RESEARCH PROTOCOL (nWMO)

PROTOCOL TITLE: Vaccine **E**ffe**CT**iveness in the p**O**pulation at **R**isk for severe COVID19

Short title	VECTOR
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Date	*11-02-2021*
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SUMMARY

Rationale: Though Phase III trials of the first approved COVID19 vaccines yielded high vaccine efficacy (VE > 90%) for preventing COVID19 infection, VE for severe COVID19 leading to hospital admission has not yet been determined. Real-world vaccine performance in a high-risk population, and in particular VE for COVID19 related hospitalization, is necessary to inform vaccination policies.

Objective: To estimate the product specific vaccine effectiveness (VE) against COVID-related hospitalization in adults at increased risk of severe disease.

Study design: Retrospective test-negative case-control study

Study population: Adults at increased risk of severe COVID19 disease due to age (>60) or comorbidities (all ages > 18 years) hospitalized with possible COVID19, according to the ECDC case definition, and with appropriate diagnostic testing for SARS-CoV-2.

Main study parameters/endpoints: Endpoint: Hospital admission with possible COVID19
Other main study parameter: Prior vaccination for COVID19

Nature and extent of the burden associated with participation, benefit and group relatedness: There will be no burden associated with participation since study data will be collected retrospectively from routinely collected information.

INTRODUCTION AND RATIONALE

In December 2020 and January 2021, the first two COVID19 vaccines (Comirnaty and COVID19 Vaccine Moderna) have been approved by the EMA and more vaccines are on their way (1). With the European approval of these first two vaccines the COVID19, the national immunization program has been started. This national immunization program will initially target healthcare providers, elderly and individuals with an increased risk of severe COVID19 due to comorbidities (2). Based on the Phase III trial results, these first two COVID19 vaccines yield an overall reduction in symptomatic SARS-CoV2 infections of >90% (3, 4). However, the effect on severe COVID19 leading to hospital admission is not yet well established as the Phase 3 trials were not powered for this endpoint. Clearly, there is an urgent need to obtain data on the real-world vaccine performance in the elderly population and in people with comorbidities, in particular their effect on COVID19 related hospitalization, to guide the design of optimal vaccination policies.

The test-negative-case-control study is a well-established epidemiological design used to evaluate, amongst others, annual influenza vaccine effectiveness (5). Here, we propose a multicenter test-negative-case-control study among vaccine eligible elderly and patients with comorbidities, who are hospitalized with possible COVID19, according to ECDC case definition, and in which the presence of SARS-CoV-2 as causative pathogen is appropriately tested to determine vaccine effectiveness against COVID19 related hospitalization.

1. OBJECTIVES

Primary Objective: The primary objective is to estimate the product specific vaccine effectiveness (VE) against COVID19-related hospitalization in adults at increased risk of severe disease due to age (>60) or comorbidities (all ages > 18 years).

Secondary Objective(s):

1. To measure product-specific VE against laboratory-confirmed SARS-CoV-2 in hospitalized patients by:
   - risk group (e.g. specific chronic conditions)
   - sex
   - age
   - time since vaccination
   - vaccine dose (one vs two)
   - Immunocompromised status
   - Specific long-term medication

2. To measure product-specific VE against more severe COVID-related outcomes (ICU admission, invasive ventilation, in-hospital mortality and 6-month)

2. STUDY DESIGN

This is a retrospective test-negative case control study that will be conducted in 7-10 Dutch hospitals using routinely collected patient medical and microbiological data. Patients and controls will be identified through regular and systematic screening of new hospital admissions with possible COVID19, according to ECDC case definition, in which the presence of SARS-CoV-2 as causative pathogen is appropriately tested. The study period will start at March 1st and will continue until the sample size has been reached.

3. STUDY POPULATION

3.1 Population (base)

Adults eligible for COVID19 vaccination according to the national immunization program, hospitalized with possible COVID19, according to ECDC case definition, and in which the presence of SARS-CoV-2 as causative pathogen is appropriately tested.

3.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Hospital admission
- Meet the ECDC possible COVID19 case definition
- Have a respiratory specimen appropriately tested for SARS-CoV2 (through PCR/LAMP-PCR) within 48hrs of admission
- Is eligible for COVID19 vaccination at the time of hospital admission.

Vaccine eligibility is determined based on age, presence of pre-existing conditions and the status of the Dutch vaccination program at the time of admission (i.e. staggered eligibility resulting from prioritization of vaccination of older age-groups and those with comorbidities) [1)]

The ECDC case definition of possible COVID19 is defined as a hospitalized person with at least one of the following symptoms:

- cough,

- fever,
- shortness of breath,
- sudden onset of anosmia, ageusia or dysgeusia.

3.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Transferred from another hospital for possible or confirmed COVID19,
- Readmitted within 14 days of a prior hospitalization for confirmed COVID19.

3.4 Sample size calculation

Assuming that 30% (conservative estimate, higher % means more power) of eligible patients are SARS-CoV-2 positive and vaccination uptake is 80% (conservative estimate, lower % means more power) we need 201 participants to demonstrate a vaccine effectiveness of 70% (conservative estimate, higher VE means more power) with 80% power and a two-sided alpha level of 5%. To account for decreasing power when adjusting for potential confounders, we add 15% to the calculated sample size, resulting in a required sample size of 232 patients. To allow for estimation for product specific vaccine effectiveness we will need 696 participants assuming 3 types of vaccines are equally distributed over the study population. We will aim for 700 inclusions. The sample size also yields 90% power to demonstrate that the vaccine effectiveness is at least 30% if the true vaccine effectiveness is 90% (i.e. to perform a significance test against a vaccine effectiveness of 30% rather than 0%).

4. METHODS

4.1.1 Main study parameter/endpoint

The primary endpoint is hospitalization due to laboratory confirmed COVID19.

Cases will be defined as patients hospitalized with COVID19, with a respiratory sample positive for (LAMP-)SARS-CoV-2 by PCR within 48 hours of hospital admission. Controls will be defined as patients hospitalized with possible COVID19, with respiratory samples taken on admission negative for SARS-CoV-2 by PCR and without a known positive COVID19 tests or close contact with a SARS-CoV-2 infected person during the 14 days prior to hospital admission.

Possible COVID19 is defined according to the ECDC case definition: *"Hospitalized person with at least one of the following symptoms: cough, fever, shortness of breath or sudden onset of anosmia, ageusia or dysgeusia"(6)*

4.1.2 Secondary study parameters/endpoints (if applicable)

- ICU admission
- invasive ventilation
- in-hospital mortality
- 6-month

4.1.3 Other study parameters

- Vaccination status
- Vaccine type
- Number of doses
- Date of vaccination of last dose
- risk group (e.g. specific chronic conditions)
- sex
- age
- Immunocompromised status
- Specific long-term medication

Definition of vaccination status

An individual will be considered as vaccinated against COVID19 with a product-specific vaccine during the current pandemic under the following categories:

- ***Fully vaccinated*** (two-dose vaccine): if they have **received both doses** at least 7 days* before onset
- ***Fully vaccinated*** (single-dose vaccine): if they have **received one dose** at least 7 days* before onset
- ***Partially vaccinated*** (two-dose vaccine only): if they have **received one of two doses** at least 7 days* before onset
- A patient will be considered as ***unvaccinated*** if s/he **did not receive COVID19 vaccine or** if s/he **was vaccinated after onset** of symptoms.

4.2 Study procedures

Eligible patients will be identified by screening all patients tested for COVID19 on inclusion and exclusion criteria.

For each identified case and control, the following data will be collected by research staff and entered in an electronic Case Report Form;

Upon inclusion:

- Birthdate, postal code (6-digit), gender, ethnicity
- BMI, presence of pre-existing conditions, smoking history, use of chronic medication, receipt of influenza and/or pneumococcal vaccine, residence type.
- Vaccination status including date of (last dose) administration, type of vaccine and brand name, and number of doses
- Symptoms on admission, date of symptom onset and date of hospital admission
- Positive SARS-CoV-2 test result within 14 days prior to hospital admission (if documented)
- Close contacts with a SARS-CoV-2 positive person within 14 days prior to hospital admission (if documented)

During follow-up;

- Length of hospital stay, ICU admission, mechanical ventilation and other live-support interventions, in-hospital mortality
- SARS-CoV-2 PCR test(s) results of samples taken during the first 48 hours of hospital admission
- Other respiratory pathogens identified within 48 hours of admission
- Medical treatment including immune modulating drugs, anti-coagulants and antivirals

Data will be collected retrospectively from electronic patient records and will be entered in an electronic Case Report Form. No additional patient-related procedures will take place. Data on 6-month mortality will be collected from Statistics Netherlands (CBS) through linkage by gender, postal code and birthdate.

5. STATISTICAL ANALYSIS

5.1 Primary study parameter(s)

This study is a case control study (test-negative design). The measure of association is an odds ratio (OR) .

$$OR = \frac{Cases\ vaccinated\ /controls\ vaccinated}{Cases\ unvaccinated\ /controls\ unvaccinated}$$

Cases are defined as patients with SARS-CoV-2 demonstrated, controls are those in which SARS-CoV-2 was not demonstrated. For vaccination as preventive factor, the VE can be computed as VE = (1 – OR)*100. A 95 % confidence interval is computed around the point estimate.

Univariable analysis will be carried out to measure the VE against being a laboratory-confirmed COVID19 case. Stratified analyses (by sex and age group, for example) can follow to better understand potential effect modifiers and confounders. Multivariable analysis will be carried out to take confounding factors and potential effect modifiers into account. This will provide adjusted ORs from which the VE can be estimated using the formula above.

5.2 Secondary study parameter(s)

Secondary endpoints will be computed the same way as the primary endpoint with univariable analysis to measure VE against being a laboratory confirmed COVID19 case though only among cases with secondary endpoints (ICU-admission, invasive ventilation, in-hospital mortality, 6-month mortality).

6. ETHICAL CONSIDERATIONS

6.1 Regulation statement

This study is non-interventional and uses routine clinical data only. The study therefore poses no burden to the study subjects and is therefore not subject to the Dutch Medical Research with Human Subjects Law (Wet Medisch-wetenschappelijk onderzoek met mensen, WMO). The study will be conducted according to the 'gedragscode gezondheidsonderzoek' and in accordance with the EU GDPR (General Data Protection Regulation).

6.2 Recruitment and consent

Obtaining individual informed consent is considered not feasible in this study because data collection is retrospective. Obtaining individual informed consent has a high risk for creating selection bias mainly because mortality within hospital admitted patients is

around 20%[7], thereby invalidating estimation of VE estimates. Given the public health importance of obtaining unbiased results for policy making and the absence of study-related procedures, data-collection complies with the exception described in Article 24 of the GDPR. We will apply for a waiver of informed consent.

7. ADMINISTRATIVE ASPECTS AND PUBLICATION

7.1 Handling and storage of data and documents

Data will be collected in a certified Electronic Data Capture tool named Castor. Personal data (postal code and birthdate) will be collected and stored in SLIM, an application widely used for storage of personal data for research-purposes, and will be linked to the case-data in Castor through a pseudonymized number. Pseudonymized data will be exported from Castor and stored in a Secured Research folder on the UMCU drive ensuring only authorized personal to have access to the data. The UMCU has a Research Agreement with the RIVM. Data will only be shared with the RIVM according to this agreement, where the data will be stored accordingly.

Personal data will uploaded from SLIM directly to the protected servers of the CBS using standardized and protocolized procedures. Authorized CBS personal will assign a unique ID on the basis of the personal information and subsequently remove all personal information, which will result in a pseudonymized dataset. This pseudonymized dataset will remain at the secured CBS servers at all time and is only available through a remote access facility. Usage of this remote access facility of the CBS is accompanied with adherence to strict rules and regulations[8]. Further, the secured CBS environment itself is compliant with strict data security and protection rules[9].

7.2 Amendments

Amendments are changes made to the research after an ethical committee gave an advice non-WMO. Any change that may cause the investigation to fall within the scope of the WMO is submitted to the ethical committee that gave the non-WMO advice.

8. REFERENCES

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