



June 9, 2022

Risk assessment of SARS-CoV-2 omicron subvariants BA.5, BA.2.12.1 and BA.4**Background**

During the spring of 2022, the omicron has changed further, and now consists of a large number of sub-variants, each of which has changes in, among other things, the spike protein, which may have an impact on proliferation, e.g. due to so-called "immune evasion". Among these, the sub-variants BA.5, BA.2.12.1 and BA.4, which can be considered as sub-variants of BA.2 in terms of evolution, are under special international surveillance, as increasing incidence of infection has been observed in several countries, coinciding with these variants constitutes an increasing relative proportion of sequenced samples.

ECDC has added BA.4 and BA.5 separately to the list of VOCs due to their potential to cause an increase in cases of infection in Europe over the summer. WHO has kept them under the omicron main variant due to their continued low prevalence globally as well as lack of data regarding their ability to cause serious illness compared to BA.1 / BA.2. Both BA.5, BA.2.12.1 and BA.4 have been observed in Denmark, and in recent weeks they have accounted for an increasing proportion of the sequenced samples (see table in appendix). Since in absolute numbers more cases of BA.5 were detected than BA.4 and BA.2.12.1

in week 21, and it is also the variant that has the highest growth rate, it is expected that this variant will become the dominant one in DK over the next 1 to 3 weeks.

Genetic and immunological characteristics of BA.5, BA.2.12.1 and BA.4 In relation to

mutations in the spike protein, BA.4 and BA.5 have characteristics that are identical, and both subvariants are more closely related to BA.2 than BA.1. Both subvariants contain the mutation S: L452R, which is also found in the delta variant as well as the mutation S: F486V. Both of these mutations are associated with decreased sensitivity to the immune system, and in addition, there is a third difference, the back mutation S: Q493R, which is probably required for strong binding to the ACE2 receptor. BA.4 and BA.5 differ from BA.2.12.1 by having the spike mutation S: F486V.

Overall, several neutralization studies show that BA.4 and BA.5 are less sensitive than both BA.1 and BA.2 to antibodies after vaccination alone and hybrid immunity (vaccination + infection). Of the EU-approved therapeutic monoclonal antibodies, evusheld has retained in vitro neutralization potency against BA.1.12.1 and BA.5 / BA.4. BA.4 and BA.5 can be captured as a group on variant PCR, and internal studies show that this is with a sensitivity above 90%.

Internationally

In several European countries, increasing proportions of BA.5 have been detected among the positive samples during the month of May. This applies i.a. Germany, France, Austria, Israel and the United Kingdom. According to the ECDC, the proportion of BA.5 in the period from week 19-20 in Portugal was: 48%, Austria: 20%, Spain: 7%, France: 6% and the Netherlands 6%. In the same period, Denmark has also seen an increasing share of BA.5 from just under 1% in week 19 to almost 3% in week 20.

During April 2022, a marked increase in cases of infection was observed in South Africa at the same time as the emergence of the subvariants BA.4 and BA.5. In December 2021, South Africa had a large omicron wave, which in contrast to Denmark was dominated by the subvariant BA.1.

Vaccination coverage in South Africa is low compared to Denmark. About 45% of the population have completed the primary vaccination program and 4.5% have received booster vaccination. The degree of natural immunity is considered to be high due to widespread spread of infection in



connection with previous waves of infection in the epidemic. Since mid-May, South Africa has had a sustained decline in infection rates and the positive percentage, and therefore now appears to be past its peak. Seen in relation to previous waves, this wave was significantly smaller. The number of cases, hospitalizations and deaths was 33%, 35% and 15% of the highest level during their BA.1 wave, respectively. However, it should be noted that the test activity was also at a significantly lower level compared to previous waves.

In Portugal, since the beginning of May, there has been an increasing spread of infection with an incidence of now approx. 250 daily cases of infection per 100,000 inhabitants. The incidence at the peak of Portugal's omicron wave in January was approx. 600 daily cases of infection per 100,000 inhabitants. As in many other countries, test activity in Portugal is at a low level, but in recent weeks a record high positive percentage of approx. 54% in week 21. According to data from ECDC, the rate of new admissions has continued to decline since the first omicron wave in February, but data is continuously updated. However, data from the COVID database "Our world in Data" (OWID) show that the number of hospitalized covid patients has increased considerably since the beginning of May, and is now almost on a par with the first omicron wave. There are no data on whether patients are admitted "with" or "off" covid. The number of inpatients has increased to a lesser extent since mid-May, but remains at a low level. According to ECDC, the number of covid-related deaths is increasing but from a low level, while data from OWID also show a possible smaller increase from a low level. Reservations must be made that the data reporting from Portugal is characterized by irregularities. According to EuroMOMO, the excess mortality rate in Portugal is stable and low.

The proportion of spike gene target failure (SGTF) positive samples, which is a proxy marker for BA.4 and BA.5 incidence on a background of widespread BA.2 infection, has increased since mid-April from a few percent to now lie at 87%. The post-registration of genome-sequenced samples has confirmed that it is BA.5 that dominates in the country. Portugal's former omicron wave was similar to the South African dominated by BA.1.

In Portugal, the vaccination coverage is almost identical to the Danish one. They started early with the booster vaccination, and had by comparison approx. 850,000 inhabitants who were booster vaccinated at the end of November 2021. A declining vaccine immunity, and a poorer immunity to BA.4 / 5 in previous BA.1 infection (compared to BA.2) are mentioned as some possible reasons for the current increase in infection. In addition, the abolition of the mask order in April and the Easter holidays are mentioned as possible contributing factors.

In Portugal, the offer of the fourth vaccination dose has been expanded in relation to the elderly and vulnerable, but so far no new restrictions have been introduced during the current wave of infections.

In the United States, BA.2.12.1 is still growing, accounting for about 59% of the sequenced samples by the end of week 21. A rapidly increasing positive percentage has been observed as well as a small increase in the number of cases of infection and hospitalizations recently, but this from a low level. The number of covid deaths is currently stably low.

BA.2.12.1's growth was first recognized in New York, where it quickly outperformed BA.1 and later BA.2. In New York, the trend in the number of infections and hospitalizations now appears to be declining again, and the peak was at a significantly lower level than during their recent omicron wave. This should be interpreted subject to a low test activity. The number of intensive care admissions and deaths has so far remained at a stable low level.



The share of BA.4 and BA.5 has also seen an increase in the US in recent weeks. Overall, they amount to 6.1% as of 28-05-2022, which is an increase from 1.9% two weeks earlier. Preliminary data from the USA indicate that BA.5 and BA.4 have a growth advantage compared to BA.2.12.1. This is also reported but it is emphasized in the from the UK in their latest technical briefing on variants¹, report that it based on few and preliminary data. The UK, like the ECDC, has classified BA.4 and BA.5 as Variants of Concern separately. They also emphasize in the report that so far there is not enough data to estimate the increase in hospital admissions that BA.4 and BA.5 may cause.

Developments in Denmark

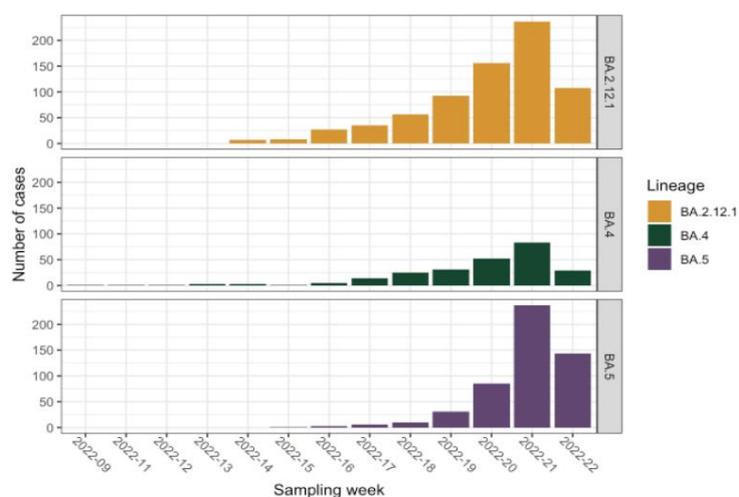
In general, the epidemic has been characterized by a prolonged period with a continuous decline in the number of new cases of infection and positive percentages. There is now an increase in the number of new cases as well as an increase in the positive percentage despite a very low and continuing decline in test activity. The incidence and positive percentage are highest among especially the older age groups, where the proportion who have achieved hybrid immunity is lowest. There are also signs of increasing positive percentage among health and care staff. In parallel, in recent weeks a signal has been seen of a flattening / slight increase in the concentration of SARS-CoV-2 in the wastewater after a continuous decrease in the period from start / mid-February to the beginning of May. However, it is worth noting that the total number of cases of infection in Denmark is still at a very low level compared with the omikron wave around the transition January-February 2022.

In Denmark, BA.5, BA.2.12.1 and BA.4 have been continuously detected in the sequenced PCR samples since March / April, respectively. BA.5 since 15 April, BA.2.12.1 since 7 April and BA.4 since 2 March. However, in recent weeks there has been a growth in the proportion of BA.5 and BA.2.12.1 among the sequenced samples, which corresponds to a doubling time of more than every and every other week, respectively, and in week 22, the sub-variants provisionally amount to 21% (BA.5) and 12.4% (BA.2.12.1) per June 8. BA.4 currently amounts to 3.7% in week 23 per. June 8, and is not considered to show the same growth as BA.5 and BA.2.12.1.

There are a total of 726 cases with BA.2.12.1 and 517 cases with BA.5 in Denmark in the period 1 March to 30 May 2022. The pattern in age and geographical distribution is comparable for BA.5 and BA.2.12.1, and also coincides with the general age and geographical distribution. The incidence of reinfections is 14% for BA.5 and 7% for BA.2.12.1 compared to 5% in general throughout the period, but reservations must be made that these are small numbers and that the majority of cases with BA.5 and BA.2.12.1 are in recent weeks, and there may thus be a greater probability of reinfections due to time alone. Among reinfections for BA.5, there is a proportion (preliminary figures corresponding to 25%), where the previous infection is in the period when omicron has been dominant.

Figure 1. below shows the development in the 3 variants in the period from week 9 to week 22. Attention is drawn to the fact that post-registration continues, and data for week 22 are therefore preliminary.

¹ https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1077180/Technical_Briefing-42-20May2022.pdf



So far, very few admissions have been registered among persons with a proven BA.5 corresponding to 1.7% (9 admitted among 517 cases) and BA.2.12.1 corresponding to 2.8% (20 admitted among 726 cases). During the same period, the proportion of admissions among other detected cases totaled 4.6% (excl. BA.4), but reservations must be made for changes in the test activity that have been declining over the period from March to the end of May.

Analysis of growth rates

The estimated growth rates for the current sub-variants are presented below, based on the method used to estimate growth rates for the omicron variants BA.1 and BA.2 in weeks 4 to 11. The method used is described in more detail in the Note Growth rates for BA.1. and BA.2 of February 8, 2022

The estimated growth rates have been converted to weekly growth rates and presented in Figure 1. It can be seen that both BA.2 and BA.2.9 have had negative growth rates throughout the period. BA.2.12.1 has been at least 2% and has had a stable positive growth during the period - however, the estimates are not significantly different from zero at the beginning of the period, which is due to the relatively small number of cases and the fact that a 14-day period is used instead of for a longer period. The latest estimated growth rates with 14-day data from 15 May to 28 May 2022 are presented in Table 1, where both BA.2.12.1 and BA.5 have statistically significant growth rates. With a weekly increase for BA.5 of 71% (95% CI [25%; 134%]), it is to be expected that BA.5 will be the most common among the current variants. However, the number of sequences is currently relatively low, so estimates may be affected by stochastic events.

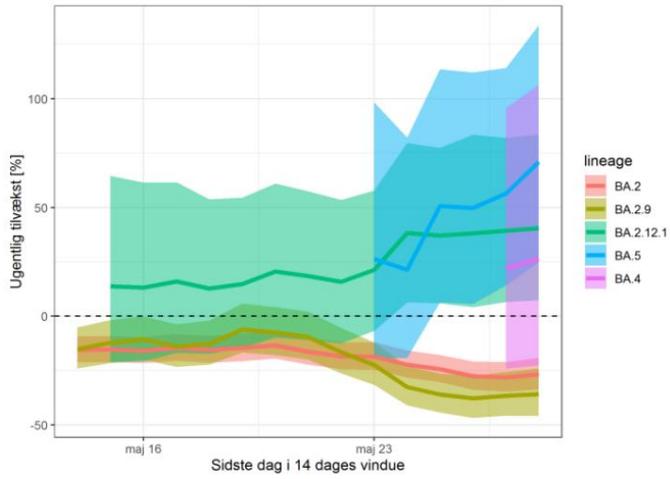
Table 1: Weekly growth rates in percent and associated 95% confidence intervals estimated from data from 15 May to 28 May. Subvariants that make up less than 2% of sequences from the period are omitted from the analysis.

Subvariant	Weekly growth	Lower	Upper
BA.2	-34%	-27%	-19%
BA.2.12.1	40%	7%	84%
BA.2.9	-36%	-46%	-24%
BA.4	26%	-23%	106%
BA.5	71%	25%	134%

² <https://covid19.ssi.dk/-/media/arkiv/subsites/covid19/risikovurderinger/2022/vkstrater-for-for-virusvariant-ba2-uge-6-2022.pdf?La=da>



Figure 1: Estimated weekly increments for sub-variants. The estimates are made with rolling windows, and the estimates are shown for the last day in the window for the sub-variants which make up more than 2% in given 14-day windows.





Overall assessment

During Denmark, there was a growth in the proportion of SARS-CoV-2 cases during May with the subvariants BA.5, BA.2.12.1 and BA.4. In particular, the subvariant BA.5 is considered to have a high growth rate, as an expression of a growth advantage compared to especially BA.2, but also compared to BA.4 and BA.2.12.1. Neutralization studies have shown that BA.4 and BA.5 appear to have a further decreased sensitivity to immunity driven by both vaccine and hybrid immunity compared to BA.1. and BA.2, which are considered to contribute to the increased growth potential of the sub-variants. Based on developments internationally, including in South Africa, the USA and Portugal, compared with the estimated growth rates for BA.5 in particular, the probability that BA.5 will become the dominant variant in the coming weeks is assessed as high.

Internationally, increasing infection and rising positive percentages have been seen despite declining testing activity in a number of countries. This pattern has coincided with an increasing proportion of BA.5 in particular among the sequenced samples. There are currently signs in Denmark of both increasing incidence of infection and increasing positive percentages based on PCR tests at the same time as a slight increase in the wastewater concentration of SARS-CoV-2. Based on these findings, compared with international data from countries where BA.5 has been dominant, it is estimated that there is a high probability of a general increase in the incidence of covid-19 driven by BA.5.

Currently, there are no signs of increased severity associated with infections with BA.5 either on the basis of international reports or the preliminary (very small) figures from Denmark. Against this background, the consequences of an increase in the epidemic in relation to serious outbreaks are assessed to be moderate for the general population, and everything else being equal is expected to be less than was the case for the wave of infection with BA.2. This is primarily due to the fact that protection against serious illness is expected on the basis of hybrid immunity. In addition, a decrease in activity in the community over the summer, combined with a seasonal effect, is expected to be able to reduce the infection in relation to the omicron wave at the beginning of 2022. However, it is likely that a larger part of the older part of the population can be infected in connection with an outbreak in the epidemic driven by BA.5 higher than during the omicron wave with BA.1 / BA.2. Currently, the older age groups have the highest positive percentage, in addition, the older age groups have not been infected to such an extent during the omicron wave with BA.2 as the rest of the population. This means that the level of hybrid immunity in this group is lower, and in addition, the probability of declining protection against serious illness is higher among the older age groups, as they were vaccinated with the 3rd bite before the rest of the population.

A new major wave of infections can therefore lead to a derived increase in hospitalizations among the elderly and vulnerable. However, there is uncertainty about the extent of a new wave of infection with BA.5 at present, i.a. given the expected seasonal effect and reduced activity in the community over the summer



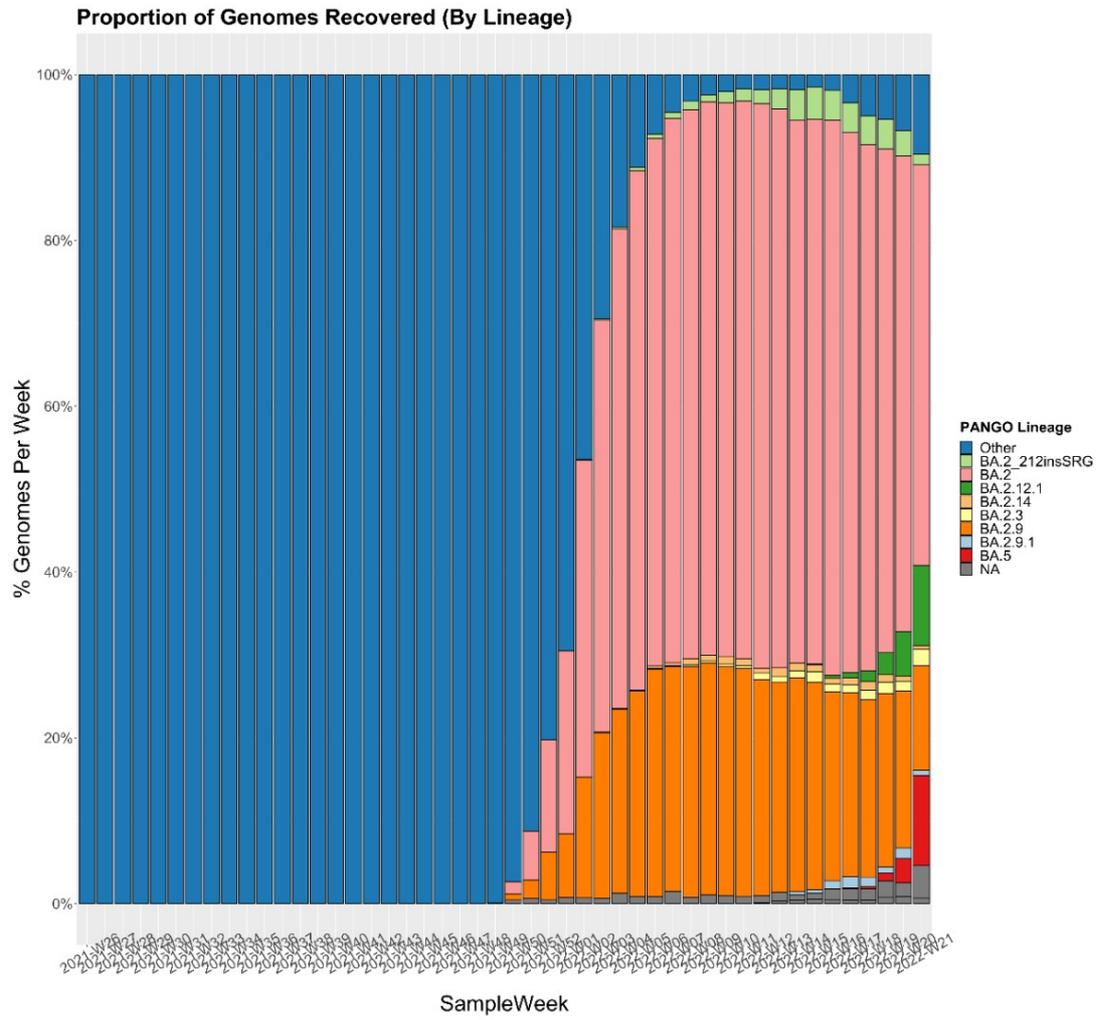
Appendix. Epidemiological and virological background data.

The development in whole-genome-sequenced samples (data from 8-06-2022)

Observed variants at WGS in the last 4 weeks

Lineage	WHO	2022-W19	2022-W20	2022-W21	2022-W22
BA.2	Omicron	2159 (60.92%)	1708 (57.49%)	1054 (47.10%)	551 (39.47%)
BA.2.9	Omicron	733 (20.68%)	568 (19.12%)	271 (12.11%)	128 (9.17%)
BA.5	Omicron	32 (0.90%)	85 (2.86%)	239 (10.68%)	287 (20.56%)
BA.2.12.1	Omicron	94 (2.65%)	156 (5.25%)	236 (10.55%)	175 (12.54%)
Unassigned		68 (1.92%)	50 (1.68%)	102 (4.56%)	94 (6.73%)
BA.4	Omicron	31 (0.87%)	52 (1.75%)	83 (3.71%)	52 (3.72%)
BA.2.3	Omicron	47 (1.33%)	34 (1.14%)	42 (1.88%)	22 (1.58%)
BA.2.18	Omicron	33 (0.93%)	48 (1.62%)	31 (1.39%)	21 (1.50%)
BA.2_212insSGR	Omicron	128 (3.61%)	95 (3.20%)	30 (1.34%)	12 (0.86%)
BA.2.31	Omicron	36 (1.02%)	18 (0.61%)	27 (1.21%)	9 (0.64%)
BA.2.12	Omicron	16 (0.45%)	20 (0.67%)	20 (0.89%)	10 (0.72%)
BA.2.13	Omicron	12 (0.34%)	11 (0.37%)	16 (0.71%)	2 (0.14%)
BA.2.23	Omicron	28 (0.79%)	23 (0.77%)	15 (0.67%)	10 (0.72%)
BA.2.9.1	Omicron	29 (0.82%)	37 (1.25%)	14 (0.63%)	3 (0.21%)
BA.2.14	Omicron	32 (0.90%)	18 (0.61%)	10 (0.45%)	4 (0.29%)
BA.2.10	Omicron	8 (0.23%)	7 (0.24%)	9 (0.40%)	0 (0.00%)
BA.2.5	Omicron	3 (0.08%)	7 (0.24%)	9 (0.40%)	4 (0.29%)
BA.2.7	Omicron	7 (0.20%)	2 (0.07%)	6 (0.27%)	1 (0.07%)
BA.2.1	Omicron	6 (0.17%)	9 (0.30%)	3 (0.13%)	3 (0.21%)
BA.2.10.1	Omicron	10 (0.28%)	1 (0.03%)	3 (0.13%)	1 (0.07%)
BA.2.11	Omicron	3 (0.08%)	3 (0.10%)	3 (0.13%)	0 (0.00%)
BA.2.22	Omicron	3 (0.08%)	7 (0.24%)	3 (0.13%)	1 (0.07%)
XG	Recombinant	4 (0.11%)	0 (0.00%)	3 (0.13%)	0 (0.00%)
BA.2.25	Omicron	4 (0.11%)	2 (0.07%)	2 (0.09%)	0 (0.00%)
BA.2.32	Omicron	2 (0.06%)	1 (0.03%)	2 (0.09%)	0 (0.00%)
BA.2.6	Omicron	3 (0.08%)	0 (0.00%)	2 (0.09%)	0 (0.00%)
BA.2.27	Omicron	0 (0.00%)	0 (0.00%)	1 (0.04%)	1 (0.07%)
BA.2.3.2	Omicron	1 (0.03%)	1 (0.03%)	1 (0.04%)	0 (0.00%)
BA.2.4	Omicron	0 (0.00%)	0 (0.00%)	1 (0.04%)	0 (0.00%)
BA.1	Omicron	0 (0.00%)	1 (0.03%)	0 (0.00%)	0 (0.00%)
BA.1.1	Omicron	1 (0.03%)	1 (0.03%)	0 (0.00%)	0 (0.00%)
BA.1.17	Omicron	2 (0.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
BA.2.2	Omicron	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.07%)
BA.2.21	Omicron	1 (0.03%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
BA.2.24	Omicron	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.07%)
BA.2.26	Omicron	4 (0.11%)	3 (0.10%)	0 (0.00%)	0 (0.00%)
BA.2.34	Omicron	1 (0.03%)	0 (0.00%)	0 (0.00%)	2 (0.14%)
BA.2.8	Omicron	2 (0.06%)	1 (0.03%)	0 (0.00%)	1 (0.07%)
BA.2.9.2	Omicron	1 (0.03%)	2 (0.07%)	0 (0.00%)	0 (0.00%)
Total		3544	2971	2238	1396

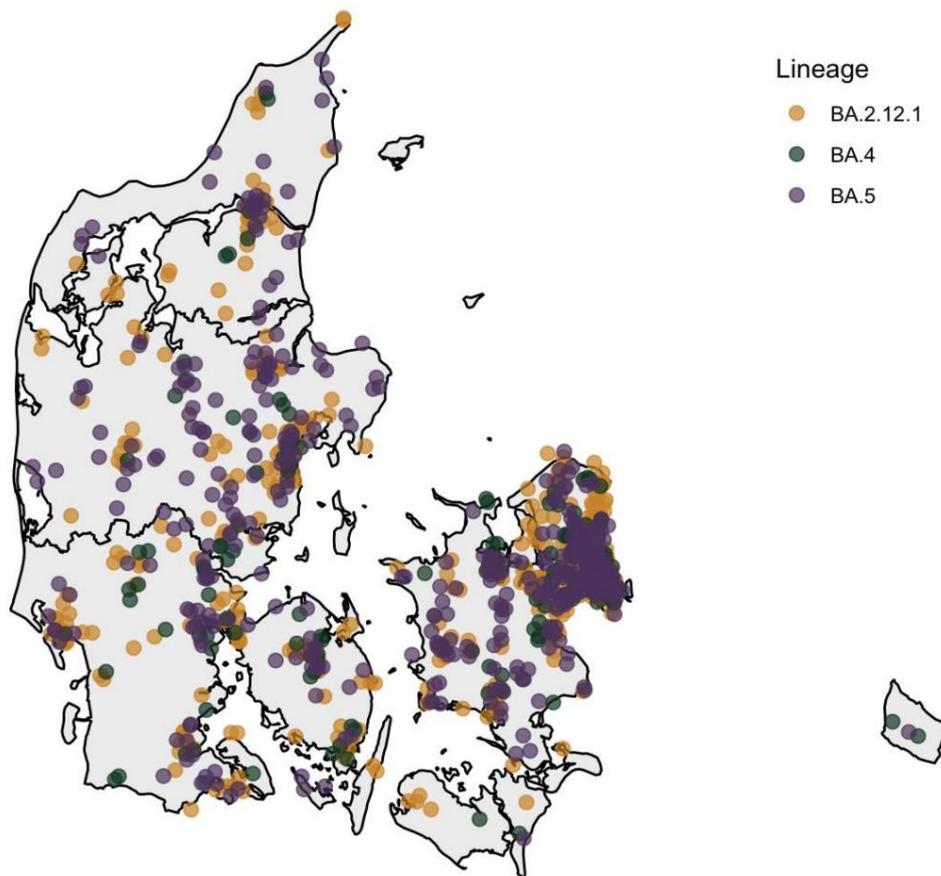
Obs: Antal varianter kan ændre sig når flere prøver bliver sekventeret og inkluderet i tabellen





Demographic inventory

Geographical distribution of selected omicron subvariants (period 17-05-2022 - 31-05-2022)



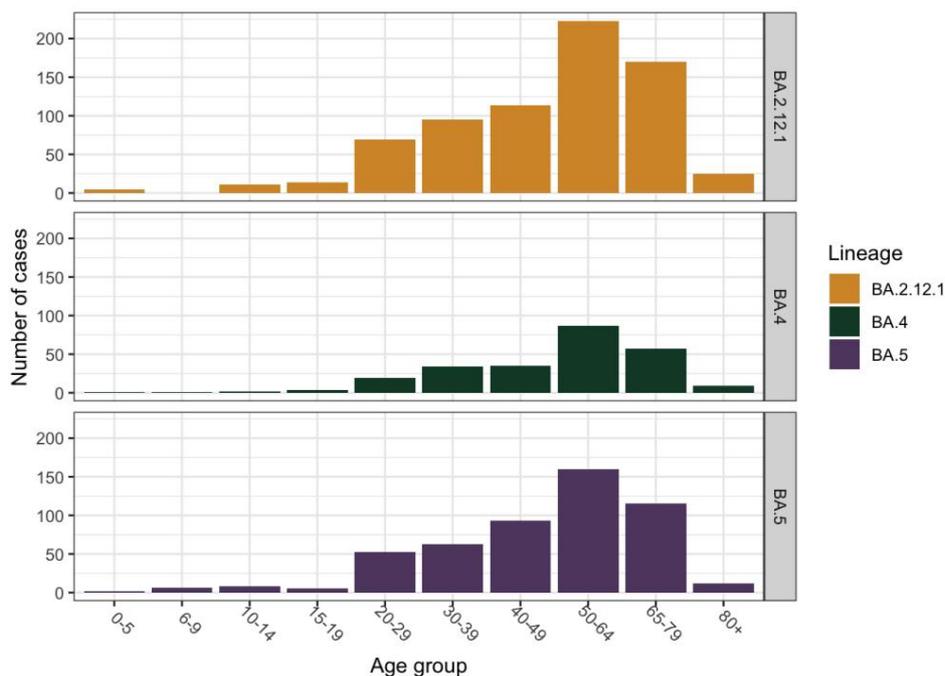


The table below shows the age distribution among cases. The category "Other" covers other cases with known variant in the period from 1 March-31. May 2022.

Age group	BA.2.12.1	BA.4	BA.5	Others
0-5	5 (1%)	1 (0%)	2 (0%)	1356 (1%)
6-9	0	1 (0%)	6 (1%)	900 (1%)
10-14	11 (2%)	2 (1%)	8 (2%)	2139 (2%)
15-19	14 (2%)	4 (2%)	5 (1%)	2506 (2%)
20-29	69 (10%)	19 (8%)	53 (10%)	11140 (10%)
30-39	95 (13%)	34 (14%)	63 (12%)	11253 (10%)
40-49	114 (16%)	35 (14%)	93 (18%)	14604 (13%)
50-64	223 (31%)	87 (35%)	1601 (31%)	33261 (30%)
65-79	170 (23%)	57 (23%)	115 (22%)	27729 (25%)
80+	25 (3%)	9 (4%)	12 (2%)	7453 (7%)



The figure below shows the age distribution for the three variants in the period 1 March-31 May 2022.



Vaccination status

The table below shows the proportion of cases that have been vaccinated. The category "Other" covers other cases with known variant in the period from 1 March-31. May 2022.

Vaccination status	BA.2.12.1	BA.4	BA.5	Others
Unvaccinated	40 (6%)	20 (8%)	36 (7%)	7829 (7%)
Started primary program	3 (0%)	0	3 (1%)	511 (0%)
Full effect, primarily program	69 (10%)	27 (11%)	54 (10%)	11121 (10%)
Full effect, booster vaccination	614 (85%)	202 (81%)	424 (82%)	92880 (83%)



Reinfections

The table below shows the proportion of cases verified as a reinfection (60+ days between two positive samples). The category "Other" covers other cases with known variant in the period from March 1 to May 31, 2022.

Reinfection	BA.2.12.1	BA.4	BA.5	Others
First infection	677 (93%)	218 (88%)	447 (86%)	106,951 (95%)
Reinfection	49 (7%)	31 (12%)	70 (14%)	5,390 (5%)

Hospital admissions

The table below shows the number and proportion of cases that have been hospitalized.

Tested positive 48 hrs or more after admission: Includes all persons who have been admitted more than 48 hours before being tested positive for Omicron. I.e. this figure covers cases of hospital-acquired omicron infection.

Tested positive prior or within 48 hrs after admission: Includes all persons who tested positive before being admitted or tested positive up to 48 hours after admission.

The category "Other" covers other cases with known variant in the period from 1 March 31 May 2022.

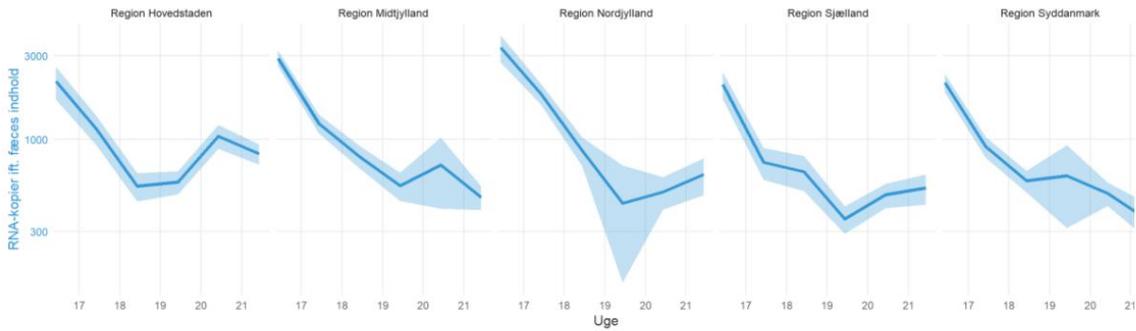
Hospital admissions	BA.2.12.1	BA.4	BA.5	Others
Have not been hospitalized	706 (97%)	245 (98%)	508 (98%)	107430 (96%)
Tested positive 48 hrs or more after admission	7 (1%)	1 (0%)	0	813 (1%)
Tested positive prior or within 48 hrs after admission	13 (2%)	3 (1%)	9 (2%)	4098 (4%)



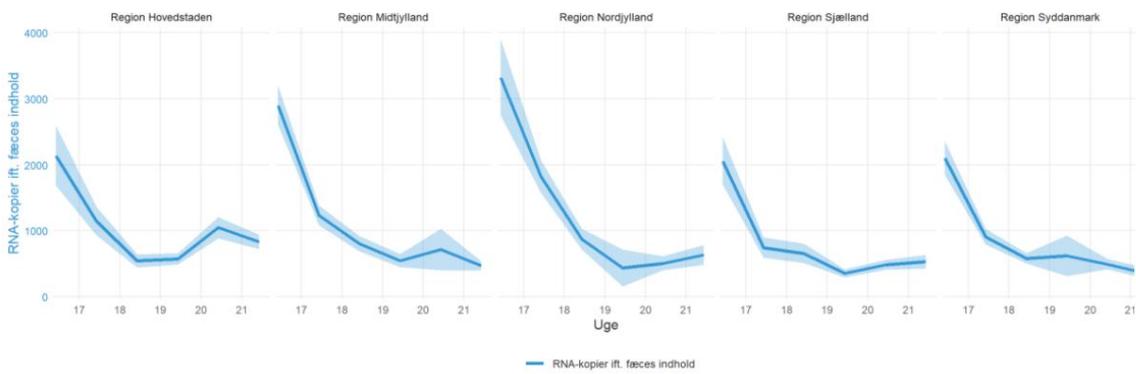
Sewage

Resultater fra spildevandsmålinger

Log skala



Normal skala



Resultater fra spildevandsmålinger - Danmark 2022

