Santé publique France

CNR Respiratory infections virus

INSTITUT PASTEUR

HCL HOSPICES CIVILS DE LYON

Risk analysis on emerging variants of SARS-CoV-2 carried out jointly by Public Health France and the CNR for respiratory infection viruses

Update of 02/23/2022

Public Health France and the National Virus Reference Center for Respiratory Infections jointly and regularly carry out a risk analysis of the different variants of SARS-CoV-2 identified in France and internationally, based on the information available on their dissemination.

The sources used for this risk analysis are as follows: data from the EMERGEN consortium including Flash surveys (see Dashboard InfoCovidFrance), results of screening RT-PCR, international virological database *"Global Initiative on Sharing Avian Influenza Data" (GISAID).* For more information on the definition of variant categories, refer to the risk analysis of 07/28/2021.

The next update of the risk analysis is scheduled in 4 weeks, unless the evolution of the situation justifies an earlier update.

Contents

1. Key points of the risk analysis dated 02/23/2022

Several highlights should be noted in this update of the risk analysis related to emerging variants of SARS-CoV-2:

Ranking of variants (Table 1):

- To date, 5 variants are classified as VOC, 1 as VOI and 1 as VUM;
- Since the last risk analysis, the **Lambda 21G (C.37)** and **Mu 21H (B.1.621*) VOIs,** as well as the VUM **20D (C.1.2)** have been downgraded, due to a lack of detection in France for more than 16 weeks and their very low circulation internationally.

Surveillance by screening for mutations of interest:

- The **screening results** illustrate the dominance of Omicron throughout the territory;
- The proportion of samples in France with a screening result compatible with Omicron in S07 was **99.8% for proxy A0C0** (99.7% in S06) and **99.1% for proxy D1** (99.1% in S06);
- The **L452R** (C1) mutation, present mainly in Delta, is now detected at low levels, with 0.2% in S07.

Epidemiology and public health impact of variants of concern (VOC) and to be monitored (VOI)

- Sequencing data confirms the dominance of **VOC 21K/L/M Omicron (B.1.1.529, BA.*)** in all regions of metropolitan France and overseas. In mainland France, it represented 99.5% of interpretable sequences in the Flash survey of 07/02/2022; • The **BA.1 sub-lineage of the** Omicron variant is still the majority in France: it represented 83% of the Omicron sequences identified during the Flash survey of 07/02. However, the proportion of the BA.2 sub-lineage is increasing, with 4.8% of Omicron sequences from the 01/24 Flash survey, 9.5% for that of 01/31 and 16% for that of 07 /02. The progression of BA.2 to the detriment of BA.1 is observed throughout metropolitan France, but at different levels depending on the region;

- The latest studies have confirmed the **higher transmissibility of Omicron's BA.2 sublineage compared to the BA.1 sublineage.** But this difference does not seem sufficient to have a major impact on the epidemic situation, as indicated by the work of modellers from INSERM and the Institut Pasteur. These two sublineages appear similar in terms immune response escape and severity;
- The **VOC 21A/I/J Delta (B.1.617.22, AY*)** is now only weakly detected, with 0.5% of the interpretable sequences of the Flash survey of 07/02/2022. VOI **20A/C (B.1.640)** has not been detected during Flash investigations since 10/01, but a few cases have been identified for other sequencing indications;
- **Recombination phenomena between two different variants of SARS-CoV-2** represent major genetic divergence events. A full discussion of this phenomenon has been included in this risk analysis. As of 01/21/2022, 10 sequences that may correspond to a Delta/Omicron recombinant have been identified in France. This signal is being investigated by the CNR and Public Health France.

Table 1: Classification of variants on 02/23/2022 and detection in metropolitan France in surveys Flash

Concerning variants (VOC)	Variations to follow (VOI)	Variants under evaluation (VUM)
20I (V1, B.1.1.7/Q.*, Alpha) Not detected since Flash S46 (15/11)	**20A/C (B.1.640)** Not detected since Flash S02 (10/01)	**20B (B.1.1.318)** Not detected since Flash S49 (06/12)
20H (V2, B.1.351*, Beta) Not detected since Flash #19 (10/08)		
20J (V3, P.1/P.1.*, Gamma) Not detected since Flash #23 (07/09)		
21A/I/J (B.1.617.2/AY.*, Delta) 0.5% of sequences (Flash S06)		
21K/L/M (B.1.1.529/BA.*, Omicron) 99.5% footage (Flash S06)		

*Update of the risk analysis on 02/23/2022. The data given concerns metropolitan France. The WHO nomenclature assigned to certain variants is added in parentheses (Greek alphabet). * indicates inclusion of sub-lineages carried out on 02/07/2022: data on 2,358 interpretable sequences.*

2. Knowledge available on VOCs, VOIs and VUMs

This chapter presents the new data available on the characteristics and public health impact of VOCs, VOIs and MUVs.

2.1. VOC Alpha, Beta, Gamma and Delta

The **Delta VOC,** which had dominated since the summer of 2021, **is now a minority** on an international scale: it represented 0.5% (2,146/423,010) of the sequences deposited on GISAID between 22/01/2022 and 21/ 02/2022, compared to 10% (94,411/974,145) for the period from 22/12/2021 to 21/02/2022. Alpha (N=2), Beta (N=0) and Gamma (N=0) were **detected very little or not** at all over the period from 01/22/2021 to 02/21/2022. For more information on the characteristics of these variants, refer to Tables 5, 6 and 7 of the risk analysis of 07/28/2021.

2.2. VOC Omicron

International epidemiological situation

The world situation today is characterized by **the dominance of VOC Omicron** on a global scale. The number of cases and the number of deaths reported by the WHO are decreasing, suggesting that the peak of the Omicron wave has passed. The majority of countries now report community spread of Omicron. This variant represented 98% (416,250/423,010) of the sequences deposited on GISAID between 01/22 and 02/21/2022, compared to 88% (861,787/974,145) for the period from 12/22/2021 to 01/21/2022. These data should, however, be interpreted in light of differences between surveillance systems in different countries, particularly sequencing capabilities, submission timelines, and sample selection biases.

Omicron VOC sublineages

As of 02/21/2022, the Omicron VOC includes a parental lineage (B.1.1.529, clade 21M) and its three sublineages: BA.1 (clade 21K), BA.2 (clade 21L) and BA.3 (no specific clade, included in 21M). Fifteen sub-lineages of BA.1, have also been defined, some of which (such as the BA.1.13 or BA.1.15 sub-lineages) also have sub-lineages (BA.1.13.1 and BA.1.15.1) (1). Given the significant circulation of Omicron in the world, genetic diversification within this variant and the progressive appearance of sub-lineages is an expected phenomenon. To date, only BA.2 appears to have different characteristics from other Omicron sublineages, with higher transmissibility.

On a global scale, the BA.1.1 sub-lineage is the most frequent with 43% of the 416,250 Omicron sequences deposited on GISAID between 01/22 and 02/21/2022. The proportion of BA.1 that did not belong to the BA.1.1 sublineage decreased from 59% of Omicron sequences during the period from 22/12/2021 to 22/01/2022 to 39% between 22/ 01 and 21/02/2022. The proportion of BA.2 has increased since the previous month: it was 4% between 22/12 and 21/01/2022, against 18% between 22/01 and 21/02/2022. These data come from the international GISAID database as of 02/21/2022 and should be analyzed in light of the differences between countries in terms of sequencing volume and potential biases in the selection of sequenced samples. **A gradual replacement of BA.1 by BA.2 is observed in many countries, particularly in Europe** (Figure 1). However, the Scandinavian countries, where the proportion of BA.2 is the highest (Denmark, Sweden, Norway), do not seem to be experiencing an epidemic rebound.
Thus, the transmissibility advantage of BA.2 does not seem sufficient to significantly modify the evolution of the incidence. Finally, only 440 sequences corresponding to the BA.3 sub-lineage are available on the international GISAID database (as of 02/21/2022) (2).

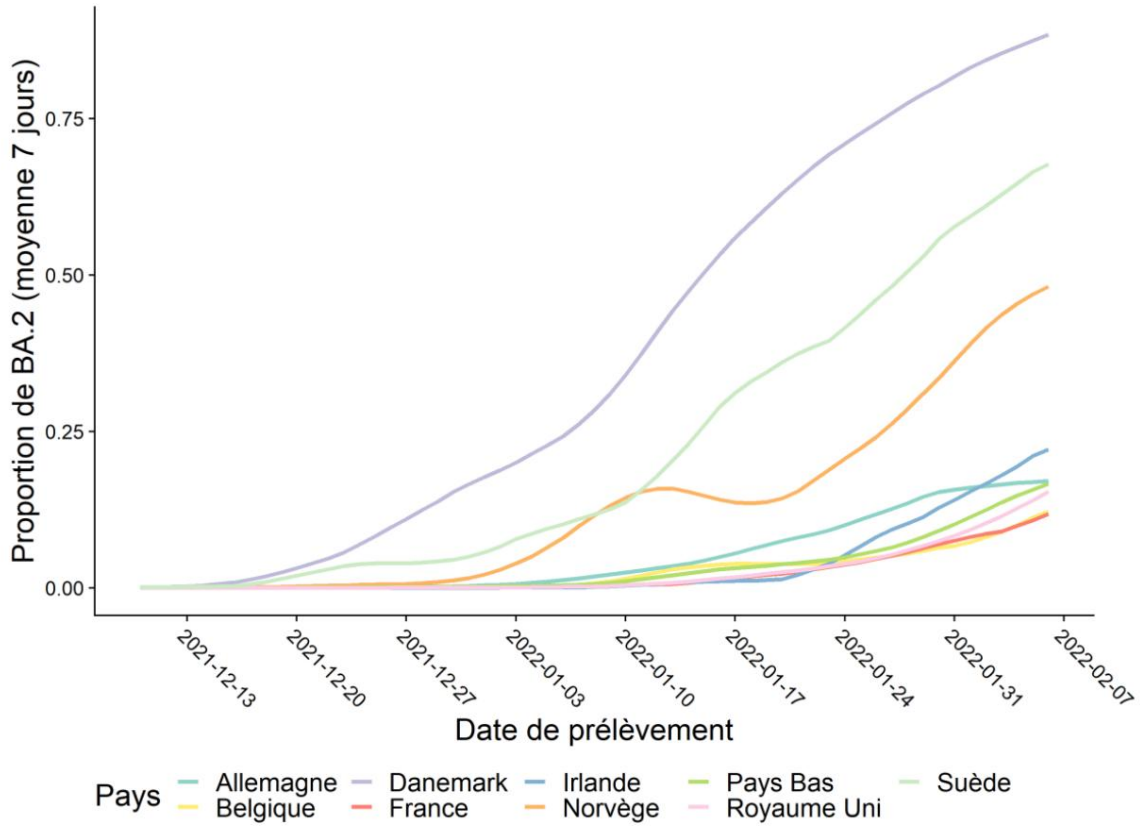

Figure 1: Proportion of BA.2 cases among the total number of sequences deposited on GISAID, by country. Data from 02/21/2022 in https:// cov-spectrum.org/.

Transmission and kinetics of infection

The rapid replacement of Delta by Omicron on a global scale illustrates the increased transmissibility of Omicron compared to previous variants (3). Secondary etch rate calculations, higher for Omicron than Delta, confirmed this observation (4, 5). If this growth advantage is partly linked to its immune response evasion properties, Omicron also seems to have intrinsic properties impacting its transmissibility potential. Knowledge gained from pre-Omicron variants indicates that increased transmissibility may be associated with several factors: higher viral shedding, better fusion ability, more efficient cleavage of the Spike protein and high affinity for the ACE2 receptor. Since the viral load of patients infected with Omicron is not higher than that of patients infected with Delta, viral shedding does not appear to be a major factor in the transmissibility of Omicron (6). *In vitro* tests have shown that Spike protein cleavage and fusogenic abilities are less efficient for Omicron compared to Delta, and therefore would not explain its transmissibility either.

increased (7). However, the affinity of Omicron's Spike protein for ACE2 appears to be better than that of VOC Alpha, Beta and Gamma, at levels similar to that of the Wuhan strain (8). The affinity of Omicron's Spike protein for its ACE2 receptor could be due to compensation for multiple mutations involved in immune escape. An *ex vivo* study also showed more efficient replication of Omicron in bronchial cells but not in lung cells, which could be involved
in Omicron's higher transmissibility and lower severity (9). The authors of this study raise the hypothesis that Omicron would enter the cells by different molecular mechanisms from the other variants. One study showed increased multiplication for Omicron compared to Delta in primary nasal epithelial cells (10). These data indicate that Omicron would enter the cells by mechanisms

molecules different from the other variants, allowing the infection of a greater number of cells of the respiratory epithelium and contributing to its increased transmissibility.

Another factor that may be involved in the replacement of one variant by another is the kinetics of infection. Two studies, one conducted in South Korea and the other in Belgium, showed a shorter serial interval (time between two cases) for Omicron compared to Delta (3 days for Omicron in the South Korean study), and therefore accelerated diffusion (11, 12). If the kinetics of transmission seem accelerated, a follow-up among healthcare professionals in the United States showed prolonged detection by antigen testing, with 43% of participants still positive between 5 and 10 days after their first positive test, whereas the instruction in the center where this study took place was a return after 5 days without the need for a negative test (13).

Within the Omicron variant, a higher growth rate was observed for the BA.2 sublineage compared to BA.1 (14, 15). A global analysis of the Omicron wave in the UK estimated the growth rate of BA.2 to be 14% higher per day compared to BA.1 (16). These data are consistent with transmission analyzes performed in Denmark, which showed a secondary attack rate of 39% for BA.2 versus 29% for BA.1 (17). An interesting observation from this analysis is that, while the secondary attack rate of BA.2 was higher than that of BA.1 regardless of the vaccination status of the contacts, this difference was observed mainly for the unvaccinated cases. Thus, vaccinated cases seem not to transmit BA.2 more efficiently than BA.1. A Japanese *in vitro* study investigated the virological characteristics of BA.2 compared to BA.1 and showed better replication of BA.2 in human epithelial cells and greater fusogenic capacities (18). However, the investigations on the possible mechanisms at the origin of these differences did not make it possible to conclude.

Efficacy of the immune response

Neutralization studies performed on Omicron since its emergence have shown that the ability of post-vaccination antibodies to neutralize SARS-CoV-2 is weaker compared to Delta. In agreement with these *in vitro results,* an increased risk of infection by the BA.1 sublineage in vaccinated or previously infected individuals was observed compared to the Delta variant (19). A similar neutralization study comparing this time BA.1 and BA.2 showed similar neutralization for these two sublineages (20). These data indicate a reduced effectiveness of the neutralization of Omicron by post-vaccination or post-infection antibodies, but the authors emphasize the importance of a booster dose of vaccination (which retains some effectiveness against Omicron) in particular for elderly (21). Israeli study found fourth dose of vaccine halved risk of symptomatic infection

and to divide by four the risk of severe forms of Covid-19 compared to three doses (22).

Beyond booster doses and non-pharmaceutical measures, the T cell response plays a major role in clinical presentation. T cells are also produced after vaccination and could be the keystone of the remarkably high protection against severe forms and death (23). In particular, we note that despite the unique mutational profile of Omicron and the reduced susceptibility of this variant to neutralizing antibodies, the T cell response induced by vaccination and infection largely targets Omicron (24, 25). Moreover, if neutralizing plasma antibodies seem to have a limited activity against Omicron, they would make it possible to extend the spectrum of recognition of the response.
immunity up to 5 months after vaccination. The first RBD-specific memory B cells
("receptor-binding domain") of the Spike protein would specifically target the Omicron RBD, and over time the RBD-specific memory B cells would diversify and could interact with more divergent RDBs.

Severity

Studies of the severity of Omicron agree on the lower risk of hospitalization, admission to intensive care and death of this variant compared to Delta. These results were confirmed more recently by a Norwegian study, which showed an 83% reduction in the risk of hospitalization for Omicron

compared to Delta (26). Similar results have been published in the United States, Canada and South Africa, with a 67-83% lower risk of ICU admission (27-30). The analyzes carried out by Santé Publique France on the probability of severe hospital events in patients infected with Omicron point in this direction, with a risk reduced by 87% compared to Delta (31). A second study by Santé Publique France aimed at describing the first cases of Omicron in France observed a mild clinical picture and the absence of serious forms (32).

Within the Omicron sublineages, a study in hamsters concluded that BA.2 was more pathogenic than BA.1 (18). However, this study was carried out on small numbers and with viruses produced by reverse genetics only carrying the S protein of BA.1 and BA.2, so it does not allow us to prejudge what would be observed with the authentic viruses. . On the other hand, preliminary analyzes from Denmark and England found similar risks of hospitalization following BA.1 or BA.2 infection (33, 34). This work on population impact is more relevant for assessing the impact of BA.2 on public health.

2.3. Co-infections and recombinants

Since the beginning of the circulation of SARS-CoV-2, different variants have circulated concomitantly.
In this context, it may happen that the same individual is infected simultaneously by several variants of SARS-CoV-2, sometimes very distinct. These co-infections can give rise to recombination phenomena: in a cell infected by two viral strains, exchanges of genetic material between the viruses can occur; the recombinant resulting from this event therefore has a “mosaic” genome, part of its genome corresponding to the genome of the first strain and another part corresponding to the genome of the second strain. This phenomenon of recombination is frequent in SARS-CoV-2, an American study carried out on 1.6 million SARS-CoV-2 genomes having identified 2.7% of recombinants (35). However, in the majority of cases, the two original strains are close and the recombinant has a profile similar to the parental strains. These recombinants are therefore difficult to detect and are generally not of public health concern. During the pandemic, the genetic divergence between the different lineages of SARS-CoV-2 has increased over time, making the

recombinations that are more easily identifiable because they come from more divergent variants (36). From sequencing data, it can be complex to distinguish co-infection with two different variants from infection with a novel recombinant, and several recombinant detections have proven to be false alarms. In 2021, a recombinant between VOC Alpha and VOC Delta was identified in Japan and a Beta/Delta recombinant in China (37, 38). Since the end of 2021, an Omicron wave has overlapped with a Delta wave in several regions of the world. This co-circulation of two variants on a large scale increases the probability of co-infections and therefore that of recombinants. Several suspected Delta/Omicron recombinants have been reported recently in the UK, USA and Australia, and others are under investigation.

Recombination phenomena between two different variants represent major genetic divergence events. It is difficult to predict what the characteristics of such a recombinant will be compared to the two parental variants and to anticipate its impact on public health. This is why SARS-CoV-2 recombinants are under close scrutiny internationally. In France, enhanced monitoring of Delta/Omicron co-infections has been implemented in order to detect possible recombinants as early as possible. Samples with a C1D1 screening result (presence of the L452R mutation associated with Delta, and one of the D mutations associated with Omicron), which are therefore suspected of co-infection, are subject to systematic sequencing. The C1D1 profile in screening was mainly identified between mid-December and mid-January, which corresponds to the period of co-circulation of Delta and Omicron (Figure 2).
As of 02/21/2021, 59 probable Delta/Omicron co-infections have been identified in France (source: EMERGEN database).

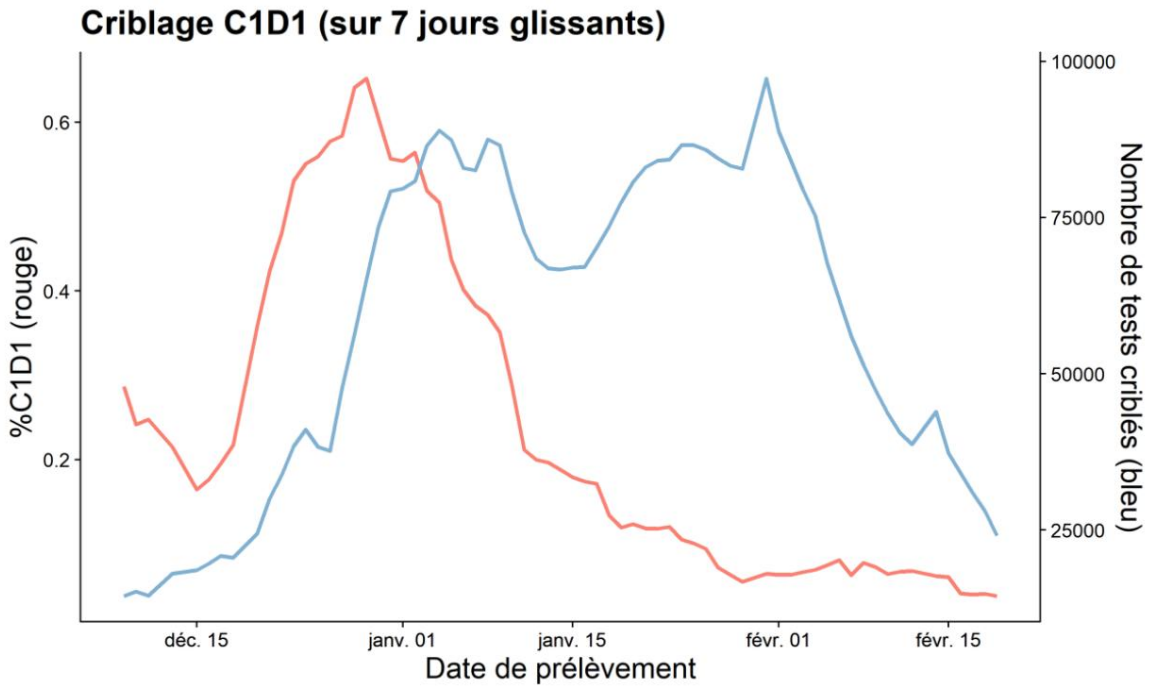

Figure 2: Proportion of C1D1 screening results (presence of L452R and one of the mutations associated with Omicron, red curve) and total number of positive samples for SARS-CoV-2 with an interpretable screening result (blue curve), by sampling date, smoothed over 7 rolling days, in metropolitan France and in the overseas departments and territories (source: SIDEP, as of 02/21/2022).

On 02/16/2022, a discussion thread was opened on the Github bioinformatics forum of the Pangolin nomenclature tool about a Delta/Omicron recombinant potential in France (39). Performed from the GISAID database, these analyzes had identified four sequences from France, four sequences from Denmark and one sequence from the Netherlands which form a separate phylogenetic branch. This signal was investigated by the Respiratory Infections Virus CNR and the RNA Virus Evolutionary Genomics Laboratory at the Institut Pasteur, which confirmed that the four sequences from France did indeed correspond to a recombinant. The majority of the genome of this recombinant corresponds to the AY.4 sublineage of the VOC Delta, and a large portion of the S gene (coding for the Spike protein) corresponds to the BA.1 sublineage of the VOC Omicron. A request to assign a specific lineage has been made. Additional analyzes were carried out on the EMERGEN database, using three mutations which seem to characterize the sequences of this recombinant: ORF1a:E352D, S:A27S, S:N764K. This "proxy mutation" is not 100% specific and sensitive in identifying this recombinant, and work is in progress to refine it. As of 02/21/2022, 10 sequences in the EMERGEN database carried these three mutations, 9 of which were sequenced during Flash surveys. These samples come from different regions and the oldest dates back to 17/01. The detection during Flash surveys and the geographic dispersion of the cases suggest that this recombinant has potentially already been circulating at very low levels since mid-January. Additional analyzes are underway to confirm these results, and this signal is being closely monitored by the CNR, the laboratories of the EMERGEN consortium and Public Health France.

2.4. VOI (variants of interest)

Lambda and Mu **VOIs** have been classified as VOIs by WHO since 2021-06-14 and 2021-08-30, respectively. VOI Lambda circulated extensively in South America (mainly Peru) in spring/summer 2021, and *in vitro* data suggested possible increased transmissibility. The VOI Mu was also detected in South America (mainly in Colombia) during the summer of 2021, and the data

available indicated immune response escape similar to VOC Beta. However, these two variants were very little detected in France (14 and 27 sequences identified in total during the Flash#11 to Flash#22 surveys, respectively). Since the end of 2021, these two VOIs have hardly been detected worldwide (23 and 35 of the 2,321,387 sequences deposited on GISAID having a sampling date between 22/11/2021 and 21/02/2022, respectively). Given the absence of detection of Lambda and Mu VOIs in France for more than 16 weeks and their very low circulation internationally, these variants are downgraded and are no longer considered VOIs in the risk analyzes of Public Health France.

Variant 20A/C (B.1.40) has been classified as VOI since the risk analysis of 05/01/2022. A total of 656 **B.1.640** sequences were deposited in the international GISAID database as of 02/21/2022, 70% of which come from France (458, Figure 3).

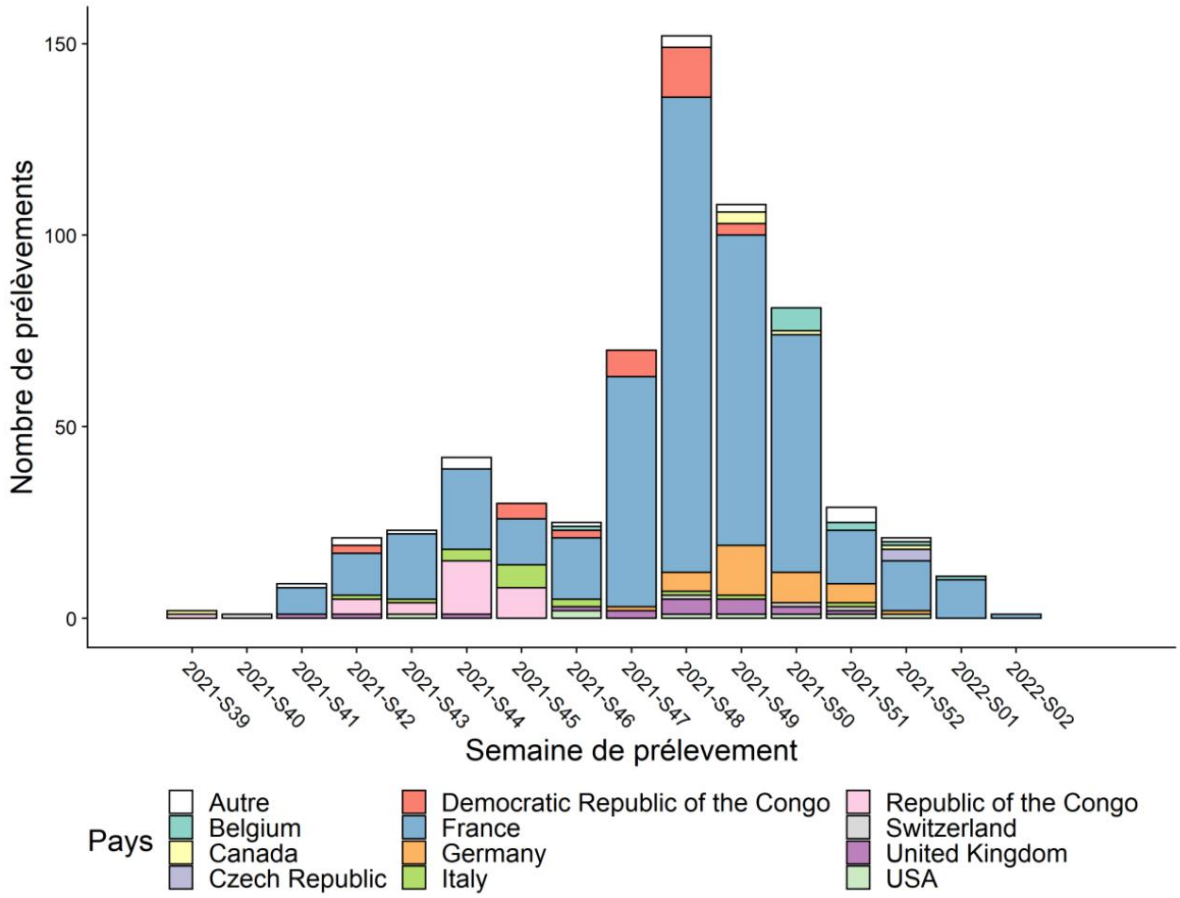

Figure 3: Number of B.1.640 sequences, by country and by sampling week (source: GISAID, as of 01/24/2022). Countries that have deposited two sequences or less are grouped in the "other" category.

The other countries that have identified this virus are the Democratic Republic of Congo (N=45), Germany (N=33) and the Republic of Congo (N=31). However, other countries in Europe, Africa, Asia and North America, some of which have limited sequencing capabilities, have detected this variant, which may suggest an underestimation of the circulation of B.1.640. The B.1.640 sequences identified mainly correspond to the B.1.640.1 sublineage with 620 sequences out of 656 (95%). Only 36 sequences of the B.1.640.2 sublineage were available on the GISAID database as of 02/21/2021, including 26 from France and 3 from the United Kingdom (40). The B.1.640.2 sublineage is characterized by the presence of the E484K mutation, for which an impact on immune response escape has been shown. But to date, no difference between the characteristics of B.1.640.2 and B.1.640.1 has been demonstrated, so they are considered to be the same variant.

2.5. VUM (variants under investigation)

VUM **20D (C.1.2)** has been classified VUM since the risk analysis of 08/09/2021 due to the presence of mutations of interest and its progression in South Africa at the time of its description. However, the latter has never been detected in France (source: EMERGEN on 02/21/2021, all sequencing indications combined). Since its classification, no evidence indicates that this VUM could have a worrying impact on public health. Internationally, C.1.2 peaked in July 2021, but has been detected very little since then. Of the 316 C.1.2 sequences available in the international GISAID database (as of 02/21/2022), only 6 correspond to samples taken after 11/22/2021, the most recent dating from 12/08/2021. Given the absence of detection of this variant in France for more than 16 weeks, its very low circulation at the international level and the absence of elements in favor of an impact on public health, this variant is downgraded and is not no longer considered VUM.

VUM 20B (B.1.1.318) was not detected internationally over the period from 22/01 to 21/02/2022 (according to the international database GISAID on 21/01/2022) .

3. Evolution of the detection of mutations of interest targeted by screening in France

A description of the screening strategy deployed in France and its changes over time is available in section 3.1 of the variant risk analysis of 05/01/2022. Screening data is available in Open Data on GEODES and data.gouv.

In addition to the presence of the E484K (A1) and L452R (C1) mutations, two screening profiles allowing the suspicion of an Omicron variant are included in the indicators monitored by Public Health France: A0C0 (absence of E484K and L452R, suspicion of Omicron) and D1 (presence of del69-70 and/or K417N and/or S371L S373P and/or Q493R, strong suspicion of Omicron).

- The proportion of detection of **the E484K** (A1) mutation has remained at very low levels since the beginning of August; it was 0.06% in S07 among all interpretable screened tests for this mutation;

- The proportion of detection of **the L452R** (C1) mutation, present mainly in Delta, is currently detected at low levels, with 0.2% in S07;
- The proportion of samples in France with a **screening result compatible with Omicron** in S07 was 99.8% for proxy A0C0 (compared to 99.7% in S06) and 99.1% for proxy D1 (compared to 99.1% in S06).

4. Evolution of the detection of VOCs, VOIs and VUMs in France within the framework of surveillance genomics

4.1. In France

In mainland France, the circulation of variants was first characterized by a dominance of **VOC Alpha** (spring 2021) then its replacement by **VOC Delta** during the summer of 2021 (Figure 4).
Beta and **Gamma VOCs** have not been detected during Flash investigations since Flash #24 (09/14/2021). The last case of **VOC Alpha** was detected during Flash S46 (11/15/2021, <0.1% of interpretable sequences). Delta remained the majority from July to December 2021, before being quickly replaced by the **VOC Omicron** during the months of December 2021 and January 2022. Today, Omicron is dominant in metropolitan France where it represented more than 99% of the sequences interpretable from Flash surveys S04, S05, S06 and S07 (Table 2 and Figure 4). This rapid replacement of Delta by Omicron was observed almost simultaneously in all regions of metropolitan France.

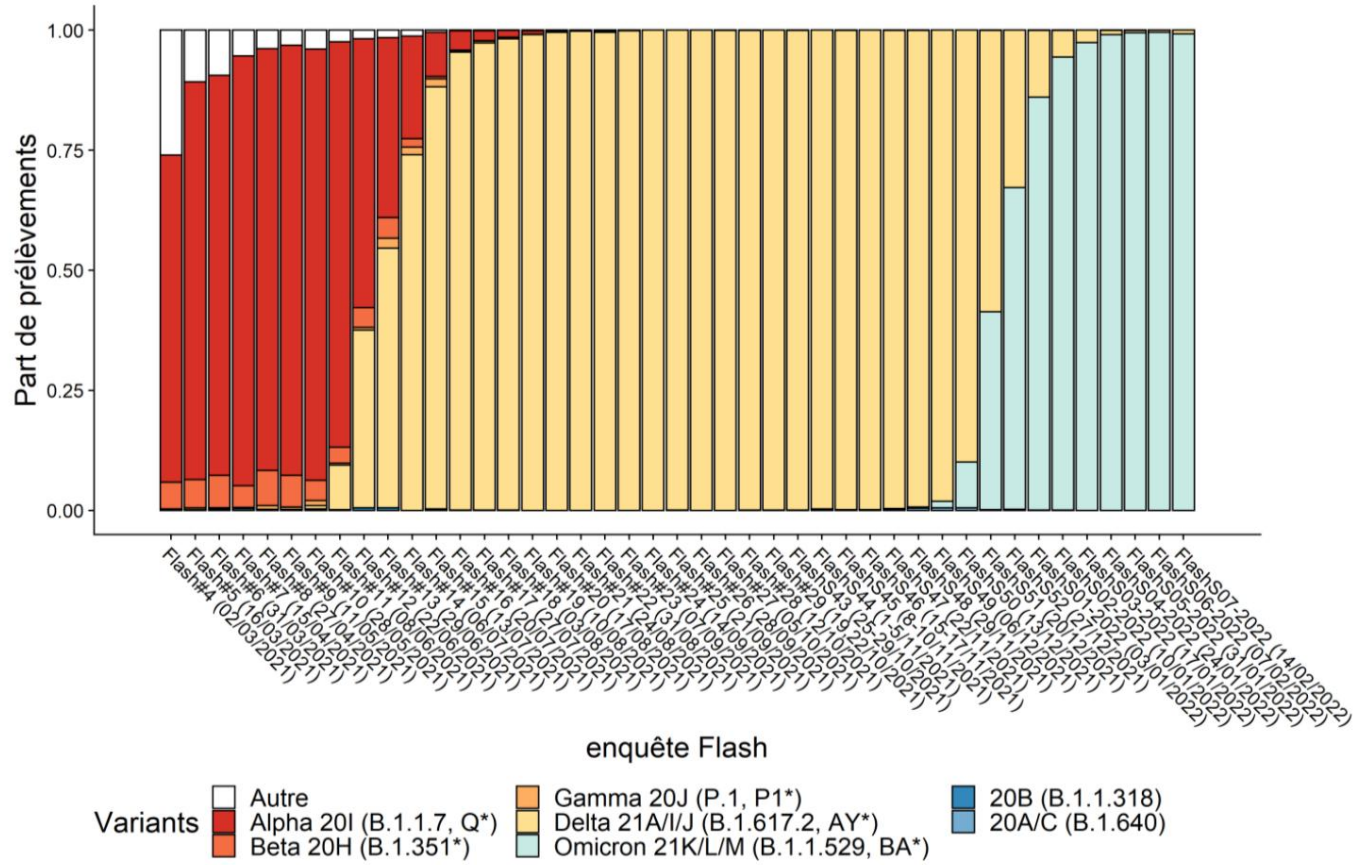

Figure 4: Evolution of the share of each VOC, VOI and VUM by Flash survey, metropolitan France (source: EMERGEN, at 02/21/2022 at 12 p.m.). Flash S06-2022 and Flash S07-2022 data are preliminary.

*

Table 2: Detection of variants during Flash S03 - Flash S07-2022 surveys, metropolitan France. indicates the inclusion of all known sublineages at this point.

Variant	Ranking	Flash S03 (01/17/2022)		Flash S04 (01/24/2022)		Flash S05 (31/01/2022)		Flash S06# (07/02/2022)		Flash S07# (02/14/2022)	
		N	%	N	%	N	%	N	%	N	%
Alpha 20I (B.1.1.7, Q*)	VOC	0	0	0	0	0	0	0	0	0	0
Beta 20H (B.1.351*)	VOC	0	0	0	0	0	0	0	0	0	0
Gamma 20J (P.1, P.1*)	VOC	0	0	0	0	0	0	0	0	0	0
Delta 21A/I/J (B.1.617.2, AY*)	VOC	118	2.57	32	0.88	16	0.53	11	0.47	6	0.8
Omicron 21K/L/M (B.1.1.529, BA.*)	VOC	4473	97.4	3620	99.0	2976	99.4	2347	99.5	740	99.2
20A/C (B.1.640)	VO	0	0	0	0	0	0	0	0	0	0
20B (B.1.1.318)	VUM	0	0	0	0	0	0	0	0	0	0
Other		0	0	3	< 0.1	1	< 0.1	0	0	0	0

Number of interpretable sequences: Flash S03: 4591; Flash S04: 3655; Flash S05: 2993; Flash S06: 2358; Flash S07: 746

#Flash S06-2022 and Flash S07-2022 data are preliminary

The Omicron sequences identified in France mainly belong to the BA.1 sub-lineage: 83% of the 2,403 Omicron sequences of the Flash S06 survey corresponded to BA.1, including 51% to its BA.1.1 sub-lineage (Figure 5). The proportion of the BA.2 sublineage has been increasing nationally since early January: it accounted for 5% of Flash S04 Omicron sequences, 10% for Flash S05, 16% for Flash S06 and 27% for Flash S07 (preliminary data). The progression of BA.2 to the detriment of BA.1 is observed in all regions of metropolitan France, but at different levels depending on the region. In particular, the proportion of BA.2 in New Aquitaine, where this sub-lineage seems to have been introduced earlier than in the other regions, exceeded 30% during Flash S06 (07/02).

A total of 14 sequences corresponding to BA.3 have been identified as of 02/21 (according to the EMERGEN database), including only two during Flash surveys. A large part of these 14 BA.3 sequences come from the same cluster and this sub-lineage remains very rare in France.

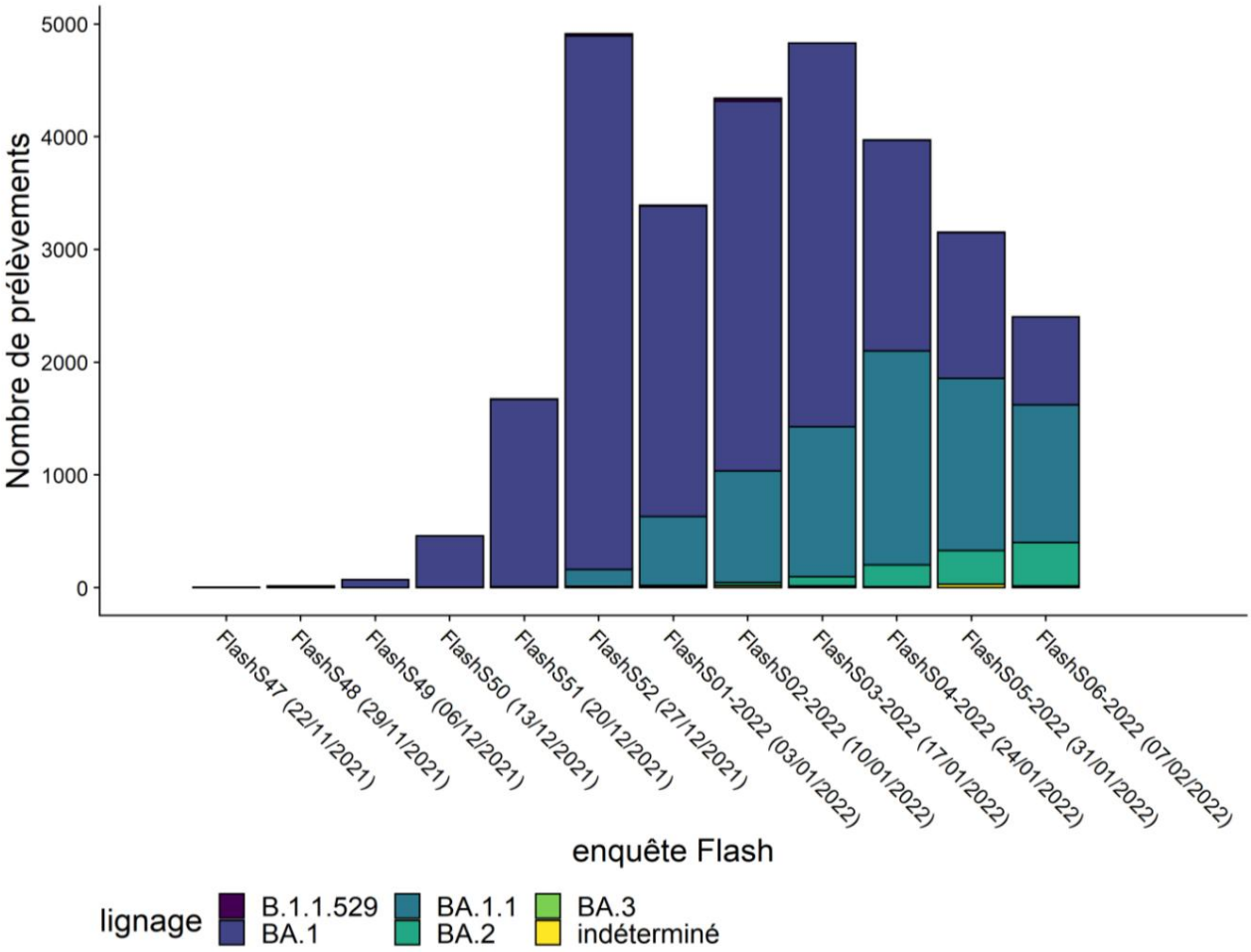

Figure 5: Sub-lineages of the Omicron variant during Flash surveys (source: EMERGEN, as of 02/21/2022 at 12)

Modeling studies have been carried out by the Institut Pasteur and INSERM to try to assess the impact of BA.2 on the Omicron wave in France, based on the evolution of the proportion of BA.2 in Flash surveys and the evolution of the number of cases. Based on data up to January 30, 2022, INSERM analyzes calculated the daily growth rate of BA.2 at 0.20 - 0.24 per day nationally, corresponding to doubling times between 3 and around 4 days, and a propagation advantage of 1.61 [1.52 – 1.69] compared to BA.1, confirming data from other countries (41). According to these estimates, BA.2 will become dominant in France around mid-February. The week of 01/31/2022, the reproduction number

of BA.2 is estimated at 1.30 [1.22-1.39], despite the decreasing overall epidemic curve (BA.1+BA.2). The results of the Institut Pasteur estimate the BA.2 doubling time to be between 4.5 and 7 days depending on the region, which is consistent with international data (42). Based on these estimates, BA.2 would become the majority in mainland France around February 24 [February 14 - March 11]. The BA.2 peak should occur around mid-February, and remain modest. The circulation of BA.2 would slow down the decrease in cases without producing a significant epidemic rebound. These conclusions remain valid for different scenarios in terms of probability of detection of Omicron and generation interval. Behavioral changes that would induce a significant increase in the transmission rate could induce an epidemic rebound, but this rebound should remain modest in size. Note that these models are built to cover only the period until April 1 , 2022. These two modeling studies confirm the growth advantage of BA.2 over BA.1, predict that BA.2 should become majority in France d 'by the end of February but underline a weak BA.2 impact on the Omicron wave.

Of the other classified variants, the **20A/C B.1.640 variant** was last detected in Flash surveys during Flash S02 (01/31, Table 2 and Figure 6). However, cases of B.1.640 infections were still detected in February 2022 outside of Flash investigations.

VUM 20B (B.1.1.318) has never been detected frequently in Flash surveys (a peak of 0.5% during Flash #12) and accounts for less than 0.1% of footage since Flash# 16 (7/20/21).

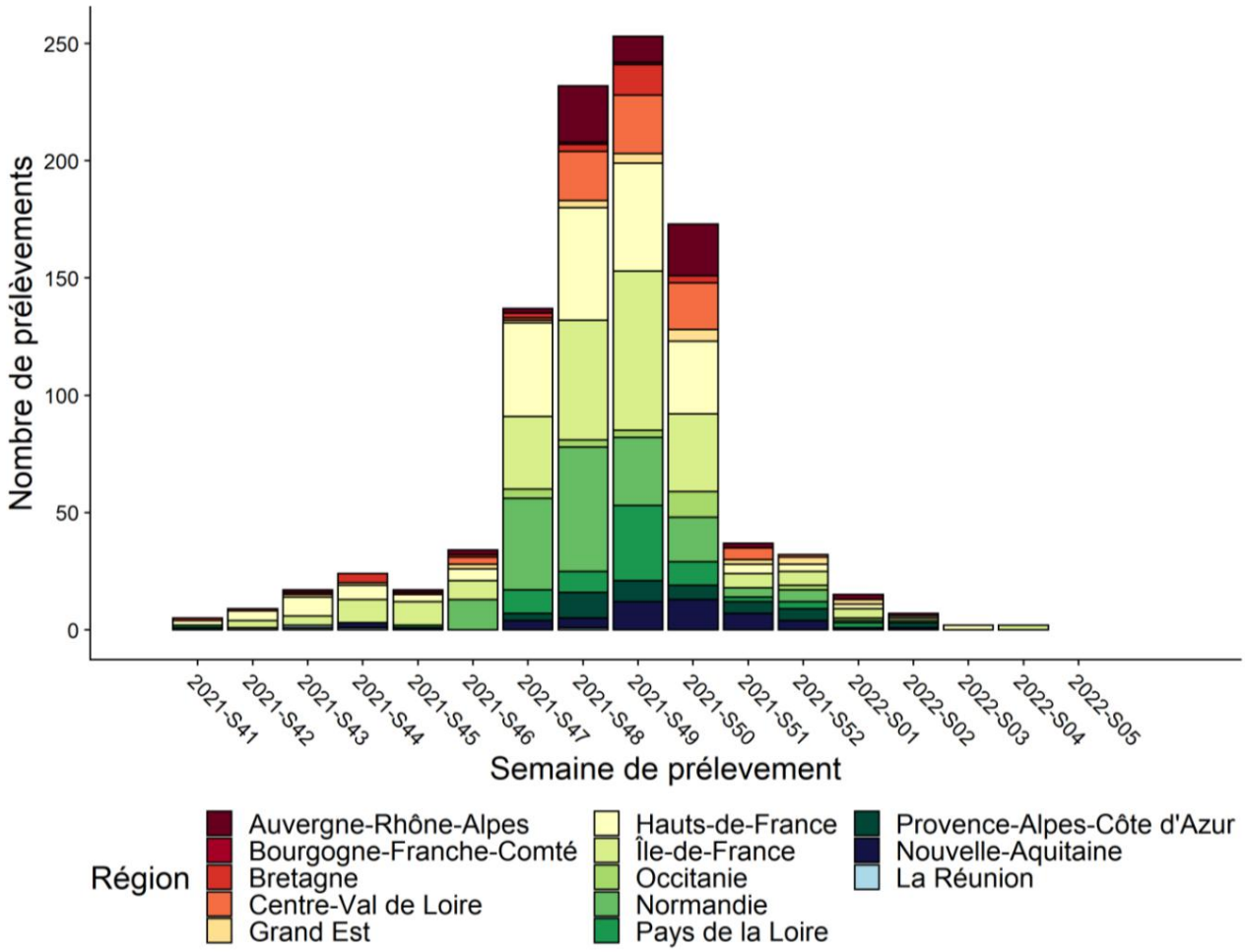

Figure 6: Number of sequenced samples classified as VOI B.1.640, by region and by week of sampling (source: EMERGEN, at 02/21/2022 at 12 p.m.)

4.2. In the DROMs

During the summer of 2021, the VOC Delta had also replaced the variants which were predominant the DROMs (Alpha in the West Indies, Beta in Reunion and Mayotte, and Gamma in Guyana). But Delta was also quickly replaced there by Omicron during December 2021/January 2022. Screening data indicates that the **Omicron VOC** is now largely in the majority in DROMs, with a proportion of A0C0 screening tests greater than 99% in S07 .

This rapid replacement of Delta by Omicron is also observed in DROMs by sequencing. Over the period from 01/10 to 02/06/2022, Omicron represented all the interpretable sequences in Mayotte (out of 17 interpretable sequences), 94% in Martinique, 94% in Reunion, 90% in Guyana and 97% in Guadeloupe (EMERGEN data as of 02/22/2022, all sequencing indications combined). Among the Omicron sequenced samples, the majority belonged to the BA.1 sub-lineage, with two BA.2 sequences identified in Guadeloupe, one in Guyana and 95 in Reunion, i.e. 4% of the Omicron sequences in this territory.

During Flash investigations S44 (01/11/2021) to S06-2022 (07/02/2022), only Delta and Omicron VOCs were detected in DROMs.

5. Conclusion as of 02/23/2022

The international situation is today characterized by a **dominance of the Omicron VOC,** which has rapidly replaced the Delta variant since its emergence at the end of November 2021. In France, Omicron has gone from less than 10% of cases to more than 90% in less than 'a month. This very rapid growth of Omicron attests to greater **competitiveness compared to Delta,** which is based on a greater escape from the immune response, both post-infection and post-vaccination, but also on intrinsic properties favoring its transmission. However, the public health impact of Omicron is mitigated by its association with less severe clinical forms, leading to a lesser impact on the health system. Thus, during the Omicron wave, a number of countries lifted the majority of control measures while the incidence was at very high levels.

As previously observed with the Delta variant, **the massive diffusion of Omicron in the world is associated with a genetic diversification within this variant and the progressive appearance of sub-lineages.** In particular, the BA.1 sub-lineage, which has mostly circulated since the emergence of Omicron, is now subdivided into more than ten sub-lineages. To date, only the BA.2 sublineage appears to have different characteristics compared to other Omicron sublineages, with higher transmissibility. **Although BA.1 was the majority until now, we are seeing a gradual replacement of BA.1 by BA.2 in European countries, including France.** Modeling studies predict that BA.2 will be predominant in France around mid-/end-February, which seems to be confirmed with the most recent epidemiological data. However, **BA.2 should only have a small impact on the decline of the epidemic wave** initiated a few weeks ago and linked to strong collective immunity generated by this large wave and the vaccination. These projections are consistent with the observations made in the Scandinavian countries, where the proportion of BA.2 is the highest, and where the incidence is decreasing. Thus, the differences between BA.1 and BA.2 do not seem sufficient to substantially modify the epidemic situation.

Until now, the genetic evolution of SARS-CoV-2 and the emergence of new variants has mainly relied on the accumulation of individual mutations. The emergence of the VOC Omicron was an atypical event, because this variant had accumulated a significant number of mutations compared to the circulating variants at the time of its detection. In coronaviruses, **recombinations are another major factor in evolutionary divergence.** When an individual is co-infected by two different variants, a new strain, whose genome is a mosaic of the two initial variants, can emerge. Before the emergence of Omicron, very few recombination events between two SARS-CoV-2 variants were reported, because the genetic proximity between the circulating viruses made the detection of recombinants impossible. But between December 2021 and January 2022, Delta and Omicron co-circulated in a large epidemic wave, which increased the likelihood of the emergence of recombinants. Several detections of Delta/Omicron recombinants have been reported, including one in France. These recombinants are subject to increased monitoring, as they constitute major evolutionary events. It is difficult to predict what their characteristics will be in relation to the variants from which they are derived, and therefore their impact on public health in the event of circulation in the population.

The situation in France in terms of circulating variants has now stabilized, with a dominance of the Omicron variant. The Omicron wave was associated with a record number of infections but also with a limited impact on the hospital system compared to Delta, in agreement with the characteristics of this variant. However, the emergence of a new different variant of Omicron cannot be ruled out. It is therefore important to maintain active surveillance of SARS-CoV-2 variants, in order to identify new variants as quickly as possible, determine their characteristics and assess their impact on public health. In France, this **effective genomic monitoring** is based on the strong sequencing activity of the EMERGEN consortium, which is currently able to detect an early signal of increased circulation of a variant, lineage or mutation.

References

1. GP designations. Omicron sublineage with potentially beneficial mutation S:346K - issue #360 2021 [Available from: https://github.com/cov-lineages/pango-designation/issues/360.
2. Desingu PA, Nagarajan K, Dhama K. Emergence of Omicron third lineage BA.3 and its importance. Journal of Medical Virology.n/a(n/a).
3. WHO. Weekly epidemiological update on COVID-19 - 22 February 2022, edition 80 2022 [Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---22-february-2022.
4. UKHSA. SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing 33. 2022. 21/02/2022 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1041307/Technical Briefing-33.pdf. Last accessed
5. Jalali N, Brustad HK, Frigessi A, MacDonald E, Meijerink H, Feruglio S, et al. Increased household transmission and immune escape of the SARS-CoV-2 Omicron variant compared to the Delta variant: evidence from Norwegian contact tracing and vaccination data. medRxiv. 2022:2022.02.07.22270437.
6. Sentis C, Billaud G, Bal A, Frobert E, Bouscambert M, Destras G, et al. SARS-CoV-2 Omicron variant, lineage BA.1, is associated with lower viral load in nasopharyngeal samples compared to Delta variant. medRxiv. 2022:2022.02.02.22269653.
7. Suzuki R, Yamasoba D, Kimura I, Wang L, Kishimoto M, Ito J, et al. Attenuated fusogenicity and pathogenicity of SARS-CoV-2 Omicron variant. Nature. 2022.
8. Han P, Li L, Liu S, Wang Q, Zhang D, Xu Z, et al. Receptor binding and complex structures of human ACE2 to spike RBD from omicron and delta SARS-CoV-2. Cell. 2022;185(4):630-40.e10.
9. Hui KPY, Ho JCW, Cheung Mc, Ng Kc, Ching RHH, Lai Kl, et al. SARS-CoV-2 Omicron variant replication in human bronchus and lung ex vivo. Nature. 2022.
10. Peacock TP, Brown JC, Zhou J, Thakur N, Newman J, Kugathasan R, et al. The SARS-CoV-2 variant, Omicron, shows rapid replication in human primary nasal epithelial cultures and efficiently uses the endosomal route of entry. bioRxiv. 2022:2021.12.31.474653.
11. Kremer C, Braeye T, Proesmans K, André E, Torneri A, Hens N. Observed serial intervals of SARS-CoV-2 for the Omicron and Delta varaints in Belgium based on contact tracing data, 19 November to 31 December 2021. medRxiv. 2022:2022.01.28.22269756.
12. Song JS, Lee J, Kim M, Jeong HS, Kim MS, Kim SG, et al. Serial Intervals and Household Transmission of SARS-CoV-2 Omicron Variant, South Korea, 2021. Emerg Infect Dis. 2022;28(3):756-9.
13. Landon E, Bartlett AH, Marrs R, Guenette C, Weber SG, Mina MJ. High Rates of Rapid Antigen Test Positivity After 5 days of Isolation for COVID-19. medRxiv. 2022:2022.02.01.22269931.
14. UKHSA. SARS-CoV-2 variants of concern and variants under investigation in England, Technical Briefing 35 - 28/01/2022 from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1050999/Technical Briefing-35-28January2022.pdf. [Available
15. (SSI) SSI. Risk assessment of Omicron BA.2 - 28/01/2022 /media/arkiv/ [Available from: https://en.ssi.dk/-subsites/covid19/risikovurderinger/2022/risk-assessment-of-omicron-ba2.pdf?la=en.
16. Elliott P, Eales O, Bodinier B, Tang D, Wang H, Jonnerby J, et al. Post-peak dynamics of a national Omicron SARS-CoV-2 epidemic during January 2022. medRxiv. 2022:2022.02.03.22270365.
17. Lyngse FP, Kirkeby CT, Denwood M, Christiansen LE, Mølbak K, Møller CH, et al. Transmission of SARS-CoV 2 Omicron VOC subvariants BA.1 and BA.2: Evidence from Danish Households. medRxiv. 2022:2022.01.28.22270044.
18. Yamasoba D, Kimura I, Nasser H, Morioka Y, Nao N, Ito J, et al. Virological characteristics of SARS-CoV-2 BA.2 variant. bioRxiv. 2022:2022.02.14.480335.
19. Eggink D, Andeweg SP, Vennema H, van Maarseveen N, Vermaas K, Vlaemynck B, et al. Increased risk of infection with SARS-CoV-2 Omicron BA.1 compared with Delta in vaccinated and previously infected individuals, the Netherlands, 22 November 2021 to 19 January 2022. Eurosurveillance. 2022;27(4):2101196.
20. Yu J, Collier A-rY, Rowe M, Mardas F, Ventura JD, Wan H, et al. Comparable Neutralization of the SARS-CoV 2 Omicron BA.1 and BA.2 Variants. medRxiv. 2022:2022.02.06.22270533.
21. Vanshylla K, Tober-Lau P, Gruell H, Münn F, Eggeling R, Pfeifer N, et al. Durability of Omicron-neutralizing serum activity following mRNA booster immunization in elderly individuals. medRxiv. 2022:2022.02.02.22270302.
22. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Amir O, Freedman L, et al. Protection by 4th dose of BNT162b2 against Omicron in Israel. medRxiv. 2022:2022.02.01.22270232.
23. Moss P. The T cell immune response against SARS-CoV-2. Nat Immunol. 2022;23(2):186-93.
24. Keeton R, Tincho MB, Ngomti A, Baguma R, Benede N, Suzuki A, et al. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. Nature. 2022.

25. Liu J, Chandrashekar A, Sellers D, Barrett J, Jacob-Dolan C, Lifton M, et al. Elicit Highly Conserved Vaccines Cellular Immunity to SARS-CoV-2 Omicron. Nature. 2022.
26. Veneti L, Bøås H, Bråthen Kristoffersen A, Stålcrantz J, Bragstad K, Hungnes O, et al. Reduced risk of hospitalization among reported COVID-19 cases infected with the SARS-CoV-2 Omicron BA.1 variant compared with the Delta variant, Norway, December 2021 to January 2022. Eurosurveillance. 2022;27(4):2200077.
27. Wang L, Berger NA, Davis PB, Kaelber DC, Volkow ND, Xu R. Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of Omicron. medRxiv. 2022:2021.12.30.21268495.
28. Ulloa AC, Buchan SA, Daneman N, Brown KA. Early estimates of SARS-CoV-2 Omicron variant severity based on a matched cohort study, Ontario, Canada. medRxiv. 2021:2021.12.24.21268382.
29. Hussey H, Davies MA, Heekes A, Williamson C, Valley-Omar Z, Hardie D, et al. Assessing the clinical severity of the Omicron variant in the Western Cape Province, South Africa, using the diagnostic PCR proxy marker of RdRp target delay to distinguish between Omicron and Delta infections – a survival analysis. medRxiv. 2022:2022.01.13.22269211.
30. Kahn F, Bonander C, Moghaddassi M, Rasmussen M, Malmqvist U, Inghammar M, et al. Risk of severe COVID 19 from the Delta and Omicron variants in relation to vaccination status, sex, age and comorbidities – surveillance results from southern Sweden. medRxiv. 2022:2022.02.03.22270389.
31. Auvigne V, Vaux S, Le Strat Y, Schaeffer J, Fournier L, Montagnat C, et al. Serious hospital events following symptomatic infection with Sars-CoV-2 Omicron and Delta variants: an exposed-unexposed cohort study in December 2021 from the COVID-19 surveillance databases in France. medRxiv. 2022:2022.02.02.22269952.
32. Maisa A, Spaccaferri G, Fournier L, Schaeffer J, Deniau J, Rolland P, et al. First cases of Omicron in France are exhibiting mild symptoms, November 2021-January 2022. Infectious Diseases Now. 2022.
33. (SSI) SSI. Now, an Omicron variant, BA.2, accounts for almost half of all Danish Omicron-cases [Available from: https://en.ssi.dk/news/news/2022/omicron-variant-ba2-accounts-for-almost-half-of-all-danish-omicron-cases.
34. UKHSA. SARS-CoV-2 variants of concern and variants under investigation in England, Technical Briefing 37 - 02/25/2022 2022 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1057359/Technical Briefing-37-25February2022.pdf.
35. Turkahia Y, Thornlow B, Hinrichs A, McBroome J, Ayala N, Ye C, et al. Pandemic-Scale Phylogenomics Reveals Elevated Recombination Rates in the SARS-CoV-2 Spike Region. bioRxiv. 2021:2021.08.04.455157.
36. Jackson B, Boni MF, Bull MJ, Colleran A, Colquhoun RM, Darby AC, et al. Generation and transmission of interlineage recombinants in the SARS-CoV-2 pandemic. Cell. 2021;184(20):5179-88.e8.
37. Sekizuka T, Itokawa K, Saito M, Shimatani M, Matsuyama S, Hasegawa H, et al. Genome Recombination between Delta and Alpha Variants of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). medRxiv. 2021:2021.10.11.21264606.
38. He Y, Ma W, Dang S, Chen L, Zhang R, Mei S, et al. Possible recombination between two variants of concern in a COVID-19 patient. Emerging Microbes & Infections. 2022;11(1):552-5.
39. GP designations. Potential Delta (AY.4) and BA.1 recombinant in European countries - issue #444 2022 [Available from: https://github.com/cov-lineages/pango-designation/issues/444.
40. Colson P, Delerce J, Burel E, Dahan J, Jouffret A, Fenollar F, et al. Emergence in Southern France of a new SARS-CoV-2 variant of probably Cameroonian origin harboring both substitutions N501Y and E484K in the spike protein. medRxiv. 2021:2021.12.24.21268174.
41. Bosetti P, Kiem CT, Andronico A, Paireau J, Emergen C, Cauchemez S. Dynamics of the BA.2 subvariant in metropolitan France. Mathematical Modeling of Infectious Diseases Unit, Institut Pasteur, University of Paris, CNRS UMR2000; 2022 02/22/2022.
42. Mattia M, Laura DD, EMERGEN, Vittoria C. Assessment of the Omicron BA.2 sub-lineage presence and growth rate in regions of France. INSERM, Sorbonne University, Pierre Louis Institute of Epidemiology and Public Health, Paris, France; 2022 02/15/2022.