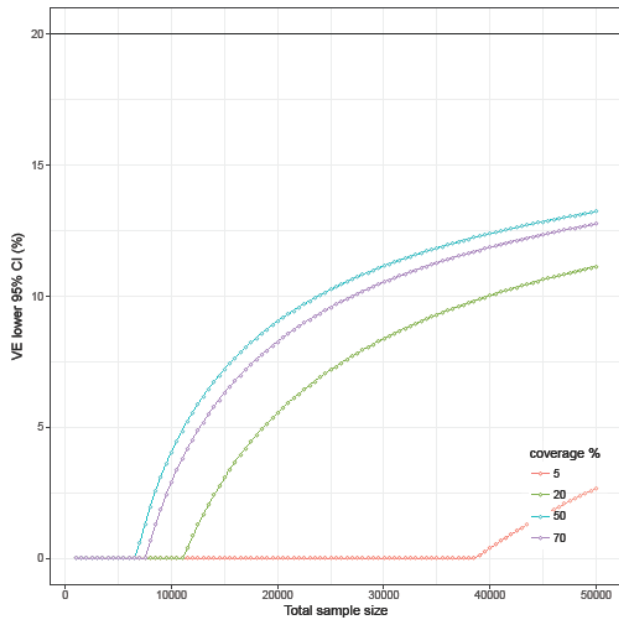
$$N_1 = N * \gamma$$

$$N_0 = N * (1 - \gamma)$$

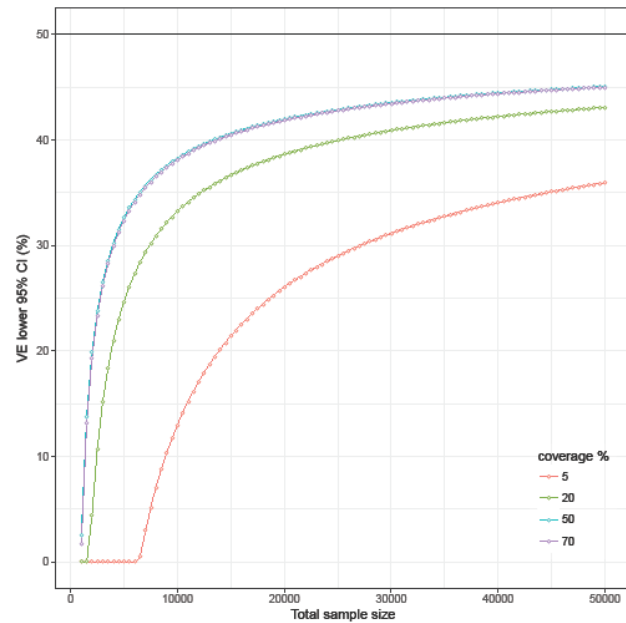
We calculated precision of the overall VE based on a two-sided 95% CI for cohort studies with the total number of subjects varying from 1000 to 50000, whilst assuming overall vaccination coverages of 5%, 20%, 50% and 70%, VE of 20%, 50% and 70%, and an attack rate in the unvaccinated of 5% and 15%. To calculate the precision of the brand-specific VE, we additionally assumed that the brand of interest accounts for 10%, 20%, 40%, 60%, 80% and 90% of the overall vaccination coverage

The results for precision of the overall VE assuming attack rates in the unvaccinated of 5% and 15% are given in Figures 4 and 5, respectively. These figures represent precision by total sample size. The results for the precision of brand-specific VE for anticipated true VE of 20%, 50% and 70%, and 5% attack rate are given in Figures 6 to 8.

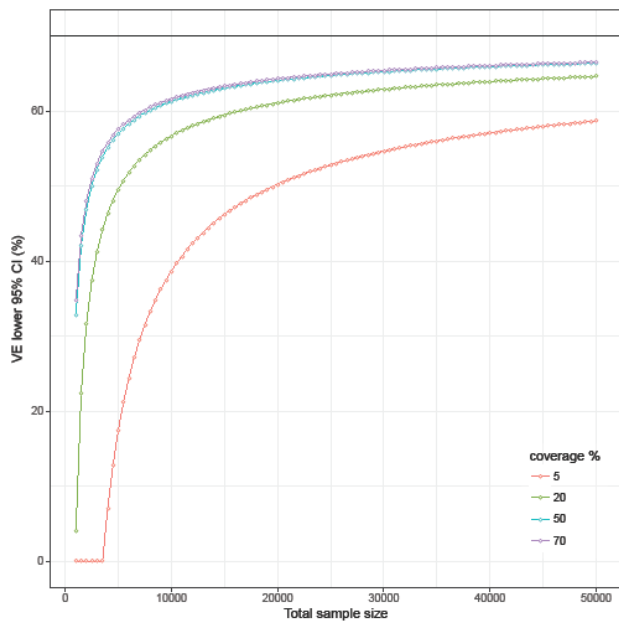




a) 20% VE

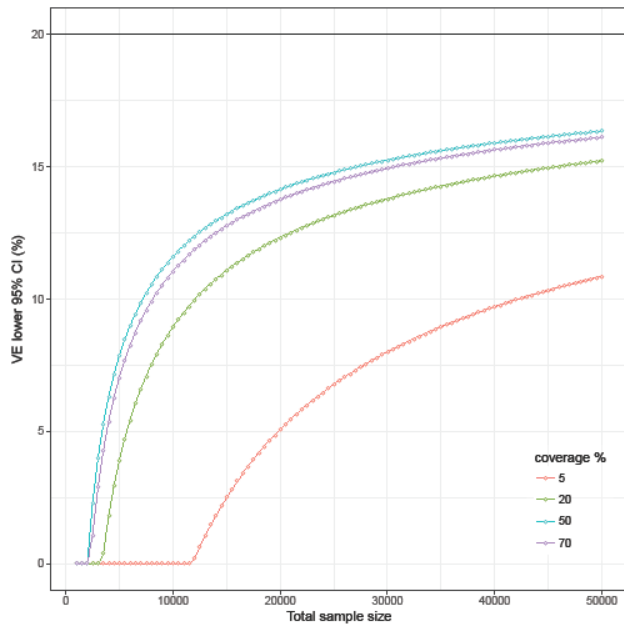


b) 50% VE

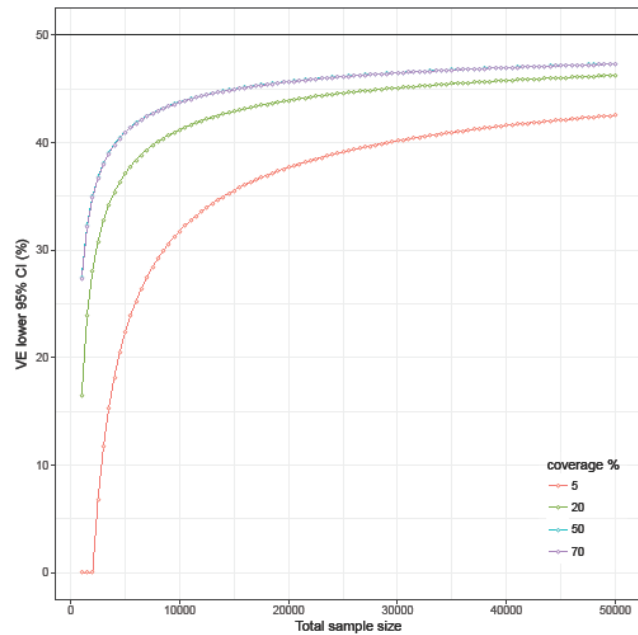


c) 70% VE

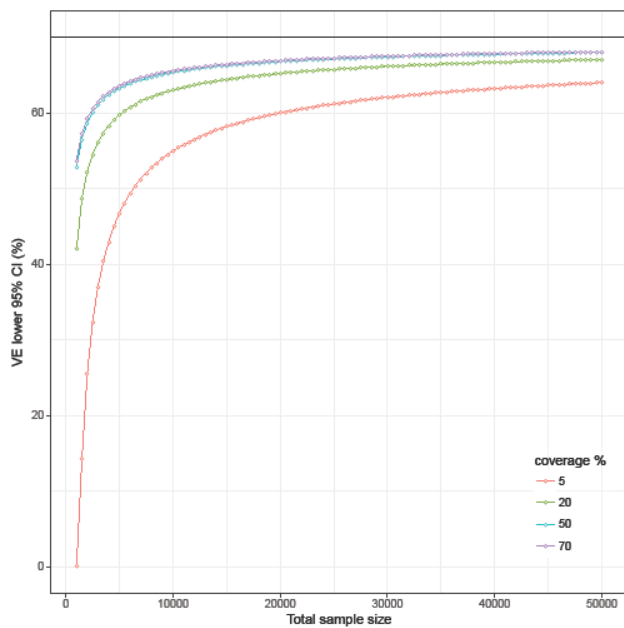
**Figure 4.** Precision of overall VE for a cohort study assuming vaccination coverage of 5%, 20%, 50% and 70%, VE of 20%, 50% and 70% (indicated with the black horizontal line), and 5% attack rate in the unvaccinated, by total sample size.



a) 20% VE

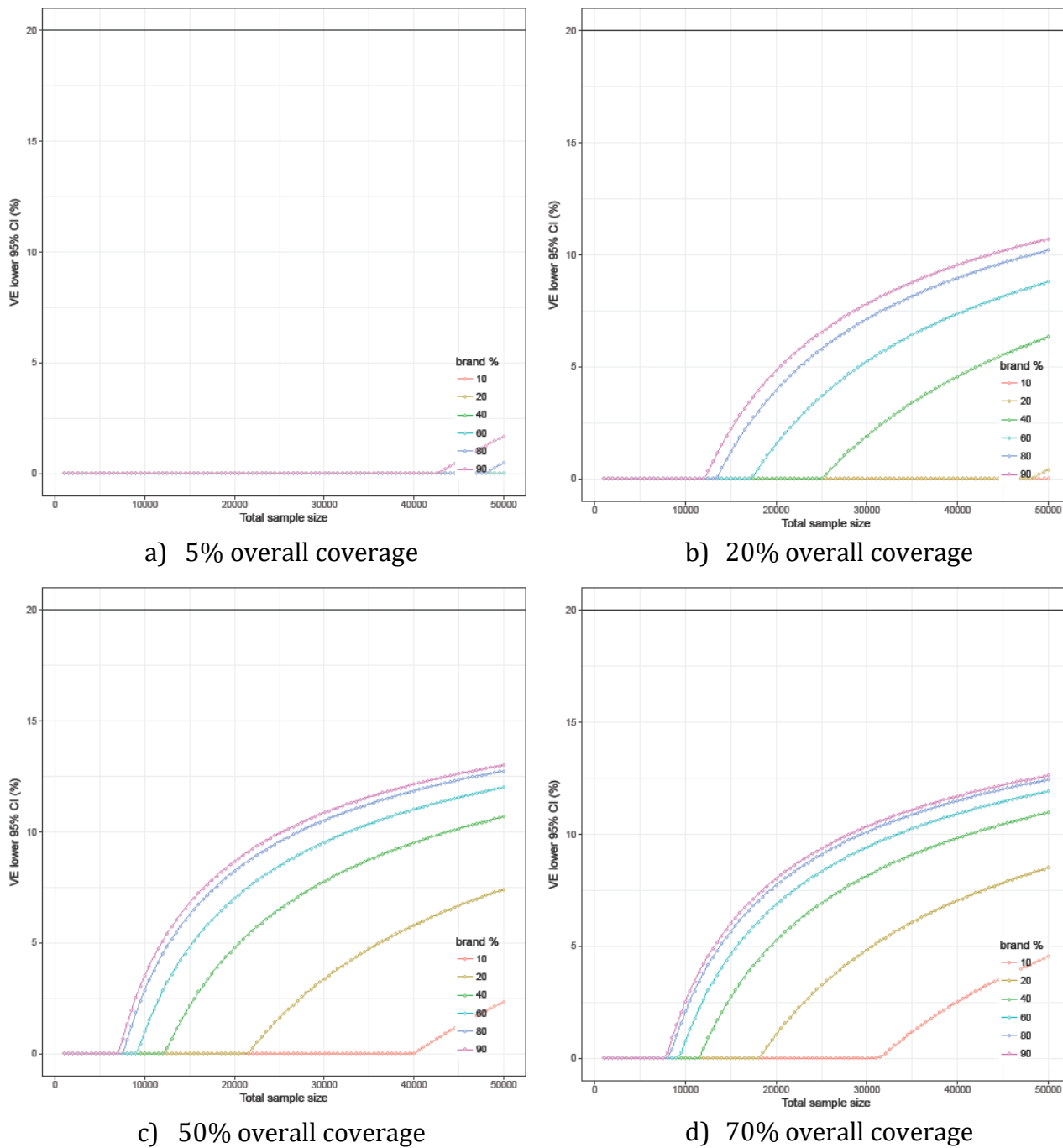


b) 50% VE

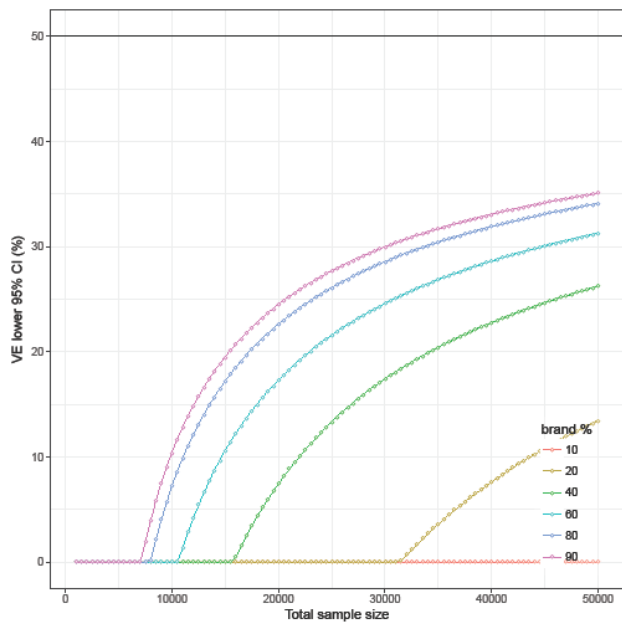


c) 70% VE

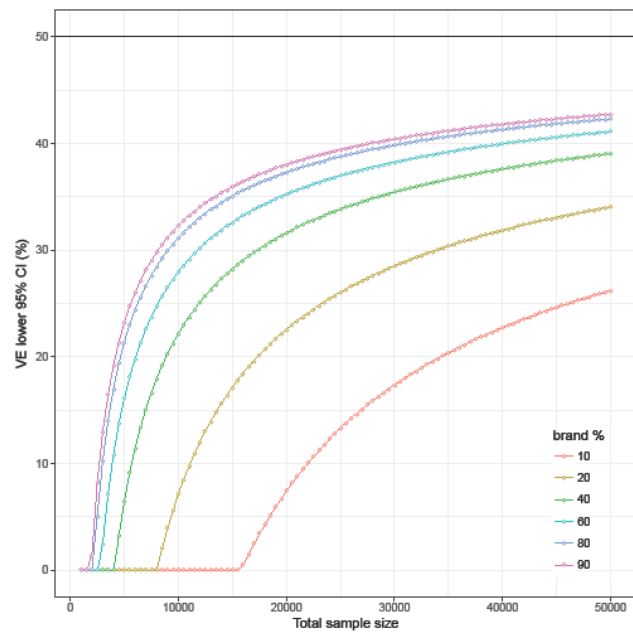
**Figure 5.** Precision of overall VE for a cohort study assuming vaccination coverage of 5%, 20%, 50% and 70%, VE of 20%, 50% and 70% (indicated with the black horizontal line), and 15% attack rate in the unvaccinated, by total sample size.



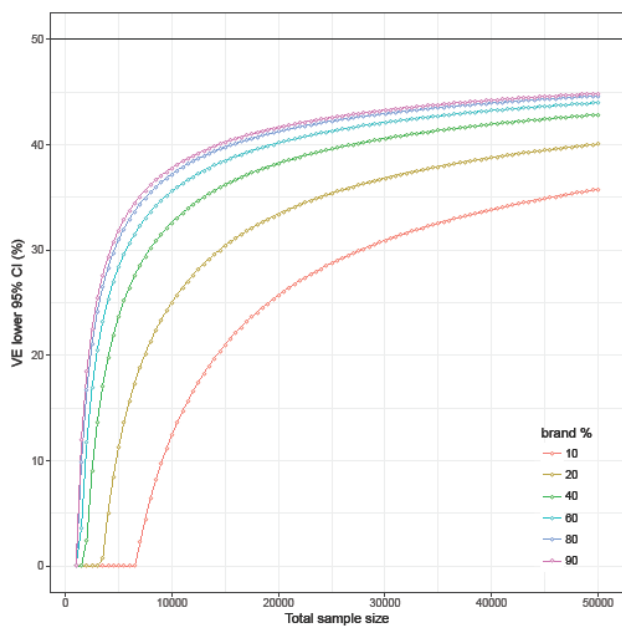
**Figure 6.** Precision of brand-specific VE for a cohort study assuming an anticipated true VE of 20% (indicated with the black horizontal line), overall vaccination coverage of 5%, 20%, 50% and 70% with the brand of interest covering 10%, 20%, 40%, 60%, 80% and 90% of the overall coverage, and 5% attack rate in the unvaccinated, by total sample size.



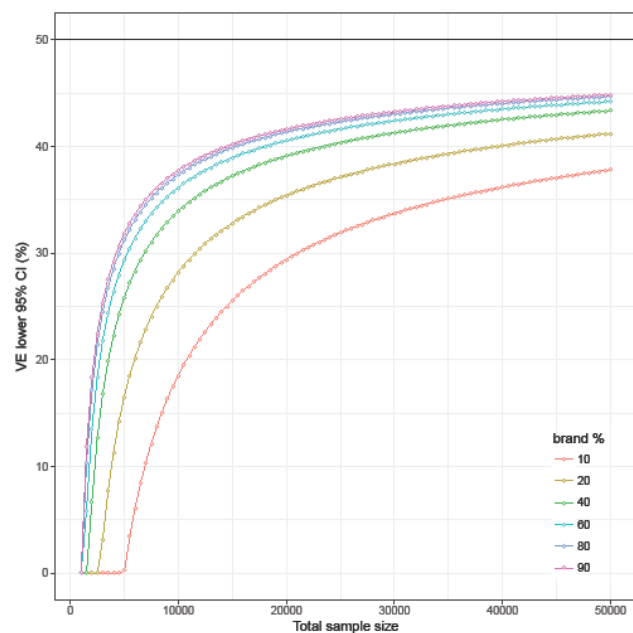
a) 5% overall coverage



b) 20% overall coverage

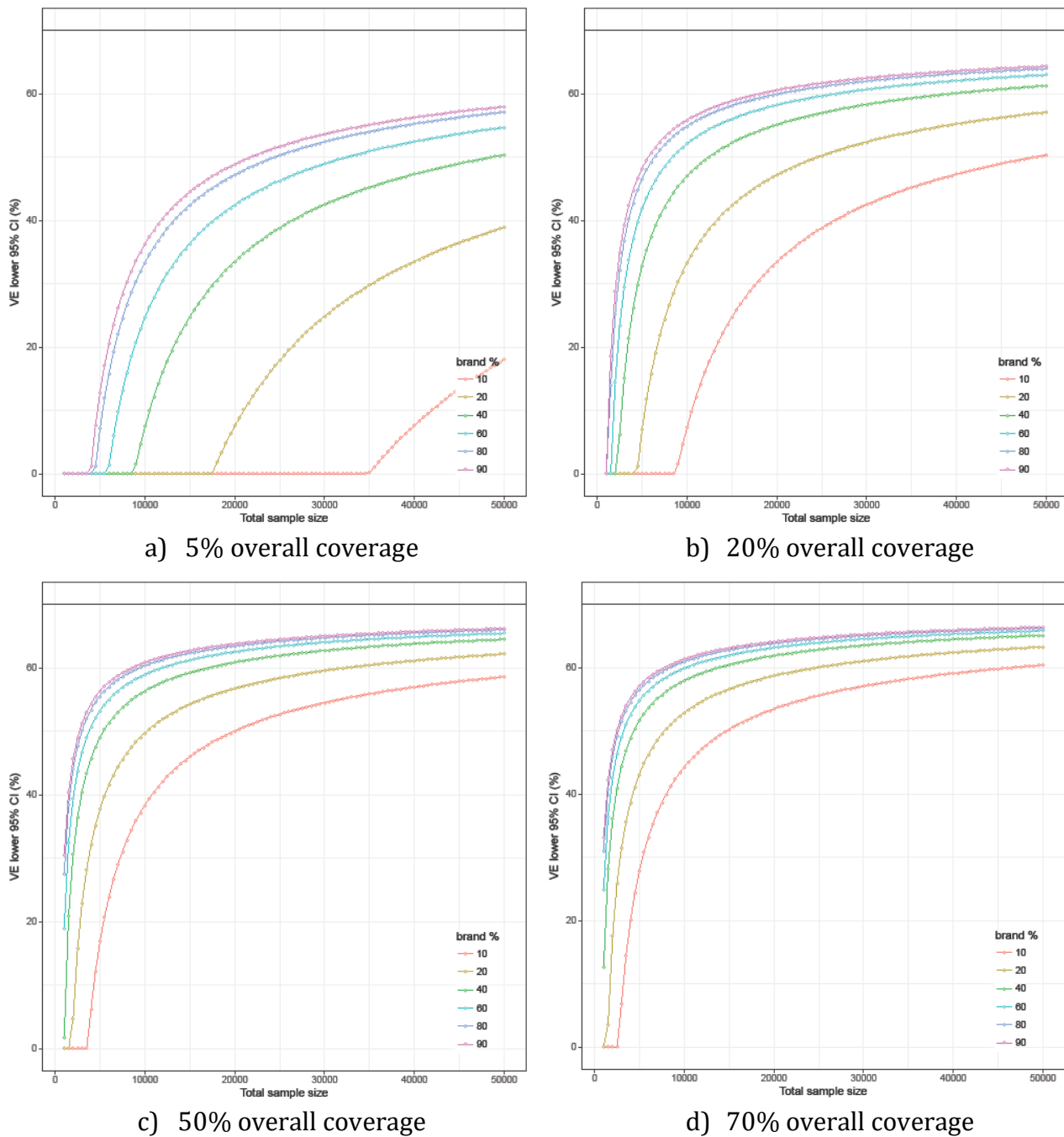


c) 50% overall coverage



d) 70% overall coverage

**Figure 7.** Precision of brand-specific VE for a cohort study assuming an anticipated true VE of 50% (indicated with the black horizontal line), overall vaccination coverage of 5%, 20%, 50% and 70% with the brand of interest covering 10%, 20%, 40%, 60%, 80% and 90% of the overall coverage, and 5% attack rate in the unvaccinated, by total sample size.



**Figure 8.** Precision of brand-specific VE for a cohort study assuming an anticipated true VE of 70% (indicated with the black horizontal line), overall vaccination coverage of 5%, 20%, 50% and 70% with the brand of interest covering 10%, 20%, 40%, 60%, 80% and 90% of the overall coverage, and 5% attack rate in the unvaccinated, by total sample size.

## Concluding remarks and recommendations

We make the following observations and recommendations based on our sample size calculations for single-site cohort studies;

- We recommend cohort studies based on 5000 subjects or more. A cohort study with 5000 subjects will result in a minimal detectable overall VE of 30-40% for an influenza attack rate of 5% and coverages >20%.
- A cohort study based on 5000 subjects will result in minimal detectable brand-specific VE of 30-40%, for an influenza attack rate of 5% and brands covering 40% to 90% of the influenza vaccines when the overall vaccination coverage is 50% or more.
- A cohort study with a total sample size of 20.000 will result in a minimal detectable VE of 18-20% for an influenza attack rate of 5% and overall vaccination coverages of 20% or more. Improvements in accuracy both in terms of minimal detectable VE and precision will be minimal when increasing sample sizes further.
- In case higher influenza attack rates (+/-15%) would be expected, lower sample sizes are needed to obtain VE estimates with acceptable precision.
- In case the VE is expected to be low (< 20%), higher sample sizes are required to obtain VE estimates with acceptable precision.
- In case interest is in VE within subgroups, the sample size calculations should be done with respect to the subgroup-specific sample size.
- IMPORTANT: These are recommendations to support the design of cohort studies on (brand-specific) influenza VE. Obtaining a minimum sample size is not a requirement for study participation.

## References

1. Woodward M. Epidemiology: study design and data analysis, 3d edition. London: Chapman & Hall, CRC Press; 2013.