

OCCURRENCE AND PATIENT CHARACTERISTICS OF COVID-19 BREAKTHROUGH INFECTIONS

18 August 2021 • Preliminary results • Legal depotnumber : D/2021/14.440/61.

Stouten V., Blot K., Haerhuis F., Serrien B., Hubin P., Vandromme M., Litzroth A., Chung J., Billuart M., Van Goethem N., Catteau L., Wyndham Thomas C

Epidemiology of infectious diseases, Sciensano

Disclaimer: This report is a rapid analysis made upon request of the Task Force Vaccination. Its objective is to give a descriptive overview of breakthrough infections occurring in Belgium. These preliminary results are to be interpreted in light of the limitations described in the text. Further analyses are still ongoing.

Key messages

1. Among 6 232 320 fully immunized persons in Belgium, breakthrough infections have been detected so-far in 0.20% (n=12 332). Median time to infection was 52 days (IQR 32-83) after receiving vaccine full dose.
2. Information on symptoms is available for over 80% of these breakthrough infections: 52.4% had COVID-19 symptoms at the time of the contact-tracing call.
3. Since the 1st of January 2021, only 2% (n=416) of all registered COVID-19 hospitalized cases were among fully immunized patients.
4. Hospitalized patients with a breakthrough infection were older (median age 82) and more frequently female (62%) when compared to unvaccinated COVID-19 hospitalized cases. The large majority had comorbidities (92%) and a substantial portion were nursing home residents (49%). Further analyses are ongoing to untangle whether these results reflect risk factors for hospitalization or rather the vaccine campaign roll-out which initially targeted the elderly and people with comorbidities.
5. Only 3 of the 416 hospitalized breakthrough cases were identified as healthcare workers.

Please cite this publication as follows:

Stouten V., Blot K., Haerhuis F., Serrien B., Hubin P., Vandromme M., Litzroth A., Chung J., Billuart M., Van Goethem N., Catteau L., Wyndham Thomas C. Occurrence and patient characteristics of COVID-19 breakthrough infections. Brussels, Belgium: Sciensano 2021. Deposit number: D/2021/14.440/61.

1. Breakthrough infections in the Belgian general population

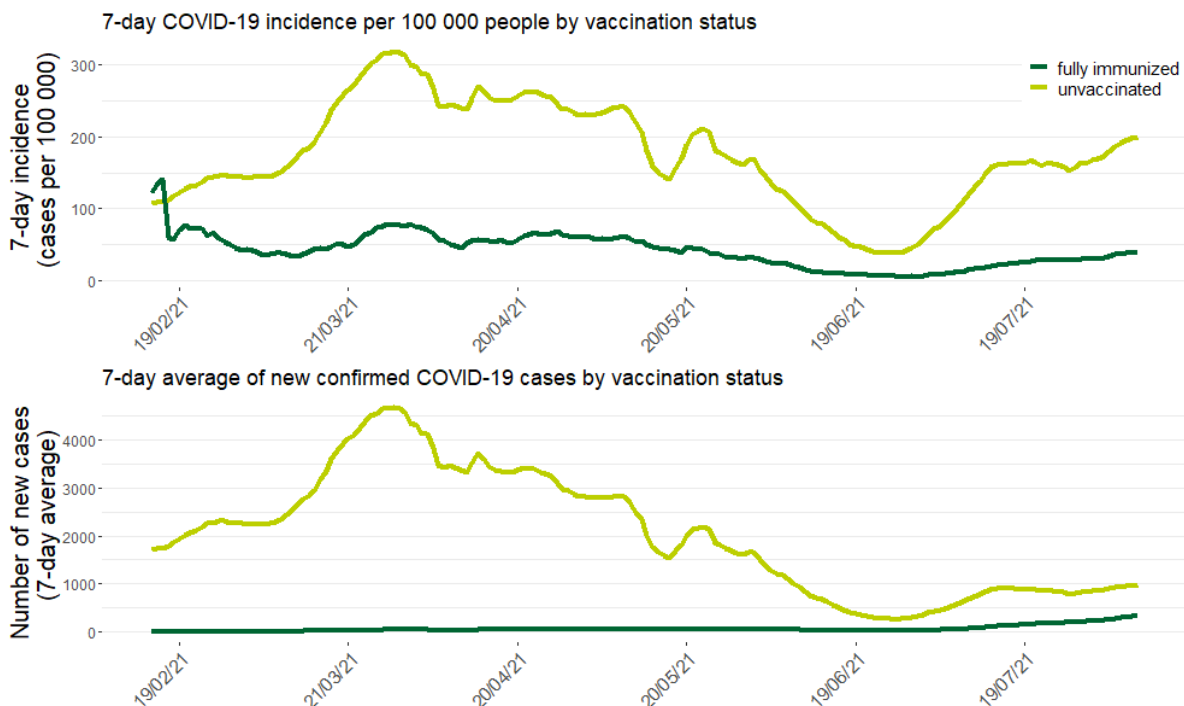
Through the [LINK-VACC project](#), Sciensano closely monitors the COVID-19 infections occurring among fully immunized persons, or breakthrough infections, by linking data from the Vaccinnet+ registry and the COVID-19 laboratory test results database. Individuals who have been fully vaccinated for at least 14 days are considered as fully immunized. A breakthrough infection is defined as a laboratory confirmed COVID-19 infection by PCR or Rapid Antigen test, occurring in fully immunized persons. Individuals who had another positive test in the 90 days prior to a breakthrough infection are excluded, as the breakthrough infection in this case is considered as a previous infection.

1.1. INCIDENCE OF BREAKTHROUGH INFECTIONS IN THE GENERAL POPULATION

By August 8, 2021, of a total of 6 232 320 fully immunized individuals in Belgium, 0.20% (12 332) have tested positive for COVID-19 during follow-up. For week 31 (August 2 to August 8), the risk of infection was reduced by 80.6% in fully immunized individuals compared to unvaccinated individuals.

Figure 1 shows the evolution of the 7-day incidence for the number of COVID-19 infections among unvaccinated individuals (light green) and among fully immunized individuals (dark green) (February 15 to August 8, 2021). On August 8 2021, the 7-day incidence rate was lower among fully immunized individuals compared to unvaccinated individuals (38.89 versus 200.46 respectively).

Figure 1 : 7-day incidence rate per 100 000 persons (top graph) and 7-day average of number of new COVID-19 infections (bottom graph), by vaccination status

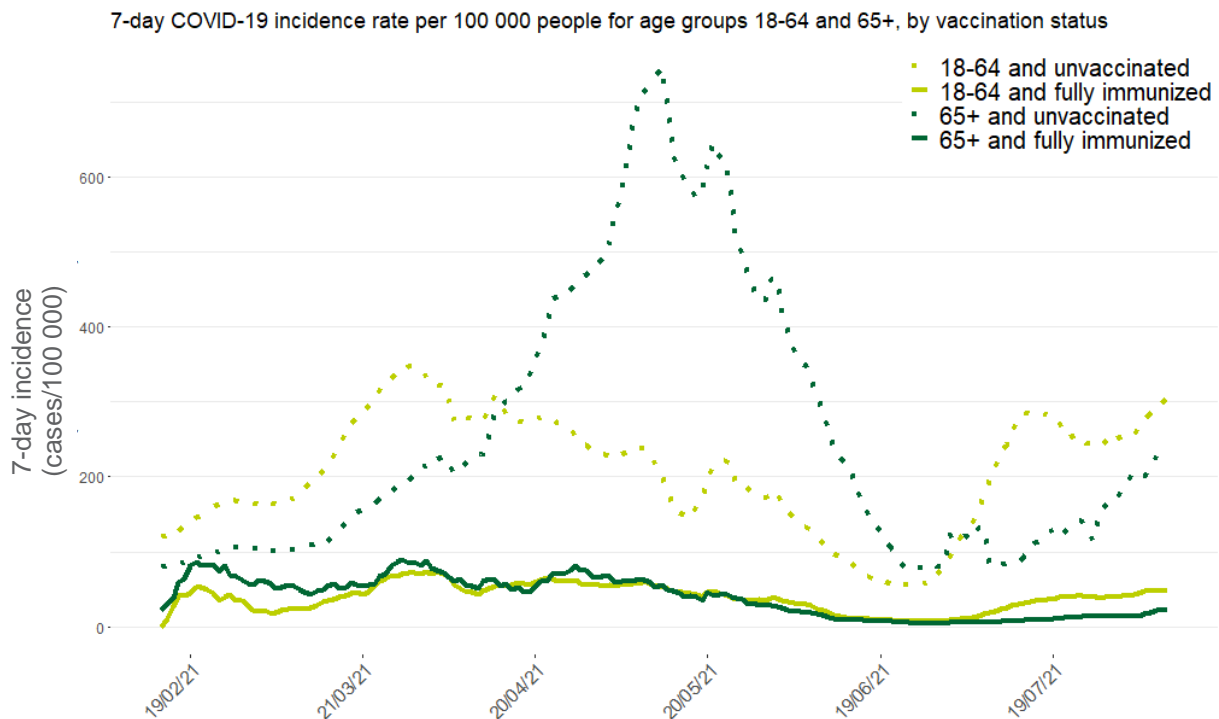


The absolute number of individuals in each of these groups (fully immunized and unvaccinated) changes over time, with the number of fully immunized individuals increasing and the number of unvaccinated individuals decreasing. This has an impact on the incidence calculation and explains the peak incidence observed at the start of the vaccination campaign in the fully immunized population.

For this reason, the evolution of the absolute number of confirmed COVID-19 cases (7-day moving average) is also shown in the bottom graph of figure 1.

Figure 2 shows the evolution of the 7-day incidence for the number of COVID-19 cases among fully immunized individuals (full lines) and among unvaccinated individuals (dotted lines) by age group for 18-64 year olds (light green) and for ≥65 year olds (dark green), from February 15, 2021. Over time, the incidence remains lower among fully immunized persons in comparison to unvaccinated persons for both age groups. Of note, on August 8, 2021, the 7-day incidence of cases was lower in ≥65 year olds than in the 18-64 year olds, both in fully immunized individuals as in unvaccinated individuals.

Figure 2: 7-day COVID-19 incidence rate per 100 000 people for age groups 18-64 and 65+, by vaccination status



1.2. CHARACTERISTICS OF BREAKTHROUGH INFECTIONS IN THE GENERAL POPULATION

As shown in point 1.1, the incidence of breakthrough cases is low. Demographic and clinical characteristics of these cases were analyzed and are summarized in Table 1 below.

Individuals with a breakthrough infection had a mean age of 53 (± 22) years. The median time to infection after final vaccine dose was 52 days (IQR 32-83). Individuals with a breakthrough infection were often female (61.7%) and the majority had been vaccinated with Pfizer-BioNTech (Comirnaty®) (71.2%). This most probably reflects the roll-out of the vaccination campaign, as Pfizer-BioNTech (Comirnaty®) is the most frequently used vaccine and women are overrepresented in the priority groups targeted within the earlier stages of the vaccination campaign (elderly and healthcare workers). Therefore, it is to be expected to see more breakthrough infections among these populations with a longer risk of exposure. Results should thus be interpreted with caution, and such factors should be considered as potential confounders.

Table 1: Demographic and clinical characteristics of individuals with a breakthrough infection as of August 8, 2021 (n=12 332)

Demographic and clinical characteristics	Number of individuals (%)
Gender	
Male	4720 (38.3)
Female	7612 (61.7)
Age (years)	
Mean (SD)	52.76 (22.18)
Median (IQR)	50 (35-70)
Age categories (years)	
00-17	41 (0.3)
18-34	3008 (24.4)
35-44	1733 (14.1)
45-54	2278 (18.5)
55-64	1585 (12.9)
65-74	1043 (8.5)
75-84	1154 (9.4)
>85	1490 (12.1)
Brand of vaccine received	
Pfizer-BioNTech (Comirnaty®)	8777 (71.2)
Moderna (Spikevax®)	670 (5.4)
Astra-Zeneca (Vaxzevria®)	1435 (11.6)
Johnson & Johnson (Janssen®)	1438 (11.7)
Prior SARS-CoV-2 infection [#]	1250 (10.1)
Time since final vaccine dose (days)*	
Median (IQR)	52 (32-83)
Mean (SD)	63.54 (41.52)

[#] Prior SARS-CoV-2 infection= as based on PCR and Rapid Antigen test as recorded in the COVID-19 Laboratory test result database. Serology and auto-tests are not considered.

*Time since final vaccine dose= time between administration of final dose of a complete vaccination scheme and occurrence of a breakthrough infection

Importantly, the breakthrough infections described in Table 1 comprise all COVID-19 laboratory confirmed infections, and therefore include asymptomatic cases. Presence of symptoms was assessed using the results of a predefined questionnaire, including the most common symptoms of COVID-19, which is administered by the contact tracing call center at the time of positive test identification. Of the 12 332 persons with a breakthrough infection, 10 186 (82.6%) had available information on symptoms. Of these persons 52.4% (5 341 / 10 186) had symptoms compatible with COVID-19 at the time of the call. Whether the demographic characteristics of the asymptomatic and symptomatic breakthrough cases differ will be further investigated. However, the surveillance system does not allow us to know whether cases that were asymptomatic at the time of the call will develop symptoms later on. Similarly the outcome of each breakthrough infection in terms of severity is not known (hospitalization or death). However, the COVID-19 Clinical Hospital Surveillance provides additional information on a subset of cases.

2. Hospitalized COVID-19 patients with breakthrough infections

Clinical information on hospitalized COVID-19 patients is collected in the COVID-19 Clinical Hospital Surveillance ([see COVID-19 surveillance frequently asked questions, section 5](#)). This surveillance does not cover all, but rather approximately 2/3rds of all hospitalized COVID-19 patients in Belgium. It also collects these data with a delay of approximately 1 week (patient demographics) and 2-3 weeks (clinical outcomes) after a patient's date of hospital admission. Linking with Vaccinnet+ data allows us to identify the vaccination status of the hospitalized cases.

From January 1 to August 8, 2021 there have been 19 723 hospitalized patients registered. Of these, 2.1% (416/19 723) were fully immunized (≥ 14 days after completing vaccination schedule). Patients with partial immunization (≥ 14 days after dose 1 and < 14 days after dose 2) accounted for 6.4% of hospitalizations (1 267/19 723).

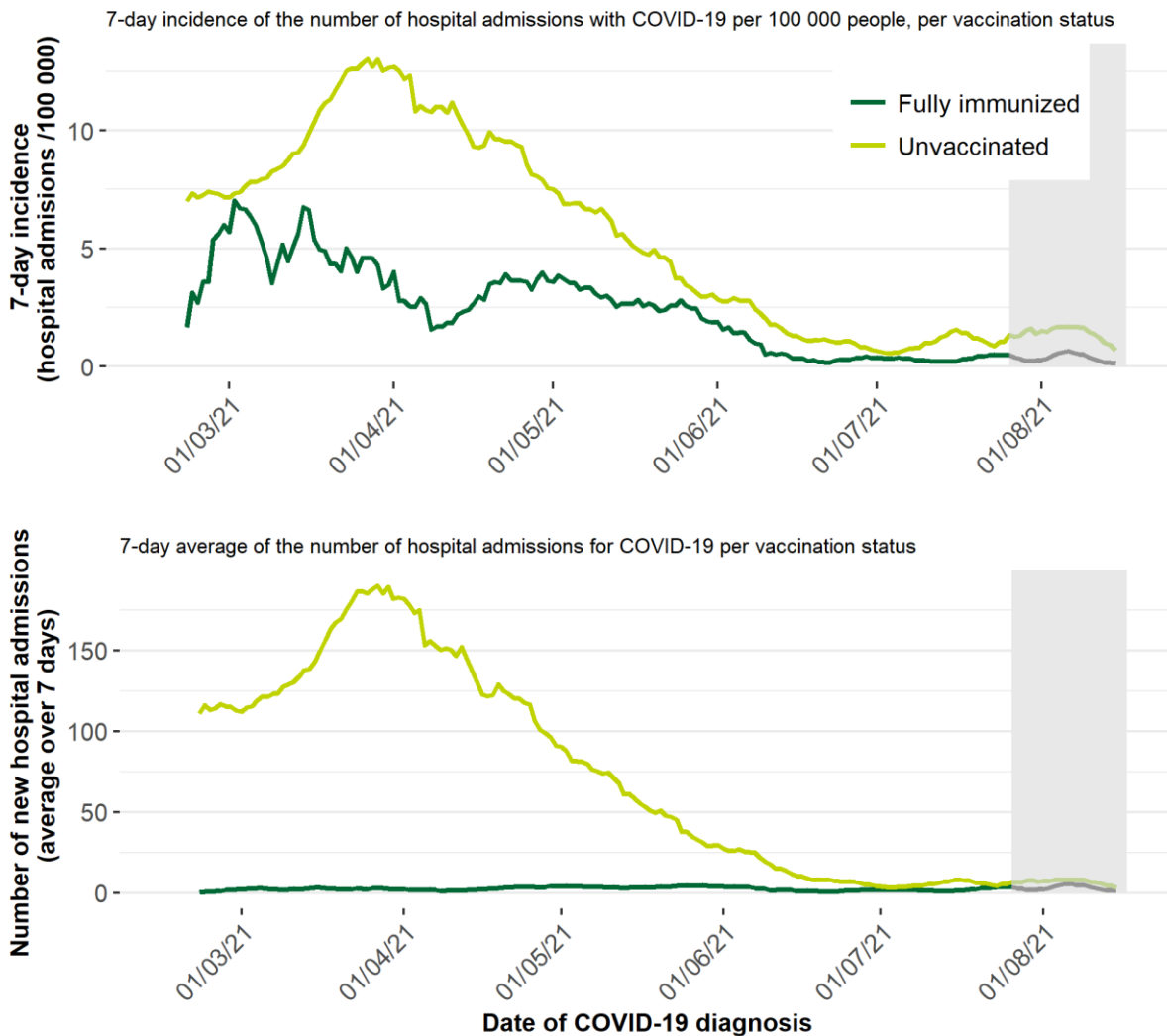
Table 2 provides an overview of the number of registered hospitalized patients according to the timing of their vaccination and the date of diagnosis of the COVID-19 infection. Since the Johnson & Johnson (J&J) vaccine brand requires only one dose, the first dose is considered to be a full dose.

Table 2. Number of hospitalized patients, sorted by date of infection diagnosis, vaccination status and vaccine brand

	Total	Pfizer	Moderna	Astra-Zeneca	J&J
Not vaccinated	16 866	-	-	-	-
Infection diagnosed <14 days after first dose	1 174	767	98	309	-
Infection diagnosed ≥ 14 days after first dose and before full dose	1 089	549	49	491	-
Infection diagnosed <14 days after full dose	178	136	20	10	12
Infection detected ≥ 14 days after full dose (= breakthrough infections)	416	370	19	14	13

Figure 2 shows the number of hospitalizations over time according to vaccination status (unvaccinated versus fully immunized). As the absolute number of fully immunized people increases over time, the incidence rate per 100 000 people was calculated per vaccination status (eg. number of hospitalized fully immunized patients per 100 000 fully immunized people). Although there are currently low absolute numbers of hospitalizations, when looking at the incidence rate per 100 000 people, there is an upwards trend of increasing hospitalizations among unvaccinated people.

Figure 2. 7-day average daily COVID-19 hospitalizations, per vaccination status, expressed as an incidence rate per 100 000 people (top graph) and as absolute numbers (bottom graph)



The grey zone identifies a time period where data is not fully consolidated and could therefore still change.

Table 3 presents the patient demographic and clinical characteristics of fully immunized compared to unvaccinated hospitalized patients. No distinction between vaccine brands was made for this analysis because the majority consisted of Pfizer-BioNtech (Comirnaty®). Please note that these descriptions are univariate analyses and thereby highly confounded (read limitations hereunder).

When considering demographics of all 416 breakthrough cases, we note that breakthrough infections, in comparison to unvaccinated hospitalized patients, were more often represented by nursing home residents (49.0% versus 3.8%), females (61.3% versus 47.1%), and older patients (median 82 years versus 64 years). There was a higher preponderance of patients with underlying comorbidities among the breakthrough cases (92.5%) compared to unvaccinated hospitalized patients (75.2%). This could be a reflection of the more elderly patient population that represents the breakthrough cases and of the vaccination roll-out targeting persons with comorbidities.

Although healthcare workers were targeted early in the vaccination campaign (and therefore had a longer and higher risk of post-vaccination exposure to COVID-19, especially during the third wave), there were up until now only three healthcare workers registered as hospitalized breakthrough cases.

Table 3. Demographic and clinical characteristics of fully immunized compared to unvaccinated hospitalized patients (January 1, 2021 – August 8, 2021)

Demographic and clinical characteristics	Number of hospitalized patients (%)		P-value
	Unvaccinated (n=16866)	Fully immunized (n=416)	
Gender			<0.001
Male	8906 (52.8)	161 (38.7)	
Female	7948 (47.1)	255 (61.3)	
Age (years)			
Mean (SD)	62 (20)	79 (14)	<0.001
Median (IQR)	64 (55-77)	82 (72-88)	<0.001
Age categories (years)			<0.001
00-17	383 (2.3)	0 (0)	
18-34	1249 (7.4)	4 (1.0)	
35-44	1428 (8.5)	8 (1.9)	
45-54	2499 (14.8)	22 (5.3)	
55-64	3093 (18.3)	29 (7.0)	
65-74	3190 (18.9)	61 (14.7)	
75-84	2901 (17.2)	120 (28.8)	
>85	2114 (12.5)	172 (41.3)	
Healthcare worker	139 (0.8)	3 (0.7)	0.99
Nursing home resident	647 (3.8)	204 (49.0)	<0.001
No underlying comorbidities	4134 (24.5)	31 (7.5)	<0.001
Reason for testing			<0.001
COVID-19 symptoms	11843 (70.2)	184 (44.2)	
Systematic screening	3553 (21.1)	209 (50.2)	
Other/unknown	1470 (8.7)	23 (5.5)	
Time since final vaccine dose (days)*			
Median (IQR)		52 (29 – 85)	
Mean (SD)		60 (37)	

* Time since final vaccine dose= time between administration of final dose of a complete vaccination scheme and occurrence of a breakthrough infection (date of infection diagnosis through PCR or rapid antigen test)

The COVID-19 Hospital Clinical Surveillance collects data from hospitalized patients with a COVID-19 infection, independent of whether COVID-19 was the reason for admission or not. It is therefore important to note that a large part of these hospitalized breakthrough cases were identified by systematic screening (50.2%, 209/416), and not because these patients had recognized symptoms compatible with a COVID-19 infection upon admission (44.2%, 184/416). Some patients were tested for other or unknown reasons (5.5%, 23/416). Among the breakthrough cases identified through systematic screening, 70.8% (148/209) were asymptomatic at the moment of hospital admission.

Nonetheless, patients identified through systematic screening may still develop severe symptoms and complications during hospitalization. The demographic profile (age, gender, comorbidities) of the 184 breakthrough cases hospitalized with COVID-19 symptoms was relatively similar to breakthrough cases identified through systematic screening. One exception was that nursing home patients represented the majority of COVID-19 patients identified through systematic screening (56.0%, 117/209) compared to patients tested because of COVID-19 symptoms (40.8%, 75/184).

Of the 416 breakthrough infections, 319 also had a completed discharge form, which allows us to analyze their clinical outcomes. Table 4 describes the clinical outcomes of fully immunized and unvaccinated hospitalized patients. Among the fully immunized patients, 7.5% were transferred to the intensive care unit (ICU) and 17.2% did not survive (all-cause death). Unvaccinated people were more often transferred to ICU (18.8%), however proportionally less patients died (14.0%). The proportion of people whose cause of death was attributed to COVID-19 was similar between the two groups. However, these numbers cannot be taken at face value because the two groups are not comparable. Patients with breakthrough infections were of older age, with more comorbidities and more often nursing home residents, which increases their risk of death. Additionally, nursing home residents are less likely to be transferred to intensive care.

Table 4. Clinical outcomes of fully immunized hospitalized patients compared to unvaccinated hospitalized patients (January 1, 2021 – August 8, 2021)

Clinical outcomes	Number of hospitalized patients (%)		
	Unvaccinated (n=15084)	Fully immunized (n=319)	P-value
ARDS	1620 (10.7)	9 (2.8)	<0.001
ICU admission	2829 (18.8)	24 (7.5)	<0.001
Death (all-cause)	2118 (14.0)	55 (17.2)	0.1
Death (due to COVID-19)	1597 (10.6)	34 (10.7)	0.99

Discharge forms with information on clinical outcomes were only available for 319 of the 419 breakthrough cases. ARDS: acute respiratory distress syndrome; ICU: intensive care unit.

3. Limitations and next steps analyses

These basic descriptive analyses cannot take into account the impact of several other factors, such as the impact of circulating variants, the changing epidemic over time which impacted age categories differently, the progress of the vaccination campaign targeting specific groups with specific vaccines, and the duration of risk of exposure post-vaccination. Moreover, the extent to which potential waning immunity over time after vaccination plays a role in the risk of a breakthrough infection or hospitalization is not currently known. As Pfizer-BioNTech is the most frequently administered vaccine in Belgium, this brand will often be represented among the breakthrough cases. Similarly, people that were fully vaccinated during a time period preceding a surge in cases, such as the third epidemic wave, could be more represented among breakthrough cases due to a higher exposure risk. In Belgium, those who were fully vaccinated prior to the third wave were nursing home staff and residents as well as

first-line healthcare workers from hospital settings. In both these populations, women are overrepresented. These factors combined can determine which patients can develop breakthrough infections and become hospitalized, which can confound the results of these basic statistics.

In order to take into account several of these potential influencing factors (although not all can be corrected for), further statistical analyses are planned to be undertaken. This would include description of the breakthrough infections in the general population and of the fully immunized cohort of hospitalized COVID-19 patients registered in the Clinical Hospital Surveillance. Through multivariable analysis the risk of a breakthrough infection or of developing severe COVID-19 (defined as acute respiratory distress syndrome, ICU admission or in-hospital death) can be determined according to demographic profiles and time between full immunization and infection. This will allow us to further investigate and understand potential determinants of breakthrough infections among the general population and among hospitalized COVID-19 patients.