Cohort profile: an observational population-based cohort study on COVID-19 vaccine effectiveness in the Netherlands – The VAccine Study COvid-19 (VASCO)

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Abstract

Purpose - VAccine Study COvid-19 (VASCO) is a cohort study with 5-year follow-up that was initiated when COVID-19 vaccination was introduced in the Netherlands. The primary objective is to estimate real-world vaccine effectiveness (VE) of COVID-19 vaccines against SARS-CoV-2 infection in the Netherlands, overall and in four subpopulations defined by age and medical risk.

Participants - The cohort consists of 45,547 community-dwelling participants aged 18-85 years who were included irrespective of their COVID-19 vaccination status or intention to get vaccinated. A medical risk condition is present in 4,289 (19.8%) of 21,679 18-59 year-olds and in 9,135 (38.3%) of 23,821 60-85 year-olds. After one year of follow-up, 5,502 participants had dropped out of the study. At inclusion, and several times after inclusion, participants are asked to take a self-collected fingerprick blood sample in which nucleoprotein and spike protein receptor binding domain-specific antibody titers are assessed. Participants are also asked to complete monthly digital questionnaires in the first year, and 3-monthly in years 2-5, including questions on sociodemographic factors, health status, COVID-19 vaccination, SARS-CoV-2-related symptoms and testing results, and behavioral responses to COVID-19 measures.

Findings to date - VASCO data has been used to describe VE against SARS-CoV-2 infection of primary vaccination, first and second booster and bivalent boosters, the impact of hybrid immunity on SARS-CoV-2 infection and VE against infectiousness. Furthermore, data was used to describe antibody response following vaccination and breakthrough infections and to investigate the relation between antibody response and reactogenicity.

Future plans - VASCO will be able to contribute to policy decision-making regarding future COVID-19 vaccination. Furthermore, VASCO provides an infrastructure to conduct further studies and to anticipate on changing vaccination campaigns and testing policy, and new virus variants.

Registration - VASCO is registered in the online Dutch clinical trials register (trialsearch.who.int) with registration number NL9279.

Strengths and limitations of this study

- Detailed sociodemographic, behavioural and clinical data are available.
- Serology data is collected regularly to identify SARS-CoV-2 (re)infections and monitor vaccination responses
- Continued SARS-CoV-2 testing by participants in the post-pandemic era
- VASCO provides an infrastructure to conduct further studies
- VASCO relies on self-reported data which may have consequences for the completeness and accuracy of data

Introduction

On 11 March 2020, the World Health Organization (WHO) declared the coronavirus disease (COVID-19) outbreak, caused by the SARS-CoV-2 virus, to be a pandemic (1). Within a year after SARS-CoV-2 emerged, the first vaccines were developed and approved after registration trials showed high efficacy against symptomatic SARS-CoV-2 infection (2-5). In the Netherlands, the COVID-19 vaccination program started on January 6, 2021. Early 2021 four different COVID-19 vaccines were approved and used in the Netherlands: Comirnaty (BNT162b2; BioNTech/Pfizer), Spikevax (mRNA-1273, Moderna), Vaxzevria (ChAdOx1-S; AstraZeneca), Janssen (Ad26.COV2-S, Janssen-Cilag International NV) and later also Nuvaxovid (NVX-CoV2373; Novavax CZ). During the various vaccination campaigns that followed, different vaccines were recommended and administered in varying age groups (6, 7).

After implementation of a vaccination program, it is important to continuously monitor the program with regards to safety, effectiveness, and epidemiological impact in real world settings (8). Pre-registration vaccine trial participants are usually not representative of the target population and usually do not include sufficient numbers of individuals of special interest (e.g. children, elderly, and individuals with comorbidities). Also, the duration of follow-up prior to vaccine registration is usually short (9, 10). Furthermore, vaccine effectiveness (VE) estimates against SARS-CoV-2 infection, disease and transmission over time, and against new virus variants, are needed, overall and for subgroups in the population (11).

We therefore established an observational population-based prospective cohort study of community-dwelling persons aged 18-85 in the Netherlands named VAccine Study COvid-19 (VASCO). The primary objective of VASCO is to estimate COVID-19 vaccine-specific VE against SARS-CoV-2 infection overall, and in four subpopulations defined by age and medical risk, over time. Secondary objectives include estimating VE by time since vaccination, severity of SARS-CoV-2 infection, and variant of infection, and monitoring of adverse events after vaccination for which medical attention was sought. VASCO was initiated during the COVID-19 vaccination roll-out in the Netherlands and is funded by the Dutch ministry of Health, Welfare and Sports. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Cohort Description

Participant recruitment and enrolment

We enrolled participants belonging to three different target populations for COVID-19 vaccination: 1) community-dwelling persons aged 60-85 years, of whom approximately half were expected to have a medical risk condition to be prioritized for COVID-19 vaccination (12), 2) community-dwelling persons aged 18-59 years with a medical risk condition, and 3) community-dwelling persons aged 18-59 years without a medical risk condition. Within each target group, we defined strata based on the primary series

vaccine brand. A sample size calculation, assuming a 6-month infection rate among unvaccinated individuals of 0.03 and a vaccination coverage of 85% and accounting for loss to follow-up and uncertainty of vaccine strata sizes resulted in the requirement of ~5,000 participants per stratum to be able to detect a VE of 70% (**Supplementary file 1**). We anticipated 10 different strata, resulting in a targeted sample size of ~50,000 participants . Participants must be able to understand Dutch, as all study materials are written in Dutch, and were included irrespective of their COVID-19 vaccination status or intention to get vaccinated.

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A random sample of the national Dutch Personal Records Database, containing all individuals with a home or postal address in the Netherlands, stratified by age group (18-39, 40-59, 60-85 years) was sent an invitation to participate in the study by regular mail. After sending the initial invitations, the number of unvaccinated persons and persons vaccinated with Spikevax, Vaxzevria and Janssen were relatively low in the VASCO study population. Therefore, two additional random samples from the Personal Records Database were taken, specifically approaching individuals who were not registered as being vaccinated and individuals registered as vaccinated with Spikevax, Vaxzevria or Janssen vaccine in the national COVID-19 vaccination Information and Monitoring System (CIMS) of the Dutch National Institute of Public Health and the Environment (RIVM). Vaccinations are registered in CIMS if the vaccinated individual provided informed consent for registration (13). In total, 770,000 individuals received a personal invitation to participate in the study. In addition, recruitment was done through (social) media. Specific recruitment of persons aged 18-59 years with a medical risk condition due to which they were prioritized for COVID-19 vaccination was done via general practitioners (GPs).

Potential participants could register themselves by entering the study website, answer some screening questions (age, not living in a health care facility), and submit their contact details. Information regarding use of the study website, the study-specific mobile phone application, and login code was sent by e-mail. Between 3 May 2021 and 15 December 2021 (**Supplementary file 2, Figure S1**), 60,390 persons subscribed on the study website and received a baseline package including study information, an informed consent form and a kit for self-collection of a blood sample. As we did not collect data on recruitment method (personal invitation or social media) until 11 June 2021, the actual response rate to the personal invitations remains unknown. In total, 46,619 (77.2%) participants signed informed consent, of which 45,547 (97.7%) completed the baseline questionnaire and 44,985 (96.5%) returned the baseline fingerprick sample.

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Data collection

Participants are followed for 5 years after enrolment. All study procedures are done remotely via a study website and mobile phone application, and self-collection of fingerprick blood samples for SARS-CoV-2 serology. At baseline, participants were asked to complete a baseline questionnaire and to donate a fingerprick sample. Follow-up information is collected using monthly online questionnaires in the first year, and three-monthly online questionnaires in years 2-5. They are asked to complete validated wellbeing questionnaires every three months. In addition to the routine questionnaires, participants are asked to report all COVID-19 vaccinations and positive SARS-CoV-2 tests via the website or app. Each time a participant reports a positive test, follow-up questions are asked about symptoms and disease course. These questions are repeated after one month and supplemented with questions on test positivity and vaccination status of household members. One month after a participant reports a new vaccination, follow-up questions are asked about side effects around the time of vaccination. An overview of the data collected through various questionnaires is presented in **Table 1**.

In addition, participants are requested to collect fingerprick blood samples at 6, 12, 18, 24 and 30 months and one month after completion of the primary vaccination series (only when at least four weeks have passed since the baseline sample). Serum from fingerprick samples is tested for the concentrations of total immunoglobulin against the receptor binding domain of the SARS-CoV-2 Spike (S1) protein and the SARS-CoV-2 Nucleoprotein (see **Supplementary file 3** for more detail).

Where relevant, data from registries on COVID-19 vaccination, SARS-CoV-2 infections, (COVID-19 related) death, and from hospitals and GPs on health status can be linked to the study data. **Supplementary file 2, Figure S2** shows examples of data collection schedules of individual participants in VASCO from start until end of the study. From April 2022 onwards, VASCO participants receive SARS-CoV-2 self-tests to be used when having symptoms in order to keep track of SARS-CoV-2 infections, as testing at Public Health Service test centers was scaled down.

Table 1. Questionnaire data collected during VASCO

Questionnaire	Timing	Topics
Baseline	Baseline	1. sociodemographic factors: age, sex, ethnicity, education, profession, 2. health status: comorbidities, medication use, pregnancy, health care consumption, medication use, previous confirmed SARS-CoV-2 infections 3. vaccination status: COVID-19, influenza, and/or pneumococcal vaccines 4. behavioural responses to COVID-19 measures (e.g. visiting public places, face mask use, contacts, travelling, and physical distancing)
Follow-up	Monthly in the first year of follow-up, 3-monthly in years 2-5 of follow-up	1. COVID-19 vaccination 2. SARS-CoV-2 testing 3. changes in health status 4. behavioural responses to COVID-19 measures (e.g. visiting public places, face mask use, contacts, travelling, and physical distancing)
Well-being	Baseline, 3-monthly	1. 12-Item Short Form Survey (SF-12) 2. Checklist Individual Strength (14-16)
COVID-19 vaccination	Whenever applicable	1. Vaccination date, vaccine product
Positive SARS-CoV-2 test	Whenever applicable	1. Type of test (either a test by a Public Health Service test centre free-of-charge, a test at a commercial test centre, or a self-test provided to schools and people with limited funds through government and widely available in stores) 2. Date of positive test 3. Reason for testing 4. Symptoms 5. Disease course
Household members	1 month after a positive SARS-CoV-2 test	1. Vaccination status of household members 2. Positive tests of household members 3. Age of household members 4. Testing of household members
Adverse events	1 month after a COVID-19 vaccination	1. Occurrence of injection site or systemic AE

		2. Occurrence of AE for which contact was sought with a health care professional
Follow-up positive SARS-CoV-2 test	1 month after a positive SARS-CoV-2 test and from May 2022 during subsequent months for as long as symptoms persist	1. Symptoms 2. Disease course

Additional data collection can easily be added during the course of the study. Some additional data collection has already been performed. In the period of December 2021 to March 2022, a subset of participants was requested to donate an additional fingerprick blood sample after confirmation of a breakthrough infection. These samples were used to assess boosting characteristics of serum SARS-CoV-2 specific antibody responses (17). In March 2022, participants were asked whether they received pneumococcal or influenza vaccination in the previous Winter season. In January 2023, all female participants <50 years who had reported to be pregnant during the study and were expected to have given birth, were invited to complete a questionnaire regarding neonatal outcomes, including questions on gestational age, birth weight, Apgar score, and hospital and NICU admission. These data are used to study the association of COVID-19 vaccination and SARS-CoV-2 infection on neonatal outcomes. Furthermore, from June 2023 onwards, participants are asked to mail in the test cartridges of positive self-tests to determine the virus variant by sequencing. This enables monitoring of circulating SARS-CoV-2 variants in the Dutch population and estimating VE by specific variant.

Follow-up

After one year of follow-up, 5,502 of the 45,547 participants had dropped out of the study, resulting in an overall attrition rate of 12.1%. The distribution of the non-time-varying characteristics of the (remaining) study population remained largely the same at baseline and 1-year follow-up (**Table 2**). Attrition analysis (**Supplementary file 4**) of 32,001 participants showed that attrition during the first year of follow-up was lower among Dutch participants compared to migrants and children of migrants, among participants with higher age, among females, among participants with intermediate education or high education. Higher test intention was associated with a lower attrition with a HR for always testing of 0.40 (95%CI 0.33 – 0.49) to a HR for rarely testing of 0.77 (95%CI 0.61 – 0.98) compared to never testing. Medical risk condition, recruitment method, and having experienced an infection did not affect the attrition rate. Some age group specific differences in attrition rate were detected. For example, attrition was higher among those with medical risk in the 60-85 year age group but lower in the 18-59 year age group (see **Supplementary file 4, Table S1**). Reasons for dropout were largely unknown (for 92% of dropouts).

Reported reasons for dropout included study duration and logistics (e.g. issues with the study app) (4.7%), personal circumstances (2.8%), or death (0.6%).

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Cohort characteristics

The main sociodemographic characteristics of VASCO participants are shown in **Table 2**. The median age is 61 years (95% range 25 – 76). Compared to the general Dutch population, VASCO participants are more often women (i.e. 62.9% vs 50.3%) (18), highly educated (56.8% vs. 40.0%) (19), and of Dutch origin (89.5% vs. 75.4%) (18). Of the participants between 18 and 60 years, 19.8% have a medical risk condition. In the age group 60-85 years, 38.3% of the participants have a medical risk condition, compared to 51% in the general population (12). The most commonly reported comorbidities in participants with a medical risk condition are cardiovascular disease (n=7,965), lung disease or asthma (n=3,576), and diabetes (n=2,210). Participants reside in all but one of the 352 municipalities of the Netherlands, with more participants residing in more densely populated areas (**Fig 1**). After one year of follow-up, the COVID-19 vaccination coverage (**Supplementary file 2, figure S3**) for at least a primary series among VASCO participants was higher compared to the Dutch adult population (97.5% vs 86.0%) and unvaccinated participants are underrepresented in VASCO (2.2% vs. 10.9%) (6). The vaccine product used for primary series vaccination was most often Comirnaty (40.1%) or Vaxzevria (34.4%). The anticipated sample size was (almost) reached for 6 out of the 10 prespecified strata (**Supplementary file 1, Table S1**). The percentage of participants who experienced a SARS-CoV-2 infection (based on self-report of a positive PCR or antigen (self) test and SARS-CoV-2 serology) increased from 16.6% at baseline to 67.3% after one year of follow-up. **Supplementary file 2, Figure S4** shows the incidence of reported positive SARS-CoV-2 tests (either PCR or antigen (self)test) during study follow-up (see www.rivm.nl/vasco/resultaten for the latest update of this graph).

Table 2. Characteristics of VASCO participants at baseline and after 1 year of follow-up.

	Baseline			Retention at 1 year follow-up (n = 40,045)	Attrition at 1 year follow up (n = 5,502)
	Total (n = 45,547)	18-59 years (n = 21,679)	60-85 years (n = 23,821)		
Sex (%)					
Male	16,881 (37.1)	6001 (27.7)	10,862 (45.6)	14,743 (36.8)	2138 (38.9)
Female	28,640 (62.9)	15,655 (72.2)	12,957 (54.4)	25,285 (63.1)	3355 (61.0)
Other	26 (0.1)	23 (0.1)	2 (0.0)	17 (0.0)	9 (0.2)
Age (years)					
18-59	21,679 (47.6)	21,679 (100.0)	0 (0.0)	18,220 (45.5)	3459 (62.9)
60-69	18,981 (41.7)	0 (0.0)	18,981 (79.7)	17,501 (43.7)	1480 (26.9)
70-85	4840 (10.6)	0 (0.0)	4840 (20.3)	4301 (10.7)	539 (9.8)
Missing	47 (0.1)	0 (0.0)	0 (0.0)	23 (0.1)	24 (0.4)
Medical risk condition[a] (%)					
Yes	13,440 (29.5)	4289 (19.8)	9135 (38.3)	11,918 (29.8)	1522 (27.7)
No	32,107 (70.5)	17,390 (80.2)	14,686 (61.7)	28,127 (70.2)	3980 (72.3)
Migrant status (%)					
Dutch	40,785 (89.5)	19,097 (88.1)	21,647 (90.9)	35,984 (89.9)	4801 (87.3)
Migrant	2482 (5.4)	1414 (6.5)	1064 (4.5)	2133 (5.3)	349 (6.3)
Child of migrant(s)	2280	1168 (5.4)	1110	1928 (4.8)	352 (6.4)

	(5.0)		(4.7)		
Educational level[b] (%)					
Low	6312 (13.9)	1479 (6.8)	4826 (20.3)	5554 (13.9)	758 (13.8)
Intermediate	13,088 (28.7)	6726 (31.0)	6348 (26.6)	11,400 (28.5)	1688 (30.7)
High	25,890 (56.8)	13,403 (61.8)	12,462 (52.3)	22,875 (57.1)	3015 (54.8)
Other	255 (0.6)	71 (0.3)	183 (0.8)	215 (0.5)	40 (0.7)
Missing	2 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)	1 (0.0)
Vaccination status[c,] * (%)					
Unvaccinated	2916 (6.4)	2541 (11.7)	371 (1.6)	871 (2.2)	208 (3.8)
Partly vaccinated	7294 (16.0)	4134 (19.1)	3150 (13.2)	124 (0.3)	204 (3.7)
Primary vaccination	27,352 (60.1)	11,254 (51.9)	16,068 (67.5)	1914 (4.8)	2106 (38.3)
One booster	7971 (17.5)	3747 (17.3)	4221 (17.7)	16,402 (41.0)	2366 (43.0)
Two boosters	13 (0.0)	3 (0.0)	10 (0.0)	15,242 (38.1)	483 (8.8)
Three boosters	1 (0.0)	-	1 (0.0)	5492 (13.7)	135 (2.5)
Vaccine product first vaccination* (%)					
Comirnaty (BioNTech/Pfizer)	17,035 (37.4)	7757 (35.8)	9254 (38.8)	16,060 (40.1)	2384 (43.3)
Spikevax (Moderna)	5905 (13.0)	5529 (25.5)	373 (1.6)	5193 (13.0)	909 (16.5)
Vaxzevria (AstraZeneca)	15,018 (33.0)	1227 (5.7)	13,776 (57.8)	13,775 (34.4)	1261 (22.9)
Jcovden (Janssen)	4608 (10.1)	4591 (21.2)	16 (0.1)	4092 (10.2)	724 (13.2)
Other	31 (0.1)	20 (0.1)	11 (0.0)	27 (0.1)	8 (0.1)

Unknown	34 (0.1)	14 (0.1)	20 (0.1)	27 (0.1)	8 (0.1)
Unvaccinated	2916 (6.4)	2541 (11.7)	371 (1.6)	871 (2.2)	208 (3.8)
SARS-CoV-2 infection[d,] * (%)					
Yes	7568 (16.6)	4523 (20.9)	3041 (12.8)	26,954 (67.3)	2470 (44.9)
No	37,979 (83.4)	17,156 (79.1)	20,780 (87.2)	13,091 (32.7)	3032 (55.1)
Recruitment method					
Personal invitation	24,661 (54.1)	9341 (43.1)	15,299 (64.2)	21,870 (54.6)	2791 (50.7)
Via social media	4621 (10.1)	4148 (19.1)	469 (2.0)	3939 (9.8)	682 (12.4)
Via family, a friend, colleague or acquaintance	2682 (5.9)	1690 (7.8)	990 (4.2)	2310 (5.8)	372 (6.8)
Other	321 (0.7)	237 (1.1)	84 (0.4)	264 (0.7)	57 (1.0)
Missing	13,262 (29.1)	6263 (28.9)	6979 (29.3)	11,662 (29.1)	1600 (29.1)
Test intention*					
Never	616 (1.4)	227 (1.0)	386 (1.6)	405 (1.0)	151 (2.7)
Rarely	598 (1.3)	290 (1.3)	308 (1.3)	1115 (2.8)	216 (3.9)
Sometimes	1138 (2.5)	609 (2.8)	529 (2.2)	2271 (5.7)	370 (6.7)
Regularly	672 (1.5)	464 (2.1)	206 (0.9)	1229 (3.1)	183 (3.3)
Often	6138 (13.5)	3811 (17.6)	2322 (9.7)	8098 (20.2)	1091 (19.8)
Always	35,806 (78.6)	16,055 (74.1)	19,715 (82.8)	26,693 (66.7)	3450 (62.7)

Missing	579 (1.3)	223 (1.0)	355 (1.5)	234 (0.6)	41 (0.7)

[a] Medical risk condition: one or more of following conditions: diabetes mellitus, lung disease or asthma, asplenia, cardiovascular disease, immune deficiency, cancer (currently untreated, currently treated, untreated), liver disease, neurological disease, renal disease, organ or bone marrow transplantation. Four most frequent conditions are presented here.

[b] Educational level was classified as low (no education or primary education), intermediate (secondary school or vocational training), or high (bachelor's degree, university).

[c] Unvaccinated (no vaccination received), primary vaccination series received (one dose of Jcovden [Janssen] 28 + days ago, or two doses of Vaxzevria [AstraZeneca], Comirnaty [BioNTech/Pfizer], or Spikevax [Moderna] 14 + days ago), primary vaccination series and one booster received (primary vaccination series + one additional dose 7 + days ago), primary vaccination series and two boosters received (primary vaccination series + two additional doses 7 + days ago), or primary vaccination series and three boosters received (primary vaccination series + three additional doses 7 + days ago)

[*]Vaccination status, vaccine product, infection status and test intention are time varying variables. The first three columns present the variable status at baseline, in the last two columns the status of the variable at time of dropout or 1 year of follow-up (whichever came first) is presented. Vaccination status was based on data from the questionnaires linked with data from CIMS (see **Supplementary file 5**).

[d] Infection status was defined using self-reported test-confirmed infections and serology data (see **Supplementary file 4**).

Findings to Date

Data collected from the cohort has contributed to multiple outputs, providing insights into effectiveness of COVID-19 vaccination and related aspects. Results contributed to vaccine policy of COVID-19 in the Netherlands, e.g. by providing input for the national health council and the COVID-19 outbreak management team. A list of publications with VASCO data can be found at www.rivm.nl/vasco/publicaties.The main findings thus far are described below.

Between July 2021 and June 2022, we found a VE of primary vaccination (all vaccine products combined) of 46% against Delta infection <6 weeks after vaccination and of 80% against Omicron infection <6 weeks after vaccination (20). VE waned over time to 71% against Delta and 25% against Omicron infection at 6 months after vaccination. VE was increased by booster vaccination (96% and 57%

against Delta and Omicron infection, respectively), although protection was rather short-lived. Even though this booster effect was also seen among medical risk groups, protection in these groups was consistently lower.

Bivalent mRNA vaccines targeting the Omicron BA.1 subvariant and the original strain of SARS-CoV-2 were introduced as booster in the Netherlands on 19 September 2022 (21). Among participants who previously received primary and one or two monovalent booster COVID-19 vaccinations we found a relative effectiveness of 31% in 18-59-year-olds and 14% in 60-85-year-olds in the first three months after introduction of the bivalent vaccine. Relative protection from a prior Omicron infection with or without bivalent vaccination was substantially higher (80-83%).

Furthermore, we showed that given an equal number of prior immunizing events, persons with hybrid immunity had a 71% to 85% lower risk (depending on number of prior immunizing events) of infection compared to persons with only vaccine-induced immunity (22). No relevant difference in effect by sequence of vaccination(s) and infection was observed. Additional immunizing events were found to increase protection against infection, but not above the level of the first weeks after the previous event. Furthermore, we showed that S-antibody concentration was associated with risk of infection in a dose-response manner.

In an analysis on VE within households, we established a VE against infectiousness of 70% for primary vaccination during the Delta period, and 45% and 64% for the primary series and first booster, respectively, during the Omicron period. However, we could not establish a VE against infection that was significantly different from zero in either period. In addition, we were not able to adjust for pervious infections in these analysis

In a sub-study with 520 vaccinated participants, we found that following breakthrough infections among those without prior infection, 82% of the participants developed N-antibodies within four weeks, which was accompanied by spike protein antibody boosting (17). In addition, relatively more antibodies to the infecting virus variant were detected, indicative of broadening of the antibody response against the spike protein of SARS-CoV-2.

We showed that antibody levels against the Spike protein shortly after vaccination were lower in participants with older age or medical risk conditions (23). In addition, our results showed that waning after the first booster was slower in participants >60 compared to younger participants. Differences in response between groups became smaller after first and second booster doses.

We described determinants of occurrence of local and systemic adverse events (AE) (24). We showed that after the second and third vaccine dose high pre-vaccination antibody levels were associated with systemic AE. Furthermore, after the third vaccination, occurrence of AE was associated with increased post-vaccination antibody levels.

Strengths and Limitations

This study has several strengths. Firstly, detailed sociodemographic, behavioural and clinical data is collected. Also, blood sampling for assessment of antibodies is done regularly to identify SARS-CoV-2 (re)infections and monitor vaccination responses. Detailed data on potential confounders and previous SARS-CoV-2 infections often lack in nationwide surveillance and observational studies. Furthermore, availability and quality of surveillance data is dependent on government decisions (i.e. closing of community testing centres, lifting of the obligation to report cases), whereas in VASCO, we instruct participants to continue to test when having COVID-19 like symptoms. Lastly, VASCO provides an infrastructure to conduct further studies and to anticipate on changing vaccination campaigns and testing policy, and new virus variants.

A limitation of VASCO is that we rely mostly on self-reported data. To reduce misclassification of the determinant (vaccination status) and outcome (SARS-CoV-2 infection) we ask the VASCO participants to use a notification button when they are vaccinated or infected. In addition, vaccination data is checked with data from the national vaccination register (13, 20). Furthermore, we use serology to detect unreported SARS-CoV-2 infections. Also, information on potential confounding variables was collected by self-report which might lead to misclassification. In addition, even though we collect information on many potential confounding factors, we might not be able to take into account all confounders and residual confounding might be an issue. Furthermore, although we oversampled people vaccinated with Spikevax, Vaxzevria or Janssen vaccine and with a medical risk condition, we did not succeed in including 5,000 participants in all strata mainly because of the unequal distribution of the vaccine types in different age and risk groups in the Netherlands. However, during the course of the pandemic, evaluating differences in VE between vaccine products became less of a priority.

Lastly, we observed some selective attrition which leads to a slight decrease of groups already less represented in the study including migrants, children of migrants, males and participants with lower education level. However, after one year of follow-up the impact of attrition on the distribution of participant characteristics was relatively small.

Abbreviations

AE – adverse events

BEBO – Beoordeling Ethiek Biomedisch Onderzoek

CIMS – COVID-19 vaccination Information and Monitoring System

GP – general practitioner

N – nucleoprotein

RIVM – National Institute of Public Health and the Environment

VASCO – VAccine Study COvid-19

VE – vaccine effectiveness

WHO – World Health Organization

Declarations

COLLABORATION

Anonymized data reported from this study can be obtained from the corresponding author upon request. The dataset may include individual data and a data dictionary will be provided. Data requests should include a proposal for the planned analyses. Data transfer will require a signed data sharing agreement.

ETHICS APPROVAL

The VASCO study is conducted in accordance with the principles of the Declaration of Helsinki and the study protocol was approved by the not-for-profit independent Medical Ethics Committee of the *Stichting Beoordeling Ethiek Biomedisch Onderzoek* (BEBO), Assen, the Netherlands (NL76815.056.21). New assessments will only be introduced into the study after approval by the Medical Ethics Committee. VASCO was registered in the online Dutch clinical trials register (trialsearch.who.int, registration number NL9279, 17/02/2021). After online registration for VASCO, participants received an informed consent by regular mail, and written informed consent was obtained from all participants prior to enrolment into the study. Participants can choose to consent to linkage of their data in national and medical databases (e.g., COVID-19 vaccination, SARS-CoV-2 infections, (COVID-19 related) death, and health status from hospitals and GPs) to their study data. For significant changes to the study (e.g. altered data collection) additional informed consent is asked. Written informed consent has been asked for additional fingerprick samples (18, 24, 30 months) and for sequencing of self-tests.

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The collection and processing of personal data from participants enrolled in the study is limited to those data that are necessary to fulfil the objectives of the study. The data are collected and processed with adequate precautions to ensure confidentiality and compliance with general data protection regulations.

A privacy impact analysis was done to measure and assess the protection of the process of personal data and to improve compliance of the privacy regulations. Appropriate procedures are implemented to protect personal data against unauthorized disclosure, access, loss or alteration.

AUTHORS' CONTRIBUTIONS

All authors have read and approved the final manuscript. AH, MNK, and CH drafted the manuscript. MNK, HdM, DG, JvdW, SH, SvdH and MJK designed the study. AH, MNK, HdM, DG, CH, RvB, GdH, JvdW, SvdH and MJK contributed to writing of the paper.

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PATIENT AND PUBLIC INVOLVEMENT

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

None declared.

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Figures

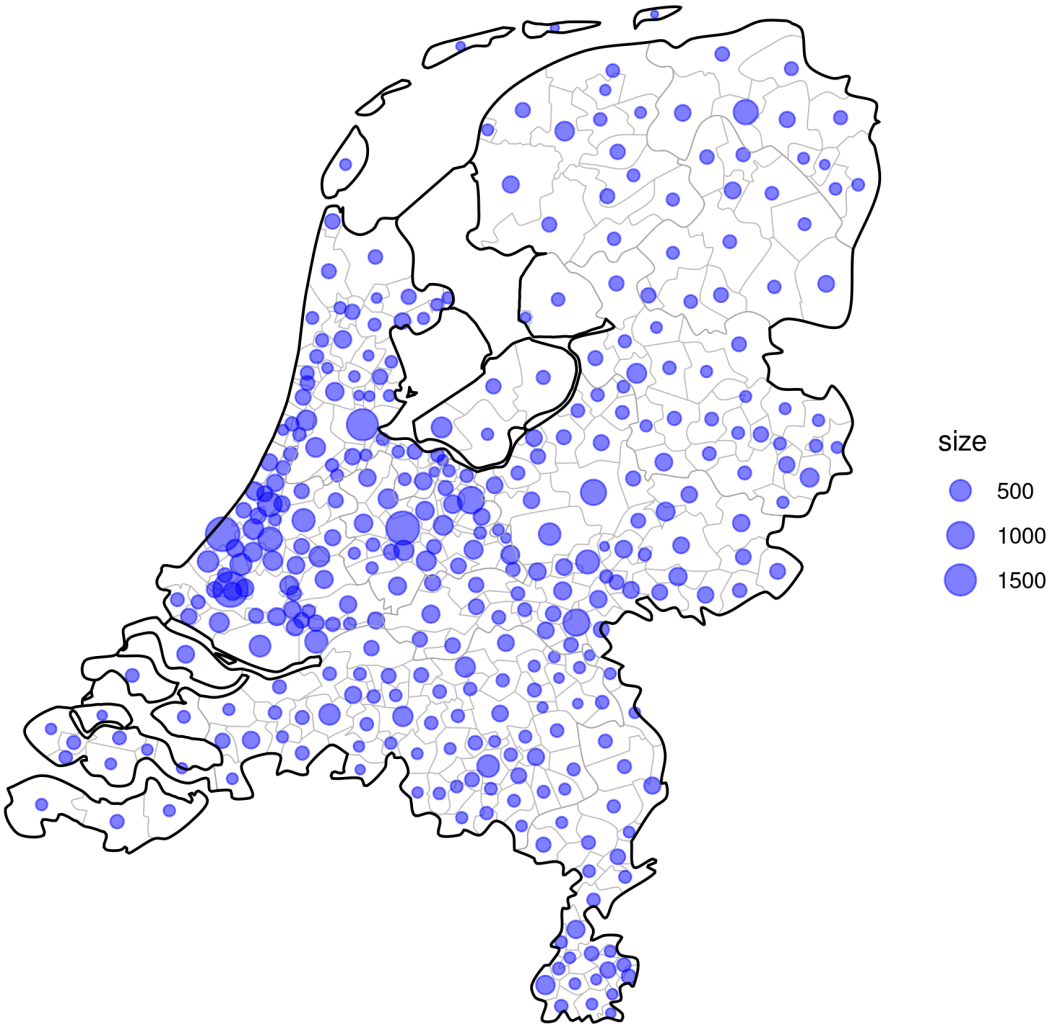

Figure 1

Distribution of participants over the municipalities in the Netherlands

Supplementary Files

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