

Genomic surveillance of SARS-CoV-2 in Belgium

Report of the National Reference Laboratory (UZ Leuven & KU Leuven)

**Situation update – 14 of December 2021
(report 2021_59)**

Executive summary

69,879 Belgian sequences of SARS-CoV-2 are now publicly available on GISAID; compared to last week's report, 1,600 sequences have been added.

1,201 sequences of positive SARS-CoV-2 samples collected between 29/11/2021 and 12/12/2021 have at this stage been analyzed in the context of baseline surveillance. Among these, B.1.1.529 (*Omicron*) represented 3.2% of the circulating strains. We estimate that during the week of 29/11/2021, *Omicron* (B.1.1.529) represented 3% of the circulating strains. This represents a 10x increase compared to the previous week. In addition to the baseline genomic surveillance, the evolution of the *Omicron* variant is followed-up on a daily basis through the percentage of diagnostic PCRs harboring the S gene target failure (rate estimated at 3% for the last 48 hours) and a complementary active investigation of local transmission clusters. During week 49, 85% of the samples presenting SGTF were further confirmed as *Omicron*. We estimate between 1,300 and 2,000 the number of *Omicron* infections in Belgium since the first infection was documented.

During the last week, a number of community clusters were highlighted, signaling that local transmission has probably become the main source of *Omicron* infections today in Belgium. We expect the total number of infections to rise importantly from January 2022.

Considering the very high level of infections foreseen during the coming weeks, we recommend:

- To accelerate the booster vaccination rollout. This will importantly contribute to decreasing the number of patients requiring hospital care.
- To reinforce infection-reduction measures as soon as possible, including with regard to masks and ventilation. Distribution of FFP2 masks is recommended.
- To consider an emergency distribution of novel effective antiviral therapies
- To prepare first line services (GPs, testing, tracing and distribution of self tests) to a very high level of activity starting in January. This preparation should include prioritization strategies as maximal capacities will very probably be reached.
- To develop adapted strategies to contain the spread of infections during the multiple social & familial small scale events associated with this season of the year.
- To prepare hospitals for a high level of activity starting end of January

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Previous reports can be downloaded using the following link:

<https://www.uzleuven.be/nl/laboratoriumgeneeskunde/genomic-surveillance-sars-cov-2-belgium>

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1. Monitoring of VOCs in Belgium

While first identified on 6 April 2021 in Belgium, the B.1.617.2 Variant of Concern (Delta) remains the dominant lineage in the country, representing 96.8% of the baseline surveillance samples sequenced (see Figure 1). Seven Omicron infections were reported through the baseline surveillance system during the week of November 29, representing 0.7% of all sequences reported during that week. For last week, 32 Omicron infections were reported, representing 13.4% of all sequences reported so far. However, these numbers are not final and can be biased due to prioritization of sequencing samples with SGTF (S gene target failure or S gene dropout).

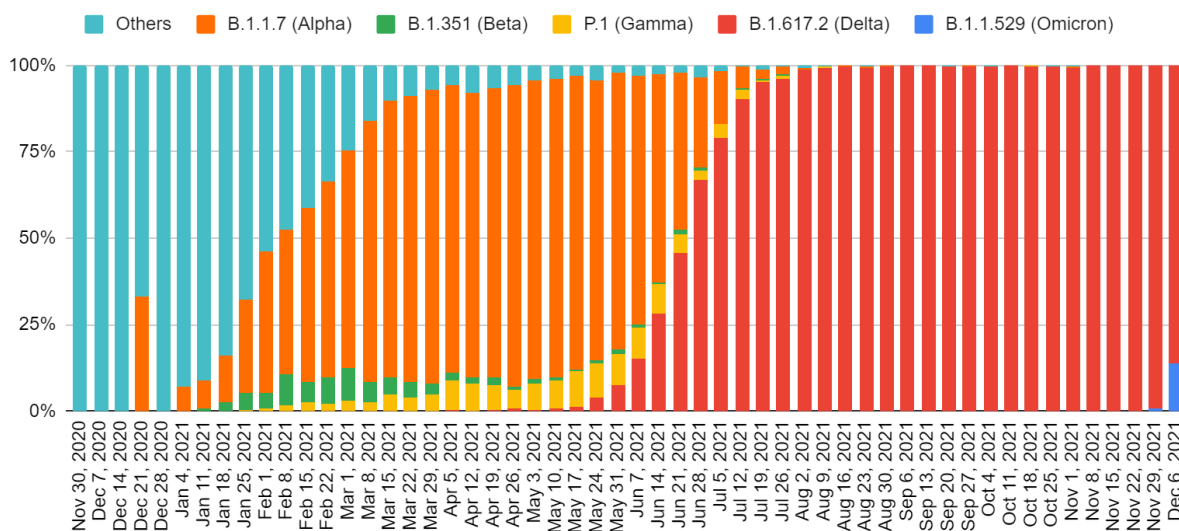


Figure 1: Weekly evolution of the frequency of variants of concern reported by the baseline surveillance network using a whole genome sequencing (WGS) approach.

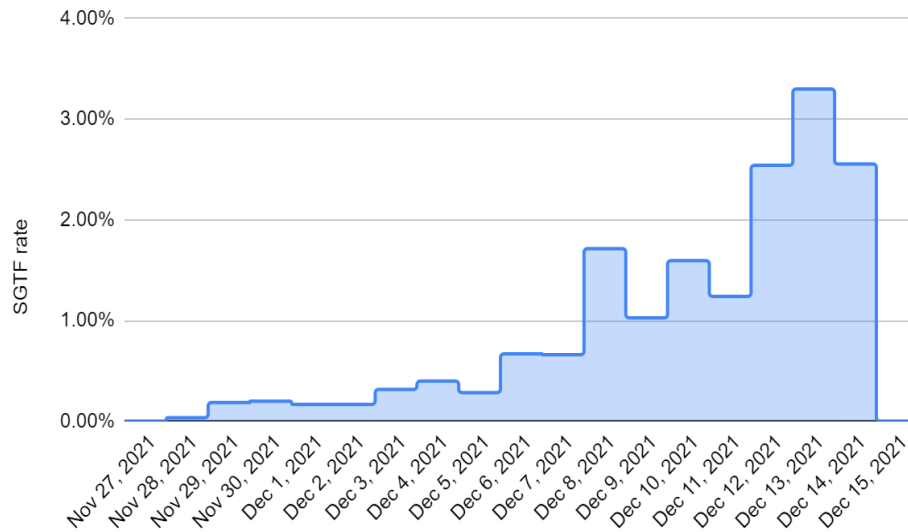


Figure 2: SGTF (S dropout with Cq <25) rate over the past 11 days in Belgium (data from the eight Federal Platform laboratories). Data for the last 2 days are preliminary and may still evolve as all data may not yet be uploaded.

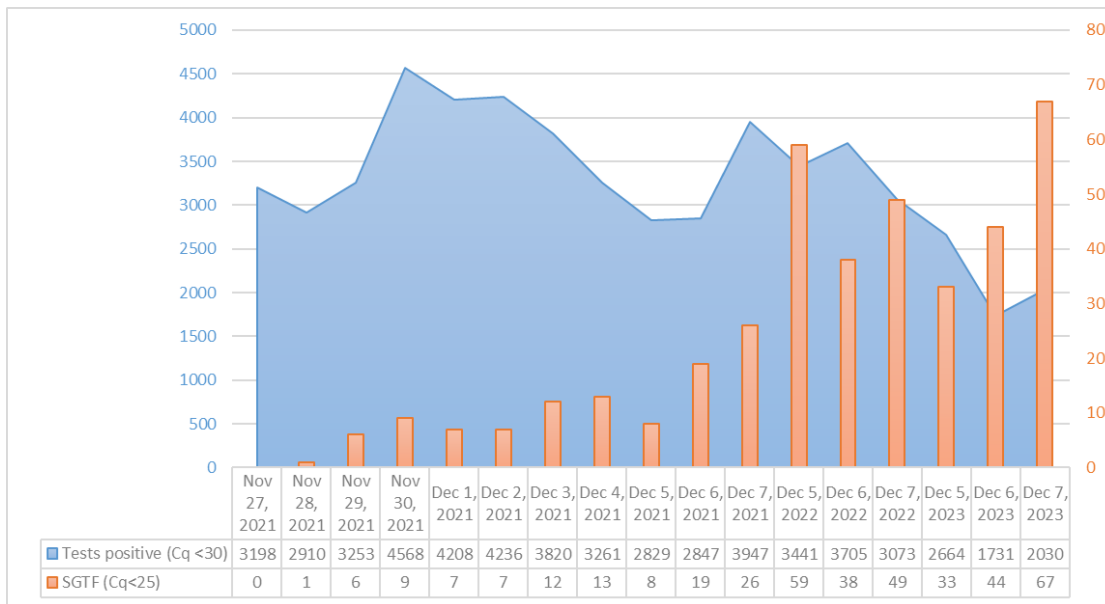


Figure 3: Evolution of the number of positive PCR results and positive samples (Cq <25) harboring SGTF in the Federal Platform laboratories. While the total number of positive samples (mainly Delta) tends to decrease, we observe an underlying and increasing trend with regard to SGTF samples.

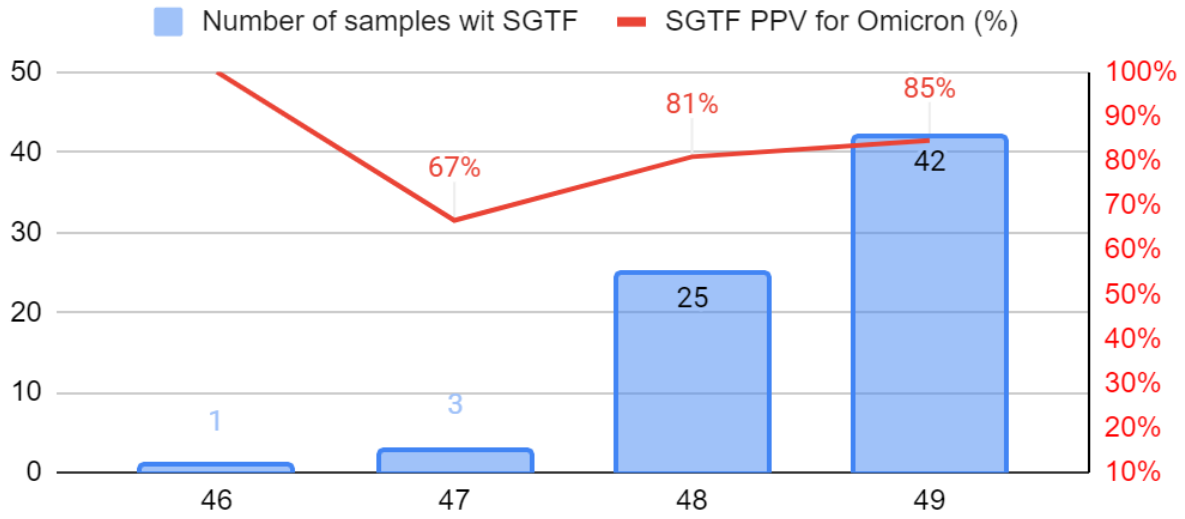


Figure 4: Weekly evolution of the percentage of samples harboring SGTF which are confirmed as Omicron by sequencing. Data from the UZ Leuven/ KU Leuven diagnostic laboratories, per epidemiological week.

2. Current status with regard to Omicron in the world

As of 14 December 2021 - 14.15 UTC, 54 countries shared 4,295 Omicron genome sequences.

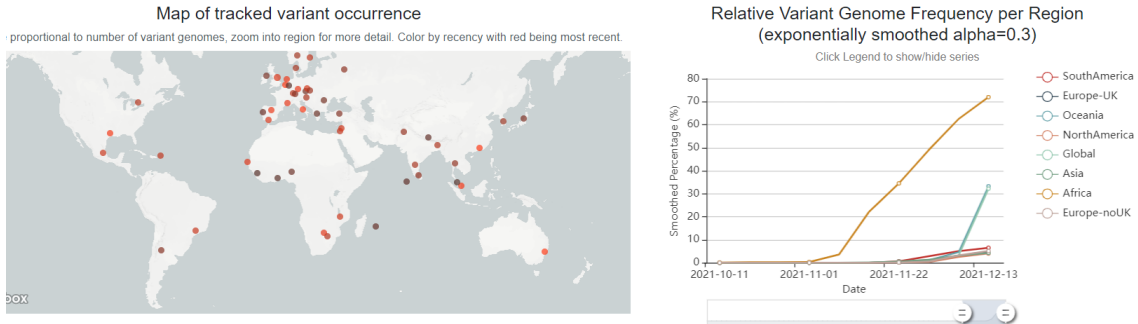


Figure 5: Countries reporting confirmed B.1.1.529 cases. Many countries, particularly in the African continent where genomic surveillance capacity is limited, probably currently under-report the real number of infections (source: GISAID)

The pace of viral population replacement is consistently faster for Omicron than what has been observed with previous variants of concern. This has been observed in South Africa, but is also observed in the United Kingdom and in Denmark. Compared to the latter two countries, the situation in Belgium is evolving with 1-2 weeks of delay, but the situation is expected to accelerate importantly during the next days and weeks.

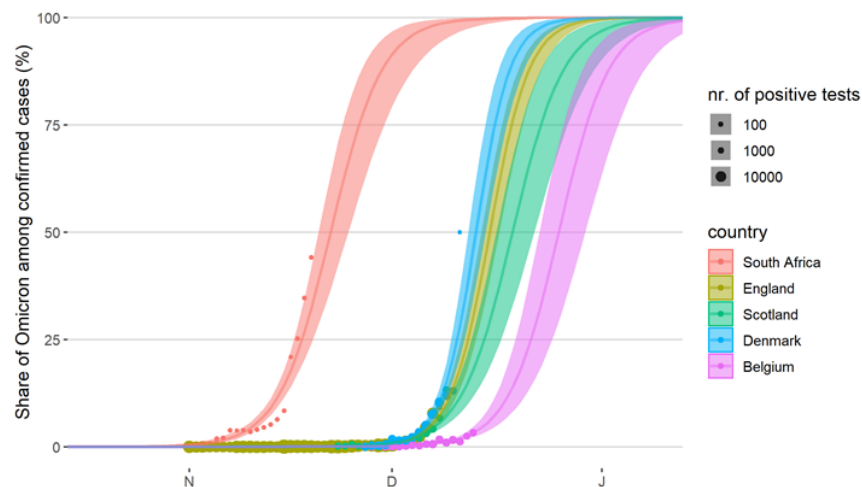


Figure 6: Logistic regression model shows the rapid rise in the share of Omicron infections among newly diagnosed infections inferred from variant-specific PCR data (for Denmark) or S dropout (SGTF) PCR test data (other countries shown). The model used allows for overdispersion via the inclusion of an observation-level random effect.

The reports on severity of Omicron-related disease are still heavily interfered by the age distribution of the cases reported. Therefore, both the inter-wave comparisons in South Africa and the over-interpretation to western European countries need to be interpreted with caution.

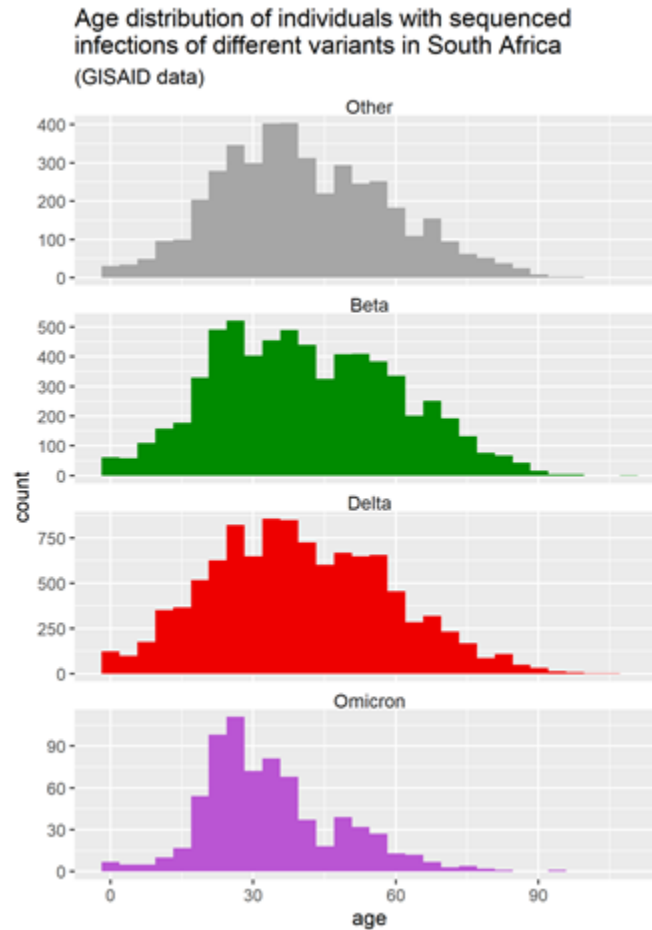


Figure 7 : Sequenced Omicron cases of South-Africa in GISAID are still very heavily skewed towards young age cohorts, compared to the sequenced cases in previous waves.

The evolution of the hospitalization rate in South Africa also needs to be closely followed-up in the coming days and weeks. Early communications indicate that the country observed a lower proportion of infected patients that require hospitalization 1 week after infection compared to the previous waves. This positive signal should nevertheless be considered in the context of an early wave of infections (peak not reached) which mainly impacted lower age groups.

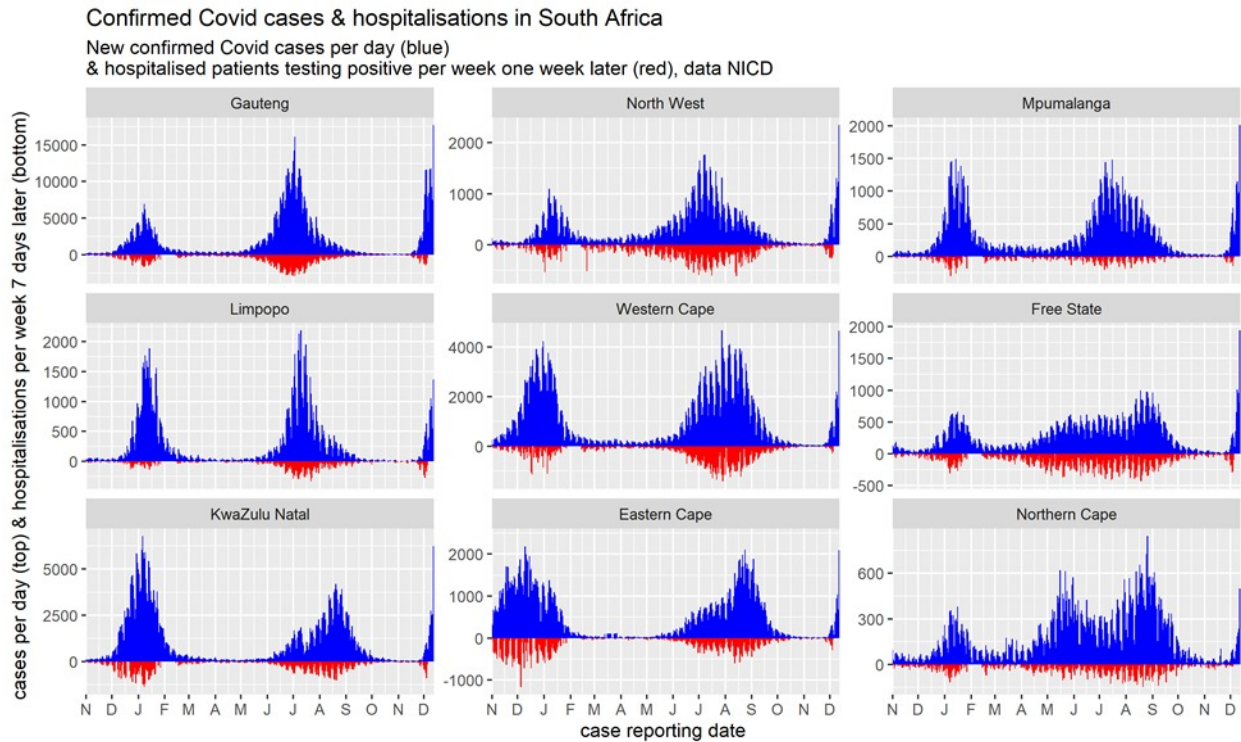


Figure 8: Confirmed cases (blue) and hospitalizations one week later (red) in South African provinces.

3. Current status with regard to Omicron in Belgium

Currently, the National Reference Laboratory has sequenced or been informed of 104 confirmed Omicron cases confirmed by sequencing in Belgium. The actual number is probably higher, as several probable Omicron infections are currently being confirmed and several clusters of local transmission could not be fully circumscribed. Of note, the baseline surveillance accuracy may currently be impacted by the very high number of Delta infections reported (lower proportion of samples sequenced) and by the interference of active case finding strategies focusing on Omicron/BA.1 (harboring SGTF) outbreaks. At this stage, no BA.2 infections have been documented through baseline surveillance.

Using the available Omicron genomic sequences on GISAID on Tuesday December 14th, we performed a detailed phylogenetic analysis to investigate how these Belgian cases are linked. This analysis currently - **based on available data and subject to change if more data become available** - reveals the presence of several Belgian transmission clusters (Figure 9), some of which we discuss and illustrate below.

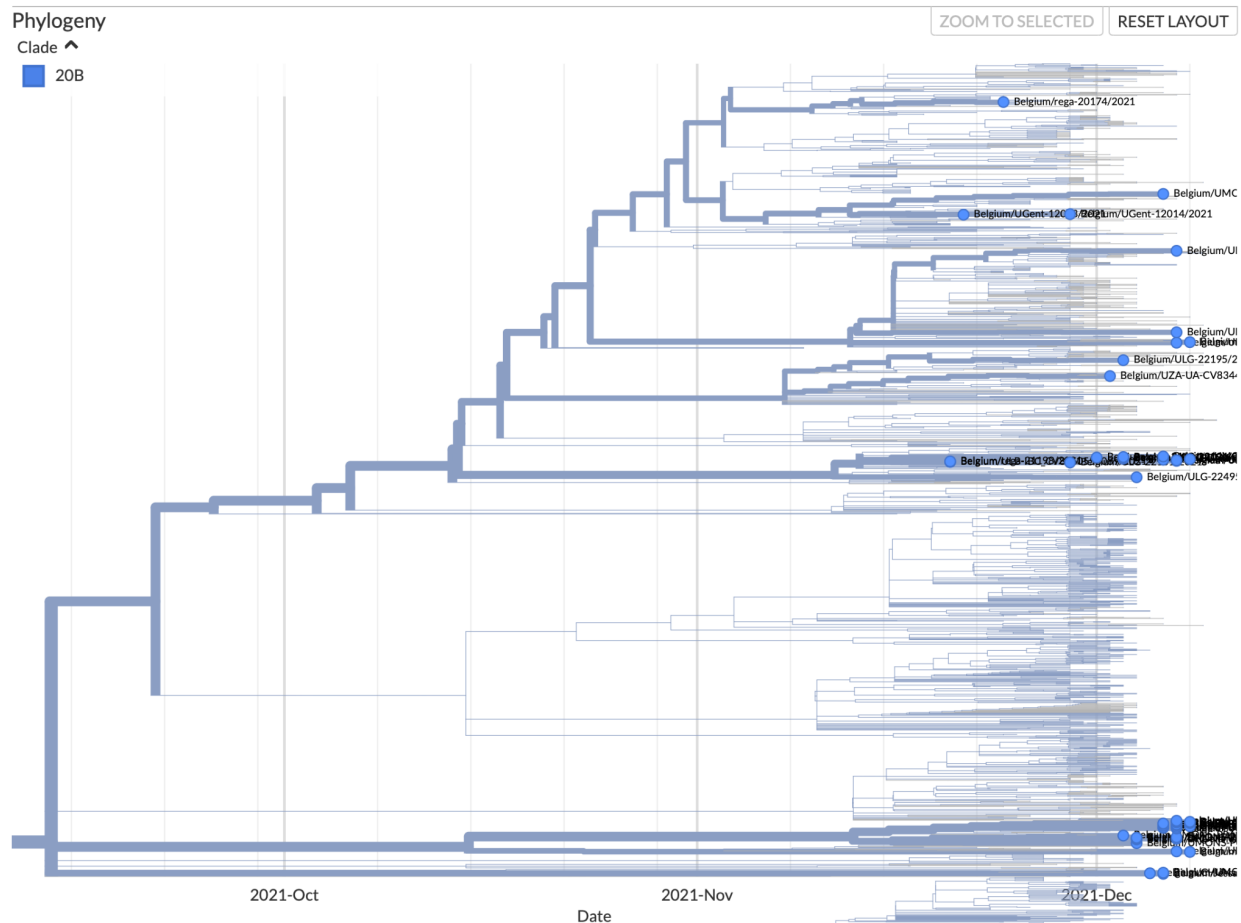


Figure 9. Visualization of the relationship between all current Belgian Omicron infections, showing an increasing number of distinct local transmission clusters, along with single introduction events.

Reports in the press recently linked two Omicron infections in the municipalities of Melle and Merelbeke to a chain of events and infections linked to an international water polo competition in Brno, in the Czech Republic. Whereas one infected Belgian participant is assumed (genomic data are not available from either two suspected Omicron-infected Belgian athletes) to have generated several secondary infections in the Brussels and Liège regions, the second infected participant could have (based on epidemiological data) generated secondary infections in Melle and Merelbeke. Genomic data however consider these infections to be part of two distinct transmission chains (Figure 7). This points to two possible scenarios: the Belgian athletes were infected with two different Omicron strains (i.e. they were not infected by the same person and did not infect one another), or the infections in Melle and Merelbeke cannot be traced back at all to the international water polo event in the Czech Republic.

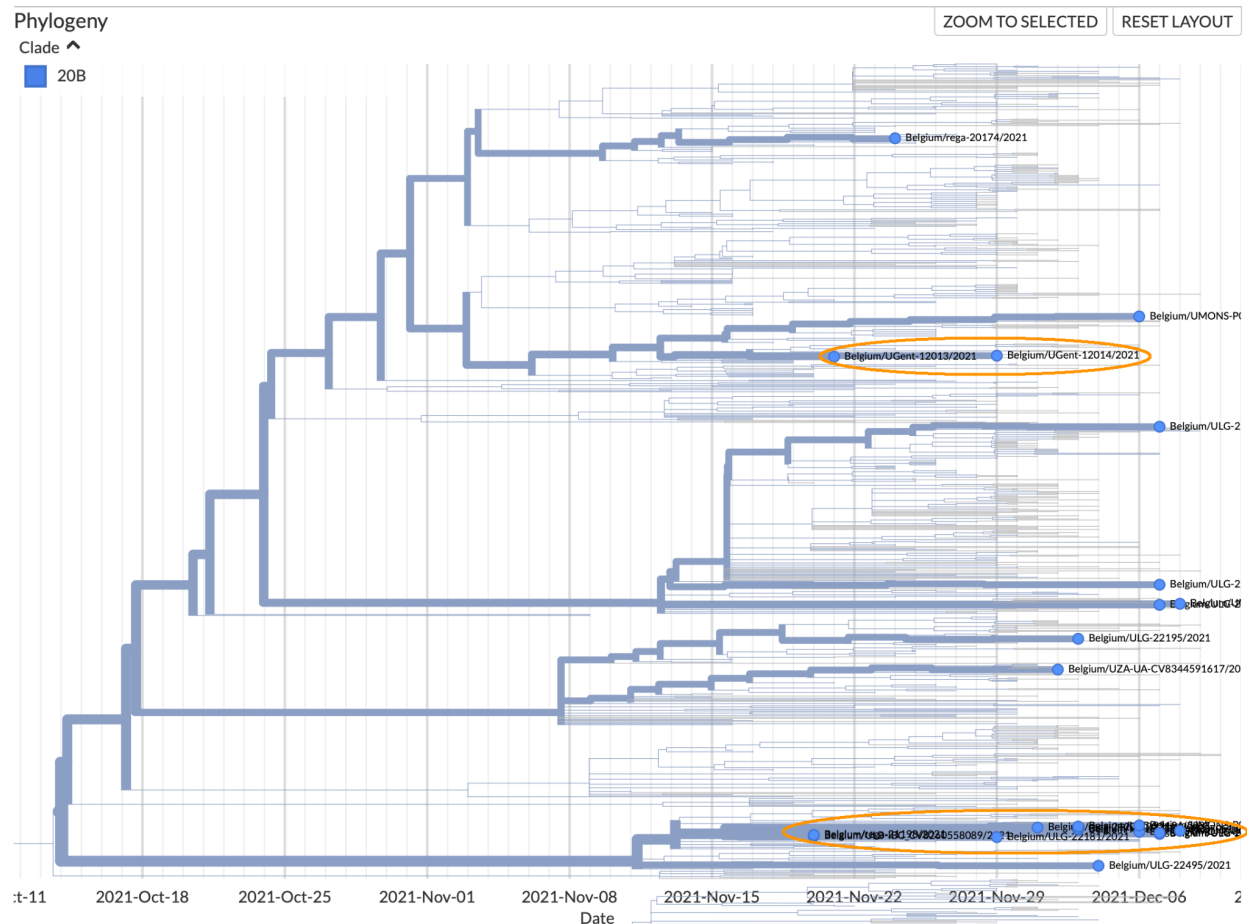


Figure 7. Based on genomic data analysis, the Omicron infections from Melle and Merelbeke (East Flanders; top orange selection) can at the moment not be linked to other transmission chains within Belgium. Notably, a link of those infections with a larger transmission cluster that involves infections in Brussels and Liège (bottom orange cluster) - as suggested in the press - cannot be confirmed.

4. Update on immune evasion of Omicron

Among the increasing number of publications, we show three early studies reporting the results of neutralization tests on Omicron. These studies show an important *in vitro* decrease in the neutralization activity of antibodies, which can be partly overcome by a booster dose and/or a natural infection. The results of these studies should be confronted with real-life data from South-Africa (public communication, not supported at this stage by peer-reviewed scientific publications) which reveal a residual (but importantly decreased compared to Delta) vaccine efficacy of 2-dosis regimens against severe forms of Omicron infection (<https://twitter.com/miamalan/status/1470684351151157252?s=20>).

Of note, a fourth recent study explored the anti-SARS-CoV-2 CD8+ T-cell response and suggests that this complementary immune response maintains its previous level of efficacy against Omicron.

4.1. The study of Cele et al.

(<https://www.ahri.org/wp-content/uploads/2021/12/MEDRXIV-2021-267417v1-Sigal.pdf>) indicates a 41-fold decline of the ability of plasma from BNT162b2 (Pfizer vaccine) vaccinated study participants to neutralize Omicron compared to ancestral D614G virus (corresponding to variants invading Europe in spring 2020). However, they did not perform a comparison with other variants of concern (VOCs). In their study, they also illustrated that sera from vaccinated people (BNT162b2, 2 doses) who also developed an infection were associated with a notably higher level of neutralization for Omicron.

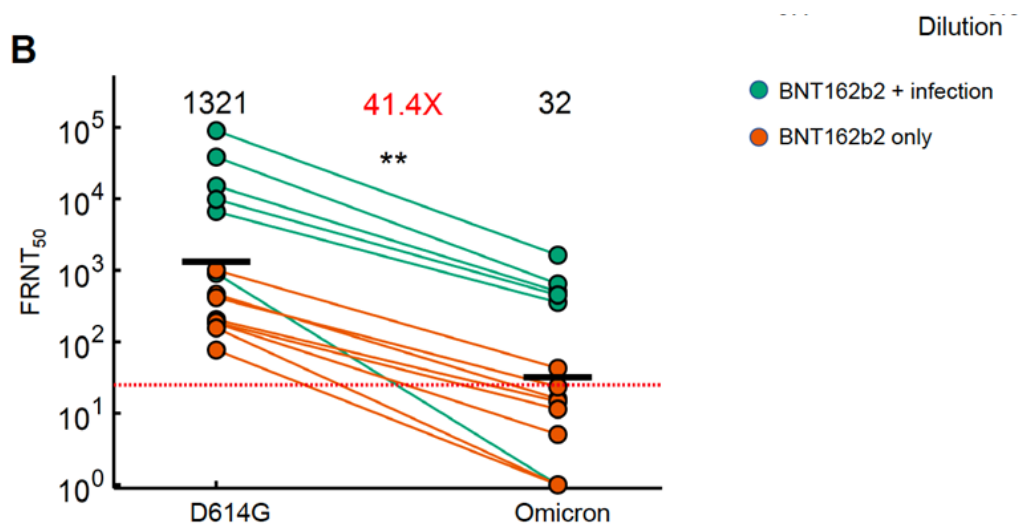


Figure 1: ACE2 dependence and partial neutralization of the Omicron variant by Pfizer BNT162b2 elicited immunity (A) Titration of live SARS-CoV-2 Omicron on H1299 parental cells and H1299-ACE2 cells. Plot shows result of titration on H1299-ACE2 cells. (B) Neutralization of the Omicron virus compared to D614G ancestral virus participants vaccinated with BNT162b2 and infected by ancestral SARS-CoV-2 (green) or vaccinated only. 14 samples from 12 participants were tested. Red horizontal line denotes most concentrated plasma tested. Numbers in black above each virus strain are geometric mean titers (GMT) of the reciprocal plasma dilution (FRNT₅₀) causing 50% reduction in the number of infection foci. Number in red denote fold-change in GMT between virus strain on the left and the virus strain on the right of each panel. $p=0.0018$ as determined by the Wilcoxon rank sum test.

4.2. The study of Wilhem et al. (<https://www.medrxiv.org/content/10.1101/2021.12.07.21267432v1>)

Compared to Delta, neutralization performed with sera from double (no-booster, sampled 6 months after last shot) or triple BNT162b2-vaccinated (sampled 0.5 or 3 months after boosting) revealed an 11.4-, 37.0- and 24.5-fold reduction for Omicron in SN titers. In the presence of high viral dose incubated with serum (4000 TCID₅₀), the percentage of serum that did not neutralize Omicron strains was 100% (no booster), 42% (booster sampled after 0.5 months) and 75% (booster sampled after 3 months) (Figure A, see below).

Sera from double mRNA1273-vaccinated (no-booster, sampled 6 months after last shot) and additionally BNT162b2-booster (sampled 0.5 month after booster vaccination) showed a 20- and 22.7-fold reduction in the neutralization capacity (Figure B). In the presence of a high viral dose incubated with serum (4000 TCID₅₀), the percentage of serum that did not neutralize Omicron strain was 100% (no booster) and 24% (booster sampled after 0.5 months).

Poor neutralization against Delta and no efficacy against Omicron were observed using sera from heterologous ChAdOx1 and BNT162b2 vaccinated individuals sampled 6 months after last shot (Figure C). Additionally, the BNT162b2- booster group showed an increase in neutralization capacity (38% of the samples neutralized omicron) but a 27.1-fold reduction in neutralization titres was observed against Omicron compared with Delta (Figure C).

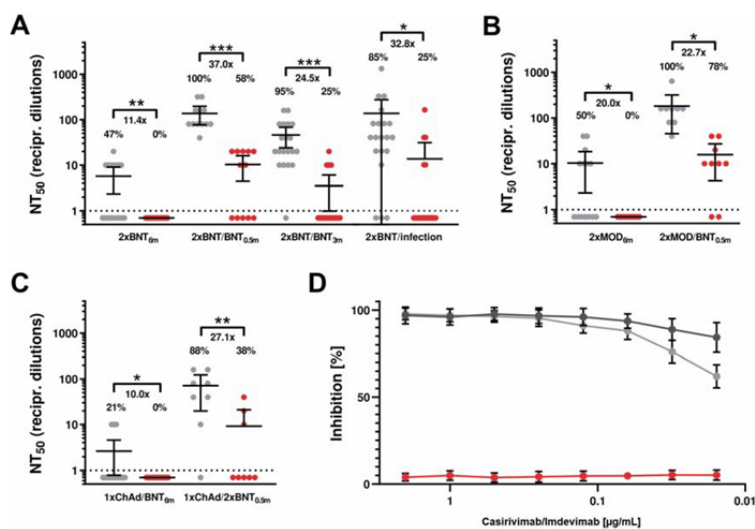


Figure 1 - Antibody-mediated neutralization efficacy against authentic SARS-CoV-2 variants Delta and Omicron. Values represent reciprocal dilutions of SARS-CoV-2 variants Delta (grey) and Omicron (red) micro-neutralization titers resulting in 50% virus neutralization (NT₅₀). **A)** Neutralization assays were performed using serum samples obtained from individuals double BNT162b2 vaccinated (2xBNT). Sera from additionally BNT162b2 boosted individuals were sampled 0.5 month (2xBNT/BNT_{0.5m}) or 3 month (2xBNT/BNT_{3m}) as well as sera from double BNT162b2 vaccinated and SARS-CoV-2 infected individuals (2xBNT/infection). **B)** Neutralization assays with sera from double mRNA-1273 vaccinated (2xMOD) and additionally BNT162b2 boosted (2xMOD/BNT_{0.5m}). **C)** Neutralization titers for sera from heterologous ChAdOx1 and BNT162b2 vaccinated (1xChAd/1xBNT_{6m}) and BNT162b2 boosted (1xChAd/2xBNT_{0.5m}) individuals. The x-fold reduction was determined using the difference between NT₅₀ values for Delta and Omicron. Only Delta neutralizing samples were considered for the calculation. Negative titers were handled as 1. The percentages indicate the relative number of sera that achieved a measurable titer. Information regarding the sera donors (sex, age, antibody titers test and sampling dates) are summarized in the Supplementary Appendix. **D)** Neutralization efficacy of monoclonal antibodies imdevimab and casirivimab against SARS-CoV-2 Omicron (red), B (dark grey), and Delta (grey). The indicated concentrations of mAbs casirivimab and imdevimab were applied in a 1:1 ratio. Mean values of two technical replicates per sample are depicted with 95% confidence intervals and SD. All experiments were verified using a second SARS-CoV-2 strain (Supplementary Table 4). Statistical significance compared to Delta was calculated by two-tailed, paired student's t-tests. Asterisks indicate p-values as * (p < 0.05), ** (p < 0.01), and *** (p < 0.001).

Eventually, Delta and Omicron neutralization was evaluated in the presence of sera obtained from infected individuals (0.7 to 7 months post infection) who received two doses of BNT162b2 (samples collected 6 months after the last shot). From these sera (n=20), 15% and 75% failed to neutralize Delta and Omicron virus preparation respectively. Neutralization titres against Omicron were 32.8-fold reduced using sera from double BNT162b2-vaccinated and infected individuals (Figure A).

This study from Ciesek's group (Wilhem et al.), showed a decreased capacity in neutralization for Omicron compared to Delta. However, the comparison between two doses protocol and three doses protocol are hampered since the delay between sampling and last shot is very different: 6 months for the 2 doses protocol, 0.5 and 3 months for the 3 doses protocol. From this set of data, it is not possible to evaluate the neutralization capacity of sera against Omicron obtained at early time points in the 2 doses protocol. In addition, the high percentages of serum that tested negative in these neutralization assays must be analyzed with caution since high doses of viral inoculum were incubated (4000 TCID₅₀). Both the relative low titers in SN assays and the absolute number of negative samples might be an overestimation.

4.3 A preliminary report (Sheward et al.) from the Karolinska Institute (Sweden) indicated also a decrease in the neutralization of Omicron variant in comparison with Wuhan and Delta strains (WT and Delta in Figure 1; <https://drive.google.com/file/d/1CuxmNYj5cpluxWXhjjVmuDqntxXwlfXQ/view>). Their assay is based on pseudotyped virions. Lentivirus particles were produced to express the spike of 3 SARS-CoV-2 variants. In their preliminary study, the authors did not report on quantification of measured SN titers.

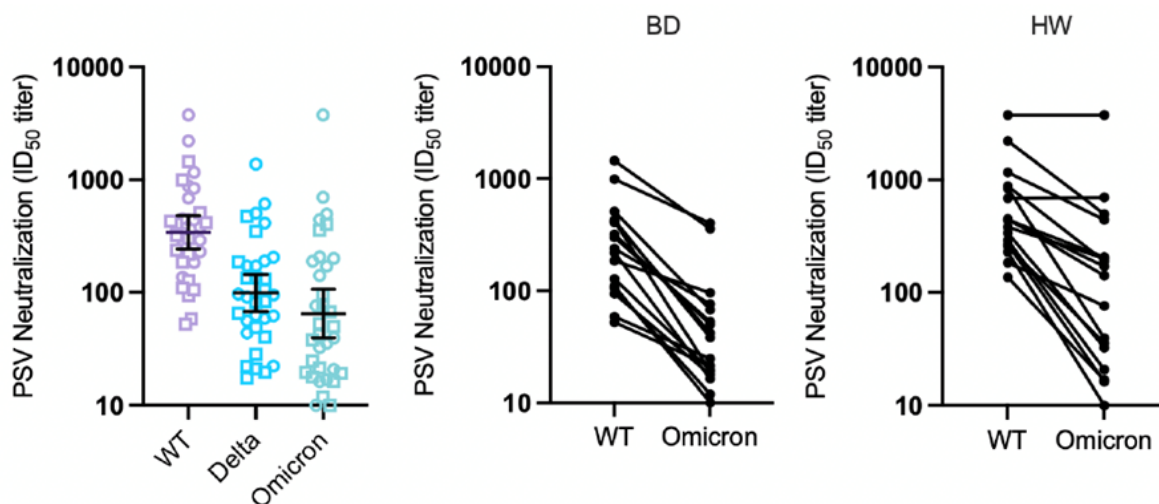


Figure 1: Pseudovirus neutralization titers for Blood Donors (BD; N=17) and Hospital Workers (HW; N=17) against the pandemic founder variant (WT), the B.1.617.2 variant (Delta) and the B.1.1.529 variant (Omicron).

4.4. T-cell response

Besides those first studies dedicated to the ability of the neutralizing antibodies to bind to Omicron, a first immunological study has now also explored the anti-SARS-CoV-2 CD8+ T-cell responses (<https://www.biorxiv.org/content/10.1101/2021.12.06.471446v1>). In their study, the authors examined if the previously identified viral epitopes targeted by CD8+ T-cells from COVID-19 convalescent patients (infected with SARS-CoV-2 in the United States in April and May 2020) are mutated in Omicron. Their data suggest that individuals with existing anti-SARS-CoV-2 CD8+ T-cell responses should recognize the Omicron VOC, and that SARS-CoV-2 has not evolved extensive T-cell escape mutations at this time.

5. Update on the efficacy of antivirals and utility to mitigate the impact of the Omicron wave of infections

Pfizer has released a press release today with regard to the efficacy of its antiviral drug Paxlovid. These data suggest an important risk reduction for hospitalization and death (89%).

These results suggest that, in the context of high risk contact or high level exposure (massive wave of infections), fragile patients would benefit from antiviral therapy, regardless of their vaccination status.

We recommend that these antivirals would be rapidly distributed in targeted high risk groups in order to contain the impact of the upcoming Omicron wave of infections.

Final data available from all high-risk patients enrolled in EPIC-HR study (n= 2,246) confirmed prior results of interim analysis showing PAXLOVID™ (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) reduced risk of hospitalization or death by 89% (within three days of symptom onset) and 88% (within five days of symptom onset) compared to placebo; no deaths compared to placebo in non-hospitalized, high-risk adults with COVID-19.

An approximate 10-fold decrease in viral load at Day 5, relative to placebo, was observed in both EPIC-HR and EPIC-SR, indicating robust activity against SARS-CoV-2 and representing the strongest viral load reduction reported to date for a COVID-19 oral antiviral agent

Source:

<https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results>