management asset

Omicron variant

Paulo Coutinho pcoutinho@marasset.com.br marasset.com.br

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Highlights

Omicron variant – the surge of the new variant in South Africa is the main risk of new Covid-19 outbreaks in the world. The fuss around the Omicron variant is that it is more transmissible and reduces the effectiveness of vaccines

Less severity – Studies based on data from South Africa and the UK estimate that those infected with Omicron have a much lower risk of being hospitalized compared to other strains.

More cases, fewer deaths – Based on the estimated parameters in terms of reduced effectiveness of vaccines for Omicron and less severity found in those studies, our simulations suggest that the Omicron wave would have a peak almost 20 times higher than that of a counterfactual of Delta in terms of cases, but with half of the deaths.

"Christmas Gift" – Data from South Africa, the only country with a more mature Omicron wave, suggest an even more positive scenario. Contrary to what the models predict, the peak of new cases was very similar to that of the Delta variant. Daily hospitalizations did not reach half of what was seen in the Delta outbreak and deaths increased only residually. The positive risk would be the repetition of these dynamics in other countries



Omicron Characteristics



Omicron variant is the highest risk related to Covid-19

• Concern regarding the emergence of a new variant can be summarized in uncertainty about two conditions:

i-Transmissibility of the disease.

ii-Effectiveness of current vaccines for severe cases.

iii-Disease lethality.

a)The speed with which Omicron has become dominant in specific regions of South Africa indicates its high transmissibility. Even sol, they are signals from a small number of cases that do not allow us to conclude that Omicron has high transmissibility.

b)In case the transmissibility is high, but the effectiveness of the vaccines is not very different, Omicron would be just another dominant variant, as well as others that we have already observed. In this scenario, countries with a high proportion of the immunized population would respond well to the virus.

c)However, a low lethality could compensate for greater transmissibility and vaccine evasion. A very positive scenario and, as we will see, it seems to be the most likely one, would be one in which Omicron was transmissible enough to become the dominant strain but generated a low number of hospitalizations/deaths due to a low virulence.

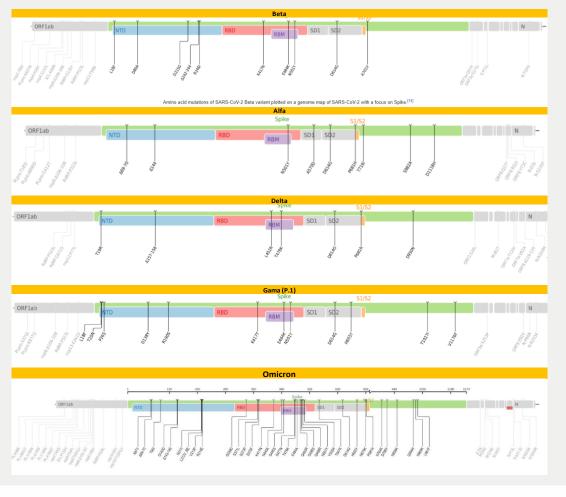
- The fuss around Omicron is that there are indications of greater transmissibility and potential for evasion on vaccines. This variant has a much higher degree of mutation than others, particularly in the spike of the virus. Scientists do not know exactly the consequences of all these mutations and the most obvious conjecture is that some of them increase their transmissibility and help the virus evade the immune system. The speed at which the variant became dominant in Gauteng turned on the warning sign regarding these characteristics.
- These conjectures were corroborated by the most recent data. Preliminary studies suggest that (i) the variant has a higher rate of transmission and (ii) greatly reduces the efficacy of the vaccine against infection. Nevertheless, these studies also suggest that the symptoms of Covid-19 in people infected with the new strain are milder. The fraction of people infected that need to be hospitalized is much smaller than in previous waves. South Africa's preliminary numbers indicate that the number of deaths is also reduced.



Omicron variant has more than 30 mutations in spike

- The number of Omicron mutations is much greater than that of other variants of concern (VoCs). In RBD alone, the new variant has 15 mutations. In comparison, the Delta had only two. It is not yet known how these mutations change the ability of the virus to transmit and evade the host's immune system.
- Some of these mutations are alike other variants of concern (alpha, gama, beta and lambda) and had been associated with higher transmissibility and resistance. Scientists do not know the precise consequence of the appearance of these mutations in the same variant. In addition, we do not know the consequences of other mutations that had not previously been observed in other variants.
- The first studies on the *in vitro* vaccine effectiveness showed a significant loss of antibody capacity of vaccines to fight the new variant. The first anecdotal evidence of closed events in which there was an outbreak of Covid-19 related to this variant corroborates the idea of relevant loss of effectiveness of the vaccines. Effectiveness data for severe cases are not yet available.

Mutations in different variants

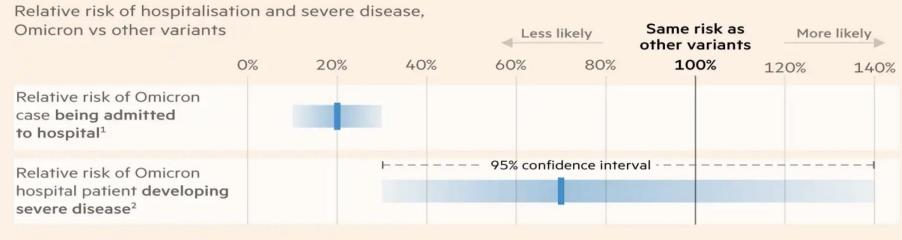




Omicron led to less severe cases in South Africa

- A study published on the severity of Omicron in real life suggests that (link):
 - i. 80% reduction in hospitalization odds if you have been infected by Omicron
 - ii. 30% reduction (not statistically significant) of developing severe disease once hospitalized.
- This result suggests that the reduction of severe cases after infection would be 86%. Even if the wave was seven times higher in terms of infected people, ICU admissions would not be much different from what was seen in the Delta outbreak.

Data from South Africa shows Omicron cases are less likely than other variants to require hospital admission



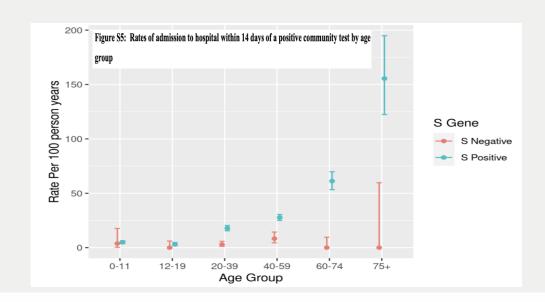
¹After controlling for age, sex, underlying health conditions, region and prior PCR positive result

²After controlling for age, sex, underlying health conditions, region, prior PCR positive result and vaccination status Source: 'Early Assessment of the Clinical Severity of the SARS-CoV-2 Omicron Variant in South Africa', by Nicole Wolter et al. © FT



UK data suggest a smaller reduction in hospitalizations

- A study published with UK data shows a 40-45% reduction in hospitalizations with more than one day of duration related to cases of Omicron (<u>link</u>). The study also shows a reduction of 50% among those who were previously infected and of about 70% in relation to those who took two doses or more of the vaccine.
- The study does not consider severe cases, which the authors themselves expect an even greater reduction among Omicron cases.
- Separately, a study using only data from Scotland suggests a 2/3 reduction in hospitalizations among those infected by Omicron (<u>link</u>).

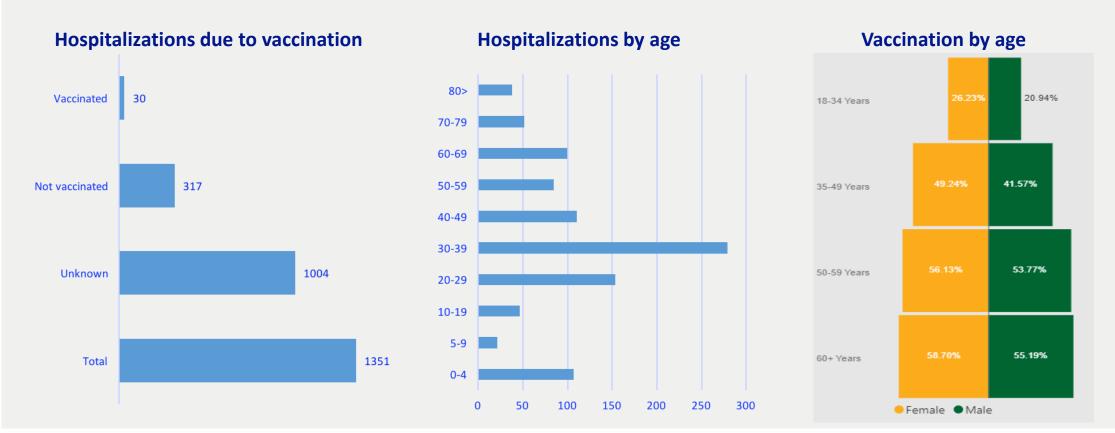


Variant	Vaccination or reinfection category	Cases	Hospital- isations	% Reinfections (cases)	% Reinfections (hosp)	HR relative to primary Delta infection in unvaccinated	p- value
All	Not reinfection	306194	3238	-	=	=	
All	Reinfection	13962	53	4.6%	1.6%	0.53 (0.47-0.61)	<1e-6
Delta	Unvaccinated	109331	1466	1.9%	0.8%	1 (1-1)	<1e-6
Delta	AZ:D1:<21	6	0	0.0%	-	-	-
Delta	AZ:D1:21+	1676	38	3.9%	5.3%	0.69 (0.58-0.81)	<1e-5
Delta	AZ:D2:<14	144	≤5	4.2%	100.0%	0.29 (0.12-0.66)	0.003
Delta	AZ:D2:14+	67717	857	2.2%	1.3%	0.38 (0.36-0.4)	<1e-6
Delta	AZ:D3:<14	13259	110	1.7%	0.9%	0.24 (0.22-0.27)	<1e-6
Delta	AZ:D3:14+	4231	70	4.1%	1.4%	0.36 (0.31-0.41)	<1e-6
Delta	PF/MD:D1:<21	2602	24	2.6%	0.0%	0.76 (0.63-0.92)	0.005
Delta	PF/MD:D1:21+	15558	109	2.4%	0.0%	0.54 (0.49-0.59)	<1e-6
Delta	PF/MD:D2:<14	1060	≤5	5.6%	0.0%	0.1 (0.05-0.18)	<1e-6
Delta	PF/MD:D2:14+	41477	293	4.6%	2.7%	0.25 (0.23-0.27)	<1e-6
Delta	PF/MD:D3:<14	2268	25	2.9%	0.0%	0.32 (0.27-0.39)	<1e-6
Delta	PF/MD:D3:14+	5691	96	3.8%	2.1%	0.3 (0.26-0.34)	<1e-6
Omicron	Unvaccinated	9585	56	18.6%	8.9%	0.59 (0.5-0.69)	<1e-6
Omicron	AZ:D1:<21	0	0	-	-	•	ı
Omicron	AZ:D1:21+	257	≤5	23.3%	0.0%	0.29 (0.11-0.77)	0.012
Omicron	AZ:D2:<14	29	0	3.4%	-	-	0.905
Omicron	AZ:D2:14+	11440	46	14.0%	4.3%	0.31 (0.27-0.36)	<1e-6
Omicron	AZ:D3:<14	2877	≤5	9.0%	0.0%	0.07 (0.04-0.12)	<1e-6
Omicron	AZ:D3:14+	2384	8	7.0%	0.0%	0.2 (0.14-0.28)	<1e-6
Omicron	PF/MD:D1:<21	293	0	14.3%	-	-	0.693
Omicron	PF/MD:D1:21+	2526	10	12.9%	20.0%	0.57 (0.42-0.78)	<1e-3
Omicron	PF/MD:D2:<14	249	≤5	20.5%	0.0%	0.44 (0.19-1.02)	0.057
Omicron	PF/MD:D2:14+	22249	60	11.9%	6.7%	0.22 (0.19-0.26)	<1e-6
Omicron	PF/MD:D3:<14	780	≤5	9.7%	25.0%	0.55 (0.36-0.85)	0.007
Omicron	PF/MD:D3:14+	2467	11	8.0%	9.1%	0.34 (0.25-0.45)	<1e-6



Gauteng data suggest 85% effectiveness for hospitalizations

• Data from hospitalizations in Tshwane suggest that the effectiveness of the vaccine is maintained at a high level. A cross-check between age and vaccination of hospitalized patients reveals that the effectiveness of the vaccine to reduce hospitalizations might be close to 85%. It is a preliminary estimate, but it would imply a strong increase in hospitalizations for the same number of cases. For example, it would triple when compared to an estimated 95% efficacy for two doses against the delta variant.

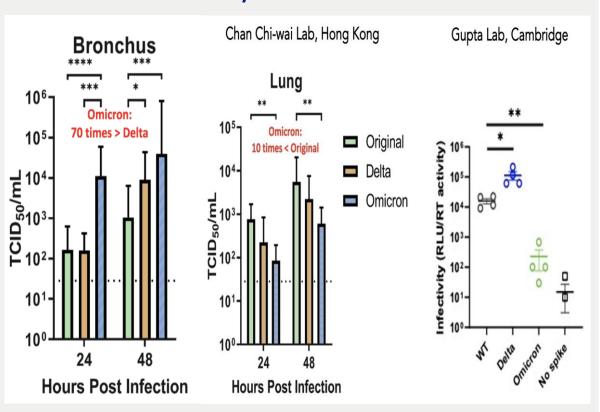




Omicron is less aggressive to the lungs of those infected

- Two studies present a potential explanation for Omicron's lower virulence (<<u>link</u> and <u>link</u>). When analyzing the degree of virus attack on lung cells, the authors of the two studies found a lower virulence of Omicron compared to other variants.
- Efficient infection of lung cells may correlate with the severity of the lung disease. Syncytium or fused cells are often observed in respiratory tissues obtained after severe disease. That is, the disease becomes less serious to the hosts.
- And how is Omicron more transmissible? The same study shows that
 it is much more effective in attacking the respiratory tract, especially
 in the first 24 hours.

Pulmonary cell infection infected by different variants





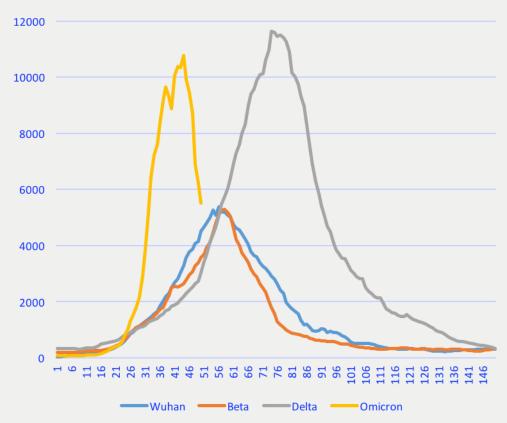
Omicron Outbreak in Africa and Europe



Omicron cases peak were similar to Delta's

• The rate of increase of cases in Gauteng in the current outbreak was higher than seen in other waves. However, the peak of the current outbreak was very similar to that of Delta, suggesting that only the speed was different, but not the cycle size.

New cases by outbreak in Gauteng



New deaths by outbreak in Gauteng

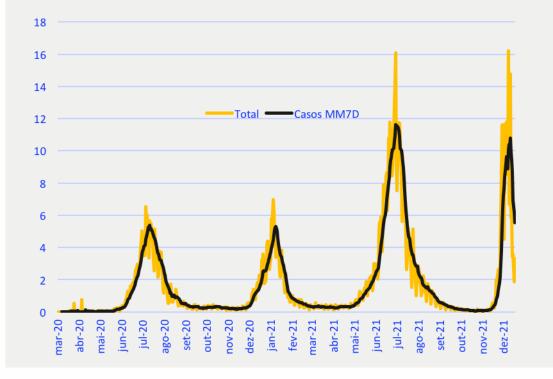




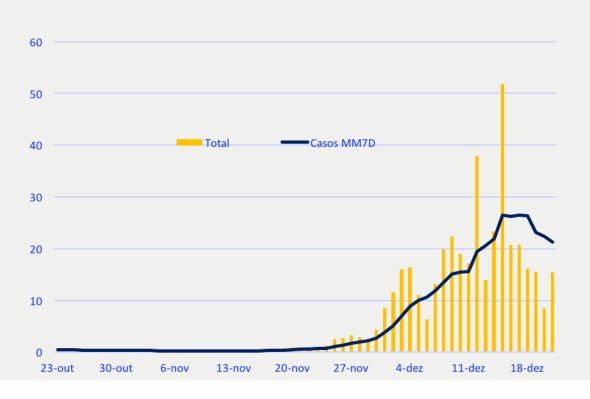
New cases already show a reduction in RSA

• Number of new cases in South Africa increased at a very rapid rate at the beginning of the outbreak. However, there was a much earlier than expected inflection and the peak of cases in the current Omicron wave was very similar to that of the Delta outbreak seen in mid-2021.

New cases of Covid-19 in South Africa (thousand)



New cases of Covid-19 in South Africa (thousand)

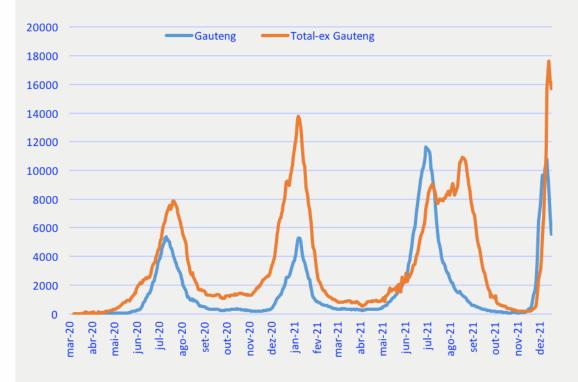




New cases show inflection in the rest of the country

• Gauteng was the epicenter of the current Covid outbreak, just as it was in the last wave. As in Gauteng, the new cases seem to have peaked much earlier than expected in the rest of the country.

New Gauteng and ex-Gauteng cases (MM 7 days)



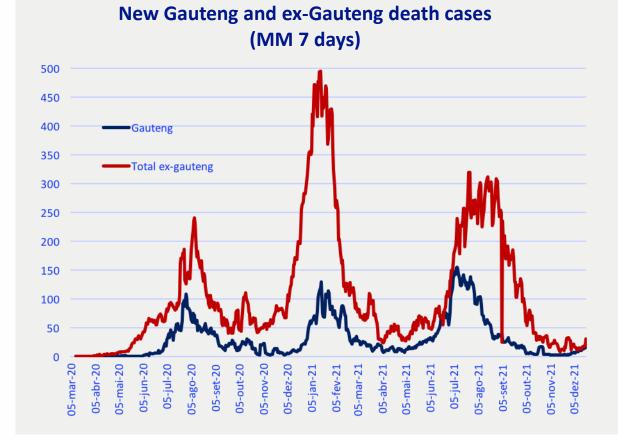
New Gauteng and ex-Gauteng cases (MM 7 days)

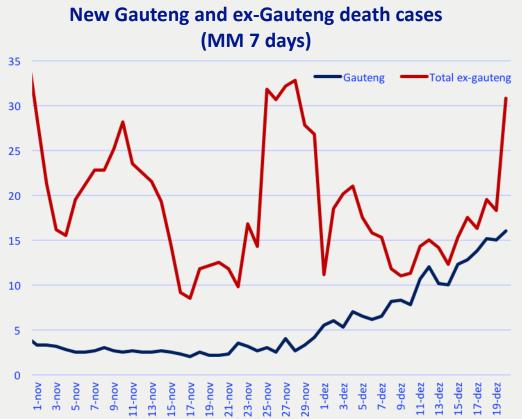




New deaths show residual increase

• New deaths have not yet shown a significant increase. Despite the natural gap between the increase in the number of new cases and deaths, it is already possible to infer that the death/case ratio will be lower in the current outbreak.



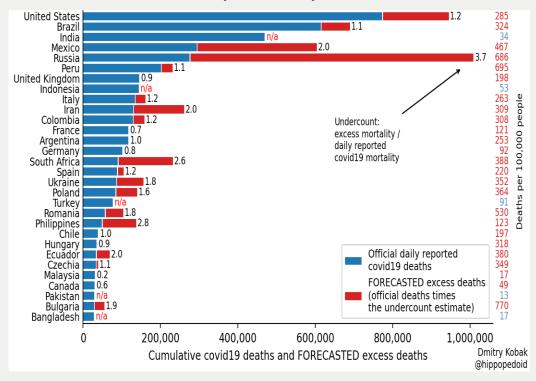




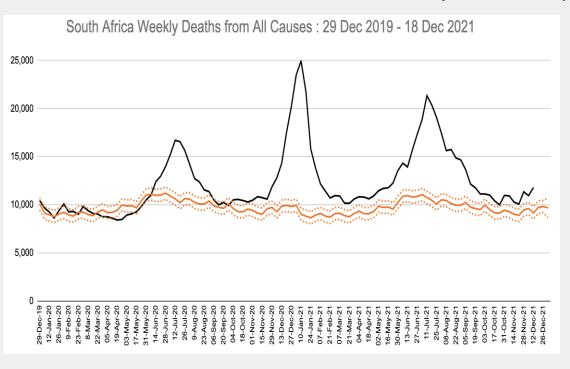
Deaths are underreported in South Africa

• Excess deaths have increased very little in recent weeks, corroborating the hypothesis of a softer outbreak. South Africa is one of the countries with the highest underreporting number of deaths from Covid-19. Using civil registration data, it is possible to calculate the number of excess deaths in the country. The total number of deaths so far has been around 250k, far above what official statistics show.

Estimates of excess deaths (thousand)



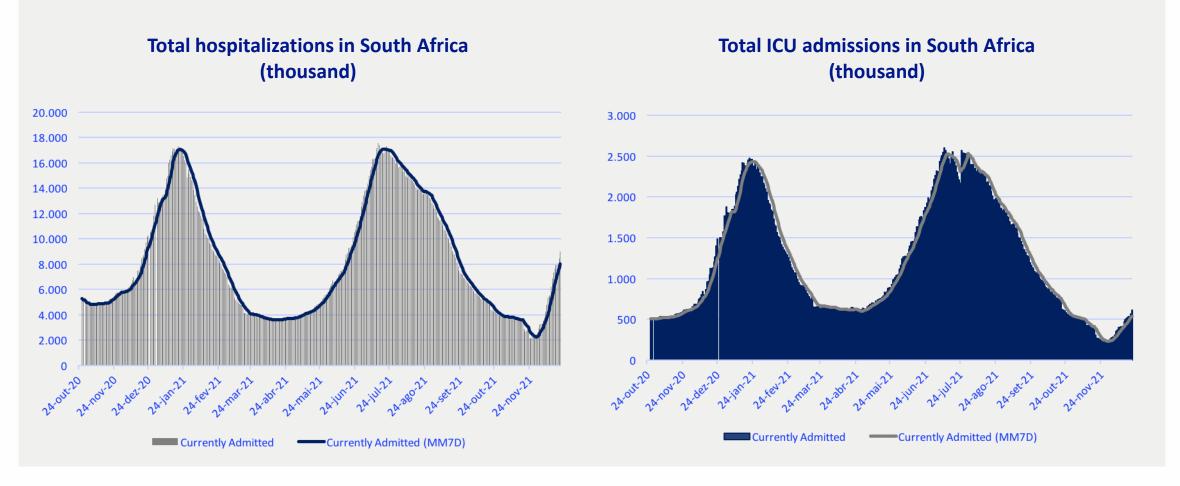
Excess deaths vs. Covid-19 deaths in South Africa (deaths/week)





Hospitalizations are below previous waves

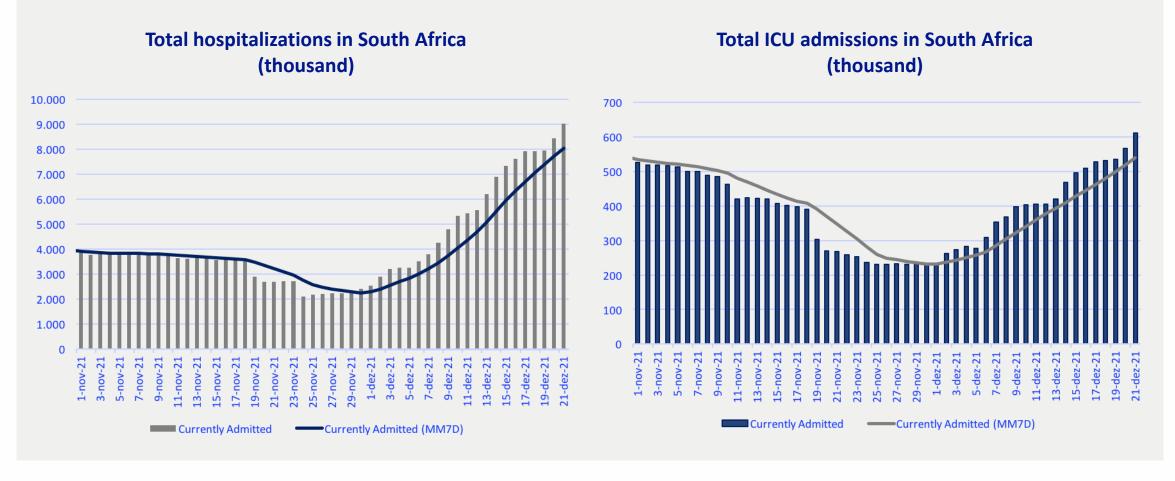
• The number of people hospitalized and admitted in the ICU remains well below the previous waves and already shows the first signs of inflection.





Hospitalizations are below previous waves 2

• The number of people hospitalized and admitted in the ICU remain well below the previous waves and already show the first signs of inflection.

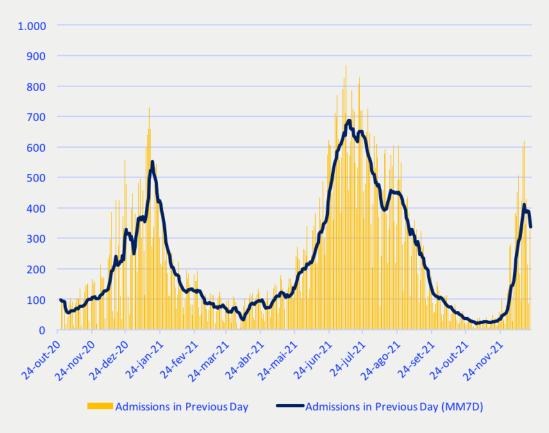




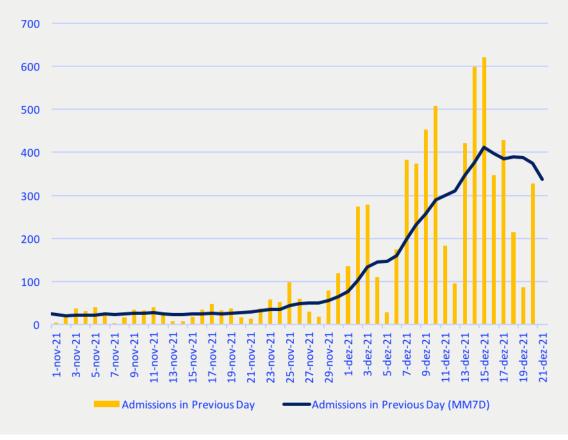
New hospitalizations already show a reduction

• The number of new hospitalizations in South Africa is already declining. This suggests that the peak of hospitalizations has also been reached and ended up being close to half that observed in the Delta outbreak.

New hospitalizations in South Africa



New hospitalizations in South Africa

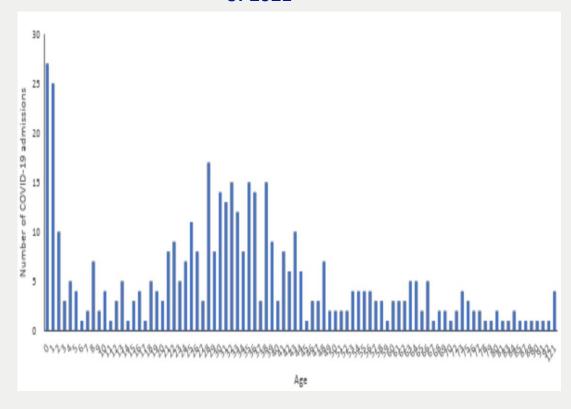




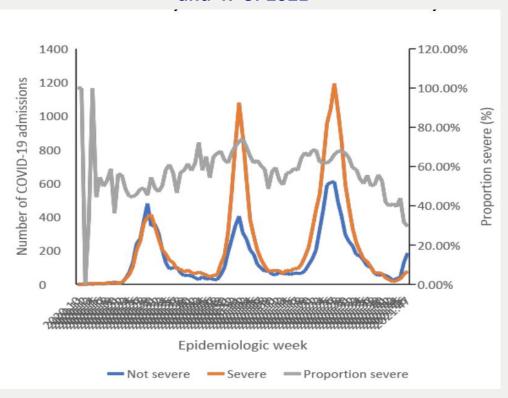
Lower severity of hospitalizations in the outbreak

• The severity of hospitalizations in Tshwane was lower than in other outbreaks. The reason for this is not clear, but it is possible to be due to a greater concentration of hospitalizations among the youngest at this beginning of the outbreak.

Admissions by age in Tshwane between weeks 40 and 47 of 2021



Degree of severity of hospitalizations between weeks 40 and 47 of 2021

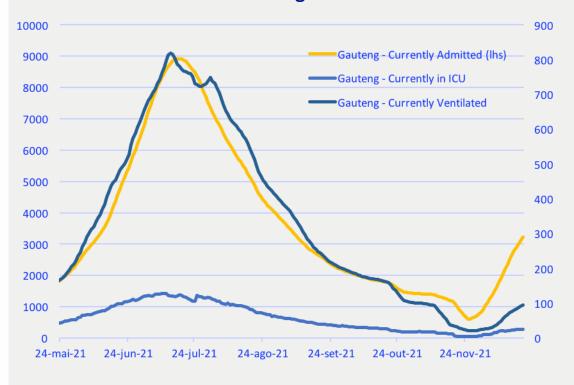




Lower severity of hospitalizations

• The ratio of ICU admissions in relation to total admissions shows a similar pattern. Currently, this ratio is at the lowest level of the historical series.

Number of patients admitted in the ICU and intubated in Gauteng



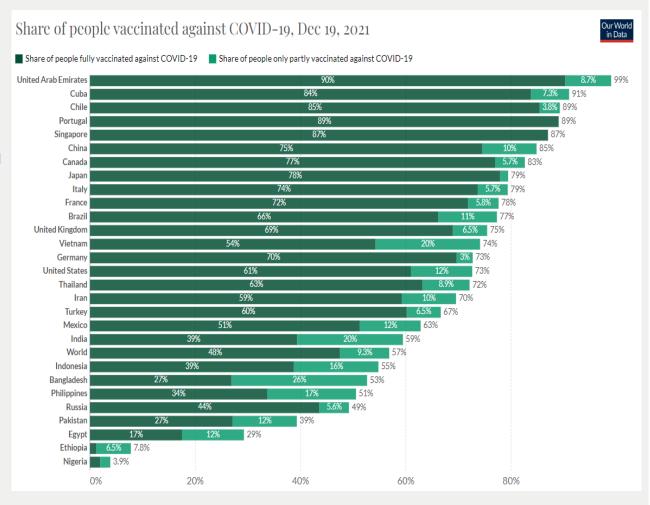
The ratio of ICU admissions in relation to total admissions (%)





Vaccination extent in South Africa is low

- One issue with the focus on South Africa is that the degree of vaccination there is quite low. Only 29% of people were vaccinated with the first dose of the vaccine.
- This is much lower than seen in Brazil, in the USA and in countries of the European Union, for example. It is possible that the higher degree of vaccination of these countries is sufficient to not allow the spread of this new variant, even in a scenario of a large outbreak in South Africa. Monitoring how this variant is transmitted in a country with higher rates of vaccines will be a better predictor of the risk it poses to, for example, Brazil and the USA.
- Nevertheless, the fact that South Africa has already experienced three severe waves of Covid-19 implies a high degree of immunization by the previous infections. Since the beginning of the pandemic, excess deaths in the country have exceeded 230k, or 0.39% of the population. Considering only the demographic pattern and the mortality rate of the virus by age group estimated by the CDC, this would imply that practically the entire population of the country would have already been infected.
- Obviously, this number is overestimated because it does not take into account reinfections nor the fact that mortality in Africa is higher due to the precariousness of treatment in relation to developed countries

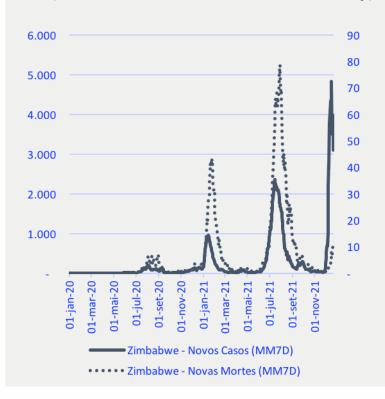




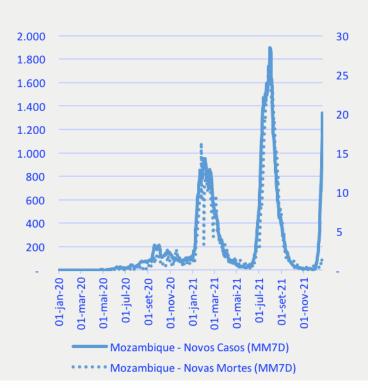
Other African countries show similar outbreaks

• Omicron variant spread very quickly to other countries in Africa. The Covid-19 outbreaks in these countries show similar characteristics to those seen in the South African outbreak – a strong and rapid increase in new cases, but with little impact on the number of new deaths. In Zimbabwe, it is already possible to see an inflection in the daily number of new cases.

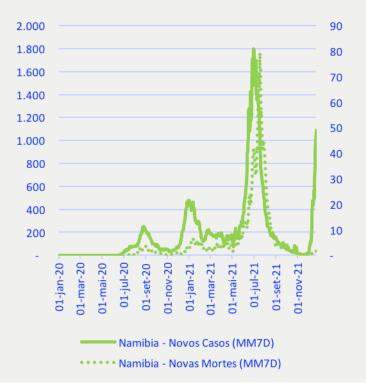
Outbreak in Zimbabwe (thousands of cases and deaths/day)



Outbreak in Mozambique (thousands of cases and deaths/day)



Outbreak in Namibia (thousands of cases and deaths/day)

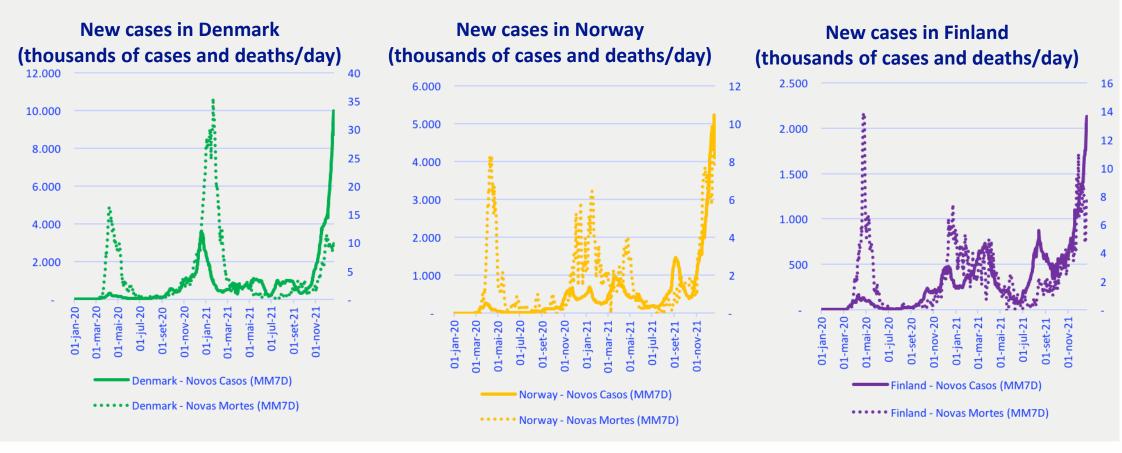


Source: John Hopkins, Mar Asset Management



Nordic countries face a wave of Delta and Omicron

• The Nordic countries will help us understand the Omicron variant ability to become dominant. The region was experiencing the worst Covid-19 wave due to the rapid spread of the Delta variant. However, the last few weeks have seen a strong advance in new cases related to Omicron. In Denmark, for example, Omicron's new cases became the majority, but there has not yet been a considerable reduction in the absolute number of new Delta cases.

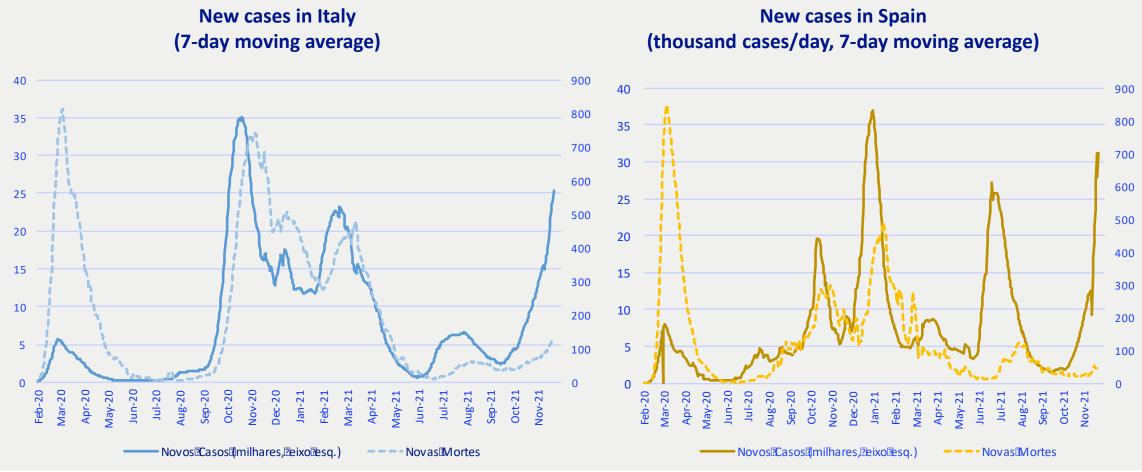


Source: John Hopkins, Mar Asset Management



New cases in Italy and Spain show an increase

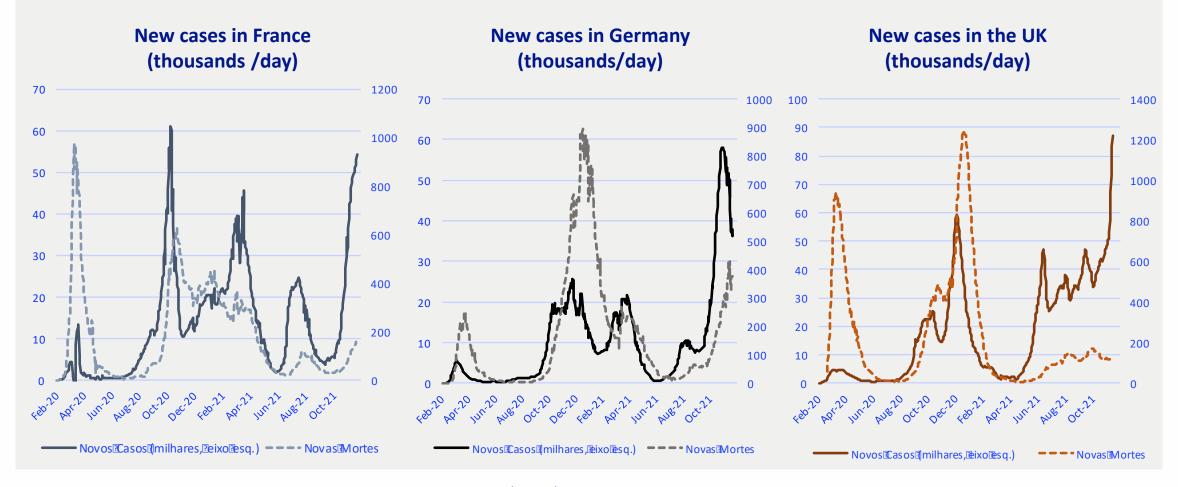
• The Omicron variant has already been transmitted to the rest of the continent. The new cases in Italy and Spain are fast approaching the peak seen during previous outbreaks. The increase has not yet been reflected in an increase in the number of new deaths.





New deaths remain in low levels in the UK

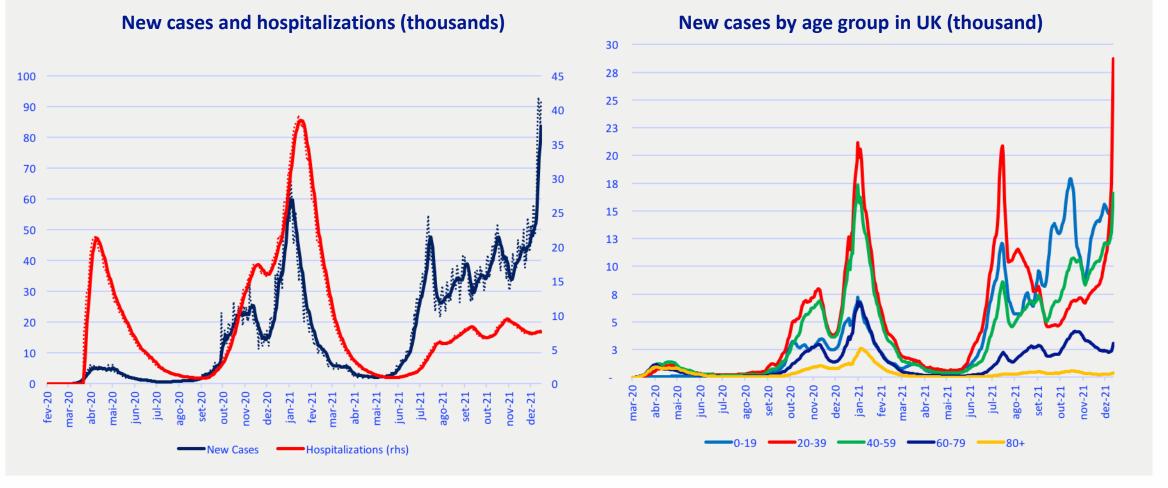
• The increase of new cases was not followed by a proportional increase in the number of deaths. The Omicron outbreak in Europe is still in the early stage, but the first pieces of evidence indicate this wave will be less severe than Delta's.





Hospitalizations still under control in UK

• Hospitalizations in England are at levels well below those recorded in the outbreak seen at the end and 2020/beginning of 2021 despite the sharp increase in cases. Some explanation is found in the higher concentration of cases among young people.

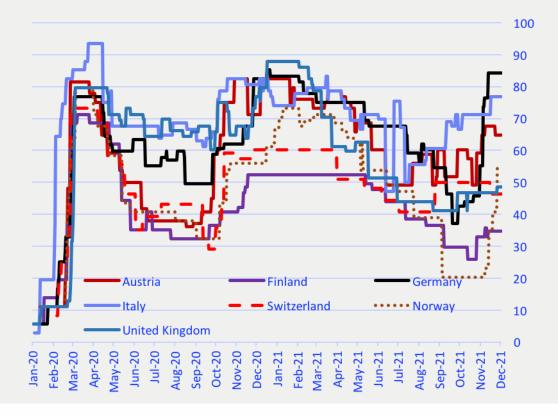




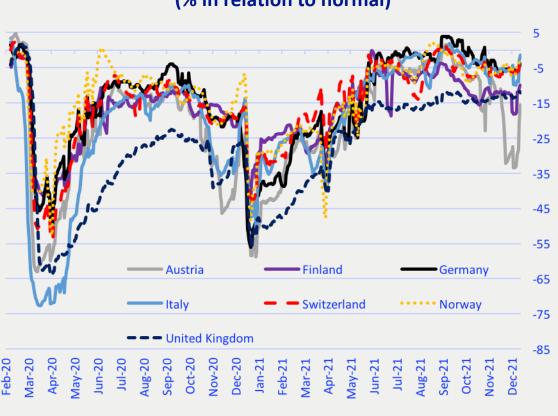
Omicron has not yet affected mobility in the EU

• The University of Oxford's Strictness Government Indexes show a tightening of official measures in order to reduce the spread of the virus. Despite the increased spread of the virus, Google's social mobility index remains at high levels.

Oxford University Covid-19 Government Response Strictness Index (0=min, 100=max)



Social mobility index (% in relation to normal)



Source: OxCGRT, Google, Mar Asset Management



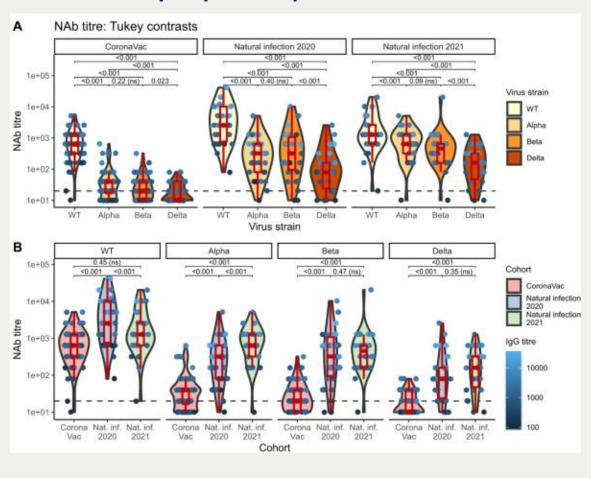
Risks



It is likely to remain effective for severe cases

- There was a relevant risk that this new variant would reduce vaccines effectiveness for symptomatic cases of Covid-19. This was the pattern observed in the emergence of VoCs in the past, such as Delta. For example, a population study by PHE shows that the effectiveness of vaccines in the UK is reduced from 49% after the first dose and 89% after the second to 35% and 79%, respectively, when compared to people infected with the delta variant in relation to the English variant (alpha).
- This does not mean that there was a loss of effectiveness for severe cases. This same study from England that the effectiveness of vaccines to reduce hospitalizations is practically unchanged.
- Coronavac's case illustrates well this dichotomy. Several studies
 have shown that this vaccine induces a very low antibody
 production, especially when confronted with the Delta variant (e.g.,
 link). Nevertheless, in practice, effectiveness against severe cases
 was high in Brazil and Chile (link).
- We will probably see something like this with Omicron. In vitro
 vaccine effectiveness studies published in recent weeks show a
 lower antibody response, but still sufficient T and B cell response suggesting loss of effectiveness against infection, but still effective
 for severe cases.

Antibody response in plasma of vaccinees

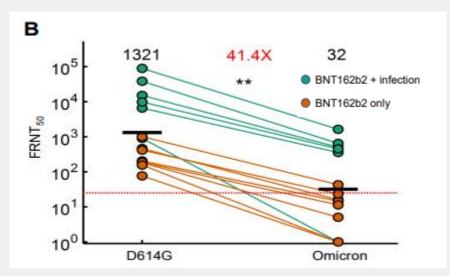




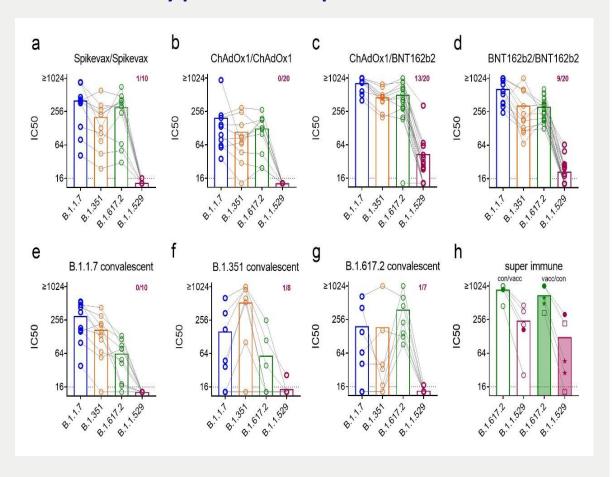
In vitro studies suggest vaccines loss of effectiveness

- In vitro studies suggest a significant loss of vaccine effectiveness against the new variant. Several studies have been published in recent weeks and almost all have reached the same conclusion.
- These studies analyze the plasma capacity of vaccinated people to fight Omicron in relation to old variants. All of them showed a strong reduction in this capacity and many of them showed zero capacity. (link, link, link).

Antibody production in plasma of vaccinees



Antibody production in plasma of vaccinees

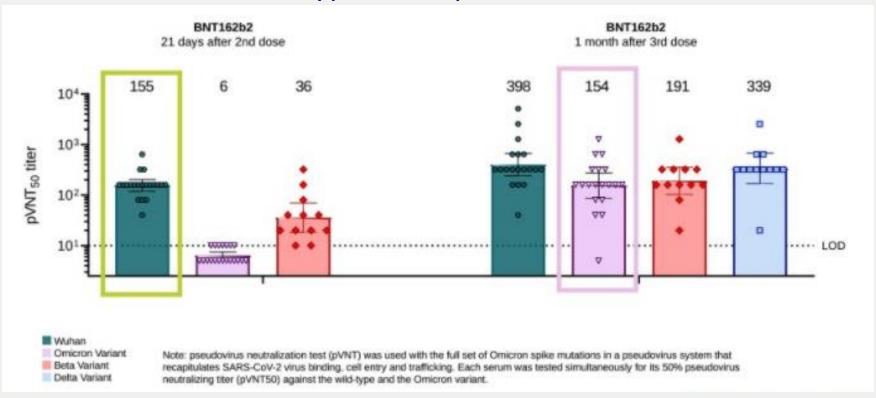




Pfizer third dose returns initial level of antibodies

• A study released by Pfizer suggests that a third dose may be able to recompose the loss of efficacy due to the new variant. Also in an *in vitro* study, the pharmaceutical company analyzed the plasma of people vaccinated with a third dose when confronted with Omicron. According to the study, the ability to neutralize this new strain of the virus is similar to that of the plasma of a person who had received only two doses of the vaccine but who was confronted with the original Wuhan variant.

Antibody production in plasma of vaccinees





Denmark casts a doubt in third dose effectiveness

- However, the first information on the effectiveness of the vaccine against Omicron in real data casts doubt on the ability of a third dose to raise the effectiveness levels observed against other variants. SSI study in Denmark suggests (link):
 - 55% effectiveness against infection in the first thirty days after the second dose.
 - Effectiveness is reduced in subsequent weeks and reaches close to zero 60 days after vaccination
 - Pfizer's third dose brings effectiveness back to 55%.

Table Estimated vaccine effectiveness for BNT162b2 and mRNA-1273 against infection with the SARS-CoV-2 Omicron and Delta variants during November 20 – December 12, 2021, Denmark.

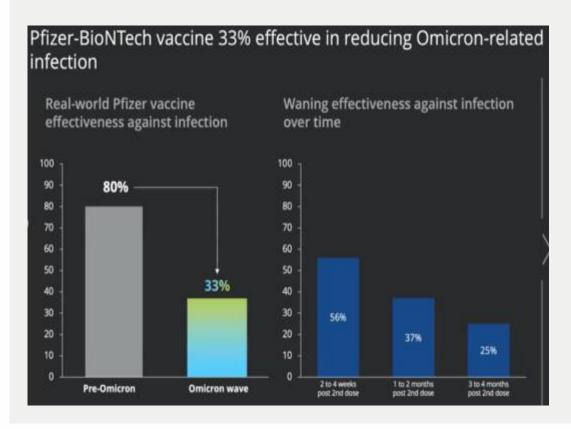
	Pfizer — BNT162b2				Moderna - mRNA-1273			
Time since vaccine	Omicron		Delta		Omi cr on		Delta	
protection	Cases	VE, % (95% CI)	Cases	VE, % (95% CI)	Cases	VE, % (95% CI)	Cases	VE, % (95% CI)
1-30 days	14	55.2 (23.5; 73.7)	171	86.7 (84.6; 88.6)	4	36.7 (-69.9; 76.4)	29	88.2 (83.1; 91.8)
31-60 days	32	16.1 (-20.8; 41.7)	454	80.9 (79.0; 82.6)	8	30.0 (-41.3; 65.4)	116	81.5 (77.7; 84.6)
61-90 days	145	9.8 (-10.0; 26.1)	3,177	72.8 (71.7; 73.8)	48	4.2 (-30.8; 29.8)	1,037	72.2 (70.4; 74.0)
91-150 days	2,851	-76.5 (-95.3;-59.5)	34,947	53.8 (52.9; 54.6)	393	-39.3 (-61.6;-20.0)	3,459	65.0 (63.6; 66.3)
1-30 days after	booster va	occin ation						
protection	29	54.6 (30.4; 70.4)	453	81.2 (79.2; 82.9)	-	-	5	82.8 (58.8; 92.9)

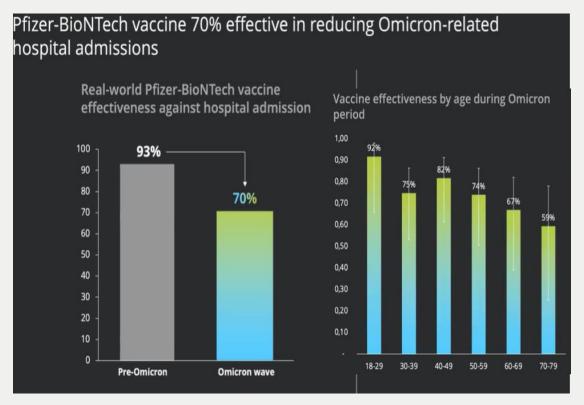
CI = confidence intervals; VE = vaccine effectiveness. VE estimates adjusted for 10-year age groups, sex and region (five geographical regions). Vaccine protection was assumed 14 days post 2nd dose. Insufficient data to estimate mRNA-1273 booster VE against Omicron.



Effectiveness of 33% and 70% for mild and severe cases

- Using data from Discovery Health, the authors calculated the effectiveness reduction of two doses of Pfizer from 80% to 33%. For cases requiring hospitalization, the effectiveness reduction goes from 93% to 70%.
- Effectiveness is lower the longer the second dose was taken and the older the person is. There is a correlation between these two variables and, therefore, it was not possible to estimate the contribution of each of these variables individually.



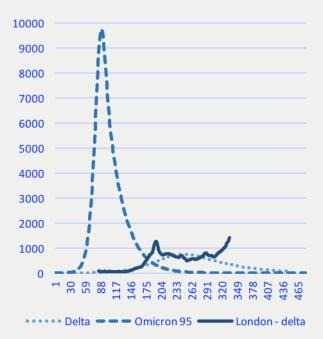




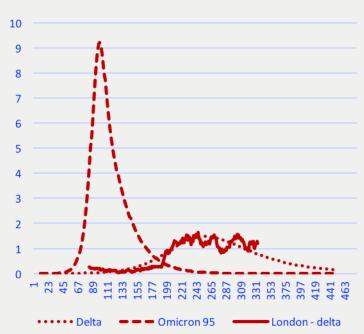
Reduced effectiveness would greatly increase number of deaths 1

- Using a SIR model for new cases evolution that considers, among other things, the effectiveness of the vaccine for new cases and deaths, we can simulate what would be the impact of a reduction in vaccines effectiveness on the dynamics of deaths/cases.
- Even in a scenario where we assume transmissibility and effectiveness of the vaccine for death prevention for Omicron is equal to that of Delta, the peak of deaths would be ten times higher if the effectiveness for infection prevention decreased from 75% to 20%. This already takes into account a greater proportion of the population vaccinated now compared to the beginning of the Delta outbreak.

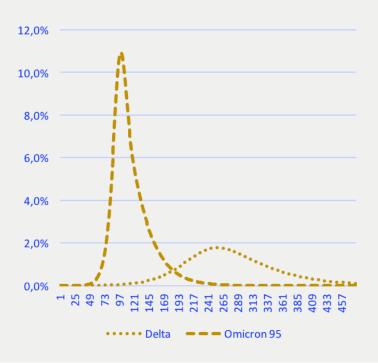
Simulations for new cases in London (million inhabitants)



Simulations for new cases in London (million inhabitants)



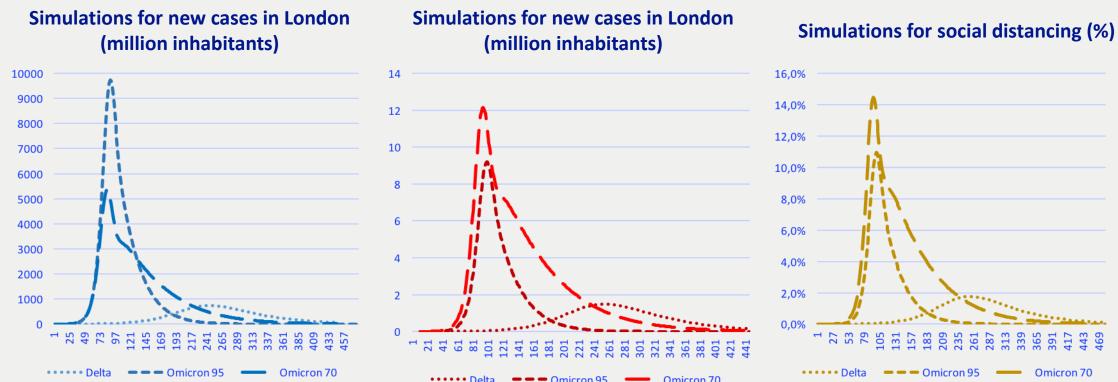
Simulations for social distancing (%)





Reduced effectiveness would greatly increase number of deaths 2

- The previous slide showed the impact on the dynamics of the Omicron outbreak if we considered only a reduction in vaccine effectiveness for infection prevention. However, it is possible that the new variant will also reduce the effectiveness of the vaccine for severe cases, which would further contribute to making a new outbreak quite dangerous.
- If the same previous simulation is performed, but also considering a reduction in vaccine effectiveness to 70%, we would have a longer wave, with more deaths and that would require a greater response from society in terms of social distance.

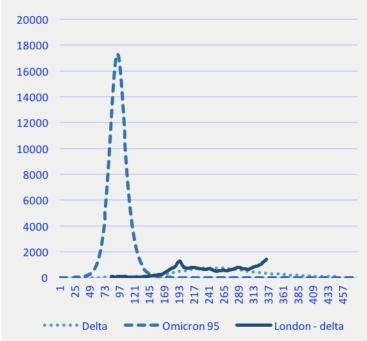




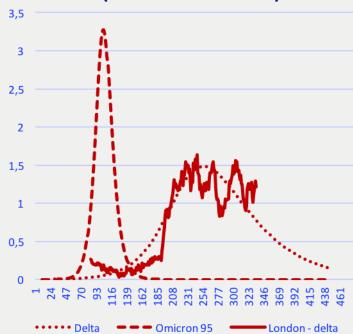
Less severity would compensate for loss of effectiveness

- Studies in South Africa and the UK suggest that the severity of Omicron is lower than that of Delta. We consider a scenario in which the vaccine effectiveness for severe cases is maintained, but with mortality five times lower than in the Delta base scenario.
- The exercise suggests that the peak of the Omicron wave would be almost 18 times higher, but the peak of deaths would only be twice as high. In addition, the wave would be much shorter, leading the total number of deaths to be half of the Delta base scenario.

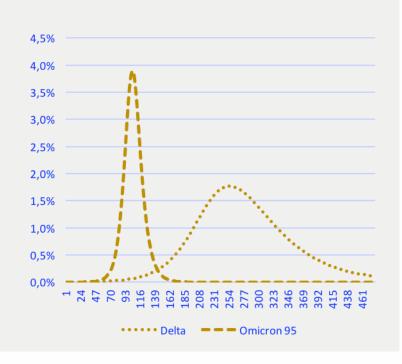
Simulations for new cases in London (million inhabitants)



Simulations for new cases in London (million inhabitants)



Simulations for social distancing (%)





Conclusions

Greater transmissibility, less severity – Preliminary studies and what we are observing suggest that Omicron emergence was beneficial. It might well be transmissible enough to become the dominant variant without causing major damage in terms of increased hospitalizations and deaths.

Effectiveness loss compensated by lower severity – a possible negative scenario would be one in which cases increased so much that, even with a lower hospitalization/case ratio, hospitalization and deaths increases greatly in an Omicron outbreak. This scenario was outlined on slides 35 and 36. However, what we have seen so far is that less severity seems more than offsetting increase in cases.

"Christmas Gift"— The outbreak in South Africa has shown three major surprises in the past week. (i) the outbreak of new cases peaked much earlier that expected and at a level similar to the Delta outbreak; (ii) the peak of new hospitalizations was half of that of Delta; (iii) the most sever hospitalizations were even lower. In particular, the surprise (i) is not consolidated. If perhaps the cycle of new cases in the rest of the world is, in fact, much smaller than expected given the transmissibility of Omicron, the scenario would be even more positive.

