CNR Respiratory infections virus

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 04/20/2022

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 04/20/2022

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, 2 variants are classified as circulating VOCs, 3 as non-circulating VOCs, 1 as VOI and 1 as VUM;
- Since the last risk analysis, VUM B.1.1.318 has been downgraded, due to an absence of detection in France for more than 16 weeks and its very low circulation internationally.

Surveillance by screening for mutations of interest:

- The screening results illustrate the almost exclusive circulation of Omicron throughout the country;
- The proportion of samples in France with a screening result compatible with Omicron in S15 was 99.8% for the A0C0 proxy and 98.5% for the D1 proxy;
- The L452R (C1) mutation, present mainly in Delta, is today detected at very low levels, with a detection proportion of 0.2% in S15.

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 100% of the interpretable sequences of the Flash survey of 04/04/2022; • The massive circulation of Omicron (first BA.1 then BA.2) around the world has led to the definition of sub-lineages within BA.1 and BA.2. This subdivision of BA.1 and BA.2 reflects the genetic diversification expected in an intensely circulating variant and is not in itself a public health signal;

- Two new sub-lines of Omicron, BA.4 and BA.5, have been defined and are under enhanced surveillance, based on their genetic profile. At this stage, no worrying epidemiological or clinical element is associated with them. As of 21/04/2022, one case of BA.4 and two cases of BA.5 have been identified in France ;
- The BA.2 sublineage of the Omicron variant is now ultra-dominant in France: it represented with its sublineages 99% of the Omicron sequences identified during the Flash survey of 04/04/2022;
- VOC 21A/I/J Delta (B.1.617.22, AY*) has not been detected since the Flash investigation of 07/03/2022. VOI 20A/C (B.1.640) has not been detected since week S06-2022;
- The VUM XD has never exceeded 0.1% during the Flash surveys of the year 2022 and does not seem to be increasing. 77 cases confirmed (by sequencing) or suspected (linked to a confirmed case) of infection by this variant were investigated by the regional cells of Public Health France in collaboration with the CNR and the laboratories of the EMERGEN consortium. A scientific article on the characterization of the XD variant is available in preprint.

Table 1: Classification of variants on 04/20/2022 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 S10 (07/03)	**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)	**recombinant AY.4/BA.1 (XD)** Not detected in Flash S14-2022
21K/L/M (B.1.1.529/BA.*, Omicron) 100% of sequences (Flash S14)	**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)		

*Update of the risk analysis on 20/04/2022. The data given concerns metropolitan France. The WHO nomenclature assigned to certain variants is added in parentheses (Greek alphabet). * indicates the inclusion of all sub-lineages carried out on 04/04/2022: data on 1,005 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 global situation today is characterized by the **dominance of Omicron VOC on a global scale,** with the majority of countries reporting almost exclusive circulation of Omicron (1). This variant represented 97.9% (239,796/244,820) of the sequences deposited on the international GISAID database between 03/20 and 04/19/2022, against 98.9% (640,628/647,811) for the period from 02/20 to 03/19/2022 (data as of 04/19/2022). **VOC Delta is now very little detected** internationally , with <0.1% (96 / 244 820) sequences deposited on GISAID between 03/20 and 04/19/2022. 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. Part of this transmissibility advantage is intrinsic to Omicron, which exhibits preferential airway infection

superior cell entry mechanisms, different infection kinetics and increased stability in the environment (2-6).

A major factor in Omicron's competitiveness is its extensive immune response evasion, as exemplified by reduced seroneutralization of Omicron by post-vaccination and post-infection antibodies. Vaccine efficacy (VE) estimates, if they vary according to the type of vaccine administered,
the number of doses and time since last dose all suggest limited protection against infection. However, estimates of VE against severe forms remain very high with Omicron.
Giving a booster dose significantly improves VE in different studies of different vaccines, especially in the elderly (7). This VE limited against infection but maintained against severe forms has also been observed in children and adolescents (8, 9). Finally, a fourth dose of messenger RNA vaccine, as recommended for immunocompromised people or people over 80 and authorized for people over 60, improves VE against Omicron infections and severe forms (10, 11). Evasion of the Omicron immune response is also associated with higher rates of reinfection with Omicron (following prior infection with another variant) than for previously circulating variants (12). Recent studies suggest that Omicron may be less immunogenic than Delta, with Omicron infection inducing weaker immunity in vaccinated and unvaccinated cases, but these observations remain to be confirmed (13, 14).

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 (15). The significant decrease in the hospitalization rate associated with Omicron compared to other variants is a major factor limiting its impact on public health (16). 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 epidemiological reports
WHO (17).

Omicron VOC sublineages

As of 04/19/2022, the Omicron VOC includes one parental lineage (B.1.1.529, clade 21M) and five sublineages: BA.1 (clade 21K), BA.2 (clade 21L), BA.3 (no specific clade, included in 21M), BA.4 and BA.5 (clade 21L). Thirty-six sublineages of BA.1 have been defined, some of which also have sublineages (18). The circulation of BA.2 following BA.1 has also led to the definition of sub-lineages (BA.2.1 to BA.2.22, some of these sub-lineages of BA.2 having themselves sub-lineages). Given the intensity of the circulation of Omicron in the world, a genetic diversification within this variant and the progressive appearance of sub-lineages is an expected phenomenon.

The first Omicron sub-lineage having circulated being BA.1, the first data available on the characteristics of Omicron correspond to this sub-lineage which serves as a reference. To date, only the BA.2 sublineage seems to have different characteristics compared to BA.1, with higher transmissibility and a shorter generation interval (time between two cases) (19-21). These differences in transmissibility and kinetics lead to a higher growth rate for BA.2 and explain the gradual replacement of BA.1 by BA.2 observed worldwide. Indeed, **the BA.2 sub-lineage is now the majority with 91%** of the Omicron sequences deposited on GISAID between 20/03 and 19/04/2022, against 65% between 20/02 and 19/03 /2022 (cov-spectrum.org data as of 04/19/2022). This difference in transmissibility appears to be due to intrinsic factors and not to greater immune escape (22, 23). If reinfections by BA.2 after an infection by BA.1 have been detected, they remain rare, which is an element in favor of cross-protection between the two sub-

lineages (24-26). No difference in terms of severity between BA.1 and BA.2 was observed. The effectiveness of monoclonal antibodies varies between BA.1 and BA.2, with Sotrovimab being slightly less effective against BA.2 while Evushield is less effective against BA.1 (27). Among the BA.2 sub-lineages, BA.2.9 is today the most frequent (38% of BA.2 sequences between 03/20 and 04/19/2022, according to GISAID on 04/19 /2022). The BA.2.9 sub-lineage was defined at the beginning of April but has been circulating in France and Europe since the end 2021/early 2022, without being associated with a particular epidemiological or clinical signal. Until now, BA.2.9 sequences were assigned to BA.2 and, following the subdivision of BA.2 into several sub-lineages, were reassigned to BA.2.9. This phenomenon of reassignment is frequently observed during changes in classification and the new sub-lineages which result from it are not in themselves signals of interest in terms of public health.

The BA.3 sublineage is little detected, with only 4,556 sequences available in total (source: GISAID on 04/19/2022). **The BA.4 and BA.5 sublineages were identified in early April 2022** (28). As of 04/19/2022, 234 BA.4 sequences and 199 BA.5 sequences have been submitted in GISAID. These data should be taken with caution, however, because the Pangolin lineage algorithms tend to assign these sublineages to poor quality BA.2 sequences. These two sub-lineages, mainly detected in South Africa, are quite similar to BA.2 but their Spike protein also has the L452R, F486V and R493Q mutations. The ECDC, based on these genetic characteristics, classified these sublineages as variants to watch (VOI) and asked that they be watched carefully (29). However, this call for vigilance is based solely on the genetic profiles of BA.4 and BA.5: no modification of the characteristics of these two sub-lineages has been described and they are not associated with a worrying epidemiological or clinical situation. in South Africa (where they circulate). Among the genetic characteristics that attracted the attention of the ECDC, the L452R mutation, carried by BA.4 and BA.5, has been described as one of the factors associated with the significant transmissibility of VOC Delta. It is essential to determine what impact this mutation may have in the genetic background of Omicron. An *in vitro* study suggests behavioral differences between Omicron viruses genetically modified to include or not the L452R mutation (fusogenicity, *in vitro infectivity,* Spike protein cleavage), but these data are very preliminary and need to be confirmed with ongoing data. real life (30). Overall, the L452R mutation has been identified in 0.2% of the Omicron sequences available on the GISAID database (as of 2022-04-19), and these profiles have not been associated with specific characteristics.

Different recombinants between the BA.1 and BA.2 sublines have been detected in several countries (UK, Denmark, Finland, Germany, Israel). There are thus: XE (470 sequences in GISAID on 04/19/2022), XG (179 sequences), XH (54 sequences), XJ (34 sequences), XK (15 sequences), XL (51 sequences), XM (32 sequences), XN (93 sequences), XP (57 sequences), XQ (59 sequences), XR (78 sequences) and XT (12 sequences). However, BA.1 and BA.2 being very similar, the probability that a BA.1/ BA.2 recombinant will have 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. For this reason, the BA.1/ BA.2 recombinants are now considered to belong to the Omicron VOC.

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

The Alpha, Beta and Gamma variants had, by their characteristics in terms of transmissibility, escape from the immune response and severity, a greater public health impact compared to the index strain (Wuhan). 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 are no longer or very little detected and are therefore classified as non-circulating VOCs. Internationally, **Alpha, Beta and Gamma were detected very little or not** at all over the period

from 03/20 to 04/19/2022 (2, 1 and 1 of 244,820 sequences, respectively). These few detections can also be assignment errors on poor quality sequences.

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

Variant 20A/C (B.1.640) has been classified as VOI since the risk analysis of 05/01/2022. A total of 909 B.1.640 sequences were deposited in the international GISAID database on 04/19/2022, of which 72% come from France (653). The most recent sequence deposited on GISAID has a collection date of 01/24/2022.

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

VUM 20B (B.1.1.318) has been classified since the risk analysis of 03/25/2021 due to the presence of the E484K mutation associated with a greater escape from the immune response. However, the latter has not been detected in France since week S49-2021 (source: EMERGEN on 04/19/2021, all sequencing indications combined). Since its classification, no evidence indicates that this VUM could have a worrying impact on public health. Internationally, B.1.1.318 experienced a peak in detection in May 2021, but has been detected very little since. Of the 3,969 sequences of B.1.1.318 available on the international GISAID database (as of 04/19/2022), the most recent has a sampling date of 11/27/2021. Given the absence of detection of this variant in France for more than 16 weeks, its very low or even zero circulation at the international level and the absence of elements in favor of an impact on public health, **this variant is downgraded** and no is no longer considered VUM.

During the period of co-circulation between Delta and Omicron, **heightened surveillance of co-infections** between these two variants had been initiated and it was extended over the period of co-circulation of the sub-lines of Omicron BA.1 and BA.2. In France, a study carried out on a sample of 21,387 sequences from Flash surveys between week S49-2021 and week S08-2022 identified 53 co-infections (31).
In this study, the proportion of Delta/Omicron co-infections was 0.18% and that of BA.1/BA.2 co-infections was 0.26%. The objective of this enhanced surveillance of co-infections is to detect recombination events as soon as possible, the follow-up of which is an important public health issue (more information in the risk analysis of 02/23/2022) . When a recombinant comes from two variants with different properties, such as Delta and Omicron, it is difficult to estimate what the characteristics of the recombinant will be compared to the parental variants. The more similar the two parental variants are (like BA.1 and BA.2), the lower the likelihood that a recombinant will have different characteristics.

Since 02/16/2022, the **XD recombinant (recombinant between the Delta and Omicron VOCs)** has been subject to heightened surveillance in France (32). 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. Isolation of this virus by the Respiratory Infections Virus CNR confirmed definitively that it was indeed a recombinant (sequence of the isolated strain available on GISAID, EPI_ISL_10819657). **An in-depth analysis of this recombinant was carried out in France in order to characterize this new variant and assess its impact on public health** (33). This study showed that neutralization of the XD variant by post-vaccination or monoclonal antibodies was similar to Omicron (BA.1). On the other hand, in the mouse model, the pathogenicity of the XD variant and its replication in the different zones of the respiratory system are different from Omicron (replication more efficient than BA.1 in the upper airways but less efficient in the lungs). On a global scale, the relatively low detection of the XD variant (26 sequences in GISAID as of 04/19/2022, including 7 from Denmark, 1 from the Netherlands and 18 from France) does not suggest a transmission advantage compared to to BA.1 or BA.2.

Two other recombinants between Delta and Omicron were detected enough to be assigned a lineage name. The XF variant, defined in March, circulates mainly in the United Kingdom with some sequences identified in the United States. The XS variant, defined at the beginning of April, currently circulates exclusively in the United States.

United. As of 04/19/2022, 35 XF sequences and 41 XS sequences have been submitted in GISAID. These recombinants have not been included in our classification due to their very low level of circulation in Europe.

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 <0.1% in S15 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 S15;
- The proportion of samples in France with a **screening result compatible with Omicron** in S15 was 99.8% for proxy A0C0 (compared to 99.7% in S14) and 98.5% for proxy D1 (compared to 98.3% in S14).

In some territories, a discrepancy between the rate of A0C0 results and that of D1 was observed. This discrepancy could be related to the fact that some laboratories use the 69-70 deletion for the D screening. As this deletion is carried by the Omicron sublineage BA.1 but not by BA.2, the BA.2 samples 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 1). According to the Flash survey for S14-2022 (07/03), it represented 100% of interpretable sequences in mainland France 1005/1005). VOC Delta, which dominated from July to mid-December 2021, in mainland France, has not been detected since the Flash S10-2022 survey (07/03).

Since the emergence of Omicron, 70 sub-lines or sub-sub-lines have been defined. **The BA.2 sub-lineage is now the majority in France,** with 99% of the 1,005 interpretable Omicron sequences from the Flash S14-2022 survey (04/04/2022, Figure 2). Within the BA.2 sublineage, the majority of sequences are not classified into sublineages and the most detected sublineages are BA.2.9 (8%), BA.2.6 (3%) and BA.2.3 (3%). A total of 189 sequences corresponding to BA.3 have been identified as of 04/19 (according to the EMERGEN database), including 82 during Flash surveys. As of 21/04/2022, one confirmed case of BA.4 (returned from South Africa) and two confirmed cases of BA.5 have been detected. The BA.1/BA.2 XE and XL recombinants were also detected, but at very low levels (one sequence of each on the EMERGEN database as of 04/19/2022).

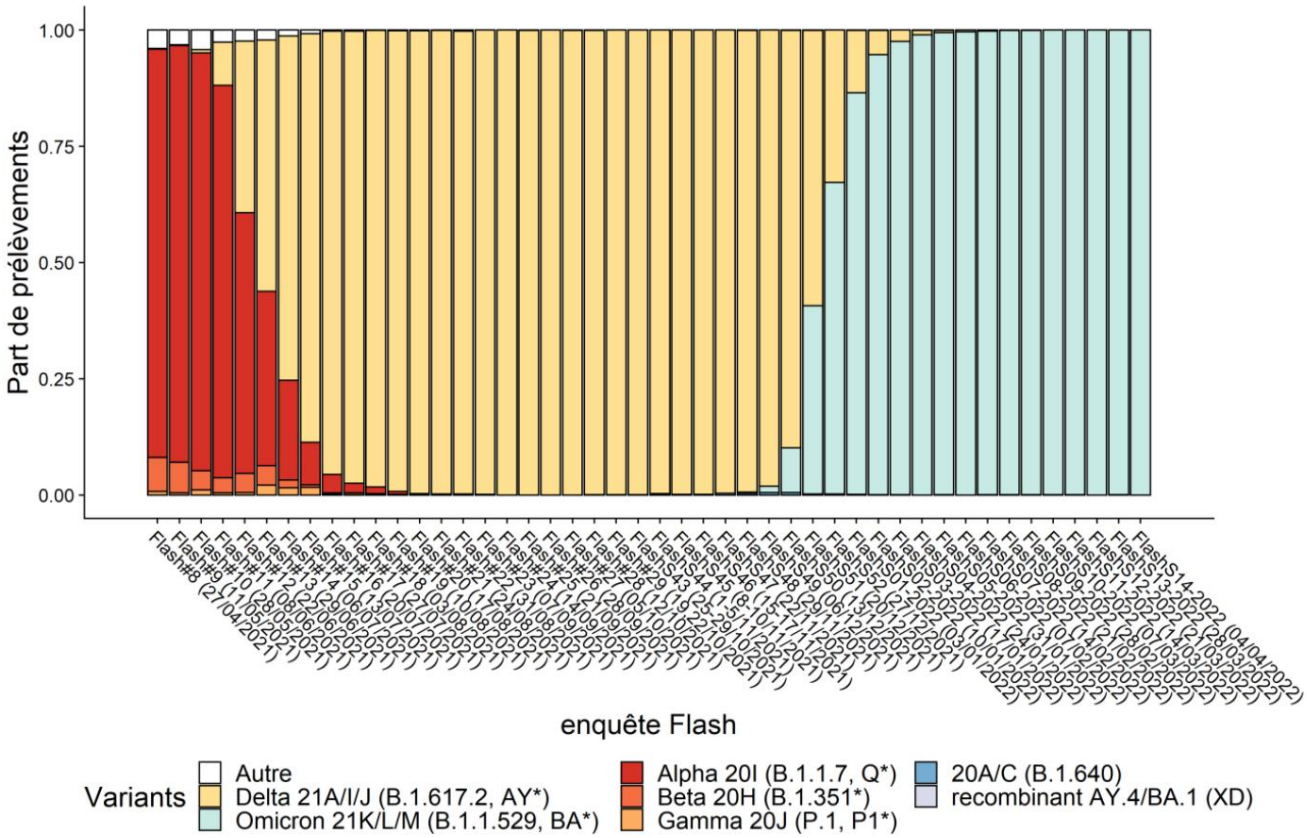

Figure 1: Evolution of the share of each VOC, VOI and VUM by Flash survey, metropolitan France (source: EMERGEN, on 04/19/2022 at 12 p.m.). Flash S13-2022 and Flash S14-2022 data are preliminary.

*Table 2: Detection of variants during Flash S10 - Flash S14-2022 surveys, metropolitan France. *indicates inclusion of all known sublineages at this point.*

Variant	Ranking	Flash S10 (07/03/2022)		Flash S11 (14/03/2022)		Flash S12 (03/21/2022)		Flash S13# (03/28/2022)		Flash S14 # (04/04/2022)	
		N	%	N	%	N	%	N	%	N	%
Delta 21A/I/J (B.1.617.2, AY*)	circulating VOC	1	<0.1	0	0	0	0	0	0	0	0
Omicron 21K/L/M (B.1.1.529, BA*)	**Circulating VOC**	**6051**	**>99.9**	**4939**	**>99.9**	**7453**	**>99.9**	**4774**	**>99.9**	**1005**	**100**
Alpha 20I (B.1.1.7, Q*)	Non-circulating VOC	0	0	0	0	0	0	0	0	0	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
Recombinant AY.4/BA.1 (XD)	VUM	3	<0.1	3	<0.1	1	<0.1	2	<0.1	0	0
Other		0	0	0	0	0	0	0	0	0	0

Number of interpretable sequences: Flash S10: 6,055; Flash S11: 4,942; Flash S12: 7,454; Flash S13: 4,776; Flash S14: 1,005

#Flash S13-2022 and Flash S14-2022 data are preliminary

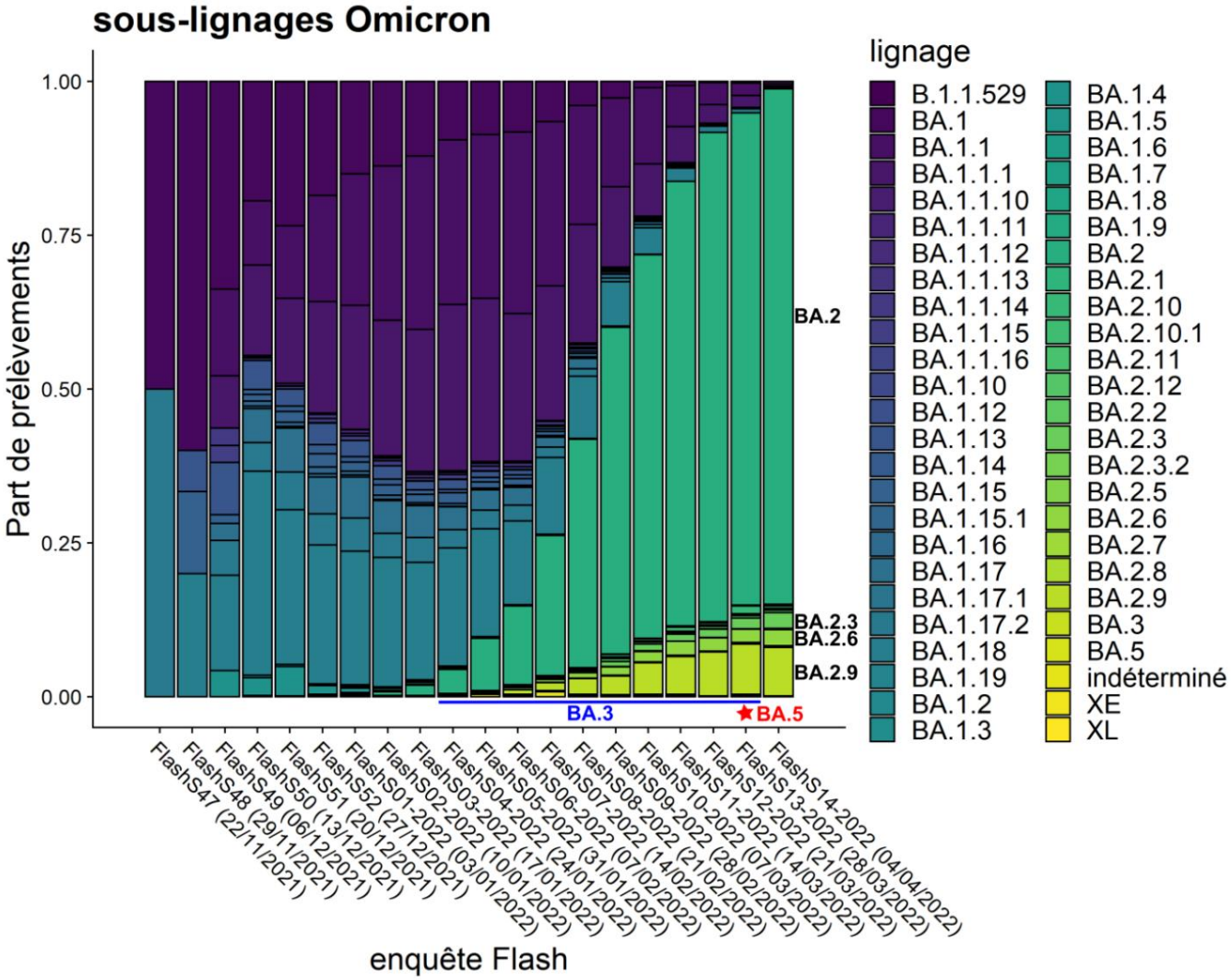

Figure 2: Sub-lineages of the Omicron variant during Flash surveys (source: EMERGEN, as of 04/19/2022 at 12). The Flash investigation where two BA.5 cases were identified is indicated by a red star. Flash surveys in which BA.3 was detected are shown in blue.

VO

The **20A/C B.1.640 variant** was last detected in Flash surveys during Flash S02-2022 (10/01). All sequencing indications combined, B.1.640 has not been detected since week S06.

VUM

The **AY.4/BA.1 (XD) recombinant** has been circulating in France since early 2022, and a total of 74 sequences have been identified. Although this variant has been detected in different regions of metropolitan France, its detection frequency during Flash surveys has never exceeded 0.1% between Flash S01-2022 (03/01/2022) and Flash S14-2022 (04/04/2022). The stable detection of the XD variant at low levels is rather in favor of a lack of competitive advantage of this variant compared to BA.2, which is the majority today.

An update of the analyzes of cases of infections by the XD variant as published in the variant risk analysis of 03/23/2022 is presented below. As of 04/15/2021, 77 cases of infection with the XD variant (54 confirmed cases and 23 suspected cases not sequenced but linked to a confirmed case) have been investigated by the cells

regional 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) (15). The regions that reported the most cases are Normandy (N=22) and Hauts-de-France (N=23), following increased contact tracing activity in these regions.

Among the 77 cases of infection by the XD variant investigated, the sex ratio was 1.1 (40 men for 37 women, Table 3). The median age was 37 years (IQS inter-quartile range 19.00-56.75), with the youngest case being 4 years old and the oldest 86 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 3).

Returning from a trip or contact with a person returning from a trip within 14 days before the positive test was reported by 6 cases of infection with the XD variant (8.2%). Among these cases, 3 reported a return from Belgium and 1 from Niger.

A large proportion of the cases investigated were associated with clusters (N=54, 72%), mostly familial. But this over-representation of clusters may be linked to the format of the investigations, which are associated with contact tracing.

Six cases of infection with the XD variant reported a previous infection with SARS-CoV-2 (8.1%, Table 3), i.e. a lower proportion than for the cases of infections with Omicron (14%, p = 0.25). The vaccination status was available for 66 cases. 4.5% of the cases investigated were unvaccinated, 4.5% vaccinated one dose, 45.5% vaccinated two doses and 33.3% vaccinated three doses. The rest corresponded to cases under the age of 12 (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 (33.3% versus 5.4%, p < 0.0001). But this difference is rather linked to the different investigation periods for the two variants (January-April 2022 for the XD variant, November 2021-January 2022 for Omicron) and the increase in the population vaccinated three doses between these two periods (7% on 11/15/2021 and 59% on 04/13/2022). The median time between the administration of the last dose and the date of the positive test was 140 days (EIQ 74-194).

Only four of the cases investigated were asymptomatic. The most frequent clinical signs were asthenia/fatigue (58%), headache (56%), fever (46%), cough (42%) and sore throat (38%, Figure 3). The main difference with previously investigated cases of Omicron infections was the higher rate of ageusia (odds ratio OR 2.4 [1.03-5.36], p=0.03) and anosmia (OR 1, 44 [0.49-3.69], not significant). Eight hospitalizations were reported among cases investigated with infection with the XD variant, four of which were part of a hospital cluster and were hospitalized for a reason other than COVID-19. No critical care admissions and no deaths were reported, but longitudinal follow-up would be needed to confirm this.

Table 3: Characteristics of 77 suspected or confirmed cases of infection with the XD variant

Features		NOT %
Region (n=77)	Auvergne-Rhône-Alpes	8 10.4%
	Brittany	1 1.3%
	Great East	4 5.2%
	Hauts-de-France	23 29.9%
	Ile-de-France	5 6.5%
	Normandy	22 28.6%
	Occitania	11 14.3%
	Provence-Alpes-Côte d'Azur	3 3.9%
Gender (n=77)	Women	37 48.1%
	Men	40 51.9%
Travel (n=73)	Yes	6 8.2%
	Nope	67 91.8%
Cluster (n=75)	Yes	54 72%
	Nope	21 28%
History of SARS-CoV-2 infection (n=74)	Yes	6 8.1%
	Nope	68 91.9%
Vaccination status (n=66)	Not vaccinated	3 4.5%
	Vaccinated one dose	3 4.5%
	Vaccinated two doses	30 45.5%
	Vaccinated three doses	22 33.3%
	Persons < 12 years old, not eligible	8 12.1%
Symptomatic (n=75)	Yes	71 94.7%
	Nope	4 5.3%
Risk factors (n=75)	Yes	24 32%
	Nope	51 68%
Hospitalization for or with COVID-19 (n=70)	Yes	8 11.4%
	Nope	62 88.6%
Intensive care (n=70)	Yes	0 0%
	Nope	70 100%

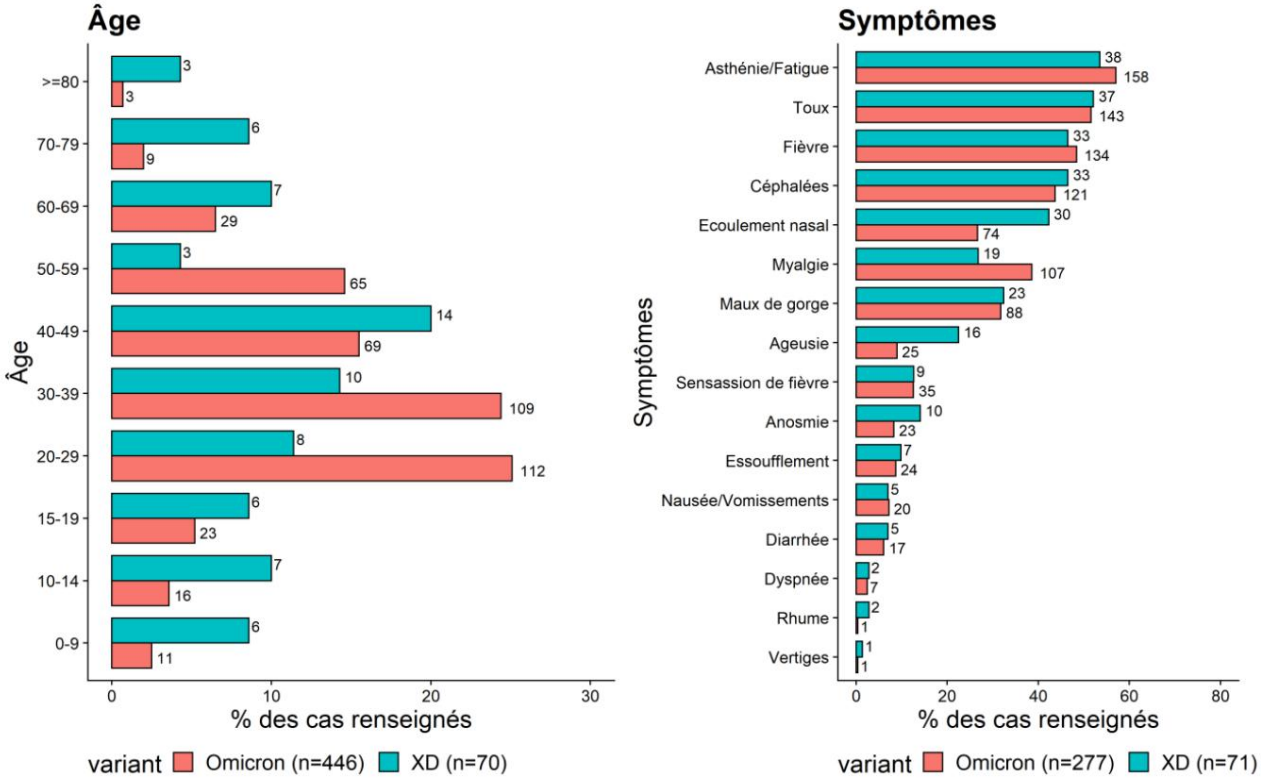

Figure 3: Age and symptoms of the 77 cases of infection with the XD variant compared to the cases of infection with Omicron previously investigated.

4.2. In the DROMs

In the DROMs as in mainland France, Delta was quickly replaced by Omicron during December 2021/January 2022 (Figure 4). 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 99% and that of D1 results over 97% since mid-March. Sequencing confirms these results, with Omicron representing 100% of interpretable sequences in Guadeloupe and Martinique since the Flash S10 survey-2022 (out of 90 and 144 interpretable sequences, respectively);
- In Réunion, since the beginning of February, the rate of D1 screened samples has been over 99%. Only Omicron has been identified during Flash investigations since Flash S10-2022 (out of a total of 555 interpretable sequences);
- In French Guiana, all the samples screened since April 1 have a D1 result and the 94 samples sequenced within the framework of Flash surveys since Flash S10 correspond to the Omicron variant;
- In Mayotte, 100% of the samples screened since February 1 have a screening result in suitability with Omicron (D1). The number of samples sequenced in Flash surveys is low (N=12), but only Omicron has been detected since Flash S02-2022.

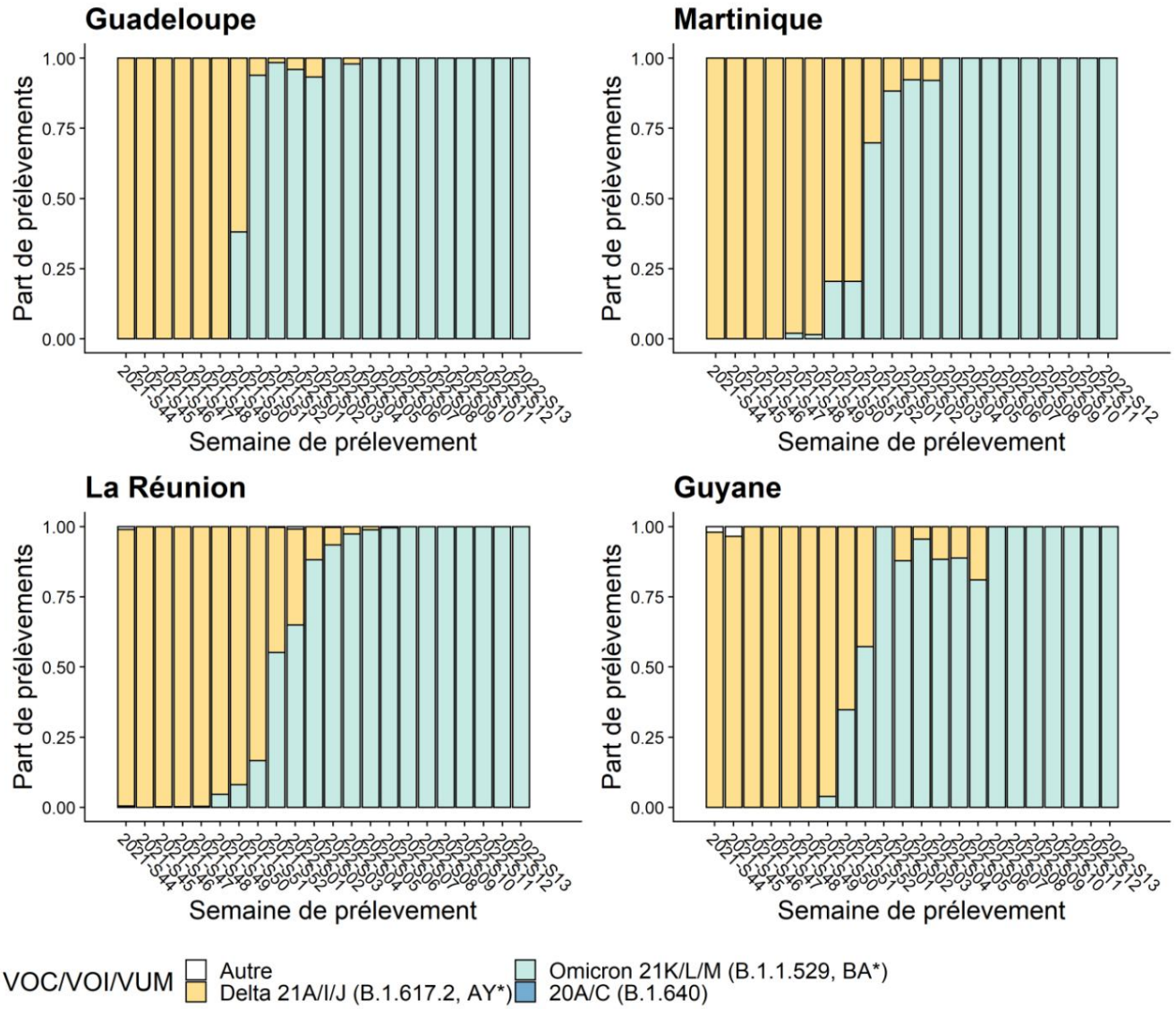

Figure 4: Evolution of the share of each VOC, VOI and VUM per week of sampling (all sequencing indications combined), by region of residence (source: EMERGEN, on 04/19/2022 at 12 p.m.). Data for weeks S12 and S13 are not consolidated.

Among the Omicron sequences, the BA.1 and BA.2 sub-lines, as well as their sub-lines, have been identified in the DROMs. The increase in BA.2 compared to BA.1 is confirmed in the Flash surveys for weeks S10 to S14-2022: the proportion of BA.2 was 41% in Martinique (BA.2, BA.2.3 and BA. 2.9), 84% in Reunion (BA.2, BA.2.2, BA.2.3, BA.2.6, BA.2.9 and BA.2.10), 88% in Guadeloupe (BA.2, BA.2.3 and BA.2.9) and 88% in Guyana (BA.2 and BA.2.9). In Mayotte, BA.2 was detected during Flash S12-2022.

5. Conclusion as of 04/20/2022

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.

Sustained circulation of a SARS-CoV-2 variant is associated with genetic diversification within that variant and the progressive appearance of sublineages. This expected phenomenon was observed for the Delta variant in the fall of 2021, for Omicron BA.1 in early 2022 and now for BA.2. In this context, **the appearance of a sub-lineage is not in itself a signal of public health interest.** However, all of these sub-lineages is followed to detect if one of them is associated with an epidemiological signal (increased circulation, detection in a specific population) or a clinical signal (more severe clinical presentation, greater vaccine escape). Two new Omicron sublineages, BA.4 and BA.5, have been identified. While the ECDC has alerted EU member countries to these two sub-lineages, this call for vigilance is based solely on the mutations carried by these two sub-lineages. To date, no modification of the characteristics of these two sub-lineages has been described. Moreover, they are not associated with a worrying epidemiological or clinical situation in South Africa, where they mainly circulate.

Following a period of co-circulation between Delta and Omicron, recombinants between these two variants emerged. Given the significant differences between Delta and Omicron, these recombinants have been subject to increased monitoring to determine their characteristics as quickly as possible, to assess their impact on public health and to take appropriate control measures if necessary. This strategy has shown its effectiveness with **the very rapid identification, monitoring and characterization of the XD variant (recombinant AY.4/BA.1).** The combination of epidemiological surveillance, case investigations, *in vitro* tests and mouse model studies by the partners of the EMERGEN consortium has made it possible to obtain a complete overview of this variant in a very short time. These results have been shared in risk analyzes and are the subject of a scientific publication (33). While the XD variant appears to have inherited some characteristics from each of its two parental variants (Delta and Omicron), its detection frequency has remained at low levels since early 2022, suggesting that it is no more competitive than Omicron. During the period of co-circulation of BA.1 and BA.2, many recombinants between these two sublineages were also identified. **BA.1 and BA.2 having very similar characteristics, it is unlikely that a recombinant will differ significantly.** 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 or public health signal.

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 where the incidence remains very high, it is therefore essential to limit the circulation of SARS-CoV-2 as much as possible, regardless of the variant.** This control involves respecting barrier gestures, and following recommendations in the event of diagnosis of infection or close contact with a case. It is also essential to continue to protect people at risk, in whom even Omicron can cause serious forms.

References

1. WHO. Weekly epidemiological update on COVID-19 - 20 April 2022, edition 88 2022 [Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---20-april-2022.
2. 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.
3. Willett BJ, Grove J, MacLean O, Wilkie C, Logan N, De Lorenzo G, et al. The hyper-transmissible SARS-CoV 2 Omicron variant exhibits significant antigenic change, vaccine escape and a switch in cell entry mechanism. medRxiv. 2022:2022.01.03.21268111.
4. Backer JA, Eggink D, Andeweg SP, Veldhuijzen IK, van Maarseveen N, Vermaas K, et al. Shorter serial intervals in SARS-CoV-2 cases with Omicron variant compared to Delta variant in the Netherlands, 13 - 19 December 2021. medRxiv. 2022:2022.01.18.22269217.
5. Button TC, Atarere J, Turcinovic J, Seitz S, Sher-Jan C, Gilbert M, et al. Viral dynamics of Omicron and Delta SARS-CoV-2 variants with implications for timing of release from isolation: a longitudinal cohort study. medRxiv. 2022:2022.04.04.22273429.
6. Hirose R, Itoh Y, Ikegaya H, Miyazaki H, Watanabe N, Yoshida T, et al. Differences in environmental stability among SARS-CoV-2 variants of concern: Omicron has higher stability. bioRxiv. 2022:2022.01.18.476607.
7. Bruel T, Pinaud L, Tondeur L, Planas D, Staropoli I, Porrot F, et al. SARS-CoV-2 Omicron neutralization and risk of infection among elderly after a booster dose of Pfizer vaccine. medRxiv. 2022:2022.03.30.22273175.
8. Simmons AE, Amoako A, Grima AA, Murison KR, Tuite AR, Fisman DN. Vaccine Effectiveness Against Hospitalization Among Adolescent and Pediatric SARS-CoV-2 Cases in Ontario, Canada. medRxiv. 2022:2022.03.24.22272919.
9. Buchan SA, Nguyen L, Wilson SE, Kitchen SA, Kwong JC. Vaccine effectiveness of BNT162b2 against Omicron and Delta outcomes in adolescents. medRxiv. 2022:2022.04.07.22273319.
10. Romero-Ibarguengoitia ME, González-Cantú A, Rivera-Salinas D, Hernández-Ruíz YG, Armendariz-Vázquez AG, Barco-Flores IA, et al. Analysis of immunization, adverse events, and efficacy of a fourth dose of BNT162b2 vaccine. medRxiv. 2022:2022.04.05.22273434.
11. Gazit S, Saciuk Y, Perez G, Peretz A, Pitzer VE, Patalon T. Relative Effectiveness of Four Doses Compared to Three Dose of the BNT162b2 Vaccine in Israel. medRxiv. 2022:2022.03.24.22272835.
12. Bastard J, Taisne B, Figoni J, Mailles A, Durand J, Fayad M, et al. Impact of the Omicron variant on SARS-CoV 2 reinfections in France, March 2021 to February 2022. Euro Surveill. 2022;27(13).
13. Lee HK, Knabl L, Walter M, Dai Y, Knabl L, Füßl M, et al. Prior vaccination enables a more robust immune response to Omicron infection. medRxiv. 2022:2022.03.24.22272837.
14. Servellita V, Syed AM, Morris MK, Brazer N, Saldhi P, Garcia-Knight M, et al. Neutralizing immunity in vaccine breakthrough infections from the SARS-CoV-2 Omicron and Delta variants. Cell. 2022.
15. 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.
16. 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.
17. WHO. Weekly epidemiological update on COVID-19. 2022.
18. SARS-CoV-2 PANGO lineages - Lineage List 2022 [Available from: https://cov-lineages.org/lineage_list.html.
19. 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.
20. Ito K, Piantham C, Nishiura H. Estimating relative generation times and relative reproduction numbers of Omicron BA.1 and BA.2 with respect to Delta in Denmark. medRxiv. 2022:2022.03.02.22271767.
21. Mesfin Y, Chen D, Bond H, Lam V, Cheung J, Wong J, et al. Epidemiology of infections with SARS-CoV-2 Omicron BA.2 variant in Hong Kong, January-March 2022. medRxiv. 2022:2022.04.07.22273595.
22. Chemaitelly H, Ayoub HH, AlMukdad S, Coyle P, Tang P, Yassine HM, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. medRxiv. 2022:2022.03.13.22272308.
23. Kirsebom FCM, Andrews N, Stowe J, Toffa S, Sachdeva R, Gallagher E, et al. COVID-19 Vaccine Effectiveness against the Omicron BA.2 variant in England. medRxiv. 2022:2022.03.22.22272691.
24. Stegger M, Edslev SM, Sieber RN, Cäcilia Ingham A, Ng KL, Tang M-HE, et al. Omicron BA.1 infection followed by BA.2 reinfection. medRxiv. 2022:2022.02.19.22271112.
25. Chemaitelly H, Ayoub HH, Coyle P, Tang P, Yassine HM, Al-Khatib HA, et al. Protection of Omicron sub-lineage infection against reinfection with another Omicron sub-lineage. medRxiv. 2022:2022.02.24.22271440.

26. UKHSA. SARS-CoV-2 variants of concern and variants under investigation in England, Technical Briefing 38 - 03/11/2022 2022 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1060337/Technical Briefing-38-11March2022.pdf.

27. Touret F, Baronti C, Pastorino B, Saba Villarroel PM, Ninove L, Nougairède A, et al. In vitro activity of therapeutic antibodies against SARS-CoV-2 Omicron BA.1 and BA.2. Research Square (https://doi.org/10.21203/rs.3.rs 1415749/v1). 2022.

28. GP designations. BA.* sublineages with S:L452R and S:F486V (79 sequences as of 2022-04-05, mainly South Africa) - issue #517 2022 [Available from: https://github.com/cov-lineages/pango-designation/issues/517.

29. ECDC. Communicable disease threats report, 3-9 April 2022, week 14. 2022 08/04/2022.

30. Zhang Y, Zhang T, Fang Y, Liu J, Ye Q, Ding L. SARS-CoV-2 spike L452R mutation increases Omicron variant fusogenicity and infectivity as well as host glycolysis. Signal Transduction and Targeted Therapy. 2022;7(1):76.

31. Bal A, Simon B, Destras G, Chalvignac R, Semanas Q, Oblette A, et al. Detection and prevalence of SARS CoV-2 co-infections during the Omicron variant circulation, France, December 2021 - February 2022. medRxiv. 2022:2022.03.24.22272871.

32. 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.

33. Simon-Lorière E, Montagutelli X, Lemoine F, Donati F, Touret F, Bourret J, et al. Rapid characterization of a recombinant Delta-Omicron SARS-CoV-2 detected in Europe. Research Square (https://doi.org/10.21203/rs.3.rs 1502293/v1). 2022.