VASCO study (VAccine Study COvid-19)

RESEARCH PROTOCOL

PROTOCOL TITLE 'VASCO study: A population-based prospective cohort study on vaccine effectiveness of COVID-19 vaccines in the Netherlands'

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Sponsor (in Dutch: verrichter/opdrachtgever)	Dutch Ministry of Welfare and Sports
Independent expert (s)	Not applicable
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AESI	Adverse events of special interest
BRP	Basis Registratie Personen
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CIMS	COVID-vaccinatie Informatie- en Monitoringsysteem
EU	European Union
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
GPs	General Practitioners
IC	Informed Consent
ICF	Informed consent form
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
VE	Vaccine Effectiveness
WHO	World Health Organisation
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Several COVID-19 vaccines have been (and will be) registered for use in the general population. COVID-19 vaccination started in the Netherlands in January 2021. Vaccination will sequentially target different groups, starting with specific groups of health care professionals and vulnerable persons. The goal is to vaccinate all adults in the course of 2021. COVID-19 vaccines have shown to be efficacious against COVID-19 in registration trials. These trials were not powered to assess efficacy in subgroups, such as age and risk groups. Also, follow-up to date has been limited to a few months, and the duration of protection is not yet known for any of the licensed vaccines. Therefore, post-marketing observational studies are needed to assess vaccine effectiveness (VE) in the real world and assess differences by vaccine and by age and risk group.

Objective: The primary objective is to estimate product-specific vaccine effectiveness (VE) of the COVID-19 vaccines that are used in the Dutch national vaccination program against symptomatic SARS-CoV-2 infection by age and medical risk group at 9 months after start of the study. Secondary objectives include estimating VE by time since vaccination, number of doses and interval between doses, and over longer follow-up time; estimating VE against SARS-CoV-2 infection by severity (asymptomatic, mild, severe); and monitoring of unsolicited adverse events for which medical attention was sought.

Study design: An observational population-based prospective cohort study. This study will use the existing SARS-CoV-2 testing infrastructure and COVID-19 vaccination strategy in the Netherlands. Preferably, participants will be included (as long as possible) before they received a first COVID-19 vaccination. At baseline, participants will be asked to take a self-collected fingerpick sample at home and to complete a baseline questionnaire via app or website. Data collected in the questionnaire includes sociodemographic variables, health status (including underlying conditions and previous SARS-CoV-2 infection), vaccination, and behaviour regarding COVID-19 measures. During follow-up participants will be asked to fill out monthly questionnaires via an app or website including questions about COVID-19 vaccination, testing for SARS-CoV-2 infection, changes in health status and behaviour regarding COVID-19 measures. Participants can also notify in the app when they tested positive for SARS-CoV-2 or when they received a COVID-19 vaccination. At 28 days and 6 months after roll out of the vaccination programme in the specific target group, participants are asked to take a self-collected fingerpick blood sample, so that a blood sample is taken for participants who decided to get vaccination and for those who decided not to get vaccination. Fingerpick blood samples are collected to measure antibodies to detect previous SARS-CoV-2 infections which were not detected by PCR or antigen tests, due to asymptomatic infections or because participants did not get tested. Furthermore, information on SARS-

CoV-2 testing and COVID-19 vaccination will be obtained through linkage with the national vaccination register and linkage with GGD-registrations where possible. Additional information about health status and hospitalization will be obtained through information from General Practitioners (GPs) and hospitals. Participants will be followed up for 5 years. Further knowledge or changes in the COVID-19 pandemic might lead to new research questions which cannot be foreseen. Sub-studies embedded into this cohort study will be designed at a later stage, for example in-depth studies investigating immunogenicity requiring more frequent blood sampling or other data collection. Such sub-studies are not described in the current protocol.

Study population: 50,000 participants will be enrolled, divided into three different target groups for COVID-19 vaccination:

1. 30,000 community-dwelling persons aged 60-80 years
2. 10,000 community-dwelling persons aged 18-59 years with a medical indication for being prioritized for COVID-19 vaccination
3. 10,000 community-dwelling persons aged 18-59 years without a medical indication for being prioritized for COVID-19 vaccination.

Participants will be recruited through a random selection from the national population registry (*Basis Registratie Personen* - BRP), stratified by age (18-39, 40-59 and 60-80 years). To enable enrolment of a sufficient number of participants in target group 2, this group will be oversampled through recruitment via GPs. Participants will also be recruited via (social) media campaigns.

Intervention (if applicable): COVID-19 vaccination will be given as part of the national vaccination program, and is not done by the study team.

Main study parameters/endpoints: The primary endpoint is symptomatic SARS-CoV-2 infection, determined by a positive PCR or antigen test in combination with COVID-19 related symptoms. Secondary endpoints are SARS-CoV-2 infections by disease severity and unsolicited adverse events of special interest following vaccination.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: At baseline and during follow-up participants are asked to complete questionnaires via app or website. In addition, participants will be asked to donate fingerpick blood (maximum of 0.5 ml/sampling timepoint) at baseline, at 28 days and 6 months after roll out of the vaccination program in the specific target group, which may cause minor discomfort. Overall, the burden for the participants will be small and is justified given the importance of assessing the VE of the different vaccines to inform (future) vaccination policy. There are no personal benefits for the participants of the study, however the participants contribute to public health insights relevant for future control of the COVID-19 pandemic, especially related to the vaccination program.

1. INTRODUCTION AND RATIONALE

The World Health Organization (WHO) has declared the current coronavirus disease (COVID-19) outbreak, caused by the SARS-CoV-2 virus, to be a pandemic and, therefore, a Public Health Emergency of International Concern. In the first half of 2020, many governments worldwide implemented general measures (such as physical distancing, hygiene measures, and face masks) and lockdowns (closures of schools, businesses, public transport, and cancellation of events) to contain their epidemics, usually with success but at great economic and social costs. Vaccination is a simple, safe, and effective way of protecting people against harmful diseases, before they come into contact with them. For a vaccination strategy to work, it needs COVID-19 vaccines that are both safe and effective. Prior to registration, efficacy and safety of COVID-19 vaccines in development are being tested in clinical trials. At present there is limited follow-up of vaccinated subjects and a urgent need for use of these vaccines as a control measure in the pandemic. In addition, most pre-registration clinical trials are conducted in a controlled population and setting. Also, these trials are not powered to assess efficacy in certain risk groups, like participants with comorbidity or elderly. This results in limited data on efficacy in these subgroups. Furthermore, follow-up in trials to date has been limited to a few months, and the duration of protection is not yet known for any of the licensed vaccines. Collection of data in a real world setting and over a prolonged period of time is therefore warranted. This also permits comparing post-marketing effectiveness of different COVID-19 vaccines.

As of February 1st 2021, three COVID-19 vaccines have been registered by the European Medicines Agency (EMA), the mRNA vaccine of Pfizer/BioNtech, the RNA vaccine of Moderna, and the vector based vaccine from Oxford/AstraZeneca. More vaccines are expected to receive approval from EMA in the near future as stated by the World Health Organization (WHO)[1]. A two-dose regimen of the Pfizer/BioNtech and Moderna vaccines showed around 95% protection against symptomatic SARS-CoV-2 infection in persons 16 years of age or older.[2,3] The vaccine of Oxford/AstraZeneca showed a vaccine efficacy of around 70% against COVID-19[4]. Once additional vaccines become available and are incorporated into the national vaccination program (e.g. vaccination strategy of Rijksoverheid[5], see **Figure 1**), they will become in scope for this study. Monitoring of real world vaccine effectiveness (VE) in the long term is necessary and therefore done for all vaccines included in national vaccination programs by national public health institutes (e.g. Rijksinstituut voor Volksgezondheid en Milieu (RIVM)) and academic institutions. In addition to the populations included in the vaccine trials for licensure, vaccines may be used in broader populations (e.g. more age groups, medical risk groups) and in other intervals. This long-term follow-up real-world study will lead to insights to emerging virus variants as well as

provide information on the duration of protection. This setting will also provide an infrastructure to conduct sub-studies, for example to assess immunogenicity of different COVID-19 vaccines. In addition, as of now unforeseen situations could occur in the following years which could be studied in this well-defined population cohort of vaccinated and unvaccinated participants.

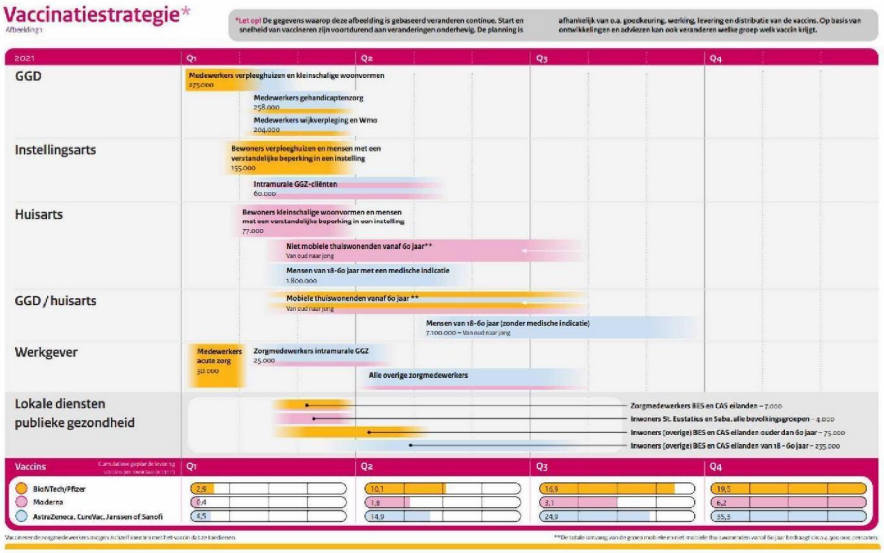


Figure 1: 'Vaccinatie strategie' of Rijksoverheid, the Netherlands version 12-01-2021[5]

2. OBJECTIVES

Primary Objective:

To estimate product-specific VE of COVID-19 vaccines used in the Dutch national vaccination program against symptomatic SARS-CoV-2 infection at 9 months after start of the study by age group (18-59, 60-80 years) and medical risk group (yes/no).

Secondary Objectives:

- Estimating product-specific VE against SARS-CoV-2 infection by disease severity (asymptomatic, mild/moderate, severe (hospitalization and death)) by age and medical risk group.
- Estimating product-specific VE against SARS-CoV-2 infection (by disease severity) by time since vaccination, interval between doses and number of doses.
- Estimating relative VE against SARS-CoV-2 infection (by disease severity) between vaccine products by age and medical risk group, and by time since vaccination.
- Estimating product-specific VE against SARS-CoV-2 infection (by disease severity) at 1-5 years after vaccination by age and medical risk group.
- Monitoring unsolicited adverse events for which medical attention is sought by product.

3. STUDY DESIGN

This study has an observational population-based prospective cohort design. Fifty thousand participants will be enrolled, divided into three different target groups for COVID-19 vaccination (**Table 1**):

1. 30,000 community-dwelling persons aged 60-80 years, irrespective of medical risk group. Approximately half of this group is expected to have a medical indication.[6]
2. 10,000 community-dwelling persons aged 18-59 years who have a medical indication for being prioritized for COVID-19 vaccination.
3. 10,000 community-dwelling persons aged 18-59 years without a medical indication for being prioritized for COVID-19 vaccination.

Participants will be included irrespective of their COVID-19 vaccination status or intention for getting vaccinated. Preferably, participants will be included before they received COVID-19 vaccination. However, the feasibility of this depends on the start-date of the study and the progress achieved by the national vaccination program by then. Participants can contribute unvaccinated as well as vaccinated person time (time varying exposure), see also **Figure 2**.

Further knowledge or changes in the COVID-19 pandemic might lead to new research questions which cannot be foreseen. Sub-studies embedded into this cohort study will be designed at a later stage, for example in-depth studies investigating immunogenicity requiring more frequent blood sampling or other data collection. Such sub-studies are not described in the current protocol and will be submitted to the METC as new protocols or protocol amendments.

Participant recruitment

A random sample will be taken from the BRP stratified by age (18-59, 60-80 years) and geographic area. The BRP contains all individuals with a home or postal address. Of persons 18-59 years, about 20% have a medical indication (see **Table 1**, according to 'vaccinatie strategie Rijksoverheid'[6]: 1.8 million with medical indication vs 7.1 million without medical indication[5]). To enable enrollment of a sufficient number of individuals in group 2, oversampling of this group is needed. Specific recruitment of persons aged 18-59 years from a medical risk group will be done through GPs. GPs have this information because they also invite persons with a medical indication for being prioritized for COVID-19 vaccination. Participants will also be recruited by a media campaign.

The vaccines which will be used in the different target groups are uncertain, but we assume that in each group 2 or 3 different vaccines will be used.

Target group	Estimated size in NL	Scheduled vaccination period	Scheduled vaccines used	Recruitment	Needed sample size (see section 4.4)
Community dwelling persons aged 60-80 years	~4 million	Feb-July 2021	BioNTech/Pfizer Moderna Other*	Random sample BRP based on age	30,000 (medical risk group yes/no, 3 vaccines)
Persons aged 18-59 years with medical indication	~1.8 million	Feb-May 2021	Other*	20% from random sample from BRP 80% from selective recruitment GP	10,000 (2 vaccines)
Persons aged 18-59 years without medical indication	~7.1 million	May-Sept 2021	Other*	Random sample BRP based on age (80% of this sample is without medical indication)	10,000 (2 vaccines)

*Other: AstraZeneca, Curevac, Janssen or Sanofi. At time of inclusion of this study uncertainty which vaccines will be used in the different target groups.

Table 1: Target group, vaccination period and used vaccines.[7]

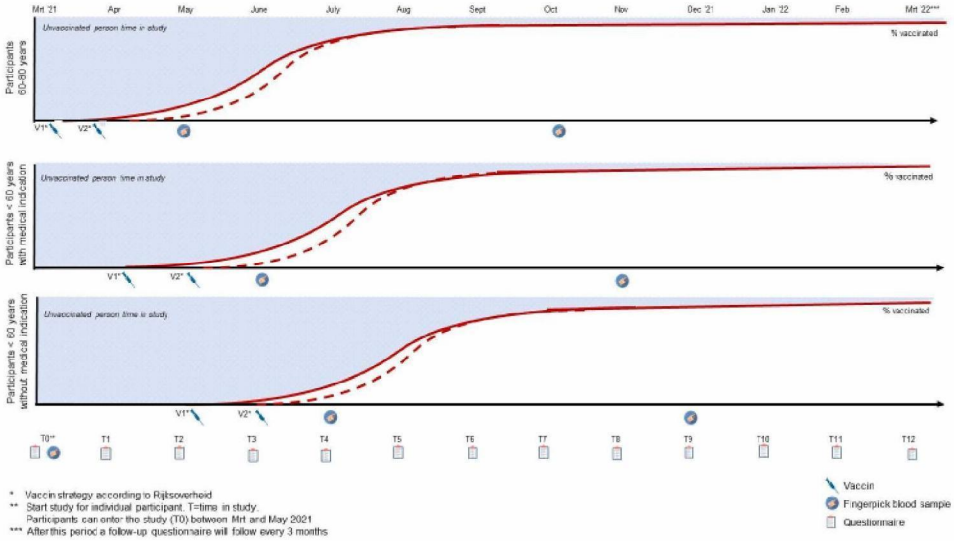


Figure 2. Study design of the VASCO study.

Data collection

This study will use the existing SARS-CoV-2 testing infrastructure and COVID-19 vaccination strategy of the Netherlands.

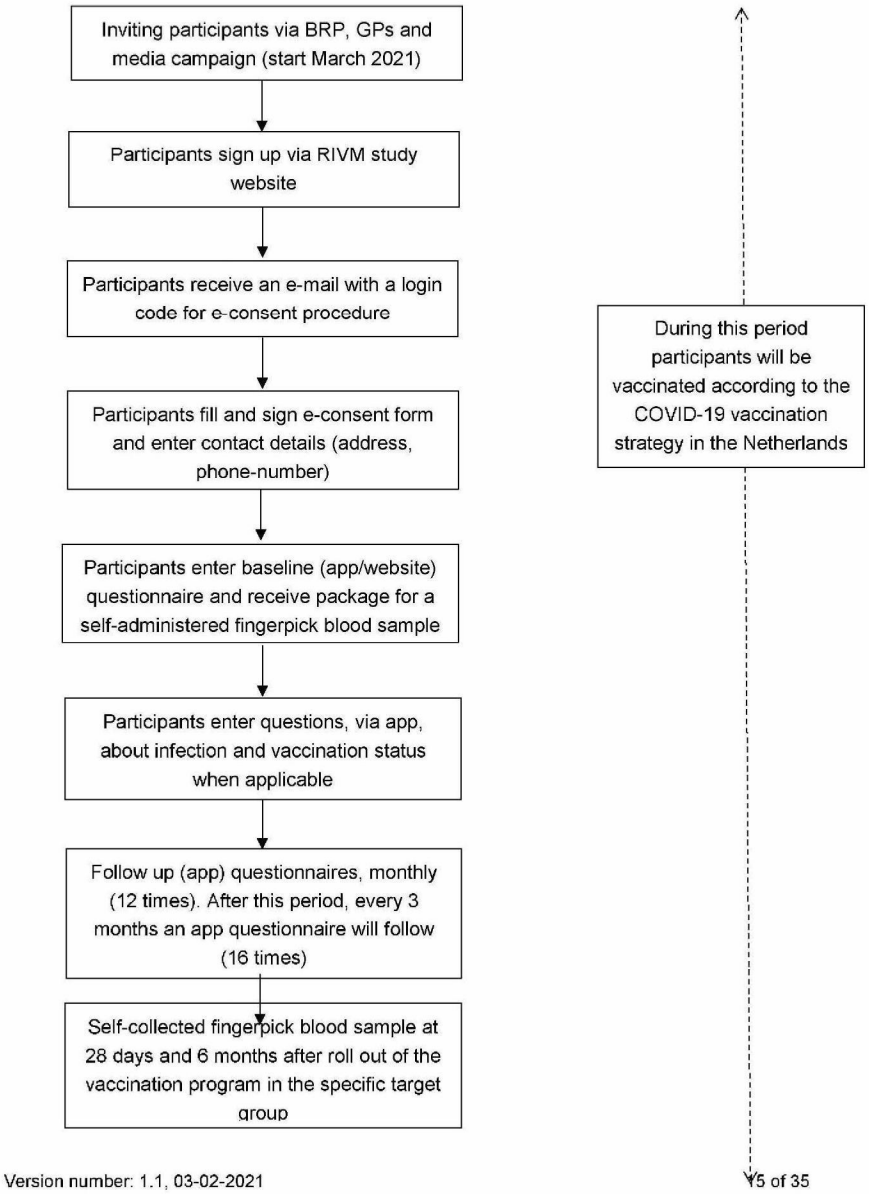
At baseline we will ask the participants the following:

- A self-collected fingerpick blood sample, for serology to detect a previous SARS-CoV-2 infection which was not detected by PCR or antigen tests, due to asymptomatic infections or because participants did not get tested.
- To fill in a baseline (digital) questionnaire via app/website: includes sociodemographic variables (age, sex, ethnicity, education, profession), health status (underlying conditions, health care consumption, medication use, previous known SARS-CoV-2 infections), vaccination status (influenza, pneumococcal, COVID-19) and behavior regarding COVID-19 measures (visiting public places, face mask use, contacts, travel, social distancing). This information is needed to adjust for differences between vaccinated and unvaccinated persons; some parameters can also change over time and should be treated as time varying confounders. See supplementary file 1 for the questionnaire.

During follow-up the following information will be collected:

- The first year participants are asked to fill out a monthly questionnaire via app/website including questions on COVID-19 vaccination, SARS-CoV-2 testing, changes in health status, and behaviour regarding COVID-19 measures.
- In addition, participants are asked to notify in the app when they have been tested positive for SARS-CoV-2 or when they received a COVID-19 vaccination.
- From year 2 until year 5 the participants fill in a follow-up (app) questionnaire every 3 months containing similar themes.
- A self-collected fingerpick blood sample at 28 days and 6 months after roll out of the vaccination program in the specific target group, for serology to detect a previous SARS-CoV-2 infection.
- Information on COVID-19 vaccination based on linkage with the national vaccination register where possible.
- Information on a SARS-CoV-2 infections based on linkage with the GGD registers where possible.
- Information about health status from hospitals and GPs.

Flow chart of inviting participants until end of study



4. STUDY POPULATION

4.1 Population (base)

Participants in the study are adults between 18 and 80 years from the general Dutch population who are or will become eligible for COVID-19 vaccination.

4.2 Inclusion criteria

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

- Community dwelling adult between 18-80 years
- Informed consent provided
- Be able to read, understand and write Dutch

4.3 Exclusion criteria

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

- Not able or willing to understand and sign the informed consent
- Not able to fill out a digital (app) questionnaire

4.4 Sample size calculation

The sample size will be determined solely by the requirements of the primary analysis, assessing VE against symptomatic SARS-CoV-2 infection at 9 months after start of the study. Using R version 3.6.3 with gsDesign (3.1.1), we can approximately assess the sample size required to achieve 90% power with 2.5% type 1 error (one-sided) with H0: VE ≤ 0% and H1: VE > 0%. When assuming the following:

- A 6-month infection rate among unvaccinated individuals of 0.03 (i.e. incidence of ~17 per 100,000 per day or ~2600 cases per day);
- A vaccination coverage of 85%;

we need 42 first infection events which is expected with 4237 participants per stratum to be able to detect a VE of 70%. We increased the sample size of each stratum by 15% (amounting to 4984 participants) to account for loss to follow up and uncertainty of vaccine strata sizes (see below).

We now anticipate the following strata:

- 60-80 year olds: medical risk group yes/no, 3 different vaccines → 6 strata
- 18-60 year olds: medical risk group yes/no, 2 different vaccines → 4 strata

When assuming equally-sized strata, we need 4984*10 strata = ~50,000 participants in total. For the strata by medical risk group and age group we can ensure equal stratum size by targeted sampling of these groups. For the stratum size by vaccine we are dependent on the implementation of the vaccination program by the government, so we cannot ensure equal stratum sizes by vaccine product.

We assumed 85% vaccination coverage in the sample size calculation but expect coverage to exceed 85% in the early phase of the vaccination campaign, which targets the most vulnerable populations. We want to make best use of these vulnerable strata and also leverage the information from the later portions of the vaccine campaign (e.g., "Persons aged 18-59 years without medical indication"). Therefore, we will also include unvaccinated person time in the analysis for persons who have not yet been vaccinated with proper accounting of participant contribution to both unvaccinated and vaccinated time via time-dependent covariate Cox proportional hazards modelling (see also **Figure 2**). Monte Carlo simulations conducted for this study suggest that such models can reliably estimate VE even under rather extremely limited unvaccinated observation time in the earlier target groups (e.g., "Community dwelling persons aged 60-80 years").

With the projected sample size, we are also able to detect with 80% power a 3.8-fold difference in infection rate between different vaccine products (e.g. VE of 90% vs VE of 62%) within the 4 strata by medical risk group and age groups when assuming an infection rate of 4.2% over one year for the worst vaccine product (11.5 infections per day per 100,000).

5. TREATMENT OF SUBJECT

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary endpoint is time to first symptomatic SARS-CoV-2 infection, determined by a positive PCR or antigen test in combination with COVID-19 related symptoms. Those infections can be detected through the national testing programme.

8.1.2 Secondary study parameters/endpoints

Secondary endpoints that will be investigated:

- SARS-CoV-2 infections by disease severity:
  - COVID-19 related death
  - COVID-19 related hospitalization
  - Mild SARS-CoV-2 infection
  - Asymptomatic SARS-CoV-2 infection
- Unsolicited adverse events for which medical attention was sought

8.1.3 Other study parameters

Other study parameters include information from questionnaires, and possibly registers, including sociodemographic variables, health status, (COVID-19) vaccination, and behaviour regarding COVID-19 measures.

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

Via the BRP potential participants will receive an invitation to participate in the study by post. Participants can also enter the study through a media campaign and sign up themselves. After signing the online informed consent form (ICF) participants will enter the online baseline questionnaire via app or website. Data collected in the questionnaire includes sociodemographic variables, health status (underlying conditions, health care consumption, medication use, previous SARS-CoV-2 infection), vaccination (influenza, pneumococcal, COVID-19), and behaviour regarding COVID-19 measures. In addition, the participants will be asked to donate a fingerpick blood sample (maximum of 0.5 ml) by

the provided self-sampling set according to the detailed instruction, and are requested to return the sample in the stamped, addressed safety-envelope provided.
During follow up participants will be asked to fill out monthly questionnaires via app/website including questions about testing for SARS-CoV-2, COVID-19 vaccination, changes in health status, and behaviour regarding COVID-19 measures (see supplementary file 1). In addition, participants are asked to notify in the app when they have been tested positive for SARS-CoV-2 by PCR or antigen test or when they received a COVID-19 vaccination. These surveys will allow the subject to self-report details of episodes related to a SARS-CoV-2 infection and COVID-19 vaccine, including which dose (i.e., first or second) and from which manufacturer. From year 2 until year 5 the participants are asked to fill out follow-up questionnaires every 3 months containing similar subjects. The participants will be asked to donate fingerpick blood samples at 28 days and 6 months after roll out of the vaccination program in the specific target group, so that a blood sample is taken for participants who decided to get vaccination and for those who decided not to get vaccination. Fingerpick blood samples are collected to measure antibodies to detect previous SARS-CoV-2 infections which were not detected by PCR or antigen tests, due to asymptomatic infections or because participants did not get tested. Serum samples will be tested for the presence of SARS-Cov-2 specific antibodies by quantitative multiplex serology (Microarray and/or Luminex or other (commercial) immune-assays), against appropriate controls (SARS/MERS and human coronaviruses). To distinguish between infection-induced immunity and vaccine-induced immunity the samples will be tested on the presence or absence of anti-N against the spikes of the coronavirus. The participants' permission will be asked explicitly in the ICF for the possibility to link their data with the COVID-vaccinatie Informatie- en Monitoringsysteem (CIMS) register, GP and hospital patient dossier and GGD registers (OSIRIS and CoronIT). Also, the participants' permission will be asked to be approached for interest in future sub studies.

8.4 Withdrawal of individual subjects

Participants can leave the study at any time for any reason if they wish to do so without any consequences.

8.4.1 Specific criteria for withdrawal

A subject will be withdrawn from the study for any of the following reasons:

- Withdrawal of consent

8.5 Replacement of individual subjects after withdrawal

There will be no replacement of participants in this study.

8.6 Follow-up of subjects withdrawn from treatment

Not applicable

8.7 Premature termination of the study

There are no criteria for terminating the study prematurely. If the study should be terminated, this will be done in consultation with the Principal Investigator and the METC will be notified.

9. SAFETY REPORTING

Not applicable.

10. STATISTICAL ANALYSIS

Below an overview is given regarding the planned statistical analyses for this population based cohort study.

General statistical approach

Appropriate statistical methods will be selected for each research question depending upon the nature of the data distribution as well as the effect that is to be characterized. Categorical variables will be presented as absolute numbers and percentages, while continuous variables will be described by number of observations, mean, standard deviation, median and range (minimum and maximum). While maximum effort will be put into the minimization of missing data, the remote nature of the study and the reliance on self-reporting by the subjects might lead to the presence of missing data. Where necessary, missing data mechanisms will be investigated and imputation methods will be used. The count and percentage of known missing data will be described. All statistical confidence intervals will be two-sided and at the 95% level. P-values will be considered significant if less than 0.05 with two-sided testing and if less than 0.025 with one-sided testing. Adjustments for multiplicity of tests are planned and will be described in more detail within a separate statistical analysis plan.

10.1 Primary study parameter(s)

The VE against symptomatic SARS-CoV-2 infection will be assessed at 9 months after the start of the study (aiming to include follow up time of on average 6 months after vaccination) using a time-dependent Cox proportional hazards model with vaccination status considered as a time-varying covariate meaning that participants can contribute both unvaccinated as well as vaccinated person-time. Analyses will be stratified by age group (18-59, 60-80 years), medical risk group (yes/no), and vaccine product. The coefficient for the hazard ratio of vaccination status will be used to estimate vaccine effectiveness. The model will use calendar time as the time-scale to account for differences in risk of exposure to SARS-CoV-2 over time. Additional assessments of vaccine effectiveness will include:

- Models with interaction terms between vaccine product, age, and/or medical risk group to assess potential vaccine effectiveness modifiers.
- Additional adjustments to the primary model and stratified models for sociodemographic variables and region (fixed or time-varying covariates).
- Exploratory additional adjustments and stratifications of behaviour regarding COVID-19 measures and health status.

10.2 Secondary study parameter(s)

Other SARS-CoV-2 infection endpoints

VE against COVID-19 related hospitalizations and deaths will be assessed using a time-dependent Cox proportional hazards model similar to the primary endpoint. Due to the rarity of these outcomes, we anticipate that vaccine product, age and medical risk group will be estimable solely as covariates and only within models containing few stratifications of the baseline hazard. The models will use calendar time as the time-scale to account for differences in risk of exposure to SARS-CoV-2 over time. Secondly we will adjust the models for sociodemographic variables and region (fixed or time-varying covariates). Third, we will explore additional adjustments and stratifications of behaviour regarding Covid-19 measures and health status.

VE against all SARS-CoV-2 infections based on PCR and antigen testing and serology (so including asymptomatic and symptomatic infections) will be assessed using a cumulative incidence approach as the exact time of infection is not known for participants positive based on serology.

Number of doses, interval between doses and time since vaccination

Analyses above will be repeated stratified by number of received doses, interval between doses and time since last dose.

Stratification based on vaccination schedule compliance is anticipated according to the following definitions:

1. Fully compliant will be defined as "receiving all intended doses within the recommended time windows for each dose".
2. Partially compliant will be defined as "receiving all intended doses but not within the recommended time windows for subsequent doses after the first". The recommended time window can change during the roll out of the vaccination program depending on shortage of vaccines, phase of the pandemic and new scientific insights.
3. Not compliant will be defined as "receiving only the first dose in a multi-dose schedule".

Long term effectiveness

Analyses above are anticipated to be repeated at least annually during the 5 years of follow up of the study.

Relative effectiveness

Relative VE comparing different products will be assessed within vaccinated persons using a Cox proportional hazards model. Similar analyses to account for effect modifiers and confounders will be done as described for the primary endpoint.

Sensitivity analysis

Analyses above will be repeated excluding participants with previous SARS-CoV-2 infection based on a self-reported positive SARS-CoV-2 PCR- or antigen-test or based on antibodies against SARS-CoV-2 at baseline.

Monitoring of adverse events of special interest

Adverse events reported after vaccination will be summarized in three ways:

1. Percentage of subjects who have reported an unsolicited adverse event with a presentation by "Any reported AE" and by classified AE terms. This will be reported overall and stratified by vaccine product, age group, and medical risk group.
2. Rate per day of subjects who have reported adverse events with a presentation by "Any reported AE" and by classified AE terms. This will be reported overall and stratified by vaccine product, age group, and medical risk group.
3. For select AE terms, a Poisson regression including terms for vaccine product, age group, and medical risk group will be conducted with an adjustment for number of days since initial vaccination.

10.3 Other study parameters

We will assess baseline differences and differences over time in sociodemographic factors, health status and behaviour regarding COVID-19 measures (including testing behaviour) between vaccinated and "never vaccinated" by age group and medical risk group using logistic regression.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and its amendments effective since 1964 and in accordance with the Medical Research Involving Human Subjects Act (WMO). The guideline ICH Good Clinical Practice (GCP) will be followed, however it is foreseen that some items cannot be adhered to, mainly because of logistical reasons. The self-collected fingerpick and completion of the questionnaires will take place at home.

11.2 Recruitment and consent

Recruitment will be done by inviting participants by post and a media campaign. Participants can show their interest to participate the study via the website (by filling in their e-mail address which will be automatically forwarded to the study team). The participants will receive an log-in code to a digital ICF and after signing the ICF participants will enter the baseline questionnaire via app or website and receive a self-sampling fingerpick set with detailed instructions.

On the website (potential) participants can find information on the study, FAQs and contact details if they need more information and they can approach the study team by email or phone for more information.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

The study is designed to include adults aged 18-80 years from the general Dutch population. The main objective can only be reached in case all targeted age groups are invited. Blood collection by fingerpick is a standard procedure which is generally accepted. The sensation of a fingerpick can be discomfortable for some participants. There are no personal benefits for the participants of the study, however the participants contribute to public health insights relevant for future control of the COVID-19 pandemic, especially related to the vaccination program.

11.5 Compensation for injury

The METC has decided that participating in the study is without risks, and has granted the RIVM dispensation from the compulsory participants' indemnification as laid down in article 7, paragraph 5 of the WMO. According to a Ministerial Order, RIVM is excluded from compulsory liability insurance for clinical research as determined by the Dutch law on Medical Investigations (WMO, section 7, paragraph 10). Any liability claims should be directed to the RIVM.

11.6 Incentives (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The collection and processing of personal data from participants enrolled in the study will be limited to those data that are necessary to fulfil the objectives of the study. The data is collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate procedures are implemented to protect the personal data against unauthorized disclosure, access, loss or alteration. Data will be captured using an eCRF, developed with Electronic Data Capture technology (EDC), VASCO web portal and laboratory results (PCR/antigen and serology antibody testing). The eCRF and the VASCO web portal are both hosted in the Your Research platform.
Data from the eCRF and the VASCO web portal will be pseudonymized (participants will be assigned a unique identification number in Your Research platform) and stored in a study database (Your Research platform). Only authorised study staff (Sponsor/Investigator, RIVM and Julius Clinical) will be allowed to enter data into the eCRF and make changes to eCRF data. These data will lack any personal identifiers. The key to connect the identification number to the subject will be stored in a separate section of the EDC and will only be available for a limited number of study staff from the Sponsor/Investigator and Julius Clinical, such as the Data manager, the Julius Clinical Data Transfer Lead and his/her delegate. Subject personal data (name and address) will also be shared with RIVM/the vendor (Mailstreet) responsible for sending the onboarding and study supplies to the participants. Since recruitment and follow-up will be completely remote, supplies will need to be sent to the participants' home addresses.
Data points that originate from a third party database (TBD for linkage), will be transferred via secure means to the investigator. Transferred data will not contain personal identifiers as only trial-specific identifiers will be used to link data between parties. Data points that are not considered part of the eCRF (e.g., derived data points and administrative data points) will be automatically calculated or entered by authorised staff of Sponsor, Investigator or it's designee.
All changes made to the eCRF data will be captured via an electronic audit trail, indicating at least date and time of change, the reason for changing the data, the individual that made the change and the old and new data value.
Source data is not applicable for this trial as all data will either be directly entered into the VASCO web portal, the eCRF or be laboratory test results.

In compliance with relevant guidelines, the study team will maintain all eCRFs as well as all study documents as specified by the applicable regulatory requirement(s). These records must be readily available for audit or inspection. If it becomes necessary for the appropriate regulatory authority to review any documentation relating to this study, the study team must permit access to such reports. The collected blood will be stored at the RIVM under appropriate conditions. All essential study documents, data and collected blood will be retained for 20 years after completion of the study, according to GCP guidelines

12.2 Monitoring and Quality Assurance

No monitoring visits will be conducted for the study. The Investigator and his study team are responsible to ensure that the study is conducted in accordance with the protocol and local regulations. The eCRF data will be reviewed internally by Clinical Team members, Data Management, Statistics, Medical and Scientific staff or their designee and, if necessary, appropriate actions will be implemented in case data entry issues are detected. Once data are concluded to be complete and accurate, the eCRF data will be locked, meaning that the data will become read-only. The VASCO web portal data, eCRF data, and laboratory data will only be accessible and verifiable by the authorized study team members and adequate back-up and security measures are implemented to prevent loss of data or unauthorised access to the data.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the study to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of participants included and numbers of participants that have completed the study, problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study

within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC. Due to the number of analyses to be performed a final report containing all the results of laboratory and epidemiology analyses might be not feasible. The results will be made public in peer reviewed journals.

12.6 Public disclosure and publication policy

This study will be registered on the clincialtrials.gov and/or clincialtrials.eu websites, which are registries of studies conducted in Europe, the United States and around the world. The results of the study will be reported in a Study Report generated by the Sponsor-Investigator or Designee. The study results will be publicly disclosed and published independent of the outcome of the study in scientific, peer-reviewed, international journals and at international conferences.

13. STRUCTURED RISK ANALYSIS

Not applicable

14. REFERENCES

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4. Knoll M.D, Wonodi C. Oxford–AstraZeneca COVID-19 vaccine efficacy. The Lancet 2021; 397: 10269: 72-74
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