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The impact of variant and vaccination on SARS-CoV-2 symptomatology; three prospective household cohorts

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ABSTRACT

Objectives: We compared age-stratified SARS-CoV-2 symptomatology of wild-type/Alpha vs Omicron BA.1/BA.2 variant infected individuals and the impact of COVID-19 booster vaccination on Omicron symptom burden.

Methods: Data from three European prospective household cohorts were used (April 2020 to April 2021 and January to March 2022). Standardized outbreak protocols included (repeated) polymerase chain reaction testing, paired serology, and daily symptom scoring for all household members. Comparative analyses were performed on 346 secondary household cases from both periods.

Results: Children <12 years (all unvaccinated) experienced more symptoms and higher severity scores during Omicron compared with wild-type/Alpha period ($P \leq 0.01$). In adults, Omicron disease duration and severity were reduced ($P \leq 0.095$). Omicron was associated with lower odds for loss of smell or taste (adjusted odds ratio [aOR]: 0.14; 95% CI 0.03-0.50) and higher but non-significant odds for upper respiratory symptoms, fever, and fatigue (aORs: 1.85-2.23). No differences were observed in disease severity or duration between primary vs booster series vaccinated adults ($P \geq 0.12$).

Conclusion: The Omicron variant causes higher symptom burden in children compared with wild-type/Alpha and lower in adults, possibly due to previous vaccination. A shift in symptoms occurred with reduction in loss of smell/taste for Omicron. No additional effect of booster vaccination on Omicron symptom burden was observed.

Introduction

Since the onset of the COVID-19 pandemic in December 2019, several SARS-CoV-2 variants of concern (VOC) have emerged [1]. With the emergence of the Omicron VOC (BA.1) and its descendants (BA.2 and further), the pandemic has taken a new turn. Omicron variants are characterized by a high number of mutations compared with the ancestral strain and are associated with immune escape and enhanced angiotensin-converting enzyme-2 (ACE-2) binding [2,3]. In addition, the Omicron variants are less capable of infecting the lower respiratory tract due to a shift in

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cellular tropism away from transmembrane protease, serine 2 (TMPRSS2) expressing cells, promoting faster replication in the upper airways but reduced replication in the lungs [4,5]. As a consequence, the clinical picture of SARS-CoV-2 infection is changing, both in vaccinated and unvaccinated individuals. To date, most studies describing the changing symptomatology of COVID-19 during the Omicron period have focused on cases in hospitals [6,7]. This restricts analyses to more severe cases and therefore provides little understanding of disease evolution in community cases, which represent the overwhelming majority of all cases, and in particular in children, who only rarely require medical care for SARS-CoV-2 infection [8].

An appropriate setting to study the COVID-19 disease spectrum across pediatric and adult age groups is within households. We used a dataset from three prospective SARS-CoV-2 household transmission studies that used similar protocols to study age-stratified symptom burden of SARS-CoV2 infections during the wild-type/Alpha dominant period compared with the Omicron BA.1 and BA.2 dominant period, considering differences in vaccination and previous infection status. Our analyses are restricted to secondary household cases to avoid index case ascertainment bias.

Materials and methods

Study design and study population

We used data from three prospective household transmission studies conducted in two different SARS-CoV-2 variant periods: the Rapid European COVID-19 Emergency Response research (RECOVER) household study and CoKids study (wild-type/Alpha period) and the SARS-coV2 variants Evaluation in pRegnancy and paeDIatrics cohorts (VERDI)-RECOVER household study (Omicron period; Supplement Figures 1-2). The primary aim of the RECOVER household study was to characterize within-household transmission of SARS-CoV-2 and the impact of implemented measures within the household to prevent transmission. From April 2020 until April 2021, data from 276 Dutch, Belgium, and Swiss households with SARS-CoV-2 were collected. Study design and results on household transmission are published elsewhere [9]. The CoKids study was set up to determine the susceptibility, transmissibility, and disease course of SARS-CoV-2 infection in children. From August 2020 until July 2021, data on 79 SARS-CoV-2 outbreaks in Dutch households with at least one child <18 years of age were collected. Study design and initial results are published elsewhere [10]. The VERDI-RECOVER household study recruited from January to March 2022 during the period when Omicron BA.1 and BA.2 were dominant. This study aims to estimate household transmission rates in partially vaccinated populations and explores the viral kinetics in Omicron variant infected subjects. During wild-type/Alpha period, vaccination became available for adults (from January 2021 onwards). During the Omicron period, booster vaccinations were available for adults (in The Netherlands from December 2021 onwards) and primary series for adolescents (in The Netherlands from July 2021 onwards). Vaccination for children aged 5 to 11 became available for medical risk groups during mid-January 2022 in The Netherlands.

In all three studies, household outbreaks had started with the identification of an index case followed by repeated sampling and daily symptom monitoring in all household members until the outbreak ended. Enrollment took place within 48 hours following a positive SARS-CoV-2 polymerase chain reaction (PCR) test of the index case. Households were excluded if one or more household members did not consent to participate. In the VERDI-RECOVER household study, the additional exclusion criterium was SARS-CoV2 positivity in any of the household members in the previous 2 weeks. Here, these three studies were used to study and compare the COVID-19 disease spectrum across pediatric and adult age groups between SARS-CoV-2 variants (wild-type, Alpha, and Omicron BA.1 and BA.2).

The studies were reviewed and ethically approved by the Medical Ethical Committee Utrecht, The Netherlands (reference number 17-069/M), the Medical Ethical Committee of the Vrije Universiteit Medical Centre (VUmc), The Netherlands (reference number A2012.901), and the Medical Ethical Committee of Erasmus Medical Centre, The Netherlands (reference number MEC-2020-0609). Written informed consent was obtained from all participating household members and/or their legal representatives.

Study procedures

Most study procedures were done remotely using self-sampling and an interactive mobile phone application to accommodate pandemic restrictions on movement, social distancing, and isolation. At baseline, each household member completed a questionnaire including age, comorbidities, recent respiratory complaints, previous infections, and COVID-19 vaccination status. During follow-up, participants reported daily on presence and severity of a set of respiratory and systemic symptoms (see Supplementary Table 1), which was continued until 21 days after last symptom onset in any household member.

A courier delivered sample kits for self-sampling at home of specimens for viral and serological testing. Self-sampling was supported by live instruction or instruction videos and leaflets delivered with the sampling material. A telephone helpdesk was available 7 days a week during working hours. In each of the studies, the core protocol included a nose-throat swab (NTS) sample at day 0 for all household members and, if applicable, an additional NTS from a household member when he/she developed symptoms during follow-up. The core protocol could be extended with additional sample time points and specimens, but this differed between studies (Supplement Table 1). Therefore, those additional results were not used in the current analysis to guarantee similarity in case detection across cohorts. Dried blood spot (DBS) samples using self-finger-prick were collected at enrollment and at the end of follow-up.

For data collection of symptoms, questionnaires, and self-sampling, we used a custom-made mobile phone application (app) compatible with Apple and Android systems, developed by the University Medical Centre Utrecht in collaboration with YourResearch Holding BV. The study app contained all study-related tasks and questionnaires along with tutorial videos, frequently asked questions, and options to contact the study team. All data entered in the study app were stored in a secured online database. Data were accessible and could be navigated by the study team in real-time by authorized login on the online portal. Daily app notifications were sent to participants to remind them to complete diary entries and self-sampling when applicable. Study teams received daily reports on participant non-compliance, which were followed up by email, phone, or text message.

Laboratory analysis

NTS samples were PCR tested for presence of SARS-CoV-2, and DBS were tested by multiplex protein microarray for antibodies as described previously [9,10] at either the Streeklab Haarlem (CoKids cohort), National Institute for Public Health and the Environment (CoKids cohort), Antwerp University (RECOVER and VERDI-RECOVER cohorts), or Erasmus University Medical Center Rotterdam (RECOVER and VERDI-RECOVER cohorts). Details on the PCR and DBS methods used can be found in Supplement 1.

Definitions

Confirmed SARS-CoV-2 infection was defined as a positive reverse transcription-PCR SARS-CoV-2 result or seroconversion defined as SARS-CoV-2 nucleoprotein (NP)-antibody negative at enrollment and positive at the end of follow-up. A secondary household case was defined as a confirmed SARS-CoV-2 infection in a household member not being the index case.

We used the daily symptom data and date of positive test result to define onset and end of a SARS-CoV-2 episode. An episode started on the day of symptom onset, which had to fall within the 7 days before, or 7 days after first positive test result. An episode ended on the last symptomatic day that was followed by at least 2 days without any symptoms. SARS-CoV-2 disease severity was categorized into symptomatic disease, pauci-symptomatic, and asymptomatic episodes. Symptomatic disease was defined as (i) onset of fever OR (ii) 2 consecutive days with one respiratory (cough, sore throat, runny or congested nose, dyspnea) and one systemic symptom (headache, muscle ache, sweats or chills, or tiredness) or with at least two respiratory symptoms. Subjects meeting the criteria for symptomatic disease additionally received a daily symptom severity score which consisted of a 5-point Likert scale per reported symptom present, except for fever, which was categorized as <38/38-39/39-40/>40 degrees Celsius. An episode was defined as pauci-symptomatic if symptoms occurred within the specified time window but remained below the threshold for a symptomatic disease episode and asymptomatic if no symptoms were reported.

Vaccination status was categorized into unvaccinated, incompletely vaccinated, primary vaccinated, or primary plus booster vaccinated. Primary vaccinated was defined as two doses of a messenger RNA (mRNA) vaccine BNT162b2 or mRNA-1273 (Pfizer-BioNtech; Moderna), two doses of the vector-based AZD1222 (AstraZeneca), or a single dose of the vector-based Ad26.COV2.S vaccine (Johnson & Johnson) at least 14 days before enrollment. Primary plus booster vaccinated was defined as a third dose of mRNA vaccine or a second dose if the primary series consisted of a single dose of Ad26.COV2.S vaccine, at least 6 months after completion of the primary series and at least 14 days before enrollment. Previous infection was determined when previous infections were reported in the questionnaire or when antibodies (NP antibodies during Omicron period) were detected in the DBS at enrollment, indicating a previous infection. Previous immunity was defined by the presence of antibodies at enrollment, being vaccinated before enrollment, and/or self-reported previous enrollment infection.

Statistical analysis

Our population for analysis included all secondary household cases from the three cohorts. Index cases were excluded because index case ascertainment strategies differed between cohorts because of testing availability, and are inherently incomplete, which may select for more severe cases. We grouped cases by dominant variant period. Secondary cases from the RECOVER and CoKids cohorts were therefore assigned to the wild-type/Alpha variant, whereas cases from the VERDI-RECOVER cohort were assigned to the Omicron BA.1 and BA.2 period (see Supplementary Figure 1 for variant prevalence over time from national surveillance [11]). Population demographic and vaccination characteristics were compared by variant period using proportions and medians with interquartile ranges (IQRs).

We compared the symptoms and severity of secondary case episodes in the wild-type/Alpha variant dominant period to those in the Omicron-dominant period stratified by age category: child (age 0-11), adolescent: (age 12-17), and adult (age above 17). We studied symptom frequency by age category and variant using bar charts, daily symptom severity scores in spline plots, and symptom frequency over time since onset, age group, and variant using heat plots.

Missing diaries and symptom severity scores were imputed using the symptoms and severity of the day before and after the missing value. Cases that did not complete any diary were excluded. For each symptomatic episode, we computed the maximum symptom severity score, referring to the day with highest reported score during the episode, and the cumulative symptom severity score, referring to the sum of symptom severity scores during the entire episode. We used chi-square test for symptom frequency and Mann–Whitney *U* test for symptom duration, number of symptoms, maximum, and cumulative symptom severity score. Next, we explored the association between variants and symptoms using binomial and Gaussian multivariable regression models. Odds ratios (ORs) were computed for each respiratory and systemic symptom to quantify the association between variant and symptom frequency, adjusted for age, gender, and previous immunity. Previous immunity was based on vaccination status, serology at baseline, and/or a reported previous positive PCR or antigen test. For unvaccinated secondary cases with missing serology at baseline and no previous positive test, we assumed no previous immunity. In sensitivity analyses, we repeated the multivariate analyses assuming the 18 persons with unknown baseline serology had a previous infection.

The multivariate analysis was repeated to assess the effect of vaccination status (primary series vs booster) on symptom burden and the symptom duration and severity. Because the distributions of disease severity and duration were skewed, the data was log-transformed before estimating the mean difference in disease severity and duration between variants. This analysis was restricted to adults during the Omicron-dominant period, as this was the only age group who were eligible for booster vaccination at the time.

Statistical analyses were performed with R version 4.0.3 (R Core Team, Vienna, Austria). The *t*-test, chi-square, and multivariate logistic regression were used for statistical analysis with Holm–Bonferroni correction ($P < 0.05$).

Results

In total, 355 secondary household cases were detected across the three cohorts. Nine cases were excluded because of missing/incomplete diaries (see details on data completeness in Supplementary Table 2) or an infection with the Delta variant (one case). For the remaining participants, data completeness was >99% for diaries and severity scores, 80-87% for NTS samples, and 66-96% for DBS. Of 346 cases included in analysis, 216 occurred during the wild-type/Alpha period and 130 during the Omicron period. Age varied between 0 and 78 years, and the majority were adults (57.8%, Table 1). The proportion of children <12 years of age was slightly higher during the Omicron period (38.5% vs 26.4%). During the wild-type/Alpha period, six cases (2.8%) had a previous SARS-CoV-2 infection, and no cases had received any vaccination. In contrast, during the Omicron period, 37.7% had a previous SARS-CoV-2 infection, 63 (96.9%) adults had received at least the primary series, and 45 (71.4%) had a booster vaccination. Of adolescents, 14 (93.3%) had received primary vaccination, whereas children <12 years were all unvaccinated. Of the individuals with available serology test results, 3.6% (6/165) had NP antibodies during wild-type/Alpha period and 35.7% (40/112) during the Omicron period.

Table 1
Baseline characteristics secondary household cases.

	Mean (SD) or No. (%)					
	Wild-type/Alpha period			Omicron period		
	Adult (≥18 years) (n = 135)	Adolescent (12-17 years) (n = 24)	Child (<12 years) (n = 57)	Adult (≥18 years) (n = 65)	Adolescent (12-17 years) (n = 15)	Child (<12 years) (n = 50)
Mean age (SD)	42.1 (13.7)	14.9 (1.6)	6.1 (3.2)	42.1 (5.0)	13.9 (1.6)	7.1 (3.1)
Female	60 (44.4%)	14 (58.3%)	23 (40.4%)	37 (56.9%)	4 (26.7%)	24 (48.0%)
Previous infection[a]						
Yes	2 (1.5%)	0 (0.0%)	4 (7.0%)	29 (44.6%)	5 (33.3%)	15 (30.0%)
No	133 (98.5%)	24 (100.0%)	53 (93.0%)	33 (50.8%)	9 (60.0%)	27 (54.0%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.6%)	1 (6.7%)	8 (16.0%)
Previous immunity[b]						
Yes	2 (1.5%)	0 (0.0%)	4 (7.0%)	65 (100.0%)	15 (100.0%)	16 (32.0%)
No	133 (98.5%)	24 (100%)	53 (93.0%)	0 (0.0%)	0 (0.0%)	34 (68.0%)
Vaccination status						
Primary plus booster series	0 (0.0%)	0 (0.0%)	0 (0.0%)	45 (69.2%)	0 (0.0%)	0 (0.0%)
Primary series	0 (0.0%)	0 (0.0%)	0 (0.0%)	18 (27.7%)	14 (93.3%)	0 (0.0%)
Incomplete primary series	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.1%)	0 (0.0%)	1 (2.0%)
No vaccination	135 (100.0%)	24 (100%)	57 (100.0%)	0 (0.0%)	1 (6.7%)	49 (98.0%)

[a] Prior infection is defined as having nucleoprotein antibodies at enrollment and/or a reported previous infection in the baseline questionnaire.
[b] Prior immunity is defined as reported vaccinated before enrollment, having nucleoprotein antibodies at enrollment, or a reported previous infection in the baseline questionnaire.

Table 2
Symptom burden of SARS-CoV-2 infections wild-type/Alpha vs Omicron variant per age group.

	No. (%) or median (IQR)								
	Adult >18 years			Adolescent 12-17 years			Child < 12 years		
	Wild-type/alpha period	Omicron period		Wild-type/alpha period	Omicron period		Wild-type/alpha period	Omicron period	
	n = 135	n = 65	*P*-value[b]	n = 24	n = 15	*P*-value[b]	n = 57	n = 50	*P*-value[b]
Disease category			0.046			0.139			0.034
Symptomatic disease	103 (76.3%)	55 (84.6%)		14 (58.3%)	13 (86.7%)		20 (35.1%)	30 (60.0%)	
Pauci-symptomatic	20 (14.8%)	10 (15.4%)		7 (29.2%)	2 (13.3%)		24 (42.1%)	12 (24.0%)	
Asymptomatic	12 (8.9%)	0 (0.0%)		3 (12.5%)	0 (0.0%)		13 (22.8%)	8 (16.0%)	
Days with symptoms	13 (7.5-21)	10 (6-18)	0.095	7 (1-12)	6 (4-8)	0.7	3 (1-7)	6 (4-11.5)	0.044
Number of symptoms	6 (3-6)	5 (4-7)	0.3	2.5 (1-5.5)	4 (3-6.5)	0.076	2 (1-3)	3 (1.5-5)	**0.004**
Maximum symptom severity score[a]	14 (10-18)	11 (9.5-15)	0.066	11 (7.5-19.5)	10 (10-12)	0.8	7 (4-11)	10 (8.5-14)	**0.011**
Cumulative symptom severity score[a]	80.5 (55.5-128)	54.0 (33.5-115)	0.024	40.5 (22-128)	34 (28-62)	>0.9	20.5 (14-49)	40.5 (28-69.5)	0.075

[a] Calculated for cases with symptomatic disease.
[b] Bold *P*-values indicate significant differences after correction for multiple testing.

Symptom burden during wild-type/Alpha and Omicron periods

Table 2 and Figures 1-3 show the SARS-CoV-2 symptom burden per period stratified by age group. Infection remained asymptomatic in 13.0% vs 6.2% (*P*-value = 0.045) of cases in the wild-type/Alpha vs Omicron period; less pauci-symptomatic and more symptomatic disease was observed in the Omicron period (63.4% vs 75.4%, *P*-value = 0.021). Overall, the symptom burden was highest in adults during the wild-type/Alpha period, and differences across age groups largely disappeared during the Omicron period. There were diverging trends in symptom burden between children and adults. Among adults, maximum and cumulative severity scores tended to be lower during the Omicron period (*P*-value = 0.06 and *P*-value = 0.024). Loss of smell or taste was significantly less common during the Omicron period (*P*-value = 0.001), whereas sore throat was more common (*P*-value = 0.017; Figures 1-3). The number of adolescents included in analysis was low, but data suggest a higher proportion of symptomatic disease during the Omicron period (86.7% vs 58.3%, *P*-value = 0.062) and a higher number of symptoms during the Omicron period (*P*-value = 0.076). In particular, cough, sore throat, cold shivers, and fever, while disease severity was not increased. In children <12 years, the number of reported symptoms and the maximum symptom severity score were significantly increased during the Omicron period ($P \leq 0.011$, Table 2 and Figures 1-3). In particular, fatigue was more common during the Omicron period (*P*-value = 0.004), and symptom duration was twice as long (3 days to 6 days, *P*-value = 0.044).

After adjustment for age, gender, and previous immunity, the Omicron variant was associated with lower odds of loss of smell or taste (OR: 0.14; 95% CI 0.03-0.50), whereas the ORs for coughing (OR: 1.85; 95% CI 0.92-3.78), fever (OR: 2.23; 95% CI 1.03-4.81), sore throat (OR: 1.89; 95% CI 0.92-3.88), nasal congestion/runny nose (OR: 1.97; 95% CI 0.89-4.59), and fatigue (OR: 2.00; 95% CI 0.98-4.14) suggest an increase in these symptoms compared with the wild-type/Alpha variant (Table 3). Sensitivity analyses assuming the 18 persons with unknown NP antibodies at enrollment as infected show equal trends in similar directions.

Vaccination status and symptom burden in adults during the Omicron period

Comparing subjects who had received the primary series of SARS-CoV-2 vaccination to those who had also received a booster

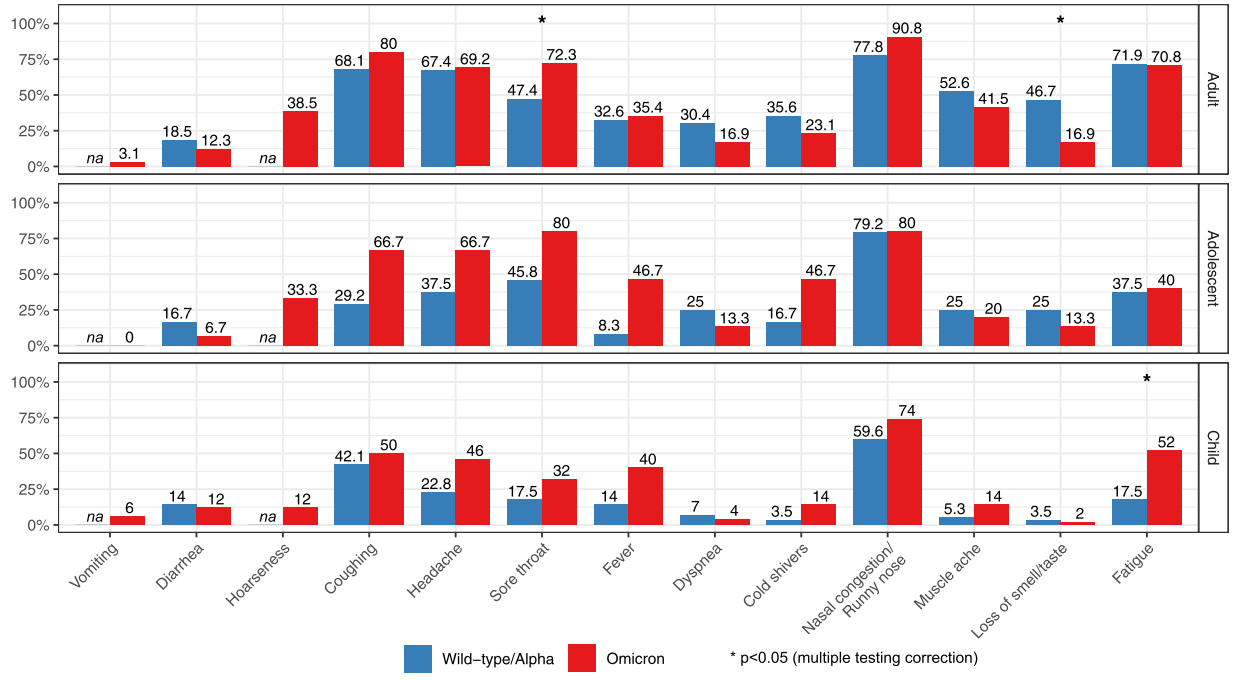

Figure 1. Symptom frequency by age category and variant (wild-type/Alpha vs Omicron). na, not available.

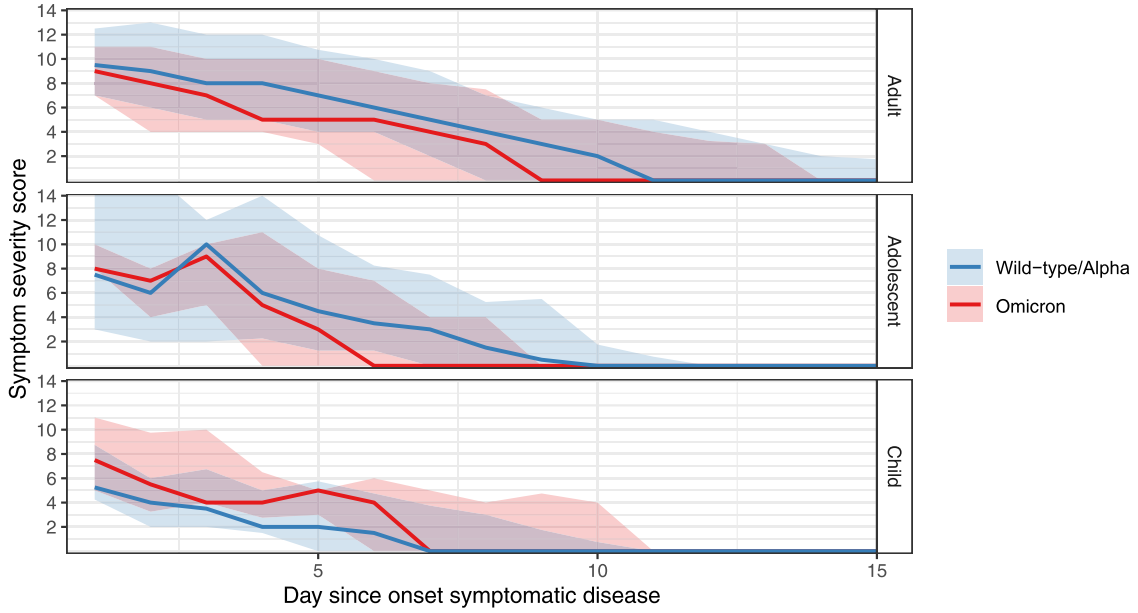

Figure 2. Symptom severity scores over time for symptomatic SARS-CoV-2 episodes by wild-type/Alpha vs Omicron variant and age group. Line indicates median and shade interquartile range.

dose, no significant differences were observed for any symptom or symptom burden outcome measure (Tables 4-5; Supplement Figures 3-5). Sensitivity analysis assuming three subjects with unknown NP antibodies at enrollment as previous immune showed similar results.

Discussion

Our analysis of symptom data of secondary household cases of SARS-CoV2 in a non-hospitalized general community, detected by comprehensive screening, provides a detailed comparison of SARS-CoV2 disease profiles in the community during two periods. During the wild-type/Alpha variant period, the population immunity was low, while in the (early) Omicron period, when BA.1 and BA.2 subvariants were dominant, a large proportion of the adult and adolescent population had been vaccinated, but not children <12 years. Interestingly, the symptom burden in children was higher during the Omicron period compared with the wild-type/Alpha period. In adults, there was a reduction in the number and duration of symptoms present during the Omicron period when nearly all of them had evidence of previous immunity from vaccination or previous infection. Trends in adolescents (93.3% vaccinated during Omicron period) were less clear, but overall numbers of infections in this age group were low. Adjusted for age, gender, and

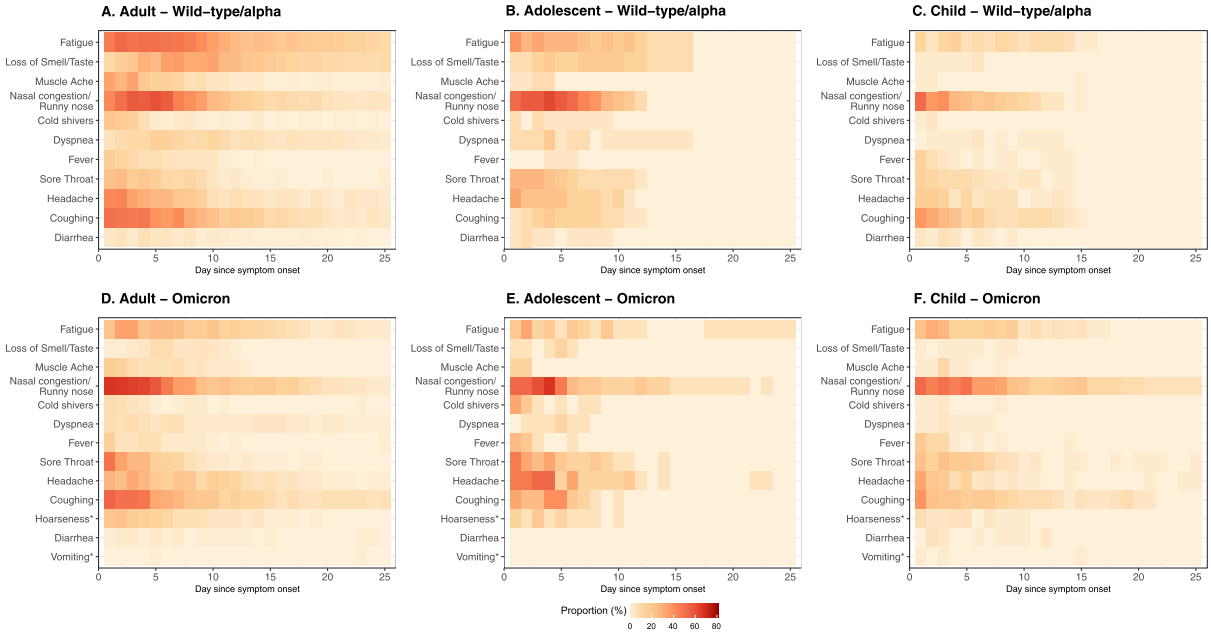

Figure 3. Symptom frequency per day since onset, age group, and variant. Includes all infected subjects (including asymptomatic cases).
*Indicate symptoms exclusively asked during Omicron period.

Table 3
Adjusted OR for symptom frequency for Omicron vs wild-type/Alpha variant. No significant OR's after correction for multiple testing.

Symptom	OR (95% CI)	*P*-value[a]
Muscle ache	0.67 (0.25-1.67)	0.4
Coughing	1.85 (0.92-3.78)	0.085
Fever	2.23 (1.03-4.81)	0.041
Sore throat	1.89 (0.92-3.88)	0.082
Nasal congestion/ runny nose	1.97 (0.89-4.59)	0.103
Dyspnea	0.60 (0.16-1.89)	0.4
Headache	1.39 (0.68-2.82)	0.4
Cold shivers	1.00 (0.37-2.56)	1.0
Fatigue	2.00 (0.98-4.14)	0.058
Diarrhea	0.93 (0.32-2.50)	0.9
Loss of smell/taste	0.14 (0.03-0.50)	0.005

An OR > 1 indicates higher odds during the Omicron period.
[a] Bold *P*-values indicate significant differences after correction for multiple testing.OR, odds ratio.

previous immunity Omicron was associated with lower odds for loss of smell or taste (OR: 0.14; 95% CI 0.03-0.50) and higher but non-significant odds for upper respiratory symptoms, fever, and fatigue (ORs varying between 1.85-2.23). No significant differences in symptoms were observed between primary vs primary plus booster-vaccinated adults during the Omicron period.

There is a general consensus that the Omicron BA.1 and BA.2 variants and its descendants cause less severe disease compared with previous variants of SARS-CoV-2 [12,13]. This notion is largely based on the lower risk of SARS-CoV-2 hospitalization and, in particular, intensive care unit admission, both in vaccinated and unvaccinated subjects, observed during the Omicron-dominant period [7]. Our results demonstrate that the average symptom burden of SARS-CoV-2 respiratory illness in the community setting has not decreased substantially and was even increased in (largely non-immune) children when compared with earlier variants. Symptoms of upper respiratory illness were more common during the Omicron period, while loss of smell and taste, a typical symptom of earlier variants, was infrequent. In adults and adolescents, there was also a nearly 50% reduction in dyspnea, but this was non-significant because of small sample size. This shift in disease symptoms for Omicron has been described by others [14] and may be explained by the altered replication and cellular tropism of the Omicron variant in different compartments of the respiratory tract compared with earlier variants [14]. Several studies have described

Table 4
Symptom burden among adults infected with SARS-CoV-2 Omicron stratified by vaccination status.

	No. (%) or median (IQR)		
	Primary series n = 18	Primary plus booster series n = 45	
			***P*-value**
Disease severity			0.5
- Symptomatic	16 (88.9%)	37 (82.2%)	
- Pauci-symptomatic	2 (11.1%)	8 (17.8%)	
- Asymptomatic	0 (0%)	0 (0%)	
			***P*-value**
Days with symptom	10 (6.5-15)	11 (6-18)	0.4
Number of symptoms	5 (4-7)	5 (4-6)	0.8
Maximum symptom severity score[a]	10 (9-12)	12 (10-15)	0.088
Cumulative symptom severity score[a]	47 (28.5-75.5)	64 (34-136)	0.24

[a] Calculated for cases with symptomatic disease.

Table 5
Adjusted OR for symptom frequency and severity in primary vs primary plus booster vaccinated subjects among Omicron-infected adults.

Symptom	OR (95% CI)	*P*-value
Hoarseness	0.56 (0.15-1.95)	0.4
Nasal congestion/ Runny nose	0.65 (0.03-5.83)	0.7
Muscle ache	1.21 (0.38-4)	0.7
Coughing	1.18 (0.27-4.58)	0.8
Fever	1.44 (0.43-5.35)	0.6
Sore throat	0.38 (0.07-1.45)	0.19
Dyspnea	0.86 (0.19-4.55)	0.8
Headache	0.62 (0.14-2.32)	0.6
Cold shivers	2.22 (0.45-14.09)	0.4
Fatigue	0.67 (0.15-2.56)	0.6
Diarrhea	1.53 (0.28-12.31)	0.6
Loss of smell/taste	5.89 (0.92-117.48)	0.12
Vomiting	∞ (0-∞)	
Duration and severity	**Absolute difference estimate (95% CI)**	***P*-value**
Days with symptom	0.11 (-0.24-0.64)	0.6
Number of symptoms	0.07 (-1.04-1.18)	0.9
Maximum symptom severity score[a]	0.16 (-0.04-0.42)	0.13
Cumulative symptom severity score[a]	25.55 (-20.78-71.87)	0.3

An OR/estimate $>$ 1 indicates higher odds/estimates for persons with booster vaccination.
[a] Calculated for cases with symptomatic disease.OR, odds ratios.

reduced replication of Omicron variants in lung parenchyma but increased replication with higher viral loads in bronchial and nasopharyngeal mucosae [15,16]. This may lead to more mucosal damage and inflammation, predominantly in the upper respiratory tract, which is then reflected in the symptom burden. The site of SARS-CoV-2 infection and replication can thus determine the kind of symptoms experienced. This is particularly evident in subjects without previous immunity, i.e., unvaccinated children $<$12 years of age in our study.

We found no difference in symptomatology between primary series vaccinated and primary plus booster series vaccinated cases during the Omicron-dominant period, but our sample size was small. A study on breakthrough infections among vaccinated healthcare workers showed that 11% of the primary series vaccinated participants were asymptomatic compared with 16% of the primary plus booster series vaccinated participants [17], suggesting a small effect of boosters on symptom burden.

The interpretation of our results has some limitations. First, it is possible that co-infections with other pathogens influence disease severity, and co-infection rates may vary over time. Based on National Virological Surveillance data from The Netherlands, most respiratory viruses circulated at lower rates during the Omicron period compared with wild-type/Alpha period [18,19]. This could, therefore, not explain the higher symptom burden in children. Second, although similar protocols were used, the samples from the cohorts were tested at different laboratories (see Supplement Table 1), this may limit comparability to some extent. Third, we based previous infection status on the results of serology testing at enrollment and on self-reported history of positive PCR or antigen tests. Availability of PCR testing was limited in the first year of the pandemic, and antibodies from previous infections may have been undetectable at the time of enrollment due to waning [20]. In our cohort, 44.6% of the adults had evidence of previous infection during the Omicron BA.1 and BA.2 period, but this is likely an underestimate. Fourth, the large majority of the adults and adolescents were vaccinated during the Omicron BA.1 and BA.2 period. This limited the extent of analyses and associations to be investigated. Last, the sample size in this study was not sufficient to detect smaller differences in symptom burden between periods and between vaccination statuses. Similarly, the low number of adolescent participants yielded insufficient power to obtain precise estimates for this age group.

Conclusion

In children, the Omicron variant causes higher symptom burden compared with the wild-type/Alpha. Adults experienced a lower symptom burden, possibly due to previous vaccination. A shift in most frequently reported symptoms occurred with a marked reduction in loss of smell or taste during the Omicron period. An additional effect of booster vaccination on symptom severity in infected adults, compared with primary series only, could not be demonstrated.

Declarations of competing interest

The authors have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.12.018.

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