Risk assessment of Omicron BA.2

Background

The Omicron SARS-CoV-2 variant has quickly become dominant in many countries including Denmark, demonstrating a significantly higher growth potential than the Delta variant. Preliminary analyses indicate that the Omicron variant is more transmissible than the Delta variant and it has shown reduced sensitivity to neutralizing antibodies. Vaccine induced protection against infection is also clearly reduced for the Omicron compared to the Delta variant. On the other hand, preliminary analyses find a 36%-80% risk reduction in hospitalization for the Omicron compared with the Delta variant, with most studies reporting a risk reduction between 45%-68%.

Omicron comprises the lineages B.1.1.529, BA.1, BA.2 and BA.3. BA.1 accounts for the majority of Omicron cases worldwide; 97% according to GISAID, whereas BA.2 accounts for approximately 2%. On 27 January 2022, 77% of all BA.2 sequences in GISAID were reported from Denmark. However, this distribution, high numbers reported from Denmark, may not accurately reflect the global distribution, but it does, however indicate that BA.2 is very frequent in Denmark. BA.2 prevalence has increased in the past month from 20% in week 52 to 66% in week 3. At the same time, BA.1 has decreased from 72% in week 52 to 33% in week 3. The same pattern - an increase in the proportion of BA.2 and a decrease in the proportion of BA.1 - is not mirrored as clearly in other countries. In the UK, Sweden and Norway, a steeper increase in the proportion of BA.2 cases relative to BA.1 has also been observed, but BA.2 still only accounts for 10%-20% of Omicron cases. BA.2 is probably also beginning to take over in Asian countries like India and the Philippines, as several European countries report BA.2 cases imported from these countries. Qatar has reported that BA.2 seems to be the dominant variant there too.

The fact that BA.2 is now the dominant variant indicates that it has an increased growth potential, either due to higher transmissibility and/or due to an increased ability to evade the immune system compared to BA.1. The difference in growth potential between countries may be linked to differences in vaccination coverage and contact patterns arising because of restrictions, population densities, etc.

Virological characteristics

According to outbreak.info, BA.1, BA.2 and BA.3 carry approximately 33, 31 and 26 mutations in their respective spike proteins, compared with the original Wuhan strain of SARS-CoV-2 from December 2019.

Compared with BA.1, BA.2 has a different distribution of mutations in the spike protein; BA.2 has more mutations in the receptor-binding domain, but fewer in the N-terminal domain. The functional consequences of these differences in the BA.2 spike protein remain unknown.

As BA.2 does not have deletion 69-70 in the spike gene it cannot be distinguished from the Delta variant by variant PCR targeting this area. Instead, Testcenter Danmark use a variant PCR targeting position L452wt, allowing Omicron and all sub-lineages to be distinguished from the Delta variant in Denmark. BA.1 and BA.2 only show limited differences in the other structural proteins (M, E and N).

BA.2 growth rates

Currently, the incidence is highest among 6-15-year-olds (11,000 cases per 100,000 inhabitants). BA.2 has gained ground rapidly across all age groups and therefore it is relevant to monitor its growth rate in various age groups to be able to identify a potential spread to the older segments of the population, which is characterized by high booster vaccination rates. Similarly, declining growth rates in other age groups may indicate that the epidemic has peaked in these groups.

The Expert Group on Mathematical Modelling has estimated growth rates along with a weekly percentage growth for the Omicron sub-variants BA.1 and BA.2. The growth rates were estimated based on sequenced samples taken from January 8 to 21 2022, and divided into five age groups (0-4 years, 5-11 years, 12-17 years, 18-59 years and 60+ years), previous infection and time since full effect of vaccination.

- The distribution of BA.2 only showed small differences on a regional level, and BA.2 is estimated to account for close to 100% of all cases by mid-February.
- The growth rate of BA.2 is much higher than BA.1 in all five age groups in the time period from 8 to 21 January. In three of the age groups, the number of cases is expected to double within less than a week.
- The difference in the growth rates between the two sub-variants corresponds to BA.2 being approximately 30% more transmissible than BA.1.
- A decline in the growth rate of BA.2 was recently observed in the youngest age group and we also expect a decline (since these estimates were calculated) in growth rates in the other age groups. Otherwise, we would have seen more cases in week 4.
- The growth rate of BA.2 is highest among the 5-17-year-olds and lowest among +60-year-olds.
- A higher growth rate of BA.2 compared to BA.1 will likely be reflected in a steeper epidemic curve with a higher peak, and it may also postpone the time at which infection rates start to decline as a larger proportion of the population needs to be infected to achieve temporary herd immunity.

Estimates of BA.2 growth rates has a number of limitations. Sufficient data to estimate the growth rates have only been available only for a short period of time. Furthermore, only a small sample size was sequenced in the reported period. Thus, in week 1 and week 2, approximately 8% of the positive samples were sequenced. The estimates will be adjusted continuously, as more sequencing results are available.

Figure 1 shows the proportion of BA.2 cases over time in the five Danish regions and a projection for future development. The figure depicts only small regional differences in the spread of BA.2 that is expected to account for close to 100% of all cases by mid-February.

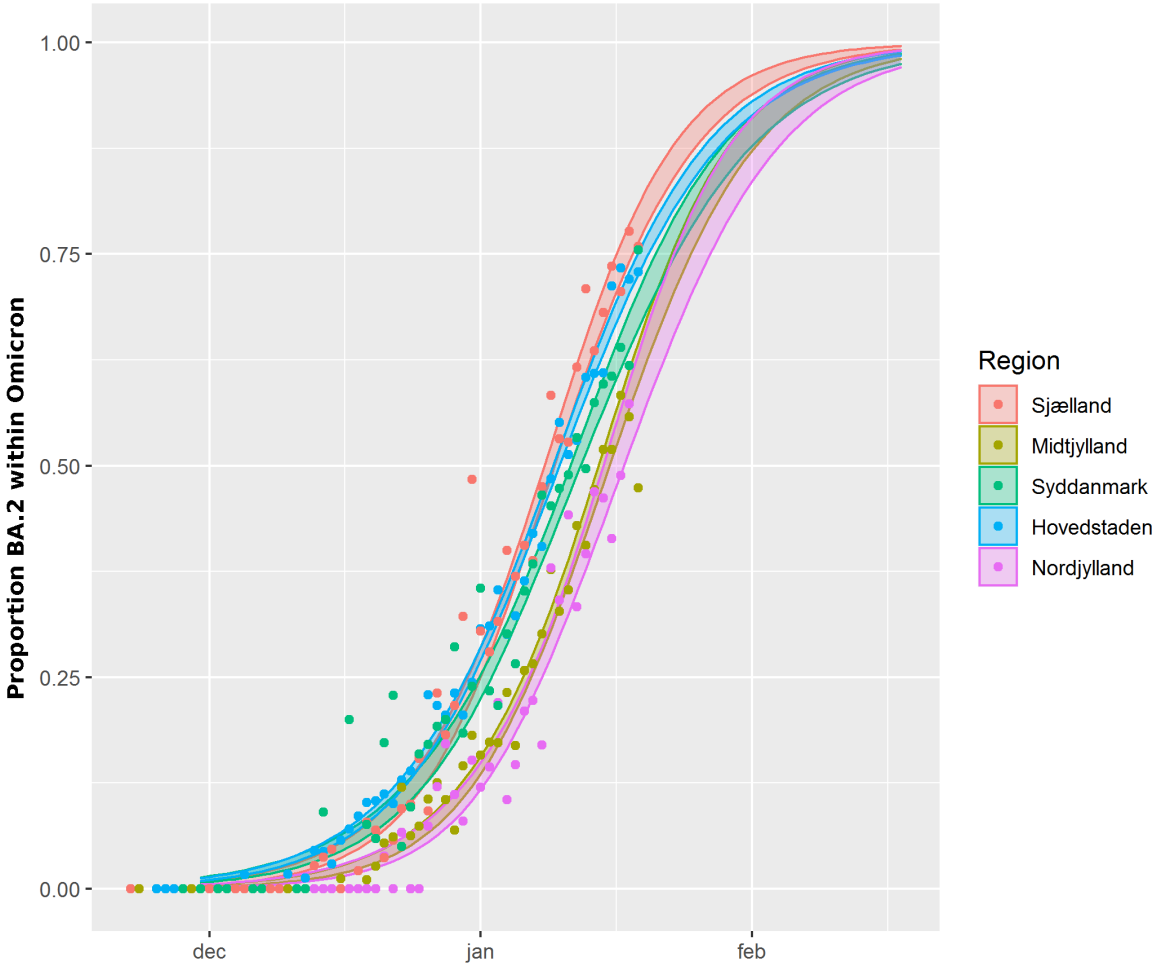

Figure 1: Projection of the proportion of BA.2 cases in the five Danish regions. The colored dots show the observed proportion of BA.2 in the regions until 21 January 2022.

Based on the sequenced samples, the Expert Group has estimated weekly growth rates of the BA.1 and BA.2 sub-variants adjusted for age group, time since second or third vaccination and confirmed previous infection (Table 1). Of note, individuals who received the first but not yet the second vaccination were excluded from the analysis, as this group was very small and dynamic. Time since full effect from the second or third vaccination was calculated using time since the second vaccination + 14 days or time since the third vaccination + 7 days for those who had a booster. In other words, the weekly growth was calculated based on time since full effect of the latest vaccination received. Of note, the estimates were calculated based on a 14-day period from 8 to 21 January.

Table 1 below shows BA.2 increasing considerably in all groups tested, thereby exhibiting a weekly growth of at least 100% in most age groups (except the +60-year-olds and the 0-4-year-olds). Among the 5-17-year-olds, BA.2 has increased by nearly 140% weekly. A different trend is seen for BA.1, showing a moderate increase in most groups. Transmission of BA.2 has thereby increased by 109% weekly among 18-59-year-olds, whereas transmission of BA.1 has remained constant in this age group.

The weekly growth rate for BA.2 is lowest among unvaccinated individuals, corresponding to a 90% weekly growth. Among individuals who received their second or third vaccination within the previous 59 days, the point estimate is around a third higher, i.e. a weekly growth of 120%. Reasons for this difference are not yet known, but one possibility could be differences in behavior. SSI will be revisiting all estimates as more data becomes available. The table also shows an approximately 20% higher weekly growth rate among individuals who have not previously been infected with BA.1 or BA.2.

Table 1: Estimated weekly growth with 95% confidence intervals in five age groups, time since second or third vaccination, and known infection status for the period from 8 January 2021 through 21 January 2022.

Group	**Weekly growth BA.2 (%)**			**Weekly growth BA.1 (%)**		
	Estimate	Lower	Upper	**Estimate**	Lower	Upper
Age group						
0-4-year-olds	**84**	59	113	**16**	-2	36
5-11-year-olds	**132**	104	164	**36**	18	58
12-17-year-olds	**142**	119	168	**33**	19	49
18-59-year-olds	**109**	96	124	**0**	-7	7
+60-year-olds	**76**	55	99	**9**	-5	26
Time since vaccination						
0-59 days	**120**	101	141	**25**	14	38
60-119 days	**118**	96	142	**24**	12	38
+120 days	**102**	85	120	**15**	5	26
Unvaccinated	**90**	76	105	**8**	0	17
Previous infection						
No	**118**	108	129	**24**	18	32
Yes	**96**	74	121	**12**	-1	26

Figure 2 shows growth rate estimates calculated based on rolling 14-day intervals. The graph shows growth rate as a function of the latest date in each of the intervals, by sub-variant and age group. The figure depicts rolling 14-day growth rates directly, and not as weekly increments. Growth rates exceeding 0 indicate that the sub-variant is growing, whereas growth rates below 0 means that the sub-variant is declining.

The figure shows that BA.2 is estimated grow continuously (on some dates, this estimate is not significant in some age groups). For BA.1, previous estimates have indicated that the variant is declining in most age groups, but the most recent findings suggest a reverse trend in some age groups, meaning that the sub-variant is growing. In the latest period, BA.2 growth rates have decreased in the youngest age groups, indicating that the sub-variant is growing slower than previously.

In all age groups BA.2 shows higher growth rates than BA.1. The difference in the growth rate between the two sub-variants corresponds to BA.2 being approx. 30% more transmissible than BA.1.

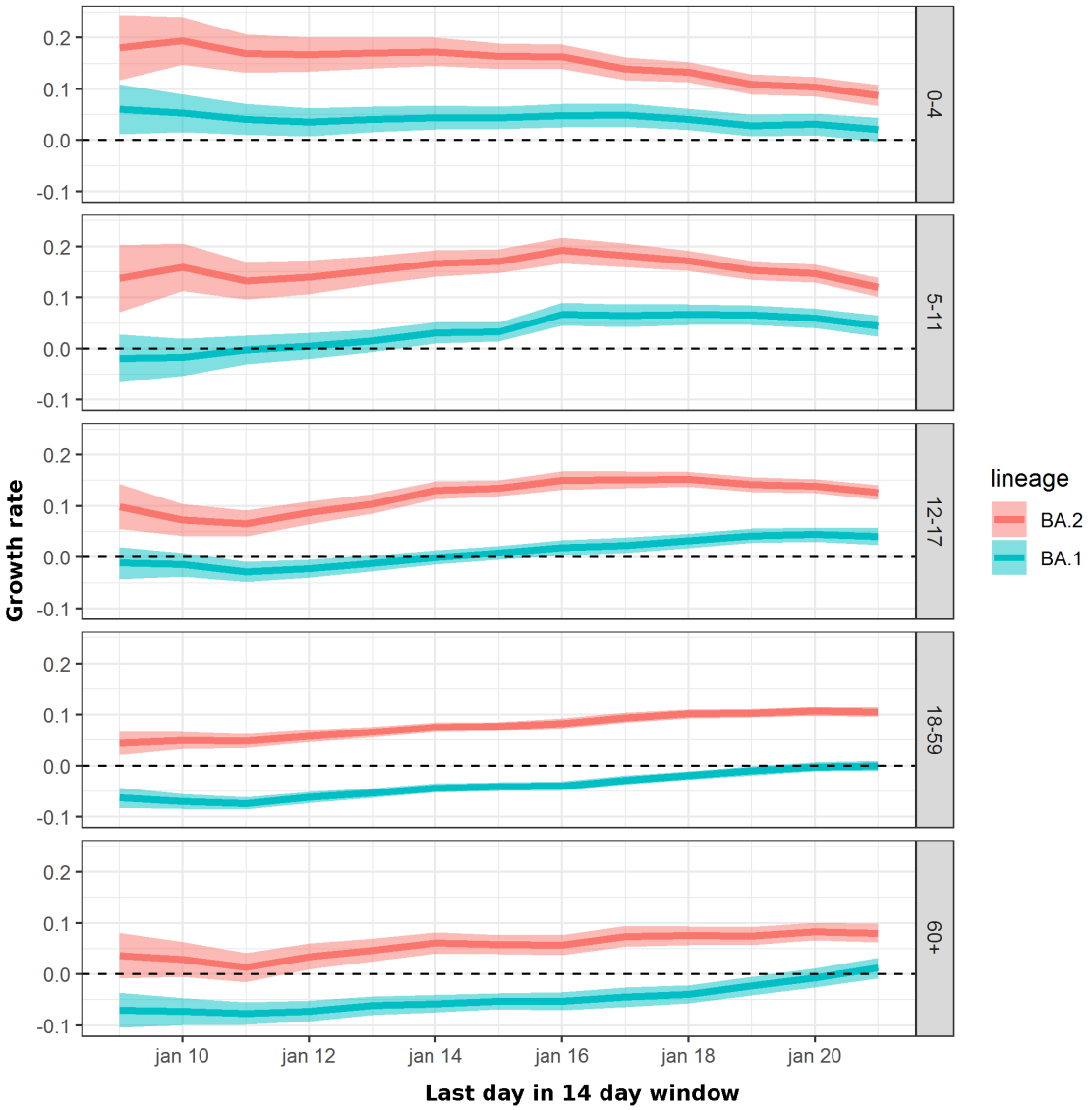

Figure 2: Development in growth rates for BA.1 (blue) and BA.2 (red). Growth rates are estimated using a 14-day interval and the figure shows the estimate for the final day of the interval. Growth rates exceeding 0 indicate that the sub-variant is growing, whereas growth rates below 0 means that the sub-variant is declining.

Household transmission with BA.1 and BA.2

Researchers from SSI, the University of Copenhagen, the Technical University of Denmark and Statistics Denmark have studied the dynamics determining how BA.1 and BA.2 have spread within Danish households [link: Transmission of SARS-CoV-2 Omicron VOC subvariants BA.1 and BA.2: Evidence from Danish Households (medrxiv.org)]. Of note, the findings of the study are preliminary and have not yet been peer reviewed. Also, analyses are based on data from the short time period during which BA.2 has been observed in Denmark and based only on a representative sample of all positive PCR tests that were whole-genome sequenced.

The study includes 8,541 households infected with the Omicron variant, estimating "secondary attack rate" (SAR) for the two sub-variants BA.1 and BA.2 from 20 December 2021 to 11 January 2022, plus a 7-day follow-up period until 18 January 2022. SAR comprises the proportion individuals in a household (potential secondary cases) testing positive 1-7 days after the first individual in a household tested positive for a specific variant (the primary case). During a 1-7-day follow-up after the primary case tested positive, a total of 5,702 secondary cases were detected among 17,945 potential secondary cases. The SAR was **29%** in households with a BA.1 infected primary case and **39%** in a BA.2 infected primary case.

Additionally, the study explores the effect of vaccination on the susceptibility (risk of becoming infected) and transmissibility (risk of transmitting infection) of the two Omicron variants. The risk of infection by either one of the two Omicron variants is higher for unvaccinated than for vaccinated individuals. Furthermore, booster vaccination (three doses) significantly reduces the risk of infection compared with fully vaccinated individuals (two doses). Even so, susceptibility is higher among potential secondary cases in BA.2 infected households than in BA.1 infected households regardless of vaccination status of the potential secondary case. This indicates that BA.2 is inherently more transmissible than BA.1.

Transmissibility is lower in fully vaccinated individuals and even lower in booster vaccinated individuals, compared to unvaccinated individuals. This is the case for both BA.1 and BA.2. Even though unvaccinated individuals transmit BA.2 infection considerably more than BA.1 infected individuals, the same pattern is not observed in vaccinated individuals. Among vaccinated individuals, the odds ratio of transmitting BA.2 is slightly lower than that of transmitting BA.1. This means that individuals who have been vaccinated are generally less likely to transmit BA.2 than BA.1.

Current knowledge about severity

Based on whole genome sequence data from the period from 21 November 2021 to 21 January 2022, when 16% of all positive PCR samples were sequenced, no difference in hospital admission risk was detected for BA.1 and BA.2 (a total of 932 patients), taking into account sex, age, vaccination status, time period, region, comorbidity and previous SARS-CoV-2 infection. Furthermore, no difference was seen between individuals who

were unvaccinated, received a single vaccination, were fully vaccinated, received a booster or among children aged 0-2 years (33 BA.2 hospital admissions). Median age was lower for individuals admitted with BA.2 than BA.1 (40 years versus 51 years), whereas no difference in sex distribution was observed.

Conclusion

The prevalence of the BA.2 Omicron sub-variant continues to increase and it is now the dominant variant in Denmark. BA.2 is expected to account for nearly 100% of all cases by mid-February 2022, as the growth rate for BA.2 is much higher than for BA.1, indicating that BA.2 may be approx. 30% more transmissible than BA.1. Consequently, this quick increase in BA.2 may lead to a steeper epidemic curve with a higher peak and may postpone the time at which infection rates decline until February.

Preliminary data shows that BA.2 is transmitted to a larger proportion of household members than BA.1, which corroborates that BA.2 is more transmissible than BA.1. Unvaccinated individuals transmit infection much more, if they are infected with BA.2 compared to BA.1, and the opposite applies in vaccinated individuals. Furthermore, vaccinated individuals are generally more susceptible to BA.2 than to BA.1.

There is still no evidence to support that BA.2 is associated with an increased risk of hospital admission.

SSI is currently attempting to grow BA.2 to conduct antibody neutralization assays, but BA.2 has proven to be very difficult to grow.

It is still relevant to closely monitor this variant and conduct/continue to perform studies on its characteristics (e.g., antibody neutralization assays and vaccine effectiveness studies). With the current evidence at hand, we recommend contact tracing of BA.2 on the same level as all other variants.