# RESEARCH PROTOCOL (nWMO)

**PROTOCOL TITLE: V**accine **E**ffe**CT**iveness in the p**O**pulation at **R**isk for severe COVID-19

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| **Short title** | VECTOR |
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## SUMMARY

**Rationale:** Though Phase III trials of the first approved COVID-19 vaccines yielded high vaccine efficacy (> 90%) for preventing COVID-19, VE for severe COVID-19 leading to hospital admission has not yet been determined. Real-world vaccine performance in a high-risk population, and in particular VE for COVID-19 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 COVID-19 disease due to age (>60) or comorbidities (all ages > 18 years) hospitalized with a respiratory infection (according to the WHO definition of SARI), and with appropriate diagnostic testing for SARS-CoV-2.

**Main study parameters/endpoints:** Endpoint: Hospital admission with laboratory confirmed SARS-CoV2

Other main study parameter: Prior vaccination for COVID-19

**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 obtained retrospectively from routinely collected information.

## INTRODUCTION AND RATIONALE

In December 2020 and January 2021, the first two COVID-19 vaccines (Comirnaty, COVID-19 vaccine AstraZeneca and COVID-19 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 COVID-19 national immunization program has been started. This national immunization program initially targets healthcare providers, elderly and individuals with an increased risk of severe COVID-19 due to comorbidities (2). Based on the Phase III trial results, these first two COVID-19 vaccines yield an overall reduction in symptomatic SARS-CoV2 infections of >90% (3, 4). However, the effect on severe COVID-19 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 COVID-19 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 elderly and patients with comorbidities eligible for COVID-19 vaccination according to the national immunization program, who are hospitalized with symptoms of a severe acute respiratory infection (SARI), , and in which the presence of SARS-CoV-2 as causative pathogen is appropriately tested to determine vaccine effectiveness against COVID-19 related hospitalization.

## 1. OBJECTIVES

**Primary Objective**: The primary objective is to estimate the product specific vaccine effectiveness (VE) against COVID-19-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 mortality)
3. To measure VE against different SARS-CoV-2 strains
4. Describe SARS-CoV-2 strains related to infection after vaccination.

## 2. STUDY DESIGN

This retrospective case control study 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 SARI symptoms, in which the presence of SARS-CoV-2 as causative pathogen is appropriately tested. The study will start at March 1st and continue until the sample size has been reached.

## 3. STUDY POPULATION

### 3.1 Population (base)

Adults eligible for COVID-19 vaccination according to the national immunization program, hospitalized with SARI symptoms 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
- SARI-symptoms defined as:
    - History of fever or measured fever of ≥ 38 C°
    - and cough or shortness of breath
    - onset within the last 10 days
- Have a respiratory specimen appropriately tested for SARS-CoV2 (through PCR/LAMP-PCR) at admission or 14 days prior to admission at the municipal health services (GGD)
- Is eligible for COVID-19 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)]

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### 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 COVID-19,
- Readmitted within 14 days of a prior hospitalization

### 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 of 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 COVID-19.

Cases will be defined as patients hospitalized with COVID-19, with a respiratory sample positive for SARS-CoV-2 by PCR/LAMP-PCR tested within 48 hours after hospital admission or positively tested for SARS-CoV-2 at the municipal health services (GGD) within 14 days prior to hospital admission. Controls will be defined as patients hospitalized with SARI symptoms, with respiratory samples taken during the first 48 hours of admission

negative for SARS-CoV-2 by PCR/LAMP-PCR and without a known positive COVID-19 tests or close contact with a SARS-CoV-2 infected person during the 14 days prior to hospital admission.

SARI symptoms are defined as:
A history of fever in combination with cough or shortness of breath, with an onset within the 10 days before hospital admission.

#### 4.1.2 Secondary study parameters/endpoints (if applicable)

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

#### 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 COVID-19 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 14 days* before onset
- ***Fully vaccinated*** (single-dose vaccine): if they have **received one dose** at least 14 days* before onset
- ***Partially vaccinated*** (two-dose vaccine only): if they have **received one dose** at least 14 days* before onset or if they received the second dose <14 days before onset

- A patient will be considered as ***unvaccinated*** if s/he **did not receive COVID-19 vaccine or** if s/he **was vaccinated within 14 days before onset or after onset** of symptoms.

### 4.2 Study procedures

Eligible patients will be identified by screening all patients tested for COVID-19 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).
- Having been in close contact with a SARS-CoV-2 positive person during the 14 days prior to hospital admission (if documented)
- Length of hospital stay, ICU admission, mechanical ventilation and other live-support interventions, in-hospital mortality
- SARS-CoV-2 PCR test(s) results during 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. For cases tested positively for SARS-CoV-2 at the GGD, the Coron-IT sample number is requested at the GGD.

Data on 6-month mortality will be collected from Statistics Netherlands (CBS) through linkage by gender, postal code and birthdate.

PCR-material of SARS-CoV-2 strains will be preserved according to clinical practice and send to the center of infectious disease research, Diagnostics and Laboratory Surveillance (IDS) for sequencing. Of patients tested positive for SARS-CoV-2 at the GGD, the IDS will

request PCR-material of SARS-CoV-2 samples at the GGD laboratories with the Coron-IT sample number.

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

Univariable analysis will be carried out to assess the VE against being a laboratory-confirmed hospitalised COVID-19 case. Stratified analyses (by sex and age group, for example) will be performed to better understand potential effect modifiers and confounders. Multivariable analyses 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 determined in the same way as the primary endpoint with univariable analysis to measure VE against being a laboratory confirmed hospitalised COVID-19 case though only among cases and controls 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 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', Wet Geneeskundige Behandelings-Overeenkomst (WGBO), and in accordance with the EU GDPR (General Data Protection Regulation) + Nederlandse uitvoeringswet AVG.

### 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 15-20%[7,8], 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.

## 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[9]. Further, the secured CBS environment itself is compliant with strict data security and protection rules[10]. For more information, see Datamanagementplan.

### 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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