Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Omicron SARS-CoV-2 variant: What we know and what we don't

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World Health Organization (WHO) designated the variant B.1.1.529 named Omicron as a variant of concern (VOC) on the 26th of November 2021 [1]. A relative rise in cases of people tested positive for SARS-CoV-2 in South Africa has been observed in regions where the Omicron variant emerged. Confounding factors are currently studied by local epidemiologists.

Expansion out of South-Africa: what is the real threat?

So far, sporadic cases observed worldwide are travel-related from southern Africa countries except for few cases with no travel history in the USA [2] or in Europe [3]. Reinforced surveillance of the Omicron variant expansion has been implemented using molecular diagnosis. Wastewater surveillance is an early surrogate marker for new variant detection that has proved useful to detect Alpha variant [4]. In France, the Omicron variant has been already detected from wastewater treatment plants since mid-November, highlighting the presence of the Omicron SARS-CoV-2 variant on the French territory while only 2 cases were reported at this time (Santé Publique France data).

Little is known regarding viral characteristics that could facilitate its expansion. The Omicron SARS-CoV-2 variant shows more than 30 mutations leading to amino-acid changes in the Spike sequence, 15 of them located in the Receptor-Binding Domain (RBD), which is key for viral-cell interaction mediated by ACE-2 receptor. Inferences to determine transmission rate have been attempted from the Omicron spike gene sequence. These data reported a cluster of mutations at the S1–S2 furin cleavage site, which may enhance viral infectivity. In addition, docking studies showed that a combination of mutations in the RBD would yield a high binding affinity with human ACE2 of this variant [5]. *In vitro* studies are needed to confirm these hypotheses. To replace the Delta variant as the main circulating variant, a huge increase in infectivity and/or transmissibility of Omicron variant would be needed.

Is there an impact on detection of Omicron variant genome variation on the diagnosis tests performances?

RT-PCR tests (NAAT tests) performance are not impacted by this new variant except for a specific S-gene target failure (SGTF) observed with the Thermo Fischer TaqPath COVID-19 assay due to the deletion in position 69–70 of the spike sequence as previously observed with the Alpha variant. This emphasizes the importance of using tests targeting at least two different genomic regions of the SARS-CoV-2 sequence in order to prevent false negativity of tests due to major changes in one of the targets.

Variant screening is the quickest way to detect and prevent expansion of a new VOC. In the current situation, SGTF can be used as a proxy to suspect an Omicron infection, similarly to the Alpha variant. The association of different mutation-specific tests can unravel the presence of the Delta (still predominant worldwide) or Omicron variants, based on the spike sequence differences between these viruses. Some of the mutation-specific tests are already available as for E484K/Q, L452R, N501Y detection, allowing a very quick implementation of an Omicron adequate screening strategy.

In addition, sequencing all suspect infections is of the utmost importance to monitor this new variant worldwide. This is enabled by the gathering of sequences on databases such as GISAID. This surveillance also allows to observe possible evolution and sublineage emergences.

Regarding tests based on antigen detection, most are rapid tests based on the detection of the nucleocapsid (N) antigen to prevent invalidation from spike protein variations. It is worthy to note that some mutations are detected on the Omicron nucleocapsid sequence. Whether these mutations could impact the ability of rapid tests to detect the Omicron variant is still not known but some firms already communicated by press release that their antigen tests were not impacted [6]. However, overall, antigen tests are known to be less sensitive than RT-PCR tests [7]. As usual, negative results from antigen tests in a context of high suspicion of infection must be confirmed with a RT-PCR test. It is then recommended to prefer RT-PCR tests when a potential Omicron infection is suspected (*e.g.*, based on travel information or contact tracing).

Does the Omicron variant emergence induce change in vaccine strategies?

As a waning of vaccine-induced immunity is now well-documented [8], it is paramount to get a booster dose in order

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to face the already ongoing and possibly speeding-up increase of cases, whatever the circulating variant should be [9]. The high frequency of mutations in the spike sequence of the Omicron variant raises concern about a potential immune escape of this variant. Indeed, it gathers amino-acids substitutions on positions already known to be involved in immune escape as E484 (E484A for Omicron variant, E484K for Beta and Gamma variants) [10]. The full combination of mutations observed in the Omicron spike gene has not been studied earlier and its impact on immune escape remains to be determined. Pharmaceutical labs are already assessing the efficacy of their vaccines against this new variant (Moderna, Pfizer and AstraZeneca) and some of them mentioned that they could adapt their vaccine design if needed (press release; Dr Sahin, BioNTech; Dr Hoge, Moderna). Another crucial question is whether heterologous vaccination could help in widening and enhancing the protection against new variants. *In vitro* serum neutralisation assays with sera from patients previously infected by different variants of SARS-CoV-2 and from people vaccinated with the distinct vaccines, including heterologous vaccination, must be carried out against the Omicron variant. As the cellular immunity is directed against different viral spike epitopes, we can assume that it may not be as impacted as humoral immunity by the virus evolutions. We already know that COVID-19 vaccines reduce infection frequency and have a great efficacy to prevent severe COVID-19 disease.

Will the Omicron variant cause more severe cases than previous SARS-CoV-2 variants?

In the first epidemiological study available, a retrospective analysis of routine epidemiological surveillance data suggest that the Omicron variant may be associated with an increase in the risk of reinfection after a primary infection [11]. This result, obtained with the data of 35,670 suspected reinfections among 2,796,982 individuals with laboratory-confirmed SARS-CoV-2 infection, suggests that the Omicron variant has an ability to evade immunity from prior infection. The results are not applicable to vaccination as vaccination coverage in South Africa was very low during the study. The question of an increase or decrease in the severity of COVID-19 arises with each new variant. It is common to hear some say, before any published data, that the new variant will lead to less severe cases while others say that it will lead to more severe cases, especially in children. At present, there are too many confounding factors to compare patients with the Omicron variant in South Africa with patients infected by other variants. In fact, COVID-19 severity and mortality vary enormously depending on the country, the prevalence of vaccination, the population's characteristics including age, socio-economic level or comorbidities, medical management guidelines or the number of simultaneous cases leading to the saturation of the health system [12]. Large-scale case-control studies, controlled for as many of these factors as possible, are essential to seriously investigate clinical severity.

The medical management of COVID-19 cases is not expected to change with this variant. Oxygen therapy associated with corticosteroids will likely remain the mainstay of therapy. Targeted anti-inflammatory drugs, such as IL-6 inhibitors (tocilizumab) or JAK inhibitors (baricitinib) may be useful in the most severe cases.

Will monoclonal antibodies and direct antiviral drugs be affected by the Omicron variant?

Monoclonal antibodies (MAbs) are the antiviral drugs with the most evidence for efficacy in COVID-19 patients. They are now available and recommended in some countries for patients at high-risk of severe COVID-19, whether as a prophylactic treatment before infection or as a treatment after proven infection. Most of the MAbs used in these therapies are targeting the RBD of the SARS-CoV-2 spike protein, which is highly mutated in Omicron variant. The impact of each single mutation has been studied on monoclonal antibodies efficacy [13] and the combination of several mutations proved to render a pseudovirus resistant to MAbs therapies *in vitro* [14]. We can expect differential susceptibility of the Omicron to MAbs *in vivo* depending on the antibody [15]. Preliminary data with single mutations in the Omicron variant suggest that VIR-7831 (sotrovimab) and VIR-7832 may retain their activity. On the other hand, no data have been published regarding Casirivimab/Imdevimab [16], while Bamlanivimab/Etesevimab are not expected to be effective against the Omicron variant as they already proved ineffective against Delta. However, neutralisation assays with the combined mutations are needed to conclude.

Regarding oral direct anti-viral therapies, the two current drugs that could provide a limited efficacy on SARS-CoV-2 are a ribonucleoside analog that inhibits the replication of SARS-CoV-2 and a protease inhibitor. Their mechanism of action targeting two non-structural proteins (protease and RNA-dependent RNA polymerase) should not be impacted as this variant shows few mutations on these genes, but their efficacy is not yet proved even in cases with the Delta variant.

Conclusion

To date, we have few data on the Omicron variant and studies must be quickly carried out to better define the threat that this variant represents. Previous experiences with Alpha and Delta lead us to believe that only time and surveillance will give us more information on transmissibility, vaccine efficacy and severity of the disease caused by this new variant. We can already affirm that protective measures and vaccination will still be the key elements to counter the spread of the new variant and to prevent new waves of severe COVID-19 cases and deaths.

The fact that Omicron emerged in a country with a low vaccination coverage is not a coincidence. Indeed, this new variant emergence strengthens the importance to give access to vaccination worldwide since letting the virus freely circulating in non-vaccinated populations, first threatens these populations of severe COVID-19 cases and deaths and, second, enables the virus to quickly accumulate mutations, which can increase viral transmissibility and infectivity, or lead to new deadly waves around the globe.

Conflicts of interest

Valentine Marie Ferré and Nathan Peiffer-Smadja declare no competing interests.

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