Early assessment of the Omicron variant's presence and growth rate in regions of France

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RESUME

En utilisant les données de surveillance génomique des enquêtes Flash jusqu'au 20 décembre, nous estimons que le temps de doublement de la croissance d'Omicron au niveau national est compris entre 1,8 et 2,2 jours, ce qui confirme la croissance rapide déjà observée dans d'autres pays. On prévoit qu'Omicron deviendra majoritaire en France à la fin de la semaine 51 (c'est-à-dire la semaine actuelle). Les données Flash suggèrent une prévalence plus élevée du nouveau variant concentrée dans les régions Île-de-France et Centre Val de Loire par rapport au reste du pays, alors que les données de dépistage ajustées avec les données génomiques indiquent une expansion plus importante et plus uniforme sur le territoire national. Seules deux régions (Île-de-France et Centre-Val de Loire) ont rapporté des fréquences Omicron exploitables pour évaluer la dynamique du variant dans le temps au sein de la région, montrant déjà une propagation importante en communauté. En utilisant les données Flash, nous estimons des temps de doublement courts, 1,8 jours en Île-de-France et 2,5 jours en Centre-Val de Loire, en accord avec les estimations nationales. Cela indique qu'Omicron est probablement devenu majoritaire la semaine dernière en Île-de-France (semaine 50, débutant le 13 décembre), et qu'il est en train de franchir le seuil des 50% la semaine actuelle en Centre-Val de Loire (semaine 51, débutant le 20 décembre). Une dynamique plus lente est prévue par les données de criblage ajustées. Des données supplémentaires seront nécessaires pour consolider les résultats, réduire les incertitudes, et fournir des estimations pour les autres régions. La situation épidémique devrait s'accélérer considérablement dans les jours et semaines à venir.

SUMMARY

Using genomic surveillance data from Flash surveys up to December 20, we estimate the doubling time of Omicron growth at the national level to be in the range between 1.8 and 2.2 days, confirming the rapid growth that was already observed in other countries. Omicron is predicted to become dominant in France by the end of week 51 (i.e. current week, starting December 20). Flash data suggest a higher prevalence

of the new variant concentrated in the Île-de-France (IDF) and Centre Val de Loire (CVL) regions compared to the rest of the country, whereas screening data adjusted with genomic data indicate a larger and more uniform expansion on the national territory. Only two regions (Île-de-France and Centre-Val de Loire) reported exploitable Omicron frequencies to assess the variant dynamics in time within the region, showing already a substantial spread in the community. Using Flash data, we estimate short doubling times, 1.8 days in Île-de-France and 2.5 days in Centre-Val de Loire, in agreement with national estimates. This indicates that Omicron has likely become dominant last week in Île-de-France (week 50, starting December 13), and it is passing the 50% threshold in current week in Centre-Val de Loire (week 51, starting December 20). Slower dynamics are predicted by the adjusted screening data. Additional data will be needed to consolidate results, reduce uncertainties, and provide estimates for the other regions. The epidemic situation is expected to accelerate considerably in the upcoming days and weeks.

INTRODUCTION

The Omicron variant is rapidly expanding in Europe[1], with several countries now witnessing a fast increase in total cases and Omicron frequency[2–4]. The aim of this report is to assess the current situation in France, based on available virological and genomic surveillance data.

METHODS

We estimate the share of Omicron cases in France based on data from virological and genomic surveillance. We use two sources of data: sequence data (from the EMERGEN Consortium[5]) and screening data performed on subsets of tested samples highlighting the absence of certain mutations.

The EMERGEN database includes the number of sequences classified by variant and analyzed by participating laboratories, provided by department and by date of collection. For each sequence, additional information on whether it belongs to a Flash survey and/or it is linked to a cluster or travel history is provided. Flash surveys weekly sequence a random sample of RT-PCR positive cases[6].

The screening protocol reveals the detection of three mutations, labelled as A, B, C and representing mutations E484K, E484Q, L452R respectively. Omicron and B.1.640 variants are known to display absence of all three mutations (coded as A0B0C0).

Based on the available data, we define three indicators to estimate the frequency of Omicron cases in the territory. The first estimate uses sequence data, considering only samples sequenced as part of Flash surveys, and further excluding those belonging to clusters or linked to travel. We compute the Omicron frequency as the ratio of Omicron sequences among all interpretable sequences (indicator shown as *Flash* in the plots):

$$Omicron\ frequency = \frac{Omicron}{interpretable\ sequences}$$

Certain laboratories prioritize sequencing on samples screened as A0B0C0 as suspected for Omicron. This will bias the Flash estimates over time towards a higher prevalence before reaching completion of the analysis on all sequences of the random sample. To account for this, we additionally compute the Omicron frequency following the definition of the first estimate, but including only the sequences provided by laboratories avoiding prioritization (*Flash (no priority)* indicator).

The third estimate is based on screening data. We consider samples screened for all three mutations with an interpretable result, i.e. presence or absence of the mutations (A01B01C01). We then take the percentage of samples showing absence of the three mutations (A0B0C0). We assume that all A0B0C0 samples are either Omicron or B.1.640 variant. We then adjust the share of A0B0C0 by the frequency of Omicron with respect to B.1.640 from Flash sequences data to exclude the portion expected for B.1.640 (*%A0B0C0 adj Flash* indicator):

$$Omicron\ frequency = \frac{A0B0C0}{A01B01C01} \times \frac{Omicron}{Omicron + B.1.640}$$

We consider data from week 44 (starting November 1, 2021) to week 50 (ending December 19), at regional and national level. Data are consolidated up to December 20. Some regions show no Omicron confirmed cases in the study period, hence estimates are considered to be equal to zero in the indicators from sequence data (*Flash, Flash (no priority)*) and also in the screening data indicator because of the adjustment (*%A0B0C0 adj Flash*). See the Limitations section for more details. Data in week 50 are not yet complete. Screening data are provided till December 17. Sequence data in week 50 include a limited number of samples; being partial, these data are not used here. We restrict the analysis to mainland France.

We estimated the growth rates and the corresponding doubling times of the Omicron variant by region and at national level with an exponential growth model[7]. We inform the effective reproductive number for the Delta variant in each area according to the estimates in week 49[8] and with generation time from Ref[9]. We use an MCMC approach maximizing the following likelihood function independently in each region and at national level:

$$L = \prod_t Binomial\ (O(t);\ N(t), p(t))$$

with p(t) defined as:

$$p(t) = 1 / \left(1 + \frac{1 - p_0}{p_0}\, e^{(r_D - r_O)t} \right)$$

where t is the weekly time step, O(t) and N(t) are the observed number of Omicron cases and total samples at time t, p_0 is the initial Omicron frequency, r_D and r_O represent the growth rate of Delta and Omicron variants, and p(t) is the predicted frequency of Omicron at time t. For each indicator, the analysis is restricted to those regions reporting at least 2 weeks of non-null Omicron data in the study period. The initial Omicron frequency p_0 is assigned in each region to the week preceding the first week with non-null

Omicron data and fitted jointly with the growth rate. We use an exponential distribution for r_0 and a uniform distribution for p_0 as prior distributions.

RESULTS

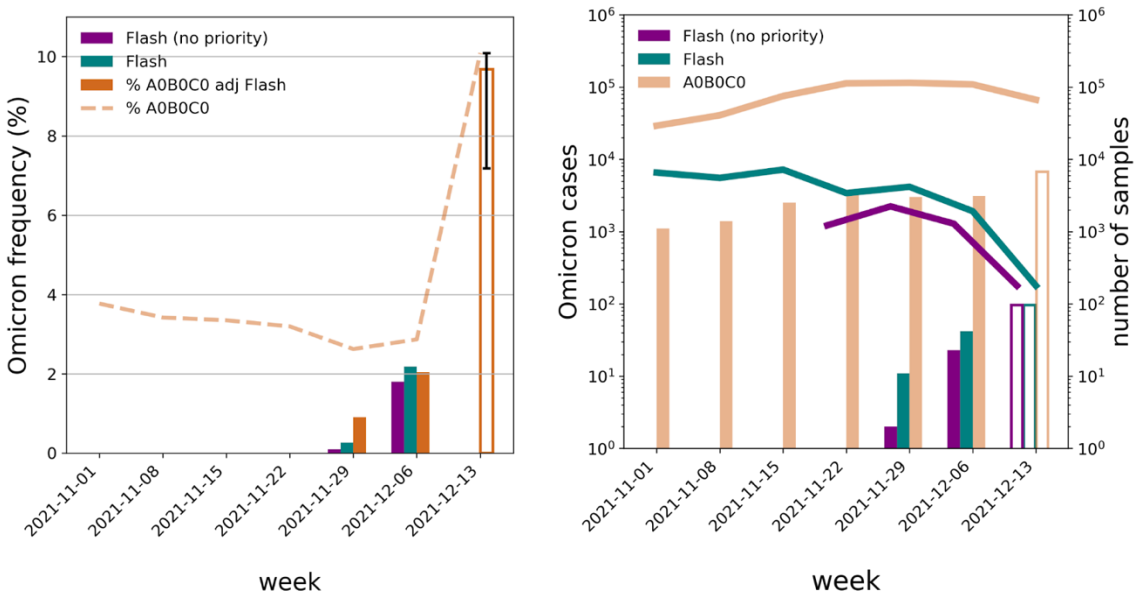

Figure 1. Omicron variant in France. Left panel: estimated Omicron frequency over time. Color indicates sequences data (teal and violet) or adjusted screening data (dark orange). Light orange indicates screening data for suspected Omicron before adjustment. Right panel: number of Omicron cases (bar plots, left y-axis) and number of samples (lines, right y-axis) over time. Color code as in left panel. In both panels, the datapoint in the week of December 13 is represented with a void bin, as screening data are not yet complete for the week (available up to December 17), and sequence data are still partial and provided by a single laboratory. In the left panel: the black error bars represent the estimated presence of Omicron in the week of December 13 based on the available screening data, assuming an adjustment factor between the one estimated in the previous week (see Figure 2) and 100%; the void bin assumes an adjustment factor computed using the limited sequence data available for the week. This partial estimate, not yet consolidated, is not used in the analysis.

Table 1. Estimated Omicron frequency in France.

Week	Flash (no priority)	Flash	% A0B0C0 adj Flash
November 29, 2021 (w48)	0.1%	0.3%	0.9%
December 6, 2021 (w49)	1.8%	2.2%	2.0%

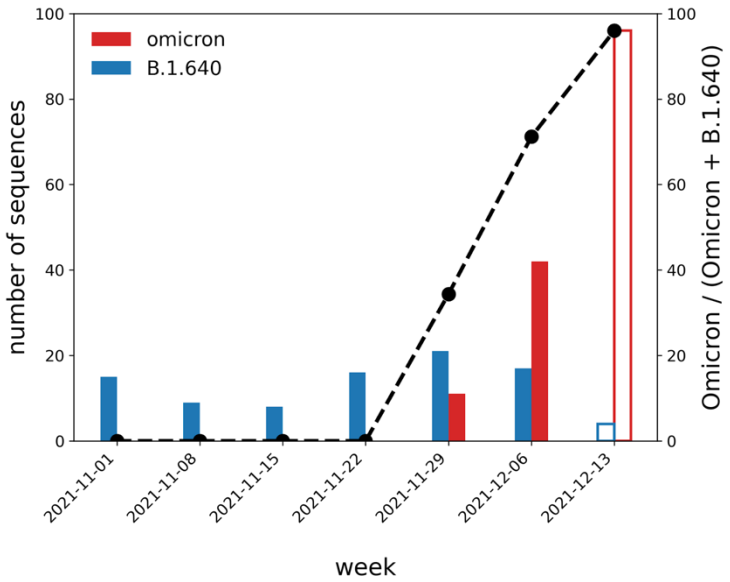

Figure 2. Omicron and B.1.640 variant. Left y-axis, bar plot: number of sequences identified as Omicron (red) or B.1.640 (blue) over time. Right y-axis: fraction of Omicron sequences (black dashed line) over time. Datapoints in the week of December 13 are represented with void bins, as sequence data for the week are still partial and provided by a single laboratory. This partial estimate, not yet consolidated, is not used in the analysis.

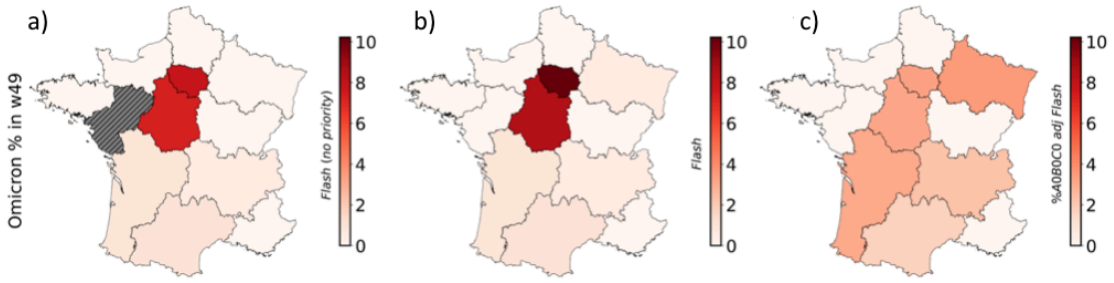

Figure 3. Estimated Omicron frequency at regional level in mainland France in week 49 (week of December 6, 2021). Left: Flash (no priority) indicator; center: Flash indicator; right: %A0B0C0 adj Flash indicator. Hatched areas indicate a sequence sample equal to zero for the region. We did not find a significant linear correlation at regional level between Flash indicators and the screening indicator, except if considering also the zero frequency datapoints, originating from the same source of data in both indicators (Pearson r=0.61, p=0.035).

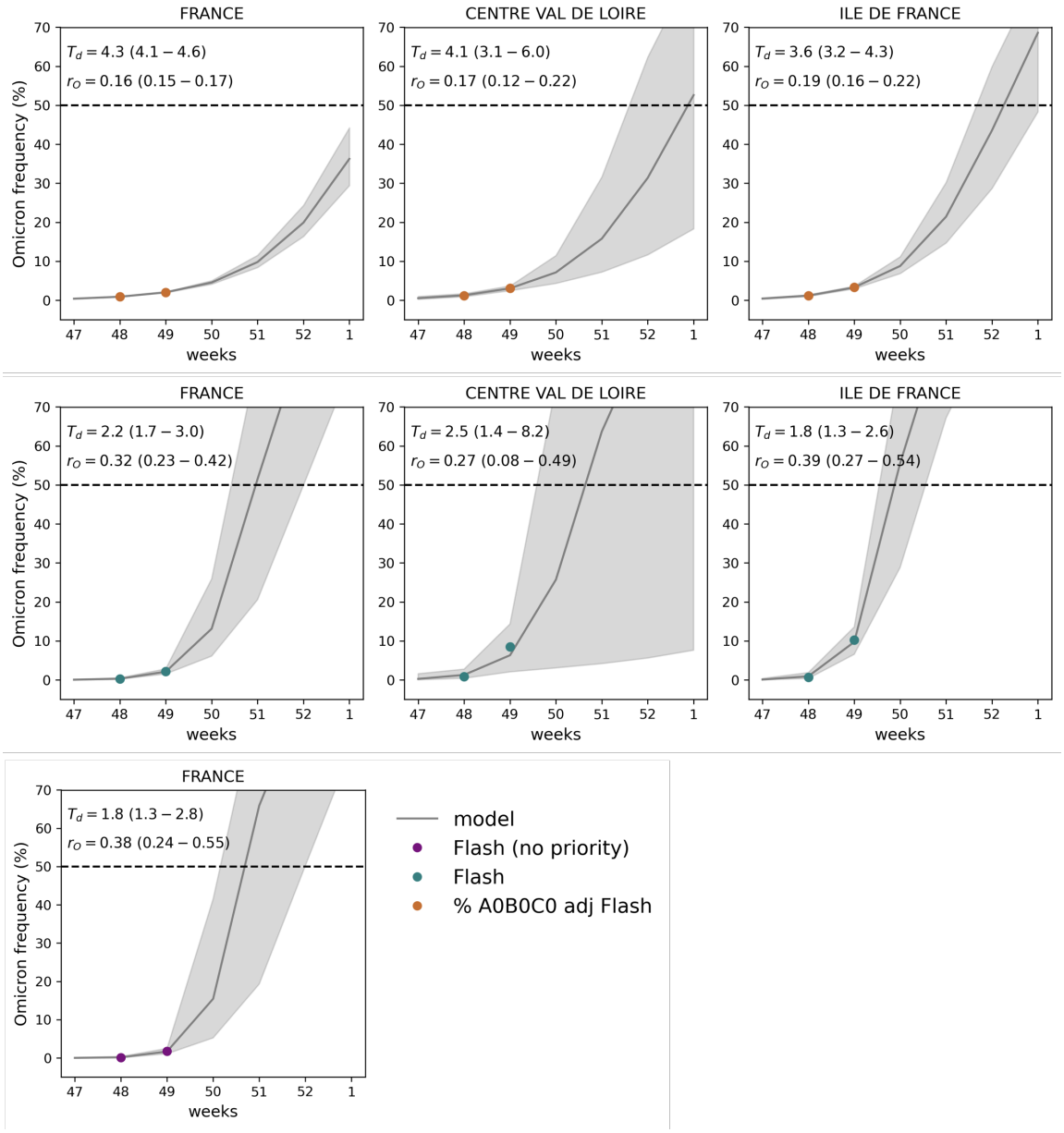

Figure 4. Estimated Omicron growth at regional and national level. Estimates of Omicron frequency from the three indicators and predicted frequency over time (median, grey line, and 95% credible interval, shaded area). Plots show only regions with at least one Omicron sequence detected in at least two weeks of observation. From top to bottom: estimates using *% A0B0C0 adj Flash* indicator (dark orange dots), *Flash* indicator (teal dots) and *Flash (no priority)* indicator (violet dots). From left to right: results at the national level, for Centre Val de Loire (CVL) and for Île-de-France (IDF) regions. T_d represents the doubling time of Omicron cases growth estimated for each area (expressed in days); r_O is the estimated daily growth rate of Omicron cases (expressed in days^{-1}).

KEY FINDINGS

- Based on Flash sequence data not subject to prioritization, we estimated the Omicron frequency in France at 0.1% in week 48 (starting November 29) and 1.8% in week 49 (December 6) (**Figure 1**, **Table 1**). Considering all Flash sequences or screening samples adjusted for the proportion of Omicron led to higher estimates (≥2%) in week 49.
- Analysis at the regional level shows a larger difference in the estimated Omicron frequency obtained from sequences or screening data (**Figure 3**). Flash data suggest a higher prevalence of the new variant concentrated in the Île-de-France (IDF) and Centre Val de Loire (CVL) regions compared to the rest of the country, whereas adjusted screening data indicate a larger and more uniform expansion on the national territory. Six regions (Bougogne-Franche-Comté, Bretagne, Hauts de France, Normandie, Pays de la Loire, Provence-Alpes-Côte d'Azur) did not report confirmed Omicron cases in Flash surveys in the study period.
- The doubling time of Omicron growth at the national level is estimated in the range between 1.8 and 2.2 days considering indicators from sequence data (**Figure 4**, *Flash* and *Flash (no priority)* indicators), confirming the rapid growth that was already observed in other countries[3,10–12]. The doubling time estimated on adjusted screening data is longer (4.3 days), and further data are needed to confirm these estimates and reduce the associated uncertainty.
- The models fitted to sequence data predict that Omicron will become dominant in France by the end of week 51 (i.e. current week, starting December 20). This is consistent with the preliminary assessment at the national level performed by the ETE (Évolution Théorique et Expérimentale) lab on AOBOCO data[13]. The epidemic situation is expected to accelerate considerably in the upcoming days and weeks.
- Only two regions (Île-de-France and Centre-Val de Loire) reported exploitable Omicron frequencies to assess the variant dynamics in time within the region, showing already a substantial spread in the community. With the *Flash* indicator we estimate short doubling times, 1.8 days in Île-de-France and 2.5 days in Centre-Val de Loire (**Figure 4**). This indicates that Omicron has likely become dominant last week in Île-de-France (week 50, starting December 13), and it is expected to pass the 50% threshold in current week in Centre-Val de Loire (week 51, starting December 20). Larger uncertainty is however associated to the dynamics in Centre-Val de Loire.
- Additional data will be needed to consolidate results and provide estimates for the other regions (see Limitations section).

LIMITATIONS

- The main limitation of the analysis lies in the data, affecting the ability to provide timely and robust estimates. Consolidation of the data used in this report is still ongoing. Flash sequence data are subject to longer delays from test to result compared to screening data, as sequencing

requires more time. In addition, they are provided on a weekly basis, thus limiting this analysis to two datapoints (i.e. two weeks) so far. In contrast, screening data are more readily available, provided on a daily basis, and with larger samples at a higher spatial resolution (region/department). However, without correcting for the Flash data to exclude B.1.640, other variants add a background noise to the screening data, especially at the start of Omicron establishment in the country, thus altering the estimate of its dynamics. Adjusting with Flash data for Omicron specificity corrects for this bias but it means, however, to lose the timeliness (as we need to wait for consolidated Flash data) and time/spatial resolution (as the correction is subject to the weekly Flash estimate, and with smaller samples by region) advantages of the screening data. For example, by December 20, only 6 regions confirmed Omicron cases in Flash data not linked to cluster nor travel history (5 regions if using *Flash (no priority)* data). All these elements pose serious limits to the assessment of the early dynamics in France of a variant spreading very rapidly, as Omicron.

- Part of Flash data are biased due to the prioritization of samples suspected as Omicron performed by certain laboratories, so that early records tend to overestimate the % of Omicron before the analysis of all sequences is complete (which inevitably requires longer time). We used the *Flash (no priority)* indicator to avoid this bias and gain in timeliness while data is consolidated, however the analysis relies on a smaller number of participating laboratories, therefore further limiting the sample.
- We assumed that all samples screened as A0B0C0 are either Omicron or B.1.640. Not considering other variants may lead to an initial overestimation of Omicron frequency, but this is expected to become rapidly negligible over time due to the rapid rise of Omicron, and its impact to be minor compared to the issues discussed above. We did not consider here data on the mutations labelled as D in the screening system due to the recent changes in protocols making results difficult to interpret at this stage.
- All the above elements: (1) limit the analysis to two weekly datapoints only, thus resulting in large uncertainties in the estimates; (2) largely reduce the possibility to estimate the Omicron dynamics spatially (at this stage the analysis cannot be extended further to other regions as they do not have enough exploitable data to capture Omicron dynamics and provide estimates of its growth rate); (3) result in differences in the reported estimates of Omicron frequencies and doubling times, which are to be considered as preliminary and subject to data limitations. The analysis can be updated as more data become available to consolidate the results and reduce such uncertainties.
- We used estimates of the effective reproductive number for Delta obtained from case incidence in w49[8], when Omicron frequency was still low in the country. Variations in the estimated reproductive number for the Delta variant at the start of Omicron expansion would impact the estimates for the growth rate of Omicron cases.

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