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Omicron: What do we know so far?

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Abstract

This policy brief comprehensively gathers and compares the results of studies on the SARS-CoV-2 variant 'Omicron' to enable a more conscious argumentation for policy measures. For this purpose, studies and reports were collected by regular screenings of medRxiv, scientific databases and websites of national health authorities.

Overall, studies reveal that compared to Delta, the risk of hospitalization is reduced by 50% to 80%, risk of ICU admission by 65% to 85% and risk of fatal course by 65% to 75% but reduced by a lower amount among older adults. Vaccine effectiveness (VE) of two doses against infection is only significant within the first months at 55% to 65% and waning over time while a 3rd dose pushes VE up to 55% to 70% again. On the contrary, VE against hospitalization seems to be more stable at 55% to 80% up to 6 months and might be increased to about 85% with a 3rd dose. Most studies report the number of ICU admissions and deaths after vaccination as too low to estimate VE. Comparing sub-lineage BA.2 to BA.1 studies mention transmission advantages for BA.2 rather than an increased immune escape and the severity of the disease is expected to be similar.

Overall, results show lower severity of infection, lower VE compared to Delta variant and importance of a 3rd dose. Nonetheless, vaccination, especially a 3rd dose, is essential to reduce the risk of severe courses and, thus, the level of population immunity is crucial to maintain the stability of health care systems without rigorous non-pharmaceutical interventions.

The possibility of relaxing non-pharmaceutical interventions can be attributed to high immunity levels within countries due to vaccination and prior infection and a lower risk of a severe course by Omicron. Nonetheless, immunity levels are expected to wane over time and, thus, a long-term vaccination strategy is necessary. On the one hand, vaccines can be adjusted to new variants that challenge current vaccines, on the other hand, future variants might turn out to be more severe than Omicron again. As data shows that protection is markedly increased by a three-dose regimen, vaccination commission should consider declaring three doses as full vaccination that should be obtained by everyone that can be vaccinated.

1 Introduction

SARS-CoV-2 has been challenging health systems and governments worldwide for about two years now. While the availability of vaccines increased, many countries have faced problems with vaccination hesitancy. Meanwhile, SARS-Cov-2 mutations are leading to changes in virus structure that potentially affect transmission dynamics, the severity of illness and vaccine effectiveness. In November 2021, a steep increase of infections with SARS-CoV-2 in South Africa was traced back to a new variant, soon denominated as 'Omicron' by the WHO. Early evidence from neutralization studies indicated enhanced immune escape compared to Delta.[1] First data from South Africa, where Omicron was detected early, indicate fast spread and less severe disease.[2] However, while the first insights refer mostly to laboratory neutralization studies, population-based studies have been increased right after to provide real-world evidence to prove findings of in vitro analyses.

So far, early population-based studies around the world have confirmed a faster spread compared to several months before the rise of Omicron, lower vaccine effectiveness (VE) against infections and lower hospitalization rates compared to previous variants.[3, 4] Several public health organizations, e.g., WHO[a], ECDC[b], CDC[c], U.K. Health Security Agency[d], provide regular updates on recently published evidence referring to Omicron. These updates and reports deliver quick insights into the latest evidence but often do not discuss and compare findings in detail, e.g., similarities and differences between studies or age groups.

This policy brief tries to capture the most important evidence referring to transmission dynamics, the severity of illness, VE against Omicron, Omicron's sub-lineage BA.2 and indications for risk of reinfection to reveal similarities and differences of widely distributed information. Reduced risk against (severe) disease after an infection is not investigated separately in this manuscript since several studies show that gained immunity by an infection can be considered at least as equal protection compared to vaccination, albeit at a higher health risk.[5-8] To summarize, this policy brief should facilitate understanding of the latest study results referring to Omicron so far and, considering this evidence, provide advice for future measures.

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[a] https://www.who.int/publications/m/item/enhancing-readiness-for-omicron-(b.1.1.529)-technical-brief-and-priority-actions-for-member-states last accessed on 17th March 2022

[b] https://www.ecdc.europa.eu/en/publications-data last accessed on 17th March 2022

[c] https://www.cdc.gov/mmwr/Novel_Coronavirus_Reports.html last accessed on 17th March 2022

[d] https://www.gov.uk/government/publications/covid-19-vaccine-weekly-surveillance-reports last accessed on 24th March 2022

Studies and reports captured in the policy brief were collected by weekly screenings of medRxiv, bioRxiv, PubMed, Google Scholar and websites of national health authorities. The used search strings were 'Omicron', BA.1', 'BA.2', 'B.1.1.528'. Further, snowball sampling was used to discover studies referring to Omicron and its sub-lineages.

In the following section, transmission dynamics in terms of different epidemiological parameters of Omicron are investigated. In section 3, studies referring to different outcomes of an infection with Omicron are reviewed. Generally, each outcome reflects some degree of severity of disease starting with an infection potentially leading to hospitalization, ICU admission and, probably, death.

In section 4 of this policy brief, VE against infection, hospitalization, ICU admission and death are summarized. Since vaccines were developed using the structure of the original (Wuhan/wild-type) coronavirus, mutations seem to be able to reduce or even circumvent protection by vaccination through adjustments of the S-antigen. Consequently, studies investigating VE are required once more each time mutations are considered as a new variant of concern.

Section 5 refers to Omicrons' sub-lineage BA.2 since at the beginning of 2022, the attention for this sub-lineage increased. Additionally, mutations in contrast to the sub-lineage BA.1 were expected to probably affect the transmission, immune escape, and severity of the disease. Studies explicitly referring to the sub-lineage BA.2 are considered within this extra section. Accordingly, results in sections 2,3 and 4 refer to studies that mostly did not further distinguish between Omicron sub-lineages, but it is assumed that they refer most likely to BA.1 since within investigated periods only BA.1 was dominant. This section further covers immune response to different sub-lineages and variants after infection with Omicron. In the last section, results are summarised and their implications for future decisions are discussed.

It has to be mentioned that most studies considered within this manuscript are not peer-reviewed but preprints from medRxiv[e]. Consequently, reported results must be treated with caution and decisions based on evidence of only one study requires some experience in dealing with academic literature and interpreting results.

[e] https://www.medrxiv.org/ last accessed on 24th March 2022

2 Transmission dynamics

A steep increase of confirmed Covid-19 infections in South Africa delivered early hints that Omicron is spreading much faster than previous variants. Thus, together with the first reports of super-spreader events in Norway and England, an increased infectiousness compared to Delta was initially assumed, while the main reason for the spread seems to be immune escape. Consequently, a wildfire-like worldwide spread of Omicron was anticipated. Accordingly, studies estimating epidemiological parameters referring to infections are considered hereafter. More precisely, doubling time, serial interval, incubation period, reproduction number, secondary attack rate and viral load are examined. However, apart from the incubation period and viral load, parameters heavily relate to the period and population they are calculated for as they are affected by vaccination rates and non-pharmaceutical interventions (NPIs).

2.1 Doubling time, serial interval, incubation period

First estimates of doubling time were available for South Africa, where Omicron was initially discovered. Early investigations referring to November and December 2021 revealed a doubling time of 1.5 days for Omicron.[9] For different regions within South Africa, doubling time was estimated to be 2.4 days in Gauteng referring to an assumed mean duration of infectiousness of 10 days and doubling time was estimated over a four-week period in another study to be 3.4 days in Gauteng and 2.7 days in KwaZulu-Natal.[10] Accordingly, the doubling time was estimated to be 3 days for Australia, 2.5 days for New York State, 2.4 days for the U.K. and 2.0 days for Denmark.[11] For December 2021 and January 2022, doubling time was estimated to be 2.7 to 3.1 days in Italy[12], respectively, for England from November 23rd to December 11th 2021 to be about 2 days,[13] and for 8 out of 9 regions in England even lower than 2 days by mid-December.[14] For Texas, U.S., the estimated case doubling time during the first three weeks in December was approximately 2.2 days.[15]

However, doubling time is dependent on several circumstances such as infectiousness and measures to reduce transmission. To be more precise, vaccination and NPIs.[16] Referring to this, in the U.K. between May and June 2021, where vaccination rates were increasing and Delta was widespread, doubling time was 11 days.[17] Overall, previously mentioned studies considered immune evasion as the most obvious reason for a shorter doubling time for Omicron compared to Delta.

The most interesting parameter in models of infectious spread is the generation time. The generation time is the interval between the infection of a person in generation x and this person infecting a person in generation x+1. As this is difficult to measure, the serial

interval is used as a surrogate. The serial interval describes the time between the same states of infection between subsequent generations, usually the time between symptom onset in a person and their secondary infections. Consequently, knowledge about infection chains, e.g., gained through contact tracing, supports the estimation of this parameter. Further, the incubation period, the time from infection to onset of symptoms, facilitates the identification of infection chains. Referring to this, a study examining 131 cases within several clusters in South Korea estimated a mean serial interval of 2.2 days.[18] Another South Korean study investigating 80 people from the end of November until mid of December revealed an incubation period of 4.2 days and a serial interval of 2.8 days.[19] Within a cluster of 111 people in Norway median incubation period was 3 days.[20] For the Netherlands, a mean serial interval was estimated to be 3.4 days for Omicron and 3.9 days for Delta.[21] In Belgium the mean serial interval for Omicron was reported to be 2.75 days compared to Delta with 3 days where serial intervals were significantly longer if individuals within infection pairs were both had received a third dose. [22] A small case study of 6 persons in Nebraska reported an incubation period for Omicron of approximately 3 days.[23]

In contrast to studies referring to Omicron, within a meta-analysis that considered 23 studies published before August 2020 and, thus, refer to the initial COVID-19 variant, a mean serial interval of 5.2 days and an incubation period of 6.5 days were estimated. [24]

2.2 Infectiousness, reproduction number, secondary attack rate, and viral load

Reproduction number and secondary attack rate are both measures showing how well an infection spreads. The reproduction number describes how many persons on average are infected by an infectious person of the previous generation. As this depends on the immunity of contacts as well as contact behaviour, the reproduction number varies, especially, over time. Thus, the basic reproduction number R_0 is distinguished from the effective reproduction number R_{eff} or R_t, the former being the reproduction number in an immune-naïve population under normal conditions, while the latter is the actual reproduction number measured, i.e., affected by contact restrictions and growing immunity. Additionally, the viral load of a contagious individual is a major factor influencing the risk of infecting other people.

Concerning reproduction number, within a South Korean study the estimated value for the Omicron outbreak was 1.9.[18] For Denmark, the reproduction number was estimated to be about 3 times higher compared to Delta under the same epidemiological conditions.[25]

A secondary household attack rate of 21.6% for Omicron and of 10.7% for Delta was reported in the U.K. by investigating routine contact tracing data.[26] Referring to this, in Denmark a secondary household attack rate of 31% was shown for Omicron and 21% for Delta. The study further revealed a significantly lower susceptibility with an odds ratio of 0.54 for households vaccinated three times compared to twice vaccinated households for Omicron, while the difference between being unvaccinated and vaccinated twice was significant with an odds ratio of 2.31 for Delta but not significant for Omicron.[27] A secondary attack rate (SAR) of 51% for Omicron and 36% for Delta was revealed by Norwegian contact tracing data. SAR was lower after three doses of vaccination for Omicron and Delta while reduction of attack rate was much higher for Delta compared to Omicron.[28] Further, a more recent study among the Norwegian population revealed a SAR of 25% for Omicron and 19% for Delta.[29] In the U.S., household attack rate was estimated to be 42.7%, 43.6% and 63.9% for being vaccinated thrice, being vaccinated twice and being unvaccinated, respectively.[30] Another study in the U.K. investigated the risk ratio of household clustering and reported a 3.54 overall risk ratio for Omicron compared to Delta.[31]

Referring to viral load, in Switzerland, a study revealed a similar amount for Omicron compared to Delta but investigated only 18 Omicron cases. [32] Further, in the U.S. lower viral loads in terms of higher CT-values were found for Omicron compared to Delta at three universities in Massachusetts.[33] A study within the National Basketball Association's occupational health program found lower peak viral loads for Omicron compared to Delta.[34] In line with previously mentioned results, among health care workers in France, viral load was significantly lower for Omicron compared to Delta. [35] In contrast to these four studies, the mean CT-value was significantly lower for Omicron compared to Delta in a study from South Africa.[2] Further, a Japanese study revealed the highest viral load 3-6 days after diagnosis or symptom onset, where contagiousness persists up to 10 days.[36]

3 Severity of an Omicron infection

To investigate the risk of hospitalization, ICU admission or death by an Omicron infection, regression models, mainly Cox regression models, are used to estimate hazard ratios for being hospitalized with an Omicron infection compared to a Delta infection. These models are mostly adjusted by several covariates., e.g., sex, age, comorbidities, vaccination, previous infection, that are assumed to increase or decrease the risk of severe outcomes according to previous findings. [37-41] Further, some studies distinguish whether Covid-19 infection is the main cause of hospitalization or might be an incidental finding. Studies reporting 'severe diseases' among hospitalized individuals are compared with and denoted as ICU cases in the following sections.

Figure 1 shows whether and how much the risk of admission to hospital and ICU is reduced for an infection by Omicron compared to Delta for different studies. The X-axis shows the amount of risk reduction compared to Delta. More precisely, a risk reduction close to zero would indicate that the risk for an outcome, mentioned on the Y-axis, is equal between Omicron and Delta and a risk reduction close to 1 would suggest that risk is 100% lower. Further, point estimates and 95% error bars are presented for each study mentioned in the box within the figure.

3.1 Risk of being hospitalized with an infection by Omicron compared to Delta

Already in 2021, two studies stressed that the risk of hospitalization is reduced by 68% and 80% for Omicron compared to Delta in South Africa and Great Britain, respectively. [2, 42] The South African study pointed out that it was not possible to adjust for vaccination status, thus, the risk reduction is likely to be overestimated.[2] A cohort study in Denmark reported an overall risk reduction of 36% independent of vaccination status and a risk reduction of 50% for people being vaccinated thrice.[43] Thereafter, at the beginning of 2022, several studies followed that revealed a risk reduction of 50% to 75%. In more detail, three studies for the U.S. reported a risk reduction of 53%, 56% and 66% and one study for each of the following countries mentioned a risk reduction of 65% for Canada, 73% for Norway, of 75% for Portugal and 59% for Great Britain.[44-50] In Norway only patients for whom a Covid-19 infection was documented as the main cause of admission were included and in the study for Canada it is mentioned that risk was further reduced after adjusting for incidental findings of a Covid-19 infection.[46, 47]

A study from South Africa showed less risk reduction compared to other studies, which was 28%. Within the study, it was assumed that this result is biased by a large number of undocumented previous infections. Thus, initial estimation without assumptions of

previous infections was 59% and, consequently, similar to results from other studies.[6] Another study from South Africa indicated a risk reduction by 44%, but with high uncertainty, most likely, due to small sample size. [51]

Another study in 2021 in the U.K. differentiated between any attendance at hospital and hospitalization with at least 1 day in the hospital. The risk of any hospital attendance with Omicron was reduced by 25% compared to Delta, while the risk was further reduced by 41% for hospital admission that was defined by attendance with at least one night in hospital. Previous infection reduced risk by 50% for any hospital attendance and by 61% for admission. In this study it was assumed that about 1/3 of all infections were detected and, thus, the number of reinfections might be higher.[7] Further, a study referring to the U.S. found an unadjusted significantly lower share of hospital admissions and need for respiratory support for Omicron infections compared to Delta.[15] A study in the U.K. among Long-Term Care residents revealed a reduced risk of hospitalization by 50% for Omicron compared to Delta.[52]

The U.S. study also examined the risk of hospital admission among different age groups. Considering all age groups, a reduced risk ratio of Omicron compared to Delta is highlighted by the share of hospitalizations with 1.75% and 3.95% for Omicron and Delta, respectively. The age group analysis revealed that risk reduction was lower for people 65 years and older with a reduction of 45% for hospital admission compared to the age group of 18 to 64 years with a reduction of 68%.[48] In line with this, a study among the population in the U.K. mentioned a risk reduction of 75% for the age group of 60 to 69 years and of 53% for the group of 80 years and older.[50] On the contrary, risk of hospitalization among a Canadian cohort study showed a reduced risk after adjusting for incidental findings of Omicron infection of 70% for people who are up to 60 years old and of 76% for people 60+ years old. Without adjusting for incidental findings reduced risk for people up to 60 years is the same, while for the older group estimated risk would be reduced only by 60%.[46]

Some of the previously mentioned studies also considered the length of hospital stay. Referring to this, the median length of stay was mentioned to be 2.8 days in the U.S. for Omicron [15], and the median duration was shorter by 3.4 days within another U.S. study for Omicron compared to Delta[44] and length of hospital stay was shorter by 4 days on average in Portugal.[45] A study in Australia disentangled length of hospital stay according to age groups for Delta and Omicron and revealed a mean duration for people up to 39 years of 3.6 days and 1.6 days, for people between 40 and 69 years of 5.8 days and 2.9 days and for people 70 years and older of 12.3 days and 6 days for Delta and Omicron, respectively.[53]

3.2 Risk of ICU admission with infection by Omicron compared to Delta

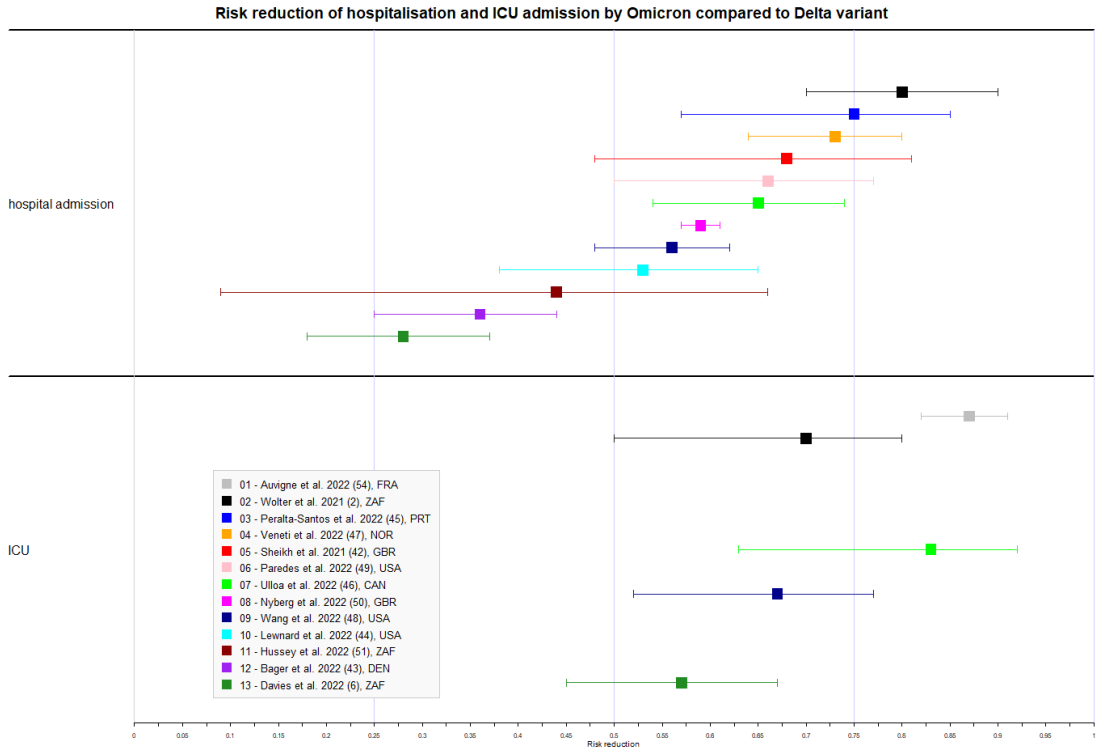
Regarding the risk of ICU admission, the number of studies was lower compared to hospital admissions. Studies displayed in Figure 1 reported a risk reduction between 57% and 87%. While the amount of risk reduction for the Canadian study, the study from the U.S. and one of the South African studies seems to be higher compared to its reduction in hospitalization, the earlier study from South Africa revealed a lower amount of risk reduction for ICU admission.[6, 46, 48] The latter might be explained by the fact that estimations for hospitalization were not adjusted by vaccination status but estimations for ICU admission were adjusted and the latter refer to the risk of an ICU admission after hospitalization. More precisely, for estimating the risk of hospitalization infected individuals without hospitalization and, thus, unknown vaccination status are compared with hospitalized individuals.[2] In France, a risk reduction of 87% against ICU admission for Omicron compared to Delta was reported where only cases with the main cause of Covid-19 were considered.[54] According to the study from the U.S., the share of ICU admission from all investigated infected cases was 0.26% and 0.78% for Omicron and Delta, respectively.[48] A Norwegian study revealed a risk reduction of 48% for being admitted to ICU for Omicron compared to Delta where only a small sample of hospitalized people with main cause SARS-CoV-2 was investigated.[55]

Referring to age groups, risk reduction for an ICU admission among people under 60 years old was reported by a Canadian study to be 95% and for people 60+ years old 72%.[46] In France, for people older than 80 years risk was estimated to be reduced by 70%.[54]

3.3 Mortality risk after infection by Omicron compared to Delta

Most studies did not further distinguish between any severe outcome and death but denote categories as 'Hospitalization or death' and 'ICU admission or death'. In previous sections, these categories were considered as hospitalization and ICU admission since category names mean that people who died after hospitalization were included in those categories. However, few studies reported the risk of death for Omicron compared to Delta. For South Africa, risk reduction was estimated to be 76% and for Portugal 86%.[6, 45] At least four studies mentioned that the number of observed deaths due to an Omicron infection was too low to estimate risk ratios.[44, 47, 48, 51]

Figure 1. Risk of hospitalization and ICU admission for Omicron compared to Delta



Source: IHS 2022

Note: Studies consecutively numbered in the box are described by the first author, year, reference number in parentheses and Alpha-3 country code

4 Vaccine Effectiveness (VE)

In this manuscript, the focus is on the VE of mRNA vaccines since these vaccines have been administered worldwide by far the most with about 88% of total vaccinations in Europe and 95% in the United States[f] and are mainly used for a 3rd dose. Referring to this, VE is only considered for two and three doses.

Not all studies mentioned in the following subsections are shown in figures since only studies that were considered comparable in terms of study design and outcome estimation are displayed. However, Figure 2 and Figure 3 provide a quick overview of the evidence of VE against Omicron, so far, and major differences between studies potentially affecting VE are mentioned in the text hereafter. VE for different age groups is only considered in the text as figures refer to the overall population of a country, sometimes limited by geographical regions.

4.1 Vaccine Effectiveness against infection with Omicron

Figure 2 shows VE compared to unvaccinated individuals against Omicron infection from seven studies according to four different countries/regions, namely Great Britain, Canada, United States of America, and Denmark, over time. The X-axis shows the percentage of VE while the Y-axis is separated into different sections. The two main sections refer to the number of vaccinations and are denoted as '2 doses' and '3 doses. The section for '2 doses' is further divided into subsections that refer to the past time since vaccination while numbers relate to VE within this month, e.g., '2 month' represents VE after 31 to 60 days. Consequently, these subsections reveal VE of 2 doses over time. Point estimates and 95% error bars of VE from each study are shown in different colours. Error bars with an arrow towards the zero-line mark non-significant estimations of VE.

Figure 2 reveals that VE after 2 doses is waning towards zero after 6 months and within 6 months classified between 10% and 25%. By administering a 3rd dose VE recovers and ranges from 54% to 82%. Error bars reveal that estimates of VE largely differ in terms of precision across studies. The most obvious reasons might be different sample sizes since earlier studies report lower sample sizes as Omicron cases had just been on the rise. Accordingly, studies published in 2021 show larger error bars compared to studies in 2022 that were able to estimate VE more precisely.[g] Further reasons might refer to study

[f] https://ourworldindata.org/grapher/covid-vaccine-doses-by-manufacturer last accessed on 4th February 2022

[g] An example of increasing precision over time with an increasing sample size is shown in Figure 4 in the appendix.

design, estimation method or estimation adjustments. For most studies, VE estimations were adjusted at least for age, sex, comorbidities, and previous infections.

One of the earliest studies investigating VE against Omicron infection in England revealed a VE decreasing from 88% within the second month after vaccination to a non-significant VE after 5 months that recovered after a 3rd dose up to 75%. High uncertainty within this study is most likely due to a small sample size of 581 Omicron cases.[56] With even higher uncertainty about VE over time, rapidly declining VE after 2 doses against Omicron infection was found in Denmark.[57] Another study from 2021 in England revealed a VE of 55% against an infection by Omicron only for up to 14 days post second vaccination. However, 14+ days after a third dose VE was estimated to be 54%.[13]

Estimations for the Canadian population revealed a rather low VE of 36% within the second month after 2nd dose that further decreased to 15% in the 6th month and vanished after 6 months. Administering a third dose led to a VE of 61%.[58] Similar results were reported among the Czech population with a VE of 43% up to two months that decreased to 9% in the following months and an increase to 56% after a third dose.[59] A study from the U.S. provided similar results for the Moderna vaccine referring to waning over time and a substantial gain by a third dose.[60] Another study from the CDC reported the highest VE compared to other studies for investigated periods and a VE of 82% after a 3rd dose but still serious waning over time.[61] Most precise estimations and in line with previously mentioned results were provided by the U.K. Health Security Agency [62] that publishes weekly updates about VE on the U.K. government's website[h]. Thus, the latest update was published on the 17th March 2022 and indicated waning of VE against infection after three doses from 62% in the first month to 40% after 4 months while waning seemed to be slower after 3 doses compared to waning after 2 doses.[63] Studies examined in 2022 revealed a monthly decline of VE, likewise studies in 2021, but reported a significant VE up to 6 months after the second dose was administered. However, all studies revealed the importance of a 3rddose to regain VE against an Omicron infection.

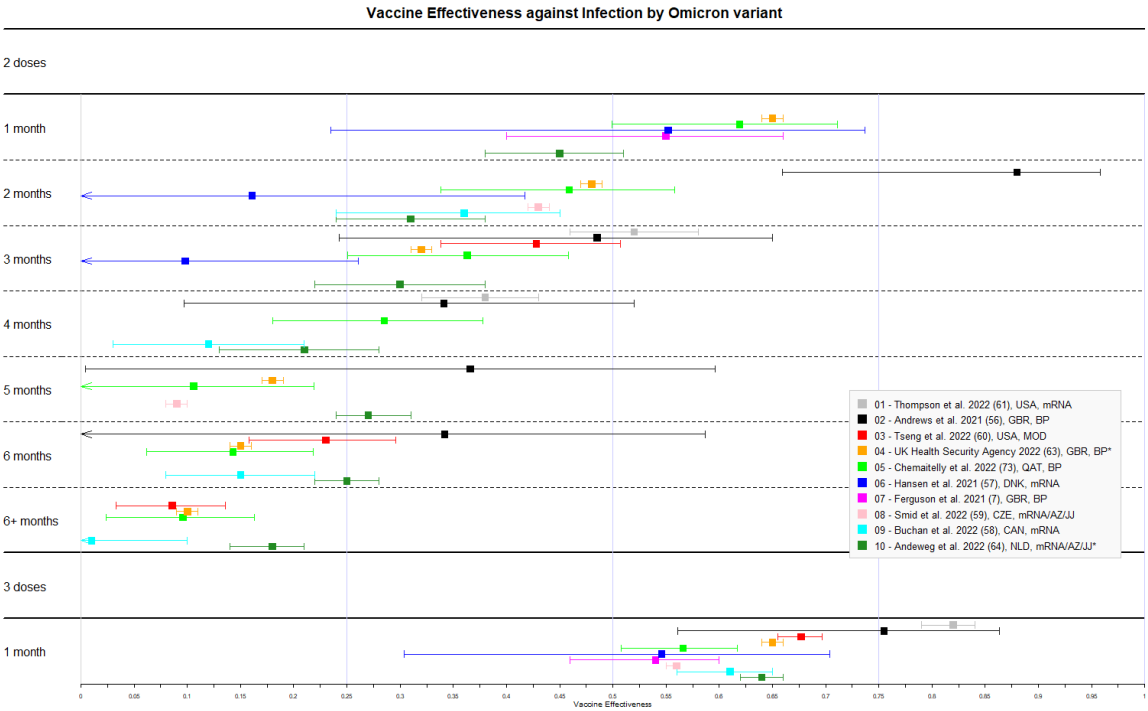
Several studies, not shown in Figure 2, investigated VE for different subgroups, e.g., age groups. Thus, VE for data from Scotland was calculated for two population subgroups. Overall, VE was estimated to be lower for the group of 50 years and older compared to the group covering people between 16 and 49 years. Within this study, VE was estimated by using 2 doses after 25 weeks as the reference group. While VE for the age group 16 to 49 years was estimated to be 53%, 33%, 15% for up to 9, 14, 19 weeks, respectively, VE increased after receiving a 3rd dose to 56% after two weeks. In contrast to this,

[h] https://www.gov.uk/government/publications/covid-19-vaccine-weekly-surveillance-reports last accessed on 24th March 2022

estimation of VE for people with 50+ years only revealed a significant result after a 3rd dose with 57% after two weeks.[42] Referring to a study from the Netherlands, VE seems to be lower for older people after two doses while, on the contrary, after a third dose VE seems to be higher for people over 60 years with about 73% compared to 68% for people between 30 and 59 years and 65% for people from 18 to 29 years.[64] Another study for people 65 years and older, VE of a 3rd dose was 64% and for individuals under 65 years 69%.[60] In contrast to this, there is also a study considering only individuals at the age between 12- and 17-year-old. VE of a third dose was estimated in contrast to individuals who received 2 doses. Accordingly, VE for a 3rd dose was estimated to be 73%.[65] Among U.S. veterans VE against Omicron infection was estimated to be 25% after 2 doses and increased to 62% after receiving a third dose. [66]

Further, several studies, compare VE against infection by Omicron to VE against infection by Delta that all conclude, doubtlessly, that VE against Omicron is much lower while VE against Delta is also waning over time.[54, 58, 62] All estimates of VE were significantly lower for Omicron compared to Delta for different periods after 2 and 3 doses. [54, 58, 61, 67]

Figure 2 Vaccine effectiveness against Omicron infection compared to unvaccinated individuals over time



Source: IHS 2022

Note: Studies consecutively numbered in the box are described by the first author, year, reference number in parentheses, Alpha-3 country code and vaccine manufacturer; *values were not available, thus, values refer to observed values from the original figure

4.2 Vaccine Effectiveness against hospitalization with Omicron

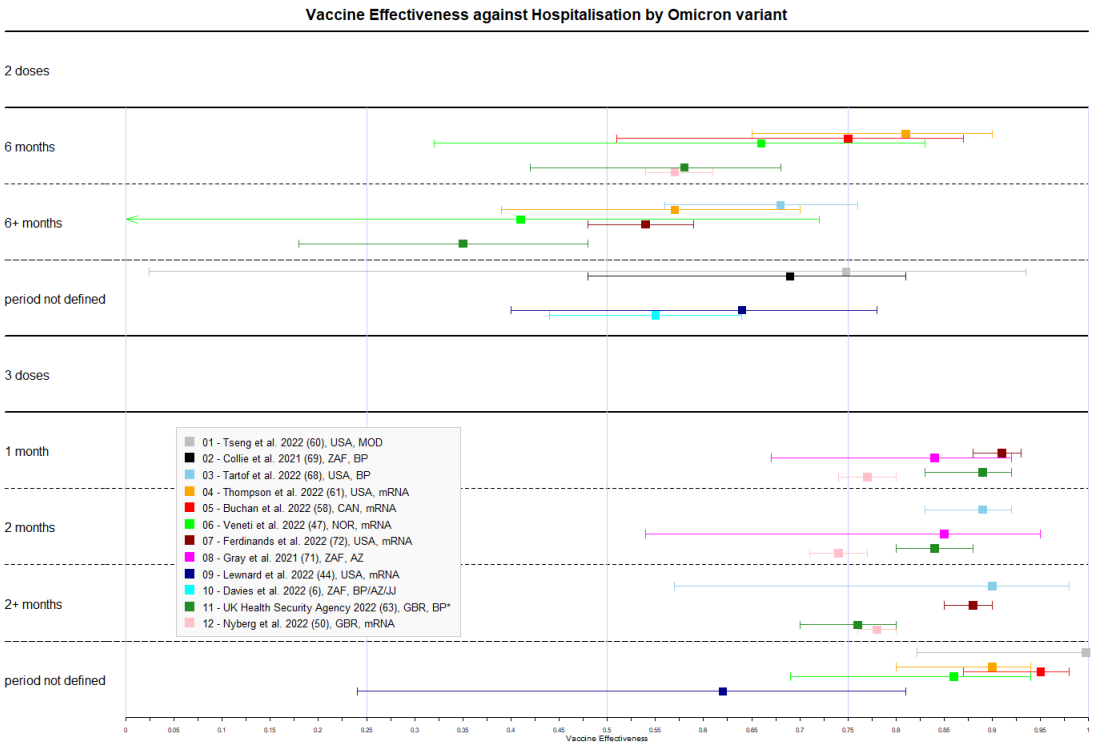
Figure 3 is built like Figure 2 (explained at the beginning of section 4.1) but shows the VE against hospitalization with Omicron and time periods on the Y-axis are chosen differently. Accordingly, VE after 2 doses up to 6 months and after 6 months and VE after a 3rd dose for the first, second and after the second month are displayed. As for both doses studies often do not refer to a clearly defined period a category denoted as 'period not defined' was added. This category mainly represents a mixture of VE for different periods that could not be separated, most likely due to small sample sizes. The number of observations for hospitalization might have been a further issue for less precise estimates of VE. However, Figure 3 reveals VE against hospitalization for populations of 5 countries/regions, namely, Canada, South Africa, the United States, Great Britain, and Norway.

Studies from Canada, U.K., U.S., and Norway revealed a VE of 55% to 80% up to 6 months after the second dose whereby the studies from the U.K. and the U.S. reported a lower VE after 6 months with about 35% and 57%, respectively.[47, 58, 61, 67] On the contrary a study from the U.S. estimates VE close to 70% even after 6 months.[68] Within the Norwegian study it was not possible to estimate VE after 6 months precise enough to reveal a significant result, most likely due to a low number of observations for this period. However, the expected VE after six months was similar within the study for the U.K. and Norway. VE against hospitalization ranges from 55% to 75% among studies without distinguished time periods and much uncertainty for the Moderna vaccine in the U.S.[6, 44, 60, 69]

VE against hospitalization after a third dose ranged from 75% to 90% for most studies independent of the point in time considered.[6, 47, 50, 58, 61, 67, 70, 71] Apart from this, one study from the U.S. revealed a lower VE of 62% with high uncertainty [44] and another study reported a VE with close to 100%.[60] The latter result indicated hardly any hospitalization of people having received a 3rd dose from the Moderna vaccine.

Referring to waning VE against hospitalization over time, studies reporting both, VE up to 6 months and after 6 months, indicated lower VE after 6 months.[47, 61, 67] Considering three doses, two studies claim stable VE within the first months [68, 71], while two studies stressed declining VE over time.[67, 72] Thus, a study from the U.S. reported a VE after 2 doses against hospitalization by 71%, 65%, 58%, 54% after one month, two to three months, four months and five months and more, respectively. Administering a 3rd dose increased VE to 91% in the first month followed by waning to 88% after two to three months and 78% after more than three months.[72]

Figure 3 Vaccine effectiveness against hospitalization by Omicron compared to unvaccinated individuals over time



Source: IHS 2022
Note: Studies consecutively numbered in the box are described by the first author, year, reference number in parentheses, Alpha-3 country code and vaccine manufacturer; *values were not available, thus, values refer to observed values from the original figure

4.3 Vaccine Effectiveness against ICU and death with Omicron

So far, there have been only a few studies reporting the impact of vaccination on severe diseases, e.g., ICU admission, or death. This might be due to a low number of available data for severe outcomes after vaccination. However, a study from South Africa reported a VE against severe admission with Omicron for individuals administered 2 doses of 72% and a VE against death of 76%.[6] By comparing hazard ratios for ICU admission with 2 doses between Omicron and Delta, a study from Canada found a reduced risk of 88% for patients vaccinated with 2 doses for Omicron.[46] A study for Qatar revealed a VE of 80% after 6 months for two doses and 91% after 1 month against severe, critical or fatal disease but did not distinguish between each of the outcomes.[73] An earlier study in Qatar estimated VE to be close to 100%.[74] In the U.K. VE against mortality was 59% after more than 6 months after receiving the second dose and 95% after three doses.[62]

5 Sub-lineage BA.2 and immune response after an infection with Omicron

Since mid of January 2022 a sub-lineage, denoted as BA.2, of Omicron has been gaining attention due to hints of faster spread and potentially lower VE and was classified as 'Variant Under Investigation' in the U.K.[75] The proportion of Omicrons' sub-lineages was estimated to be 32.7% for BA.1, 39.6% for BA.1.1 and 27.7% for BA.2 among all infections in February 2022 in England.[76] First real-world data from the U.K., Denmark, South Africa and Qatar were analysed according to transmission, vaccine effectiveness (VE) and severity of the disease.[62, 75, 77-80] Further, protection after BA.1 infection against reinfection with BA.2 and protection against previous variants was investigated, while the latter only refers to in-vitro studies.[81, 82]

5.1 Sub-lineage BA.2

The generation time of BA.2 was estimated to be 0.85 of the length of BA.1 and the effective reproduction number was mentioned to be 1.26 times larger than that of BA.1 in Denmark, both indicating a faster spread of BA.2 compared to BA.1.[83] Investigation of secondary attack rates in England indicated an attack rate of 13.4% for BA.2 while attack rate for other Omicron lineages was estimated to be 10.3%.[75] Accordingly, in Denmark secondary attack rate within households was reported to be 39% for BA.2 and 29% for BA.1, the initial Omicron lineage.[77] A Danish study revealed significantly higher transmissibility and susceptibility for unvaccinated individuals compared to individuals administered two or three doses for both lineages. Comparing VE against infection of BA.2 relative to BA.1, susceptibility was significantly higher after three doses for BA.2 but not for transmissibility.[77] In contrast to this, in England VE against infection was estimated to be 10% and 18% after two doses after 6 months, 69% and 74% in the first month after a third dose, 61% and 67% in the second month and 49% and 46% after two months for BA.1 and BA.2, respectively.[84] VE against hospitalization with BA.1 after 2 doses was estimated to be 32% after 6 months and after 3 doses VE was estimated to be 83% in the first month, 81% in the second month and 73% after two months while VE after 2 doses against hospitalization with BA.2 was estimated to be 50% after 6 months and after a third dose was estimated to be 87% in the first month, 83% in the second month and 70% after two months.[85] In Qatar, protection against infection from vaccination and prior infection was mentioned to be similar for BA.1 and BA.2. Accordingly, an effectiveness of 50% and 46% after prior infection and an effectiveness of 60% and 52% after three doses were reported for BA.1 and BA.2, respectively.[86] Considering the severity of disease, no significant differences in hospitalization and more severe outcomes, ICU admission and death, between BA.1 and BA.2 were revealed in

South Africa.[78] Additionally, laboratory-based studies reported BA.2 to be more replicative in human nasal epithelial cells and fusogenic than BA.1 and suggested higher transmissibility of BA.2 compared to BA.1 rather than enhanced immune escape.[87, 88] In line with this, in Qatar a significantly lower CT-value was found for BA.2 compared to BA.1 indicating a higher viral load for BA.2.[80]

5.2 Immune response after an infection with Omicron

In Qatar, immune response after an Omicron BA.1 infection was estimated to be effective at a level of 94% against reinfection with BA.2 and effective at a level of 86% the other way round.[81] A Danish study investigating reinfections with BA.2 after more than 20 days and less than 60 days of a BA.1 infection mentioned that reinfections were more likely in unvaccinated and younger population but investigated sample size was small.[89] An in vitro study among 27 people in South Africa reported that protection after Omicron infection against prior variants, Beta and Delta, was significantly higher for vaccinated people compared to unvaccinated while effectiveness against reinfection with Omicron seems to be unaffected by vaccination.[90] Similarly, an investigation in India found substantial levels of neutralising antibodies against BA.1, BA.2 and Delta after an Omicron infection but low levels of neutralising antibodies after a Delta infection against Omicron.[82] In line with this, another in-vitro study, comparing immune responses after Delta and BA.1, reported neutralising antibody responses to be weakest against BA.2 after a Delta infection while immune response after BA.1 was similar against BA.2 and Delta. Convalescent neutralisation titers were generally lower for unvaccinated compared to vaccinated people.[91]

6 Conclusions

Evidence for characteristics of the SARS-Cov-2 variant Omicron evolved quickly. Early estimations of doubling times in November and December ranged from 2 to 3 days, a serial interval of 2 to 3 days, an incubation period of about 3 to 4 days and a reproduction number of 1.9 marked the Omicron wave in December and January in many countries.[11, 18, 20] Higher infectiousness was revealed by secondary attack rates in Denmark and the U.K. [26, 77] that is mainly based on immune escape and not on higher viral loads. [33-35] Accordingly, epidemiological parameters referring to infections for Omicron were affected much more by non-pharmaceutical interventions (NPIs) than vaccination rates. Referring to this, the estimated doubling time for Australia was expected to be higher compared to Denmark due to a higher level of NPIs in Australia at the time of calculation. Nevertheless, secondary household attack rates were mentioned to be reduced for individuals after a third dose indicating importance of a 3rd dose to counter immune evasion.[27] To summarize, Omicron was spreading faster than previous variants mainly due to immune escape.[10, 11, 20, 27] Roughly spoken, more susceptible individuals were available compared to Delta, where vaccination was more effective. [11, 27 21]

Early investigations in South Africa and the U.K. gave a hint that the risk of hospitalization with an Omicron infection is lower compared to Delta but with the limitation of not being able to adjust for vaccination and previous infection.[2, 42] Later on, studies revealed a risk reduction of 50% to 80% for Omicron compared to Delta for being hospitalized. On the one hand, studies show the positive impact of vaccination and previous infection on the risk of a severe outcome, on the other hand, they reveal that the assumptions about undocumented previous infections and incidental findings of infection affect estimated effect size.[6, 56] While undocumented previous infections are suggested to further reduce risk, incidental findings are mentioned to lead to an underestimation of risk reduction.[46] Amount of risk reduction is mentioned to be higher for the younger population, although one study indicates that incidental findings of an infection at the time of hospitalization are more likely for older adults.[46, 48] Nonetheless, it is revealed that length of hospital stay is shorter for Omicron compared to Delta.[44, 45] Considering ICU admission by Omicron risk is reduced by 65% to 85% and risk for death is estimated to be reduced by 75% to 85%. Referring to the latter, in some studies, it was mentioned that numbers of ICU admissions and deaths due to Omicron were too low to estimate risk ratios.[51 48] The latter further supports the evidence of considerably lower severity of Omicron.

Vaccine effectiveness against Omicron can be summarized by three main findings. First, VE against infection is about 55% to 65% only within the first month after receiving the 2nd dose. Thereafter, VE is waning over time to a VE of 10% to 25% up to 6 months after the second dose. Administering a 3rd dose increases VE up to 55% to 70% with two

studies reporting an even higher VE of 76% and 82%.[56, 61] Second, VE against hospitalization was estimated to be 55% to 80% after 2 doses up to 6 months. A third dose increased VE up to about 85% with some indications of waning over time. Third, hardly any study considering VE for ICU admission or death was available, most likely due to low numbers of ICU admissions and deaths for Omicron after receiving at least 2 doses. However, studies were hard to compare in more detail since there are many differences between countries, e.g., population characteristics, availability of vaccines by manufacturer, and, depending on data availability, possibilities to adjust estimation of VE. However, in the end, findings were similar, and no contradicting findings were revealed. Nonetheless, sample sizes were very different and, thus, some studies were able to estimate VE only with high uncertainty. Referring to this, within a study from Canada it was revealed how estimates become more precise in the second version of the paper with increased sample size.[58] While this is overall good news, it is likely and indicated in the most recent study from the U.K. Health Security Agency[63, 85] that VE will wane similarly to previous variants.

Sub-lineage BA.2 revealed higher secondary attack rates in England and higher household attack rates in Denmark, so far.[67, 75, 77] According to the report from the U.K., VE after a third dose seems not to be affected significantly by BA.2 compared to BA.1 even though estimates of VE against BA.2 infection have been subject to higher uncertainty so far. Accordingly, waning immunity has to be considered as one possible reason for higher susceptibility after three doses for BA.2 compared to BA.1 as time since vaccination is not considered in the Danish study. Generally, studies suggest transmission advantages of BA.2 compared to BA.1 rather than increased immune escape.[80, 87] Further, a study among the population in South Africa reported no significant differences between BA.1 and BA.2 referring to the severity of the disease.[78] Nonetheless, immune response after Omicron infection seems to be effective against its different lineages and previous variants, especially for vaccinated people.[81] Thus, vaccination is mentioned to significantly improve immune response after infection.

7 Policy implications and future perspectives

Established immunization against infection by vaccination and/or previous infection was revealed to be less protective against Omicron than against previous coronavirus variants, but still provide good protection against severe outcomes. The risk of severe outcomes, such as hospitalization, ICU admission or death in general seems to be reduced with Omicron compared to Delta. In addition, being vaccinated thrice reduces the previously mentioned risks significantly and immune response to different SARS-CoV-2 variants after an infection seems to be further improved by vaccination. Accordingly, populations with high immunization levels, specifically within groups that are associated with a higher risk of severe outcomes, are not expected to be burdened by a high number of infected individuals as few of these will be admitted to the hospital or ICU. Thus, it is very important to ensure that risk groups, e.g., older adults, people with certain comorbidities, gained immunization by vaccination to further reduce the risk of hospitalization and ICU admission. Given the strong effect of a third dose on vaccine effectiveness, three doses should be considered “full vaccination” rather than two. Immunization gaps within risk groups are expected to be more challenging for health systems than within younger population. This claim is justified by simple considerations of risk ratios revealed in this manuscript. In addition, a high incidence increases the risk of an infection for an exposed individual who is more likely to experience a severe course. Consequently, getting an infection after being vaccinated is mentioned to comprise more issues for the environment than the person itself.

It seems advisable that countries remain aware of immunity levels within their population to consider the necessity of additional measures. Additionally, with reduced NPIs, monitoring the spread of Omicron and the detection of future variants will be necessary to act quickly enough if case numbers surge again.

Given waning immunity but also good vaccine effectiveness after 3 doses against new variants so far, a vaccination strategy should be devised such that the pool of susceptible individuals is lowest when the next wave will likely hit.

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9 Appendix

Table 1. Data according to Figure 1

		Severity of disease	
Study	**95% Confidence Interval**	**hospitalization**	**ICU**
Auvigne et al. 2022, FRA	**mean**		**87%**
	lower		82%
	upper		91%
Bager et al. 2022, DEN	**mean**	**36%**	
	lower	25%	
	upper	44%	
Davies et al. 2022, ZAF	**mean**	**28%**	**57%**
	lower	18%	45%
	upper	37%	67%
Hussey et al. 2022, ZAF	**mean**	**44%**	
	lower	9%	
	upper	66%	
Lewnard et al. 2022, USA	**mean**	**53%**	
	lower	38%	
	upper	65%	
Nyberg et al. 2022, GBR	**mean**	**59%**	
	lower	57%	
	upper	61%	
Peralta-Santos et al. 2022, PRT	**mean**	**75%**	
	lower	57%	
	upper	85%	
Sheikh et al. 2021, GBR	**mean**	**68%**	
	lower	48%	
	upper	81%	
Ulloa et al. 2022, CAN	**mean**	**65%**	**83%**
	lower	54%	63%
	upper	74%	92%
Veneti et al. 2022, NOR	**mean**	**73%**	
	lower	64%	
	upper	80%	
Wang et al. 2022, USA	**mean**	**56%**	**67%**
	lower	48%	52%
	upper	62%	77%
Wolter et al. 2021, ZAF	**mean**	**80%**	**70%**
	lower	70%	50%
	upper	90%	80%

Source: IHS 2022

Table 2. Data according to Figure 2

Study	95% Confidence Interval	Period since 2 doses: 1 month	2 months	3 months	4 months	5 months	6 months	6+ months	Period since 3 doses: 1 month
Andeweg et al. 2022, NLD, mRNA/AZ/JJ*	**mean**	**45%**	**31%**	**30%**	**21%**	**27%**	**25%**	**18%**	**64%**
	lower	38%	24%	22%	13%	24%	22%	14%	62%
	upper	51%	38%	38%	28%	31%	28%	21%	66%
Andrews et al. 2021, GBR, BP	**mean**		**88%**	**49%**	**34%**	**37%**	**34%**		**76%**
	lower		66%	24%	10%	0%	-5%		56%
	upper		96%	65%	52%	60%	59%		86%
Buchan et al. 2022, CAN, mRNA	**mean**		**36%**		**12%**		**15%**	**1%**	**61%**
	lower		24%		3%		8%	-8%	56%
	upper		45%		21%		22%	10%	65%
Chemaitelly et al. 2022, QAT, BP	**mean**	**62%**	**46%**	**36%**	**29%**	**11%**	**14%**	**10%**	**57%**
	lower	50%	34%	25%	18%	-2%	6%	2%	51%
	upper	71%	56%	46%	38%	22%	22%	16%	62%
Ferguson et al. 2021, GBR, BP	**mean**	**55%**							**54%**
	lower	40%							46%
	upper	66%							60%
Hansen et al. 2021, DNK, mRNA	**mean**	**55%**	**16%**	**10%**					**55%**
	lower	24%	-21%	-10%					30%
	upper	74%	42%	26%					70%
Smid et al. 2022, CZE, mRNA/AZ/JJ	**mean**		**43%**			**9%**			**56%**
	lower		42%			8%			55%
	upper		44%			10%			56%
Thompson et al. 2022, USA, mRNA	**mean**			**52%**	**38%**				**82%**
	lower			46%	32%				79%
	upper			58%	43%				84%
Tseng et al. 2022, USA, MOD	**mean**			**43%**			**23%**	**9%**	**68%**
	lower			34%			16%	3%	66%
	upper			51%			30%	14%	70%
U.K. Health Security Agency 2022, GBR, BP*	**mean**	**65%**	**48%**	**32%**		**18%**	**15%**	**10%**	**65%**
	lower	64%	47%	31%		17%	14%	9%	64%
	upper	66%	49%	33%		19%	16%	11%	66%

Source: IHS 2022

Note: *values were not available, thus, values refer to observed values from the original figure

Table 3. Data according to Figure 3

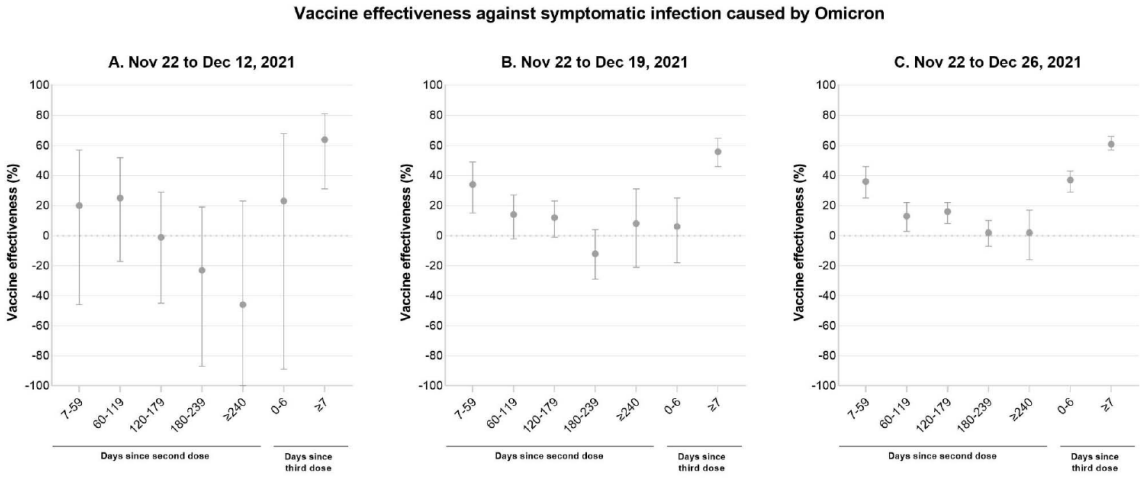
		Period since 2 doses			Period since 3 doses			
Study	**95% Confidence Interval**	**6 months**	**6+ months**	**period not defined**	**1 month**	**2 months**	**2+ months**	**period not defined**
Buchan et al. 2022, CAN, mRNA	**mean**	**75%**						**95%**
	lower	51%						87%
	upper	87%						98%
Collie et al. 2021, ZAF, BP	**mean**			**69%**				
	lower			48%				
	upper			81%				
Davies et al. 2022, ZAF, BP/AZ/JJ	**mean**			**55%**				
	lower			44%				
	upper			64%				
Gray et al. 2021, ZAF, AZ	**mean**				**84%**	**85%**		
	lower				67%	54%		
	upper				92%	95%		
Lewnard et al. 2022, USA, mRNA	**mean**			**64%**				**62%**
	lower			40%				24%
	upper			78%				81%
Nyberg et al. 2022, GBR, mRNA	**mean**	**57%**			**77%**	**74%**	**78%**	
	lower	54%			74%	71%	76%	
	upper	61%			80%	77%	80%	
Tartof et al. 2022, USA, BP	**mean**		**68%**			**89%**	**90%**	
	lower		56%			83%	57%	
	upper		76%			92%	98%	
Thompson et al. 2022, USA, mRNA	**mean**	**81%**	**57%**					**90%**
	lower	65%	39%					80%
	upper	90%	70%					94%
Tseng et al. 2022, USA, MOD	**mean**			**75%**				**100%**
	lower			2%				82%
	upper			94%				100%
U.K. Health Security Agency 2022, GBR, BP*	**mean**	**58%***	**35%***		**89%***	**84%***	**76%***	
	lower	42%*	18%*		83%*	80%*	70%*	
	upper	68%*	48%*		92%*	88%*	80%*	
Veneti et al. 2022, NOR, mRNA	**mean**	**66%**	**41%**					**86%**
	lower	32%	-22%					69%
	upper	83%	72%					94%

Source: IHS 2022

Note: *values were not available, thus, values refer to observed values from the original figure

Figure 4. Screenshot of Buchan et al. 2022 showing more precise estimates over time with an increasing sample size

Figure 2. Estimates of vaccine effectiveness (VE) against symptomatic Omicron infection by cumulative time period to demonstrate the impact of adding data from successive weeks to VE estimates (panel A: November 22 to December 21, 2021; panel B: November 22 to December 19, 2021; panel C: November 22 to December 26, 2021)



The lower 95% confidence limit for vaccine effectiveness against symptomatic Omicron infection ≥240 days after a second dose was -174

Source: Buchan et al. 2022[58], Figure 2