THREAT ASSESSMENT BRIEF

Implications for the EU/EEA of the spread of the SARS-CoV-2 Omicron XBB.1.5 sub-lineage

13 January 2023

Summary

The XBB.1.5 Omicron sub-lineage was first detected in samples in the United States (US) in October 2022. This sub-lineage has been growing in proportion in the US and many countries around the world since then, including in several EU/EEA countries and the UK. XBB.1.5 is a sub-lineage of XBB, which is a recombinant of two earlier lineages of the Omicron variant of concern (VOC), with an additional spike receptor-binding domain (RBD) change S486P. The reported proportion of XBB.1.5 in the EU/EEA has been lower than 2.5% for the last two weeks of 2022.

XBB.1.5 currently exhibits a daily growth advantage of 12% in the US compared to other circulating variants. It is plausible that the difference in growth rate between XBB and XBB.1.5 is mainly explained by a difference in transmissibility. In addition, XBB and XBB.1 demonstrate the most substantial immune escape observed amongst Omicron sub-lineages to date, with significant reductions in the neutralising capacity of serum from vaccinated individuals. Preliminary *in-vitro* data show the immune escape properties of XBB.1.5 are equivalent to XBB.1.

While there are currently no vaccine effectiveness (VE) estimates for XBB.1.5, the available vaccines still remain effective against severe disease due to previous and current Omicron variants dominant in the EU, even though there is some evidence of waning over time.

There are currently no signals that the infection severity of XBB.1.5 is different than that of previously circulating Omicron sub-lineages. Regarding therapeutics, no specific data exist on the effectiveness of therapeutics such as nirmatrelvir/ritonavir or remdesivir for XBB.1.5, however the variant is expected to be as susceptible to these antivirals as XBB has shown to be.

Mathematical modelling performed by ECDC provides estimates of when XBB.1.5 might become dominant (i.e. causes more than 50% of infections) in the EU/EEA by using a broad range of scenarios with hypothetical values of the growth rate advantage and of the current proportions of XBB.1.5 in the EU/EEA.

Suggested citation: European Centre for Disease Prevention and Control. Implications for the EU/EEA of the spread of the SARS-CoV-2 Omicron XBB.1.5 sub-lineage for the EU/EEA – 13 January 2023. ECDC: Stockholm; 2023.

Risk assessed

What risk does the spread of the Omicron variant sub-lineage XBB.1.5 pose to the general population and to vulnerable individuals in the EU/EEA?

According to the current ECDC assessment, there is moderate probability of XBB.1.5 becoming dominant in the EU/EEA and causing a substantial increase in the number of COVID-19 cases within the next one to two months. The impact of XBB.1.5 infection on the general population is assessed as low, due to the overall low incidence of severe disease caused by the Omicron VOC and prior immunity. For recently vaccinated vulnerable individuals, the impact of infection is assessed as moderate, while for vulnerable individuals unvaccinated or incompletely vaccinated according to the recommended schedule for their population group, it is assessed as high. Therefore, the overall level of risk associated with the spread of XBB.1.5 sub-lineage in the EU/EEA is assessed, with a high degree of uncertainty, as **low** for the general population and **moderate-to-high** for vulnerable individuals.

Several gaps in knowledge exist in relation to XBB.1.5 and this assessment may change in the coming weeks as more evidence becomes available. Predictions based on early growth advantage estimates for variants are always uncertain and will need to be revised as data from further countries become available.

Options for response

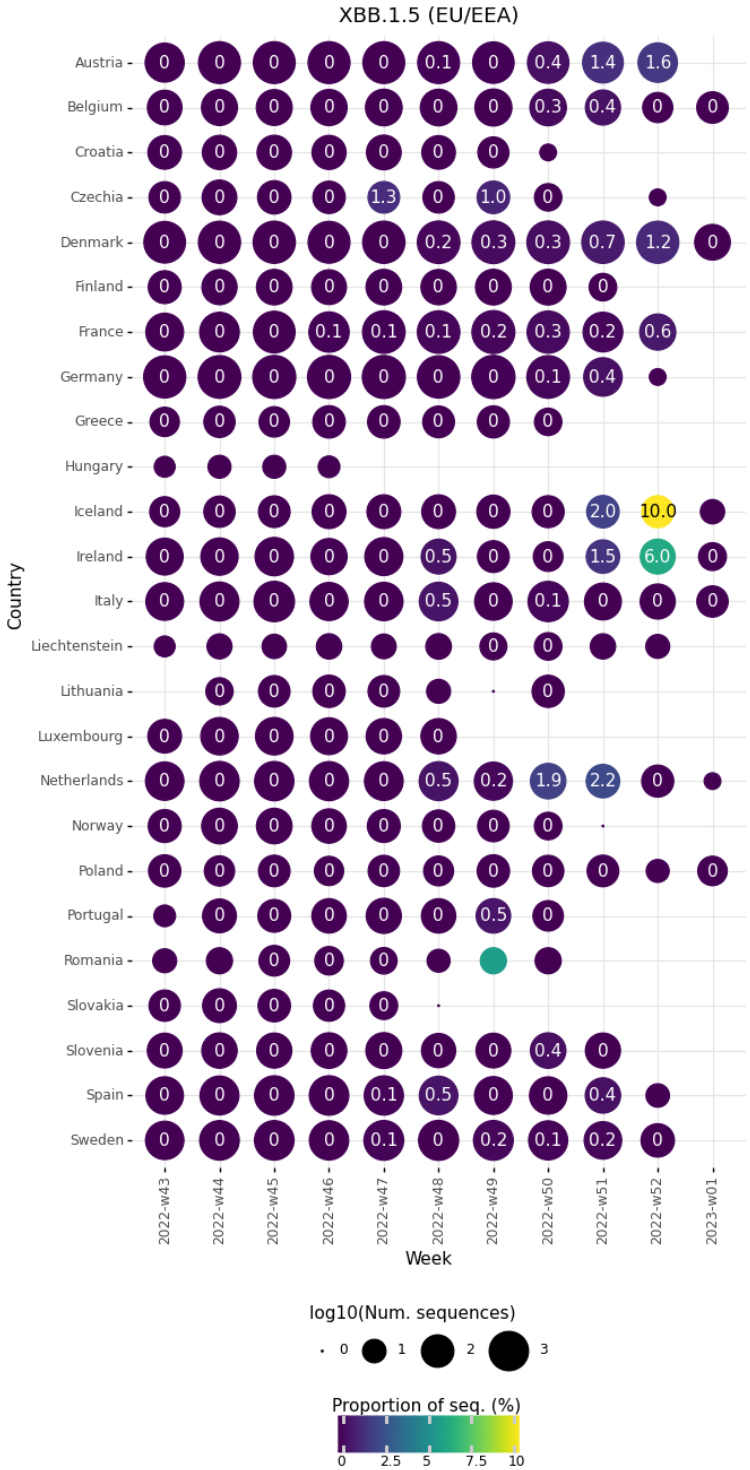
In view of the expected spread of SARS-CoV-2 Omicron sub-lineage XBB.1.5, the following options for response are proposed for public health authorities in the EU/EEA:

- Conduct appropriate risk communication activities for health professionals and the general public, with a balanced overview of the situation including the existing gaps in our knowledge about XBB.1.5. Provide information to health professionals about treatment options.
- Maintain or improve appropriate levels of testing and sequencing of SARS-CoV-2 according to explicit target thresholds as outlined in the guidance for representative and targeted genomic SARS-CoV-2 monitoring. Countries should continue strengthening their representative genomic sequencing efforts, particularly the sequencing of primary and secondary care sentinel specimens and share data in a timely way.
- Improve the timely uptake of COVID-19 vaccines, including primary course and booster doses according to national guidelines, particularly targeting eligible vulnerable individuals who have not yet received them. Ensuring that eligible individuals are up to date with their vaccination is of key importance to ensure the strongest protection. The existing vaccines are very likely to continue to protect against severe outcomes for this sub-lineage, too.
- Consider time-limited and targeted non-pharmaceutical interventions for the community such as teleworking, appropriate use of face masks and good ventilation of indoor spaces, tailored to the epidemiological and healthcare system situation and needs in the community.
- Follow appropriate infection prevention and control (IPC) guidance for healthcare settings which apply a holistic approach that addresses risks from the transmission of all respiratory viruses.

Event background

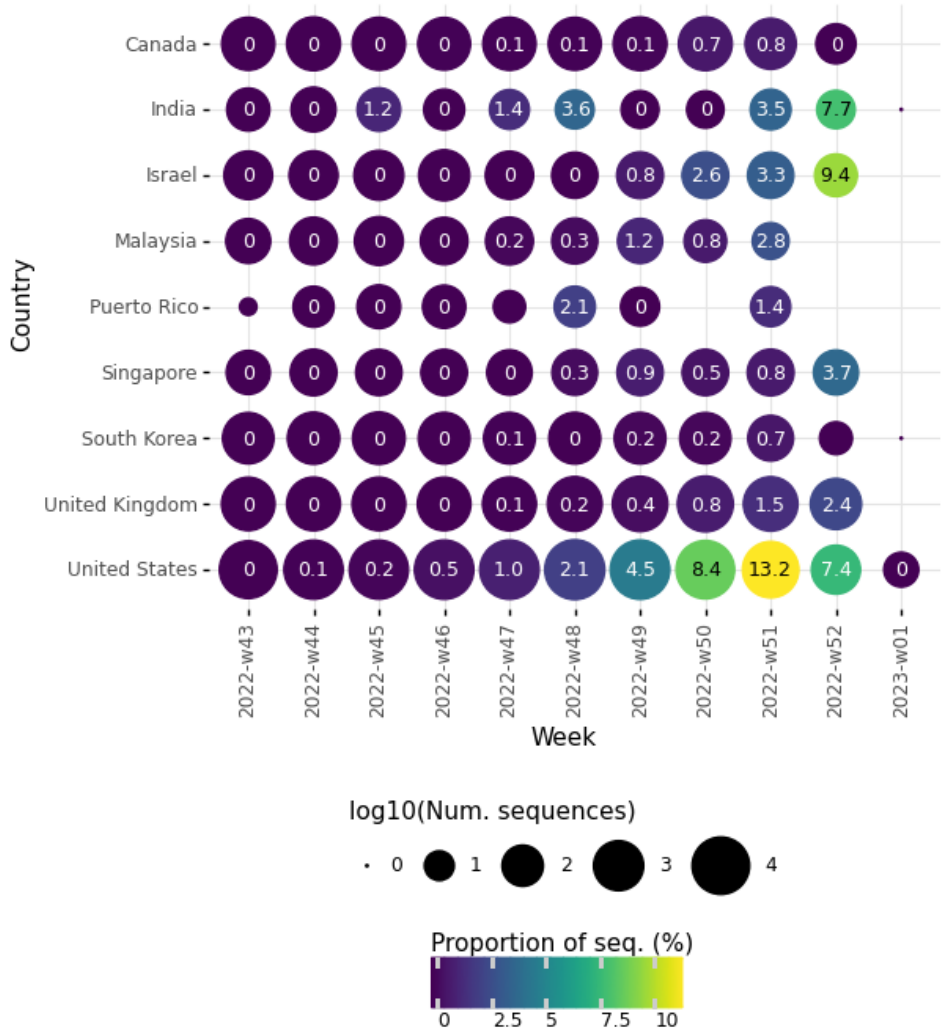
As of 9 January 2023, 4 770 sequences belonging to XBB.1.5 with the mutational profile in spike protein region - Q183E, F486P and F490S have been deposited in GISAID EpiCoV. Most of these submissions are from the United States (4 111 sequences, 86%), and the United Kingdom (202 sequences, 4%), with the variant also detected in several other countries, including the following EU/EEA countries – Austria, Belgium, Czechia, Denmark, France, Germany, Iceland, Ireland, Italy, the Netherlands, Portugal, Romania, Slovenia, Spain, and Sweden. The proportion of the sub-lineage in the EU/EEA has been lower than 2.5% for the last two weeks of 2022 for all countries where variant proportions at this low level can be accurately estimated, based on their sequencing volumes (Figure 1). Iceland and Ireland report higher levels (10% and 6%, respectively) for week 52. However, rapid increases spanning only a single week, especially in week 52 which is a public holiday week with possibly reduced sampling and sequencing activities, are more likely to be caused by results from targeted surveillance, or outbreaks involving the variant, rather than increased community transmission of the variant.

Figure 1. Proportion of XBB.1.5 in EU/EEA countries reported to GISAID EpiCoV, as of 9 January 2023



The colour scale indicates the weekly proportion of sequences that belong to XBB.1.5, and the size of the bubbles indicates the number of sequences from samples collected during each week (logarithmic scale).

Figure 2. Proportion of XBB.1.5 in selected non-EU/EEA countries reported to GISAID EpiCoV, as of 9 January 2023

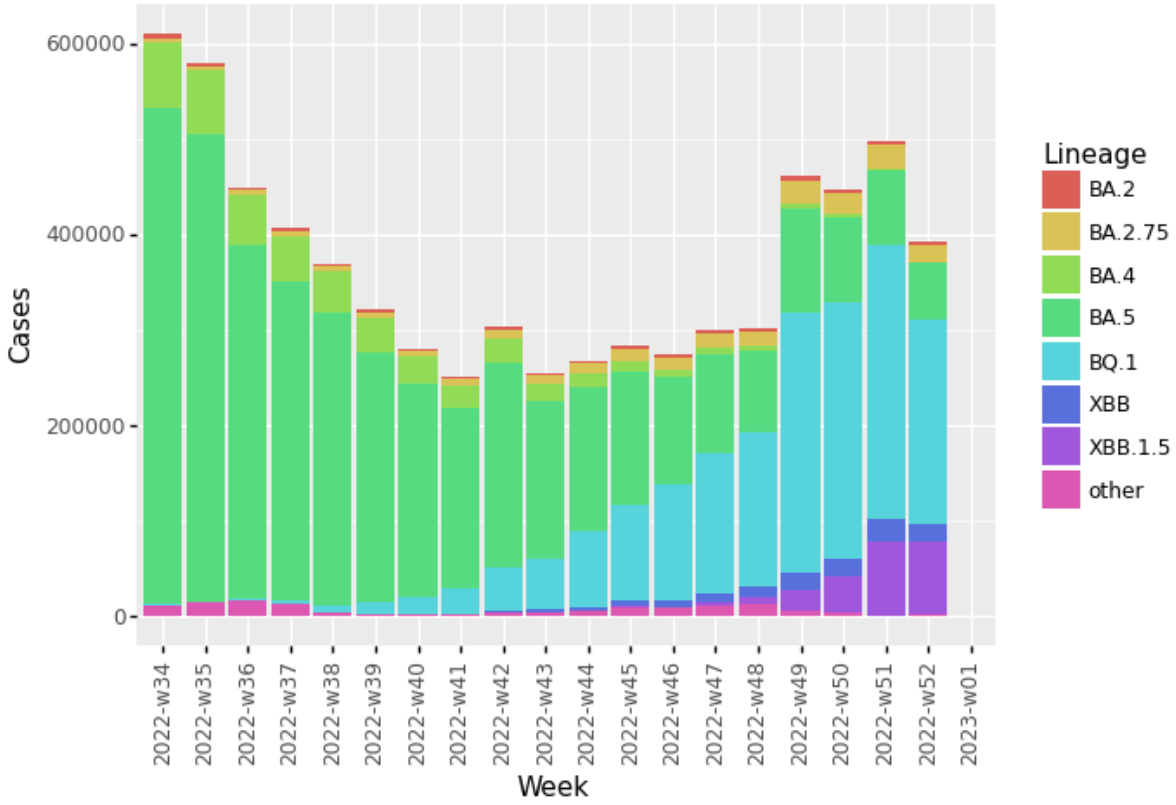


Countries reporting XBB.1.5 sequences from 19 December 2022 and onward are included. The colour scale indicates the weekly proportion of sequences that belong to XBB.1.5, and the size of the bubbles indicates the number of sequences from samples collected during each week (logarithmic scale).

Outside of the EU/EEA, several countries have recently reported cases of XBB.1.5 to GISAID EpiCoV (Figure 2). Since many countries report no or insufficient data to accurately detect variants at low proportions, it is highly likely that the variant is present in many more countries around the world. Since the sampling strategies behind these data are not known, it is also likely that the proportions shown here are not fully representative of the cases in each country. It is, however, clear that XBB.1.5 is widely distributed geographically.

The highest proportion of XBB.1.5 is currently found in the US, where it is estimated to account for about 28% of overall cases, reaching up to 73% of detected cases in the northeast states (data from CDC COVID Data Tracker on 13 January 2023). An estimation of the number of cases of COVID-19 caused by different variants of concern (VOC) and variants of interest (VOI) in the US from sequences reported to GISAID EpiCoV and weekly cases reported to the WHO as of 9 January 2022 is shown in Figure 3. The numbers of cases estimated to be caused by XBB.1.5 grew significantly during weeks 49-51 of 2022, reducing slightly in week 52 (though winter holidays generally have a reducing effect on testing and number of reported cases). As a comparison, estimated cases of BQ.1 remained stable from week 49 to 51.

Figure 3. Estimated weekly cases of COVID-19 in the US reported to WHO caused by VOC and VOI as defined by ECDC, and XBB.1.5, week 34/2022–week 01/2023



Note that the XBB category shown here includes all XBB lineages except XBB.1.5, the BA.5 category includes all BA.5 lineages except BQ.1 with sub-lineages and the BA.2 category includes all BA.2 lineages except BA.2.75 with sub-lineages.

The XBB.1.5 variant

SARS-CoV-2 XBB lineage is a recombinant of two earlier lineages of the Omicron VOC, BA.2.10.1 and BA.2.75, [1] which became dominant mostly in south- and east-Asian countries (Singapore, Malaysia, Indonesia, India, Bangladesh) during the winter months of 2022, but did not reach levels higher than ~10% in any EU/EEA country [2]. XBB.1.5 is a sub-lineage of XBB with an additional spike RBD change S486P. This lineage was first detected in the US with the earliest sample collection date of 22 October 2022, and this lineage has increased in numbers in the US and worldwide since then.

The 486P amino acid variant has been rare during the pandemic, probably due to it requiring two nucleotide substitutions in the same codon to change from phenylalanine, present in the original virus, to proline, present in XBB.1.5. However, other variants with this change have emerged before without becoming successful, so it is not likely that this change alone would provide a significant advantage to the virus.

Since the lineage is frequently misclassified in the Pangolin [3] implementation in GISAID EpiCoV, likely due to parts of some of the genome sequences not being covered, a mutational proxy can be used to identify the lineage more sensitively. ECDC currently uses the spike mutational proxy Q183E, F486P and F490S [4] inclusively to detect XBB.1.5. Phylogenetic analysis of all sequences available in GISAID EpiCoV as of 9 January 2023 matching this proxy (N=4770), show that only two sequences are clearly false positive hits that belong to other lineages.

ECDC has been monitoring the entire XBB lineage as a variant of interest. As of 12 January 2023, ECDC has classified XBB.1.5 as a separate VOI in order to gather and evaluate evidence separately from other XBB lineages. For the latest classification of variants for the EU/EEA, see ECDCs webpage on variants [5].

Diagnostics

According to WHO, the diagnostic accuracy of routinely-used RT-PCR assays does not appear to be impacted by Omicron [6] and FIND, the global alliance for diagnostics, maintains a directory of diagnostic assays functional for different SARS-CoV-2 variants [7]. The EU Joint Research Centre (JRC) also monitors the performance of RT-PCR assays and displays information, including for variants XBB and XBB.1 [8,9], on the JRC dashboard. These in silico analyses identified seven out of 20 and 19 assays that may have reduced sensitivity or fail to detect XBB and XBB.1, respectively [8,9]. The US Food and Drug Administration (FDA) reports reduced, but not failed, performance for the DxTerity SARS-CoV-2 RT PCR CE Test (DxTerity Diagnostics, Inc.) for the Omicron variant and sub-variants as well as reduced performance for the Clip COVID Rapid Antigen Test (Luminostics, Inc.) [10]. There are, however, certain assays that may be impacted by the mutations that Omicron lineage XBB.1.5 carries, and reports on the performance of diagnostic tests specifically for XBB.1.5 are warranted. Therefore, laboratories are urged to validate the performance of their diagnostics in use.

Growth rate

The observed growth rate advantage of a new variant is a combined effect of potential increased inherent transmissibility, immune escape, and changes in the generational time or infectious period. It could also be an artifact of e.g. biased testing, founder effects, or super-spreading events.

According to estimates provided by covSPECTRUM [11], based on data reported by the US to GISAID EpiCoV [12], XBB.1.5 (using the mutational proxy described under the heading *The XBB.1.5 variant* above) currently exhibits a daily growth advantage of 12% (95%CI 11-13%) in the US compared to other circulating variants. As a comparison, BQ.1.1 exhibits a daily growth advantage of 5.6% (95%CI 5.3-5.7%), CH.1.1 of 5.0% (95%CI 4.6-5.3%), and XBB (excluding XBB.1.5) of 4.2% (4.0-4.3%).

Transmissibility

According to a preliminary study, XBB and XBB.1.5 have very similar antigenic properties, while XBB.1.5 exhibits significantly stronger binding to the human ACE2 receptor, similar to that of BA.2.75 [13]. It is therefore plausible that the difference in growth rate between XBB and XBB.1.5 is mainly explained by a difference in transmissibility. If the difference in observed growth rate would be completely explained by an increase in inherent transmissibility, it would correspond to an increase of between 27% and 62% in the basic reproduction number (R0) compared to other XBB variants circulating in the US, using an assumed generation time range between two published estimates of 3.3 and 6.8 days [14,15]. No direct estimates of the transmissibility of XBB.1.5 from secondary attack rates in specific settings are currently available.

Early growth advantage can be overestimated due to the influence of founder and stochastic effects, though these are less likely as explanations when there are already high levels of circulation of the virus in the population. It is also possible that the assumption that the observed difference in growth rate between XBB.1.5 and other XBB lineages can be explained by an intrinsic transmissibility advantage is not true. For these reasons, the estimated increase in the basic reproductive number is associated with a high level of uncertainty.

Immune escape properties

In vitro data

Studies evaluating the capacity of human serum to effectively neutralise SARS-CoV-2 virus in vitro provide an early indication of whether newly-emerged lineages can evade infection-induced or vaccine-induced neutralising antibodies, which are critical for protection against infection.

A number of studies have shown that XBB and XBB.1 demonstrate the most substantial immune escape observed amongst Omicron sub-lineages to-date, with significant reductions in the capacity of serum from vaccinated individuals (two to four doses monovalent mRNA vaccines targeting the original strain of SARS-CoV-2) to neutralise both viruses when compared to ancestral Omicron variants [16-20]. Only a modest increase in neutralising performance measured by vaccine-induced neutralising antibodies has been reported for serum from individuals receiving at least one dose of the latest bivalent mRNA booster vaccines. For XBB and XBB.1, the best performing sera are sampled from individuals that have experienced a prior BA.4/5 infection coupled with recent receipt of a bivalent mRNA booster, however, it is difficult to translate marginal increases observed in neutralisation studies to improved clinical protection against infection [16].

Only one preprint article reports on the immune escape properties of XBB.1.5 specifically, testing both monoclonal antibodies and sera from hybrid immune individuals (two to four doses monovalent mRNA vaccines with a prior BA.5 infection). Yue et al established that the immune escape properties of XBB.1.5 are equivalent to XBB.1. Both are resistant to Evusheld (tixagevimab /cilgavimab) and bebtelovimab, while sotrovimab remains weakly reactive in vitro [13].

Whilst neutralising antibodies in serum contribute to protection from infection, few in vitro studies assess the additional immune protection derived from non-neutralising antibodies and T cells, the majority of which are conserved across all SARS-CoV-2 variants and play an important role in protection against severe disease. One small study comparing the impact of monovalent versus bivalent mRNA vaccine boosters on neutralising antibody, CD4 and CD8 T cell responses to BA.1 and BA.5 Omicron sub-lineages, suggests that whilst both markedly increased antibody responses, they did not substantially augment T-cell responses [20]. No T cell studies are available for XBB.1.5 specifically.

Vaccination uptake data

As of 12 January 2023, the cumulative uptake of the primary COVID-19 vaccination course in the total population in the EU/EEA reached 73.0%. Approximately 61.4 million adults in the EU/EEA had received a second booster dose of a COVID-19 vaccine, of these 78% in the 60+ age group. The uptake of the second booster in the 60+ age group reached 34.4%. Table 1 shows a summary of the cumulative uptake of the primary course, first, second and third booster dose in the total population, adults (18+), and older adults (60+ and 80+ years).

Approximately 26.8 million doses of Comirnaty bivalent vaccines and 863 000 doses of Spikevax bivalent vaccines targeting the Omicron subvariants BA.1 and BA.4/BA.5 have been administered in the EU/EEA (18 countries reporting), which represents approximately 83% of the total number of vaccine doses administered in EU/EEA countries since mid-September 2022 (data from ECDC Vaccine Tracker).

Table 1. Summary table of COVID-19 vaccine uptake in EU/EEA countries, as of 12 January 2023

Population group	Uptake of primary course (range)	Uptake of first booster (range)	Uptake of second booster (range)	Countries reporting	Uptake of third booster (range)	Countries reporting
Persons aged 60+ *	**91.1%** (38.4 - 100%)	**84.8%** (13.6 - 100%)	**34.4%** (0.3 - 86.3%)	**30**	**2.0%** (<0.1 - 33.2%)	**20**
Persons aged 80+ *	**94.0** (26.7 - 100%)	**83.8%** (8.0 - 100%)	**45.1%** (0.3 - 96%)	**29**	**3.5%** (<0.1 - 53.7%)	**18**
Adults (18+)**	**82.4%** (35.8 - 96.1%)	**65.4%** (11.3 - 87.0%)	**16.5%** (0.2 - 41.7%)	**30**	**1.7%** (<0.1 - 10.6%)	**20**
Total population**	**73.0%** (30 - 86.3%)	**54.7%** (9.2 - 75.8%)	**13.5%** (0.1 - 33.5%)	**30**	**1.4%** (<0.1 - 8.6%)	**20**

** Values are the median across the reporting countries*
*** Note that not all countries actively promote second/third booster vaccination for these age groups*

Vaccine effectiveness data

While there are no vaccine effectiveness (VE) estimates for XBB.1.5 yet, the currently available vaccines remain effective against severe disease due to previous and current Omicron variants dominant in EU, with some evidence of waning over time. It is very likely that this will also be the case for XBB.1.5. A US VE study on the Omicron updated mRNA BA.1 bivalent COVID-19 vaccines indicates that bivalent boosters in the short term restore the previously waned protection against symptomatic infection with absolute VE estimates ranging from 43% in younger age groups to 22% amongst those aged 65+ years [21]. In another US study, VE of a bivalent booster dose (after two, three of four doses of the COVID-19 mRNA vaccine targeting the original strain of SARS-CoV-2) against hospitalisation for COVID-19–associated illness was 57% compared with no vaccination and 45% compared with receipt of last original vaccine doses, with last dose ≥11 months earlier [22]. The incremental protection conferred by the mRNA bivalent BA.1 COVID-19 vaccine estimated relative to those with waned immunity was 57% against hospitalisation, as published in a UK report [23]. The incremental (or relative) VE is the level of protection that the booster dose adds in addition to the remaining protection conferred by previous doses. These estimates therefore, appear lower and are not directly comparable with estimates where VE is calculated relative to the unvaccinated. A recently published pre-print study from Israel found a reduction of severe outcomes (hospitalisation and death) amongst individuals 65 years and older who were vaccinated with a bivalent booster as compared to those eligible for, but not having received the bivalent booster [24]. However, the currently available studies are not investigating XBB.1.5 but include all Omicron subvariants circulating at the time of the study.

Severity

There are currently no signals that the infection severity of XBB.1.5 is different than that of previously circulating Omicron sub-lineages. However, an increase in cases caused by increased transmissibility or immune escape would be expected to lead to an increase in the number of severe cases. In hamsters, the virological characteristics *in vivo* and intrinsic pathogenicity of XBB is comparable to the BA.2.75 sub-lineage, and lower than Delta VOC based on body weight, pulmonary function, efficacy of viral spread in the respiratory tissues and histopathological assessments reported in a preprint study [25]. The results suggest that XBB is less pathogenic than Delta and comparable with BA.2.75. To our knowledge, no *in vitro* or *in vivo* studies have yet been reported for the XBB.1.5 sub-lineage specifically.

Therapeutics

No specific data are currently available on the effectiveness of EU-authorised COVID-19 antivirals nirmatrelvir/ritonavir or remdesivir for XBB.1.5. However, recent data indicate that the susceptibility of XBB to nirmatrelvir, remdesivir and molnupiravir (authorised in the US) is similar to ancestral strains [26]. The effectiveness of monoclonal antibodies targeting the spike protein is expected to be considerably limited [27].

Modelling insights

We make use of mathematical modelling to estimate the time until the XBB.1.5 sub-lineage is expected to cause more than 50% of all SARS-CoV-2 infections in the EU/EEA. The relative growth advantage of the XBB.1.5 sub-lineage compared to other circulating SARS-CoV-2 variants in the EU/EEA is assumed to be constant over time. Utilising the methodology detailed in the ECDC technical report Spread of the SARS-CoV-2 Omicron variant sub-lineage BQ.1 in the EU/EEA [28], the evolution of the proportion of SARS-CoV-2 infections that are due to XBB.1.5 depends on two factors: the growth rate advantage of XBB.1.5 in the EU/EEA and the current proportion of XBB.1.5 cases in the EU/EEA. As both factors are highly uncertain, we explore the impact of hypothetical values for these two factors on the time until XBB.1.5 becomes dominant in the EU/EEA.

Table 2 shows the resulting estimated time until XBB.1.5 becomes dominant (i.e. if it causes more than 50% of all SARS-CoV-2 infections in the EU/EEA) for a broad range of hypothetical values of the growth rate advantage of XBB.1.5 and the current proportion of XBB.1.5 in the EU/EEA. For example, the fourth row shows that, given a hypothetical proportion of 1% SARS-CoV-2 infections due to XBB.1.5 in the EU/EEA and a daily growth advantage of at least 8% in the EU/EEA, the XBB.1.5 sub-lineage is estimated to become dominant by 1 March 2023. More evidence is needed to estimate which of the hypothetical values for the current proportion of XBB.1.5 in the EU/EEA and its daily growth advantage in the EU/EEA are most accurate. Given the current reported proportions of XBB.1.5 in the EU/EEA (see Figure 1) and its estimated growth rate advantage (of approximately 12%, with large uncertainties across the EU/EEA), there is a moderate probability of XBB.1.5 becoming dominant in the EU/EEA after one to two months and causing a substantial increase in the number of COVID-19 cases.

Table 2. Modelling results for the expected time until the XBB.1.5 sub-lineage becomes dominant

XBB.1.5 sub-lineage becomes dominant (>50%) in the EU/EEA	*Hypothetical* current proportion of infections due to the XBB.1.5 sub-lineage in the EU/EEA (on 1 Jan 2023)	*Hypothetical* daily growth advantage of the XBB.1.5 sub-lineage in the EU/EEA
One month (1 February 2023)	1%	>17%
	0.1%	>26%
	0.01%	>36%
Two months (1 March 2023)	1%	>8%
	0.1%	>13%
	0.01%	>17%
Four months (1 May 2023)	1%	>4%
	0.1%	>6%
	0.01%	>8%

The expected time until the XBB.1.5 sub-lineage becomes dominant in the EU/EEA (first column) in dependency of two parameters: the current proportions of SARS-CoV-2 infections due to the XBB.1.5 in the EU/EEA (second column) and its daily growth rate advantage in the EU/EEA (third column), which is a combined effect of increased inherent transmissibility, immune escape, and changes in the generational time or infectious period. Only hypothetical values for the two parameters are considered since both parameters are highly uncertain at the time of writing. Each of the nine rows corresponds to one hypothetical parameter setting. For example, the fourth row shows that, given a hypothetical proportion of 1% SARS-CoV-2 infections due to XBB.1.5 in the EU/EEA and a daily growth advantage of at least 8% in the EU/EEA, the XBB.1.5 sub-lineage is estimated to become dominant by 1 March 2023. The first column shows coarse estimates of the time until the XBB.1.5 sub-lineage becomes dominant, since the mathematical model relies on several simplifying assumptions, including: a well-mixed homogeneous population; the absence of super-spreader events (or other erratic effects on the incidence); a similar effect of human behaviour and non-pharmaceutical interventions on the relative growth of different variants; the absence of other competing variants; and the same growth rate

advantage across the EU/EEA (which depends on the inherent transmissibility of XBB.1.5, its evasion of naturally-acquired and vaccine-induced immunity and the overall immunity landscape of the population).

Risk assessment for the EU/EEA

This assessment is based on evidence available to ECDC at the time of publication and is informed by mathematical modelling as described above. It follows the ECDC rapid risk assessment methodology, with relevant adaptations, where the overall risk is determined by a combination of the probability and its impact [29].

What risk does the spread of the Omicron variant sub-lineage XBB.1.5 pose to the general population and to vulnerable individuals in the EU/EEA?

The number of countries in the EU/EEA reporting XBB.1.5 cases has increased in the past weeks. However, a severe limitation in this assessment is the decreased number of countries achieving an adequate percentage of sequenced samples at the national level. XBB.1.5 exhibits a large daily growth advantage in the US relative to previously circulating lineages (estimated at 12%), although estimates are associated with significant uncertainty.

Indications from preliminary data suggest that the increased growth rate may be caused by an increase in intrinsic transmissibility for XBB.1.5, combined with the already high level of immune escape exhibited by XBB.

There is a **moderate** probability of XBB.1.5 becoming dominant in the EU/EEA and causing a substantial increase in the number of cases of COVID-19. This is likely to occur after one to two months given the current reported proportions of XBB.1.5 in the EU/EEA and its estimated growth rate. Due to the heterogeneity of former COVID-19 waves, differences in vaccine uptake and population immunity, etc. XBB.1.5 may spread differently in different countries.

Evidence around the severity of the infection associated with XBB.1.5 is currently lacking, but there are no indications that it is different from previously circulating Omicron sub-lineages. Therefore, infection in the general population in the EU/EEA is expected to have a **low** impact, due to low incidence of severe disease with the Omicron VOC and prior immunity (either through vaccination, prior infection or both).

Based on the few available studies performed during the recent Omicron period that are not including XBB.1.5, individuals who recently received an updated bivalent mRNA vaccine have restored their immunity against symptomatic infection and hospitalisation. Antivirals, along with other treatment options (dexamethasone, immune modulators, etc.) can be used for treatment of severe COVID-19 disease, but the effectiveness of monoclonal antibodies targeting the spike protein appears to be considerably limited, according to studies carried out in vitro [27]. Therefore, the impact of XBB.1.5. infection on vulnerable individuals, including immunocompromised, people with comorbidities, individuals 65 years of age and older, who have received a recent COVID-19 vaccine dose is assessed as **moderate.** The impact on vulnerable individuals who are incompletely vaccinated according to the recommended schedule for their population group or unvaccinated is assessed as **high**.

Therefore, the overall risk is assessed as **low** for the general population and **moderate to high** for vulnerable population groups depending on their immunity against SARS-CoV-2. This assessment is currently associated with a high degree of uncertainty.

An increasing number of COVID-19 cases will add pressure to the EU/EEA healthcare systems which are already strained by the co-circulation of multiple respiratory viruses (RSV, seasonal influenza, other coronaviruses, etc.).

Several knowledge gaps exist in relation to XBB.1.5 and it is possible that the assessment may change in the coming weeks as more evidence becomes available. Early growth advantage estimates for variants are always uncertain and will need to be revised as data from further countries become available.

Options for response

In view of the expected spread of SARS-CoV-2 Omicron sub-lineage XBB.1.5 the following options for response are proposed for public health authorities in the EU/EEA:

- Conduct appropriate risk communication activities for health professionals and the public.
- Maintain /or improve appropriate levels of testing and sequencing of SARS-CoV-2 according to explicit target thresholds as outlined in the guidance for representative and targeted genomic SARS-CoV-2 monitoring.
- Improve the timely uptake of COVID-19 vaccines, including primary course and booster doses according to national guidelines, particularly targeting eligible vulnerable individuals who have not yet received them.
- Consider time-limited and targeted non-pharmaceutical interventions for the community if appropriate.

- Follow appropriate infection prevention and control (IPC) guidance for healthcare settings which apply a holistic approach that addresses risks from the transmission of all respiratory viruses.

Risk communication activities

Risk communication to the public should provide a balanced overview of the available information on the XBB.1.5 variant including the significant limitations due to lack of robust evidence about the disease caused by this variant. Communication to health professionals should inform them about the available therapeutic options such as antivirals (nirmatrelvir), which are expected to be effective when used appropriately, as well as dexamethasone, immune modulators etc. [30].

Public health efforts should also aim to actively promote vaccinations against seasonal influenza and COVID-19. Information campaigns should be in place to promote these vaccinations for healthcare workers and eligible population groups.

Basic hygiene measures such as respiratory etiquette, appropriate hand hygiene and good ventilation of closed spaces should be emphasised.

Testing and sequencing

Diagnostic testing - i.e. testing of people with symptoms compatible with COVID-19, or asymptomatic people with high-risk exposure - remains key to identifying COVID-19 cases, enabling prompt treatment, particularly as new therapeutic options become available, and putting in place measures to prevent further transmission (i.e. isolation). RT-PCR assays remain accurate diagnostic tools for Omicron variants including XBB.1.5, as well as RADTs included in the EU list [31] of reliable antigen tests.

EU/EEA countries should focus on the early detection of any new variants. As new variants can appear anywhere around the world, the cornerstone for such detection is laboratory testing with effective sentinel surveillance variant monitoring, which will continue to guide and inform public health response measures. Routine population-based representative sampling and sequencing of positive specimens from sentinel systems in primary and secondary care in EU/EEA countries remain the most effective way to monitor transmission and virus evolution in a timely manner, and may be supplemented by targeted sequencing approaches as described in the joint ECDC and WHO Operational considerations for respiratory virus surveillance in Europe [32,33]. Member States should maintain or improve their representative genomic sequencing according to explicit target thresholds, particularly sequencing of primary and secondary care sentinel specimens. Timely sharing of data (ideally within one week) through GISAID, TESSy and other publicly accessible databases including the COVID-19 data portal through the European Nucleotide Archive (ENA) is vital.

As other circulating respiratory viruses such as influenza and RSV may cause additional challenges for healthcare providers, multiplex RT-PCR assays for respiratory viruses are beneficial for diagnosis of respiratory infections in primary care and hospitalised patients.

Virus characterisation services are available through ECDC; please contact ECDC at Covid.Microbiology@ecdc.europa.eu, if clinical specimens or isolates are available. Additionally, countries are encouraged to perform and share results of virus characterisation and laboratory assay assessments to improve the understanding of the variant's intrinsic characteristics including immune evasion and antigenic characterisation, impact on diagnostic methods, or other relevant characteristics.

All genomic sequencing results should be notified by the designated data managers of national public health authorities to TESSy RESPISURV (case-based) or NCOVVARIANT (aggregated) on a weekly basis. Cases of XBB.1.5 variant can be reported as XBB.1.5 Virus Variant or, until this is implemented in the TESSy metadata, as XBB specifying XBB.1.5 in the 'VariantOther' variable. Countries of the EU/EEA may also use the EpiPulse event (2023-IRV-00004) on XBB.1.5 to informally discuss and share information, including partial and preliminary data, preferably also indicating if data posted in EpiPulse can be shared in the ECOVID-Net or -LabNet and SARS-CoV-2 Virus Characterisation Working Group.

Wastewater surveillance can complement the regular surveillance activities for monitoring of variants through testing of wastewater in designated sites capturing circulating variants in the general public and in travellers [34,35].

Vaccination

The currently available COVID-19 vaccines are very likely to continue to protect against severe outcomes including for this subvariant of Omicron, albeit with waned effectiveness over time. However, an overall increase in COVID-19 cases can result in a rise in hospitalisations, ICU admissions and deaths. As for the previously circulating Omicron subvariants, VE against infection is likely to be low for XBB.1.5, and wane with time since vaccination. Hybrid immunity could provide an additional layer of protection, but due to the lack of studies at this point, the

extent of this potential protection is unclear. Data emerging on VE against XBB.1.5 for various outcomes will continue to be assessed.

The objective of COVID-19 vaccination campaigns continues to be the reduction of COVID-19 hospitalisations, severe disease and deaths, and the protection of health systems. Improving the vaccine uptake of the primary course and booster doses in eligible individuals remains a priority, especially for population groups at higher risk of severe disease, who are yet to receive them, and for countries with lower uptake of primary course and first booster dose. Ensuring that eligible individuals are up to date with their vaccination is of key importance, to ensure the strongest protection.

Non-pharmaceutical interventions

Good hygiene practices and NPIs implemented in EU/EEA countries have proven to be an effective public health tool for reducing the spread of SARS-CoV-2 and other respiratory viruses since the beginning of the pandemic. Appropriate NPIs and targeted guidance for risk groups and caregivers of vulnerable groups should be considered in all countries experiencing a worsening epidemiological situation due to the simultaneous circulation of multiple respiratory viruses, including new sub-lineages of SARS-CoV-2. This guidance should be tailored according to the local epidemiological situation, the setting, and the pressure on the healthcare system and other essential services, bearing in mind the positive short-term and negative long-term effects of certain NPIs. Good hand and respiratory hygiene, including appropriate use of face masks [36]; good ventilation in indoor spaces; allowing employees and students to stay home when sick and teleworking where possible; avoidance of crowded public spaces, including public transport, are measures that may be taken depending on the local epidemiological situation.

Overall, the key to NPI effectiveness is community engagement and prompt implementation of these measures when incidence of respiratory infections rises.

Infection prevention and control in healthcare settings

It is important that healthcare facilities implement effective measures to mitigate the risk of respiratory virus transmission to healthcare staff but also to other people (patients and visitors), applying an integrated approach that addresses risks from transmission of all respiratory viruses not only focusing on SARS-CoV-2.

Early detection of COVID-19 and other respiratory viral infection cases, such as influenza and RSV using rapid antigen detection or other tests facilitates the optimal management of admitted patients and the appropriate room/bed allocation according to the IPC recommendations.

Standard precautions, and in particular meticulous hand hygiene and respiratory hygiene, are key for the prevention of respiratory tract infection transmission and should be applied for all patients. The use of medical face masks by healthcare workers for source control and personal protection should be strongly considered in clinical areas during all routine activities (targeted clinical masking) as a measure for reducing transmission within healthcare settings, particularly during periods of high community transmission. Universal masking by staff, visitors and patients can be considered.

Appropriate ventilation, in accordance with the applicable hospital regulations, should be ensured at all times (at least six air changes per hour in regular patient rooms [37]).

Transmission-based precautions should be applied taking into consideration the microorganism, as well as factors that can affect transmissibility such as the time and proximity of contact, the need for high-risk procedures, the immune status of the patient and the clinical presentation. Patients with viral respiratory infections should ideally be placed in single rooms or cohorted with other patients with the same infection.

Limitations and knowledge gaps

This risk assessment is undertaken based on the evidence known to ECDC at the time of publication. There remains many scientific uncertainties and knowledge gaps around what is known about this variant.

Some of these evidence gaps include:

- Lack of sufficient sequencing volume on SARS-CoV-2 allowing for detection of virus variant prevalence over 5% from most EU/EEA countries, which affects forecasting and estimation of the growth advantage of XBB.1.5 in the EU/EEA context.
- Lack of reliable growth advantage estimates from other settings than the USA for XBB.1.5 sub-lineage.
- Lack of epidemiological and clinical studies to assess severity and transmissibility of the XBB.1.5 sub-lineage.
- Lack of laboratory studies to fully assess the antigenic properties of the XBB.1.5 sub-lineage.
- Lack of vaccine effectiveness studies specifically for XBB.1.5.
- Lack of pathogenicity studies specifically for XBB.1.5.

The WHO Technical Advisory Group (TAG) on virus evolution has in a recent rapid risk assessment on XBB.1.5 [38] identified these further priority activities to fill some of the knowledge gaps:

- Estimation of the growth advantage of XBB.1.5 in further countries than the US.
- In-vitro neutralisation studies using human sera representative of the affected population and live XBB.1.5 virus.
- Comparative assessment of severity indicators to detect any changes in infection severity.

Source and date of request

ECDC internal decision, 05 January 2023.

Consulted experts

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Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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