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Vaccine effectiveness against onward transmission of SARS-CoV2-infection by variant of concern and time since vaccination, Belgian contact tracing, 2021

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ABSTRACT

Background: During the first half of 2021, we observed high vaccine effectiveness (VE) against SARS-CoV2-infection. The replacement of the alpha-'variant of concern' (VOC) by the delta-VOC and uncertainty about the time course of immunity called for a re-assessment.
Methods: We estimated VE against transmission of infection (VET) from Belgian contact tracing data for high-risk exposure contacts between 26/01/2021 and 14/12/2021 by susceptibility (VEs) and infectiousness of breakthrough cases (VEi) for a complete schedule of Ad26.COV2.S, ChAdOx1, BNT162b2, mRNA-1273 as well as infection-acquired and hybrid immunity. We used a multilevel Bayesian model and adjusted for personal characteristics (age, sex, household), background exposure, calendar week, VOC and time since immunity conferring-event.
Findings: VET-estimates were higher for mRNA-vaccines, over 90%, compared to viral vector vaccines: 66% and 80% for Ad26COV2.S and ChAdOx1 respectively (Alpha, 0–50 days after vaccination). Delta was associated with a 40% increase in odds of transmission and a decrease of VEs (72–64%) and especially of VEi (71–46% for BNT162b2). Infection-acquired and hybrid immunity were less affected by Delta. Waning further reduced VET-estimates: from 81% to 63% for BNT162b2 (Delta, 150–200 days after vaccination). We observed lower initial VEi in the age group 65–84 years (32% vs 46% in the age group 45–64 years for BNT162b2) and faster waning. Hybrid immunity waned slower than vaccine-induced immunity.
Interpretation: VEi and VEs-estimates, while remaining significant, were reduced by Delta and waned over time. We observed faster waning in the oldest age group. We should seek to improve vaccine-induced protection in older persons and those vaccinated with viral-vector vaccines.

1. Introduction

Understanding the magnitude of vaccine-induced protection over time and against SARS-CoV2-variants of concern (VOC) is a public health priority [1]. Vaccine effectiveness against the onward transmission (VET) of infection during contacts can be separated into two components; infectiousness (VEi) and susceptibility (VEs). Early analyses showed that vaccines reduced susceptibility of vaccinated persons and, if a breakthrough infection occurred, they reduced infectiousness of breakthrough cases [2]. From Belgian contact tracing data collected during the first half of 2021, we estimated the VET to be over 90% for the mRNA-vaccines BNT162b2 and mRNA-1273 [3]. We could however only include data collected from recently vaccinated persons and on infections that were likely caused by the alpha-VOC (Alpha). These early studies were also limited by the small number of breakthrough cases. This was especially true for the viral-vector vaccines, ChAdOx1 and Ad26.COV2.S, which were included later in the vaccination campaign and used less. In addition to the uncertainty around

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the early VE-estimates, two important evolutions required further investigation of VE-estimates: the delta-VOC (Delta) replaced Alpha from mid-2021 onwards in Belgium and early reports on the waning of neutralizing vaccine-induced-antibodies were published [4–6].

VET-estimates are obtained by explicitly including the potential 'infectors' and their vaccination status into the model. Data for these models typically comes from either household-surveys or contact tracing. In Belgium, contact tracing started in May 2020. During 2021, all persons with a positive test (PCR or antigenic) for SARS-CoV-2 were called and asked to report their high-risk exposure contacts (contacts for >15′ at <1.5m without face masks, or direct physical contact, close contacts) [7]. We refer to the initial cases as index cases and to their high-risk exposure contacts as HREC. Index cases with a recent infection (positive PCR or antigenic test in the past 90 days), were excluded from contact tracing and recently infected HREC were not required to get tested.

Belgium's vaccination campaign started in January 2021 and the vaccination strategy prioritized nursing home residents and healthcare workers after which an age- and risk-based approach was taken to vaccinate the general population. By 30 November 2021, 86·7% of the adult and 75% of the total Belgian population was fully vaccinated. There was a three- to five-week interval between doses for the mRNA-vaccines and a eight to 12-week interval for ChAdOx1. For further details on the strategy we refer to the Scientific Institute of Public Health FAQ [8]. Belgium started administering additional doses to persons with reduced immunity and booster doses to selected populations, including nursing home residents, healthcare workers and those aged 65 years or older from mid-September 2021 onwards. Eventually booster-vaccination was offered to all Belgian adults.

1.1. Objectives

We estimated VE against transmission of SARS-CoV-2-infection by VOC and time since vaccination for the four vaccine brands used in Belgium (Ad26.COV2.S, ChAdOx1, BNT162b2, mRNA-1273) and compared VE-estimates to protection offered by previous infection (=infection-acquired immunity) and by the combination of vaccine-induced and infection-acquired immunity (=hybrid immunity).

2. Methods

2.1. Data included

We included data from 26 January 2021 to 14 December 2021. From 26 January 2021 onwards a second PCR-test was required when the first test was negative. The first test was carried out as soon as possible. The second test was carried out seven days after the last contact. A single negative test sufficed for vaccinated persons during the summer holidays (July-August) and if there had been no contact with the index case in the last three days. We included test results of first and second tests from fully vaccinated and unvaccinated persons. Persons who received a single dose of a two-dose vaccine schedule (incomplete vaccination) or an additional or booster dose at the time of testing were excluded.

Alpha was the dominant strain during the first months of 2021, being detected in 60–85% of sequenced samples. Delta was first detected in Belgium in April 2021. We defined 18 June 2021, the date at which 20% of the sequenced samples were identified as Delta, as the end of the Alpha-dominant period. On 15 July 2021, 86% of the sequenced samples were identified as Delta. This percentage increased to 99.6% by 30 November 2021. We defined the period from 15 July to 14 December 2021 as the period during which Delta was dominant. On 15 December 2021, 4% of sequenced sampled were identified as Omicron. Samples collected between the Alpha and Delta-dominant periods, from 19 June 2021 to 14 July 2021, were excluded.

Contacts with a negative duration of exposure were excluded: (1) when the HREC was tested earlier than the index case and (2) when the date of last contact between index and HREC was more than three days before the date of symptom onset of the index case. For index cases with more than three HREC, we randomly selected three HREC for inclusion and excluded the other HREC.

2.2. Variables included

Person-level data on test-results (result of the test, sampling and testing date) were linked to data from the vaccination registry (vaccine brand and date of vaccination) and contact tracing data (age, sex, date of symptom onset, date of last contact, household-membership) by National Registry Number (NRN).

A person was considered fully vaccinated 14 days after the second dose of ChAdOx1/ mRNA-1273, seven days after the second dose of BNT162b2 and 21 days after a single dose of Ad26.COV2.S [9]. A previous SARS-CoV2-infection was defined as having had a positive PCR or antigenic test more than 90 days prior to the date of sampling.

Biological sex and age at sampling were obtained from the national registry. Age groups were 0–5, 6–11, 12–24, 25–44, 45–64 and 65–84 years old. As we could only include a small number of persons aged 85 years and older, these were excluded from the analysis. VEs was not estimated for persons younger than 12 years as this age group was not eligible for vaccination during the study period.

We included a dummy variable to indicate if the index case and HREC were part of the same household. We included whether the test was a first test or a second test (in combination with the test result of the first test). Calendar time, the week during which the sample was taken, was included as a random effect into the model. Finally, the background exposure was included as the positivity rate (centered 7-day moving average) of all PCR and antigenic tests of the province of the HREC at the sampling date.

2.3. The model

We fitted a multilevel Bayesian regression model to the test results of the HREC. The probability of a positive test was a function of characteristics of the index and HREC (age, sex, household, vaccination and previous infection ($pC.Vacc$)), the dominant VOC, background exposure and the calendar week.

$$\begin{aligned} P_{postestHREC} \sim\ & age_{index} + sex_{index} + age_{HREC} + sex_{HREC} + household \\ & + VOC + backgroundexposure + calendarweek \\ & + (Index)Imm_{AgeGroup,Sex,pC.Vacc,t,VOC} \\ & + (HREC)Imm_{AgeGroup,Sex,pC.Vacc,t,VOC} \end{aligned}$$

2.3.1. The effect of vaccination and previous Covid-19 infection

The effect of the immunity-conferring event (Imm) was included for the index case (effect on infectiousness) and the HREC (effect on susceptibility) as an initial effect ($pC.Vacc + age + sex$) in interaction with the VOC ($VOC_{pC.Vacc}$) and waning ($Waning_{Age,Sex,pC.Vacc,t}$).

$$\begin{aligned} Imm_{Age,Sex,pC.Vacc,t,VOC} = & (pC.Vacc + age + sex) * Waning_{Age,Sex,pC.Vacc,t} \\ & * VOC_{pC.Vacc} \end{aligned}$$

Previous infection and vaccination (*pC.Vacc*) were included as a factor with 10 factor-levels (2 * 5: yes/no previous infection and unvaccinated/Ad26.COV2.S/ChAdOx1/BNT162b2/mRNA-1273). $Waning_{Age,Sex,pC.Vacc,t}$ is included as a linear spline over 50-day periods since the last immunity-conferring event with a single knot at 150 days. The spline's coefficients are determined by age, sex and the combination of vaccination and previous infection.

$$Waning_{AgeGroup,Sex,pC.Vacc}\ AgeGroup + Sex + pC.Vacc$$

One way to interpret the model is to look at its three levels. The first level represents a baseline for transmissibility/infectiousness/susceptibility defined by age, sex (of index case and HREC), household, VOC, background exposure and calendar week. The second level represents the initial effect of the vaccination/previous infection (first 50 days after last immunity-conferring event). The third level represents the waning of this initial effect. Note that variables such as age, sex, vaccination (brand)/previous infection are included on all three levels. The model allows age to be associated with changes in susceptibility, changes in vaccine effectiveness and faster or slower waning. Other variables, such as the VOC, were included on two levels (1) baseline transmissibility/infectious ness/susceptibility and (2) 'vaccination/previous infection'-effect. The model allows for a different VOC-effect on infection-acquired immunity, vaccine-induced immunity and hybrid immunity. The model does not allow VOC-specific waning.

We reported 95% credible intervals as CI. The Bayesian model was fitted using the R-package nimble. Code for the model and the priors used can be found in supplementary material.

Females aged 45–64 years old without a previous infection were used as reference category in this paper. Whenever VE is reported without additionally mentioning sex, age group and previous infection, it refers to females aged 45–64 years of age. BNT162b2 is the most frequently administered vaccine in Belgium and is therefore often used as reference in this study.

2.4. Role of the funding source

This study was supported by the Belgian Federal and Regional Authorities through funding for the LINK-VACC project and organizing and financing of contact tracing. The funding source had no role in the study design, collection, analysis, interpretation, writing of the report or deciding to submit the paper.

3. Results

3.1. Numbers included and characteristics of those included

Over the study period 1,281,260 Covid19-cases were recorded. A total of 931,518 (72%) index cases were successfully contacted, 85.6% reported contacts (low and/or high-risk) and 50% reported HREC. A median of 3 HREC were reported per index case reporting HREC. A total of 1,341,084 HREC were to be contacted. To be included in the analysis, the HREC needed to be successfully contacted and provide a NRN. This was available for 1,037,677 HREC (78.5% of all HREC).

Adherence to the testing strategy was high: test results were available for 90.3% of HREC with an NRN (N = 934,285). Among those testing negative on a first test, a test result of a second test was available for 65%.

Over the study period 1,446,605 test results were available. Results were excluded because of missing variables for the HREC (N = 5920), missing variables for the index case (N = 144,380), sampling during a period in which the dominant VOC was unclear (N = 24,884), incomplete vaccination or booster vaccination (N = 144,411), second tests in fully vaccinated persons during summer (N = 21,618), an index case or HREC aged 85 years or older (N = 10,150), more than 3 HREC per index case (N = 188,926) and misclassification (e.g. testing of HREC before testing of index case, N = 78,683). We included 941,320, of which 194,128 positive, test results (20.6%) from 321,279 index cases and 567,986 HREC in the analysis.

We included a number of descriptive tables on previous infection and vaccine brand by age group for HREC and index case (Tables 1 and 2). More descriptive statistics on age, sex, index case-HREC interactions and the temporal evolution of the unadjusted attack rate in HREC are provided in supplementary material. Notably, persons included in the analysis were most frequently aged around either 15 or 42 years. Also, about 66% of HREC were household-members of the index case and most tests were from March-April (3rd Belgian Covid19-wave) and October-November 2021 (4th Belgian Covid19-wave).

3.2. Baseline susceptibility and infectiousness

The baseline susceptibility and infectiousness as obtained from the multivariate model (adjusted for VOC, vaccination/previous infection, background exposure, household-membership and characteristics of index/HREC) were lowest for the youngest age group and highest for the oldest age group (Fig. 1). Susceptibility was lower in males (OR 0·96, CI 0.95–0.97) compared to females, infectiousness was not-significantly different (OR 1.01, CI 0.99–1.02).

The odds of transmission during the period when Delta was dominant increased with 40.4% (CI 38.9–41.8) compared to the period when Alpha was dominant.

3.3. First 50-day effects of vaccine and previous infection on susceptibility, alpha-VOC

In persons without previous infection, during the Alpha-dominant period, we observed significant differences in VEs-estimates by vaccine brand. mRNA-1273 offered the highest VEs (82%, CI 79–84) and VEs was lowest for Ad26.COV2.S (38%, CI 34–44). The VEs-estimates for BNT162b2 and ChAdOx1 were 72% (CI 70–74) and 56% (CI 51–59) respectively. Infection-acquired immunity did not offer significantly different protection compared to mRNA-1273-vaccination. The estimated reduction in susceptibility for re-infection was 83% (CI 80–88). Hybrid immunity provided the highest protection; in previously infected persons, VEs was estimated around 87%, without significant differences between vaccine brands.

In addition to reducing susceptibility, the infectiousness of breakthrough cases without previous infection, was reduced by 76% (CI 72–79) for mRNA-1273 and 44% (CI 41–48) for Ad26.COV2.S. The VEi-estimates for BNT162b2 and ChAdOx1 were 71% (CI 68–74) and 53% (CI 49–57) respectively. Infection-acquired immunity reduced infectiousness with 73% (CI 68–82). The reduction associated with hybrid-immunity was estimated around 80%, without significant differences between vaccine brands.

3.4. VOC-effects

The protective effects of vaccines were smaller for Delta compared to Alpha. The observed decrease was greatest for persons without previous infection and was greater for VEi (19–25 percentage points) compared to VEs (5–8 percentage points).

The dominance of the delta-VOC also resulted in a decrease in protection conferred by previous infection but to a lower extent and 95% credible intervals overlapped (Fig. 2).

Table 1
Number of the included index cases (upper) and High-Risk Exposure Contacts (bottom) by previous infection and age group (at the time of high-risk exposure contact). The positivity rate of the first test of the HREC (or HREC reported by the index case) is presented in brackets (%). Index cases are included once per tested HREC. Belgian contact tracing, 26/01/2021–14/12/2021.

Index case	0–5	6–11	12–24	25–44	45–64	65–84
No prev. Infection (% HREC positive)	24,145 (19%)	120,391 (17%)	115,502 (17%)	202,067 (24%)	120,951 (25%)	23,031 (27%)
Prev. Infection (% HREC positive)	102 (17%)	1570 (9%)	3317 (9%)	5394 (12%)	2476 (12%)	329 (10%)
HREC	0–5	6–11	12–24	25–44	45–64	65–84
No prev. Infection (% positive)	28,912 (27%)	77,622 (31%)	124,959 (21%)	193,047 (20%)	131,711 (20%)	32,682 (22%)
Prev. Infection (% positive)	218 (11%)	2024 (10%)	6994 (7%)	12,717 (7%)	7429 (5%)	960 (5%)

Table 2
Number of the included index cases (upper) and High-Risk Exposure Contacts (HREC bottom) by vaccination status (vaccine brand or unvaccinated) and age group (at the time of high-risk contact). The positivity rate of the first test of the HREC (or HREC reported by the index case) is presented in brackets (%). Index cases are included once per tested HREC. Belgian contact tracing, 26/01/2021–14/12/2021.

Index case	0–5	6–11	12–24	25–44	45–64	65–84
Unvaccinated (% HREC pos)	24,247 (19%)	121,958 (17%)	91,307 (18%)	114,679 (27%)	64,393 (30%)	10,675 (30%)
Ad26.COV2.S (% HREC pos)	NA	NA	3826 (11%)	4614 (22%)	5286 (21%)	135 (30%)
ChAdOx1 (% HREC pos)	NA	NA	1698 (10%)	11,713 (20%)	15,520 (20%)	3413 (25%)
BNT162b2 (% HREC pos)	NA	NA	21,100 (11%)	69,077 (20%)	34,889 (19%)	8649 (25%)
mRNA-1273 (% HREC pos)	NA	NA	888 (10%)	7378 (17%)	3339 (14%)	448 (18%)
HREC	0–5	6–11	12–24	25–44	45–64	65–84
Unvaccinated (% positive)	29,130 (27%)	79,639 (30%)	82,413 (26%)	89,862 (24%)	60,805 (24%)	12,372 (28%)
Ad26.COV2.S (% positive)	NA	NA	2422 (16%)	4031 (20%)	5007 (20%)	196 (20%)
ChAdOx1 (% positive)	NA	NA	792 (13%)	9336 (17%)	16,296 (18%)	5373 (17%)
BNT162b2 (% positive)	NA	NA	44,606 (9%)	90,037 (15%)	50,603 (15%)	14,449 (19%)
mRNA-1273 (% positive)	NA	NA	1720 (7%)	12,498 (11%)	6429 (11%)	1252 (12%)

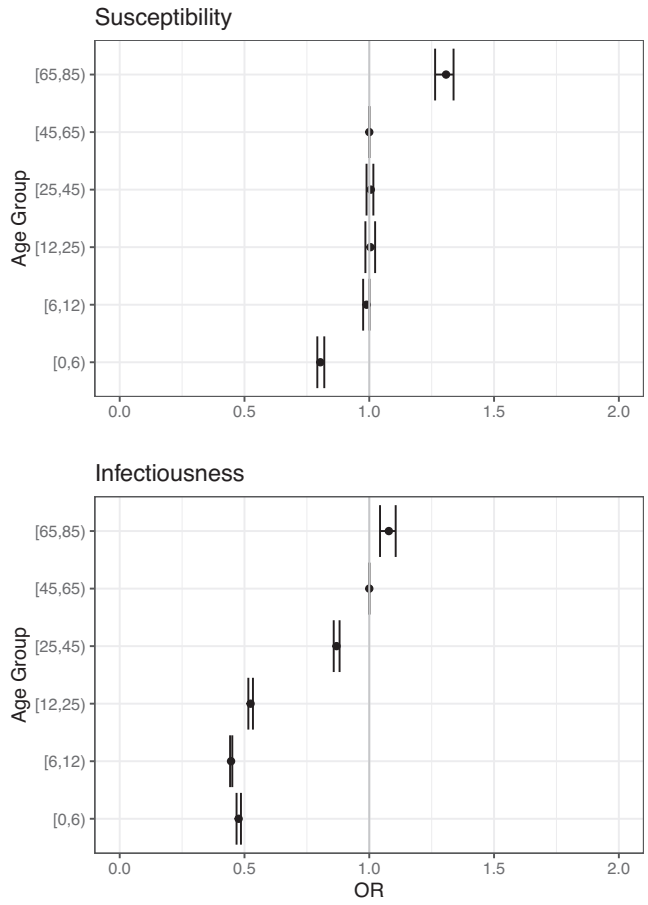

Fig. 1. Baseline Odds Ratio (95% CI) for susceptibility (upper) and infectiousness (bottom) by age group, Belgian contact tracing, 26/01/2021–14/12/2021.

3.5. Waning of initial effects

We observed waning of vaccine-induced and immunity-acquired protection for both VEi and VEs. Over a period of 150–200 days after vaccination, VEs decreased by 11–20 percentage points and VEi decreased by 1–12 percentage points (depending on the brand). The VET-estimate for BNT162b2 decreased from 81% to 63% (for females 45–64 years old, Delta). The reduction in susceptibility ((1-RR) * 100) by previous infection to Delta-infection without vaccination went from 79% (CI 74–83) to 64% (CI 61–66). For hybrid immunity, we observed waning from 87% (CI 84–88) to 82% (81–83) (BNT162b2, Delta, 150–200 days). There is considerable uncertainty surrounding these estimates with wide 95% credible intervals (Figs. 3 and 4).

3.6. Effects of age groups and sex on vaccine effectiveness/effect of previous infection

Male sex was associated with higher VEs (lower odds of infection after vaccination of HREC compared to females OR 0.83 CI 0.84–0.93), but lower VEi (higher odds of infection after vaccination of index cases compared to females OR 1.08 CI 1.01–1.17). In addition, faster waning of VEs was observed in males compared to females, but the size of the effect was small.

Faster waning of VEi and VEs was observed in the oldest age group. This observation was accompanied by a lower initial VEi in the oldest age group. We observed higher VEs in the youngest age group (12–25 years) (Fig. 5).

3.7. Vaccine and previous infection effectiveness against transmission

The combined initial effects of VEi and VEs resulted in VET-estimates of 90% (CI 89–92) for high-risk contacts between fully vaccinated (BNT162b2) females aged 65–84 years without previ-

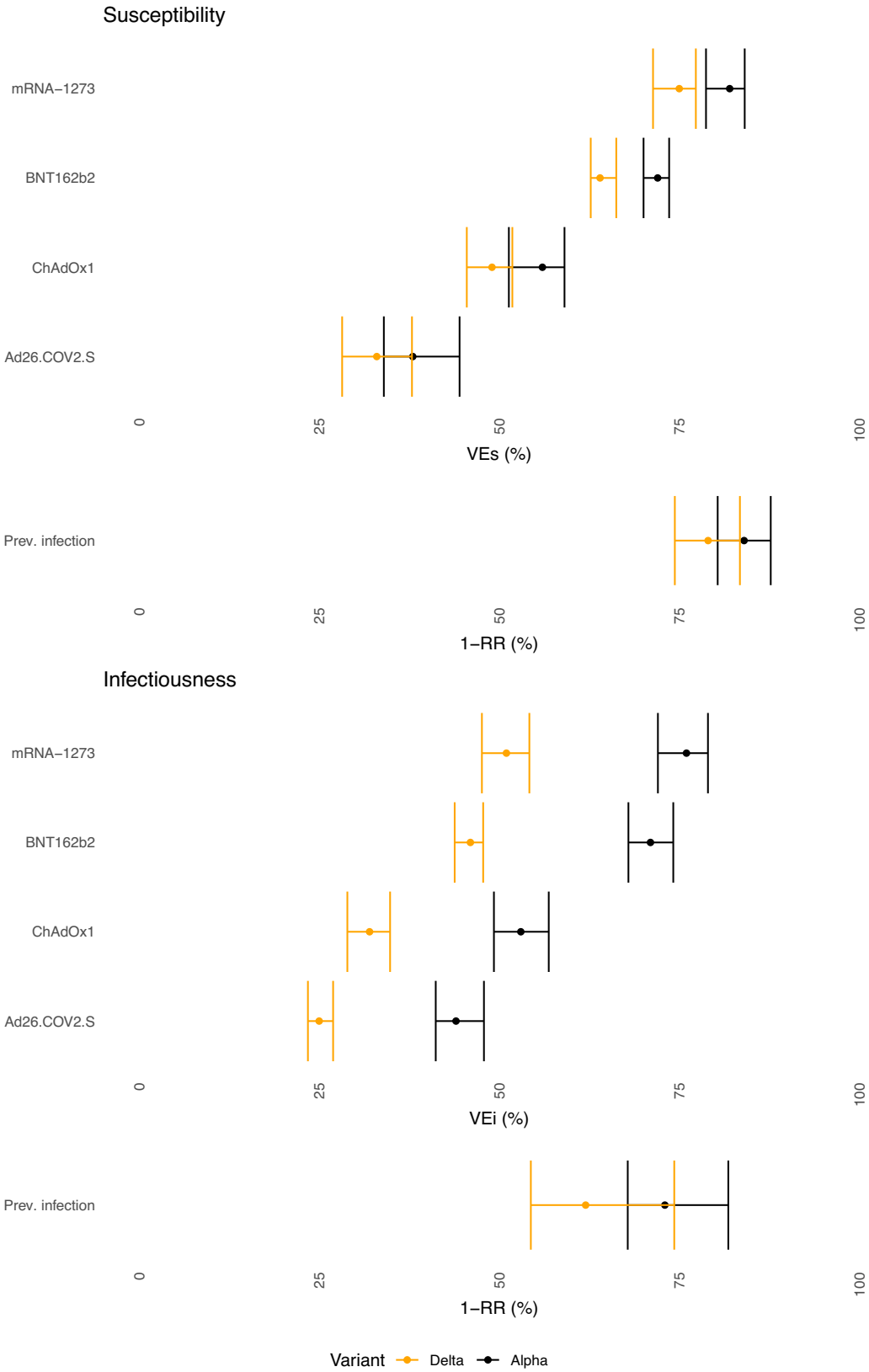

Fig. 2. (Top) VE-susceptibility (95% CI) and (Bottom) VE-infectiousness (95% CI) by vaccine brand and previous infection and by VOC, 0–50 days after vaccination (alpha = black, delta = orange, hybrid immunity not presented), Belgian contact tracing, 26/01/2021–14/12/2021. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

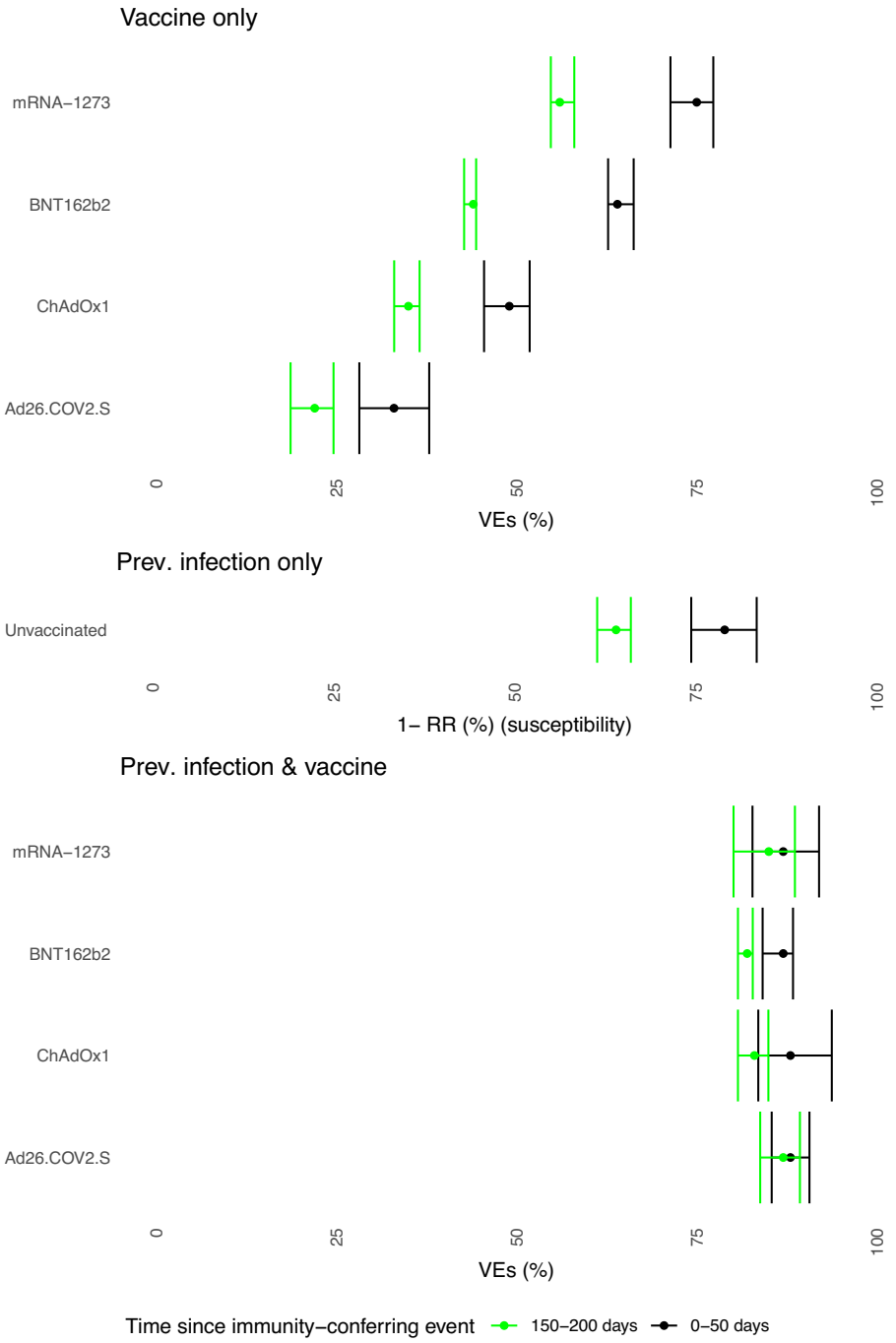

Fig. 3. VE-susceptibility (95% CI) by vaccine brand and previous infection and by time since vaccination (0–50 days (black) and 150–200 days after vaccination/infection (green), Delta), Belgian contact tracing, 26/01/2021–14/12/2021. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ous infection for Alpha. For Delta and 150–200 days after full vaccination, these estimates were reduced to 54% (CI 50–57). The largest part of the reduction in VET for this age group is associated with waning. For younger age groups, the VOC-effect and waning over a 150–200 days period were more equally associated with the decrease (Figs. 6 and 7).

4. Discussion

In this study, we estimated the effects of vaccination on transmission of SARS-CoV2 during high-risk exposure contacts from Belgium's contact tracing data. We found that, while the delta-VOC and time since vaccination lowered vaccine-induced protection, significant protection remained. We first discuss the initial effect of vaccination and then discuss how this effect waned over time. Finally, we discuss infectiousness of vaccinated cases.

Initial vaccination effects differed by VOC and by vaccine type. Delta was associated with a decrease of 19–25 percentage points for VEi and 5–8 for VEs. mRNA-vaccines offered more protection than viral-vector vaccines. The lowest VE-estimates were associated with the single dose viral-vector vaccine Ad26.COV2.S. This has been observed in other studies [10,11]. Also in accordance with

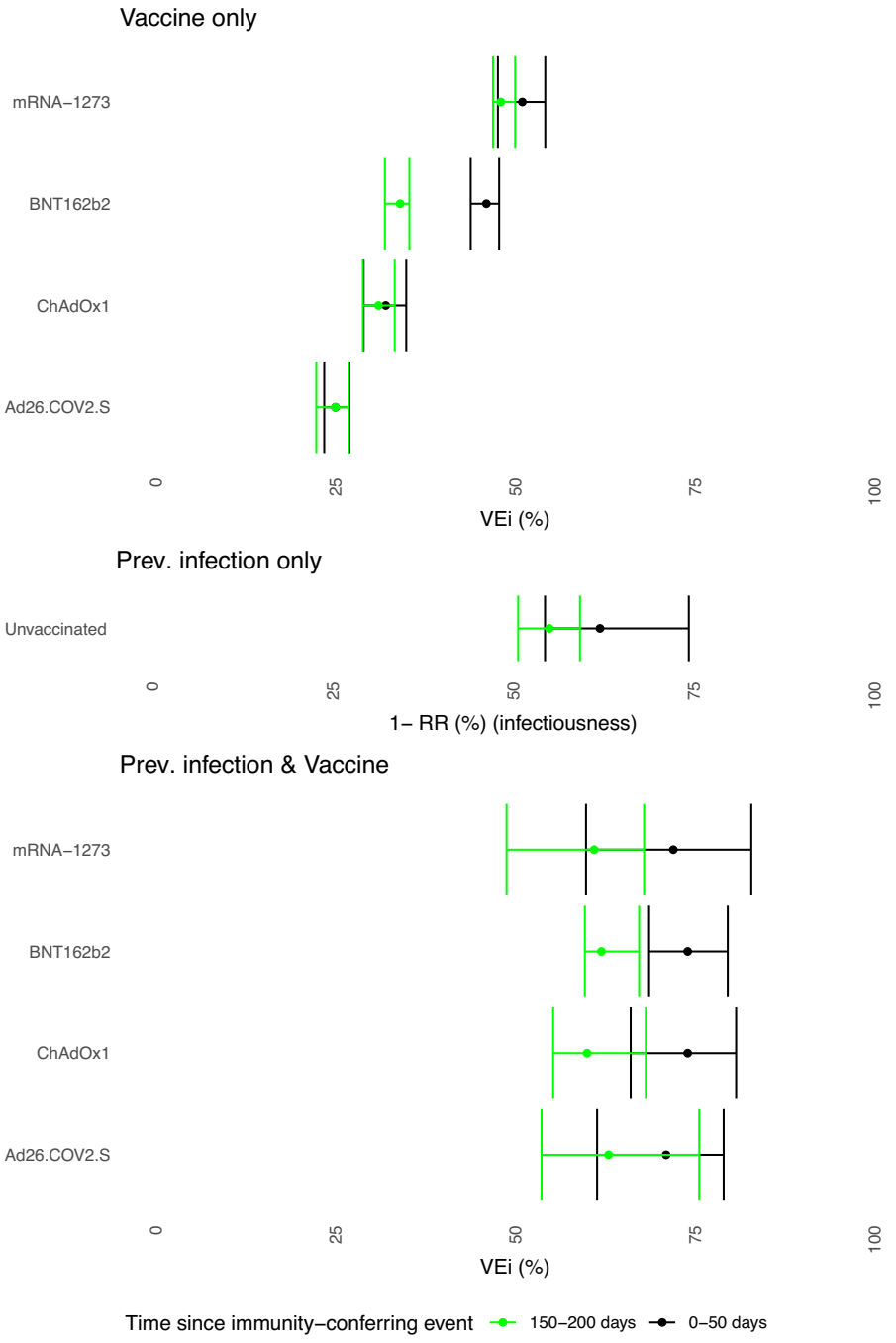

Fig. 4. VE-infectiousness (95% CI) by vaccine brand and previous infection and by time since vaccination (0–50 days (black) and 150–200 days after vaccination/infection (green), Delta), Belgian contact tracing, 26/01/2021–14/12/2021. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

other studies [12–15], we observed a high level of protection against re-infection after vaccination. We estimated VEs at 85% for hybrid immunity (BNT162b2, Delta), with non-significant differences between vaccine brands. Hybrid immunity offered more protection than previous infection or vaccination alone. Without vaccination, protection by previous infection was comparable to protection by mRNA-1273. Our estimate for infection-acquired relative risk reduction for susceptibility (1-RR: 83%, Delta) was at the lower limit of the range (80–100%) reported by an overview study [16]. While we observed more cross-neutralization between Alpha and Delta by infection-acquired compared to vaccine-induced immunity, this finding cannot be extrapolated to other VOCs [17]: neutralizing antibody responses are strongest against variants sharing certain spike mutation with the immunizing exposure [18].

We observed waning for both VEi and VEs. The waning observed for VEi was age-specific: increasing with age and not significant for the youngest age groups. Because, compared to HREC, a lower number of vaccinated index cases were included, our estimates for VEi are more uncertain. This is especially true for the viral-vector vaccines which were administered less. We observed an initial steep decrease of VET-estimates over the first 4 months, a loss of around 20%. Estimates continued to wane, but at a slower speed. Our waning estimate is within the 20–30% range over a six

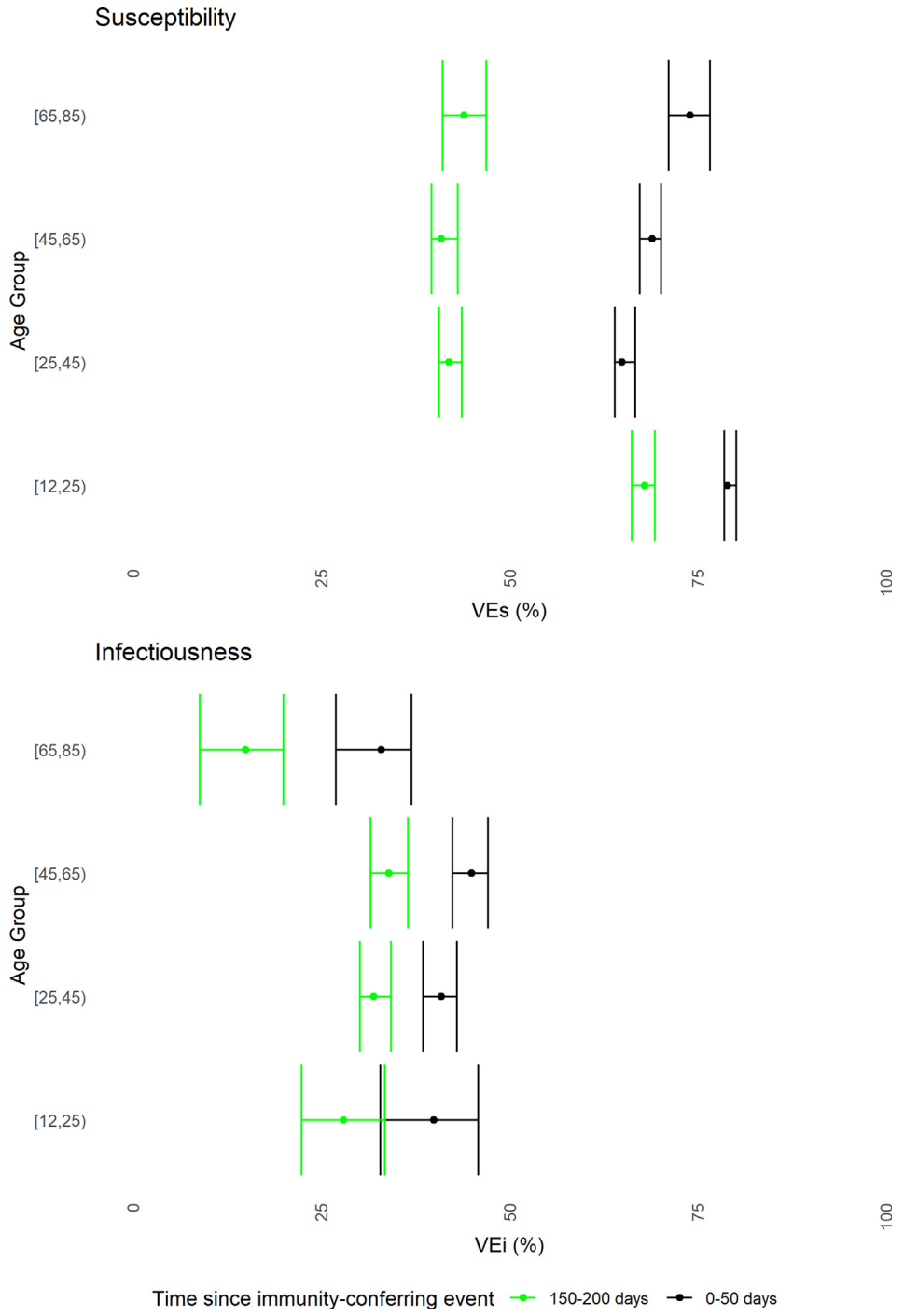

Fig. 5. (Top) VE-susceptibility (95% CI) and (Bottom) VE-infectiousness (95 %CI) for the different age groups (index case and HREC from the same age group, 0–50 (black) and 150–200 (green) days after full vaccination, fully vaccinated with BNT162b2 no previous infection, Delta), Belgian contact tracing, 26/01/2021–14/12/2021. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

month period reported by a systematic review [19]. Other studies reported faster or comparable waning of VE-estimates. Over five months, from February to October 2021, VE declined from 80% to 43% in the UK [20] and 81% to 46% in the USA [5]. Another UK study reported waning 20 weeks after full vaccination to 44.3 (CI 45–50) and 66.3 (CI 69–71) against the Delta variant for ChadOx1 and BNT162b2 respectively [21]. A population study from Sweden reported waning after vaccination with BNT162b2 from 92% to 47% 121–180 days later [22]. Serum antibody levels have been shown to decline by 57% in six months [23]. For persons aged over 65 years, we report faster waning. We associated hybrid immunity with slow waning. It was identified as the most durable form of immunity by an Israeli study [24]. Even among older people [preprint] [25] and after a single dose [26], hybrid immunity was associated with a durable IgG response [20].

We found significant VEi-estimates against both Alpha and Delta. Other studies have also reported significant VEi against Alpha; an Israeli study found VEi-estimates of 23% [27], UK studies on households and healthcare workers found estimates of 35–60% [28–30]. Studies on Delta have reported no significant or, com-

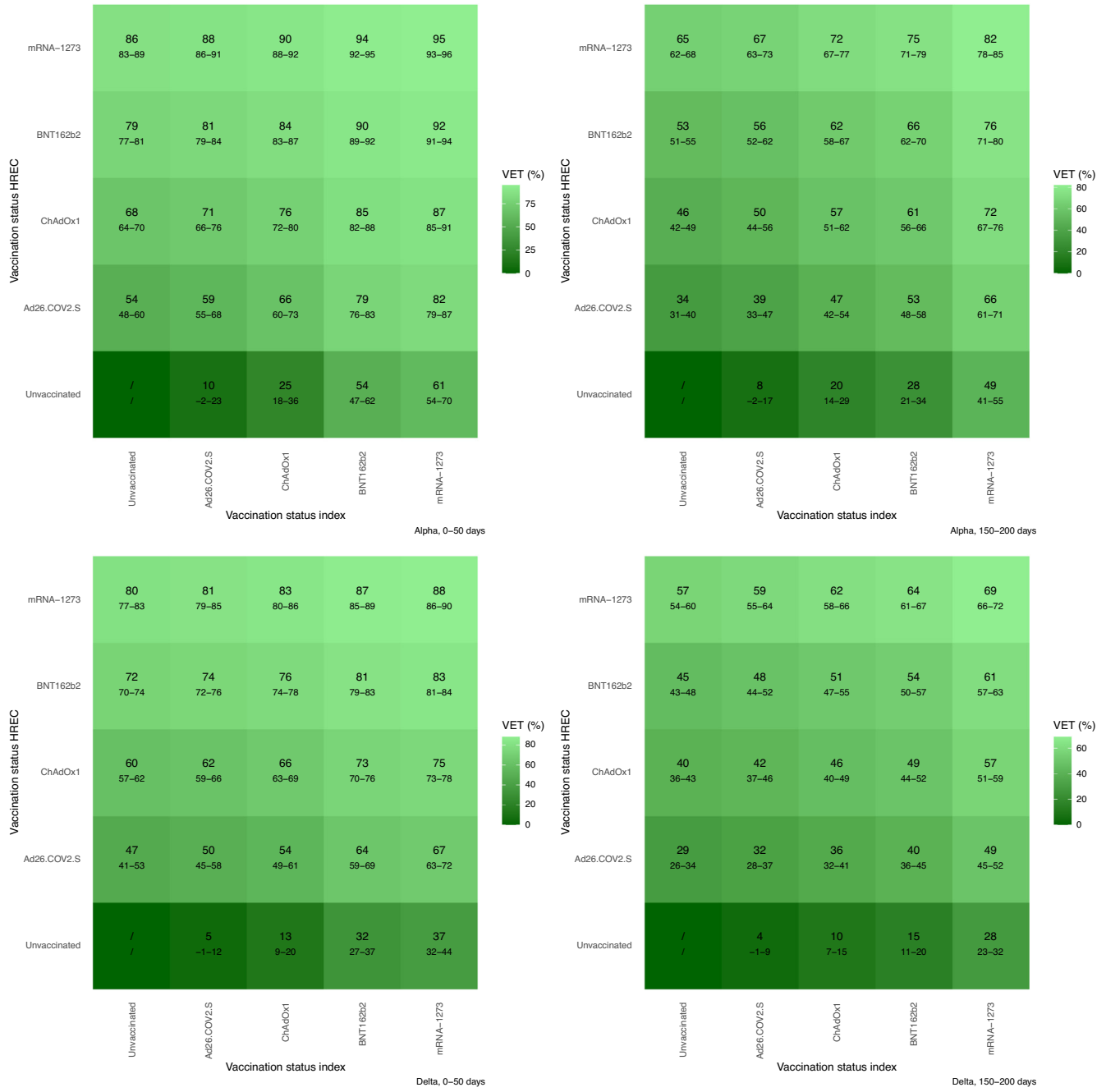

Fig. 6. VE-Transmission (95% CI) for females aged 65–84 years old without previous infection, by vaccine brand, VOC and time since vaccination (0–50 and 150–200 days), Belgian contact tracing, 26/01/2021–14/12/2021. The first column presents VE-estimates against susceptibility (protection of the HREC by vaccination against exposure from an unvaccinated index case), the first row presents VE-estimates against infectiousness (protection of unvaccinated HREC through reduced infectiousness of an index case by vaccination).

pared to Alpha, lower VEi-estimates. A Singapore, Isreali and a UK household-study found no significant VEi-estimates [27,31,32], while another UK household-study reported VEi-estimates around 40% for two doses of BNT16b2 and ChAdOx1 [preprint] [28]. Estimates from contact tracing data in the Netherlands found significant VEi-estimates: 63% in unvaccinated household-contacts and 40% in vaccinated household-contacts [33]. This was a significant decrease however from the estimates they reported for Alpha [2]. We estimated VEi at 25–51% against Delta for 25–44 year olds. Estimates for the 65–84 years old were considerably lower (5–37%) and waned faster. Comparable results on waning of VEi were obtained from an English study on contact testing. They found an initial significant reduction in transmission for BNT162b2 (aRR = 0·50) and ChAdOx1 (aRR = 0·76). These estimates were lower than those obtained for the index cases infected with Alpha and VEi was no longer significant after 12 weeks for ChAdOx1 and attenuated substantially for BNT162b2 [34].

4.1. Strengths and limitations

We offer detailed estimates of VEi/VEs/VET for four different vaccine brands obtained from systematic and repeated testing of HREC regardless of vaccination status and symptomatic state. We adjusted baseline infectiousness/susceptibility-, VE- and waning-estimates for personal characteristics. This detailed analysis was possible because we could include a large number of person-

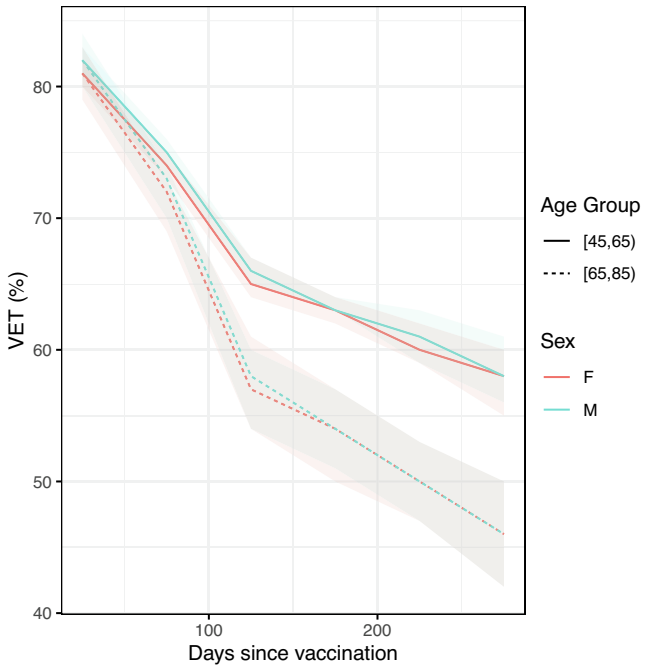

Fig. 7. VE-Transmission (95% CI) over time since vaccination by age groups and sex (HREC and Index case fully vaccinated with BNT162b2, from the same age group and same sex), Belgian contact tracing, 26/01/2021–14/12/2021.

level observations into a multilevel model. The use of contact tracing data limited possible confounding by test seeking and contact behavior differences between vaccinated an unvaccinated persons. In addition, VEi/VEs-estimates avoid a confounding-bias between the vaccination statuses of the potential infector and at-risk person. An unadjusted VE-estimate will be a combination of the VEs-estimate of the at-risk person and the VEi-estimate of the (unidentified) infector. For example, some studies have reported faster waning of VE-estimates in older age groups [35–37], while others found no significant difference [11]. We did observe significantly faster waning of VEs in older age groups, but the faster decrease of VET for older age groups was mostly linked to the faster waning of VEi. The distinction between VEi and VEs also allows for a more detailed analysis of Delta's transmissibility. Adjusted for vaccination, the odds of transmission compared to Alpha increased with 40%. While other studies have reported even larger increases [38], in our study this finding is accompanied by a large decrease in VEi against Delta.

We also investigated susceptibility and infectiousness for baseline, adjusted for vaccination, rates and found them to increase with age. Comparable observations, have been made from Belgian case data [preprint] [39] and internationally [31,34,38,40]. While we accounted for some of the characteristics of the potential infector, we cannot exclude a remaining effect of within 'index case' clustering of HREC. We included a maximum of three HREC per index case to limit such an effect. Possible misclassification; e.g. a HREC infecting the index case or an unknown common infector is another limitation of this study.

Undetected infections remain a possible cause of, typically downward, biased VE-estimates. In our study the age group from 25 to 44 years reported both the lowest effect of vaccination and the slowest waning. This observation could be explained both by a larger relative (to other age groups) amount of undetected infections and/or age-specific immunological effects. In addition, even with 90% of HREC taking a first test, symptomatic HREC might still be more likely to get tested, biasing our VE-estimates against infection towards VE-estimates against symptomatic infection.

Our model did not allow for VOC-vaccine brand interactions or VOC-specific waning. The VOC had different effects on VEi and VEs, but effects were assumed equal for the included brands. We explored more complex models, but these exploratory analyses and the observation by Cromer et al. [41] that "whether immunity was acquired through infection or vaccination (and which vaccine was used) was not significantly associated with the loss of neutralization" (by VOC) indicated that this assumption was acceptable [42].

For hybrid immunity, we did not differentiate infection followed by vaccination from vaccination followed by infection. In addition, the time between vaccination and previous infection is discarded and only the time since the last immunity-conferring event (either vaccination or previous infection) is used. Likewise, we did not focus on the time between vaccination doses. We did not include corrections for underlying medical conditions or clinically vulnerable groups. We did not differentiate between severe and mild infections. VE-estimates against severe outcomes (hospitalization and deaths) are not included in this study. We excluded persons over 84 years. Only small number were available for this age group since we excluded persons who received booster vaccination and long-term care facilities have separate contact tracing systems. Our study period precedes significant circulation of Omicron.

5. Conclusion

We report significant VEi and VEs-estimates for both Alpha and Delta. Both increasing time since vaccination and Delta were associated with a decrease in VET-estimates. In addition, Delta increased baseline transmission. Infection-acquired immunity was less affected by Delta and, in combination with vaccination, showed slower waning compared to vaccine-induced immunity. VET-estimates were highest for hybrid immunity. We observed the fastest waning of VET in persons aged 65 to 84 years, mainly because the effect of vaccination on the infectiousness of breakthrough cases waned fastest in this age group.

Statements

Data sharing statement

The person-level contact tracing data will not be shared. General descriptive statistics from the contact tracing are available from https://covid-19.sciensano.be/nl/covid-19-epidemiologische-situatie. Code for the nimble-model is provided in supplementary materials.

Authors' contributions

TB, KP, DvC, LuC and CWT have conceptualized the study. TB, KP, RB, PH, MB, AD, RM, EB, NH were responsible for data curation and investigation and did the formal data analysis. KP, TB, RB, MB, PH accessed and verified the data. TB, LaC, VS, JvL, TB, CWT prepared the initial draft of the manuscript. LuC, DvC, HvO, CWT oversaw the project. TB, LuC, RB, JvL, KP, LaC, HvO, VS, PH, MB, AD, RM, EB, NH, DvC, CWT reviewed and edited the manuscript.

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Role of the funding source

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Ethics committee approval

Data linkage and collection within the data-warehouse has been approved by the information security committee.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.04.025.

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