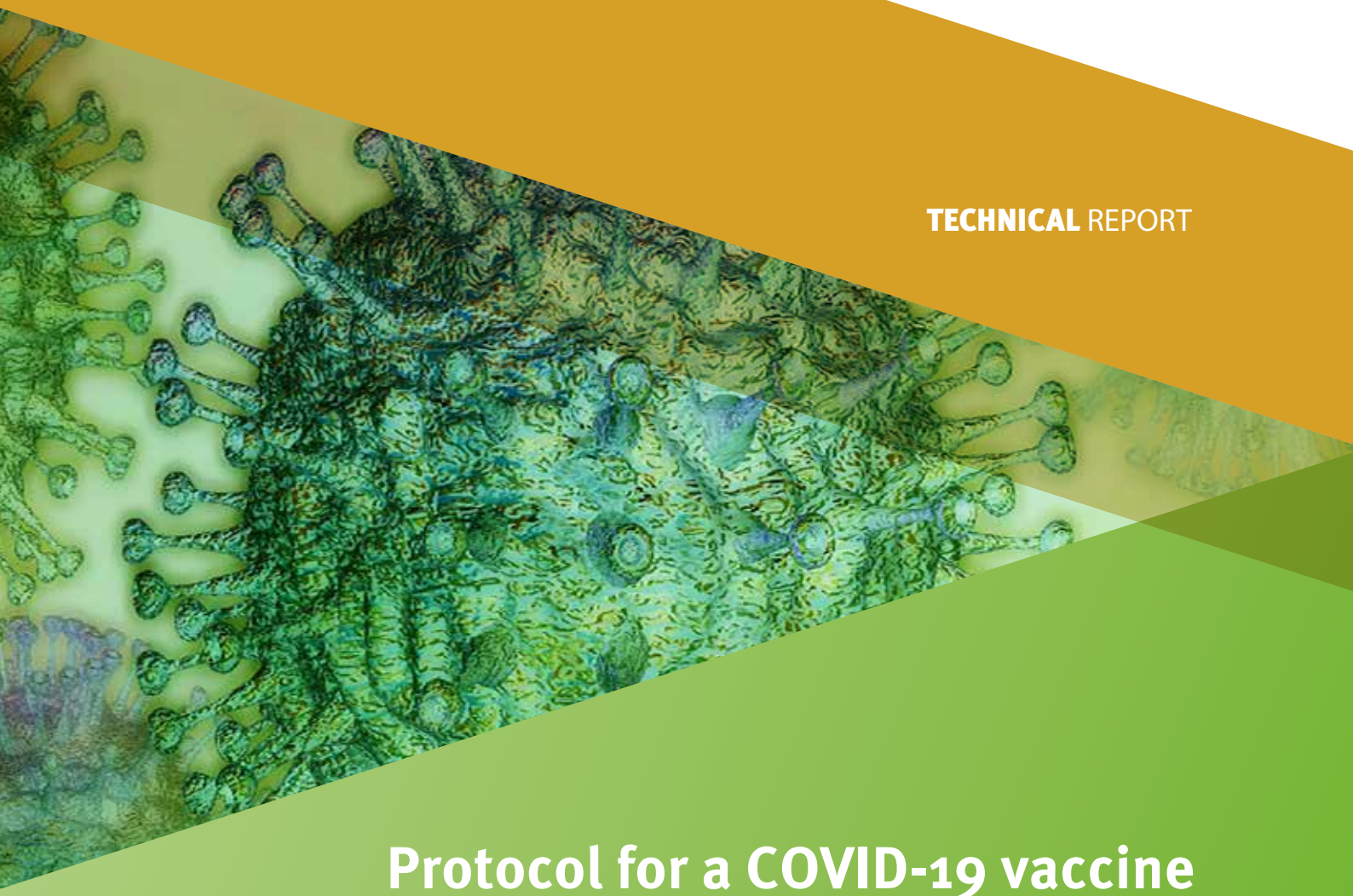


TECHNICAL REPORT

Protocol for a COVID-19 vaccine effectiveness multi-country cohort study in the paediatric population aged 5–17-years using electronic health records in EU/EEA countries

www.ecdc.europa.eu

ECDC TECHNICAL REPORT

Protocol for a COVID-19 vaccine effectiveness multi-country cohort study in the paediatric population aged 5–17 years using electronic health records in EU/EEA countries

This protocol was commissioned by the European Centre for Disease Prevention and Control (ECDC), as part of the activities within the Framework Contract (FWC) ECDC/2021/018 'Vaccine Effectiveness, Burden and Impact Studies (VEBIS) of COVID-19 and Influenza Lot 4'. Production of the protocol was coordinated by Nathalie Nicolay.

Authors
Patrícia Soares (PS), Ausenda Machado (AM), Irina Kislaya (IK), Baltazar Nunes (BN) (Instituto Nacional de Saúde, Portugal), Anthony Nardone, Alexis Sentis, Esther Kissling, James Humphreys (Epiconcept, France), Susana Monge Corella, Mario Fontan Vela (Instituto de Salud Carlos III, Spain), Iván Martínez-Baz, Itziar Casado, Aitziber Echeverría, Camino Trobajo-Sanmartín, Jesús Castilla (Instituto de Salud Pública de Navarra – IdiSNA – CIBERESP, Pamplona, Navarre-region, Spain), Christian Holm Hansen, Katrine Finderup Nielsen (Statens Serum Institut, Denmark), Massimo Fabiani, Alberto Mateo Urdiales, Chiara Sacco (Istituto Superiore di Sanità, Rome, Italy), Ala'a Al Kerwi, Susanne Schmitz (Ministry of Health, Directorate of Health, Service of Epidemiology and Statistics, Luxembourg), Hinta Meijerink, Anja Bråthen Kristoffersen (Norwegian Institute of Public Health, Norway).

Suggested citation: European Centre for Disease Prevention and Control. Protocol for a COVID-19 vaccine effectiveness multi-country cohort study in the paediatric population aged 5–17-years using electronic health records in EU/EEA countries. Stockholm: ECDC; 2024.

Stockholm, March 2024

ISBN 978-92-9498-696-2
doi: 10.2900/455798
Catalogue number TQ-02-24-383-EN-N

Contents

Abbreviations iv
Executive summary 1
Background 1
Objectives 2
Principal objective 2
Secondary objectives 2
Methodology 2
Study design 2
Study period 3
Study population 3
Vaccination status 4
Outcome 4
Stratification variables 5
Potential confounding variables (for adjustment) 5
Data sources 5
Construction of the cohort 6
Analysis plan 7
Description of the sample selection 7
Description of the study population 7
Estimation of the vaccine effectiveness 7
Data checking and validation 9
Potential biases and limitations 10
Data sharing to pool results at the European level 10
References 11
Annex 1. Vaccination campaign and coverage in each study site 13
Annex 2. Eligibility criteria for each study site 14
Annex 3. Outcome definition by study site 15
Annex 4. Variant of Concern dominance period 16
Annex 5. Confounding variables for adjustment 17
Annex 6. Data sources on reference population, vaccination, outcome and confounders 19
Annex 7. Data linkage methods 22
Annex 8. Pooled analysis power calculations 23
Annex 9. Reporting templates 26

Tables

Table 1. Implementation example of time-dependent variables and the outcome 7
Table 2. Minimum level of vaccine effectiveness detectable with a Power of 80% and a Type I error of 5%r 9
Table 1.1. Vaccination campaign rollout by country and age groups 13
Table 1.2. Vaccination coverage for one dose, complete primary course and first booster dose of COVID-19 vaccine by country and age groups as of 2023-06-16 13
Table 2.1. Eligibility criteria for complete vaccination with and without previous infection 14
Table 2.2. Minimum time interval recommended between doses 14
Table 3.1. Outcome definition by site 15
Table 4.1. VOC dominance period of 80% or higher by study site 16
Table 5.1. Indicators of socioeconomic status 17
Table 5.2. Definition of comorbidity by study site 17
Table 5.3 Factors used to adjust for confounding in each study site 18
Table 6.1 Source of information on the reference population 19
Table 6.2 Source of information and limitations on vaccination, outcome and confounders 20
Table 7.1 Data linkage method used in each study site 22
Table 8.1 Number of events, person-years and COVID-19 hospitalisation rate in the unvaccinated group 24
Table 8.2 Minimum level of vaccine effectiveness detectable at study site 25
Table 9.1 Mock-up table describing the distribution of the total number of persons or person-time during the follow-up period by sociodemographic and clinical characteristics of the study population 26
Table 9.2 Format for data reporting 27

Abbreviations

COVID-19	Coronavirus disease 2019
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
HR	Hazard Ratio
ICD	International Classification of Diseases
IPTW	Inverted Probability of Treatment Weighting
IRR	Incidence Rate Ratio
RT- PCR	Reverse-transcription polymerase chain reaction
SARI	Severe acute respiratory infection
SARS-CoV-2	Severe acute respiratory syndrome – coronavirus 2
VEBIS	Vaccine Effectiveness, Burden and Impact Studies
VOC	Variant of Concern
VOCs	Variants of Concern
VPS	Vaccination Propensity Scores

Executive summary

This protocol describes the common methodology to be applied to established health data registries across seven participating European Union/European Economic Area (EU/EEA) Member States to estimate vaccine effectiveness for Coronavirus disease 2019 (COVID-19) in children and adolescents aged 5-17 years old. This work was performed within the Vaccine Effectiveness, Burden and Impact Studies (VEBIS) project [1].

The study design is a retrospective cohort study using data from paediatric populations aged under 18 years old and eligible for COVID-19 vaccination, collected routinely in electronic health records databases. The study started at the beginning of the vaccination campaign for each age cohort and country (5-11 years old, 12-17 years old) and ended one year after. The outcome of interest is hospital admission due to COVID-19. Data collected, besides the outcome of interest, included sociodemographic (age, sex), clinical (comorbidities, previous history of severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2) infection) and COVID-19 vaccination history (brand, number and dates of dose administration).

The protocol outlines the methodology for analysing data at the country level and includes a plan for the pooled analysis. This master protocol was primarily intended to guide the implementation of one study within the VEBIS project. However, ECDC encourages, using this protocol as a basis to conduct vaccine effectiveness studies in countries that do not currently plan to participate in ECDC-funded studies. Consistent protocols will facilitate comparability of results across studies, countries and sites.

Background

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. The pandemic had resulted in over 6 million deaths by May 2023 [2]. More than three years after the start of the pandemic, WHO declared that COVID-19 was no longer a public health emergency of international concern in May 2023 [3]. Despite the ongoing high global risk assessment, the risk to human health was deemed reduced due to high population immunity obtained through infection and vaccination against SARS-CoV-2 [3]. In December 2020, the European Medicines Agency (EMA) authorised several vaccines against COVID-19 for use in the European Union [4]. Since then, COVID-19 vaccines have been studied for their effectiveness in different age groups, for their effectiveness against different variants of concern (VOCs) and for vaccination strategies (primary vaccination and booster). Overall, evidence points to high vaccine effectiveness against severe outcomes, such as hospitalisation and death (vaccine effectiveness varying between 76% and 99% respectively), and a decrease in effectiveness against SARS-CoV-2 infection and severe outcomes over time [5-8]. Several studies estimated COVID-19 vaccine effectiveness against infection in children and adolescents. However, few studies were focused on COVID-19 vaccine effectiveness in children and adolescents against COVID-19-related hospitalisation. Most of the studies analysing vaccine effectiveness against COVID-19-related hospitalisation were conducted in Singapore and the USA [9-16], with only a few studies conducted in Europe [17-18].

Within the paediatric population, COVID-19 vaccine effectiveness against hospitalisation varied between 40% and 93% [9-18]. Variations in vaccine effectiveness were observed analysing different subgroups. For children aged between three and 11 years old, vaccine effectiveness varied between 68% and 76%, and for adolescents between 12 and 18 years old, vaccine effectiveness varied between 40% and 93% [10-12]. Klein et al. also analysed adolescents between 12 and 15 years old and 16 and 17 years old and found similar vaccine effectiveness against hospitalisation for both age groups in the first five months after vaccine administration (92% and 94%, respectively). However, vaccine effectiveness decreased respectively to 73% and 88% after 150 days. Most studies were conducted when the dominant variant was Omicron [9, 12-15, 17]. Fewer studies looked at vaccine effectiveness during the Delta dominant period [10, 12, 13, 15]. Different results were found comparing Delta and Omicron post-infection-related hospitalisation, with a higher effectiveness against Delta-variant associated hospitalisation (vaccine effectiveness was around 83%, while vaccine effectiveness against Omicron-related hospitalisation ranged between 68% to 75%) [11, 13, 14]. Most of the studies evaluated the vaccine performance up to six months after vaccination [9-12, 14-17] , with one study evaluating the effectiveness up to nine months after vaccination [13].

Given the high variability of reported vaccine effectiveness estimations and several European countries' strategies regarding recommendation of vaccination in the paediatric population [19], it is crucial to evaluate and describe the effect of vaccines against severe outcomes in this age group.

This protocol describes a common methodology to estimate vaccine effectiveness against hospital admission due to COVID-19 for European children and adolescents using routinely collected vaccination status and outcome data from electronic health registries. This methodology has been used to monitor COVID-19 vaccine effectiveness in adults in Europe with robust estimation [6, 7].

Objectives

Principal objective

To estimate COVID-19 vaccine effectiveness against hospital admission due to the disease in the paediatric population eligible for vaccination (5–11 and 12–17 years old) without previous SARS-CoV-2 infection using information routinely collected in EU/EEA Member State electronic health registries in. Vaccine effectiveness was estimated for partially vaccinated individuals with primary series of COVID-19 vaccine (one dose) and individuals completely vaccinated with primary series of COVID-19 vaccine (two doses).

Secondary objectives

To estimate COVID-19 vaccine effectiveness (if sample size allows):

- Among individuals with previous SARS-CoV-2 infection and eligible for vaccination;
- By time since completion of primary vaccination series to describe waning immunity – (0–89), (90–179), (180–365) days, corresponding approximately to (0–3), (3–6) and (9–12) months;
- By vaccine products;
- Against different SARS-CoV-2 Variants of Concern: Delta, Omicron BA.1/BA.2 and Omicron BA.4/BA.5;

Study sites may contribute to all or only a subset of objectives.

Methodology

Study design

A retrospective cohort study was performed using data collected routinely in electronic health records registries . Data included the paediatric population eligible for vaccination during the study period, categorised into two age groups: 5 to 11 years old and 12 to 17 years old, given the vaccination schedule and vaccine type. We used a fixed cohort approach, defining the eligible population by their age at the start of the vaccination campaign, per the age criteria described.

Two different cohorts were analysed: a cohort of individuals without previous infection at baseline (principal objective) and a cohort of individuals with a previous infection at baseline (secondary objective). These cohorts are represented in Figure 1 and Figure 2, respectively.

Figure 1. Cohort diagram for individuals without previous infection at study baseline

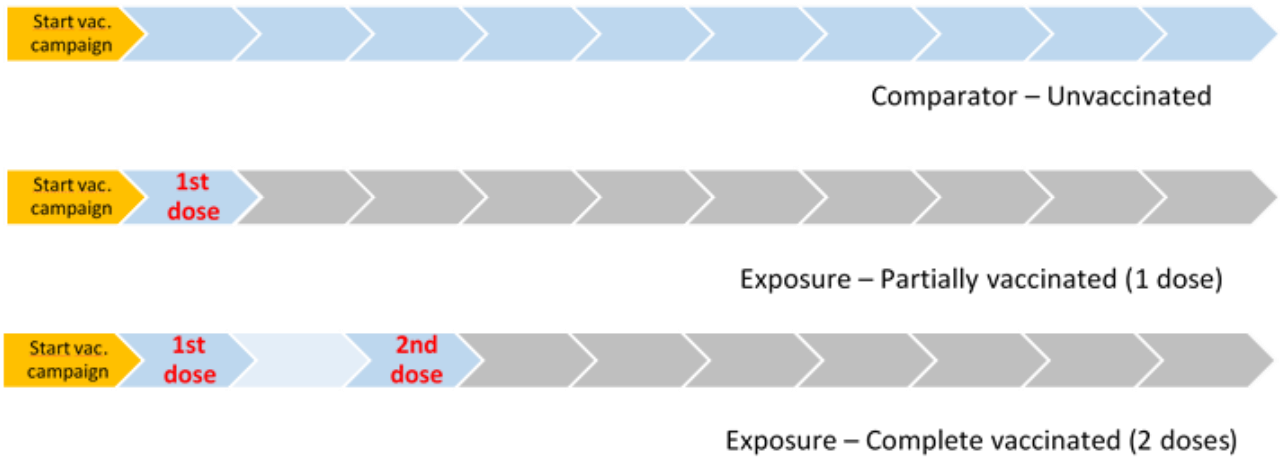
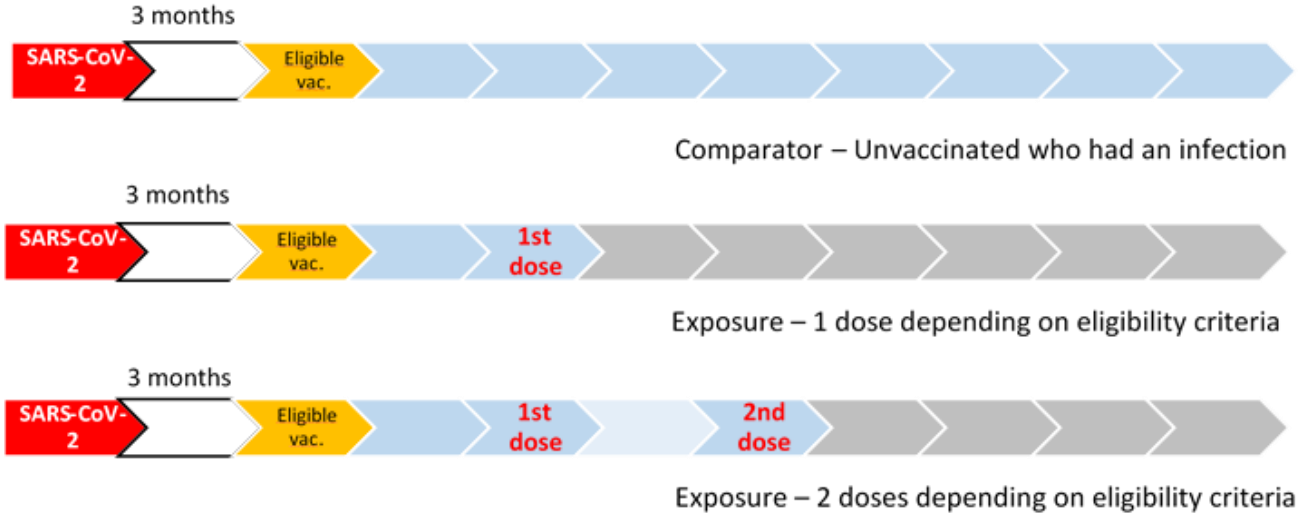


Figure 2. Cohort diagram for individuals with previous infection at study baseline



Study period

The study period started after the deployment of the COVID-19 vaccination campaign for each age group cohort and study site, and ended 12 months thereafter. The respective vaccine campaign start dates and vaccine coverage for each age group and site are reported in Annex 1.

Study population

Inclusion criteria

The study population included the paediatric reference population registries fulfilling the following criteria during the study periods:

- Aged between 5 and 17 years old at the beginning of the vaccination campaign;
- Resident in any of the participating EU/EEA countries covered in the study (definition of residency for each study site can be seen in Annex 6);
- Eligible for vaccination at the start of the vaccination campaign (study baseline) as indicated by each study site recommendation for each age group (Annex 2);
- For the analysis of vaccine effectiveness among those with a previous SARS-Cov2 infection, inclusion criteria will be a previous documented infection and being eligible for vaccination at the study baseline, according to national recommendations (Annex 2).

Exclusion criteria

- Individuals with an interval between the first and second dose not compatible with national recommendations in place in each age group (Annex 2);
- Individuals with inconsistent or missing data on vaccination (vaccination status unknown, any vaccination date unknown, any vaccine brand unknown, and number of doses unknown);
- Individuals vaccinated with a number of doses higher than the total number recommended for their age group (Annex 2);
- Individuals who received any vaccine product not approved by EMA and/or those for which the combination of vaccine products received is not possible when following the recommended schedule (may vary by age group) will be excluded (Annex 2);
- Individuals vaccinated before the beginning of the study period;
- Individuals with a previous documented SARS-CoV-2 infection (principal objective);
- Individuals who had a previous SARS-CoV-2 infection in the previous 90 days before the study will no longer be eligible to enter the previous infection cohort (one of the secondary objectives).

Vaccination status

The vaccination status was based on the number of vaccine doses administered up to when vaccination status is assessed (as a time-changing variable), according to the following classification:

Cohort without previous infection

- **Unvaccinated:** person-time of children and adolescents without any registered COVID-19 vaccine dose.
- **Partially-vaccinated with primary series of COVID-19 vaccine:** person-time of children and adolescents who received one dose of Comirnaty or Spikevax adult or children's dose depending on the age group during the study period. The completion status is achieved 14 days after administration of the dose.
- **Complete vaccination with primary series of COVID-19 vaccine:** person-time of children and adolescents who received two doses of Comirnaty or Spikevax adult or children's dose depending on the age group during the study period. The two doses should be administered according to respective age group and country recommendation (Annex 2). The completion status of the primary series is achieved 14 days after administration of the second dose required for complete primary series vaccination.

Cohort with previous infection

- **Unvaccinated:** Person-time of children and adolescents without any registered COVID-19 vaccine dose
- **Partially-vaccinated with primary series of COVID-19 vaccine:** person-time of children and adolescents with a documented previous infection who received one dose of Comirnaty or Spikevax during the study period (Annex 2). The completion status of the primary series is achieved 14 days after administration of the final dose required for complete primary series vaccination.
- **Complete vaccination with primary series of COVID-19 vaccine:** person-time of children and adolescents with a documented previous infection who received two doses of Comirnaty or Spikevax during the study period (Annex 2). The completion status of the primary series is achieved 14 days after administration of the final dose required for complete primary series vaccination.

Time since vaccination

- Time since completion of the primary vaccination will be calculated at each time point and classified into the following categories:
- From time 14 days, as previously defined, to ≤89 days after time 0 (i.e., <13 weeks, approximately three months);
- 90 to 179 days after time 0 (i.e., ≥13 weeks & <26 weeks, approximately three to six months);
- 180 to 365 days (i.e. ≥26 weeks & <52 weeks, approximately six to 12 months);

By vaccine product

Primary series vaccine effectiveness overall, and by time since vaccination, was estimated by vaccine brand (Comirnaty and Spikevax) if the number of events allowed.

Children with Comirnaty (or Spikevax) complete vaccination primary series were defined as those aged 5 to 17 years old that received two doses of the same paediatric Comirnaty (or Spikevax) vaccine formulation, with time between doses as recommended, according to the relevant national guidelines (Annex 2).

Outcome

The outcome of interest was defined as admission to a hospital:

- with a laboratory-confirmed infection using reverse-transcription polymerase chain reaction (RT-PCR), or antigen test, between 24 hours after or ≤up to 14 days before pre- or ≤24 hours post-admission, in which admission criteria are compatible with severe acute respiratory infection (SARI) (based on similar criteria as in SARI surveillance, International Classification of Diseases (ICD) coding or similar);
  OR
- in which COVID-19 is the main diagnosis in the discharge record (for example, based on ICD coding or similar).

The outcome date was the earliest between the hospitalisation date and the laboratory diagnosis date (i.e. the sample date or, if the sample date is unavailable, the date of laboratory result of the first positive test that resulted in hospital admission), with a maximum interval of 30 days. If no positive test was available but the cause of hospitalisation was COVID-19, the outcome date was the date of hospitalisation (outcome definition per country/study site in Annex 3).

Stratification variables

Age group

Age was calculated at the beginning of the study period using the date of birth and was categorised into two age groups: 5 to 11 years old, and 12 to 17 years old. Study sites that started the vaccination campaign at different dates in 12–15 years old and 16—17 years old should construct different cohorts for each age group and merge them for analysis.

Variants of Concern

Estimates of COVID-19 vaccine effectiveness was presented with study time stratified by the period of circulation of Variants of Concern (VOC) predominance. This study considered the Delta, Omicron BA.1/2 and BA.4/5 dominance period. A period of VOC dominance was defined by the set of weeks starting with the first week where the proportion of SARS-CoV-2 cases that belonged to the specific VOC was higher or equal to 80% and ended with the last week where the VOC prevalence was higher or equal to 80%. Variant of Concern dominance period per study site is available in Annex 4.

Potential confounding variables (for adjustment)

A set of variables was used to account for confounding bias, adapted to each country/ study site context. This may include sociodemographic, health status, comorbidities and health-seeking behaviour. Specific confounding variables are presented in Annex 5.

Sociodemographic

- Sex;
- Age;
- Indicators of social socioeconomic status, at individual or area-level;
- Region;
- Country of birth and/or nationality.

Comorbidities and health-seeking behaviour

Different variables can be used to account for comorbidities. Annex 5 lists the definition of comorbidities per study site.

Data sources

The study used routinely data collected in various population health registries available at the study site, national or subnational level. Each database should contain a unique identifier for each individual to allow data linkage between databases.

Sources of information on the reference population

The reference population database (census database, health coverage database, etc.) with individual records of the target study population for each study site is present in Annex 6.

Sources of information on the vaccination status

Information on vaccination status is found in the vaccination registry or vaccination record databases with records of children and adolescents, including dates of COVID-19 vaccination and vaccine brand. Annex 6 summarises the different datasets used in each study site.

Sources of information on the outcomes

Data was extracted from different electronic health record databases (Annex 6 for specific data sources per study site):

- COVID-19 laboratory-confirmed infection;
- Hospital admission/discharge.

Sources of information on confounders

- Electronic databases on comorbidities: possibly primary healthcare records, data on medication prescriptions, or any other population-based data source that can provide information on comorbidities for all cohort individuals;
- Electronic databases on healthcare-seeking behaviour: possibly healthcare administrative database (i.e. the number of consultations), laboratory records (i.e. the number of tests performed) or non-COVID-19 vaccination records (i.e. other vaccines administered).

Construction of the cohort

Identification of individuals and characteristics at baseline

The reference population database was linked with the electronic databases on vaccination, comorbidities and/or health-seeking behaviour, SARS-CoV-2 laboratory tests and results, hospitalisations and other vital registries using unique identifiers by employing a deterministic data linkage procedure (no random component in the linkage procedure).

Children and adolescents entered the study in their corresponding group of vaccination status based on the data available in the vaccination registry. The start period for 5–11 years old and 12–17 years old also differed according to the start of the vaccination campaigns for those age groups (Annex 1). Study sites that started the vaccination campaign on different dates for 12–15 years old and 16–17 years old also entered the study at different times, since individuals cannot be at risk before the start of the vaccination campaign for their age group. An example can be seen in Table 1.

Variables to be measured at baseline include age, sex, region (if relevant), previous documented SARS-CoV-2 infection and SARS-CoV-2 infection date, comorbidities, and other socioeconomic or health-seeking behaviour variables that were used to adjust vaccine effectiveness estimates to stratify or account for confounding.

Annex 7 specifies the different data linkage methods used in each study site.

Time-changing characteristics and identification of outcomes during follow-up

Vaccination status and time since vaccination was assessed, and children and adolescents were classified into the same or updated vaccination status daily, generating a new record in the dataset for each new assessment.

The time-varying variable was created for each age group. Study sites that started the vaccination campaign on different dates for 12–15 years old and 16–17 years old also created this variable separately. In these cases, the date of study entry was added as a covariate to account for any influence of the actual calendar date. An example of the time-varying variable can be seen in Table 1.

Person-time exposure to first and second dose between 0–13 days as excluded from the analysis. In Table 1, these times correspond to the categories 'Partially vaccinated 0–13' and 'Completely vaccinated 0–13'.

Information for identifying outcomes and the dates they occurred was obtained by data linkage between the cohort built previously and the databases containing information on the respective outcomes. Outcome classification for each child and adolescent was assessed from the start of the vaccination campaign for each age group. Table 1 displays an example of the dataset for the outcome and the vaccination status.

For each VOC predominance period, the analysis cohort corresponded to a subset of the cohort created for the principal objective, filtered based on the VOC dates reported in Annex 4 (secondary objective 4).

Censoring events

All children and adolescents were followed from the start of the vaccination campaign for each age group (or the start of the VOC-specific study period, for secondary objective 4) until:

- Hospitalisation date, or SARS-CoV-2 laboratory diagnosis date, as defined above, which corresponded to the event date;
- At the end of the study, 12 months after the start of the vaccination campaign, or at the end of the VOC-specific study period;
- On the date of death, by any cause;
- Discontinuation in the administrative database, such as emigration;
- SARS-CoV-2 laboratory diagnosis date during the study period if no hospitalisation occured;
- Date of COVID-19 vaccine booster dose.

Table 1. Implementation example of time-dependent variables and the outcome

ID	Age group	age	Start time	End time	Start study	Vaccination status	Time since vaccination	Event	Other variables classified at baseline (e.g., age, sex, or comorbidities)
1	12–17	16	0	365	13/07/2021	Unvaccinated	Unvaccinated	0	Constant
2	12–17	13	30	60	12/08/2021	Unvaccinated	Unvaccinated	0	Constant
2	12–17	13	61	74	12/08/2021	Partially vaccinated 0–13	Partially vaccinated 0–13	0	Constant
2	12–17	13	75	100	12/08/2021	Partially vaccinated	Partially vaccinated 14–89	0	Constant
2	12–17	13	101	114	12/08/2021	Completely vaccinated 0–13	Completely vaccinated 0–13	0	Constant
2	12–17	13	115	190	12/08/2021	Completely vaccinated	Completely vaccinated 14–89	0	Constant
2	12–17	13	191	211	12/08/2021	Completely vaccinated	Completely vaccinated 90–179	1	Constant

Analysis plan

Description of the sample selection

The total number of children and adolescents fulfilling the inclusion criteria at the study baseline was calculated for each database. The number and proportion of children and adolescents excluded after applying each selection criteria was recorded.

Description of the study population

The number of persons, total person-time of follow-up, and the number of events by vaccination status and age group was calculated following the format in Annex 9. Distribution of the number of persons and total person-time of follow-up was described by baseline variables in each vaccination status group defined in the study. To estimate the total number of persons, the vaccination status group at the end of each person-time follow-up was considered.

The proportion of the missing data was used to determine if each specific variable can be included in the model and how (e.g., missing could eventually be included in the model as a category). Imputation to address missing data was not planned as a means for increasing data quality.

Estimation of the vaccine effectiveness

A complete case analysis as performed considering all variables included in the final model used to estimate adjusted-confounding vaccine effectiveness.

Groups compared and subgroup analysed

vaccine effectiveness was estimated by comparing the hazard rate of the outcome in children and adolescents with COVID-19 primary vaccination (exposed group) for any vaccine or by vaccine brand (secondary objective 3) with the hazard rate of the outcome in unvaccinated children and adolescents (reference group).

In the analysis of vaccine effectiveness by time since vaccination (secondary objective 2), vaccine effectiveness was estimated by comparing the hazard rate of the outcome in children and adolescents with COVID-19 primary vaccination for each group from the time since vaccination 14 to 89, 90 to 179 and 180 to 365 days (exposed group) in comparison with the outcome hazard rate in unvaccinated children and adolescents (reference group).

For secondary objectives, the analyses was stratified by age group (5–11, 12–17) and VOC period of predominance (Delta, Omicron BA.1/2 and Omicron BA.4/5).

Crude hazard ratio

Cox proportional hazards regression models was used to estimate the hazard ratio (HR), considering the event as the first hospitalisation due to COVID-19 and the exposure as the vaccination status. The crude HR of vaccinated vs. unvaccinated was estimated for each outcome of interest during the study period at each study site, without adjusting for other factors or covariates [6].

Vaccine effectiveness

vaccine effectiveness was estimated as one minus the confounder-adjusted HR of vaccinated vs. unvaccinated for each outcome of interest.

vaccine effectiveness = (1-aHR) x 100

Cox proportional hazards regression model was used to estimate the confounder-adjusted HR. The event was the first hospitalisation due to COVID-19 and the exposure was vaccination status (primary vaccine and time since vaccination). Two sets of confounding factors were considered. First, partially adjusted HR was estimated e.g adjusting by age, sex and country region, whenever appropriate. Second, a fully adjusted HR estimate was produced e.g. adjusting variables related to socioeconomic condition, comorbidities and health-seeking behaviour as relevant at each study site (Annex 5). For additional variable selection for adjustment, it is recommended to fit models with and without each covariate to see its effect on the vaccine effectiveness estimate.

Alternative method to adjust for confounding

Given the expected low frequency of events in each study site and the need to adjust for several potential confounders, an alternative approach applying an Inverted Probability of Treatment Weighting (IPTW) could also be used. In this situation, a generalised linear model with multinomial distribution and logit link can be used to estimate COVID-19 vaccination propensity scores (VPS) using individuals' baseline characteristics as predictors. Predictors can include age, sex, country region, socioeconomic condition, comorbidities and health-seeking behaviour. Predictors might vary for each study site.

Inverted Probability of Treatment Weighting corresponds to the ratio between P(V=0)/P(V=0|Cov), P(V=1)/P(V=1|Cov) and P(V=2)/P(V=2|Cov) for the unvaccinated, vaccinated with one dose and vaccinated with two doses, respectively P(V=x), with x=0, 1 or 2 is estimated from the multinomial logistic regression model only with the constant and P(V=x|cov) is estimated from a multinomial logistic model with vaccination status as outcome and the covariates as predictors [20]. Extreme values of the IPTW weights (higher than the 95% percentile) will be replaced by the 95% percentile value. Confounder-adjusted HR estimates could be obtained by weighting the Cox proportional hazards regression models by the IPTW weight.

Methods for pooling estimates

Country-specific HRs and standard errors for the effect of COVID-19 vaccination obtained from the study sites will be combined in a model using meta-analysis techniques.

Given the expected heterogeneity of the vaccine effect at the country level due to different database systems, vaccination history, SARS-CoV-2 VOCs circulation periods and epidemic phase, between-site vaccine effectiveness estimate heterogeneity is expected. Considering this, a random-effects model will be used as the first approach. To account for the two sources of variability (within-study and between-studies), the variance will be divided into two components: the individual study-specific variances and the variance of the random study effects (τ^2). I^2 represents the proportion of the total variance that is not attributable to random variation between study effects estimates but due to heterogeneity in the effect. τ^2 and I^2 will be used to report between-site statistical heterogeneity, along with the p-value of Cochrane's heterogeneity test.

A fixed-effects approach will also be used, as a comparator, by computing a simple weighted average across studies. To do this, the site-specific vaccination status-disease effects (HRs) will be weighted by the inverse of their marginal variances (generic inverse variance method). This will give the pooled HR and a standard error. The confidence interval around the pooled effect (the range of values that contain the true average HR with 95% certainty) will then be calculated.

Potential factors or specific pilot site characteristics that could be the source of qualitative heterogeneity will be described, as covered in the descriptive part of the data analysis in this protocol.

The country-specific vaccine effectiveness, their confidence intervals, and the pooled vaccine effectiveness, will be presented graphically in a forest plot. The crude effect, the basic adjusted effect (age, sex, region) and the fully adjusted effect (adding the rest of available covariates) will be compared to assess the degree of confounding by different factors and guide the hypothesis around the explanation of differences across sites.

Pooled vaccine effectiveness power analysis

The power analysis was developed for the principal objective considering the measure of effect vaccine effectiveness = 1 - incidence rate ratio (IRR primary course vaccine vs unvaccinated).

From each study site and age group, the number of events and person-years in the unvaccinated group, the total person-years in the vaccinated group and the total person-years observed in the total cohort over 12 months was used (Annex 8). The power was calculated at the study site and age group, for each possible value of the vaccine effectiveness from 1% to 99%.

To produce power calculations for pooled estimates, the recommendations presented in Valentine J, Pigott and Rothstein 2010 [21] were followed.

Four scenarios of heterogeneity between vaccine effectiveness estimates at the study site were considered:

1) No heterogeneity (fixed effect model), and three levels of heterogeneity (random effects model);

2) low heterogeneity – $I^2 = 25\%$,

3) medium heterogeneity – $I^2 = 50\%$ and 4) high heterogeneity – $I^2 = 75\%$.

Methodological details can be found in Annex 8.

Results are presented regarding the minimum level of vaccine effectiveness detectable with a power of 80% and a Type I error of 5%. At the study site, the power calculations show that the minimum detectable value of vaccine effectiveness varied between 92% (Navarra, Spain) to 22% (Italy) for the age group 12–17 years old, and from 98% (Luxembourg) to 17% (Italy) for the age group 5–11 years old (Annex 8).

Pooled vaccine effectiveness estimated power analysis showed that minimum detectable vaccine effectiveness according to different levels of heterogeneity varied from 20% to 30% in the 12–17 years old and 16% to 26% in the 5–11 years age group (Table 2). Even for high levels of heterogeneity between studies, the minimum detectable vaccine effectiveness was below the vaccine effectiveness estimates reported in the literature (40% to 93%) in these age groups.

Table 2. Minimum level of vaccine effectiveness detectable with a Power of 80% and a Type I error of 5%, for the four levels of vaccine effectiveness heterogeneity between studies and the study site with the highest power

Type of Analysis	Age group 12 to 17	Age group 5 to 11
Individual study with maximum power	22	17
No heterogeneity (fixed effect model)	**20**	**16**
Low heterogeneity $I^2 = 25\%$ (random effect model)	**22**	**18**
Medium heterogeneity $I^2 = 50\%$ (random effect model)	24	20
High heterogeneity $I^2 = 75\%$ (random effect model)	30	26

Data checking and validation

Each study site should conduct the following data checking and validation before analysis:

- Identification of inconsistencies (e.g., earlier dates for second doses than for first doses);
- Unusual values and outliers;
- Missing values, missing clinical details, missing laboratory results;
- Duplicate cases and multiple admissions;
- A delay between the symptom's onset date and lab specimen collection date that is too long;
- Consistency of and among dates (onset, admission, discharge, swabbing);
- Missing data for essential variables that can lead to excluding the records from the analyses.

Ethical requirements

Each study site received ethical approval and conformed to national and EU ethical and data protection requirements.

Potential biases and limitations

- The granularity and availability of each registry used in the study may vary, as they were designed for purposes other than this study. As a result of the inherent between-site variability of registry data, pooled estimates must be interpreted with care.
- Control for confounding will also be limited since many relevant variables are not monitored or available in the registries.
- Previous infections may not be adequately recorded. Thus, identifying individuals with a previous SARS-CoV-2 infection may be imperfect due to limitations in the availability of data and different testing policies among participating countries. As a result, individuals with a previous SARS-CoV-2 infection (though unregistered) may be erroneously classified as belonging to the cohort with no previous SARS-CoV-2 infection – biasing vaccine effectiveness estimates.
- Given the rollout of COVID-19 vaccination in most European countries, there is collinearity between age, time of infection, type of vaccine used and VOC predominance periods. Therefore, the interpretation of effects by time since vaccination, age and during VOC predominance periods needs to be done cautiously from a causal perspective.
- The unvaccinated children and adolescents will be the reference group in the analysis. However, they might be increasingly different from the vaccinated population. For example, they may take fewer preventive precautions, be more at risk, and have a higher underlying risk of COVID-19 – leading to an overestimation of vaccine effectiveness. On the other hand, they could be children and adolescents with a previous SARS-CoV-2 infection that remained unidentified in the registries (something likely after the widespread use of self-tests), thus underestimating vaccine effectiveness.

Data sharing to pool results at the European level

The specific information to be shared with the European collaboration includes:

- Point estimation (HR) for all analysed effects (for each outcome, in every subgroup), i.e. exponential coefficient from the Cox proportional hazards regression models.
- Lower and Upper limits of the confidence interval of every estimation, i.e. exponential lower and upper limits of the confidence intervals estimated from the Cox proportional hazards regression models.
- Number of persons, of person-days of follow-up and events in each analysis.

References

1. European Centre for Disease Prevention and Control (ECDC). Pilot Protocol for a COVID-19 Vaccine Effectiveness Study Using Health Data Registries.; 2022. doi:10.2900/125804. Available at: https://www.ecdc.europa.eu/en/publications-data/protocol-covid-19-vaccine-effectiveness-study-using-health-data-registries
2. World Health Organization (WHO). COVID-19 Weekly Epidemiological Update.; 2021. https://www.who.int/publications/m/item/covid-19-weekly-epidemiological-update
3. World Health Organization (WHO). Statement on the fifteenth meeting of the IHR (2005) Emergency Committee on the COVID-19 pandemic. Published 2023. Accessed May 19, 2023. https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic
4. European Medicines Agency (EMA). COVID-19 vaccines: authorised. [Accessed May 10, 2023]. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised
5. Au WY, Cheung PPH. Effectiveness of heterologous and homologous covid-19 vaccine regimens: Living systematic review with network meta-analysis. BMJ. Published online 2022. doi:10.1136/bmj-2022-069989
6. Nunes B, Rodrigues AP, Kislaya I, Cruz C, Peralta-Santos A, Lima J, et al. mRNA vaccine effectiveness against COVID-19-related hospitalisations and deaths in older adults: A cohort study based on data linkage of national health registries in Portugal, February to August 2021. Eurosurveillance. 2021;26(38):1-7. Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.38.2100833
7. Kissling E, Hooiveld M, Martinez-Baz I, Mazagatos C, Naoma W, Vilcu A, et al. Effectiveness of complete primary vaccination against COVID-19 at primary care and community level during predominant Delta circulation in Europe: multicentre analysis, I-MOVE-COVID-19 and ECDC networks, July to August 2021. Eurosurveillance. 2022;27(21). Available at: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.21.2101104
8. Ssentongo P, Ssentongo AE, Voleti N, Groff D, Sun A, Djibril M, et al. SARS-CoV-2 vaccine effectiveness against infection, symptomatic and severe COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2022;22(1):1-12. doi:10.1186/s12879-022-07418-y
9. Yan VKC, Cheng FWT, Chui CSL, Tsz F, Lai T, King Ho Wong C, et al. Effectiveness of BNT162b2 and CoronaVac vaccines in preventing SARS-CoV-2 Omicron infections, hospitalizations, and severe complications in the pediatric population in Hong Kong: a case-control study. Emerg Microbes Infect. 2023;12(1). doi:10.1080/22221751.2023.2185455
10. Price AM, Olson SM, Newhams MM, Halasa V, Boom J, Sahni L, et al. BNT162b2 Protection against the Omicron Variant in Children and Adolescents. N Engl J Med. 2022;386(20):1899-1909. doi:10.1056/nejmoa2202826
11. González S, Olszevicki S, Gaiano A, Baino A, Regairaz L, Salazar M, et al. Effectiveness of BBIBP-CorV, BNT162b2 and mRNA-1273 vaccines against hospitalisations among children and adolescents during the Omicron outbreak in Argentina: A retrospective cohort study. Lancet Reg Heal - Am. 2022;13:100316. doi:10.1016/J.LANA.2022.100316
12. Klein NP, Stockwell MS, Demarco M, Gaglani M, Kharbanda A, Irving S, et al. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA Vaccination in Preventing COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Nonimmunocompromised Children and Adolescents Aged 5–17 Years — VISION Network, 10 States, April 2021–January 2022. MMWR Morb Mortal Wkly Rep. 2022;71(9):352-358. doi:10.15585/MMWR.MM7109E3
13. Chiew CJ, Premikha M, Chong CY, Wycliffe E Wei, Ong B, Lye D, et al. Effectiveness of primary series and booster vaccination against SARS-CoV-2 infection and hospitalisation among adolescents aged 12–17 years in Singapore: a national cohort study. Lancet Infect Dis. 2023;23(2):177-182. doi:10.1016/S1473-3099(22)00573-4
14. Tan SHX, Cook AR, Heng D, Ong B, Lye DC, Tan KB. Effectiveness of BNT162b2 Vaccine against Omicron in Children 5 to 11 Years of Age. N Engl J Med. 2022;387(6):525-532. doi:10.1056/NEJMOA2203209/SUPPL_FILE/NEJMOA2203209_DISCLOSURES.PDF
15. Jara A, Undurraga EA, Flores JC, ubizarreta J, González C, Pizarro A, et al. Effectiveness of an Inactivated SARS-CoV-2 Vaccine in Children and Adolescents: A Large-Scale Observational Study. SSRN Electron J. 2022;21:100487. doi:10.2139/ssrn.4035405
16. Jara A, Undurraga EA, Zubizarreta JR, et al. Effectiveness of CoronaVac in children 3–5 years of age during the SARS-CoV-2 Omicron outbreak in Chile. Nat Med. 2022;28(7):1377-1380. doi:10.1038/s41591-022-01874-4
17. Nordström P, Ballin M, Nordström A. Safety and effectiveness of monovalent COVID-19 mRNA vaccination and risk factors for hospitalisation caused by the omicron variant in 0.8 million adolescents: A nationwide cohort study in Sweden. PLoS Med. 2023;20(2):1-14. doi:10.1371/journal.pmed.1004127
18. Sacco C, Del Manso M, Mateo-Urdiales A, Rota M, Petrone D, Riccardo F, et al. Effectiveness of BNT162b2 vaccine against SARS-CoV-2 infection and severe COVID-19 in children aged 5–11 years in Italy: a retrospective analysis of January–April, 2022. Lancet. 2022;400(10346):97-103. doi:10.1016/S0140-6736(22)01185-0
19. European Centre for Disease Prevention and Control (ECDC). Overview of the implementation of COVID-19 vaccination strategies and deployment plans in the EU/EEA. 3 March 2023. Stockholm: ECDC; 2023. Available from:

https://www.ecdc.europa.eu/en/publications-data/overview-implementation-covid-19-vaccination-strategies-and-deployment-plans

20. Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC. 2020. [Preprint]. Available at: https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/
21. Valentine JC, Pigott TD, Rothstein HR. How many studies do you need? A primer on statistical power for meta-analysis. J Educ Behav Stat. 2010;35(2):215-247. doi:10.3102/1076998609346961
22. Conseil Superieur des Maladies Infectieuses. Recommandation Du CSMI Concernant La 2ème Dose de Vaccin Contre La COVID-19 Chez Des Personnes Présentant Une Contre-Indication à l'administration Du Vaccin Vaxzevria.; 2021. [Accessed October 4, 2023]. https://sante.public.lu/dam-assets/fr/espace-professionnel/recommandations/conseil-maladies-infectieuses/covid-19/covid-19-annexes/CSMI-recommandation-2ieme-dose-post-vaccin-AZ.pdf
23. Statistics Norway. Concept variable: Crowded dwelling. 2020. [Accessed July 28, 2023]. https://www.ssb.no/a/metadata/conceptvariable/vardok/3462/en
24. Ribeiro AI, Mayer A, Miranda A, Pina M de F de. The Portuguese Version of the European Deprivation Index: An Instrument to Study Health Inequalities. Acta Med Port. 2017;30(1):17-25. doi:http://dx.doi.org/10.20344/amp.7387

Annex 1. Vaccination campaign and coverage in each study site

Table 1.1. Vaccination campaign rollout by country and age groups

Study site	16–17 years	12–15 years	5–11 years
Denmark	**04/06/2021**	28/07/2021	28/11/2021
Italy	09/06/2021	**07/07/2021**	16/12/2021
Luxembourg	17/08/2021	**17/08/2021**	**06/01/2022**
Navarra (Spain)	02/08/2021	06/08/2021	**15/12/2021**
Norway	**18/08/2021**	*	*
Portugal	13/07/2021	12/08/2021	18/12/2021
Variation start of the vaccination campaign	**10.6 weeks**	**5.9 weeks**	**5.6 weeks**

**12–15–year-olds only recommended one dose. Vaccination was not universally recommended among 5–11-year-old in Norway.*

Table 1.2. Vaccination coverage for one dose, complete primary course and first booster dose of COVID-19 vaccine by country and age groups as of 2023-06-16

Study site	<18 years			15–17 years			10–14 years			5–9 years		
	At least one dose	Primary course	First booster	At least one dose	Primary course	First booster	At least one dose	Primary course	First booster	At least one dose	Primary course	First booster
Denmark	40.3	36.7	0.2	85.9	84.5	0.9	60.6	54.7	0.1	27.9	21.7	0.0
Italy	47.0	50.8	20.8	-	-	-	-	-	-	-	-	-
Luxembourg	35.6	33.7	15.1	84.8	82.7	51.5	60.1	57.3	24.8	19.5	16.8	0.0
Spain	59.7	47.2	0.9	92.4	79.2	3.7	85.2	75.9	0.8	57.9	32.3	-
Norway	31.4	13.4	-	-	-	-	-	-	-	-	-	-
Portugal	61.4	48.6	0.6	96.4	85.6	1.7	89.0	74.2	0.7	56.1	33.4	0.2

Source: ECDC Vaccine Tracker

Annex 2. Eligibility criteria for each study site

Table 2.1. Eligibility criteria for complete vaccination with and without previous infection

Study site	Eligibility criteria for complete vaccination – two doses, without previous infection	Eligibility criteria for complete vaccination, with previous infection
Denmark	All children and adolescents.	All children and adolescents receive two doses.
Italy	All children and adolescents.	Children and adolescents with a SARS-CoV-2 infection more than 12 months earlier were recommended two doses. Those with the infection 12 months or earlier were recommended to get one dose only.
Luxembourg	All children and adolescents. The schedule was different depending on the health status of the children.	All children and adolescents receive two doses. The schedule was different depending on the health status of the children.
Navarra (Spain)	All children and adolescents.	All children and adolescents receive one dose.
Norway	In 2021: recommendation two doses for 16-17 years, one dose for 12-15 years. Two doses recommended for all 5-17 years with underlying medical conditions. From the start of 2022: two doses were also available for 12-15 years. Recommendation for those with underlying risk, but (freely) available for all.	In 2021: recommendation two doses for 16-17 years, one dose for 12-15 years. Two doses recommended for all 5-17 years with underlying medical conditions. From the start of 2022: two doses were also available for 12-15 years. Recommendation for those with underlying risk, but (freely) available for all.
Portugal	All children and adolescents.	All children and adolescents receive one dose. However, children and adolescents immunocompromised two doses.

Table 2.2. Minimum time interval recommended between doses

Study site	12–17 years	5–11 years
Denmark	No less than 19 days apart	No less than 19 days apart
Italy	No less than 21 days for Pfizer and 28 days for Moderna	No less than 21 days
Luxembourg	No less than 28 days [22].	No less than 28 days [22].
Navarra (Spain)	No less than 19 days apart for Comirnaty and 22 days for Spikevax,	No less than 19 days apart
Norway	The interval for 16–17-year-olds was recommended to be between 8–12 weeks between the first and second dose.	*
Portugal	No less than 19 days apart	The interval for 5–11-year-olds was recommended to be between six to eight weeks between the first and second dose.

**12–15-year-olds only recommended one dose. Vaccination was not universally recommended among 5–11-year-old in Norway.*

Annex 3. Outcome definition by study site

Table 3.1. Outcome definition by site

Study site	Outcome definition
Denmark	Laboratory-confirmed infection 24 hours after hospital admission or three weeks before admission, lasting for a minimum of 24 hours and in which admission is classified with ICD-10 codes B342 and B972 or one of the sub-codes under these. The COVID-19-related ICD-10 codes have to be both primary diagnosis and action code.
Italy	Hospital admission with SARS-CoV-2 confirmed infection through RT-PCR or antigenic test and clinical manifestations of the respiratory tract or other organs directly associated with SARS-CoV-2 infection
Luxembourg	Hospitalised due to COVID-19 with a positive RT-PCR test within 14 days before and 24 hours after admission
Navarra (Spain)	Hospital admission with laboratory-confirmed COVID-19 infection by RT-PCR, reviewed by a medical doctor who concluded that the hospitalisation was due to COVID-19
Norway	Hospital admission due to COVID-19 with laboratory-confirmed SARS-CoV-2 infection
Portugal	COVID-19 is the main diagnosis in the discharge record

Annex 4. Variant of Concern dominance period

Table 4.1. VOC dominance period of 80% or higher by study site

Study site	Delta			Omicron BA.1/2			Omicron BA.4/5		
	Start	End	Period (in weeks)	Start	End	Period (in weeks)	Start	End	Period (in weeks
Denmark	2021-27	2021-49	22	2021-52	**2022-21**	22	2022-25	2022-42	17
Italy	2021-27	2021-50	23	2022-01	**2022-21**	20	**2022-26**	2022-42	16
Luxembourg	**2021-29**	2021-50	21	2021-52	2022-20	21	2022-23	2022-42	19
Navarra (Spain)	2021-28	2021-49	21	2021-52	2022-20	21	2022-25	2022-41	16
Norway	2021-28	2021-50	22	2022-01	**2022-21**	20	2022-25	2022-42	17
Portugal	**2021-25**	2021-50	25	2021-52	**2022-17**	18	**2022-22**	2022-40	18
Variation start/end dates	**4 weeks**	**1 week**		**1 week**	**4 weeks**		**4 weeks**	**2 weeks**	

Data extracted on 24/07/2023 from the ECDC website (GISAID and TESSy databases)

Annex 5. Confounding variables for adjustment

Table 5.1. Indicators of socioeconomic status

Study site	*Indicators of socioeconomic status*
Denmark	Not available
Italy	Deprivation Index at the municipality level provided by the Italian Institute of Statistics (Istat)
Luxembourg	Not available
Navarra (Spain)	Income level of the family
Norway	Living conditions – individuals are considered to live in crowded conditions if the number of rooms is lower than the number of residents or one resident lives in one room, and the number of square metres (P-area) is below 25 sq. m. per person. If the number of rooms or the P-area is not specified, a household will be regarded as crowded if one of these criteria is met [23].
Portugal	European Deprivation Index at the municipality-level [24]

Table 5.2. Definition of comorbidity by study site

Study site	No comorbidities	Low-medium risk comorbidities	High risk comorbidities
Denmark	No comorbidities	The presence of at least one of the following conditions: tuberculosis, haematological, coagulation, diabetes, adipose, endocrinological, ischemic heart disease, heart problems, chronic lung diseases, alcoholic liver, liver condition, neurological condition, kidney condition, Congenital, COPD, contact regarding influenza vaccination, cancer, missing lung, missing kidney, alcohol consumption	The presence of at least one of the following conditions: HIV, Immunological suppression, Irradiation, Transplantation
Italy	+	+	+
Luxembourg	*	*	*
Navarra (Spain)	No comorbidities related to increased risk of COVID-19	Other comorbidities that are associated with the risk of COVID-19 but different from immunocompromising conditions: diabetes, severe obesity, cancer, stroke, dementia, kidney disease, haematological cancers, heart disease, chronic respiratory disease, liver disease and rheumatic arthritis.	Immunocompromising conditions
Norway	No comorbidities related to increased risk of COVID-19	The presence of at least one of the following conditions: chronic liver disease or significant hepatic impairment, diseases requiring immunosuppressive therapy, diabetes, chronic lung disease including cystic fibrosis and severe asthma, which have required the use of high dose inhaled or oral steroids within the past year, obesity with a body mass index (BMI) of ≥35 kg/m2, dementia; chronic heart and vascular disease (except for high blood pressure), and stroke	The presence of at least one of the following conditions: organ transplant, immunodeficiency, haematological cancer in the last five years, other active cancers, neurological or neuromuscular diseases that cause impaired cough or lung function (e.g. ALS and cerebral palsy), chronic kidney disease, or significant renal impairment.
Portugal	No comorbidities	The presence of at least one of the following conditions without immunosuppression: anaemia, dementia, diabetes, cardiac disease, neuromuscular disease, rheumatologic disease, obesity, tuberculosis, stroke, pulmonary disease, asthma, liver disease and hypertension	The presence of at least one of the following immunocompromising conditions: HIV, renal disease, and cancer

*+Italy only has access to comorbidities for vaccinated individuals, *Luxembourg does not have access to comorbidities. Additionally, study sites can adjust for variables that translate to different health-seeking behaviour. Portugal will also consider the number of SARS-CoV-2 tests performed during the previous year (0, 1, 2 to 4, ≥5).*

Table 5.3 Factors used to adjust for confounding in each study site

Study site	Factors and covariates used to adjust for confounding
Denmark	Sex, age, region, and comorbidities
Italy	Sex, age, region and deprivation index
Luxembourg	Sex, age, country of birth, and nationality
Navarra (Spain)	Sex, age, comorbidities/immunocompromised, country of birth, income level, and pneumococcus vaccine
Norway	Sex, age, living condition, country of residence, and comorbidities
Portugal	Sex, age, region, European deprivation index, comorbidities, and number of SARS-CoV-2 tests performed in the previous year

Annex 6. Data sources on reference population, vaccination, outcome and confounders

Table 6.1 Source of information on the reference population

Study site	Source of information	Residency definition
Denmark	The Danish Civil Registration System (CPR)	Residency is defined as an individual who is registered as currently living in the country (as the main country of residency). It is impossible to live in Denmark for a prolonged period without being registered as a resident.
Italy	Official population statistics provided by the Italian Institute of Statistics (Istat)	The database includes the size of the population residing in Italy at the beginning of each calendar year (1st of January) by sex, age and municipality/region. According to the Istat definition, the resident population is made up of people, of Italian and foreign citizenship, having habitual residence in the national territory even if temporarily absent.
Luxembourg	Administrative dataset collected by the national social security, IGSS "Inspection génerale de la sécurité sociale"	The identification of non-residents is possible thanks to "i_residence_country" variable.
Navarra (Spain)	Administrative database	Residents covered by the Navarra Health Service. This Service covers 98% of the population in the region, with an unbiased distribution by sex and geographical areas. The database contains variables that allow the identification of non-residents or temporary residents.
Norway	The National Population Register	Individuals should have a valid national identity number and be registered in the National Population Registry as living in Norway.
Portugal	National Health Service User (NHSU) dataset	Residents in mainland Portugal who had contact with the healthcare system in the previous three years.

Table 6.2 Source of information and limitations on vaccination, outcome and confounders

Study site	Variable	Source of information	Limitations
Denmark	COVID-19 vaccination	Nationwide electronic health register – Danish vaccination register	Vaccines administered abroad may not be registered, they have to be registered after the fact by a health professional or the person themselves.
	Hospitalisation	Danish national patient register – DNPR	Risk of misclassifications and different coding practices, though these risks are thought to be less for COVID-19-diagnosis as they are new and specific
	Comorbidities	Danish national patient register – DNPR	
	Region	The Danish Civil Registration System (CPR)	
Italy	COVID-19 vaccination	National Vaccination Registry (ANV)	
	Hospitalisation	COVID-19 Surveillance System	
	Sex, age, region	For vaccinated individuals: National Vaccination Registry (ANV) For unvaccinated individuals: yearly estimates of the resident population from the Italian Institute of Statistics - Istat (calculated by subtracting the vaccinated individuals from the total resident population in each age/sex/municipality stratum.	
	Deprivation index	Italian Institute of Statistics (Istat)	Deprivation Index measured at the municipality level might not represent the individual socio-economic conditions because, especially in large municipalities, it could not be homogeneous across sub-areas within the same municipality.
Luxembourg	COVID-19 vaccination	National vaccination registry – MSVAC	
	Hospitalisation	Hospitals Epidemiological surveillance platform (MSINF) (use of normal care, admissions to intensive care)	
	Sex, age, country of birth, and nationality	Administrative dataset collected by the national social security, IGSS "Inspection génerale de la sécurité sociale"	The status of residency and place of living is defined for September 2021. An update on this may be available in the future.
Navarra (Spain)	COVID-19 vaccination	Vaccination registry	
	Hospitalisation	Enhanced COVID-19 surveillance with individual revision of events	Low number of hospitalisation in children and adolescents. Several months should be pooled to reach statistical power.
	Age (date of birth), sex, country of birth, and comorbidities, income level	Administrative database	This database is updated annually at the beginning of each season. Only the comorbidities registered in the General Practitioners records are taken into account.
	Pneumococcal vaccine	Vaccination registry	
Norway	COVID-19 vaccination	The National Immunisation Register - SYSVAK	
	Hospitalisation	Norwegian Intensive Care and Pandemic Registry – NIPaR Norwegian Surveillance System for Communicable Diseases - MSIS	From June 2023 only registration of hospital admission due to COVID-19, does not include hospital admission with another reason, but with positive test. This does not include those who self-tested positive through at-home testing. Since January 2022 no recommendation to confirm with RT-PCR.
	Age, Sex, County of residence, Country of birth	The National Population Register	The county of residence was updated in January 2022, which might lead to some errors for individuals who have moved in the last half year.
	Living condition	Statistics Norway (SSB)	Used to identify the living conditions of individuals as a proxy for SES.

Study site	Variable	Source of information	Limitations
	Comorbidities	Norwegian Patient Registry (NPR): individual level data from all public specialist health-care services in Norway.	Only includes data from specialised services and specified ICD10 codes, therefore dependent on clinical diagnoses.
Portugal	COVID-19 vaccination	National Vaccination Registry – VACINAS	The database presents inconsistencies, such as the number of inoculations per user greater than expected and/or several inoculations with different brands on the same day.
	Hospitalisation	National database of hospital discharges – BIMH	There is a delay in the update of this database.
	Age, sex and municipality	National Health Service User (NHSU) dataset	NHSU contains the unique mandatory health number (NHS) attributed to each individual in Portugal. However, this database could have update issues, and can also include occasional/temporary NHS users.
	EDI	European Deprivation Index	This index is based on 2011 Census.
	Comorbidities	Primary Care Information System (SIM@SNS)	
	SARS-CoV-2 tests performed in the previous year	National Information System for Epidemiologic Surveillance	Only notified cases are present. It's possible that previous infections occurred but were not reported due to the widespread use of autotests.
	BCG or pneumococcus vaccine	National Vaccination Registry – VACINAS	

Annex 7. Data linkage methods

Table 7.1 Data linkage method used in each study site

Study site	Data linkage method
Denmark	The reference population database will be linked with the electronic databases on vaccination, comorbidity and/or health-seeking behaviours registries using the unique identifier and a deterministic data linkage procedure (no random component in the linkage procedure). The CPR-number from the Danish Civil Registration System (CPR)is used as a unique identifier and linkage between registries.
Italy	Deterministic record linkage through the individual tax code (unique individual identifier), or through the municipality code (for the deprivation index measured at municipality level)
Luxembourg	The different databases are linked daily, using the unique identifier and a deterministic data linkage procedure (no random component in the linkage procedure).
Navarra (Spain)	A unique individual identifier is used for linkage of all information for each person. All datasets used in the analyses are anonymised.
Norway	The reference population database will be linked with the electronic databases on vaccination, comorbidity and/or health-seeking behaviour registries using the unique identifier and a deterministic data linkage procedure.
Portugal	Each of the registries considered contains a unique individual's identifier (NHS), allowing deterministic data linkage between registries. Data extraction and linkage is performed monthly by the Shared Services of the Ministry of Health in accordance with national legal requirements. All data is anonymised prior to transfer to INSA research team for analysis.

Annex 8. Pooled analysis power calculations

The power analysis was developed for the principal objective considering the measure of effect VE=1-incidence rate ratio (IRR primary course vaccine vs unvaccinated).

From each study site and age group, we used the number of events and person-years in the unvaccinated group, the total person-years in the vaccinated group and the total person-years observed in the total cohort over a period of 12 months. The power was calculated at the study level for each possible value of the vaccine effectiveness from 1 to 99%. For each possible value of the vaccine effectiveness, the number of events in the vaccinated group (a_v) was estimated by $a_v = IRR\ I_{uv} py_v$, were I_{uv} and py_v are respectively the incidence and the total person-years observed among the unvaccinated and vaccinated individuals. Power at the study level was calculated by:

$$P_{site} = 1 - \Phi(c_{1-\alpha/2} - z) + \Phi(c_{\alpha/2} - z)$$

Where $c_{1-\alpha/2}$ and $c_{\alpha/2}$ are the critical values of the standard normal distribution, $\Phi(\ \ )$ is the cumulative standard normal distribution and $z = \frac{ln(IRR)}{SE(ln(IRR))}$, $SE(ln(IRR))$ is the standard error of the logarithm of the incidence rate ratio.

To produce power calculations for pooled estimates, we followed the recommendations presented in Valentine J, Pigott and Rothstein 2010[20]. The pooled variance was calculated as $v_{.} = \frac{1}{\sum_{i=1}^{k} \frac{1}{v_i}}$, where k is the number of study sites and $v_i = SE(ln(IRR_i))^2$ is the variance of the vaccine effectiveness estimate at study level.

Pooled power calculations were obtained by:

$P_{pooled} = 1 - \Phi\left(c_{1-\frac{\alpha}{2}} - z_{pooled}\right) + \Phi\left(c_{\frac{\alpha}{2}} - z_{pooled}\right)$, were $z_{pooled} = \frac{ln(IRR_{pooled})}{\sqrt{v_{.}}}$

We considered four scenarios for the heterogeneity level between vaccine effectiveness estimates at the study level – the no heterogeneity (fixed effect model) and three levels of heterogeneity (random effects model) were v_i is substituted by $v_i^* = v_i + \tau^2$, and τ^2 defines the level of heterogeneity in the following way:

1. Low heterogeneity $I^2 = 25\%$, $\tau^2 = 0.33 \times v_{.}$
2. Medium heterogeneity $I^2 = 50\%$, $\tau^2 = 1 \times v_{.}$
3. High heterogeneity $I^2 = 75\%$, $\tau^2 = 3 \times v_{.}$

This calculation are based on the result that $I^2 = \frac{\tau^2}{v_{.} + \tau^2}$

Results are presented in terms of the minimum level of vaccine effectiveness detectable with a power of 80% and a Type I error of 5%.

Table 8.1 Number of events, person-years and COVID-19 hospitalisation rate in the unvaccinated group, and total person years observed in the 12 months after the start of the vaccination campaign in each age group cohort and study site

Study site	Age group	Number of events unvaccinated group	Person years unvaccinated	Rate per 100.000 person years in unvaccinated	Person years in total
Denmark	12 to 17	15	116,469	12.9	217,707
Italy	12 to 17	237	536,191	44.2	1,380,454
Luxembourg	12 to 17	2	39,156	5.1	54,497
Navarra	12 to 17	4	10,922	36.6	42,735
Portugal	12 to 17	39	132,732	29.4	520,860
Total	**12 to 17**	**297**	**835,470**	**35.5**	**2,216,253**
Denmark	5 to 11	16	50,859	31.5	226,049
Italy	5 to 11	667	2,125,876	31.4	3,540,956
Luxembourg	5 to 11	2	7,747	25.8	44,442
Navarra	5 to 11	16	26,909	59.5	33,923
Portugal	5 to 11	59	287,743	20.5	469,867
Total	**5 to 11**	**760**	**2,499,134**	**30.4**	**4,315,237**

Figure 8.1 Study level and age cohort power curves.

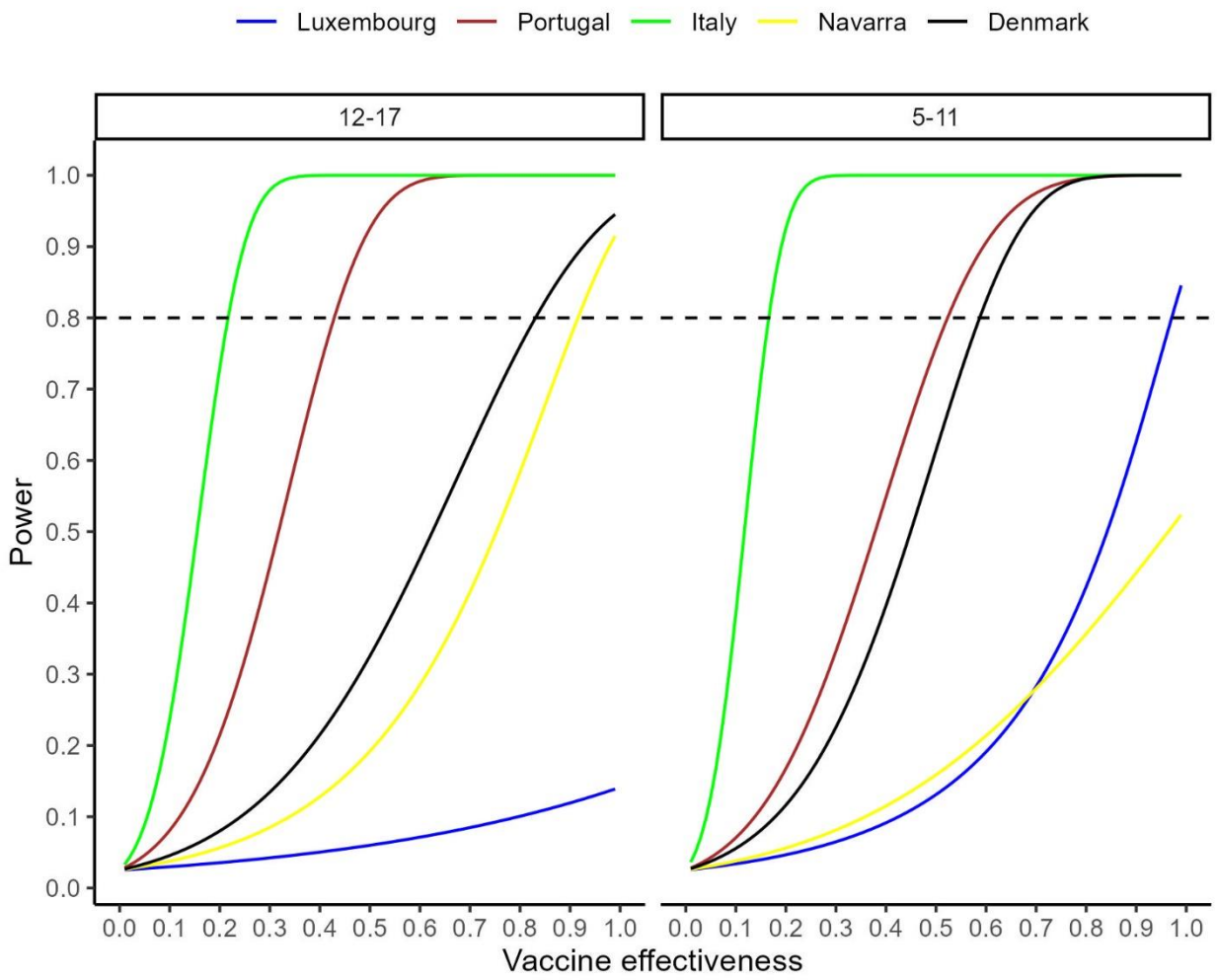
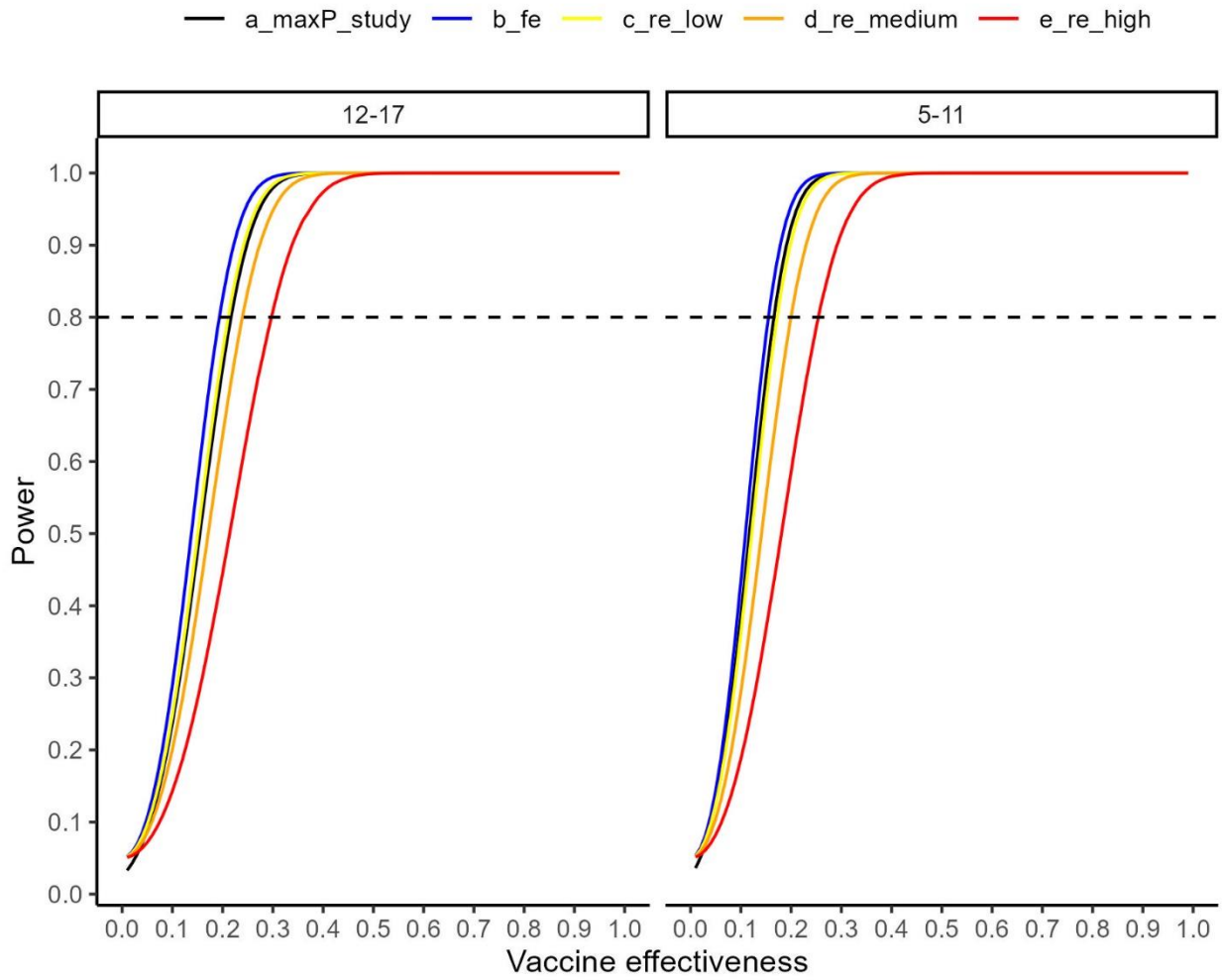


Table 8.2 Minimum level of vaccine effectiveness detectable at study site with a Power of 80% and a Type I error of 5%

Study site	Age group	Minimum vaccine effectiveness (%)
Denmark	12 to 17	84
Italy	12 to 17	**22**
Luxembourg	12 to 17	not found
Navarra	12 to 17	92
Portugal	12 to 17	43
Denmark	5 to 11	59
Italy	5 to 11	**17**
Luxembourg	5 to 11	98
Navarra	5 to 11	not found
Portugal	5 to 11	53

Figure 8.2 Power curves for pooled analysis considering the four levels of vaccine effectiveness heterogeneity between studies and the study site with the highest power



Annex 9. Reporting templates

Table 9.1 Mock-up table describing the distribution of the total number of persons or person-time during the follow-up period by sociodemographic and clinical characteristics of the study population included by vaccination status (one table per study site, age group – 5 to 11 and 12 to 17, and different cohorts – principal objective, secondary objective 1 and 4)

	Unvaccinated	Vaccination with one dose	Complete vaccination with two doses
	N (total number of persons) or PY (total number of person-years)	N (total number of persons) or PY (total number of person-years)	N (total number of persons) or PY (total number of person-years)
Site			
Total of children and adolescents			
Sex			
Male			
Female			
Missing			
Age-group			
5 to 9 (or 12 to 15)			
10 to 11 (or 16 to 17)			
Country of birth			
Native			
Non-native			
Missing			
Nationality			
National			
Non-national			
Missing			
Vaccine product (only including individuals who achieved full vaccination before end of study period)			
Comirnaty children dose (Comirnaty adult dose for those >=12 yoa)	NA		
Spikevax childrens dose (Spikevax adult dose for those >=12 yoa)	NA		
Other	NA		
Missing	NA		
Comorbidities			
No comorbidity			
Low-medium risk comorbidities /non-immunocompromising			
High-risk comorbidities/ immunocompromising			
Missing			

Table 9.2 Format for data reporting (one table per study site, age group – 5 to 11 and 12 to 17, and different cohorts – principal objective, secondary objective 1 and 4)

AGE GROUP												
Exposure categories	N*	person-days	Events	HR crude			HR adjusted1**			HR adjusted2***		
				Estimate	95%CI low	95%CI high	Estimate	95%CI low	95%CI high	Estimate	95%CI low	95%CI high
Unvaccinated				REF	REF	REF	REF	REF	REF	REF	REF	REF
Vaccinated one dose												
Complete vaccination two doses												
Unvaccinated				REF	REF	REF	REF	REF	REF	REF	REF	REF
Vaccinated one dose, ≤89 days after time 0												
Vaccinated one dose, days 90 – 179 after time 0												
Vaccinated one dose, days 180 – 365 after time 0												
Complete vaccination two doses, ≤89 days after time 0												
Complete vaccination two doses, days 90 – 179 after time 0												
Complete vaccination two doses, days 180 – 365 after time 0												
Unvaccinated				REF	REF	REF	REF	REF	REF	REF	REF	REF
One dose of Comirnaty – children dose (one dose of Comirnaty – adult dose for those >=12 years)												
Two doses of Comirnaty – children dose (two doses of Comirnaty – adult dose for those >=12 years)												
One dose of Spikevax – children dose (one dose of Spikevax – adult dose for those >=12 years)												
Two doses of Spikevax – children dose (two doses of Spikevax – adult dose for those >=12 years)												

**Number of individuals contributing to each group. Because exposure is time-varying, the sum of N in all categories will be greater than the total sample size in the study.*
***HR adjusted1: Adjusted by age, sex and region according to each study site.*
***HR adjusted2: Additionally adjusted by the rest of confounding variables according to each study site.*

PDF TQ-02-24-383-EN-N

European Centre for Disease Prevention and Control (ECDC)

Gustav III:s Boulevard 40, 16973 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
www.ecdc.europa.eu

An agency of the European Union
www.europa.eu

Subscribe to our publications
www.ecdc.europa.eu/en/publications

Contact us
publications@ecdc.europa.eu

Follow us on Twitter
@ECDC_EU

Like our Facebook page
www.facebook.com/ECDC.EU

ECDC is committed to ensuring the transparency and independence of its work

In accordance with the *Staff Regulations for Officials and Conditions of Employment of Other Servants of the European Union* and the *ECDC Independence Policy*, ECDC staff members shall not, in the performance of their duties, deal with matters in which they may, directly or indirectly, have a personal interest that could impair their independence. Declarations of interest must be received from any prospective contractor before a contract can be awarded.
www.ecdc.europa.eu/en/aboutus/transparency

Publications Office of the European Union

PDF ISBN 978-92-9498-696-2