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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 03/23/2022

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 03/23/2022

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):

- The VOC category of the variant classification system has been subdivided into two sub-categories: circulating VOCs and non-circulating VOCs;
- To date, 2 variants are classified as circulating VOCs, 3 as non-circulating VOCs, 1 as VOI and 2 as VUM;
- Since the last risk analysis, the recombinant AY.4/BA.1 (XD) has been classified as VUM, due to its genetic characteristics derived from the parental VOCs (Delta AY.4 and Omicron BA.1).

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 S11 was 99.5% for the A0C0 proxy and 98.4% for the D1 proxy;
- The L452R (C1) mutation, present mainly in Delta, is currently detected at very low levels, with a detection proportion of 0.2% in S11.

Genomic surveillance and public health impact of variants (VOC, VOI, VUM)

- The sequencing data confirm 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 99.8% of interpretable sequences in the Flash survey of 07/03/2022; • The BA.2 sub-lineage of the Omicron variant is now the majority in France: it represented 73% Omicron sequences identified during the Flash investigation of 07/03/2022;
- VOC 21A/I/J Delta (B.1.617.22, AY*) has not been detected since the Flash investigation of 02/14/2022. VOI 20A/C (B.1.640) has not been detected during Flash surveys since 01/10/2022, but a few cases have been identified for other sequencing indications;
- As of 03/21/2022, 44 sequences corresponding to VUM XD have been identified in France. It has never exceeded 0.1% during Flash surveys and does not appear to be increasing. 54 cases confirmed (by sequencing) or suspected (linked to a confirmed case) of infection by this variant were investigated by the regional units of Public Health France in collaboration with the CNR and the laboratories of the EMERGEN consortium.

Table 1: Classification of variants on 03/23/2022 and detection in mainland France in surveys Flash

Variants of concern (VOC)		Variations to follow (VOI)	Variants under evaluation (VUM)
circulating	**Not circulating**		
21A/I/J (B.1.617.2/AY.*, Delta) Not detected from Flash S07 (02/14)	**20I (V1, B.1.1.7/Q.*, Alpha)** Not detected since Flash S46 (15/11)	**20A/C (B.1.640)** Not detected from Flash S02 (10/01)	**20B (B.1.1.318)** Not detected since Flash S49 (06/12)
21K/L/M (B.1.1.529/BA.*, Omicron) 99.8% of sequences (Flash S10)	**20H (V2, B.1.351*, Beta)** Not detected since Flash #19 (10/08)		**XD (recombinant AY.4/BA.1)** <0.1% of sequences (Flash S10-2022)
	20J (V3, P.1/P.1.*, Gamma) Not detected since Flash #23 (07/09)		

*Update of the risk analysis as of 03/23/2022. The data given concerns metropolitan France. The WHO nomenclature assigned to certain variants is added in parentheses (Greek alphabet). * indicates points of this lineage carried out on 03/07/2022: data on 2,233 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. Circulating VOCs (variants of concern): Delta and Omicron

International epidemiological situation

The world situation today is characterized by the **dominance of VOC Omicron on a global scale,** VOC Delta being the only other VOC detected at non-negligible levels (1). In terms of impact Overall cases, the situation is contrasted between the different regions: incidence still falling for the Africa, Americas, South-East Asia and Eastern Mediterranean regions, re-increase in the number of cases in the Western Pacific and stabilization in Europe. The majority of countries now report almost exclusive distribution of Omicron. This variant represented > 99.9% (278,752/278,865) of the sequences deposited on the international GISAID database between 02/22 and 03/21/2022, compared to 98.2% (903,591/920,058) for the period from 01/22 to 02/21/2022 (data as of 03/21/2022). **VOC Delta is very little detected** today internationally, with <0.1% (110/278,865) of sequences deposited on GISAID between 02/22 and 03/21/2022, compared to 0.4% (3,976/920,058) for the period from 22/01 to 21/02/2022. These data should, however, be interpreted in light of the differences between the surveillance systems of different countries, in particular sequencing capacities, submission deadlines and sample selection biases.

Omicron VOC Features

The Omicron variant is characterized by a transmission advantage compared to previously circulating variants, in particular the Delta variant which was predominant when Omicron emerged. This advantage explains the rapid replacement of Delta by Omicron observed worldwide. While part of this transmissibility advantage is intrinsic to Omicron, which also exhibits increased stability in the environment (2), a major factor is Omicron's extensive evasion of the immune response. Indeed, *in vitro* studies have shown reduced serum neutralization of Omicron by post-vaccination and post-infection antibodies. Vaccine efficacy (VE) estimates, while they vary according to the type of vaccine administered and the number of doses, are all in favor of limited protection against infection. EV estimates
against Omicron remain very high for severe forms. Booster administration significantly improves VE in different studies of different vaccines, but more data are needed to estimate whether this response is sustained over time. Evasion of the immune response is also associated with rates of reinfection with Omicron (following prior infection with another variant)
higher than for previously circulating variants.

The clinical presentation of Omicron infections differs from that of previously circulating variants: anosmia (loss of smell) and ageusia (loss of taste) are less common, and severe forms are rarer. The significant decrease in the hospitalization rate associated with Omicron compared with other variants is a major factor limiting its impact on public health (3). In terms of treatments, studies on the efficacy of monoclonal antibodies reported retained neutralizing activity for three monoclonal antibodies with broad neutralizing activity (Sotrovimab, S2X259 and S2H97) but reduced efficacy for the others. No differences in antiviral efficacy have been reported. Finally, the effectiveness of diagnostic tests (PCR or antigenic) does not seem to be reduced for Omicron.

In summary, the three major characteristics of Omicron are its high transmissibility, its immune escape and its lower severity. More detailed information on the characteristics of Omicron can be found in previous risk analyzes and, in English, in the WHO epidemiological report of 08/03/2022 (1).

Omicron VOC sublineages

As of 03/21/2022, 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). Thirty-six sub-lineages of BA.1 have also been defined, some of which also have sub-lineages (BA.1.1, BA.1.13, BA.1.15, BA.1.16 and BA.1.17) (4). 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.

On a global scale, **the BA.2 sub-lineage is today the most frequent with 66%** of the 278,752 Omicron sequences deposited on GISAID between 02/22 and 03/21/2022, compared to 22% between 01/22 and 02/21/2022 (data as of 03/21/2022). The increase in BA.2 came at the expense of BA.1, which was previously the majority sub-lineage. Between 02/22 and 03/21, 9% of Omicron sequences corresponded to the BA.1 sublineage and 23% to its BA.1.1 sublineage, compared to 32% and 5% between 01/22 and 21 /02/2022. The BA.3 sublineage is little detected, with only 648 sequences available in total (source: GISAID on 03/21/2022)

The first circulating Omicron sub-lineage being BA.1, the first available data on Omicron's characteristics correspond to this sub-lineage, which serves as a reference. To date, only the BA.2 sub-lineage seems to have different characteristics compared to BA.1. Indeed, the available data indicate that BA.2 is more transmissible than BA.1 (secondary attack rate of 39% for BA.2 against 29% for BA.1) (5). A study also estimates that the generation interval (time between two cases) of BA.2 is 15% lower than that of BA.1 (6). These differences in transmissibility and kinetics are at the origin

higher growth rate for BA.2 and explain the gradual replacement of BA.1 by BA.2 observed worldwide (7-9). The molecular mechanisms behind this growth advantage of BA.2 are not yet fully elucidated, although some differences have been identified in terms of
replication and fusogenicity (10).

This difference in transmissibility seems to be due to intrinsic factors and not to a greater immune escape. Indeed, several *in vitro* studies have shown a similar serum neutralization of BA.1 and BA.2 by post-vaccination and post-infection antibodies (11, 12). Vaccine efficacy analyzes from Qatar also support similar vaccine efficacy against symptomatic infections for BA.1 and BA.2 (13). If BA.2 reinfections after BA.1 infection have been detected, they remain rare, which is another element in favor of cross-protection between the two sublineages (14-16).

In terms of severity, preliminary analyzes from Denmark and England found similar risks of hospitalization following BA.1 or BA.2 infection (17, 18). A study in South Africa confirmed these findings of similar severity of the two Omicron sublines (19). In terms of treatment, a French study showed differences in the effectiveness of four monoclonal antibodies (out of nine tested): Cilgavimab (effective against BA.2 but not BA.1), Imdevimab (better effectiveness against BA.1 than BA. 2), Adintrevimab and Sotrovimab (effective against BA.1 but not BA.2) (20). The combination Evusheld (Cilgavimab + Tixagevimab), used for prophylaxis in immunocompromised patients, remained effective against BA.1 and BA.2.

Different recombinants between the BA.1 and BA.2 sub-lines have been detected in several countries (United Kingdom, Denmark, Finland, Germany, Israel). However, BA.1 and BA.2 having very different characteristics similar, the likelihood that a BA.1/BA.2 recombinant will have completely different characteristics is low. In the absence of clinical impact, the identification of such recombinants is an illustration of quality genomic monitoring, which makes it possible to detect complex signals at low frequency levels, in the absence of a clinical signal. or public health.

2.2. Non-circulating VOCs (variants of concern): Alpha, Beta and Gamma

The **Alpha, Beta** and **Gamma** variants have, by their characteristics in terms of transmissibility, escape from the immune response and severity, a greater impact on public health compared to the Wuhan strain. For more information on the characteristics of these variants, refer to Tables 5, 6 and 7 of the risk analysis of 07/28/2021. These intrinsic characteristics justify their VOC classification.
However, these three VOCs have not been detected in mainland France or in the DROMs during Flash surveys for more than 16 weeks (since Flash S46, Flash #23 and Flash #24, respectively). They are therefore today classified as **non-circulating VOCs.** Internationally, Alpha, Beta and Gamma were **detected very little or not** at all over the period from 02/22 to 03/21/2022 (3, 0 and 0 of 278,865 sequences, respectively).

2.3. VOI (variants to follow): B.1.640

Variant 20A/C (B.1.40) has been classified as VOI since the risk analysis of 05/01/2022. A total of 818 **B.1.640** sequences were deposited in the international GISAID database as of 03/21/2022, of which 66% come from France (540, Figure 1).

The other countries that have identified this virus are the Republic of Congo (N=42), Germany (N=33) and the United States (N=30). Old sequences from India and the United States seem to have been reassigned to the B.1.640 lineage, but this observation should be taken with caution. The B.1.640 sequences identified mainly correspond to the B.1.640.1 sublineage with 719 sequences out of 769 (93%). Only 50 sequences of the B.1.640.2 sublineage were available on the GISAID database as of 02/21/2021, including 36 from France and 3 from the United Kingdom. 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.

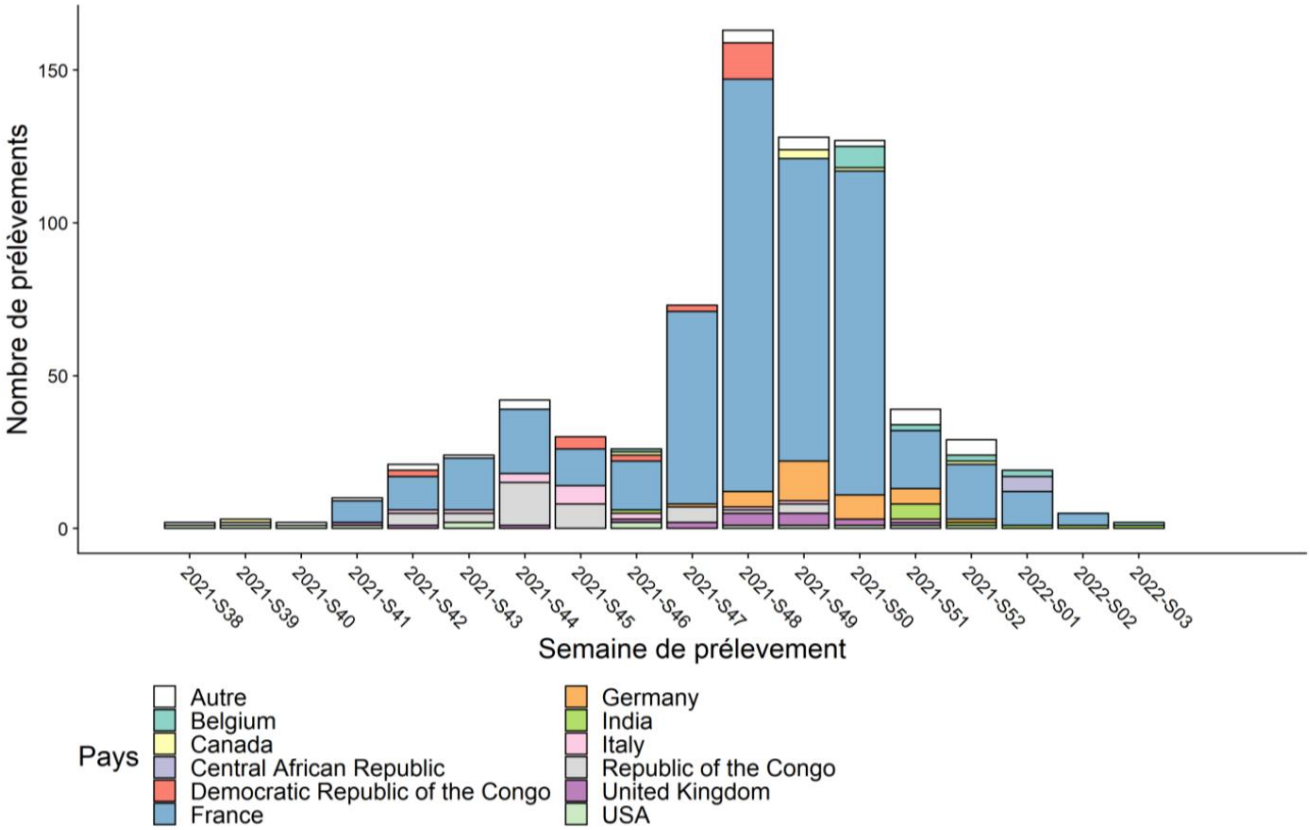

Figure 1: Number of B.1.640 sequences with a sampling date after 09/01/2022, by country and by week of sampling (source: GISAID, at 03/23/2022). Countries that have deposited two sequences or less are grouped in the "other" category.

2.4. VUM (variants under investigation): B.1.1.318 and XD

VUM 20B (B.1.1.318) was not detected internationally over the period from 22/02 to 21/03/2022 (according to the international database GISAID on 21/03/2022) .

Since 02/16/2022, a **recombinant between VOC Delta and Omicron** has been subject to enhanced monitoring in France (21). The **Pangolin XD** lineage has been assigned to this recombinant. The majority of the XD variant genome 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. The isolation of this virus by the CNR Virus des Infections Respiratoires made it possible to definitively confirm that it was indeed a recomb (sequence of the isolated strain available on GISAID, EPI_ISL_10819657). Thus, the XD variant has genetic characteristics from the two parental VOCs Delta and Omicron, but very little data is currently available on its characteristics. These genetic characteristics justify the classification of the XD variant as VUM, and this classification will be re-evaluated as new data become available.

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 0.4% in S11 among all interpretable screened tests for this mutation;

- The proportion of detection of **the L452R** (C1) mutation, present mainly in Delta, is detected today at very low levels, with 0.2% in S11;
- The proportion of samples in France with a **screening result compatible with Omicron** in S11 was 99.5% for proxy A0C0 (compared to 99.4% in S10) and 98.4% for proxy D1 (compared to 98.5% in S10).

In some territories, a discrepancy between the rate of A0C0 results and that of D1 was observed. This discrepancy could be linked to the fact that some laboratories use the 69-70 deletion for the D screening: as this deletion is carried by the Omicron BA.1 sub-lineage but not by BA.2, the BA.2 samples have an A0C0 and D0 screening result. The presence of BA.2 in these territories could therefore induce a difference, with a rate of samples screened D1 lower than the rate of samples screened A0C0.

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

4.1. In France

circulating VOCs

The **VOC Omicron currently dominates in France.** Since week S05, it has represented more than 99% of samples sequenced within the framework of Flash surveys (Table 2 and Figure 2). According to the S10 Flash survey (07/03), it represented 99.9% of interpretable sequences in mainland France (2,230/2,233).
VOC Delta, which dominated from July to mid-December in mainland France, has not been detected since the Flash S07 survey (14/02).

As the trends of the previous weeks suggested, **the BA.2 sub-lineage is now the majority in France,** with 73% of the 2,229 interpretable Omicron sequences in the Flash S10 survey (07/03/2021, Figure 3) . 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. The BA.1 and BA.1.1 sublineages now accounted for only 7% and 20% of the 2,229 Omicron sequences in the Flash S10 survey, respectively. Other recently defined BA.1 sublineages (BA.1.3, BA.1.13, BA.1.14, BA.1.15 and BA.1.15.1) have also been detected, but they remain rare. A total of 18 sequences corresponding to BA.3 have been identified as of 03/21 (according to the EMERGEN database), including only two during Flash surveys. A large proportion of these BA.3s come from the same cluster and this sub-lineage remains very rare in France.

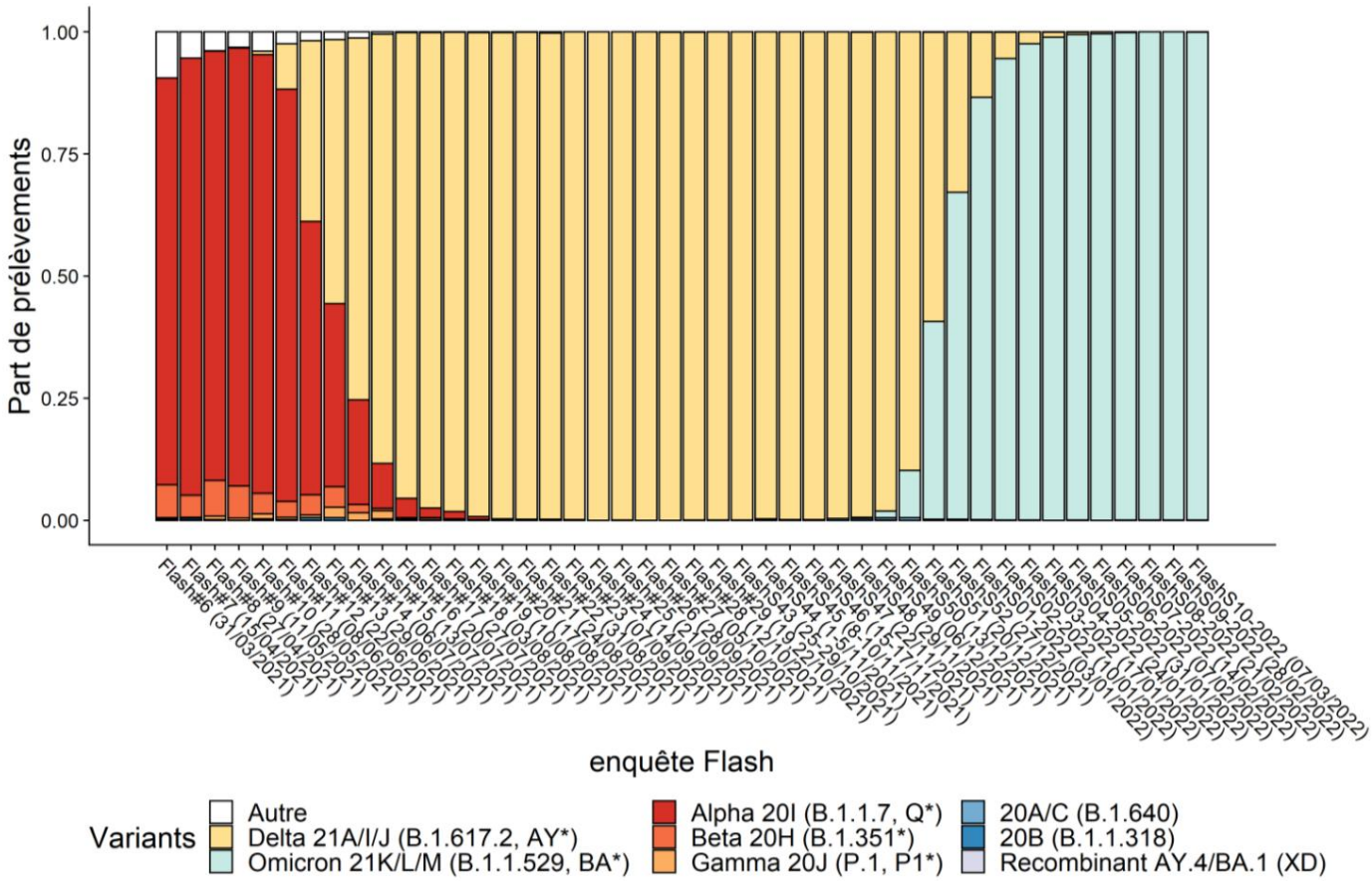

Figure 2: Evolution of the share of each VOC, VOI and VUM by Flash survey, metropolitan France (source: EMERGEN, as of 03/21/2022 at 12 p.m.). Flash S09-2022 and Flash S10-2022 data are preliminary.

*Table 2: Detection of variants during Flash S06 - Flash S10-2022 surveys, metropolitan France. *indicates inclusion of all known sublineages at this point.*

Variant	Ranking	Flash S06 (07/02/2022)		Flash S07 (02/14/2022)		Flash S08 (02/21/2022)		Flash S09# (28/02/2022)		Flash S10# (07/03/2022)	
		N	%	N	%	N	%	N	%	N	%
Delta 21A/I/J (B.1.617.2, AY*)	circulating VOC	19	0.4	7	0.2	0	0	0	0	0	0
Omicron 21K/L/M (B.1.1.529, BA*)	**Circulating VOC**	**5027**	**99.6**	**4220**	**99.7**	**5061**	**99.9**	**3159**	**99.9**	**2230**	**99.8**
Alpha 20I (B.1.1.7, Q*)	Non-circulating VOC	1	0	0	0	0	0	0	0	1	0
Beta 20H (B.1.351*)	Non-circulating VOC	0	0	0	0	0	0	0	0	0	0
Gamma 20J (P.1, P.1*)	Non-circulating VOC	0	0	0	0	0	0	0	0	0	0
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
Recombinant AY.4/BA.1 (XD)	VUM	0	0	2	<0.1	3	<0.1	2	<0.1	2	<0.1
Other		0	0	0	0	0	0	0	0	1	<0.1

Number of interpretable sequences: Flash S06: 5,047; Flash S07: 4,229; Flash S08: 5064; Flash S09: 3,161; Flash S10: 2,233

#Flash S09-2022 and Flash S10-2022 data are preliminary

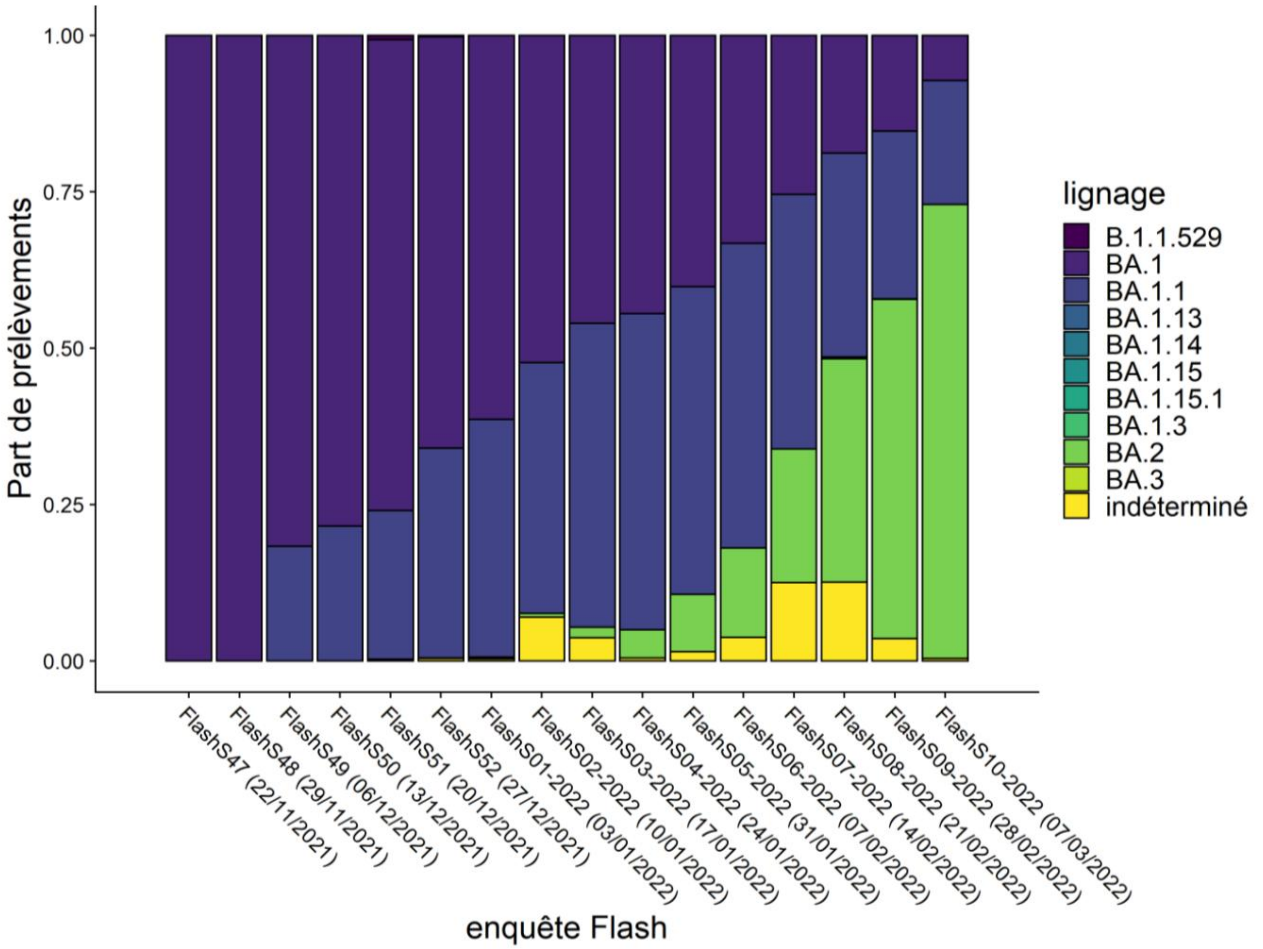

Figure 3: Sub-lineages of the Omicron variant during Flash surveys (source: EMERGEN, as of 03/21/2022 at 12).

VO

The **20A/C B.1.640 variant** was last detected in Flash surveys during Flash S02 (01/31, Table 2). All sequencing indications combined, B.1.640 has not been detected since week S06.

VUM

VUM 20B (B.1.1.318) was never detected frequently during Flash surveys (a maximum of 0.5% during Flash #12) and has not been detected since Flash S49 (06/ 12/2021).

The lineage name of the **recombinant AY.4/BA.1 (XD)** was assigned very recently and is therefore not yet available in bioinformatics analysis tools. A proxy was therefore developed to be able to follow the **VUM XD** on the basis of the detection of three mutations: ORF1a:I2820V, S:A27S and S:N764K As of 03/21/2022, 44 sequences from the EMERGEN database carried these three mutations, 21 of which were sequenced during the Flash investigations (Flash S01 to Flash S10). These samples come from different regions of metropolitan France and the oldest dates back to 03/01. The detection during Flash surveys and the geographic dispersion of the cases may suggest that this recombinant has already been circulating at very low levels since the beginning of January. However, the frequency of detection of the XD variant during Flash surveys does not seem to have increased between S01 and S10.

As of 03/21/2021, 54 cases of infection with the XD variant (36 confirmed sequenced cases and 18 suspected cases not sequenced but linked to a confirmed case) had been investigated by the regional units of Public Health France with a standardized questionnaire. Since this questionnaire had already been used during the emergence of Omicron to investigate the first cases in France, the characteristics of the cases of infections by the XD variant could be compared to those of the cases of infections by Omicron (during the investigation period mainly BA.1) (22). The oldest case was sampled on 03/01/2022 and the first investigation was carried out on 09/02/2022. The regions that reported the most cases are Normandy (N=20) and Hauts-de-France (N=13), following increased contact tracing activity in these regions.

Among the 54 cases of infection by the XD variant investigated, the sex ratio was 1.2 (29 men for 25 women, Table 3). The median age was 32 (interquartile range 18-44), with the youngest case being 4 years old and the oldest 66 years old. The median age was similar to that of cases of Omicron infections investigated between November 2021 and January 2022 (35 years), but with a different distribution (Figure 4). The proportion of XD variant cases under 20 years of age (30.6%) was significantly lower than that of Omicron cases (11.3%, p=0.0004). No case of the investigated XD variant was over 70 years old, compared to 2.7% for the Omicron cases. Returning from a trip or contact with a person returning from a trip within 14 days before the positive test was reported by 5 cases of infection with the XD variant (10%). Among these cases, 3 reported a return from Belgium, 1 from Niger and the travel history of the 5th case was unknown. A significant proportion of the cases investigated were associated with clusters (N=35, 67.3%), mostly familial. But this overrepresentation of clusters can be linked to the format of the investigations, which are based on tracing the chains of transmission and monitoring contacts.

Three cases of infection with the XD variant reported a previous infection with SARS-CoV-2 (5.9%, Table 3), i.e. a lower proportion than for the cases of infections with Omicron (14%). The vaccination status was available for 46 cases. Cases under 12 years old were excluded (N=5) because vaccination coverage is still low. 6.5% of the cases investigated were unvaccinated, 4.3% vaccinated one dose, 54.3% vaccinated two doses and 23.9% vaccinated three doses (Table 3). The proportion of cases infected with the XD variant who received three doses of vaccine was significantly higher compared to cases infected with Omicron (23.9% versus 5.4%, $p < 0.0001$). But this difference is rather linked to the different investigation periods for the two variants (January-March 2022 for the XD variant, November 2021-January 2022 for Omicron) and the increase in the proportion of the population vaccinated three doses between these two periods (7% on 11/15/2021 and 58% on 03/01/2022). The median time between the administration of the last dose and the date of the positive test was 168 days (interquartile range 89-209).

Only two of the cases investigated were asymptomatic, both children under the age of 10. The most frequent clinical signs were asthenia/fatigue (58%), headache (56%), fever (46%), cough (42%) and sore throat (38%, Figure 4). The main difference with previously investigated cases of Omicron infections was the higher rate of ageusia (odds ratio OR 2.4 [1.027-5.358], p=0.03) and anosmia (OR 1.44 [0.489-3.694], no significant). Three hospitalizations were reported among the investigated cases of infection by the XD variant. The first case was hospitalized for a reason other than COVID-19 and tested upon admission. The second case, vaccinated with one dose (Jansen), was hospitalized for less than 24 hours for fever and vomiting. The third case, vaccinated with three doses (last dose at the end of December), suffered from chronic respiratory problems and was also hospitalized for less than 24 hours. No critical care admissions and no deaths were reported, but longitudinal follow-up would be needed to confirm this. In addition, other cases are being investigated, including a hospital cluster in Auvergne-Rhône-Alpes.

Table 3: Characteristics of 54 suspected or confirmed cases of infection with the XD variant

Features		NOT	%
Region (n=54)	Brittany	1	1.9%
	Great East	4	7.4%
	Hauts-de-France	13	24.1%
	Ile-de-France	4	7.4%
	Normandy	20	37%
	Occitania	9	16.7%
	Provence-Alpes-Côte d'Azur	3	5.6%
Sex (n=54)	Women	25	46.3%
	Men	29	53.7%
Travel (n=50)	Yes	5	10%
	Nope	45	90%
Cluster (n=52)	Yes	35	67.3%
	Nope	17	32.7%
History of SARS-CoV-2 infection (n=51)	Yes	3	5.9%
	Nope	48	94.1%
Vaccination status (n=46)	Not vaccinated	3	6.5%
	Vaccinated one dose	2	4.3%
	Vaccinated two doses	25	54.3%
	Vaccinated three doses	11	23.9%
	Persons < 12 years old, not eligible	5	10.9%
Symptomatic (n=52)	Yes	50	96.2%
	Nope	2	3.8%
Risk factors (n=52)	Yes	11	21.2%
	Nope	41	78.8%
Hospitalization (n=49)	Yes	3	6.1%
	Nope	46	93.9%
Intensive care (n=49)	Yes	0	0%
	Nope	49	100%

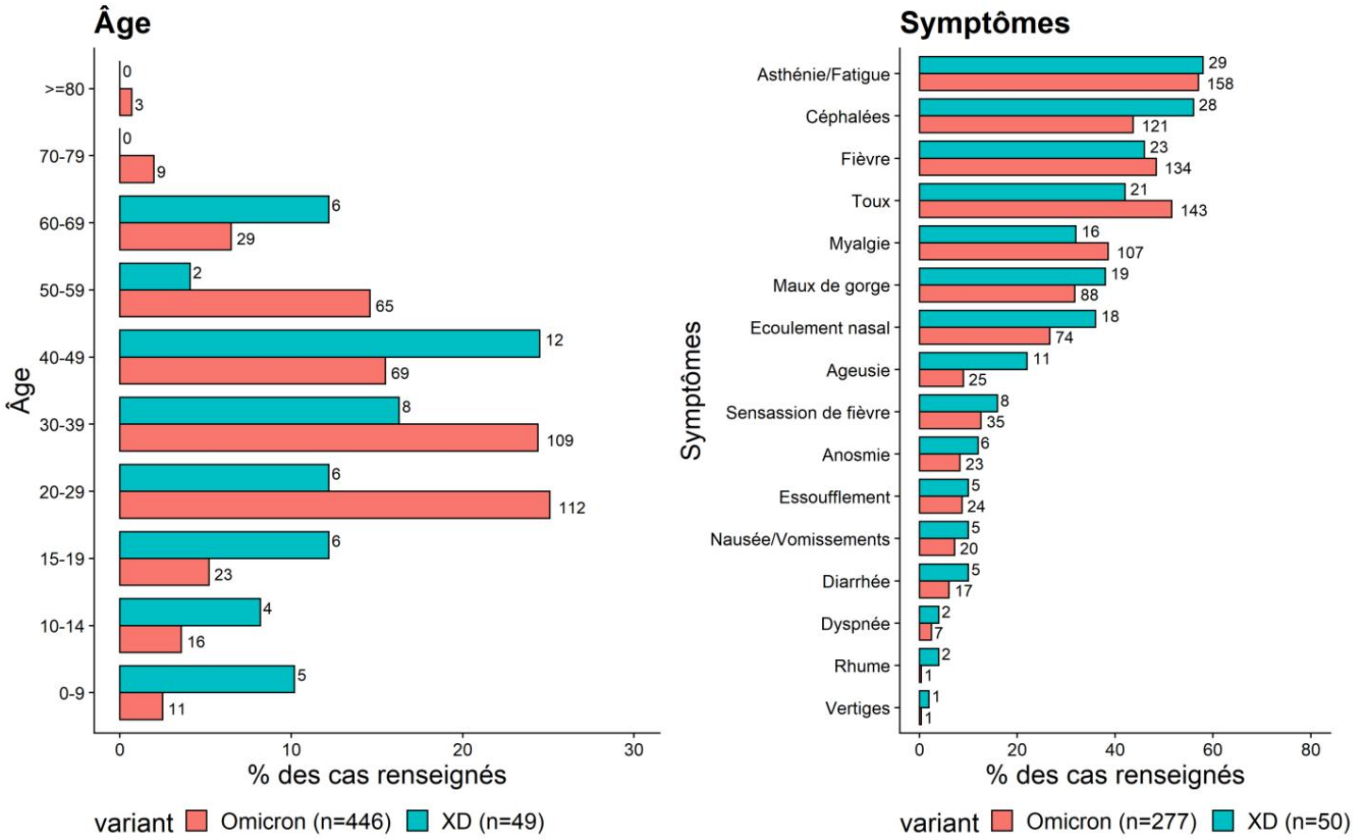

Figure 4: Age and symptoms of the 54 cases of infection with the XD variant compared to the cases of infection with Omicron previously investigated.

4.2. In the DROMs

During the summer of 2021, VOC Delta had also replaced the variants that were predominant in 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 (Figure 5). We find the **predominance of Omicron in all the DROMs :**

- In Martinique and Guadeloupe, the screening results indicate that Omicron is dominant. The rate of samples with an A0C0 screening result has been over 98% and that of D1 results over 95% since the beginning of February. Sequencing confirms these results, with Omicron representing 100% of interpretable sequences since the Flash S05 survey (out of 183 interpretable sequences);

- In Réunion, since the beginning of February, the rate of D1 screened samples has been over 99%. The percentage of Omicron among the samples sequenced during Flash surveys has been over 95% since Flash S04 (out of a total of 519 interpretable sequences);
- In French Guiana, all the samples screened since February 1 have a D1 result and the 79 samples sequenced within the framework of Flash surveys since Flash S04 correspond to the Omicron variant;

- In Mayotte, 100% of the samples screened since February 1 have a screening result in line with Omicron (D1). The number of samples sequenced in the context of Flash surveys since Flash S02 is low (N=9), but only Omicron has been detected.

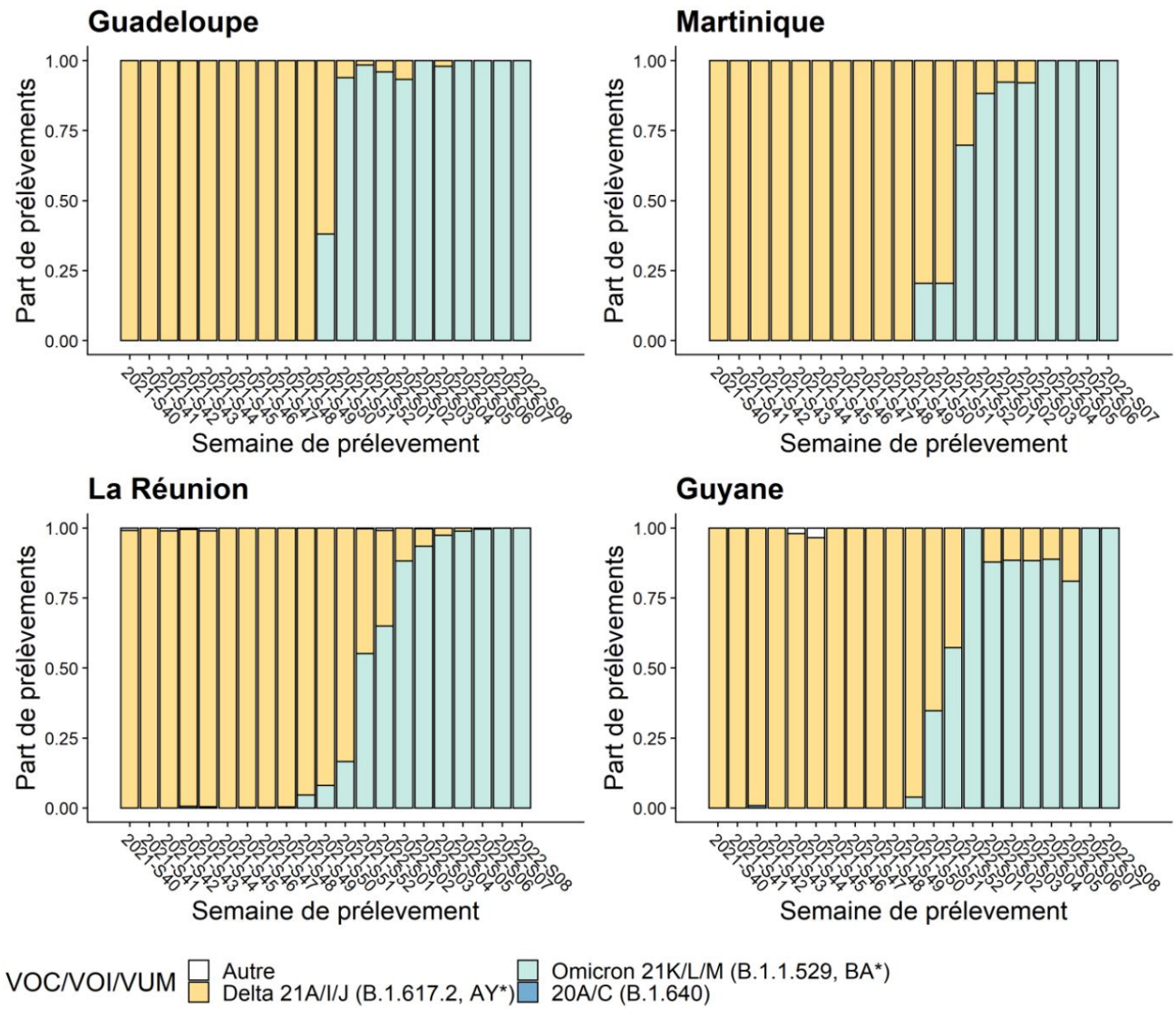

Figure 5: Evolution of the share of each VOC, VOI and VUM per sampling week (all sequencing indications combined), by region of residence (source: EMERGEN, as of 03/21/2022 at 12 p.m.). Data for weeks S07 and S08 are not consolidated.

Among the Omicron sequences, the BA.1, BA.1.1 and BA.2 sublineages have been identified in the DROMs. Despite the low numbers, the overall trend seems to be an increase in BA.2 compared to BA.1 and BA.1.1. In the Flash surveys for weeks S07 to S10, the proportion of BA.2 was 1.5% in Martinique, 17% in Guadeloupe, 18% in Réunion and 25% in Guyana. By comparison, during the Flash surveys S03 to S06, BA.2 was not detected in Martinique and Guyana, and represented 4% of the sequences in Guadeloupe and 6% in Reunion. In Mayotte, BA.2 has not yet been detected.

5. Conclusion as of 03/23/2022

The situation in France and internationally is today characterized by a **dominance of VOC Omicron,** which quickly replaced the Delta variant. The higher competitiveness of Omicron compared to Delta 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.

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 sublineage, which has mostly circulated since the emergence of Omicron, is now subdivided into more than 30 sublineages. To date, only the BA.2 sublineage appears to have different characteristics compared to other Omicron sublineages, with higher transmissibility. This difference has led to a gradual replacement of BA.1 by BA.2, and BA.2 is today the majority in international sequencing data, in the majority of European countries and in France. The transmissibility of BA.2 raises the question of its role in reversing epidemiological trends in recent weeks, marked by a rebound in incidence. However
based on modeling studies, BA.2 alone cannot explain these trends. On the other hand, **a change in the rate of transmission, linked to a decrease in respect for barrier gestures and control measures, has a strong impact on this dynamic and may be at the origin of a new wave.**

Recombinants between different variants of SARS-CoV-2 are subject to increased surveillance, 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. It is therefore crucial to maintain quality genomic monitoring in order to detect and characterize them early. The genomic monitoring in place in France via the EMERGEN consortium has enabled the identification of a **recombinant between the AY.4 sub-lineages of Delta and BA.1 of Omicron, named XD.** This recombinant has been detected during Flash surveys since the beginning of January 2022, but its prevalence does not currently seem to be increasing over time. Epidemiological analyses, *in vitro* tests and *in vivo* experiments are underway to precisely determine the characteristics of this recombinant and assess its impact on public health.

The situation in France in terms of circulating variants is currently stable, with a dominance of the Omicron variant. Since the Omicron variant is associated with less severity, its impact on the hospital system is therefore lower compared to Delta. However, the low hospitalization rate with Omicron is partly driven by the effectiveness of vaccination against severe forms. It is therefore essential to maintain high levels of immunity, among other things by administering booster doses as soon as necessary. In addition, the emergence of a new different variant of Omicron, whether or not resulting from a recombination event, cannot be excluded. **In the current epidemiological context of rising incidence, it therefore remains essential to limit the circulation of SARS-CoV-2 as much as possible, regardless of the variant.** This control involves respecting barrier gestures, in particular for people at risk and during contact with them, and by following the recommendations in the event of diagnosis of infection or close contact with a case.

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