SUNDHEDSSTYRELSEN

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Assessment of population immunity to SARS-CoV-2 in Denmark

On 11 March 2020, the World Health Organization, WHO, declared the COVID-19 outbreak a pandemic. As the condition was caused by a novel virus disease in humans, no part of the world population had achieved protective immunity, and the pandemic therefore spread rapidly, also in Denmark. Subsequently, immunity in the Danish population has increased considerably owing to comprehensive vaccination coverage and because a large share of the population has become infected with SARS-CoV-2.

SARS-CoV-2 is an unstable virus, and several different variants of the virus have dominated during the pandemic. The Delta variant was dominant from the summer to the winter of 2021 and proved to be more infectious and more pathogenic (virulent) than any of the previous variants. Concurrently, vaccine-induced immunity proved to be less effective in preventing transmission with the Delta variant, whereas it provided strong protection against serious COVID-19 disease following infection with the Delta variant.

The Omicron variant spread in Denmark from late November 2021 at a previously unseen speed and has been the vastly predominant variant in Denmark since late December 2021. The rapid spreading of the Omicron variant was probably due to various factors, including the ability of the variant to evade the immunity achieved by vaccination and infection (immune escape), that less time passes from infection with the variant before a person may transmit the virus, that the variant more effectively infects the upper airways and that a greater share of those infected are asymptomatic or only slightly symptomatic. Additionally, the immunity induced by Omicron infection has proven to be highly effective in preventing infection with the more virulent Delta variant, which has therefore been repressed in Denmark.

The Omicron variant hit Denmark at a time when we had already established a high level of population immunity, either through infection (acquired immunity) with SARS-COV-2 or vaccination (induced immunity). The extremely high primary vaccination coverage reached in Denmark in the autumn of 2021 along with the extended and advanced booster vaccination programme initiated in the early winter of 2021 contributed considerably to the strong population immunity that Denmark enjoyed at the beginning of the 2021/22 winter season. We assess that this starting point has been pivotal in ensuring that Denmark has fared well in the

current third wave, avoiding overly comprehensive social restrictions and limiting the disease burden.

Our understanding of the pandemic is challenged by the dominance of the Omicron variant, the comprehensive community infection observed and the special characteristics of the variant including immune escape, increased infectiveness and a considerably reduced virulence. In this light, we have re-assessed both the risk and the measures needed to continue preventing a high COVID-19 disease burden. A pivotal element in this understanding is assessing the strength and duration of population immunity. In the following, we therefore aim to describe and estimate population immunity.

The below presentation should be considered in conjunction with our previous assessments from June, September and November 2021 when we prepared population immunity estimates for Denmark as part of the efforts made to lay the groundwork for our previous decisions about the target groups for and timing of the vaccination efforts made[1]. These previous estimates were prepared to elucidate possible levels of population immunity as a basis for assessments of, e.g., vaccination offers for children or booster vaccination for adults.

About epidemics

Infectious diseases may occur sporadically, endemically or epidemically. Sporadic occurrence is when a disease only occurs rarely, at random and displays no clear pattern. Tetanus (lockjaw) and rabies are examples of infectious diseases that may occur sporadically in Denmark.

Endemic occurrence is when a relatively constant base level of infection is observed in a geographical area or in a population group without cases being imported to the affected group. Chicken-pox is an example of an endemically occurring disease in Denmark.

Mathematically, endemics may be described by the basic reproduction number (R_0 - pronounced “R naught”), i.e. the number of persons that an infected person will him- or herself infect in a population in which everyone is susceptible (non-immune). If R_0 equals 1 in a population in which everyone is susceptible, the prevalence of the disease will remain constant. If only part of the population is susceptible, then the effective contact number (R_e) needs to be equal to one for infections to remain constant. R_e is calculated as R_0 multiplied by the share of susceptible people.

[1] Danish Health Authority, 17 June 2021, Concerning vaccination of children aged 12-15 years (Sundhedsstyrelsen, 17. juni 2021, Vedr. vaccination af børn på 12-15 år), Danish Health Authority, 28 September 2021, Concerning COVID-19 booster vaccination (Sundhedsstyrelsen, 28. september 2021, Vedr. revaccination mod covid-19), Danish Health Authority Concerning booster vaccination of persons aged 18 years or more, 25 November 2021 (Sundhedsstyrelsen Vedr. revaccination af personer på 18 år og derover, d 25. november 2021) and Danish Health Authority, 26 November 2021, concerning vaccination of children aged 5-11 years (Sundhedsstyrelsen, 26. november 2021, Vedr. vaccination af børn på 5-11 år).

In endemic spreading, an infectious disease spreads more rapidly and more comprehensively than the normal base level. Influenza, RS virus, norovirus (acute infectious gastroenteritis) and COVID-19 are examples of epidemic diseases in Denmark. The concepts of outbreak and epidemic are often used interchangeably. However, in Danish language, an *outbreak* (udbrud) is typically a more limited and delimited occurrence of infection, whereas *epidemic* (epidemi) is the term used to describe more comprehensive community transmission. An epidemic wave describes a period with persistent exponentially increasing transmission followed by a corresponding persistent decline. Mathematically, an epidemic wave may therefore be described as an extensive unbroken period (e.g., several weeks) with $R > 1$ followed by another extensive and unbroken period in which $R < 1$.

An infectious disease may shift between being endemic and epidemic, as is the case in Denmark for RS virus or influenza, which are characterised by seasonal variation with nationwide epidemics in the winter season and more limited epidemics occurring in some population groups, e.g., in daycare institutions or at nursing homes, etc.

A pandemic is a global epidemic caused by a novel disease that spreads across borders and spans regions and continents. Influenza epidemics, which are seasonal and occur concurrently in many countries, are not considered pandemics. Even so, if a new type of influenza virus, for which the global perceptibility is higher, spreads across borders, it may be considered a pandemic.

Criteria published by the World Health Organization (WHO) denote an influenza pandemic as probable when sustained community infection is seen by a new influenza strain in a minimum of two countries; and a current influenza pandemic is when community infection with the same new virus strain is observed in a minimum of two WHO regions. The so-called “Spanish disease” (the 1918-1920 influenza pandemic) and COVID-19 are examples of pandemics.

Pandemics caused by virus diseases such as influenza may cause comprehensive morbidity and mortality, and are typically seen several times each century. Thus, influenza pandemics were recorded in 1918-20, 1957-58, 1968-69, 1977-79 and 2009-10. Influenza pandemics arise when new variants of influenza virus spread from animals (e.g., pigs or ducks) to humans, who are susceptible because any extant immunity from previous infection or vaccination is insufficient. As a pandemic spreads, effective population immunity will follow, and the new influenza variant will eventually become endemic and give rise to seasonal influenza epidemics.

As is the case for pandemic influenza, SARS-CoV-2 has spread from animals to humans (zoonosis), probably originating from bats. SARS-CoV-2 may also be transmitted back from humans to animals as we observed with the Danish mink population.

In humans, coronavirus was initially described one hundred years ago, but it probably existed long before that. Currently, seven strains are known that may cause disease in humans. Four

of these strains cause common cold, in Denmark as elsewhere. Since 2003, three new zoonotic strains have been detected that may cause serious disease in humans. These strains are characterised by severe lower airway infection (pneumonia and pulmonary damage) as the typical clinical manifestation. The diseases were coined SARS, MERS and COVID-19. SARS has not been observed in humans since 2004. Since its appearance in 2012, MERS has only caused limited outbreaks.

The virus causing COVID-19 is termed SARS-CoV-2. As is the case for other viruses, the characteristics of SARS-CoV-2 constantly change due to changes (mutations) in its genetic makeup (RNA) that arise due to errors during repeated RNA copying as the virus replicates. If the RNA mutations are advantageous to the virus, the mutations may gain foothold as a new virus variant. As RNA codes for the virus' surface proteins (antigens), mutations may give rise to more or less significant changes in the properties of the virus (so-called *antigen drift*), including the ability of the virus to infect specific cells in the body and the body's ability to neutralise virus with antibodies and immune cells.

Population immunity

Immunity to a virus disease like COVID-19 may be acquired by passing the infection. Immunity may also be induced by vaccination or added by antibodies in the form of plasma products from other persons who have passed the infection or by industrially produced monoclonal antibodies.

The immunity activated by vaccination and infection alike is both cell-borne (cellular) and plasma-borne (antigens). During an infection, the body's immune cells (among others lymphocytes, a type of white blood cells) are exposed to the surface proteins of the virus (antigens). Vaccination uses the same principle, as the immune cells are stimulated, e.g., by live but attenuated whole virus, inactivated dead virus, synthetically produced antigens or where the vaccine stimulates the production of antigens in the cells of the body (mRNA vaccines).

Several types of lymphocytes exist. B lymphocytes are stimulated to form neutralising antibodies that are released into the blood stream, whereas T lymphocytes are activated either directly to break down cells that have become infected by virus or indirectly by stimulating B cells. Whereas antibodies are gradually degraded in the body, cellular immunity may have "memory" and may therefore be prolonged. The different types of immunity may also explain differences in, e.g., the strength and duration of different types of protection against infection, disease, etc.

The strength and duration of immunity, both acquired by infection and induced through vaccination, may vary from one infectious disease to the next and from one variant of a single virus to another. Thus, you acquire lifelong immunity after having diseases like measles,

mumps, chicken-pox or mononucleosis; and you will also enjoy lifelong immunity after vaccination against, e.g., measles, mumps, polio and small pox. Other vaccines, such as tetanus need to be boosted at multiple-year intervals to uphold their protective effect, whereas vaccinations against diseases characterised by considerable *antigen drift*, e.g. influenza, need to be changed continually to provide protection against new variants.

Several factors thus affect the strength and duration of both acquired and induced immunity, including vaccine technology, virus properties and the characteristics of the condition. In many cases, including COVID-19, it is therefore important not to understand immunity as an absolute entity, according to which you are either immune or non-immune, but as a continuum where immunity may be of varying strength and duration. Individual factors may also play a part, including age as the immune system is generally weakened with time; and disease or treatment that compromises the immune response.

The very rapid growth and dominance of the Omicron variant is due to several characteristics of this virus variant, but the immunity conditions are pivotal to understanding the dominance of the new variant. Omicron is a so-called *immune escape* variant because comprehensive mutations in the code for the *spike* surface protein weaken the ability to neutralise the virus of both vaccine-induced immunity (based on *spike*) and acquired immunity from previously dominant variants. In contrast, the immunity acquired by people who become infected by Omicron seems to have a strong effect on Delta infection, which probably plays a part in explaining how Omicron has repressed the previously dominant variant so rapidly.

The overall immunity against COVID-19 in the population is comprised by infection-acquired and vaccine-induced immunity, and many citizens will have hybrid immunity owed to vaccination as well as infection, and possibly also re-infection with new variants.

Additionally, some measure of cross immunity may be expected, i.e. that immunity developed after vaccination against or infection by other variants may provide partial protection against the condition, particularly against serious COVID-19 and death, even though the virus has changed.[2] Cross immunity is also known from other viruses, e.g., influenza virus where a sufficiently high level of immunity is achieved at the population level owing to cross immunity following previous infection/vaccination and where repeated vaccination campaigns may therefore be targeted at selected risk groups who carry an increased risk of running a serious disease course.

We have previously prepared population immunity estimates in Denmark to determine possible levels of immunity in the population as a basis for assessments of, e.g., vaccination offers for children or booster vaccination of adults. We then used the concept of population immunity as an umbrella term describing the overall expected level of immunity in the population,

[2] Knowledge Paper on Infection with and Evolution of the Virus 12 Sep 2021 (Videnspapir om smitte og virusevolution 12 Sep 2021): https://fm.dk/media/25159/videnspapir-smitte-og-virusevolution.pdf.

stated on the basis of knowledge about the number of vacinees and their vaccination status, and knowledge about the number of persons who have become infected with SARS-CoV-2. We aimed to estimate approximate levels of population immunity at relevant time points during the epidemic and to illustrate how expanding the vaccination programme would contribute to the total population immunity.

The concept of population immunity is occasionally used interchangeably with the concept of herd immunity. However, herd immunity is used with several different meanings, and is thus, among others, used to describe both specific epidemic control strategies, to denominate only infection-acquired immunity and to describe the epidemic threshold level (see page 2). In the following, we have therefore generally used the concept of population immunity to denominate the total immunity achieved from all sources, whereas we will be using the concept of herd immunity threshold to describe the theoretical level of an epidemic[3], cf. also page 2.

For relatively stable viruses with no animal reservoir, and for which the acquired or induced immunity is strong and long-lasting, a population immunity that exceeds the herd immunity threshold may mean that the disease may be curbed by *elimination* (reduction to no or very few cases within a geographical area), which may, in turn, lead to its *eradication* (complete and permanent reduction to no cases world-wide). In 1979, small-pox was eradicated thanks to a global vaccination effort, and polio is also close to being eradicated. Measles and rubella have been eliminated in Denmark through the childhood vaccination programme, which means that these diseases can no longer circulate in Denmark periodically and that any outbreaks based on imported cases can rapidly be controlled. For the very infectious measles disease, this is possible owed to the extremely high Danish vaccination coverage, of nearly 95%[4].

As SARS-CoV-2, in line with influenza, is an unstable virus with potentially large animal reservoirs, current knowledge and available technologies are unlikely to eliminate COVID-19, and even less likely to eradicate the condition in a globalised world.

Even so, it is important to describe the strength and duration of population immunity to SARS-CoV-2 in Denmark and internationally, as both the transmission of the infection and the disease burden may be controlled at acceptable levels by population immunity.

The COVID-19 pandemic in Denmark

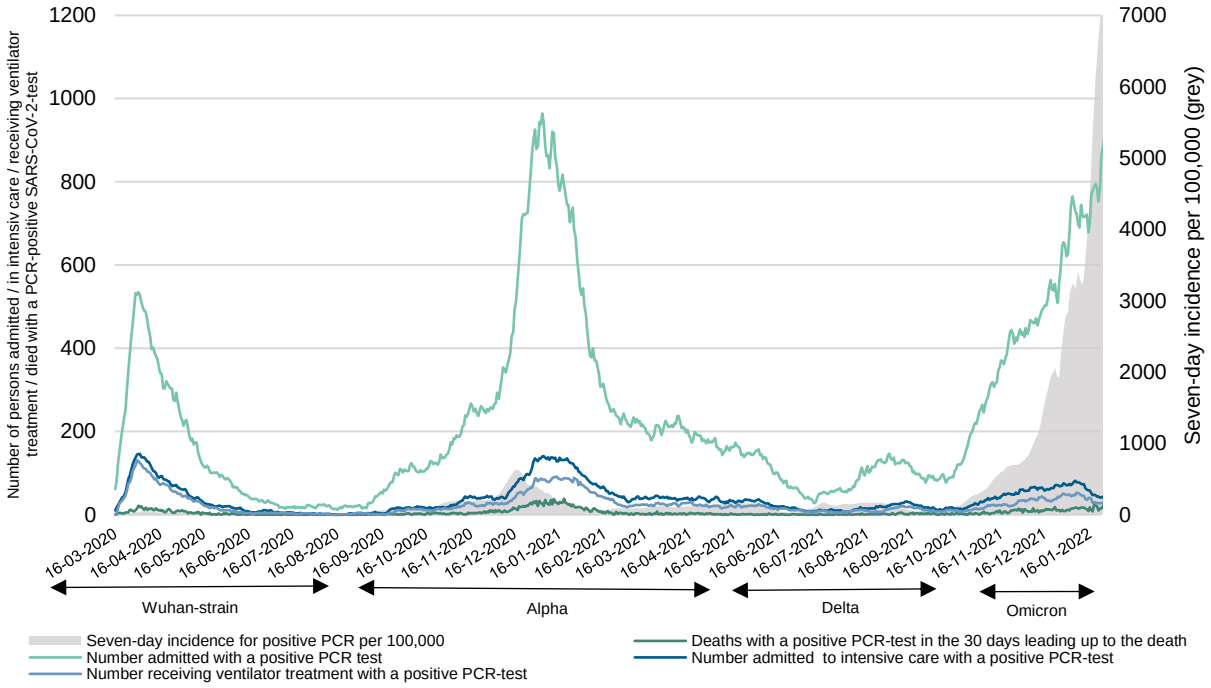
The importance of COVID-19 for the disease burden and hospital capacity in Denmark may be illustrated by various different types of data reports, each of which comes with a number of advantages and drawbacks. Figure 1 provides an overview of the number of persons who have

[3] Fine P, Eames K, Heymann DL. "Herd Immunity": A Rough Guide. Clin Infect Dis. 2011 Apr 1;52(7):911-6

[4] MMR1, Vaccination coverage - Monitoring in figures, graphs and maps (ssi.dk) (MFR 1, Vaccinationstilslutning - Overvågning i tal, grafer og kort (ssi.dk).

tested positive to SARS-CoV-2 by PCR throughout the pandemic, and the share hereof who have been admitted to hospital, to an intensive care unit or have died. The four virus variants that have been dominant in Denmark in the various stages of the epidemic are shown in the figure. In the course of the pandemic, reports may have been affected by shifts in testing activity, including changing guidelines for screening tests of admitted patients.

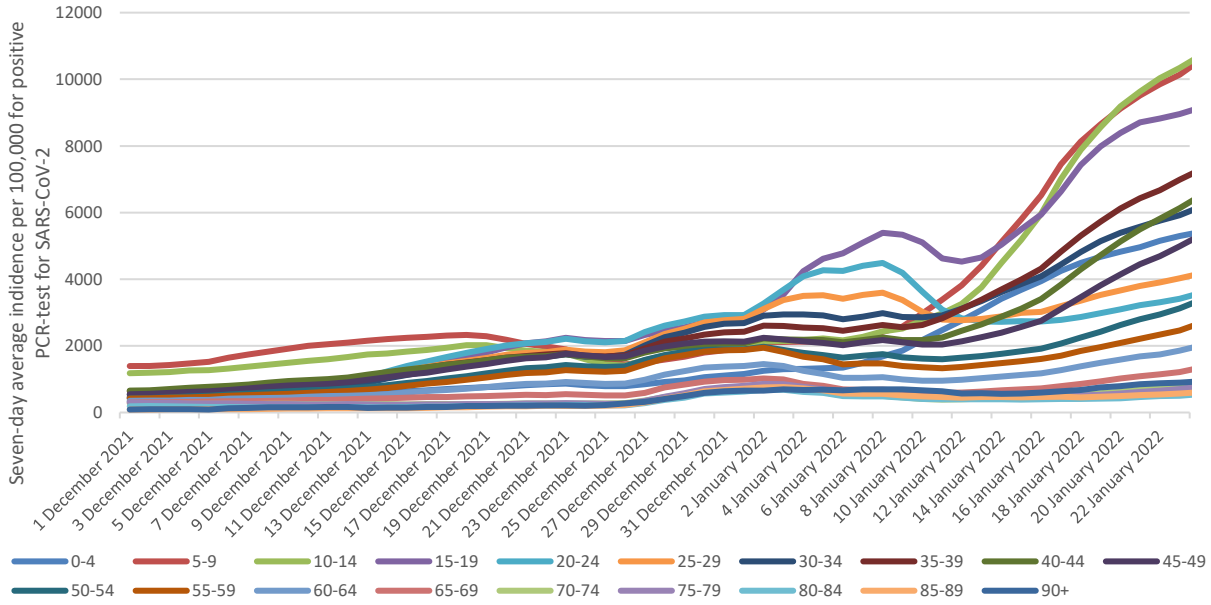
Figure 1. Test incidence, admitted, and deceased with a SARS-CoV-2 positive PCR test, calculated as per 24 January 2022.



Note for Figure 1: Patients were included if they had a SARS-CoV-2-positive PCR test conducted within the 14 days leading up to their admission or during their admission. The number of patients admitted to an intensive care unit is comprised by the total number of patients admitted to hospital, and the number of patients receiving ventilator treatment is comprised by the number of patients admitted to an intensive care unit. Data on deaths are stated as deaths occurring within 30 days from a SARS-CoV-2-positive PCR test.

During the pandemic, both the Southern and the Northern Hemisphere have observed a clear seasonal variation, with epidemic development at our latitude being observed at the transition from autumn to winter, though it should be noted that the first wave hit Denmark at the transition from winter to spring. Currently, the third epidemic wave is still following an increasing trend.

Figure 2. Test incidence by age groups, calculated as per 24 January 2022



Presently, the highest test incidence and the largest increase in the number or patients with a SARS-CoV-2-positive PCR test is seen among children and adolescents below 20 years of age, which is probably related to the return to schools, recreative activities, etc.Also of note, an interesting stabilisation is seen of the test incidence among 20-29-year-olds, who may be expected to have a high number of daily contacts. This may be an indication of a high immunity in this age group.

Furthermore, the test incidence among persons aged 50 years or more has levelled out, which may both be because of the very high booster vaccination rate in the oldest part of the Danish population and because of a high measure of transmission-preventive behaviour.

Earlier in the epidemic, we observed a very close association between test incidence and number of persons admitted to hospital with a SARS-CoV-2 positive PCR test, but now this association is less clear. This decoupling is probably owed to the comprehensive population immunity achieved and the reduced ability of the Omicron variant to cause disease (virulence). Particularly, a very clear decoupling is observed between test incidence and the number of patients admitted to an intensive care unit with a SARS-CoV-2-positive PCR test.

Contribution from acquired infection

Table 1 presents the number of persons in Denmark who, in the course of the pandemic, have tested PCR-positive to SARS-CoV-2, by age groups.

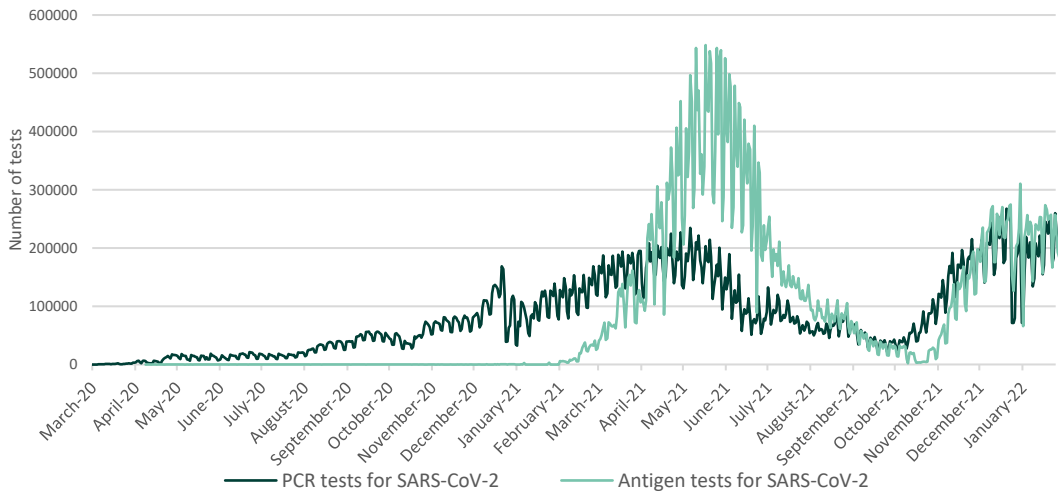
Table 1. Test incidence by age groups, calculated as per 24 January

Age group (years)	Population 4th quarter 2021	First-time PCR positive to SARS-CoV-2	Share
0-4	311,093	74,018	24%*
5-17	839,838	348,887	42%
18-39	1,634,256	501,895	31%
40-64	1,893,507	406,190	21%
65-79	904,301	79,443	9%
80+	291,906	26,555	9%
Total	**5,874,901**	**1,436,988**	**24%**

*In the course of the pandemic, low testing activity has been observed in the age group. Therefore, the dark figure is probably relatively higher in this age group than in other age groups.

Throughout the pandemic, the test criteria and recommendations as well as age limits, supply and demand have varied extensively. The varying testing activity appears from Figure 3. The test incidences should therefore be interpreted with caution, and the number of persons who have tested PCR-positive to SARS-CoV-2 in the course of the pandemic (Table 1) should be considered a minimum estimate of the acquired population immunity during the pandemic. Many persons may have become infected with SARS-CoV-2 without testing positive; this so-called "dark figure" needs to be taken into account.

Figure 3. Daily tests calculated as per 24 January 2022

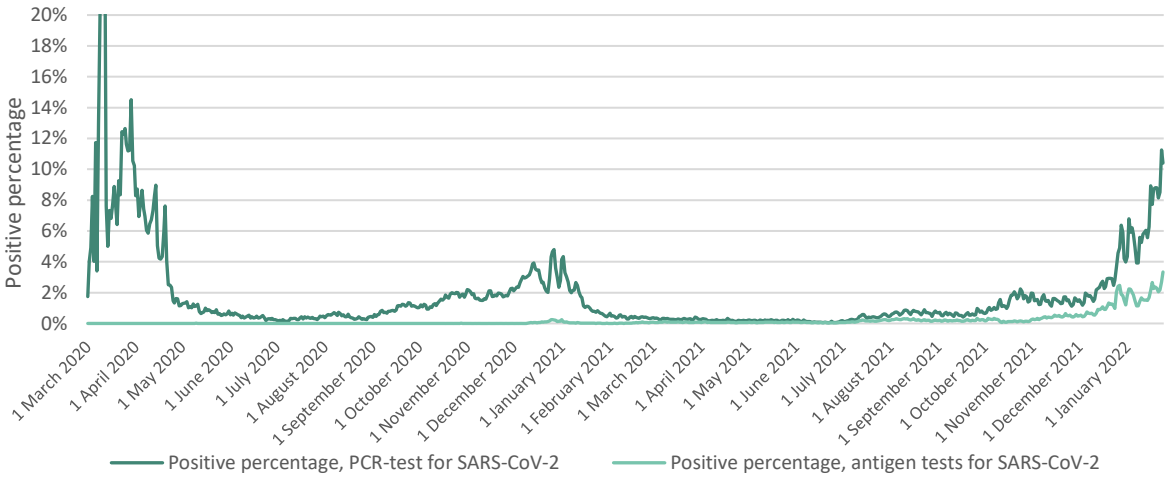


The positive percentage, i.e. the share of those tested who test positive to SARS-CoV-2, must be considered in conjunction with the testing activity and the testing guidelines, as was seen in the early phases of the pandemic when testing was mainly done on indication. Even so, at a

high positive percentage despite a stable or increasing screening activity, as has been the case during the current third wave, a high positive percentage will reflect considerable and extensive community infection, and therefore also a higher dark figure.

Changes in the properties of the virus may also affect the dark figure, particularly so if the shares of asymptomatic or slightly symptomatic infected people rise. Unfortunately, no systematic or validated registration has been made of test indications during the pandemic.

Figure 4. Positive percentage for PCR and antigen test, calculated as per 24 January 2022



Note for Figure 4: Before 1 March 2021, only positive antigen tests were recorded.

Figure 4 shows that the positive percentage is considerably higher during the third wave for PCR tests as well as antigen tests. This may, among others, be due to the rapid growth of the epidemic wave following the appearance of the Omicron variant, and the fact that in the period self tests have been used more extensively. Thus, a larger part of the test-negatives from the opportunistic screening disappears from the PCR-tested population.

By measuring SARS-CoV-2 antibodies in unvaccinated people and comparing results with PCR testing data, the dark figure may be estimated. Even so, it should be taken into account that this is done as a snapshot made at a certain point in time during the epidemic, whereas a number of factors may, as mentioned above, affect the distribution between known and unknown cases of infection.

In five rounds from May 2020 to July 2021, the SSI studied the occurrence of SARS-CoV-2 antibodies among randomly selected unvaccinated people aged 12 years or more. Until July 2021, researchers found that approx. 8.6% (95% confidence interval (CI): 7.6-9.6%) of the included population had SARS-CoV-2 antibodies[5]. Based on these data, the dark figure in early December 2020 was estimated to be around one unacknowledged infection per acknowledged

[5] Statens Serum Institut: Covid 19 Prevalence Study (ssi.dk) (Prævalensundersøgelse af covid-19 (ssi.dk))

infected case[6]. However, in a prevalence study from May 2021, the dark figure was estimated to be somewhat lower than one unacknowledged case per confirmed case [7].

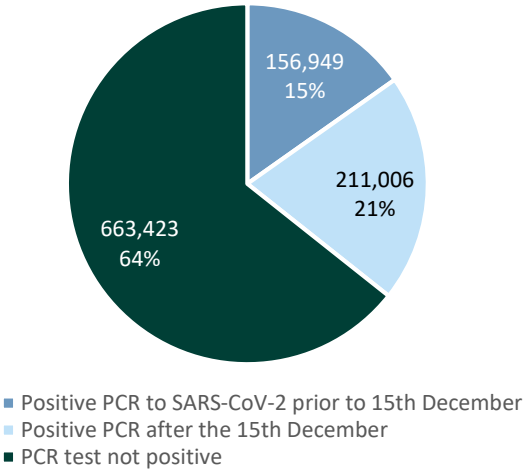
A range of provisos mean that using the above estimates to project the dark figure to the current third wave is difficult, including the current massive occurrence of community infection with the less virulent Omicron variant, changed guidelines for testing and tracing, and the increasing use of self testing. Generally, most of these factors tend to lead to underestimation of the dark figure, which is why we currently assess that the population-level dark figure must be at least one unacknowledged case for every confirmed infection.

As described below, approx. one fourth of both unvaccinated and vaccinated people have tested positive to SARS-CoV-2 by PCR in the course of the epidemic. The interpretation of this figure needs to take into account a considerable underestimation of the number of unvaccinated people who have become infected, as more than half of the total group of unvaccinated people is currently children aged 0-4 years, who are tested much more rarely than the rest of the population. Therefore, it seems fair to assume that the dark figure for unvaccinated people is currently even higher, probably reaching at least two unacknowledged cases per acknowledged infection case.

Acquired immunity among unvaccinated people

Figure 5 shows that more than a third of the persons who were still unvaccinated on 24 January 2022 had tested SARS-CoV-2 positive by PCR. Data were divided as per 15 December 2021, using this date as a surrogate marker for non-Omicron versus Omicron infection.

Figure 5 - Test incidence among unvaccinated people calculated as per 24 January

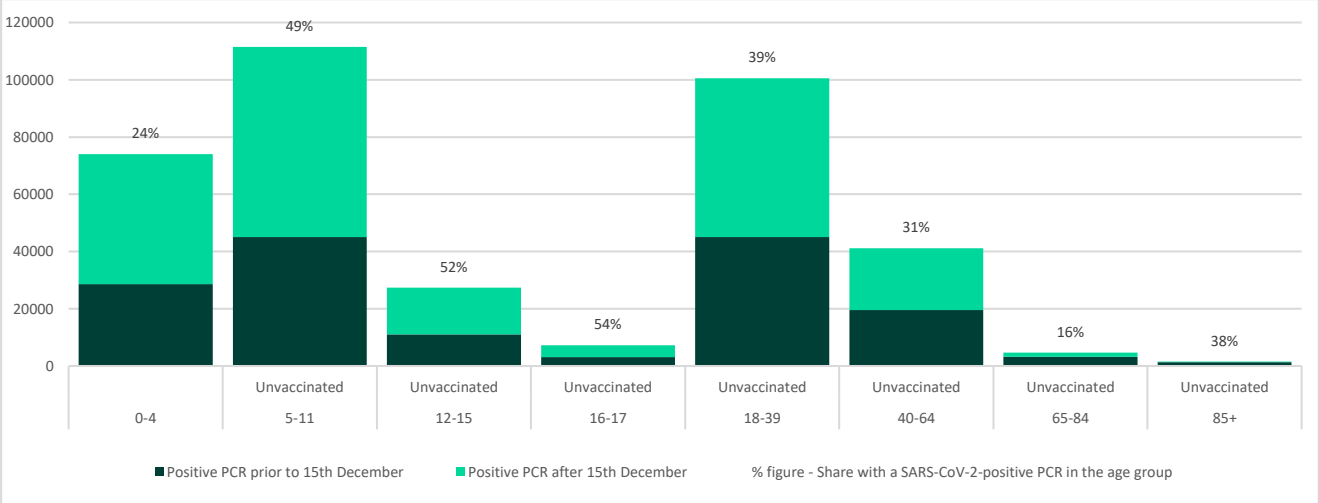


[6] L. Espenhain et al, Prevalence of SARS-CoV-2 antibodies in Denmark: nationwide, population-based seroepidemiological study: Prevalence of SARS-CoV-2 antibodies in Denmark: nationwide, population-based seroepidemiological study - PubMed (nih.gov)

[7] Staten Serum institut: Memo on the fifth round of the National Danish Prevalence Study: Results from the Fifth Round of the National Danish Prevalence Study Comprising 75,000 Selected Citizens, Week 19-223, 2021 (ssi.dk) (Notat vedr. den nationale prævalensundersøgelse 5. runde: Resultaterne fra 5. runde af prævalensundersøgelsen med 75.000 udtrukne borgere, uge 19-23, 2021 (ssi.dk))

Figure 6 reveals that the share of confirmed infected people among unvaccinated people is particularly high in the 5-17-year-olds age group, whereof more than half are presumably recent Omicron infectees.

Figure 6 - Test incidence among unvaccinated people, by age groups, calculated as per 24 January 2022



Reinfection

Several studies have shown that whereas previously the risk of reinfection was low once you had become infected with SARS-CoV-2 (regardless of variant), the risk of reinfection with the Omicron is markedly higher if you have previously become infected by another variant.

The risk is estimated to be 2-5 times increased compared with the other variants. One study has shown a protective effect of previous infection against the Omicron variant of 19% (95% CI: 0-27%)[8], whereas previous studies have reported a protective effect of approx. 85% to previous variants.

Laboratory studies and epidemiological data indicate that the immunity achieved by becoming infected by the Omicron variant protects effectively against infection with the Delta variant, which explains why the Omicron variant has repressed the Delta variant. Also see our Memo of 21 January 2022[9].

[8] Ferguson N. Report 49: Growth and Immune Escape of the Omicron SARS-CoV-2 Variant of Concern in England. Imperial College London; 2021. doi:10.25561/93038 https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/covid-19/report-49-Omicron/

[9] Danish Health Authority, Memo on the Fourth COVID-19 Vaccination Shot for Selected Persons (Sundhedsstyrelsen Notat vedr. vaccination med 4. stik mod covid-19 til udvalgte personer)

Contribution from vaccine-induced immunity

The development of the primary COVID-19 vaccination programme was initiated in Denmark on 27 December 2020. Due to limited vaccine supplies in the period leading up to the summer of 2021, vaccination efforts were prioritised according to the risk of running a serious COVID-19 disease course, age and critical occupations (front-line staff in the healthcare elderly and parts of the social sector).

In the summer of 2021, the primary COVID-19 vaccination programme was extended to comprise children and adolescents aged 12-15 years[10] and then children aged 5-11 years in the autumn of 2021[11].

In the course of 2021, improved data became available on the duration of immunity following the primary vaccination course (the initial two vaccination shots). The data revealed, among others, that the risk of breakthrough infection (PCR positivity) increased by time since the second shot, whereas the protective effect against serious and admission-requiring COVID-19 largely remained in place. Furthermore, the vaccine effectiveness in relation to breakthrough infection was shown to be lower for the then emerging and more virulent Delta variant. The decline in protective effect was more pronounced among the oldest age groups and among persons with underlying conditions.

On that basis, in 2021 we decided to offer booster vaccination to heavily immunocompromised persons, nursing home residents and anyone aged 85 years or more. The third shot was initially offered six months after the second shot, cf. the approval basis. At this point in time, the aim of the booster vaccination programme was primarily to prevent serious COVID-19 disease and death[12].

Subsequently, additional data became available showing that the decline in immunity following primary vaccination was observed in all adult age groups and that booster vaccination across age groups reduced the risk of breakthrough infection (PCR positivity) and breakthrough illness in the form of a serious disease course and death due to COVID-19. On 21 October 2021, we therefore decided to extend the booster vaccination programme by recommending a third vaccination shot approx. six months after the second shot to everyone covered by the vaccination programme. At that point in time, the booster vaccination programme primarily comprised persons aged 65-84 years, persons carrying a specially increased risk of a serious COVID-19 disease course and healthcare and nursing staff, i.e. some of the groups that had received primary vaccination early[13]. In late December 2021, the booster vaccination

[10] Danish Health Authority, 17 June 2021: Concerning vaccination of children aged 12-15 years (Sundhedsstyrelsen, den 17. juni 2021: Vedr. vaccination af børn på 12-15 år)

[11] Danish Health Authority, 26 November 2021: COVID-19 vaccination of children aged 5-11 years (Sundhedsstyrelsen, den 26. november 2021: COVID-19 vaccination af børn på 5-11 år)

[12] Danish Health Authority, 28 September 2021: Concerning COVID-19 booster vaccination (Sundhedsstyrelsen, den 28. september 2021: Vedr. Revaccination mod COVID-19)

[13] Danish Health Authority, 15 October 2021: Plan for COVID-19 booster vaccination (Phase II) (Sundhedsstyrelsen, den 15. oktober 2021: Plan for revaccination mod COVID-19 (Fase II))

programme was additionally extended by recommending the third shot to everyone aged 18 years or more[14].

In light of the very rapidly advancing Omicron immune escape variant, causing a steep increase in community transmission in the early winter, and due to lacking knowledge about the virulence of the new variant, in December 2021 we decided to advance booster vaccination by shortening the recommended interval between the second and shirt shot to 140 calendar days (approx. 4.5 months); initially, starting on 17 December 2021, for persons aged 40 years or more, and then, from 22 December 2021[15], for all persons aged 18 years or more[16]. The aim of advancing the third shot was to rapidly achieve a broad population immunity, primarily to increase protection against serious COVID-19 infection in the adult population. Furthermore, the shortened interval was expected to contribute to overall population immunity and thereby prevent transmission in January and February 2022, when the load on Danish healthcare was expected to peak.

As per 18 January 2022, approx. 81% of the total population has received the second shot, corresponding to around 4.7 million persons. Furthermore, primary vaccination efforts are still advancing, as approx. 120,000 persons have received their first shot as per 18 January 2022. As per 20 January 2022, approx. 4 million persons have received an invitation for booster vaccination, among whom 3.4 million persons have received the third shot, corresponding to approx. 85% of those invited.

Overall, vaccination coverage increases with increasing age. In the primary vaccination programme, the coverage among persons aged 65 years or more is at least 93%. Among nursing home residents and persons aged 85 years or more, 97% have received primary vaccination, and 98% hereof have also received the third shot. The lowest coverage is observed among the youngest children aged 5-11 years. In this age group, 47% have initiated their vaccination course, i.e. have received either the first or the first two shots.

[14] Danish Health Authority, 25 November 2021: Booster vaccination of persons aged more than 40 years (Sundhedsstyrelsen, den 25. november 2021: Revaccination af personer over 40 år)

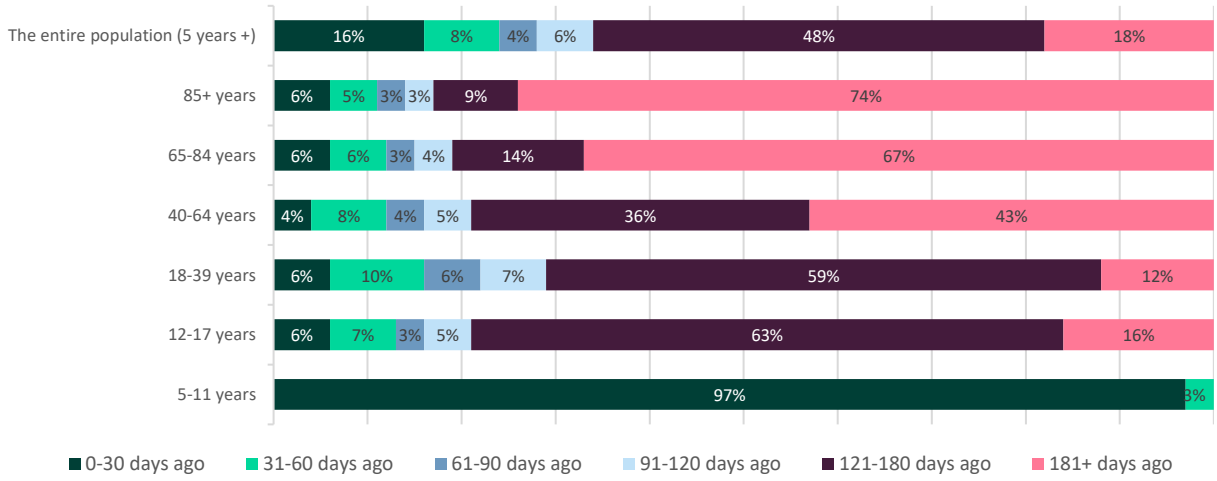
[15] Danish Health Authority, 13 December 2021: Vedr. fremskyndelse af 3. dosis covid-19 vaccine af Comirnaty® og Spikevax® for personer på 40 år og ældre (Sundhedsstyrelsen, den 13. december 2021: Vedr. fremskyndelse af 3. dosis covid-19 vaccine af Comirnaty® og Spikevax® for personer på 40 år og ældre)

[16] Danish Health Authority 22 December 2021: Vedr. fremskyndelse af 3. dosis covid-19 vaccine af Comirnaty® og Spikevax® for personer i alderen 18-39 år (Sundhedsstyrelsen, den 22. december 2021: Vedr. fremskyndelse af 3. dosis covid-19 vaccine af Comirnaty® og Spikevax® for personer i alderen 18-39 år)

Quality of vaccine-induced immunity

Vaccine effectiveness declines over time and has already declined considerably a few months after vaccination[17]. Figures 7 and 8 present the time passed since the second and third vaccination shot, respectively, by age groups. We have not included an overview of time passed since the first shot, as this group only comprises approx. 2% of the total population.

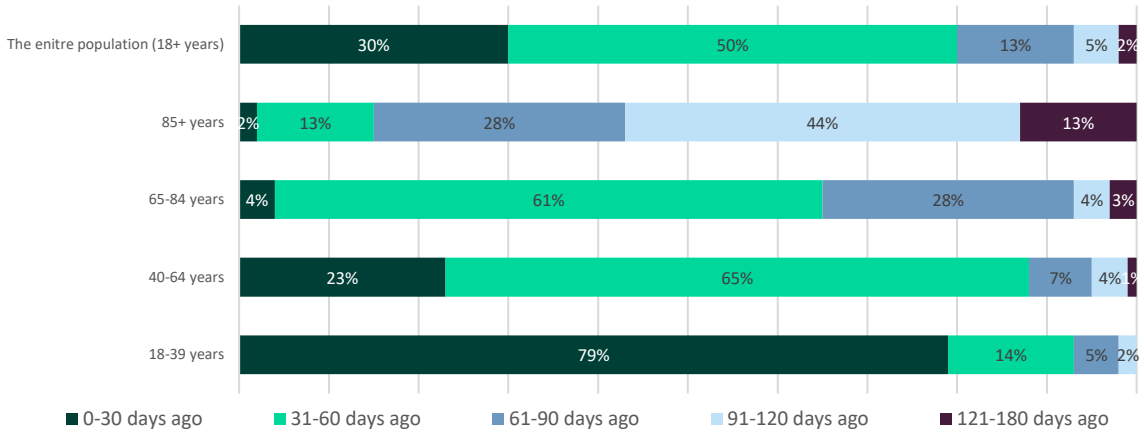
Figure 7. Time since the second vaccination shot, by age groups (persons who had received the third shot were excluded), calculated as per 24 January 2022



Barring the 5-11-year-olds who were not offered vaccination until 25 November 2021, it is evident that a very large share of the persons who have not yet received their third shot received their second shot more than 120 days ago. However, booster vaccination efforts are still progressing successfully and are characterised by a very high coverage across age groups. Therefore, this group is probably shrinking rapidly. Due to the currently very high level of community transmission, some delay may be expected in the coverage of the third shot, as you must have remained symptom free for one month before booster vaccination is recommended.

[17] Danish Health Authority, 6 January 2022: The Danish Health Authority's recommendations on the duration of corona passport following vaccination and following infection (Sundhedsstyrelsen, 6. januar 2022: Sundhedsstyrelsens anbefalinger om varighed af coronapas efter vaccination og efter infektion)

Figure 8. Time since third shot, by age groups, calculated as per 24 January 2022

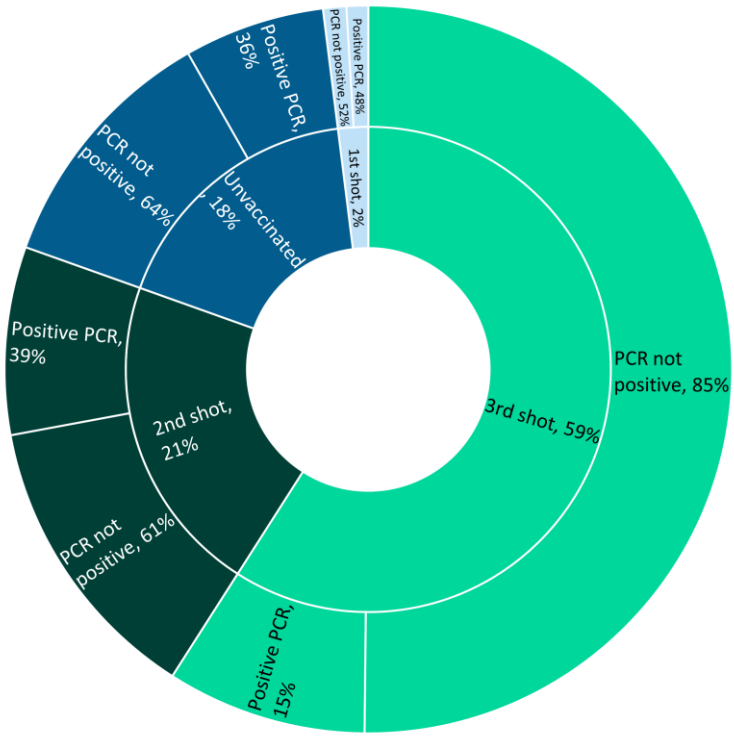


The distribution of time passed since the third shot presented in Figure 8 reflects the sequence of the prioritised roll-out of booster vaccinations, which was initially limited to people aged 85 years or more.

Acquired immunity among vaccinated people

Figure 9 presents the share with a positive PCR test for SARS-CoV-2, by vaccination status.

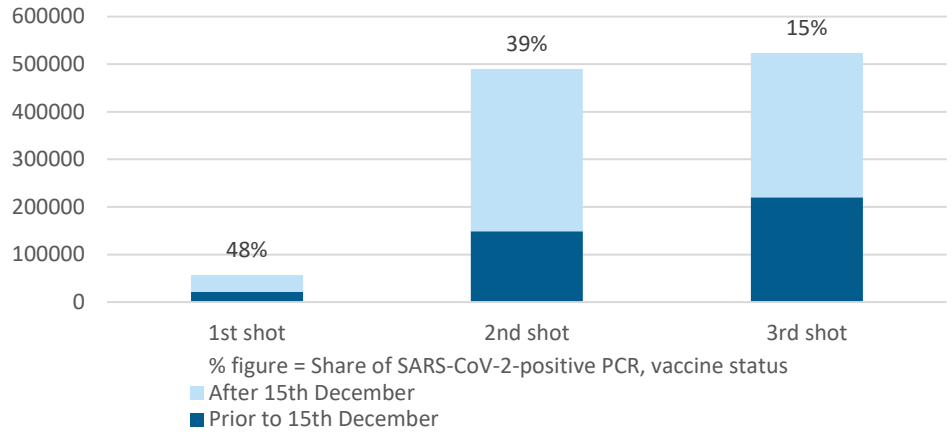
Figure 9. Test incidence by vaccination status (calculated as per 24 January 2022)



On the calculation date, more than a third of both unvaccinated (36%) and primarily vaccinated people (39%) had tested positive to SARS-CoV-2 by PCR. These figures should be interpreted taking into account considerable underestimation of the number of unvaccinated people who have become infected as more than half of the overall group of unvaccinated people are children aged 0-4 years who are tested much less frequently than the rest of the population.

Figure 10 presents the distribution of persons who have tested positive to SARS-CoV-2 by PCR in the course of the pandemic. The data in the figure are presented by vaccination status and furthermore divided into Omicron and non-Omicron infections using the 15 December 2021 as a surrogate marker. Persons with a positive PCR test may have become infected before or after being vaccinated.

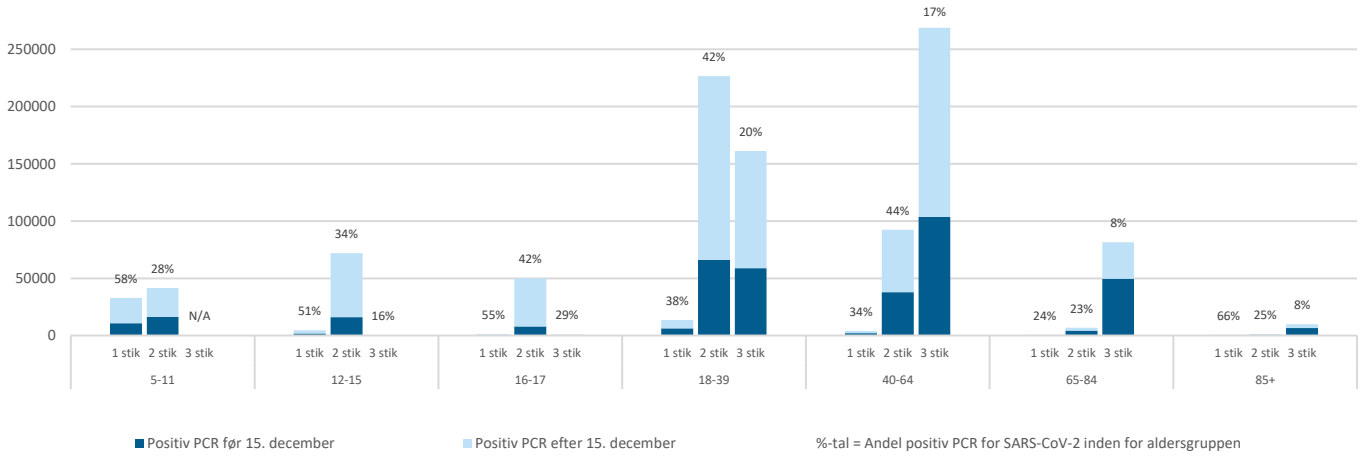
Figure 10. Test incidence by vaccination status before and after the Omicron variant became dominant (data calculated as per 24 January 2022)



Note: *% figures denote the share of the total group who have tested positive to SARS-CoV-2 by PCR in the course of the pandemic.

Figure 11 presents the same data, but by age groups.

Figure 11. Test incidence by vaccination status and age group (calculated as per 24 January 2022)



Vaccine effectiveness to transmission with Omicron

The Omicron variant has considerably more mutations in the spike protein than the other known variants. Many of these mutations are located to the receptor-binding domain, which is important to infectiousness. Additionally, mutations were found in several parts of the spike protein which may influence the effect of vaccine-induced immunity.

Preliminary analyses from the SSI based on Danish data from 11 January 2021 show a vaccine effectiveness (VE) with respect to infection (positive PCR test) with the Omicron variant of approx. 40% in the first three months (90 days) after primary vaccination (two doses) with Comirnaty® has been concluded. After 121 days, the VE had declined to 17%. Analyses were not conducted for Spikevax®. The VE was higher after the third dose, but also followed a declining trend (53% 14-30 days after, 40% 61-90 days after and 32% 91-120 days after concluded primary vaccination). Also see our Memo of 21 January 2022[18].

The results are comparable to international data. A US study found a lower VE for infection with the Omicron variant. Specifically, the study reported 30% within 14-90 days after the second dose, increasing to 63% after the third dose. The latest reports from the UK, released on 14 January 2021, show a higher VE for infection with the Omicron variant: 65-70% immediately (2-4 weeks) after the second dose of Comirnaty®, but declining to approx. 10% among patients who had received the second dose 20 weeks ago. Among patients who had received the third dose within 2-4 weeks, the VE was approx. 65-75%, declining to 55-65% at 5-9 weeks and 45-50% at 10+ weeks[19]. Of note, the VE among patients who had received two doses of Vaxzevria® and subsequently a third dose with an mRNA vaccine was comparable to VE among those receiving three doses of mRNA vaccine.

The VE for serious COVID-19 disease is higher than that for asymptomatic or slightly symptomatic transmission. A South-African study found a VE for admission with the Omicron variant of 70% after two doses of Comirnaty®[20]. The above-mentioned report from the UK found a VE against admission of 64% at 2-24 weeks after the second dose, declining to 44% after 25+ weeks. For persons who have received the third dose, the VE against admission was 92% after 2-4 weeks, declining to 83% after 10+ weeks. In the UK report, all vaccine types were combined. Due to the composition of the British vaccination programme, a large share of those receiving two doses received Vaxzevria® exclusively, which means that the figures cannot simply be extrapolated to the Danish setting. Even so, cf. the above findings, it may be assumed that after the third dose with an mRNA vaccine, the VE is comparable for persons who have previously received Vaxzevria® and an mRNA vaccine.

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[18] Memo on COVID-19 vaccination by a fourth vaccination shot, for selected person groups - Danish Health Authority (Notat vedr. vaccination med 4. stik mod covid-19 til udvalgte personer - Sundhedsstyrelsen)

[19] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1046853/technical-briefing-34-14-january-2022.pdf (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1046853/technical-briefing-34-14-january-2022.pdf)

[20] Collie S, Champion J, Moultrie, H, et al. Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa. NEJM December 29, 2021. DOI: 10.1056/NEJMc2119270

Overall assessment of population immunity

Below, we aim to estimate the extent and quality of the total population immunity to COVID-19, including contributions from immunity acquired from infection and vaccine-induced immunity, and we focus on the time dimension, taking into account shifting dominant virus variants. Contributions from passively achieved immunity (plasma products and antibodies) are negligible in relation to total population immunity and have therefore not been considered in the estimation.

The calculations provided below must be interpreted with caution and taking into account, e.g., incomplete knowledge, data and reporting methods; and simplified calculations. Thus, the calculations serve only to illustrate the possible extent and quality of the current overall population immunity in Denmark.

Assumptions and estimates related to population immunity

The calculations are based on data for primary and booster vaccinations as per 24 January 2022. At the time data were collected, approx. 2% of the population had received one vaccine shot only. Persons aged 16 years or above who have only received a single shot are considered not to have been vaccinated as most of the people in this group received their first shot a long time ago. Persons aged 5-15 years who have only received their first shot are included as having completed their primary vaccination as their first shot was given recently and because the majority will presumably receive their second shot in the near future.

The calculations rely on two different VE indicators: A person with a SARS-CoV-2-positive PCR test is used as surrogate marker for spreading of the infection, whereas admission to hospital of a person with a positive PCR test is used as a surrogate marker for COVID-19 illness. Both of these assumptions come with provisos. In other reports of Danish and international data, delimitations may be different, e.g., to distinguish serious from treatment-demanding disease.

Based on Danish data from the period from 21 December 2021 to 8 January 2022, the SSI has analysed VE against infection with Omicron following primary vaccination and booster vaccination, including the decline in VE over time, which is used to estimate the quality of the immunity achieved.

Furthermore, due to lacking Danish reports on VE for admission-requiring Omicron illness, we use English data showing VEs of 64% (95% CI: 54-71) 2-24 weeks after the second dose, declining to 44% (95% CI: 30-54) after 25+ weeks and 92% (95% CI: 89-94) 2-4 weeks after the third dose, declining to 83% (95% CI: 77-87) after 10+ weeks (see Table 2). As a large

share of the English population received Vaxzevria® as primary vaccination, these data may underestimate the VE in a Danish context[21].

Data on the prioritised roll-out of the Danish vaccination programme are used to describe the time passed since primary or booster vaccination, cf. Figures 7 and 8 (and summarised in Table 2) as a basis for the estimation of the overall and weighted VE. As VE varies with primary or booster vaccination and time passed since vaccination, the calculations assume a VE against infection (PCR positivity) of 42% immediately after primary vaccination and 53% immediately after booster vaccination, declining with time (waning immunity), as described in Table 2. A similar method was used to estimate the overall weighted VE against illness due to Omicron.

[21]Data from England are stated for persons aged 18 years or above who tested positive between 27 November 2021 and 6 January 2022. The analysis comprises 760,647 persons with confirmed Omicron infection based on whole-genome sequencing, genotyping or S-gene target analysis. Test data were linked to data on acute admissions, excluding admissions due to accidents.

Table 2 - Time since primary or booster vaccination and estimated VE - calculated as per 24 January 2022

		Time since primary or booster vaccination**						Weighted average, VE, %
		0-30 days	31-60 days	61-90 days	91-120	121-180	+181	
		VE Omicron infection (positive PCR test to SARS-CoV-2)						
Primary vaccination (second shot)	Vaccine effectiveness (VE), (%)	42.0 (39.4-44.4)	40.7 (38.0-43.3)	39.5 (36.6-42.2)	32.8 (31.0-34.6)	17.1 (15.8-18.3)	-*	~ 24.8
	Population of primary vaccinated people	16%	8%	4%	6%	48%	18%	
Booster vaccination (third shot)	Vaccine effectiveness (VE), (%)	53.2 (52.2-54.0)	46.3 (44.8-47.7)	40.3 (37.8-42.7)	31.7 (26.7-36.6)	-*	-*	~ 46.6
	Population of booster vaccinated people (%)	30%	50%	13%	5%	2%	0%	
		VE Omicron disease (admitted with a positive PCR test to SARS-CoV-2)						
Primary vaccination (second shot)	Vaccine effectiveness (VE), (%)	64 (54-71)	-*	-*	-*	-*	44 (30-54)	~ 60.4
	Population of primary vaccinated people	16%	8%	4%	6%	48%	18%	
Booster vaccination (third shot)	Vaccine effectiveness (VE), (%)	92 (89-94)	-*	83 (77-87)	-*	-*	-*	~ 90.2
	Population of primary vaccinated people	30%	50%	13%	5%	2%	0%	

*Estimate for the period in question not calculated. For use in subsequent calculations, we assume the same estimate as in the preceding period.

**The percentage distribution in the population over time since primary and booster vaccination are presented in Figures 7 and 8.

Estimates of acquired immunity in the unvaccinated part of the population have been up-adjusted considerably since the calculations made in our previous memo, when we found that approx. 15% had tested positive by PCR[22]. As the Omicron variant has advanced among the unvaccinated part of the population, we now find that at least one third of the unvaccinated part of the population have become infected by SARS-CoV-2, among whom at least half have recently become infected by Omicron (see Figures 5 and 6).

As described on page 11, various estimates may be made of unacknowledged infection (the dark figure). Currently, the dark figure must be assumed to constitute at least two unacknowledged cases per case acknowledged by SARS-CoV-2 positive PCR test among unvaccinated people.

In our adjustment of the estimates of protective immunity acquired through infection among unvaccinated people, we thus take into account both the immunity-reducing virus variant, time since infection and the dark figure (see footnote to Table 3). Calculations do not take into account the total estimated dark figure at the population level (corresponding to one unacknowledged case per confirmed infection, cf. page 10).

In the calculation of the estimates, we have also not taken into account hybrid immunity, which means that the contribution to immunity from vaccinated people may be considerably underestimated, as one fourth of those who have received primary vaccination have probably also become infected with Omicron, cf. also page 11 and Figures 9 and 10. Finally, we have not taken into account any contribution to immunity from the increasing number of reinfected people.

[22] Danish Health Authority, 28 September 2021: Concerning COVID-19 booster vaccination (Sundhedsstyrelsen, den 28. september 2021: Vedr. Revaccination mod COVID-19)

Table 3 - Estimated total protection (population immunity) against Omicron infection and disease, calculated as per 24 January 2022

	Population with vaccine-induced immunity N (% of the total population*)	VE immediately after vaccination, %	Weighted VE, % (see table 2)	Total protective vaccine-induced immunity, 5 years or more, %	Total protective vaccine-induced immunity, all of the population*, %	Total protective immunity following infection among unvaccinated people, all of the population, %***	Total protective immunity, all of the population, %
A) Estimated protection against infection with Omicron (SARS-CoV-2 positive PCR test) at population level							
Primary vaccination	1,321,993 (22.5)**	42.0 (39.4-44.4)	~ 24.8	~ 40.6	~ 33.1	13.4	~ 46.5
Booster vaccination	3,469,373 (59.1)	53.2 (52.2-54.0)	~ 46.6				
B) Estimated protection against falling ill with Omicron (admitted with positive PCR test for SARS-CoV-2) at population level							
Primary vaccination	1,321,993 (22.5)**	64 (54-71)	~ 60.4	~ 82.0	~ 67.0	13.4	~ 80.4
Booster vaccination	3,469,373 (59.1)	92 (89-94)	~ 90.2				

*The entire Danish population counting 5,874,901 citizens as per 24 January 2022.

**1,256,751 (primary vaccinated people) + 56,411 (5-11-year-olds who have received their first shot) + 8,831 (12-15-year-olds who have received their first shot)

***Cf. Figure 5, at the time of reporting on 24 January 2022, a total of 156,949 persons had tested positive by PCR before 15 December 2021, and 211,006 had tested positive by PCR as from 15 December, whereof the latter may be presumed to have become infected by the Omicron variant. As Omicron is now the completely dominant immune escape variant and in the light of waning immunity, we have used only a third of the population infected before 15 December 2021 but all of the population infected after 15 December 2021 in the calculation of the estimation of the overall protective population immunity against Omicron infection. However, we corrected by factor 3 (cf. page 11) to take into account the considerable dark figure among unvaccinated people, i.e. (156,949/3) + 211,006) * 3 = 789,967 = 13.4% of 5,874,90

Overall assessment

Keeping in mind the stated provisos, we find that at the time of the calculations on 24 January 2022, Denmark had a population level protection (population immunity) against transmission with Omicron (SARS-CoV-2 positive PCR test) of 46.5% and against Omicron disease of 80.4%.

Both are probably underestimations, keeping in mind the development in the subsequent weeks and among others because booster vaccination efforts are still progressing and because considerable community transmission occurs with the Omicron variant. Both of these developments will further strengthen the overall population immunity among both vaccinated and unvaccinated people. Of note, the largest contribution to overall population immunity was achieved through vaccination.

Furthermore, our current 46.5% estimate for population immunity against transmission with Omicron is lower than our corresponding 65% estimate made in late November 2021, when the Delta variant was dominant.

Even so, we still report a relatively high estimate for population level protection against falling ill due to Omicron. It should also be noted that this estimate applies to the total Danish population, but in actual fact the protection and the prophylactic potential will be considerably higher in the risk population comprised, e.g., by persons older than 40-50 years.

We expect the continued and comprehensive community transmission will be dominated by Omicron, and in conjunction with the lower virulence and the continued very high population immunity against serious disease, this will further increase the overall population immunity. We expect that immunity will increase gradually without reaching a critical level of morbidity and mortality. We will continue to monitor developments very closely, both with respect to the prevalence of treatment-demanding illness caused by Omicron infection and the virulence of any new virus variants.

An increasing share of the population may be expected to develop hybrid immunity following vaccination in combination with previous SARS-CoV-2 infection, thereby contributing further to curbing the current Danish epidemic winter wave before spring. We expect that Danish as well as international data will add to our knowledge of the duration and quality of hybrid immunity, thereby allowing us to update and further qualify our population immunity assessments.

Without any further initiatives, the current estimated population immunity is insufficient to ensure an endemic base level, i.e. achieve an R_e of or below 1, cf. page 2. The necessary level of population immunity (herd immunity threshold), i.e. the share of the total population that is not susceptible to transmission, may theoretically be estimated as $1 – 1/R_0$. The R_0 of the

Omicron variant has yet to be established, but assuming that it is somewhat larger than the R_0 of the Delta variant, e.g., R_0(Omicron) = 7, we achieve a threshold of approx. 85%.

The future will show if is possible to achieve population immunity (achieved through vaccination and infection) of a strength and duration that will reduce the prevalence of SARS-CoV-2 to a permanent, low level in Denmark, or if the condition will give rise to larger seasonal epidemics that affect the population in general, as is the case for, e.g., influenza.