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Note: DOCUMENT TRANSLATION WITH DeepL

Opinion of the AvATher Group of 16 January 2023

Response to the request for additional advice from the DGS dated 6 December 2022 concerning the target population for Paxlovid® and the use of Evusheld ® in pre-exposure prophylaxis

REMINDER - Circulation of classified variants in France (SPF)[1]

- In week 52, 2022, the slowdown in the circulation of SARS-CoV-2 continued across France. The incidence rate has fallen sharply across all age groups, against a backdrop of a significant drop in the screening rate, particularly in the under-60s.

- Sequencing data confirms the exclusive circulation of the Omicron variant of concern (or VOC) in all regions of mainland France and the French overseas territories. In mainland France, it represented 100% of the interpretable sequences in the Flash S50 survey published on 05 January 2023.

- Within the Omicron variant, the BA.5 sub-lineage is in the majority: it represented (all sub-lineages included) 93% of the interpretable sequences in the Flash S50-2022 survey published on 05 January 2023.

- The increase in BQ.1.1* continues at a steady pace, with 48%, 53%, 60%, 62%, 67% and 70% of interpretable sequences in the Flash S45, S46, S47, S48, S49 and S50 2022 surveys respectively. This increase in the detection of BQ.1.1* was observed in all regions of mainland France and in other European countries, but at a slower rate than that observed for other Omicron sub-lineages. The BF.7, BQ.1 and BA.5.2 variants were identified in 2%, 6% and 5% of sequencing respectively.

- The Omicron BA.4 sublineage (including all its sublineages) is currently detected at low levels, with 1% of the interpretable sequences in the Flash S48-2022 survey. The recombinant XBB*, which circulates widely in Asia, is detected at low levels in mainland France. The majority of XBB* sequences correspond to its XBB.1 sublineage, which was initially detected in Flash S41 and has stabilised at low levels in recent Flash surveys (2% in Flash S48).

- The Omicron BA.2.75 subline continues to circulate in France (9% of sequences deposited in the GISAID database between 13/11 and 12/12/2022). This BA.2.75.2 sublineage is being monitored more closely because of its mutation profile.

[1] https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-5-janvier-2023

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Notice concerning the target population for Paxlovid® .

Since the beginning of 2020, there have been several epidemic waves involving different variants around the world, and particularly in France. The definition of groups particularly at risk of adverse outcomes was established on the basis of the first studies, particularly during the first wave. Since autumn 2021, the Omicron variant has therefore become the overwhelming majority, with a succession of sub-variants that may have evolved over time in terms of pathogenicity and sensitivity to the various antivirals. Clinical data have recently been published, adding to the previous data used to establish the place of Paxlovid® in the therapeutic arsenal. This justifies updating the recommendations on the use of Paxlovid® in the Omicron period, taking into account changes in the severity of COVID-19, as well as the clinical efficacy of Paxlovid® in populations most at risk of an unfavourable outcome. It should be noted, however, that data concerning the most recent sub-variants (BA.5, BQ1.1 or XBB.1.5) are currently scarce or non-existent.

a) **Did the severity of COVID-19 decrease between the alpha to delta waves and the omicron wave?**

Direct comparison of the severity of COVID-19 is made difficult by changes in the immune status (particularly post-vaccination) of populations at different periods in the epidemic. Among the studies published, three (one Canadian - Ulloa AC et al -, one American - Strasser Z et al - and one Mexican - Ascencio-Montiel IJ et al) directly compared hospitalisation rates in the same population during the delta and omicron waves (BA.1 and BA.2). They found that the hospitalisation rate rose from 2.8 to 0.3%, from 5.9 to 3.3% and from 9.9 to 1.9% respectively, while the mortality rate fell from 0.5 to 0.03%, from 0.7 to 0.4% and from 4.3 to 0.32%. A large English study (Agrawal U et al.) observed rates of severe forms (hospitalisation, death) close to those of the Canadian study (0.3%). A Danish study (Hansen CH et al.) reported a hospitalisation rate in the BA.5 period of 1.9%, slightly higher than in the BA.2 period (1.4%). All in all, depending on the location, vaccination coverage rate, healthcare resources and criteria used, the "gross" severity observed in the Omicron era was 2 to 10 times less than that observed in the Delta era (without adjusting for the degree of protection of the population, which increased over time). This reduction in severity has also been observed in France (Bouzid D et al.), but does not prevent a mortality rate which, although falling, is nonetheless significant (around one hundred hospital deaths for COVID-19 per day in France at the end of December 2022). The population most at risk of severe forms of the disease remains the immunocompromised. In a French multicentre study analysing the profile of patients hospitalised in intensive care for infection with an Omicron variant, 43.2% were immunocompromised, and the mortality rate for these immunocompromised patients in intensive care was 46.9% compared with 26.2% for immunocompetent patients (De Prost N et al.).

b) Are the populations at risk the same in the Omicron era as in the first waves?

Some studies have analysed the risk factors associated with the severity of COVID-19 in the Omicron era in the general population (Agrawal U et al.) or on the basis of hospitalised patients (O'Leary AL et al., Stepanova M et al., Colnago M et al.). All found age (with a threshold of 60 or 65 depending on the study) and incomplete vaccination status to be risk factors. In the most

In a major study involving more than 29 million British people (Agrawal U et al.), in addition to age and vaccination status, all the risk factors identified during the first wave remain associated with an increased risk of severe disease, in particular obesity, renal, cardiac and hepatic failure, diabetes, cancer and immunodepression.

In the end, there is still an increased risk of severe disease in people with the comorbidities listed in the previous recommendations, even though the reduction in overall severity probably means that more people need to be treated to avoid hospitalisation or death.

c) What are the clinical efficacy data for Paxlovid® in the Omicron era?

Several studies in Israel (Arbel R et al., Najjar-Debbiny et al.), Canada (Schwartz KL et al.), the USA (Dryden-Peterson S et al., Bajema KL et al., Dryden-Peterson S et al.) and Hong Kong (Wong CKH et al.) have evaluated the efficacy of Paxlovid® in the Omicron period. The studies by Najjar-Debbiny R et al, Schwartz KL et al, and Shah MM et al involved more than a hundred thousand people (treated with Paxlovid® vs untreated, 4,737 vs 175,614, 8,876 vs 168,669, 198,927 vs 500,921, respectively). All confirmed the clinical benefit in the Omicron era of administering this treatment within the first 5 days after the onset of symptoms, with a reduced relative risk of hospitalisation and/or death (from 0.21 to 0.56), in a predominantly vaccinated population. The observed rates of hospitalisation or death ranged from 0.56 to 2.7% with Paxlovid® versus 0.96 to 4.1% without treatment (or 0.015-0.016 versus 0.029-0.059 /100 person-days). The benefit was also observed in cases of co-morbidities, including diabetes, neurological impairment, heart/renal failure, cancer and immunodepression (assessed independently only in the Israeli studies). All the studies confirm the protective role of immunity (post-infectious and/or up-to-date vaccination status).

With regard to age, all but one (Dryden-Peterson S et al.) reported an objective benefit in people aged 65 and over, whether or not they had been vaccinated (except in the Hong Kong study).
- Wong CKH et al - where the benefit was no longer statistically significant in fully vaccinated people, and in Shah's American study where there was no benefit in people aged 65 and over without comorbidity).

Three studies point to a significant benefit in younger people: the Canadian study (in people under 70, rate of hospitalisation or death of 0.3% with Paxlovid® vs 0.8% in controls, OR = 0.34 [0.15-0.79]) (Schwartz KL et al), the Dryden study (under 65, RR = 0.33 [0.15 to 0.74], but without adjustment for other risk factors) (Dryden-Peterson S et al.), and the study with the largest number of patients (50-64 years, HR hospitalisation = 0.40 [0.34-0.48], and 18-49 years, HR hospitalisation = 0.59 |0.48-0.71]) (Shah MM et al.). However, in the latter study, this benefit was no longer observed when there were no at least 2 comorbidities (18-49 age group) or at least one (50-64 age group). In addition, the benefit was significant in patients who had not been vaccinated as well as in those vaccinated with 2 doses (or even ≥ 3 doses for the 50-64 age group), but without detail on the sequence and post-vaccination delay, and with a relatively low event rate.

In the under-65 age group, the data vary from study to study. The
The "weight" of co-morbidities in the risk of progression to a severe form is significant in the

main study. The number of people who need to be treated to avoid an event is potentially high, even though there is still a lack of experience of adverse effects. This leads us to recommend administration to people under 65 if they have at least one co-morbidity at risk of severe disease, regardless of vaccination status.

In conclusion, based on an analysis of the latest data available during the Omicron period ;

1) **Paxlovid® remains the first-line curative treatment for people with mild to moderate COVID-19, whatever the SARS-CoV-2 variant or sub-variant.**
2) **Treatment with Paxlovid® is particularly indicated regardless of vaccination status in patients :**
   - **aged 65 and over, or**
   - **are immunocompromised, whatever their age, or**
   - **with another comorbidity at high risk of severe disease, whatever their age.**

Paxlovid® should be administered as soon as possible after the diagnosis of COVID-19, ideally within 5 days of the onset of symptoms and for a further 5 days.

Advice on the use of Evusheld® for pre-exposure prophylaxis

The phase 3 TACKLE trial (Montgomery H et al.) was conducted in a "pre-Omicron" era in unvaccinated patients. It showed a 50.5% (14.6-71.3) reduction in the risk of severe COVID-19 or death. As a reminder, several studies (Bruel T el al., Planchais C et al.) had shown a weak neutralising activity of Evusheld® on BA.1 and a better activity of Evusheld® on BA.2 compared with BA.1. Subsequently, various studies (Tuekprakhon A et al. Gruell H et al.) demonstrated a higher activity of Evusheld® on BA.4/BA.5 compared with that observed on BA.1, but lower than that observed on BA.2. In general, the activity of Evusheld® on Omicron sub-variants is mainly based on Cilgavimab, Tixagevimab having almost completely lost its activity and the synergistic effect of the combination remaining modest.

The initial results of the French PRECOVIM study (ANRS166s PRECOVIM cohort; de Lamballerie X et al.), looking at the neutralising activity of the serum of immunocompromised patients 1 month after prophylactic administration of Evusheld® 300mg (150 + 150 mg), are in line with the *in vitro* data available and indicate very low activity against BA.1, partially recovered against BA.2, but falling back to levels close to BA.1 for the BA.5 variant, and a complete absence of neutralisation against BQ.1.1 after administration of Evusheld® 600mg (300 + 300 mg). Other recent studies have confirmed the total loss of neutralising activity of Cilgavimab on the BQ.1.1 variant (Cao Y et al, Wang Q et al, Imai M et al, Touret F et al).

Finally, data on the follow-up of cases of adverse reactions to drugs used in the management of Covid-19 (ANSM 8 December 2022)[2] lists 121 adverse reactions to Evusheld® (of which 52% were serious and 5% fatal). Of these, 32 cardiovascular and/or thromboembolic adverse events were reported, including 5 deep vein thromboses (DVT), 5 pulmonary embolisms, 2 of which occurred in the context of DVT, and 4 myocardial infarctions/coronary syndromes, which continues to lead to the recommendation that the benefits and risks should be carefully assessed before initiating EVUSHELD® in people at high risk of cardiovascular or thromboembolic events.

In conclusion:

- The persistence of the concomitant circulation of BA.5 at a significant level at the same time as the emergence of BQ1.1 justified the recommendation to continue prophylaxis with Evusheld® in the most fragile patients (DGS referral to the mAbTher group on 23/10/22).

Considering :

- a significant increase in the proportion of BQ1.1, representing almost 70% of circulating variants,
- resistance of BQ.1.1 to neutralisation by Tixagevimab and Cilgavimab,
- the reduction in the incidence of SARS-CoV-2 infection at national level,
- and the persistence of a pharmacovigilance signal relating to cardiovascular adverse events in patients who received Evusheld® (even if infrequent)

The AvATher group does not recommend the continuation of pre-exposure prophylaxis with EVUSHELD in people who have so far been eligible, as the benefit/risk balance is probably no longer favourable.

[2] https://ansm.sante.fr/actualites/suivi-des-effets-indesirables-des-medicaments-utilises-dans-la-prise-en-charge-du-covid-19-en-date-du-8-12-2022

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