Genomic surveillance of SARS-CoV-2 in Belgium

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

Situation update – 2nd of February 2021
(6th report of 2021)

Executive summary

Genomic surveillance in Belgium is based on whole genome sequencing (WGS) of a selection of representative samples, complemented with targeted active surveillance initiatives and molecular methods aiming to early detect and precisely monitor the presence of variants of concern (VOCs). Currently, 3.827 sequences of samples collected in Belgium since the start of the epidemic are available on GISAID in open access.

Since the 1st of December 2020, an increasing number of 501Y.V1 (754) and 501Y.V2 VOCs (99) have been confirmed by WGS. The evolution of the 501Y.V1 (B.1.1.7), which is currently the most prevalent VOC in Belgium, is followed on a daily basis using the proportion of "S dropout" signals among positive PCR results performed in the federal PCR platform composed of 8 geographically spread laboratories and representing +- 1/3 of all positive results reported in Belgium. The proportion of presumptive 501Y.V1 among newly diagnosed patients is estimated between 15% and 28%, a proportion which has increased significantly during the last month, although at a slower pace since +- 10 days.

Belgium has recently experienced multiple introductions of variants of concern, particularly since the last days of 2020. The consolidated genomic and epidemiological data are consistent with a rapidly increasing number of events of local transmission. VOCs widely circulate in Belgium, and the situation is evolving towards a full replacement of current viral populations in the coming weeks. This shift in viral populations constitutes an objective epidemiological risk, although the impact of this phenomenon on overall COVID-19 incidence could be mitigated through a combination of interventions taking into account the higher infectiousness of emerging variants (infection control policies, broadened testing strategies, rapid outbreak management, vaccination).

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1. International context

Since the end of the year, 4 variants of concern (VOCs) have arisen independently of one another in the United Kingdom (501Y.V1), South Africa (501Y.V2) and Brazil (501Y.V3 and 20B/S.484K). These variants harbour a number of mutations and deletions associated with higher infectiousness and immune escape. All variants are spreading internationally, with 501Y.V1 and 501Y.V2 having been detected to date in Belgium.

The figures below (source : https://covariants.org/per-country) show for several countries including Belgium, the proportion of total number of sequences (not cases), over time, that fall into defined variant groups. Viral strains harbouring the 501Y mutation (common to all VOCs, coloured in pink) have increased in most countries as a consequence of higher infectiousness compared to other circulating strains.

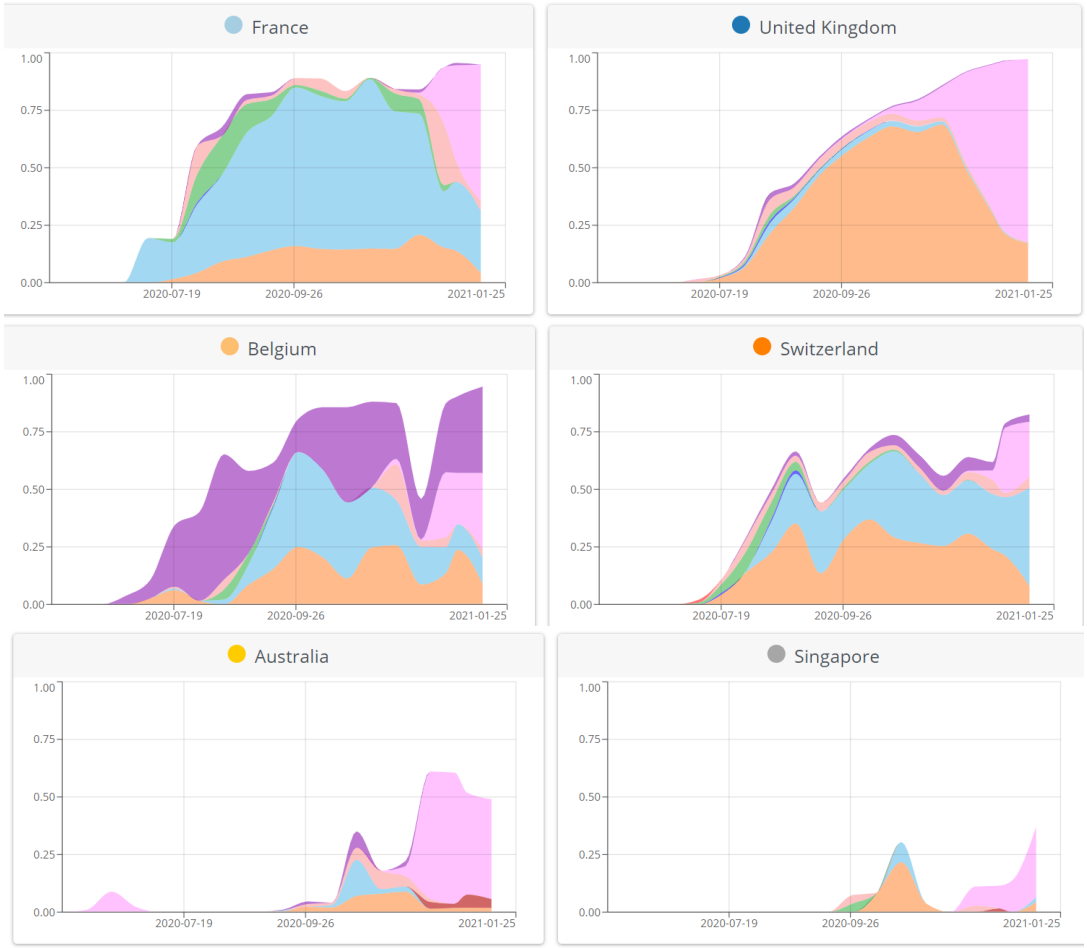

Figure 1: Evolution over the months of viral populations in different countries. Variants harbouring the 501Y mutation (pink) are more infectious compared to other circulating populations, and are therefore progressively evolving to become the dominant populations.

The UK has very recently communicated about independent events of acquisition of the S:E484K mutation among 501Y.V1 samples. To date, 21 501Y.V1 (lineage B.1.1.7) sequences harbouring E484K were made available by UK colleagues on GISAID (19 from England, 2 from Wales).
This mutation is located in the receptor binding domain (RBD), important to ACE2 binding and antibody recognition. To date, no 501Y.V1 sequences from Belgium harbour this mutation of concern, and the situation is being monitored (https://nextstrain.org/community/GuyBaele/sars-cov-2-belgium/voc?c=gt-S_484&f_country=Belgium&label=clade:20I/501Y.V1) .

2. Belgian genomic surveillance

The National Reference Centre hosted at UZ Leuven – KU Leuven has put in place genomic surveillance at the national level since the first introduction of the virus in February 2020. Along the way, other university centres have contributed to this surveillance effort through complementary initiatives, and the federal government has recently supported a scale-up of this network, built upon the federal platform laboratories. While baseline surveillance will be continued and strengthened using WGS, active surveillance and monitoring of VOCs is to be performed using PCR-based techniques currently in validation. To date, 3.827 sequences originating from Belgian laboratories were uploaded on GISAID and are available in open access.

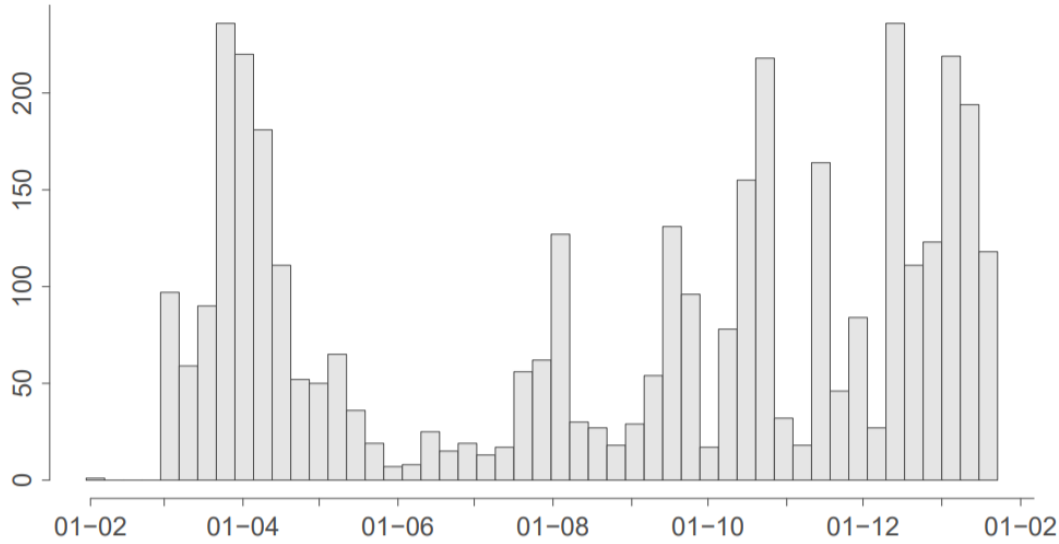

Figure 2: Number of Belgian sequences deposited on GISAID per week since the first case was diagnosed in the country.

Baseline Surveillance. A representative sampling of the positive cases in Belgium organised with the collaboration of a sentinel network of laboratories, allows to follow over the time the trends in the genetic diversity of circulating strains of SARS-CoV-2. 24 pre-selected labs were contacted by the National Reference lab and agreed to refer 5% of their positive samples for the baseline surveillance system. Most labs have started sending these baseline surveillance samples. The selection of participating labs was made to ensure an optimal geographical coverage and a diversity of clinical severity patterns (university hospitals, regional hospitals, GPs and community-based testing centres). The aim is to cover at all times 2-5% of all positive cases in Belgium, with a current major attention to consolidate uniform geographical coverage.

Active surveillance aims to promptly identify the introduction of emergence of (possible) variants of concern (VOCs). This surveillance is available for all clinical laboratories and does not systematically require WGS testing. Currently, active surveillance in Belgium focuses on:

- Systematic screening of VOCs among returning travellers
- Systematic screening of VOCs among atypical PCR or antigen diagnostic test results (including "S dropouts")
- Genetic characterization of a subset of strains in the situation of outbreaks
- Genetic characterization among patients experiencing re-infection or infection after vaccination
- Genetic characterization among patients presenting a higher risk of chronic infection and mutant selection (e.g. immunocompromised, antiviral therapy)

3. Evolution of VOCs in Belgium

Since the 1st of December 2020, an increasing number of 501Y.V1 (754) and 501Y.V2 VOCs (99) have been confirmed by WGS.

Since the 1st of January 2021, 583 sequences have been uploaded on GISAID by the participating sequencing laboratories.

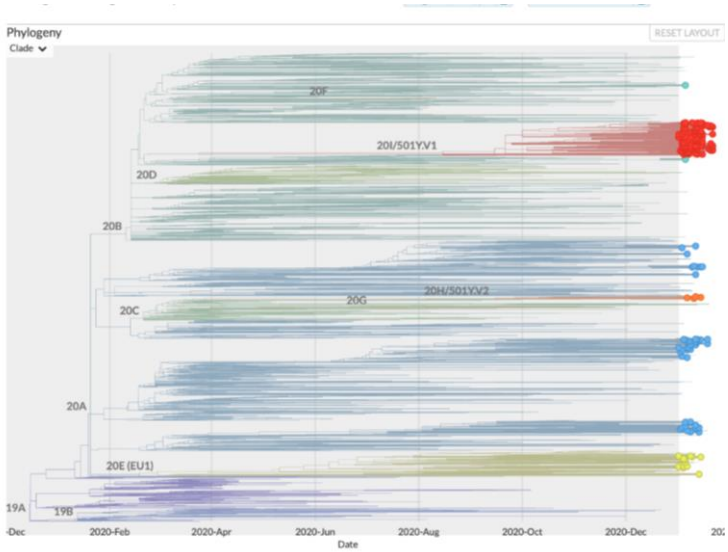

Figure 3 : Characterization of recent Belgian sequences uploaded on GISAID (from 1/1/2021). There are currently 2 VOCs circulating in Belgium: 501Y.V1 (red) and 501Y.V2 (orange) together with other strains (blue and yellow)

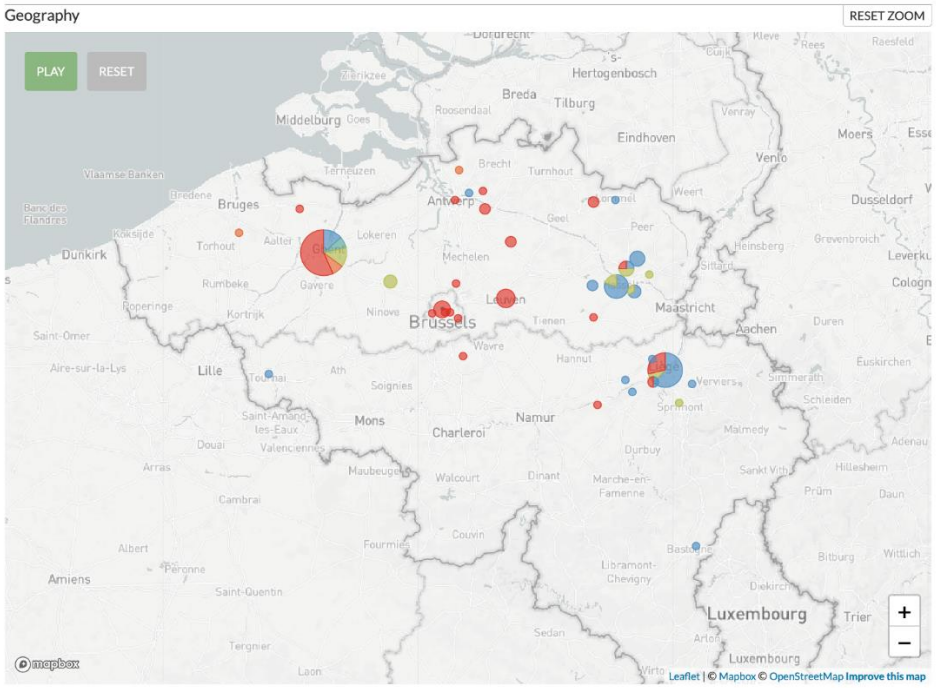

Figure 4. Coverage of WGS and characterization by province since 01/01/2021. 501Y.V1 is coloured in red. The proportion between types of strains is biased by active selection of S dropout and returning travellers and should therefore not be considered as representative of current situation.

Increase over time in share of S-dropout samples confirmed to be 501Y.V1

S-dropout is caused by the presence of a H69- deletion in the S gene of SARS-CoV-2. This deletion is present in the 501Y.V1 mutant and other non-VOC strains circulating in Belgium. When looking at the sequences of the last months (uploaded sequences on GISAID), 80% of H69- deletions are related to 501Y.V1.

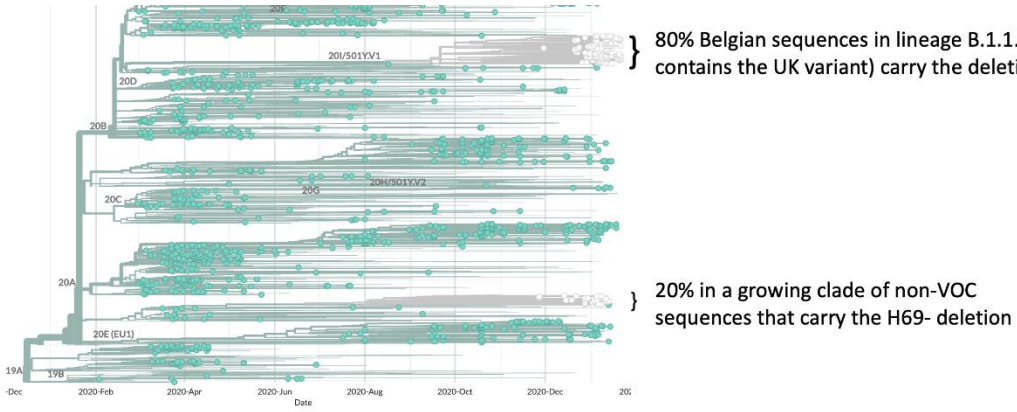

Figure 5: Presence of H69- deletion in non-501Y.V1 strains in Belgium

When looking at the more recent sequencing results of S-dropout samples, we observe the share of S-dropout samples that are actually the 501Y.V1 UK SARS-CoV2 variant has been rapidly increasing, with an estimate of up to 97% [93-99%] 95% CLs predictive value for samples analysed on 1/2/2021. S-dropout in Belgium can therefore now be used as a reliable proxy for a sample being the 501Y.V1 variant.

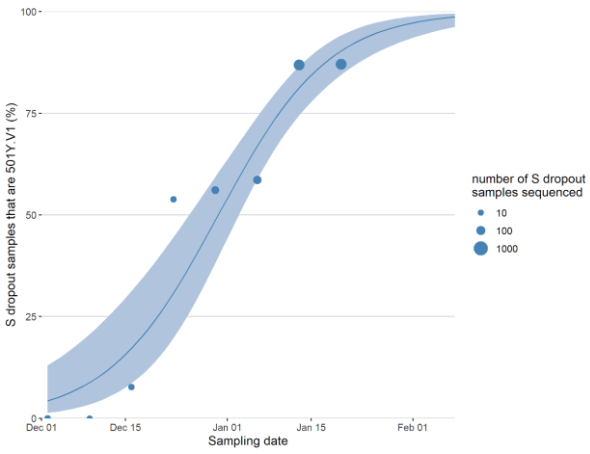

Figure 6. Rapid increase over the last weeks in the proportion of S dropout samples confirmed to be 501Y.V1 variant by sequencing (binomial GLMM with 95% confidence intervals).

Evolution over time in share of S-dropout among positive PCR results

Across the 8 laboratories composing the federal testing platform (over 528.000 PCR tests performed since 1/12/2020), the proportion of “S dropouts” among positive SARS-CoV-2 PCR remained between 15% and 25% over the last 12 days.

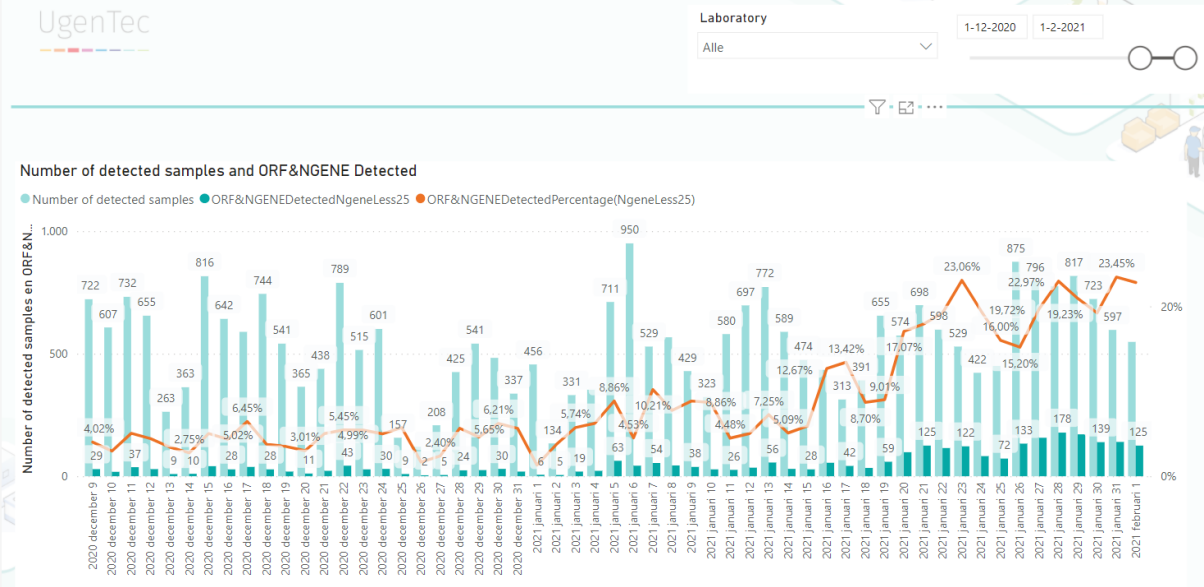

Figure 7 : Evolution of the share of S dropout over time in the federal platform laboratories.

Evolution over time of the age distribution of positive PCR results (S-dropout and non-S-dropout)

We received the distribution by age and week for “S dropouts” and “non S dropouts” positive PCR results from all platform bis laboratories for the last 4 weeks. This data supports numerous introductions of 501Y.V1 during the first week of the year (returning travellers) followed by a spread in all age groups. During the last week, we have seen no increase in absolute numbers of “S dropout” results in the 20+ age groups, but an increase of 39% in the 0-19 group. It is probable that this increase is the result of increased testing in schools rather than massive spread, as the “non S dropout” results have increased by 60% during the same period of time in the same age group.

Week	Namur	# S-gene dropouts						# non S-gene dropouts				
		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years
28-12 – 3/1	1	0	1	0	0	0	175	29	74	49	22	1
4/1 – 10/1	17	1	6	5	1	4	367	47	167	105	42	6
11/1 – 17/1	15	0	3	0	4	8	275	55	97	87	35	1
18/1 – 24/1	22	3	2	3	2	12	269	48	71	92	47	11
25/1 – 31/1	36	1	14	10	8	3	343	113	106	92	27	5

Week	Leuven	# S-gene dropouts						# non S-gene dropouts				
		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years
28-12 – 3/1	6	1	2	2	1	0	177	31	60	48	29	9
4/1 – 10/1	5	3	1	0	1	0	227	40	77	60	30	20
11/1 – 17/1	21	1	10	3	5	2	257	53	98	62	26	18
18/1 – 24/1	62	28	9	11	7	7	246	35	92	56	23	40
25/1 - 31/1	165	85	34	32	5	9	403	119	107	87	44	46

Week	Liège	# S-gene dropouts						# non S-gene dropouts				
		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years
28-12 – 3/1	0	0	0	0	0	0	25	2	5	9	6	3
4/1 – 10/1	0	0	0	0	0	0	150	9	28	40	26	47
11/1 – 17/1	3	0	3	0	0	0	112	11	20	38	15	28
18/1 – 24/1	5	2	2	1	0	0	67	12	12	7	12	24
25/1 - 31/1	24	4	4	3	6	7	76	16	21	20	8	11

Week	ULB	# S-gene dropouts						# non S-gene dropouts				
		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years
28-12 – 3/1												
4/1 – 10/1												
11/1 – 17/1	168	28	58	56	14	12	449	53	195	143	42	16
18/1 – 24/1	172	19	50	57	18	28	362	53	139	108	32	30
25/1 - 31/1	18	4	4	5	2	3	37	5	15	12	2	3

Week	Mons	# S-gene dropouts						# non S-gene dropouts				
		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years
28-12 – 3/1	5	0	1	3	1	0	405	49	154	124	62	16
4/1 – 10/1	5	0	2	2	1	0	514	46	189	172	85	22
11/1 – 17/1	10	0	3	4	2	1	512	80	179	138	91	24
18/1 – 24/1	14	2	5	4	2	1	530	101	141	176	78	34
25/1 - 31/1	26	8	7	5	4	2	764	199	218	201	99	47

Week	UCL	# S-gene dropouts						# non S-gene dropouts				
		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years
28-12 – 3/1	6	1	1	3	1	0	339	52	141	113	27	6
4/1 – 10/1	0	0	0	0	0	0	597	80	281	175	55	6
11/1 – 17/1	34	0	23	5	6	0	806	96	396	239	61	14
18/1 – 24/1	69	14	30	20	5	0	454	69	174	128	52	31
25/1 - 31/1	45	7	19	18	0	1	244	62	85	63	17	17

Week	Antwerp	# S-gene dropouts						# non S-gene dropouts				
		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years
28-12 – 3/1	14	5	4	4	0	1	427	58	127	122	54	66
4/1 – 10/1	25	9	10	5	1	0	556	73	177	186	59	61
11/1 – 17/1	60	11	26	22	1	0	530	85	171	142	65	67
18/1 – 24/1	136	63	32	35	5	1	485	137	143	124	41	40
25/1 - 31/1	181	72	42	57	10	0	560	212	153	133	50	12

Week	Gent	# S-gene dropouts						# non S-gene dropouts				
		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years
28-12 – 3/1	2	0	0	0	2	0	11744					
4/1 – 10/1	7	0	4	3	0	0	13354					
11/1 – 17/1	2	0	1	1	0	0	9607					
18/1 – 24/1	18	3	3	5	1	6	10366					
25/1 - 31/1	37	5	6	6	2	18	10312					

Week	Total	# S-gene dropouts					Total	# non S-gene dropouts				
		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years		0 – 19 years	20 - 39 years	40 - 59 years	60 – 79 years	80 – 99 years
28-12 – 3/1	34	7	9	12	5	1	13292	221	561	465	200	101
4/1 – 10/1	59	13	23	15	4	4	15765	295	919	738	297	162
11/1 – 17/1	313	40	127	91	32	23	12548	433	1156	849	335	168
18/1 – 24/1	498	134	133	136	40	55	12779	455	772	691	285	210
25/1 - 31/1	532	186	130	136	37	43	12739	726	705	608	247	141

Table 1 : Age distribution of S dropout results for the last 8 weeks.

Estimation of the growth rate advantage and increased transmissibility of 501Y.V1

The increase over time in the true positive rate, i.e. of the share of S-dropout samples that were actually 501Y.V1 were either estimated from sequencing data of S-dropout samples using a binomial generalized linear mixed model (GLMM) with sample date included as a covariate and an observation-level random effect included to take into account overdispersion (for the Belgian data) or were estimated from the S dropout data itself (for the UK data, method as described in [1])

The estimated growth rate advantage of the 501Y.V1 variant (i.e. the difference in Malthusian growth rate per day of 501Y.V1 minus that of the wild type variants) was estimated from the S gene dropout data using a binomial GLMM of the proportion of cases that are consistent with being 501Y.V1. This model used the counts of S dropout samples, multiplied by the estimated probability of being 501Y.V1 (as estimated by a separate binomial GLMM fit on S gene dropout sequencing data in function of sample data), as a proportion of the count of all positive tests on a given day. Sample date and laboratory were included as fixed effects and an observation-level random effect was included to take into account overdispersion. A natural cubic spline in function of sample date with an appropriate number of knots was included if this provided a superior fit. A model with or without an interaction effect between laboratory and sample date (or a spline in function of sample date) were both fitted to test if the rate at which 501Y.V1 displaces other strains occurs at the same rate throughout Belgium or not. The growth rate advantage is given by the slope in function of time in this binomial GLMM (Davies et al. [1]).

The estimated transmission advantage (increase in transmissibility in terms of multiplicative effect on the effective reproduction number Rt), assuming an identical generation time, can be shown to be equal to exp(r.T) [1], where T is the mean generation interval (here taken to be 4.7 days, Nishiura et al. 2020 [2], which is the value that historically has been used throughout the epidemic by the Public Health Institute of Belgium, Sciensano, and therefore provides the best point of reference). This transmission advantage is assumed to be independent of mitigation measures, as these would typically be expected to affect all variants equally. Hence, this method automatically controls for variation in absolute number of new infection due to nonpharmaceutical interventions or possible changes in testing strategy, and is therefore much more accurate than trying to calculate the Rt values of each variant separately and then calculating their ratios.

A common-slope binomial GLMM fitted the available data best based on the Bayesian Information Criterion (BIC). In addition, in a model with separate-slopes per laboratory (region), there were no labs with a significantly above or below average slope of the binomial GLMM in function of time, except for the UGhent lab, which had a somewhat higher than average slope (effect contrast, z ratio = 3.1, Sidak p value = 0.01, all other $p > 0.05$), perhaps due to this lab being heavily involved in active surveillance of 501Y.V1 infection clusters. Hence, we can conclude that the variant 501Y.V1 is displacing other strains at approximately the same rate across the whole of Belgium, and that any deviations from this pattern are likely caused by bias in the data. The common-slope binomial GLMM (Figure 2) had a marginal slope of 0.12 [0.10-0.13] 95% CLs (observation-level random effect variance: 0.42), which implies that the 501Y.V1 variant has a 12% [10-13%] higher growth rate than the previous SARS-CoV2 wild types. This estimate is compatible with other international data, which demonstrate a growth rate advantage of the 501Y.V1 variant of 11% [10-12%] in the UK (Davies et al. Table S1, [1], range 9-15% across different NHS regions), 8% [7-10%] in Denmark (Davies et al. Table S1, [1]), 8% [7-10%] in Portugal (Borges et al., [3]) and 8% [7.5-9.5%] in the US (T. Bedford, pers. comm.).

Figure 8. Estimated increase in the relative abundance of the 501Y.V1 variant in Belgium based on S dropout data across different regions (labs where samples were analysed)

(mean and 95% confidence intervals, binomial GLMM with laboratory and sampling date included as fixed effect and an observation-level random effect included to take into account overdispersion, with correction for the expected proportion of true positives, logit Y scale).

If we assume that the 501Y.V1 variant has the same generation as the SARS-CoV2 wild type (which models have shown is compatible with the epidemiological data, Davies et al. [1]), and assuming a generation interval of T=4.7 days (following Nishiura et al. 2020 [2]), the estimated growth rate advantage r for Belgium would be expected to have a multiplicative effect on the effective reproduction number Rt of exp(r.T)=1.74 [1.61-1.87] 95% CLs, implying an increased transmissibility of 74% [61-87%] 95% CLs. The fitted model indicates that at this moment (1/2/2021), 28% [24-33%] 95% CLs of all newly diagnosed infections are compatible with being variant 501Y.V1, whilst among all new infections (taking into account a time of approx. 7 days between time of infection and diagnosis), already 45% [38-53%] would be estimated to be with variant 501Y.V1. By February 3d [31st of January - 7th of February] 95% CLs, we estimate that overall >50% of all new infections will be by variant 501Y.V1 (at time of infection), while by the 23d of February [18th of February - 2nd of March], we estimated that >90% of all new infections will be by this variant. If we look at the model predictions split up by region (hospital where samples were analysed), we can tell from the intercepts that the variant was likely introduced almost simultaneously in most regions except Mons, where it arrived noticeable and statistically significantly later (z ratio = -8.97, FDR corrected $p < 0.0001$), while in Ghent, Antwerp and Brussels, the variant arrived sooner than average (all FDR corrected p values at least < 0.05) (Figure 3).

Given that the estimated growth trajectory of the 501Y.V1 variant still has relatively broad confidence intervals, we also carried out a combined analysis of the Belgian S-dropout data and the Pillar 2 (i.e. community testing) UK S dropout data (data October 1 2020 - 24th of January 2021), to be able to further narrow down the predictions. For both the Belgian and UK data, we multiplied the S dropout counts in the numerator of the binomial fractions with the probability of the S dropout samples actually being the 501Y.V1 variant (i.e. the true positive rate). This probability was estimated from a binomial GLM fitted to counts of sequenced S dropout samples, while for the UK data, the probability was estimated as described in [1]. For this dataset, a binomial GLMM with a 3 degree of freedom natural cubic spline in function of sample date, region (UK NHS region or Belgium as a whole) and their interaction coded a fixed effects and an observation-level random effect included to take into account overdispersion was found to fit the data best based on the BIC criterion. With such a model, we estimated that at this moment (1/2/2021), the 501Y.V1 variant in Belgium experiences a growth advantage of 9.6% per day [7-12%] (observation-level random effect variance: 0.01), which with a generation time of 4.7 days would translate into an increased transmissibility of 57% [42-73%]. This growth advantage is also slightly lower than the one that the model estimates for the beginning of January (1/1/2021), namely 17% per day [11-24%]. Possible, stochastic effects could cause an upward bias in the estimation of the growth advantage during the early stages of its spread (Bodin & Rocklöv 2021). By comparison, under this model, the 501Y.V1 variant was estimated to experience a growth advantage of 8.6% [8.4-8.9%] in the South East of the UK in mid-November (14/11/2020), where it likely first originated, which would translate into a transmission advantage of 50% [49-52%]. Based on this binomial spline GLMM, we estimate that by February 4th [1st of February - 9th of February] >50% of all new infections will be by this variant (at time of infection), while by the 27th of February [20th of February - 11th of March], >90% of all new infections would be by the variant. In a model without any spline terms, but merely with region-specific slopes, the growth advantage of the 501Y.V1 variant was estimated at 12.6% [11.5-13.6%] for Belgium and 8.8%-10.4% for the different UK NHS England regions. The fitted slope for Belgium in this model was significantly higher than the slopes of all NHS regions except the East of England and the Midlands. It is possible though that this merely reflects the fact that the Pillar 2 UK S dropout samples may have been collected more randomly than is the case in Belgium, where some labs also engage in active surveillance and targeted analysis of 501Y.V1 infection clusters, which may also cause an upward bias in our estimate.

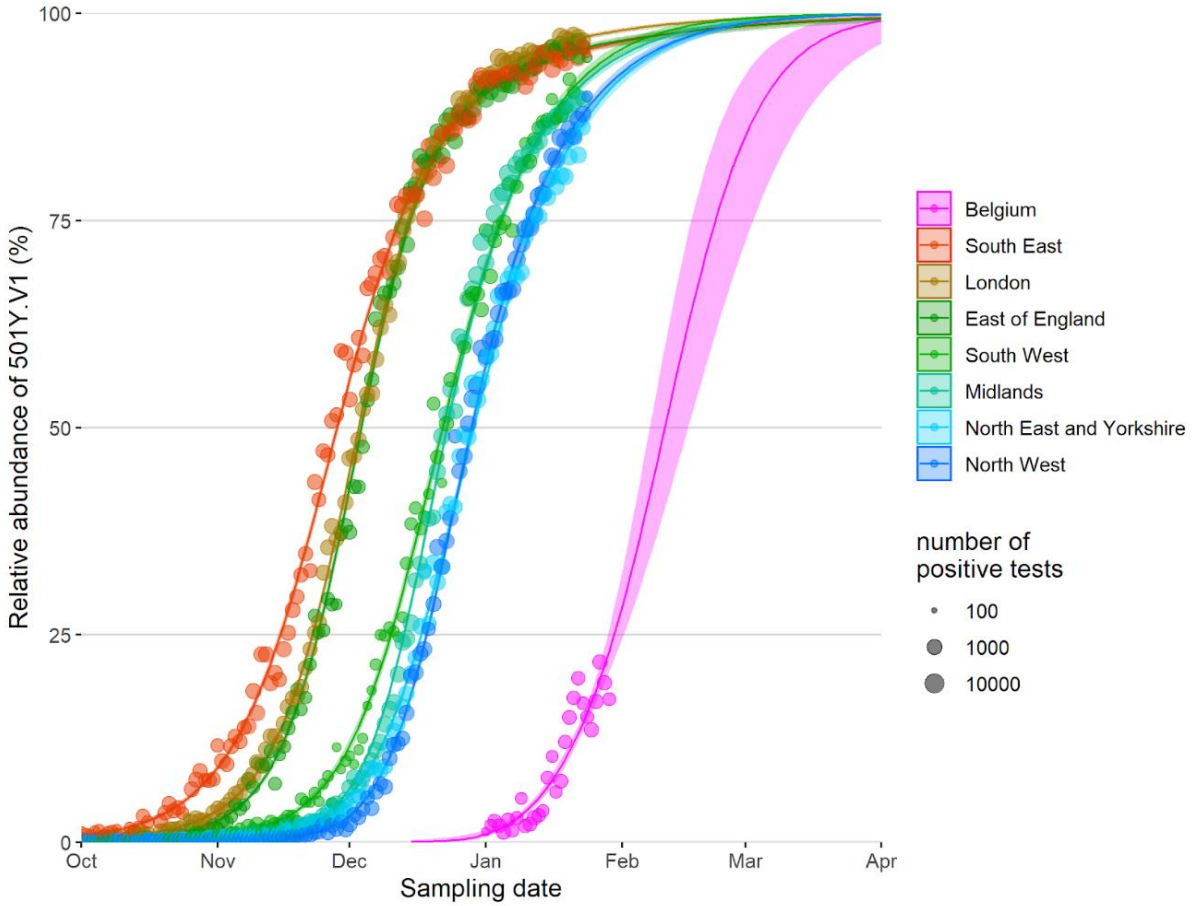

Figure 9. Estimated increase (plus 95% confidence intervals) in the relative abundance of the 501Y.V1 variant in the UK and Belgium, based on a joint analysis of S dropout data from Belgium and the UK (binomial GLMM with region (or country) and a 3 degree of freedom natural cubic spline in function of sampling date plus their interaction coded as fixed effects and with an observation-level random effect included to take into account overdispersion). The introduction of the 501Y.V1 variant in Belgium occurred with a delay of about 2.5 months compared to the initial spread in the South East of the UK.

<u>Conclusion of the predictive analysis (based on current data – will be revised weekly)</u>

Based on early 501Y.V1 data for Belgium, we observe that this variant is rapidly spreading, and will likely become the dominant strain in a short timespan, being projected to reach 90% of all newly diagnosed infections by the end of February. It could already make up 28% of all new lab diagnoses and 45% of all new infections at this moment (1/2/2021). The growth advantage relative to other strains, based on a joint fit of the Belgian and UK S dropout data, is on the order of 9.6% [7-12%] per day at this moment, which would translate into an increased transmissibility of ca. 57% [42-73%].

Our work has several limitations. First, we cannot exclude selection bias because, at least in part, our data pertain to specific outbreaks with a suspicion of 501Y.V1; e.g. because of travellers returning from the UK after end of year holidays. Minimising bias could be done provided data on the reason for testing would be available. Patient meta-data is also urgently needed to be able to estimate possible differential age-susceptibility and estimate possible effects on hospitalisation or mortality rates. Despite the fact that our data do not constitute a random sample of the population, the inferred increase in transmissibility is entirely in line with estimates found for other countries based on the observed growth advantage there (typically 8-11% per day, cf. above). A big advantage of our method

of estimating the transmission advantage from the growth advantage is that this controls for the effect of various non-pharmaceutical interactions on absolute infection numbers [1]. Hence, one expects our estimated growth and transmission advantage to be largely independent of any mitigation measures, unless these were specifically targeted towards 501Y.V1 infection clusters. Mitigation measures, however, could be very successful in pushing down the overall baseline basic reproduction rate, and which should be pursued to be able to contain the spread of 501Y.V1 and other variants, such as the South African 501Y.V2 and the Brazilian 501Y.V3. Further work should focus on explicitly accounting for the emerging new strain using mathematical modelling as, e.g., done by [4,5]. Nevertheless, the resulting figures are worrisome, as they would imply that, given current vaccine scarcity, substantial efforts need to be made to mitigate the spread of SARS-CoV-2.

We should note that earlier preprints in which the increased transmissibility of 501Y.V1 were estimated do not always use correct procedures and often use differing generation times, which is a major cause of the differences in the estimates obtained [6]. For example, Volz et al. [7] calculated an additive change in the Rt value based on the product of the difference in growth rate and generation time, while the actual relationship is multiplicative [1]. If we would recalculate the given additive change in Rt s in their Table 2, calculated for a generation time of 6.5 days, to a multiplicative increase in Rt for a generation time of 4.7 days we use here, we would obtain an expected increase in the Rt values of exp(s.4.7 / 6.5), which works out at 30% to 64%, and which encompasses the estimate that we obtain for Belgium. Likewise, Walker et al. [8] analysed ONS S gene dropout data from the UK, but did not filter out samples with single-gene amplifications (indicative of random gene dropout due to very low virus titers, e.g. linked to old infections), which resulted in an underestimation of the current incidence of the 501Y.V1 variant (reporting ca. 60% prevalence across England among new infections, while the Pillar 2 S gene target failure data show figures >90%, Fig. 4) as well as of its contagiousness (K. Pouwels, pers. comm.). This is currently being addressed by the study authors, in consultation with the ONS, who have to adapt their definition of S dropout samples. We make these points to demonstrate that if the same procedure is used to estimate the growth and transmission advantage of the 501Y.V1 variant, highly concordant estimates are obtained across different countries and regions. We therefore believe our conclusions to be reliable and robust.

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