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

Anne J Huiberts ,[1] Christina E Hoeve,[1] Marjolein N Kooijman,[1] Hester E de Melker,[1] Susan JM Hahné,[1] Diederick E Grobbee,[2] Rob van Binnendijk,[1] Gerco den Hartog,[1] Janneke HHM van de Wijgert ,[1,2] Susan van den Hof,[1] Mirjam J Knol[1]

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[1]Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
[2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands

Correspondence to
Dr Mirjam J Knol;
mirjam.knol@rivm.nl

ABSTRACT

Purpose VAccine Study COVID-19 (VASCO) is a cohort study with a 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 4289 (19.8%) of 21 679 individuals aged 18–59 years, and in 9135 (38.3%) of 23 821 individuals aged 60–85 years. After 1 year of follow-up, 5502 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 concentrations 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 behavioural responses to COVID-19 measures.

Findings to date VASCO data have 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 were 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 respond to changes in vaccination campaigns and testing policy, and new virus variants.

Trial registration number NL9279.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Detailed sociodemographic, behavioural and clinical data are available.
⇒ Serology data are collected regularly to identify SARS-CoV-2 (re)infections and monitor vaccination responses.
⇒ Continued SARS-CoV-2 testing by participants in the postpandemic era.
⇒ VAccine Study COVID-19 (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 WHO declared the 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 programme started on 6 January 2021. In 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), Jcovden (Ad26.COV2-S, Janssen-Cilag International NV). Later, Nuvaxovid (NVX-CoV2373; Novavax CZ) was also introduced. During the various vaccination campaigns that followed, different vaccines were recommended and administered to varying age groups.[6 7]

After the implementation of a vaccination programme, it is important to continuously

monitor the programme with regard to safety, effectiveness and epidemiological impact in real-world settings.[8] Preregistration vaccine trial participants are usually not representative of the target population and usually do not include sufficient numbers of individuals of special interest (eg, children, elderly and individuals with comorbidities).[9 10] Also, the duration of follow-up prior to vaccine registration is usually short. Furthermore, estimates of vaccine effectiveness (VE) against SARS-CoV-2 infection, disease and transmission over time—and against emerging virus variants—are needed, both overall and for population subgroups.[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 a variant of infection, and monitoring of adverse events (AEs) 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 prioritised 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, based on a 6-month infection rate of 0.03 among unvaccinated individuals, a vaccination coverage of 85% and adjustments for loss to follow-up and uncertainty in vaccine strata sizes, indicated the need for approximately 5000 participants per stratum to detect a VE of 70% (online supplemental 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.

A random sample from the national Dutch Personal Records Database, which includes all individuals with a home or postal address in the Netherlands, was stratified by age group (18–39, 40–59 and 60–85 years) and sent an invitation to participate in the study via regular mail. After sending the initial invitations, the number of unvaccinated persons and persons vaccinated with Spikevax, Vaxzevria and Jcovden was 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 Jcovden vaccine in the national COVID-19 vaccination Information and Monitoring System (CIMS) of the Dutch National Institute of Public Health and the Environment. Vaccinations are registered in CIMS if the vaccinated individual provides 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 prioritised for COVID-19 vaccination was done via general practitioners (GPs).

Potential participants could register themselves by entering the study website, answering some screening questions (age, not living in a healthcare facility) and submitting their contact details. Information regarding use of the study website, the study-specific mobile phone application and login code was sent by email. Between 3 May 2021 and 15 December 2021 (online supplemental file 2, figure S2), 60 390 persons subscribed to 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 the 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.

Data collection

Participants are followed for 5 years after enrolment. All study procedures are done remotely via a study website and mobile phone application. For the self-collection of fingerprick blood samples for SARS-CoV-2 serology, a kit was sent by regular mail including a detailed instruction (including a link to an instruction video on our website: https://www.rivm.nl/vasco/informatie-voor-deelnemers) and a stamped, addressed safety-envelope to return the sample. 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 3 monthly online questionnaires in years 2–5. They are asked to complete validated well-being questionnaires every 3 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 1 month and supplemented

Table 1 Questionnaire data collected during VASCO

Questionnaire	Timing	Topics
Baseline	Baseline	► Sociodemographic factors: age, sex, ethnicity, education, profession ► Health status: comorbidities, medication use, pregnancy, healthcare consumption, medication use, previous confirmed SARS-CoV-2 infections ► Vaccination status: COVID-19, influenza and/or pneumococcal vaccines ► Behavioural responses to COVID-19 measures (eg, 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	► COVID-19 vaccination ► SARS-CoV-2 testing ► Changes in health status ► Behavioural responses to COVID-19 measures (eg, visiting public places, face mask use, contacts, travelling and physical distancing)
Well-being	Baseline, 3-monthly	► 12-Item Short Form Survey ► Checklist Individual Strength[23–25]
COVID-19 vaccination	Whenever applicable	► Vaccination date, vaccine product
Positive SARS-CoV-2 test	Whenever applicable	► 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) ► Date of positive test ► Reason for testing ► Symptoms ► Disease course
Household members	1 month after a positive SARS-CoV-2 test	► Vaccination status of household members ► Positive tests of household members ► Age of household members ► Testing of household members
Adverse events	1 month after a COVID-19 vaccination	► Occurrence of injection site (eg, pain, redness and swelling at the injection site or axillary region) or systemic (eg, headache, myalgia, fatigue, nausea, diarrhoea and other symptoms of malaise) AE ► Occurrence of AE for which contact was sought with a healthcare 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	► Symptoms ► Disease course

AE, adverse event; VASCO, VAccine Study COVID-19.

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 1 month after completion of the primary vaccination series (only when at least 4 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 online supplemental 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. Online supplemental file 2, figure S2 shows examples of data collection schedules of individual participants in VASCO from the start to the 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 centres was scaled down.

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.[14] 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.

Patient and public involvement

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

Follow-up

After 1 year of follow-up, 5502 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 (online supplemental file 4) of 32 001 participants showed that attrition during the first year of follow-up was lower among Dutch participants compared with migrants and children of migrants, among participants with higher age, among females and among participants with intermediate education or high education. Higher test intention was associated with a lower attrition with an HR for always testing of 0.40 (95% CI 0.33 to 0.49) to an HR for rarely testing of 0.77 (95% CI 0.61 to 0.98) compared with never testing. Medical risk conditions, recruitment methods 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 years age group but lower in the 18–59 years age group (see online supplemental file 4, table S2). Reasons for dropout were largely unknown (for 92% of dropouts). Reported reasons for dropout included study duration and logistics (eg, issues with the study app) (4.7%), personal circumstances (2.8%) or death (0.6%).

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 with the general Dutch population, VASCO participants are more often women (ie, 62.9% vs 50.3%),[15] highly educated (56.8% vs 40.0%)[16] and of Dutch origin (89.5% vs 75.4%).[15] Among participants aged 18–59 years, 19.8% have a medical risk condition, while this is 38.3% of participants aged 60–85 years. In the general population, approximated proportions based on healthcare utilisation and medication prescription data are 19% for 18–66 years and 49% for those aged 67 years and older.[17] The most commonly reported comorbidities in participants with a medical risk condition are cardiovascular disease (n=7965), lung disease or asthma (n=3576) and diabetes (n=2210). Participants reside in all but 1 of the 352 municipalities of the Netherlands, with more participants residing in more densely populated areas (figure 1). After 1 year of follow-up, the COVID-19 vaccination coverage (online supplemental file 2, figure S3) for at least a primary series among VASCO participants was higher compared with 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 (online supplemental 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 1 year of follow-up. Online supplemental 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).

FINDINGS TO DATE

Data collected from the cohort have contributed to multiple outputs, providing insights into effectiveness of COVID-19 vaccination and related aspects. Results contributed to vaccine policy for COVID-19 in the Netherlands, for example, 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 80% against Delta infection <6 weeks after vaccination and 46% against Omicron infection <6 weeks after vaccination.[18] VE waned over time to 71% against Delta and 25% against Omicron infection at 6 months after vaccination.

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=5502)
	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* (%)					
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 (5.0)	1168 (5.4)	1110 (4.7)	1928 (4.8)	352 (6.4)
Educational level† (%)					
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§‡ (%)					
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¶‡ (%)					
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)

Continued

Table 2 Continued

	Baseline			Retention at 1-year follow-up (n=40 045)	Attrition at 1-year follow-up (n=5502)
	Total (n=45 547)	18–59 years (n=21 679)	60–85 years (n=23 821)		
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)

*Medical risk condition: one or more of the 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.
†Educational level was classified as low (no education or primary education), intermediate (secondary school or vocational training) or high (bachelor's degree, university).
‡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 online supplemental file 5).
§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)
¶Infection status was defined using self-reported test-confirmed infections and serology data (see online supplemental file 4).
VASCO, VAccine Study COVID-19.

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 boosters in the Netherlands on 19 September 2022.[19] 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 years and 14% in 60–85 years in the first 3 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 immunising events, persons with hybrid immunity had a 71%–85% lower risk (depending on a number of prior immunising events) of infection compared with persons with only vaccine-induced immunity.[20] No relevant difference in effect by sequence of vaccination(s) and infection was observed. Additional immunising 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 of 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

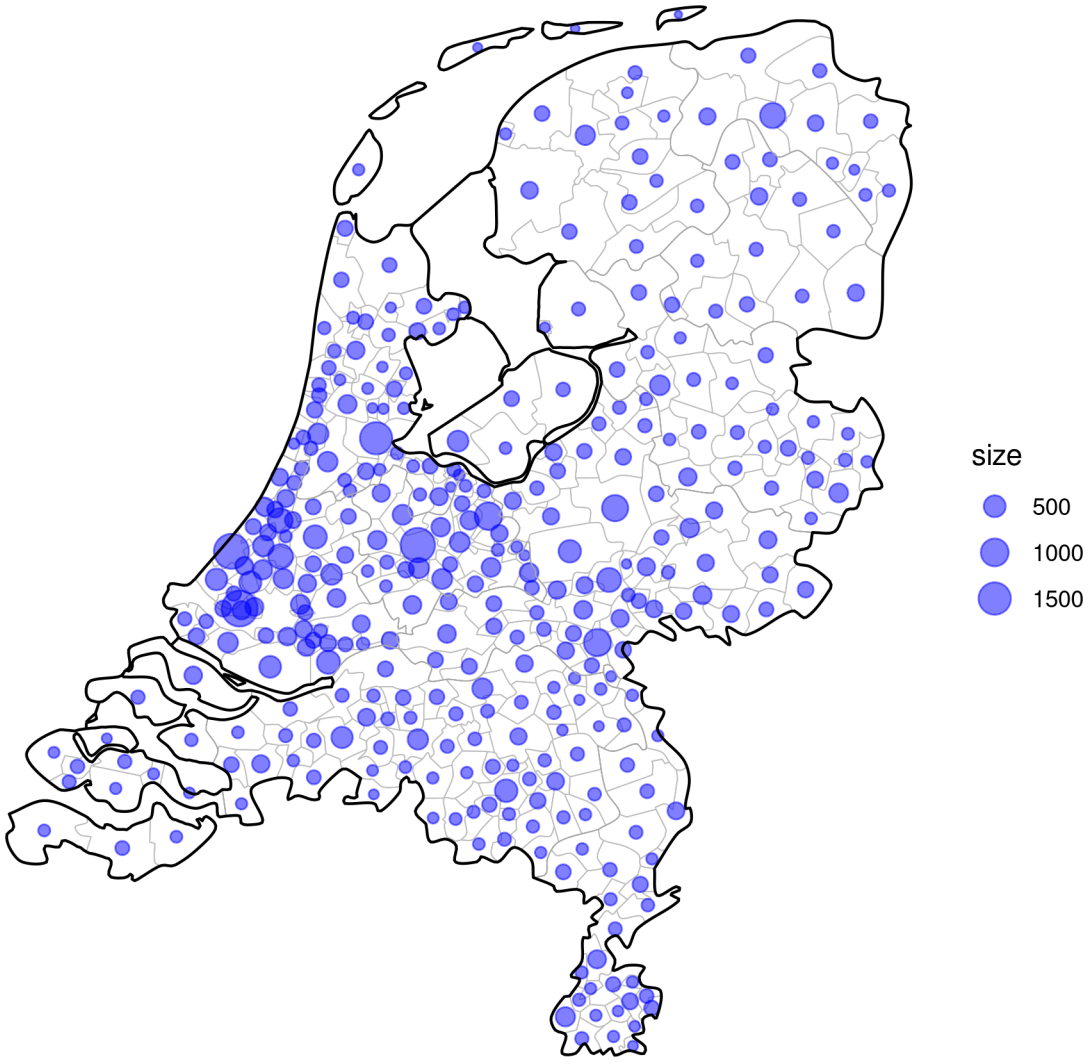

Figure 1 Distribution of participants over the municipalities in the Netherlands.

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 previous infections in these analyses.

In a substudy with 520 vaccinated participants, we found that following breakthrough infections among those without prior infection, 82% of the participants developed N-antibodies within 4 weeks, which was accompanied by spike protein antibody boosting.[14] In addition, relatively more antibodies to the infecting virus variant were detected, indicative of a 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.[21] In addition, our results showed that waning after the first booster was slower in participants >60 compared with younger participants. Differences in response between groups became smaller after first and second booster doses.

We described determinants of occurrence of local (eg, pain, redness and swelling at the injection site or axillary region) and systemic (eg, headache, myalgia, fatigue, nausea, diarrhoea and ther symptoms of malaise) AEs.[22] We demonstrated that high prevaccination antibody levels were associated with systemic AE following the second and third vaccine doses. Furthermore, after the third vaccination, the occurrence of AE was associated with increased postvaccination antibody levels.

STRENGTHS AND LIMITATIONS

This study has several strengths. First, detailed sociodemographic, behavioural and clinical data are 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, the availability and quality of surveillance data are dependent on government decisions (ie, 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 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 are checked with data from the national vaccination register.[13 18] 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 Jcovden vaccine and with a medical risk condition, we did not succeed in including 5000 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 led to a slight decrease in groups already less represented in the study including migrants, children of migrants, males and participants with lower education levels. However, after 1 year of follow-up, the impact of attrition on the distribution of participant characteristics was relatively small.

COLLABORATION

Anonymised data reported from this study can be obtained from the corresponding author on 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.

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Contributors All authors have read and approved the final manuscript. AJH, MNK and CEH drafted the manuscript. MNK, HEdM, DEG, JHHMvdW, SJMH, SvdH and MJK designed the study. AJH, MNK, HEdM, DEG, CEH, RvB, GdH, JHHMvdW, SvdH and MJK contributed to writing of the paper. MJK is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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 (eg, 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 (eg, 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. 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 with the privacy regulations. Appropriate procedures are implemented to protect personal data against unauthorised disclosure, access, loss or alteration.

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Data availability statement Data are available on reasonable request. Anonymised data reported from this study can be obtained from the corresponding author on 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.

ORCID iDs

Anne J Huiberts http://orcid.org/0000-0003-3206-9777
Janneke HHM van de Wijgert http://orcid.org/0000-0003-2728-4560

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