International Journal of Infectious Diseases 133 (2023) 36–42

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Vaccine effectiveness of primary and booster COVID-19 vaccinations against SARS-CoV-2 infection in the Netherlands from July 12, 2021 to June 6, 2022: A prospective cohort study

Anne J. Huiberts[1], Brechje de Gier[1], Christina E. Hoeve[1], Hester E. de Melker[1], Susan J.M. Hahné[1], Gerco den Hartog[1], Diederick E. Grobbee[2], Janneke H.H.M. van de Wijgert[1,2], Susan van den Hof[1], Mirjam J. Knol[1,*]

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

ARTICLE INFO

Article history:
Received 8 February 2023
Revised 13 April 2023
Accepted 18 April 2023

Keywords:
COVID-19
SARS-CoV-2
Vaccine effectiveness

ABSTRACT

Objectives: We estimated vaccine effectiveness (VE) of primary and booster vaccinations against SARS-CoV-2 infection overall and in four risk groups defined by age and medical risk condition during the Delta and Omicron BA.1/BA.2 periods.

Methods: VAccine Study COvid-19 is an ongoing prospective cohort study among Dutch adults. The primary end point was a self-reported positive SARS-CoV-2 test from July 12, 2021 to June 06, 2022. The analyses included only participants without a previous SARS-CoV-2 infection based on a positive test or serology. We used Cox proportional hazard models with vaccination status as the time-varying exposure and adjustment for age, sex, educational level, and medical risk condition.

Results: A total of 37,170 participants (mean age 57 years) were included. In the Delta period, VE <6 weeks after the primary vaccination was 80% (95% confidence interval 69-87) and decreased to 71% (65-77) after 6 months. VE increased to 96% (86-99) shortly after the first booster vaccination. In the Omicron period, these estimates were 46% (22-63), 25% (8-39), and 57% (52-62), respectively. For the Omicron period, an interaction term between vaccination status and risk group significantly improved the model (P <0.001), with generally lower VEs for those with a medical risk condition.

Conclusion: Our results show the benefit of booster vaccinations against infection, also in risk groups; although, the additional protection wanes quite rapidly.

Introduction

After implementation of a vaccination program, real-world vaccine effectiveness (VE) should be monitored to inform further vaccination policy [1]. The COVID-19 vaccination program in the Netherlands started on January 6, 2021. Different vaccines were recommended and administered in varying age groups [2,3]. The first booster campaign for adults was initiated on November 18, 2021, prioritizing health care workers and those aged ≥60 years. From March 4, 2022, a second booster vaccination was offered to adults aged ≥60 years [2,4].

Since the start of the vaccination program, various new SARS-CoV-2 variants of concern emerged, including the Delta (B.1.617.2) and Omicron (B.1.1.529) variants. The Delta variant was first detected in the Netherlands in April 2021 and replaced the Alpha variant as the dominant strain in July 2021 [5]. The Omicron variant was first detected in late November 2021 and caused 90% of the infections 6 weeks later.

As in other countries, the nationwide COVID-19 surveillance data in the Netherlands, including testing and contact tracing data, have been used to monitor and evaluate VE against SARS-CoV-2 infections [6–8]. The advantages of using national surveillance data are the large sample size and data availability in real time. The disadvantages are dependence on testing infrastructure and testing behavior. For example, the Dutch government scaled down free-of-charge testing at community test centers from April 11, 2022 on-

* Corresponding author.
E-mail address: mirjam.knol@rivm.nl (M.J. Knol).

https://doi.org/10.1016/j.ijid.2023.04.401

wards; the general public was encouraged to self-test when having symptoms from that date onwards.

The VAccine Study COvid-19 (VASCO) is a large population-based prospective cohort study collecting extensive data, including demographics, vaccination data, and positive (self-)tests that enabled us to study VE, irrespective of available registration data [9]. Here, we report on the VE of primary, as well as first and second booster vaccination, against self-reported SARS-CoV-2 infection by time since vaccination and in four subpopulations defined by age and medical risk condition, during July 12, 2021 to June 6, 2022, the period in which the Delta and Omicron BA.1 and BA.2 variants were sequentially dominant.

Methods

Study design and study population

VASCO is an ongoing population-based prospective cohort study with a 5-year follow-up [9]. The study was initiated during the roll-out of the COVID-19 vaccination program in the Netherlands. Between May 3, 2021 and December 15, 2021, 45,552 community-dwelling adults aged 18-85 years were included. Participants had to be able to understand Dutch because all study materials were written in Dutch. Participants were asked to complete monthly online questionnaires in the first year and 3-monthly online questionnaires in years 2-5, including questions on sociodemographic factors, health status, COVID-19 vaccination, SARS-CoV-2-related symptoms, testing results, and test intention. At inclusion, 6 and 12 months after inclusion, and 1 month after primary vaccination, participants were asked to take a self-collected finger prick blood sample at home. Samples were tested for SARS-CoV-2 antibodies by Elecsys Anti-SARS-CoV-2 immunoassay (Roche Diagnostics, Vienna, Austria) using the NIBSC 20/136 WHO standard for quantification. In the current analysis, serology data were used to identify participants who had had a SARS-CoV-2 infection before the study period by determining the presence of immunoglobulin antibodies against the SARS-CoV-2 nucleocapsid protein. Written informed consent was obtained from all participants before enrollment into the study. 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, Assen, the Netherlands.

Vaccination status

Self-reported vaccination data were linked to vaccination data registered in the Dutch national COVID-19 vaccination information and monitoring system (CIMS) [3]. Vaccination data from the CIMS registry were considered the primary source, except when the participant did not provide written informed consent for vaccination registration in CIMS or for linking study and CIMS data. If CIMS and/or self-reported data were incomplete, data from both sources were combined (see Additional file 1 and Table S1 for a detailed description). Vaccination status was categorized as 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), or primary vaccination series and two boosters received (primary vaccination series + two additional doses 7+ days ago) [2,3]. For individuals with a severe immune deficiency, the primary vaccination consisted of three doses. Therefore, a third dose administered before the start of the general public booster campaign (November 18, 2021) was considered an additional primary series vaccination and not a booster vaccination. A second booster vaccination in the spring of 2022 was only available for individuals aged ≥60 years and some highly vulnerable groups. The 7, 14, or 28 person-days between vaccine administration and obtained vaccination status were excluded because we assumed that immunity was not yet fully established. Participants were excluded if they reported to have received more doses than possible according to the Dutch vaccination strategy [2].

SARS-CoV-2 infections

The primary end point was a self-reported positive SARS-CoV-2 test. Participants were asked to notify all positive SARS-CoV-2 tests through the study website or app (either a test by a community testing center free-of-charge, a test at a commercial test center, or a self-administered antigen test). Community testing was scaled down from April 11, 2022 onward. To facilitate testing after that date in case of symptoms associated with COVID-19 and/or contact with a person infected with SARS-CoV-2, the study team provided self-tests to participants from May 2022 onward. Reported infections were considered Delta infections if the positive test date was between July 12, 2021 and December 19, 2021, the period in which >90% of the cases was caused by the Delta variant [10]. Reported positive tests from January 10, 2022 until June 6, 2022 were attributed to the Omicron BA.1 or BA.2 variant. Participants who had reported a positive test or tested positive for antibodies against the SARS-CoV-2 nucleocapsid protein before start of follow-up in the current analysis were excluded from the analysis in order to estimate effects of vaccination only.

Covariates

Sociodemographic data were collected at baseline and during follow-up. Educational level was classified as low (no education or primary education), intermediate (secondary school or vocational training), or high (bachelor's degree, university). A medical risk condition was present when a participant reported to have one or more of the following conditions: diabetes mellitus, lung disease or asthma, asplenia, cardiovascular disease, immune deficiency, cancer (currently untreated but treated in the past, currently treated, untreated), liver disease, neurological disease, renal disease, organ or bone marrow transplantation. Four risk groups were defined by age (18-59 and 60-85 years) and presence of a medical risk condition (present or absent).

Statistical analyses

Cox proportional hazard models were used to estimate the VE of the primary series and the first and second booster vaccination against SARS-CoV-2 infection in the Delta and Omicron BA.1/BA.2 period. Vaccination status was included as a time-varying exposure. Participants entered the study at the start of the study period (July 12, 2021) or the date of completion of the baseline questionnaire, if they became a participant later than July 12, 2021. Participants were followed up until the date of the first reported positive test. If no positive test was reported, participants were followed up until the most recent questionnaire completion date plus the median time between follow-up questionnaires (to include only person-time in which participants were assumed to be active) or the end date of the study period (June 06, 2022), whichever came first. The median time between follow-up questionnaires was determined per person and separately for year 1 and years 2-5 because frequency of follow-up questionnaires differed. Calendar time was used as the underlying timescale for the Cox regression. This effectively means that on each date, participants with different vaccination statuses were compared, thereby

Table 1
Baseline characteristics of participants included in analysis.

	Total (n = 36,816)	18-59 years (n = 16,575)	60-85 years (n = 20,241)
Sex (%)			
Male	13,874 (37.7)	4633 (28.0)	9241 (45.7)
Female	22,922 (62.3)	11,923 (71.9)	10,999 (54.3)
Other	20 (0.1)	19 (0.1)	1 (0.0)
Median age (years; interquartile range)	61 (15)	48 (17)	65 (7)
Medical risk condition[a] at inclusion, yes (%)	11,078 (30.1)	3307 (20.0)	7771 (38.4)
Cardiovascular disease	6612 (18.0)	1322 (8.0)	5290 (26.1)
Lung disease or asthma	2852 (7.7)	1289 (7.8)	1563 (7.7)
Diabetes mellitus	1820 (4.9)	393 (2.4)	1427 (7.1)
Immune deficiency	697 (1.9)	336 (2.0)	361 (1.8)
Educational level[b] (%)			
Low	5151 (14.0)	1105 (6.7)	4046 (20.0)
Intermediate	10,328 (28.1)	4976 (30.0)	5352 (26.4)
High	21,119 (57.4)	10,441 (63.0)	10,678 (52.8)
Other	218 (0.6)	53 (0.3)	165 (0.8)

[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).

adjusting for factors changing over time during the pandemic, *i.e.*, infection pressure and the number of vaccinated persons in the population. Potential violation of assumptions regarding proportional hazards was checked using graphical diagnostics based on the scaled Schoenfeld residuals.

Models were stratified by Delta and Omicron periods and by time since the start of the vaccination status in 6-week intervals. The analyses were first adjusted for sex, educational level, and age group, and then additionally for the presence of a medical risk condition. Age group and the presence of a medical risk condition were included as time-varying confounders. Risk group membership based on age (18-59 and 60-85 years) and medical risk condition (present or absent) was examined as a potential effect modifier by extending the model with an interaction term and by stratified analysis. In the sensitivity analyses, analyses were repeated in two specific subpopulations. First, in participants who reported to (almost) always test for SARS-CoV-2 infection in case of SARS-CoV-2 related symptoms. Second, in participants who had received only Comirnaty vaccine doses versus unvaccinated participants. We also present the VE estimates stratified by sex and the VE estimates of the primary vaccination series stratified by vaccine product (Comirnaty, Spikevax, Vaxzevria, and Jcovden) and the VE estimates of first booster vaccination stratified by vaccine product of the booster (Comirnaty or Spikevax) and primary vaccination series (mRNA vaccine or Vaxzevria).

VE was calculated as 100% × (1 − hazard ratio). All statistical analyses were performed in statistical package R version 4.1.3, using packages Epi and survival.

Results

Study population

Of the 44,633 participants participating (partly) during the study period without missing covariates, 6826 participants (15.3%) reported to have had a positive SARS-CoV-2 test before start of follow-up in the current analysis. In addition, 991 (2.2%) tested positive for antibodies against the SARS-CoV-2 nucleocapsid protein before the start of follow-up. Consequently, 36,816 participants were included in the analyses (Table 1). The median age of the participants at inclusion was 61 years. More women (62%) than men were included, and 57% of the participants was highly educated. At the start of the study period, 12,152 participants were included in the study, of which 11,908 (98.0%) had completed their primary vaccination series, and 244 (2.0%) were unvaccinated (Additional file 1, Figure S1). At the start of the Omicron period, the cohort consisted of 27,646 active participants. Of those, 3802 (13.8%) participants had only completed their primary vaccination series, 23,352 (84.5%) participants had additionally received a first booster vaccination, and 492 (1.8%) participants were unvaccinated. Of all participants that contributed vaccinated person-weeks during the study period (n = 36,109), the first vaccine dose was most often Comirnaty (41.5%). Other first vaccination products were Vaxzevria (33.7%), Spikevax (13.0%), Jcovden (9.9%), other (0.01%), or unknown (0.1%).

Participants had a median follow-up time of 27.7 person-weeks. This was relatively short because participants were included over a period of 7 months and were censored after a reported positive SARS-CoV-2 test. During a total of 1,032,976 person-weeks of follow-up, 13,756 first SARS-CoV-2 infections were reported, corresponding with an infection rate of 13.3 infections per 1000 person-weeks. Reported positive tests were often a polymerase chain reaction test (72.7%) or antigen test (can be self-administered) (26.1%), with the share of antigen tests increasing sharply during the Omicron period (Additional file 1, Figure S2). The largest proportion of reported infections (12,129, 88.2%) occurred during the Omicron BA.1/BA.2 period (Figure 1). Infection rates were higher during person-weeks for unvaccinated than person-weeks for vaccinated individuals (Figure 1; Additional file 1, Table S2).

Vaccine effectiveness

The fully adjusted VE in the Delta period was estimated to be 80% (95% confidence interval [CI] 69.3-87.0) <6 weeks after completing the primary series, counting from the start of the vaccination status not vaccine administration (Figure 2). This decreased to 71% (95% CI 64.7-76.8) 18-23 weeks after the completion of the primary vaccination series. VE increased again to 96% (95% CI 86.1-98.6) <6 weeks after the booster vaccination. The VE estimates for the Omicron period were substantially lower than those in the Delta period. VE <6 weeks after completing the primary vaccination series was estimated to be 46% (95% CI 21.7-62.7) and decreased to 25% (95% CI 7.7-39.1) 18-23 weeks after completion of the primary vaccination series. VE increased to 57% (95% CI 51.9-62.3) <6 weeks after booster vaccination and decreased to 31% (95% CI 16.6-43.5) at 18-23 weeks. For the participants aged ≥60 years, the VE against Omicron infection within 6 weeks after the second booster vaccination was 50% (95% CI 34.0-62.1) (Additional

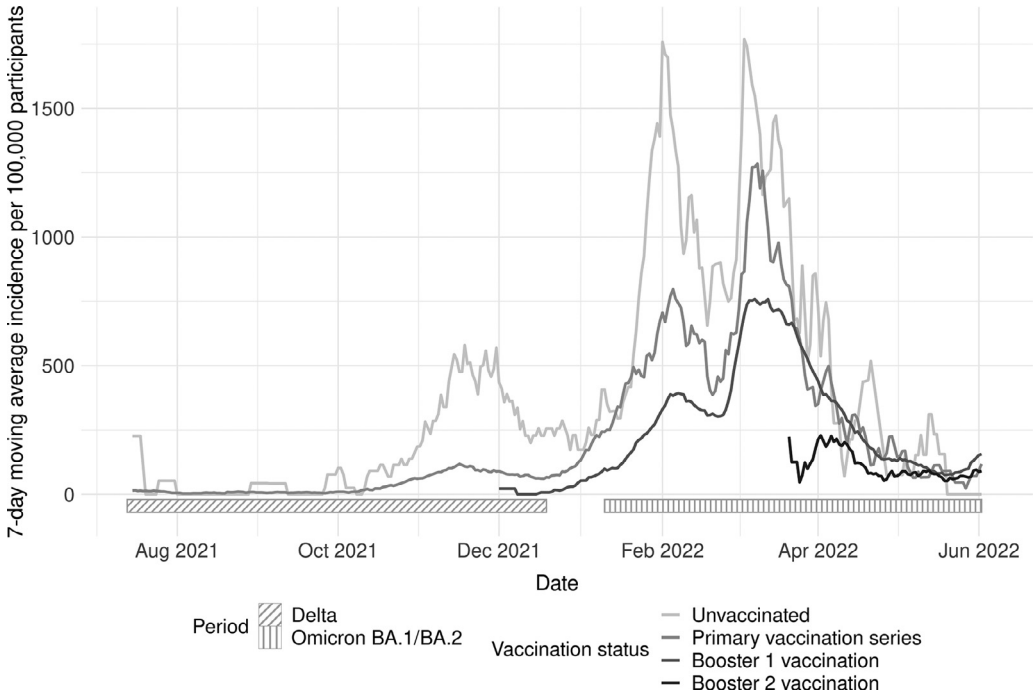

Figure 1. The 7-days moving average of number of infections reported per 100,000 VAccine Study COvid-19 (VASCO) participants by vaccination status from July 12, 2021 to June 06, 2022

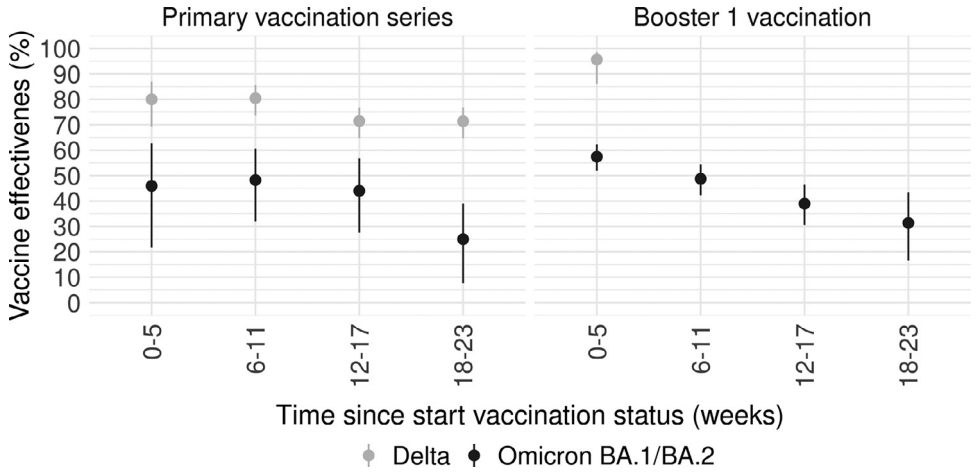

Figure 2. Vaccine effectiveness[a] for primary vaccination series and first booster vaccination in Delta and Omicron BA.1/BA.2 period from July 12, 2021 to June 06, 2022
[a]Adjusted for age group, sex, educational level, medical condition.

file 1, Figure S3 and Table S3). The Delta VE estimates of the models with and without medical risk condition as confounder were comparable (Additional file 1, Table S2). VE estimates for Omicron were slightly lower when additionally adjusting for the presence of a medical risk condition.

VE estimates showed a similar pattern in the sensitivity analysis restricted to participants with a high intention to test in case of symptoms (n = 26,520, median age = 61), except that the VE estimates for the Omicron infection were higher in this specific population (Figure 3). The higher estimates in this sensitivity analysis were in line with a higher intention to test in vaccinated participants (Additional file 1, Figure S4).

In the sensitivity analysis restricted to participants who only received Comirnaty vaccine doses (as primary series and as a booster[s] if a booster[s] was received) (n = 14,652 (39.8% of full analysis population), median age = 60), the VE estimates for the Delta period were comparable to the VE estimates of the complete study population (Additional file 1, Table S4). For the Omicron period, the VE estimates for the booster vaccination were slightly but consistently lower in the Comirnaty subpopulation than the total study population. VE estimates stratified by vaccine product of the primary series and first booster vaccination are given in Additional file 1, Tables S5 and S6. Generally, the estimates were higher for Spikevax as the primary series and lower for Vaxzevria and Jcovden than Comirnaty. For the booster vaccination, the estimates for Spikevax as booster were generally higher than for Comirnaty as booster, irrespective of the vaccine product of the primary series.

For the Delta period, the models with and without an interaction term between vaccination status and risk group did not differ significantly. For the Omicron period, the interaction term did significantly improve the model ($P < 0.001$). The interaction term was significant between at least two risk groups for all periods after booster vaccination (Additional file 1, Table S7). When stratifying the model according to risk group, the VE of booster vaccination in

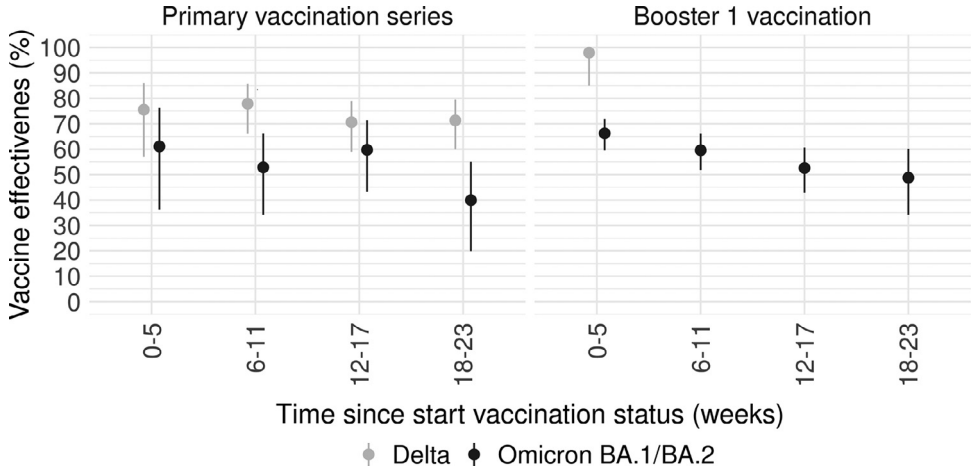

Figure 3. Vaccine effectiveness[a] for primary vaccination series and first booster vaccination in Delta and Omicron BA.1/BA.2 period in participants with high intention to test if experiencing symptoms from July 12, 2021 to June 06, 2022.
[a]Adjusted for age group, sex, educational level, medical condition.

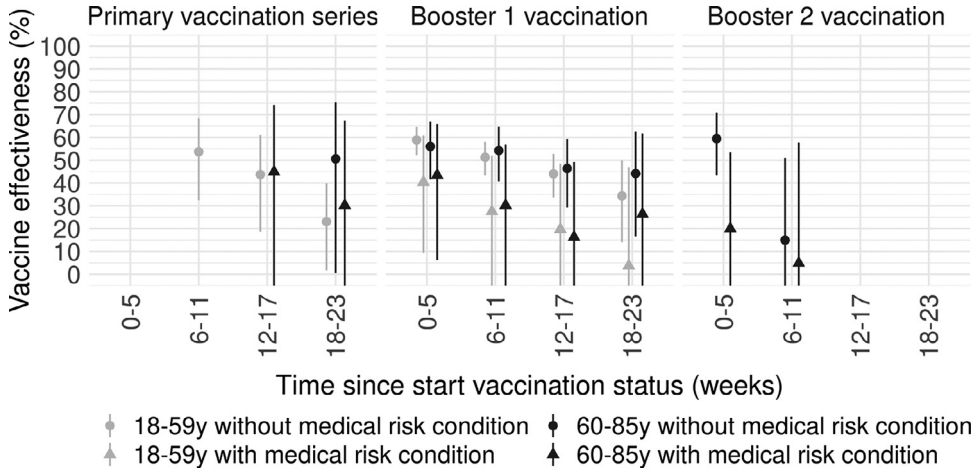

Figure 4. Vaccine effectiveness[a] for primary vaccination series, booster and second booster vaccination per risk group in the Omicron BA.1/BA.2 period from January 10, 2022 to June 06, 2022.
[a]Vaccine effectiveness was not reported when number of person-weeks <500; Adjusted for age group, sex, educational level.

the Omicron period was lower among participants with a medical condition than those without (Figure 4). The number of infections and person-weeks in unvaccinated persons with medical risk condition were relatively small, resulting in large CIs around the VE. The VE estimates for males and females were comparable for both the Delta and Omicron period (Additional file 1, Table S8).

Discussion

We evaluated the effectiveness of COVID-19 vaccines against Delta and Omicron BA.1/BA.2 SARS-CoV-2 infection in a real-world setting overall and in four risk groups based on age and presence of medical risk condition. Compared with unvaccinated individuals, having completed the primary vaccination series was associated with protection against Delta and Omicron BA.1/BA.2 SARS-CoV-2 infection. However, protection against the Omicron infection was markedly lower than protection against Delta infection. VE decreased over time after completing the primary vaccination series but increased again after receiving a first booster vaccination, also in risk groups. In those aged ≥60 years, the VE increased again after receiving a second booster. The VE of booster vaccinations also decreased over time since vaccination. Our data showed that unvaccinated participants had a lower intention to test if having symptoms than vaccinated participants. Indeed, when restricting our analysis to participants with a high intention to test, the VE against Omicron infection was higher. Despite the large CIs, the VE against Omicron BA.1/BA.2 infection appeared lower among participants with a medical risk condition than participants without, which was visible both in younger and older individuals. Our estimates concern effects of vaccination only because previous infections were excluded.

Our study results are in line with national [6] and international surveillance data [11–15], showing a higher VE against Delta infection than Omicron infection, resulting from considerable immune escape by the Omicron variant [16,17]. The reported estimates for VE shortly after completion of a primary series ranging from 78% to 91% against Delta infection and 40% to 66% against Omicron infection are consistent with our findings of 80% to 46%, respectively. The VE estimates of the booster vaccination against Delta (96%) and Omicron infection (57%) were consistent with those found using surveillance data (86-99% and 56-72%, respectively) [6,11–15]. Similar to our findings, other studies have shown waning of the effectiveness of both primary and booster vaccination [11–13]. One preprint reported a VE of second booster vaccination against Omi-

cron BA.2 infection in adults. The VE decreased from 64% (95% CI 50.7-74.2) to 51% (95% CI 35.5-63.0) 14-30 to 31-90 days after the fourth dose [18]. Our estimates were slightly lower (50% after 0-5 weeks and 16% after 6-11 weeks) but were based on data of adults aged ≥60 years only.

Only two other prospective cohort studies have reported VEs against the Delta infection [19,20]. In both studies, nose and/or throat swabs for polymerase chain reaction testing were regularly collected, irrespective of having symptoms, allowing the detection of symptomatic and asymptomatic infections. The VE of Comirnaty primary vaccination series in the Delta period reported in the ONS CIS study decreased from 85% at 14 days after the second dose to 75% at 90 days [20]. The results of our sensitivity analysis in participants who had only received Comirnaty vaccine doses were consistent with the ONS CIS Comirnaty estimates (81% at 0-5 weeks and 79% at 6-11 weeks after the primary series). The VE estimate in the HEROES-RECOVER study was lower (66%, 95% CI 26-84), but the time since vaccination was not taken into account and the study population consisted of health care workers only with likely high exposure [19]. The ONS CIS study further showed that the VE of Vaxzevria primary vaccination series was considerably lower than for Comirnaty (68% at 14 days and 61% at 90 days), which was consistent with our results. Our results showed that the VE of Comirnaty booster vaccination was lower than the VE of Spikevax booster vaccination. This is consistent with literature showing higher antibody levels after a Spikevax booster [21].

There are limited data on the VE against infection in medical risk populations. One test-negative case-control study found a significant interaction between immunocompromised status and vaccination status in both the Delta and Omicron periods. The stratified analysis showed a lower three-dose VE against infection in immunocompromised individuals (Delta: 70.6%, 95% CI 31.0-87.5; Omicron: 29.4%, 95% CI 0.3-50.0) compared with immunocompetent individuals (Delta: 93.7%, 95% CI 92.2-94.9; Omicron: 70.5%, 95% CI 68.6-72.4) [12]. The differences between the groups were larger than the differences we observed; yet, our definition of medical risk was broader than immunocompromised individuals only. An Israelian historic cohort study showed a lower VE of two doses against infection in both individuals with diabetes and cardiovascular disease (82%, 95% CI 62-92) and immunocompromised individuals (71%, 95% CI 37-87) than overall (92%, 95% CI 83-96) [22]. Taking into account the increased risk for severe COVID-19 outcomes [23], our results support the Dutch vaccination strategy to recommend booster vaccination for high-risk groups.

This study has several strengths. In this cohort study, we were able to adjust for (time-varying) confounders using extensive data from monthly questionnaires. Also, serological data enabled us to exclude participants with previous unreported SARS-CoV-2 infections. A recent study by Kahn *et al.* emphasized the added value of serological testing to exclude participants with previous infection [24]. Also, we were able to include self-administered antigen tests as an outcome so we were not dependent on the testing infrastructure, and we facilitated the use of self-tests by providing those to the participants. Furthermore, the questionnaire on test behavior allowed an analysis restricted to participants with a consistently high intention to test in case of symptoms.

Some limitations need to be discussed. Although the Cox proportional hazards models were adjusted for potential confounders, the differences in (time-varying) factors between vaccinated and unvaccinated participants, including test frequency and infection exposure, can still confound the results. The vaccinated individuals in our cohort had a higher intention to test when the symptoms occurred than unvaccinated individuals, possibly because they are more health-conscious. Still, vaccination may have reduced testing if breakthrough infections are more often mild or asymptomatic. In other contexts, vaccinated individuals may test less frequently, if public health authorities request more frequent testing of unvaccinated individuals (corona check app). These behavioral factors might have resulted in either an underestimation or overestimation of the VE. Furthermore, vaccinated individuals may become more heavily exposed to the virus, if they feel safer to attend (high-risk) exposure activities [25]. Even though it is suggested that there is little change in behavior early after vaccination [26] and a recent study showed that the differences in chance of SARS-CoV-2 exposure due to behavior did not relevantly confound the VE estimates in a test-negative setting [27], this phenomenon might decrease the benefit of vaccination [28]. Furthermore, the ease and availability of self-administered antigen tests is likely to have encouraged testing among those with no or mild symptoms, possibly increasing the proportion of asymptomatic and mild infections during the Omicron period compared with the Delta period and therefore partly explaining the differences between the VE during Delta and Omicron period. A sensitivity analysis restricting to symptomatic infections only, however, showed a minimal increase in the VE estimates in both the Delta and Omicron period. In this study, no data were available on hospitalization, against which the VE also remained high also during the Omicron period, according to literature [12,14].

Overall, our results show that VE was lower against Omicron infection than Delta infection, and both the first and second booster vaccination increased waned effectiveness again; although the additional protection was rather short-lived. Importantly, this booster effect was also seen among risk groups but the protection of vaccination against Omicron infection was consistently lower among risk groups. Thus, our data show the benefit of booster vaccination in preventing SARS-CoV-2 infections, also in risk groups.

Funding

This work was supported by the Dutch ministry of Health.

Ethical 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, Assen, the Netherlands (NL76815.056.21).

Author contributions

All authors have read and approved the final manuscript. HdM, DG, JvdW, SH, SvdH, and MK designed the study. AH, BdG, and CH cleaned and analyzed the data. AH drafted the manuscript. BdG, CH, HdM, SH, GdH, JvdW, SvdH, and MK critically reviewed the manuscript.

Declarations of competing interest

The authors have no competing interests to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.04.401.

References

[1] Hahné S, Bollaerts K, Farrington P. *Vaccination programmes: epidemiology, monitoring, evaluation*. 1st ed. London: Routledge; 2021.
[2] Pluijmaekers A, de Melker H. *The National Immunisation Programme in the Netherlands. Surveillance and developments in 2021–2022*. The Hague: Rijksinstituut voor Volksgezondheid en milieu RIVM; 2022.

[3] Valk A, van Meijeren D, Smorenburg N, Neppelenbroek N, van Iersel S, de Bruijn S, et al. *Vaccinatiegraad COVID-19 vaccinatie Nederland, 2021*. The Hague: Rijksinstituut voor Volksgezondheid en milieu RIVM; 2022.
[4] Rijksinstituut voor volksgezondheid en milieu *Archief wekelijkse update vaccinatiecijfers 2022*; 2022 *https://www.rivm.nl/covid-19-vaccinatie/archief-wekelijkse-update-vaccinatiecijfers-2022* [accessed 24 June 2022].
[5] RIVM COVID-19 epidemiologie en surveillance team *Effectiviteit van COVID-19-vaccinatie tegen SARS-CoV-2 infectie in de Delta periode*. The Hague: Rijksinstituut voor Volksgezondheid en milieu RIVM; 2021.
[6] Andeweg SP, de Gier B, Eggink D, van den Ende C, van Maarseveen N, Ali L, et al. Protection of COVID-19 vaccination and previous infection against Omicron BA.1, BA.2 and Delta SARS-CoV-2 infections. *Nat Commun* 2022;**13**:4738. doi:10.1038/s41467-022-31838-8.
[7] de Gier B, Andeweg S, Joosten R, Ter Schegget R, Smorenburg N, van de Kassteele J, et al. Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. *Euro Surveill* 2021;**26**:2100640. doi:10.2807/1560-7917.ES.2021.26.31.2100640.
[8] de Gier B, Andeweg S, Backer JA, Hahné SJ, van den Hof S, de Melker HE, et al. Vaccine effectiveness against SARS-CoV-2 transmission to household contacts during dominance of Delta variant (B.1.617.2), the Netherlands, August to September 2021. *Eurosurveill* 2021;**26**:2100977. doi:10.2807/1560-7917.ES.2021.26.44.2100977.
[9] Huiberts A, Kooijman M, Melker H, Hahne S, Grobbee D, Hoeve C, et al. Design and baseline description of an observational population-based cohort study on COVID-19 vaccine effectiveness in the Netherlands - the VAccine Study COvid-19 (VASCO). Research Square. 19 May 2022. https://www.researchsquare.com/article/rs-1645696/v1 [accessed 23 January 2023].
[10] Rijksinstituut voor volksgezondheid en milieu *Varianten van het coronavirus SARS-CoV-2*; 2022 *https://www.rivm.nl/coronavirus-covid-19/virus/varianten* [accessed 29 July 2022].
[11] Suarez Castillo M, Khaoua H, Courtejoie N. Vaccine-induced and naturally-acquired protection against Omicron and Delta symptomatic infection and severe COVID-19 outcomes, France, December 2021 to January 2022. *Euro Surveill* 2022;**27**:2200250. doi:10.2807/1560-7917.ES.2022.27.16.2200250.
[12] Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. *Nat Med* 2022;**28**:1063–71. doi:10.1038/s41591-022-01753-y.
[13] Andrews N, Stowe J, Kirsebom F, Toffa S, Rickeard T, Gallagher E, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med* 2022;**386**:1532–46. doi:10.1056/NEJMoa2119451.
[14] Gram MA, Emborg HD, Schelde AB, Friis NU, Nielsen KF, Moustsen-Helms IR, et al. Vaccine effectiveness against SARS-CoV-2 infection or COVID-19 hospitalization with the Alpha, Delta, or Omicron SARS-CoV-2 variant: A nationwide Danish cohort study. *PLOS Med* 2022;**19**:e1003992. doi:10.1371/journal.pmed.1003992.
[15] Young-Xu Y, Zwain GM, Izurieta HS, Korves C, Powell EI, Smith J, et al. Effectiveness of mRNA COVID-19 vaccines against Omicron and Delta variants in a matched test-negative case-control study among US veterans. *BMJ Open* 2022;**12**:e063935. doi:10.1136/bmjopen-2022-063935.
[16] Yu J, Collier AR, Rowe M, Mardas F, Ventura JD, Wan H, et al. Neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 Variants. *N Engl J Med* 2022;**386**:1579–80. doi:10.1056/NEJMc2201849.
[17] Netzl A, Tureli S, LeGresley E, Mühlemann B, Wilks SH, Smith DJ. Analysis of SARS-CoV-2 omicron neutralization data up to 2021-12-22. bioRxiv. 03 January 2022. https://www.biorxiv.org/content/10.1101/2021.12.31.474032v1 [accessed 23 January 2023].
[18] Tseng HF, Ackerson BK, Bruxvoort KJ, Sy LS, Tubert JE, Lee GS, et al. Effectiveness of mRNA-1273 vaccination against SARS-CoV-2 omicron subvariants BA.1, BA.2, BA.2.12.1, BA.4, and BA.5. *Nat Commun* 2023;**14**:189. doi:10.1038/s41467-023-35815-7.
[19] Fowlkes A, Gaglani M, Groover K, Thiese MS, Tyner H, Ellingson KHEROES-RECOVER Cohorts. Effectiveness of COVID-19 vaccines in preventing SARS-CoV-2 infection among frontline workers before and during B.1.617.2 (Delta) variant predominance — eight U.S. locations, December 2020–August 2021. *MMWR Morb Mortal Wkly Rep* 2021;**70**:1167–9. doi:10.15585/mmwr.mm7034e4.
[20] Pouwels KB, Pritchard E, Matthews PC, Stoesser N, Eyre DW, Vihta KD, et al. Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Nat Med* 2021;**27**:2127–35. doi:10.1038/s41591-021-01548-7.
[21] Wei J, Matthews PC, Stoesser N, Newton JN, Diamond I, Studley R, et al. Correlates of protection against SARS-CoV-2 Omicron variant and anti-spike antibody responses after a third/booster vaccination or breakthrough infection in the UK general population. medRxiv. 30 November 2022. https://www.medrxiv.org/content/10.1101/2022.11.29.22282916v1 [accessed 23 January 2023].
[22] Chodick G, Tene L, Rotem RS, Patalon T, Gazit S, Ben-Tov A, et al. The effectiveness of the two-dose BNT162b2 vaccine: analysis of real-world data. *Clin Infect Dis* 2022;**74**:472–8. doi:10.1093/cid/ciab438.
[23] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430–6. doi:10.1038/s41586-020-2521-4.
[24] Kahn R, Schrag SJ, Verani JR, Lipsitch M. Identifying and alleviating bias due to differential depletion of susceptible people in postmarketing evaluations of COVID-19 vaccines. *Am J Epidemiol* 2022;**191**:800–11. doi:10.1093/aje/kwac015.
[25] Ioannidis JPA. Factors influencing estimated effectiveness of COVID-19 vaccines in non-randomised studies. *BMJ Evid Based Med* 2022;**27**:324–9. doi:10.1136/bmjebm-2021-111901.
[26] Goldszmidt R, Petherick A, Andrade EB, Hale T, Furst R, Phillips T, et al. Protective behaviors against COVID-19 by individual vaccination status in 12 countries during the pandemic. *JAMA Netw Open* 2021;**4**:e2131137. doi:10.1001/jamanetworkopen.2021.31137.
[27] van Ewijk CE, Kooijman MN, Fanoy E, Raven SF, Middeldorp M, Shah A, et al. COVID-19 vaccine effectiveness against SARS-CoV-2 infection during the Delta period, a nationwide study adjusting for chance of exposure, the Netherlands, July to December 2021. *Euro Surveill* 2022;**27**:2200217. doi:10.2807/1560-7917.ES.2022.27.45.2200217.
[28] Ioannidis JPA. Benefit of COVID-19 vaccination accounting for potential risk compensation. *npj Vaccines* 2021;**6**:99. doi:10.1038/s41541-021-00362-z.