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COVID-19-vaccination

Evidence update for the Health Council of the Netherlands

RIVM letter report 2024-0220

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Colophon

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Synopsis

COVID-19-vaccination

Evidence update for the Health Council of the Netherlands

In 2024, certain groups in the Netherlands were advised to get vaccinated against the coronavirus during the autumn. These groups included people aged 60 years and older, people aged 18–59 who are invited every year to get the seasonal flu vaccine, children and adults who could become very ill due to the coronavirus (for example due to severely impaired immunity) and healthcare workers who have direct contact with vulnerable patients. Since April 2024, the advice no longer applies to pregnant women. Vaccination against the coronavirus was available from 16 September until 6 December 2024 (autumn round).

In 2025, the Health Council will again advise the Ministry of Health, Welfare and Sport on coronavirus vaccination. In preparation for this, the National Institute for Public Health and the Environment (RIVM) has collected the most recent information about the coronavirus in the Netherlands in this document. This includes, among other things, the number of people that got the coronavirus vaccine in the autumn round of 2024, the extent to which the coronavirus was present, information about hospital admissions and the protective effect of the coronavirus vaccine.

During the autumn round of 2024, more than 2,5 million people were vaccinated against the coronavirus. The burden of disease among the Dutch population due to COVID-19 has declined in recent years, but it is still higher than the burden of disease due to influenza. The burden of disease indicates the number of years of good health lost due to illness or premature death due to COVID-19.

In 2023, people aged 60 years and over and infants below 6 months of age had the highest risk of hospitalisation with a coronavirus infection. The number of hospital admissions during the periods in 2024 when many people were ill was about half the number during the peaks in 2022 and 2023. Unlike the annual flu wave, which usually occurs only during winter, the number of coronavirus infections goes up outside the winter period as well.

The risk of developing post-COVID after COVID-19 is now smaller than at the beginning of the pandemic (2020–2021). Vaccination and natural immunity seem to have helped to reduce this risk. Changes in virus variants may also have contributed to this.

Keywords: coronavirus vaccination, coronavirus, COVID-19, background information, Health Council of the Netherlands, advice, immune response, spread, virus load, vaccine effectiveness, vaccination coverage

Publiekssamenvatting

COVID-19-vaccinatie

Kennisupdate voor de Gezondheidsraad

In 2024 kregen bepaalde groepen mensen in Nederland het advies om in het najaar een coronaprik te halen. Dat waren mensen vanaf 60 jaar en ouder, en mensen van 18 tot en met 59 jaar die elk jaar een uitnodiging voor de griepprik krijgen. Het advies gold ook voor kinderen en volwassenen die erg ziek kunnen worden door corona (bijvoorbeeld door een ernstige afweerstoornis) en voor zorgmedewerkers die direct contact hebben met kwetsbare patiënten. Sinds april 2024 geldt het advies niet meer voor zwangeren. De coronaprik werd aangeboden van 16 september tot en met 6 december 2024 (de najaarsronde).

In 2025 gaat de Gezondheidsraad het ministerie van VWS opnieuw adviseren over de coronavaccinatie. Als voorbereiding daarop heeft het RIVM nieuwe gegevens over corona in Nederland verzameld. In dit 'basisdocument' staat onder andere hoeveel mensen de coronaprik tijdens de najaarsronde hebben gehaald, de mate waarin het virus in Nederland aanwezig was, het aantal ziekenhuisopnames en hoe goed de vaccinatie werkte.

Tijdens de najaarsronde van 2024 zijn ruim 2,5 miljoen coronaprikken gehaald. De ziektelast van de Nederlandse bevolking door corona is de afgelopen jaren gedaald, maar is nog steeds hoger dan de ziektelast door griep. De ziektelast geeft het aantal jaren in goede gezondheid aan dat verloren is gegaan doordat mensen ziek waren of vroegtijdig zijn overleden door corona.

In 2023 hadden mensen die ouder zijn dan 60 en baby's onder de zes maanden de grootste kans om met corona in het ziekenhuis terecht te komen. Het aantal ziekenhuisopnames was tijdens de perioden in 2024 dat veel mensen ziek waren, ongeveer de helft van het aantal tijdens de pieken in 2022 en 2023. In tegenstelling tot de jaarlijkse griepgolf, die meestal alleen in de winter voorkomt, leeft het aantal besmettingen met het coronavirus ook buiten de winterperiode op.

De kans om na corona post-COVID te krijgen is nu kleiner dan in het begin van de pandemie (2020-2021). Vaccinatie en natuurlijk opgebouwde immuniteit tegen het virus lijken te hebben geholpen om de kans daarop te verkleinen. Ook veranderingen in varianten van het virus kunnen daaraan hebben bijgedragen.

Kernwoorden: coronavaccinatie, corona, COVID-19, basisdocument, Gezondheidsraad, advies, immuunrespons, verspreiding, virusvracht, vaccineffectiviteit, vaccinatiegraad

Contents

Summary

This letter report presents evidence on COVID-19 and COVID-19 vaccination that became available since the most recent evidence update published by RIVM in March 2024.

In the Netherlands, the target groups for vaccination in the 2024 autumn round were mostly the same as those for the autumn 2023 vaccination round, except that in this 2024 autumn round COVID-19 vaccination was no longer recommended for all pregnant women. Vaccination recommendations in 2024 in surrounding countries were broadly similar regarding the definition of older adults and medical risk groups with an indication for COVID-19 vaccination. However, most northern European countries recommendations for 2024 included COVID-19 vaccination in pregnancy, and some had a spring round for the highest risk groups in addition to an autumn round.

There is a continuing risk of hospital admission and death in the existing demarcated high-risk groups. In particular older adults (60 years and over) and people with immunosuppression remain highly vulnerable. In addition, the age-group specific incidence of COVID-19 hospitalisation is relatively high in infants below 6 months of age (with most below 3 months of age). It should be noted that the actual contribution of SARS-CoV-2 infection to the need for hospitalisation is uncertain; this holds for COVID-19 hospitalisations in other age-groups also. Studies performed in the Delta and earlier Omicron era found that COVID-19 vaccination in pregnancy reduced the risk of severe COVID-19 in infants.

We report the results of ongoing studies by the RIVM into determinants and attitudes towards COVID-19 vaccination in the Netherlands, with a focus on medical risk groups and populations with a migration background. Results indicate that among people aged 60 and older, those less likely to be vaccinated were: younger persons, migrants with two foreign-born parents, inhabitants of highly or extremely urbanized areas and persons with low medical risk, lower income and lower education level.

SARS-CoV-2 circulation does not have a stable seasonal pattern yet and increases are also observed outside the respiratory season. In summer 2024 a new wave of SARS-CoV-2 infections occurred, with, however, lower infection levels than observed in the wave at the end of 2023. The optimal timing of booster vaccinations depends on the seasonality of infection and the waning of protection subsequent to booster vaccination.

Antibodies induced against previous Omicron variants are less able, in vitro, to neutralise more recent Omicron variants, although some neutralisation capacity remains. However, vaccine effectiveness (VE) studies still show considerable protection against hospitalisation and death due to COVID-19, also when caused by more recent variants. The protection against severe disease is higher and lasts longer than

protection against infection and milder disease. Prior infections are also protective against new (severe) disease.
The RIVM corona vaccination studies monitor and evaluate the immunological responses induced by the vaccines delivered as part of the national COVID-19 vaccination programme in healthy participants of all ages eligible for vaccination. All older age groups show an increase in SARS-CoV-2 specific IgG antibody concentrations after the 2023 autumn round. This is observed for IgG antibodies directed against (and T cells that react to) the S-protein of the vaccine strain but also against the Omicron variant BA.1 and the original Wuhan strain that were part of the bivalent and previous monovalent vaccines. Following repeated vaccination, adults produce increasing amounts of IgG4, an antibody subclass that is less capable of activating immune cells involved in killing of virus-infected cells. It is not clear what this implies for actual protection against COVID-19.

This evidence update includes updated estimates of the COVID-19 burden of disease in 2023, and, for the first time, an initial cost-effectiveness analysis (CEA) of COVID-19 vaccination. The annual burden of disease from acute COVID-19 within the Dutch population decreased from approximately 200,000 DALYs in 2020 to 37,800 DALY's in 2023. The burden of disease from acute COVID-19 in 2023 was still significantly higher than that of an average influenza season in the entire population (~9,000 DALYs). The results of the initial CEA suggest that the net costs per DALY averted of the COVID-19 vaccination programme remained below the generally used threshold value for preventive interventions of 20.000 euro per DALY, provided the vaccination costs are below €100 per vaccinated person. The results may differ if a full CEA were performed according to the Dutch cost-effectiveness guideline, including the disease burden from mild episodes and post-COVID, including non-healthcare costs (societal perspective), and accounting for time preferences (discounting).

Several studies have now estimated the prevalence of post-acute sequelae of COVID-19 (PASC) in the Netherlands and beyond. When extrapolated, an estimated 80.000 – 127.000 adults have a severe form of PASC in the Netherlands. The risk of post-COVID per infection is presently lower than early pandemic estimates. Vaccination is thought to have contributed to this risk-reduction as well as natural immunity, viral adaptations and other time variable factors.

Introduction

This letter report contains an evidence update regarding COVID-19, COVID-19-vaccination and immunity against SARS-CoV-2. It includes evidence that became available after the previous evidence update, published on 20 March 2024, about SARS-CoV-2 variants, immunogenicity of COVID-19 vaccines, vaccine effectiveness, the duration of protection, burden of disease and initial cost-effectiveness, and long-COVID.

We refer also to the annual report "The National Immunisation Programme in The Netherlands. Surveillance and developments" where some similar as well as additional information is provided.
After publication of this letter report, RIVM continues to collate and review relevant scientific evidence as soon as this becomes available.

1 COVID-19-vaccination: target groups and vaccines

1.1 Target groups for the COVID-19-vaccination round in autumn 2024

The COVID-19 vaccination round in autumn 2024 ran between 16 September and 6 December 2024. Vaccination was recommended for the following groups:

- People aged 60 years and older
- People between the age of 18 and 59 who receive an annual invitation to have the flu vaccine
- Children and adults with a high medical risk for severe COVID-19 (such as severely immunocompromised persons)
- Healthcare workers who are directly in contact with vulnerable patients

This target group in 2024 was the same as for the 2023 autumn round, except that in the 2024 autumn round COVID-19 vaccination was no longer recommended for all pregnant women (only for those with underlying illnesses).

1.2 Vaccines

In the autumn 2024 vaccination round, the JN.1 monovalent mRNA vaccine Comirnaty (BioNTech/Pfizer) is used. Information regarding the adverse events after COVID-19-vaccination can be found in the NIP report 2023-2024, chapter 9.8.

2 Policies on COVID-19-vaccination (WHO and Northern Europe)

Surrounding countries have implemented various COVID-19 vaccination strategies. Some have already included COVID-19 vaccination in their routine immunization schedule, while other countries adjust and plan their vaccination strategy annually. The Strategic Advisory Group on Immunization (SAGE) of the World Health Organisation (WHO) also published a roadmap in which they share their general recommendations for the optimal implementation of COVID-19 vaccination, based on current evidence. This will be adapted in case of new developments. WHO/SAGE published their roadmap with recommendations on COVID-19 vaccination late 2023 [1]. WHO/SAGE divided target populations into three priority groups based on age and health condition:

The first target population within the high priority group consists of the oldest adults (cut-off often 75 or 80 years) and older adults with multiple comorbidities. They propose to revaccinate this population every 6 to 12 months after the previous dose. The other target populations within the high priority group are older adults (age cut-off to be decided by countries: often it is 50 or 60 years) and adults with a comorbidity. This group is advised to be vaccinated 12 months after their previous dose.
The medium priority group includes healthy adults and individuals aged 6 months to 17 years with a comorbidity.
The low priority group includes healthy individuals aged 6 months to 17 years. SAGE advises that neither the medium nor the low priority group should receive routine COVID-19 vaccinations.
They also distinguish three additional high priority subgroups each having special considerations, including people with immunocompromising conditions, pregnant people and healthcare workers with direct patient contact. For those with immunocompromising conditions, revaccination is recommended every 6 to 12 months after the previous dose. Healthcare workers are advised to be revaccinated after approximately 12 months. Lastly, pregnant people are advised a single dose during their pregnancy, preferably in the second trimester.
An updated WHO SAGE roadmap on COVID-19 vaccination is expected in 2025.

In the UK, people aged 75 years and over, people in care homes, and those aged 6 months and over with a weakened immune system were offered a COVID-19 vaccine in spring 2024. For autumn 2024, the Joint Committee on Vaccination and Immunisation (JCVI) recommended to offer vaccination to adults aged 65 years and over, residents in a care home for older adults and individuals aged six months to 64 years who have underlying health conditions leading to greater risk of disease or mortality [2]. In September 2024, new guidelines for COVID-19 vaccination were published in the UK [3]. Compared to the previous autumn campaigns, household contacts of the immunosuppressed, and

frontline health and social care workers are no longer recommended a COVID-19 vaccination.

JCVI will continue to review the optimal timing and frequency of COVID-19 vaccination. Based on the most recent cost-effectiveness assessment for autumn 2024, vaccination was likely to be cost-effective when recommended to the groups; adults aged over 70, adults aged 65 years and over in a clinical risk group and individuals with immunosuppression aged 15 years and over. However, JCVI decided to recommend vaccination to all adults aged 65 years and over, rather than limiting it to those who are 70 years old and over. Their decision to use this cut-off was based on the fact that a significant number of older adults belong to a clinical risk group, and by the high participation rates seen in other universal age-based programmes. Vaccination offered to individuals below 65 years old in the clinical risk group is unlikely to be cost-effective. Nonetheless, the clinical risk groups display a high level of diversity, with the risk of severe illness varying greatly both within and between groups. With changing population immunity, the significance of various underlying health conditions may also vary. Thus, individuals in a clinical risk group aged 6 months and over are offered vaccination in autumn 2024. This includes women who are pregnant regardless of their stage of pregnancy, while recognising that the risk of severe COVID-19 in both pregnant women and neonates is currently substantially lower than previously seen in these groups. The JCVI advised to not vaccinate those living and working with vulnerable people.

The most recent JCVI statement (November 2024) for autumn 2025 and spring 2026 is based on the use of a standard cost-effectiveness assessment instead of the non-standard cost-effectiveness assessment that was used since autumn 2023 [4]. The use of this standard is in line with other routine vaccinations in the national immunisation programme in the UK. Using the standard cost-effectiveness assessment, JCVI advises to offer a COVID-19-vaccination in autumn 2025 and spring 2026 to adults aged 75 years and over, residents in a care home for older adults and individuals aged 6 months and over who are immunosuppressed. Increasing age continued to be the most important risk factor associated with COVID-19 mortality. JCVI advises to offer COVID-19 vaccination as far as possible as a universal aged-based programme. In the older age group a high proportion of individuals are in a COVID-19 at-risk group and those who are not in an at-risk group are still at risk of mortality from COVID-19 because of their age.

Certain surrounding countries have included COVID-19 vaccination in their routine immunisation schedule. The Standing Committee on Vaccination (STIKO) in Germany recommends an annual vaccination in the autumn [5]. The groups for which vaccination is recommended vaccination are: all people aged 60 and over, residents of long-term care facilities, individuals aged 6 months and over with underlying health conditions, and those living and working with vulnerable people. Women of reproductive age and pregnant women are not recommended an additional booster in the autumn of each year but ‘basic immunity’ (through vaccination or through infection, at least one exposure through vaccination).

The French National Authority for Health (HAS) also recommends an annual vaccination in autumn. They advise to vaccinate people aged 65 years and over and people with comorbidities [6]. An interval of at least 6 months since the last dose or the last COVID-19 infection is recommended. This interval is reduced to 3 months for people aged 80 and over, immunocompromised people, residents of long-term care facilities and people at very high risk of severe disease. HAS advises for these groups an additional dose in the spring. COVID-19-vaccinations are recommended during pregnancy.

The Scandinavian countries Sweden and Finland also have a vaccination strategy for autumn 2024. The Public Health Agency of Sweden has updated their recommendations on COVID-19 vaccination in June 2024 and these recommendations apply until further notice [7]. This autumn, vaccination is recommended for people aged 65 and over and medical risk groups aged 18 to 64 years (such as the conditions diabetes mellitus, renal failure, immunosuppressive disease and pregnancy). An additional vaccination is recommended in the spring for people aged 80 years and over and residents of care homes.

In Finland, the Institute for Health and Welfare (THL) recommends a booster dose in autumn 2024 for specific target groups. They will use a stepwise approach, where they will prioritise certain groups to be vaccinated first. The target groups which are suggested to be vaccinated as soon as the vaccines arrive in Finland are people in long-term care facilities, people aged 80 or over and severely immunocompromised individuals [8]. People aged 75 to 79 should be vaccinated earlier than in previous autumn rounds. Afterwards, all people aged 65 years and over are able to receive a vaccination as well as people aged 18 years and over who have an underlying health condition that increases the risk of severe disease. Conditions that are expected to increase the risk of severe COVID-19 in persons 18 and over are, for example, organ transplant or stem cell transplant, Down’s syndrome, morbid obesity, pregnancy and severe chronic kidney disease.

Table 2.1 Overview of COVID-19 vaccine recommendations in spring/autumn round 2024.

Country	**Recommendations for spring round in 2024**	**Recommendations for autumn round in 2024**	**COVID-19-vaccination recommended for all pregnant women?**	**COVID-19-vaccination recommended for those living or working with vulnerable people?**
Belgium[1]	No	People aged ≥ 65; Residents of long-term care facilities; People under 65 years of age with underlying health conditions.	No	Persons working in the healthcare sector, in or outside a healthcare facility; Persons living with someone with an underlying health problem.
Denmark[2,3]	No	People aged ≥ 65; People under 65 years of age with underlying health conditions.	Yes	Not mentioned
Finland[4,5]	No	Persons aged ≥ 75; People living in nursing homes or regular home care; Persons with immune deficiency (booster vaccine is also offered for people aged ≥ 65 and with and those in medical risk groups aged ≥ 18)	Yes	Not mentioned
France[6,7]	People aged ≥ 80; Immunocompromised people;	People aged ≥ 65; People under 65 years of age with underlying health conditions.	Yes	Relatives of vulnerable people and professionals in the medical and social sectors.

Country	Recommendations for spring round in 2024	Recommendations for autumn round in 2024	COVID-19-vaccination recommended for all pregnant women?	COVID-19-vaccination recommended for those living or working with vulnerable people?
	Residents of nursing homes and long-term care facilities; People at very high risk of severe disease.			
Germany[8,9]	No	People aged ≥ 60; Residents of long-term care facilities; People under 65 years of age with underlying health conditions.	No	Persons with a higher occupational infection risk on account of their work in health or long-term care; Family members and close contacts of persons for whom COVID-19 vaccination is unlikely to produce a protective immune response.
Netherlands[10]	No	People aged ≥ 60; People under 60 years of age with underlying health conditions.	No	Healthcare workers who are directly in contact with vulnerable patients.
Norway[11]	No	People aged ≥ 65; Nursing home residents; People under 65 years of age with underlying health conditions.	Yes	People who live with (or are similarly close) immunosuppressed; Only healthcare personnel who belong to a risk group themselves.
Sweden[12]	People aged ≥ 80 years; Residents of care homes.	People aged ≥ 65 years;	Yes	Not mentioned.

Country	Recommendations for spring round in 2024	Recommendations for autumn round in 2024	COVID-19-vaccination recommended for all pregnant women?	COVID-19-vaccination recommended for those living or working with vulnerable people?
		People under 65 years of age with underlying health conditions.		
United Kingdom[13]	People aged ≥ 75 years; People in care homes; People aged 6 months and over with a weakened immune system.	People aged ≥ 65 years; Residents in a care home; People under 65 years of age with underlying health conditions.*	Yes	No

*In the UK, JCVI advises to offer COVID-19-vaccination in autumn 2025 and spring 2026 to adults aged 75 years and over, residents in a care home for older adults and individuals aged 6 months and over who are immunosuppressed.

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3 Medical (high)-risk groups definition

3.1 Medical (high)-risk groups for severe SARS-CoV-2-infection: definitions used in the Netherlands

Soon after the start of the COVID-19 pandemic, it became clear that older age and certain underlying medical conditions were risk factors for a severe course of SARS-CoV-2 infection. During the vaccination program, several risk groups were defined based on the data available in an unvaccinated population. The first demarcation of high-risk groups was formulated by a RIVM-coordinated working group on COVID-19-vaccination together with medical specialists and published by the Health Council in February 2021. These medical high-risk groups were prioritized for vaccination.

The classification of medical (high)-risk groups at increased risk of severe COVID-19 was updated in the Netherlands in 2022 (see the advisory note Determining adult medical risk groups COVID-19 vaccination campaign). The current definition of this group, applicable to the autumn 2024 vaccination round, can be found in the RIVM guideline for all professionals involved in the implementation of the COVID-19-vaccination (see COVID-19-vaccination | LCI guidelines (rivm.nl)).

3.2 Medical (high)-risk groups for severe SARS-CoV-2 infection: literature update

In the March 2024 evidence update, a descriptive analysis by age, medical risk and vaccination status of hospitalisation was performed by linking the NICE COVID-19- dataset, CIMS and CBS microdata (September – December 2023). This suggested that unvaccinated medical high-risk groups retained the highest risk of hospitalisation, more than unvaccinated people from the general population or people from other medical risk groups (who are invited annually for influenza vaccination via their general practitioner). Age 60 years or older was also a dominant predicting factor for hospitalisation due to COVID-19. However, also in persons below the age of 60 years hospitalisation rates were high in medical high risk groups (immunocompromised) and second highest in the group eligible for influenza and COVID-19-vaccination.

Much of the evidence to define medical high-risk groups was derived from the OpenSAFELY platform from the United Kingdom, in which primary care records linked to other data were made available for research from March 2020 onwards. A May 2023 publication by Nab et al. using the OpenSAFELY platform, reports changes in COVID-19-related mortality risks across population subgroups in several waves of the pandemic, between March 2020 and August 2022 [9]. Compared with the first wave of the pandemic, the overall population-based mortality risk declined substantially in the last wave, also in most clinical risk groups. People who received organ transplants across successive waves, people with chronic kidney disease, people with haematological malignancies, and people with immunosuppression remained highly

vulnerable. In addition, for groups of people with low vaccination coverage the decline in COVID-19-related mortality risk was smaller than for the overall population. The authors do not draw any conclusions on removing the indication for COVID-19 vaccination for certain clinical risk groups.

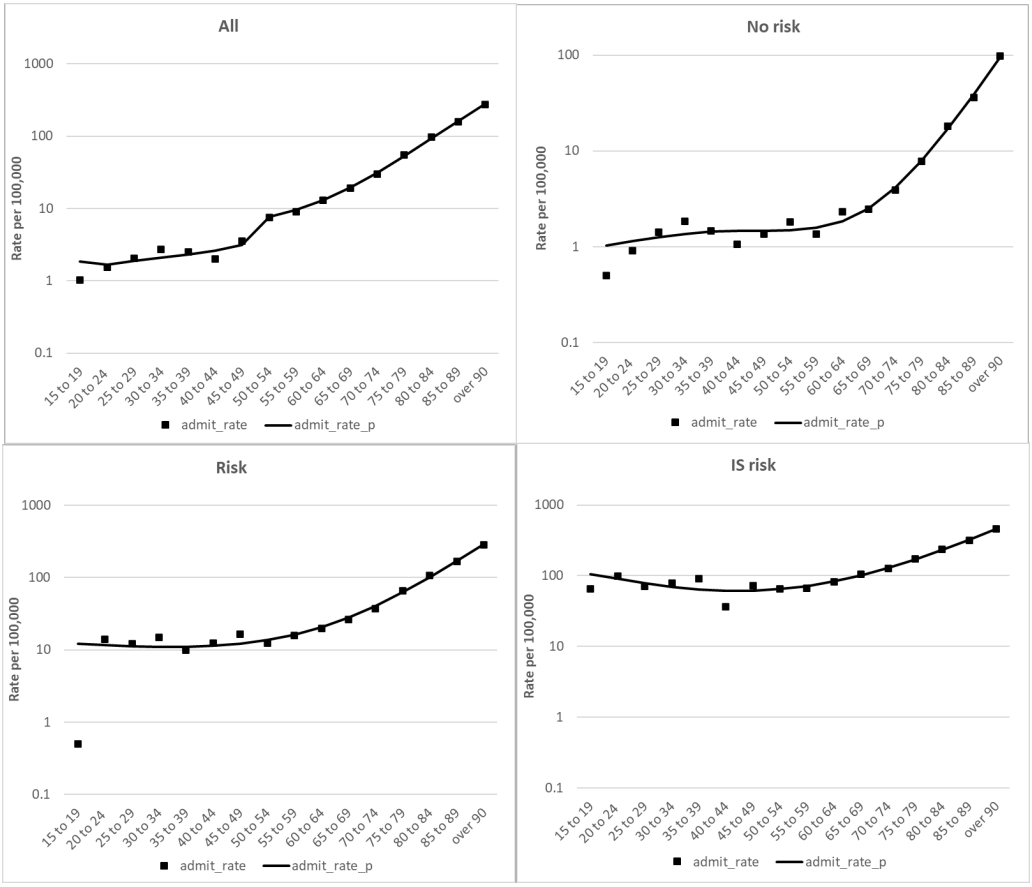
There is a continuing risk of hospital admission and death in the existing demarcated high-risk groups. This is evident from two recently published studies with international data. A French study shows that despite a booster dose between January and October 2022 and a less virulent circulating variant (i.e. Omicron), there was still a residual risk of hospitalisation for COVID-19 among the older segment (≥55 years) of the population and in those with comorbidities [10]. The highest risk of hospital admission was in the high-risk groups, as included in the Dutch risk categorization: Down syndrome, chronic respiratory disease, transplant recipients, active cancer, immunosuppressive treatment, neurodegenerative disease (included in the Dutch categorization as 'long term care facilities'), and dialysis.

An English study (published January 2024) highlights that the risk of COVID-19 death, compared to all other causes of death, remains highest in certain groups aged 50-100 years with underlying health conditions despite a booster dose in autumn 2022 (data up to April 26th, 2023): Down syndrome or learning disabilities, active lung/oral cancer, neurodegenerative disease, liver cirrhosis and cancer of blood or bone marrow [11]. All these conditions are currently included in the Dutch (high) risk categorization.

Evidence in the literature to add or remove risk groups (or to refine the current risk group definition) is scarce. A major limitation is that coding differs between studies and countries, making it difficult to interpret findings. In addition, even when the same disease codes are used, groups may differ in terms of disease stage and treatment, or in national differences in access or eligibility for COVID-19 antiviral treatment that may also influence clinical outcomes.

In May 2023, results of analyses to estimate the number needed to vaccinate (NNV) to prevent hospitalisation, severe hospitalisation and death due to COVID-19 were published by the UK Health Security Agency [12,13], based on incidence in the period 15 November 2022 – 14 January 2023. These estimates were used to inform decisions around the autumn 2023 booster round in the UK. The NNV estimates were stratified by age and clinical risk (no risk; risk but no immunosuppression; immunosuppression). As expected, the incidence of hospitalisation increases by age. Interestingly, the incidence of hospitalisation due to COVID-19 is particularly high for people with immunosuppression, also in people below the age of 60, which is less the case in people with no medical risk and those with a medical risk but no immunosuppression (Figure 3.1).

Figure 3.1 COVID-19 hospitalisation rates (registered and predicted) by age and medical risk group, UK, 15/11/2022-14/1/2023. IS risk: immunosuppressed. Please note the y-axis is on a logarithmic scale and that the y-axis scale differs for the 'no risk' group.



Note: the image is taken from the UKHSA report estimating the number needed to vaccinate to prevent COVID-19 hospitalisation for booster vaccination in autumn 2023 in England, 5 October 2023 [12].

On August 2nd, 2024, JCVI published new estimates of the NNV by medical risk groups, based on an adjusted estimate of the incidence observed in winter 2022-2023 (Table 3.1) [13]. These estimates are substantially higher than NNVs based on unadjusted incidence data for winter 2022-2023 [3]. The relative NNV of people with a medical risk but not immunosuppression compared to those with immunosuppression increases much by younger age.

Table 3.1 Number Needed to Vaccinate (NNV) estimates for hospitalisation by age and medical risk group, UKHSA, August 2024, based on adjusted winter 2022/2023 data. IS: immunosuppressed.

Age (years)	No risk	Risk (not including IS)	IS	All
15-19	113,700	9,800	1,100	63,500
20 to 24	102,900	10,200	1,300	69,900
25 to 29	93,800	10,500	1,500	62,100
30 to 34	86,700	10,700	1,700	56,000
35 to 39	82,100	10,700	1,800	50,800
40 to 44	80,000	10,400	1,900	45,100
45 to 49	80,200	9,600	1,900	37,100
50 to 54	79,700	8,600	1,800	15,500
55 to 59	75,000	7,200	1,600	12,300
60 to 64	63,700	5,700	1,400	9,000
65 to 69	46,700	4,200	1,200	6,000
70 to 74	28,500	2,900	910	3,800
75 to 79	14,900	1,900	690	2,200
80 to 84	7,000	1,200	500	1,300
85 to 89	3,000	690	360	730
Over 90	1,200	410	260	420

The UK autumn 2024 campaign was also informed by an adapted cost-effectiveness assessment [14]. Since the vaccines were already purchased, costs for these for included as sunk costs. An initial cost-effectiveness analyses for the Netherlands is presented in Chapter 7 of this report.
In September 2024 an analysis of the effect of the spring booster campaign in 2022 and 2023 suggested significant reductions in the number of hospitalisations due to these campaigns. Since the method of analyses was an age-discontinuity design, these results clearly indicate impact on preventing additional hospitalisations by spring boosters for the eligible age-groups [15].
In the October 2024 meeting of the JCVI, newer estimates of the NNV were presented in draft minutes. NNV estimates to prevent hospitalisation were <4,000 in not at-risk adults aged ≥80 years, and in at-risk but not immunosuppressed adults aged 60 years and over. For immunosuppressed individuals, NNVs were <4,000 in almost all age groups.

3.2.1 Young infants

No vaccine is currently licensed for use among infants aged <6 months [16]. A recent publication from the US reported that infants under 6 months of age have high COVID-19 hospitalisation rates [16]. Weekly COVID-19 hospitalisation rates from October 2022 to April 2024 were substantially higher for infants aged <6 months than for children and adolescents in older age groups. Compared across all age groups, cumulative COVID-19 hospitalisation rates between October 2023 and April 2024 among infants <6 months (320 per 100,000 infants) were comparable to hospitalisation rates among adults aged 65-74 years (284 per 100,000 persons), and higher than in any other age group except among the elderly aged ≥75 years (940 per 100,000 population). The infant COVID-19 hospitalisation rate did decrease compared to the

previous respiratory virus season (414 per 100,000 infants between October 2022 and April 2023). Twenty-two percent of admissions between October 2022 and April 2024 were ICU admissions. In this study, laboratory-confirmed COVID-19 hospitalisation is defined as documentation of a positive SARS-CoV-2 test during hospitalisation or ≤14 days preceding hospital admission [14]. Hereby it is important to note that the pathogenic role of the Omicron variant is not always clear, since we know that SARS-CoV-2 infections can be asymptomatic or only mildly symptomatic. It has been described that viral and bacterial co-occurrence may drive symptomatology of human coronavirus (HCoVs-) associated infections including COVID-19 in infants [17].The aforementioned US study finds that 93% of hospitalized infants (excluding those diagnosed during delivery) had COVID-19 symptoms. In 30% of the infants, ≥1 respiratory coinfection that may explain these symptoms, primarily RSV, was recorded [16].

Previous analyses based on data from the same US hospital surveillance network found similar patterns of hospitalisation rates across age groups [18,19]. Most, though not all, other studies conducted in 2021 and 2022 show that infants are at increased risk of severe COVID-19 as well, but these findings may not be equally applicable to the present epidemiological situation and SARS-CoV-2 variant [20,21,22]. Also recent data from the UK suggest relatively high rates of COVID-19 hospitalisation and severe COVID-19 hospitalisation in infants <6 months of age, whilst the incidence of COVID-19 deaths is very low in this age group [3]. In the Netherlands in 2023, incidence of COVID-19 hospitalisation was also higher among infants aged <6 months compared to other age groups, exceeded only among persons aged ≥80 years (Table 5.1 in chapter 5.1 of this document).

In addition to being unable to determine whether the SARS-CoV-2 infection alone was the reason for admission or that other infections like RS or influenza virus coincided, other partial explanations for the high COVID-19 hospitalisation incidence are conceivable. Among very young infants, underlying medical conditions (approximately one quarter of patients in the recent US publication [16]) may lead to a lower threshold for hospitalisation, concern for complications and/or more severe manifestations of a SARS-CoV-2 infection [23]. More generally, the increased rates of hospitalisation in infants aged <6 months or <1 year compared to older children might partially reflect the smaller size of the respiratory tract leading more easily to respiratory problems and/or feeding difficulties in case of infection and infants may be more likely to be hospitalized with milder respiratory disease [24,25]. On the other hand some studies suggest higher COVID-19 severity among infants <6 months of age [19,20]. The aforementioned recent US study found that severe outcomes were common, with 22% of hospitalisations being ICU admissions and 21% requiring high flow nasal canula or BiPAP/CPAP, although these figures were not compared across age groups and part of these outcomes may have been caused by a simultaneous infection with another virus [16].

Multiple studies find that maternal COVID-19 vaccination during pregnancy reduces the risk of SARS-CoV-2 infection and severe COVID-19 in infants (aged <4 or <6 months), although these studies were

conducted when Delta and previous Omicron variants dominated [26,27,28,29,30,31,32,33]. Most studies that stratified by variant period found that vaccination during pregnancy provided some protection during the Omicron (XBB) dominated period, but was less effective than during the Delta-dominated period [28,30,31,32]. One US study found no significant effect of vaccination during pregnancy on SARS-CoV-2 infection in infants below 6 months of age when Omicron dominated [26]. VE of a booster (third) dose during pregnancy ranged between 44% (95%CI: 26-58) and 78% (95%CI: 57-88) and between 46% (95%CI: 26-60) and 80% (95%CI: 64-89) against SARS-CoV-2 infection and against COVID-19 hospitalisation in the first 6 months of life, respectively [28,29,30,32]. Effectiveness waned over time since vaccination, resulting in a decrease in effectiveness as infants aged [28,29,30,31]. A case-control study conducted between March 2022 and May 2023 (Omicron period) found a VE of a second or higher COVID-19 vaccine dose during pregnancy of 54% (95%CI 32-68%) against COVID-19 related hospitalisation in infants <3 months of age [34]. In Scandinavian countries, France and UK pregnant women are up to autumn/winter 2024/2025 recommended to receive a COVID-19-vaccination either during pregnancy or only during an autumn vaccination round. For autumn 2025, JCVI has recommended that for the UK vaccination during pregnancy is no longer advised. For other countries recommendations for autumn 2025 are not known yet.

The risk of multiple adverse foetal and neonatal outcomes, including preterm birth, neonatal intensive care admission, small for gestational age status and several composite neonatal morbidity and mortality indices, have been found to be higher among women who had a SARS-CoV-2 infection during pregnancy compared to uninfected pregnant women [35,36,37,38]. COVID-19 vaccination during pregnancy may protect against these outcomes by preventing SARS-CoV-2 infection or COVID-19 in pregnancy [39]. The effects of vaccination during pregnancy on these outcomes has also been analysed in the context of vaccine safety. However, recent evidence on the effects of COVID-19 vaccination on foetal and neonatal outcomes is scarce. Most studies were conducted in 2021-2022, comparing women who received any vs. no vaccination in pregnancy, and none specifically analyse the effects of the COVID-19 booster vaccinations offered in 2022 or 2023 compared to no booster vaccination during pregnancy.

Two meta-analyses including studies from 2021 and 2022 found no evidence of any harmful effect of COVID-19 vaccination during pregnancy on foetal and neonatal outcomes [40,41]. Moreover, vaccination during pregnancy had a protective effect on neonatal intensive care unit admission [40,41], stillbirth and preterm birth [41]. One recent study stratified by dominant variant period during which the largest share of the pregnancy occurred. During Omicron dominance, lower rates of preterm birth were observed among mothers vaccinated in pregnancy (RR=0.85, 95%CI: 0.79-0.91 compared to never vaccinated mothers, RR=0.48 95%CI: 0.34-0.68 compared to mothers vaccinated after pregnancy) [42]. The difference in stillbirth rates was not significant [42].
Recent estimates from the UK on the NNV for maternal vaccination can be found in preliminary minutes of the JCVI.

Two analyses of the first booster in Israel (pregnancies in Alpha and Delta periods) indicated no effect, neither harmful nor beneficial, of receiving the booster in pregnancy as compared to having had the primary course only, on several foetal and neonatal outcomes [43,44]. A study among women who delivered between January 2021 and October 2022 (mostly Omicron period) found no effect of the first booster on preterm birth or very low birth weight rates, but lower rates of stillbirth among booster recipients (RR=0.60, p<0.025) [45]. In a Canadian study among women pregnant during Delta or Omicron dominance (deliveries December 2022 – August 2022), most effect estimates were around the null, but booster vaccination during pregnancy had a protective effect on preterm birth (HR=0.91, 95%CI: 0.84-0.99), stillbirth (HR=0.56, 95%CI: 0.39-0.81) and small for gestational age status (HR=0.86, 95%CI: 0.79-0.93) [46].

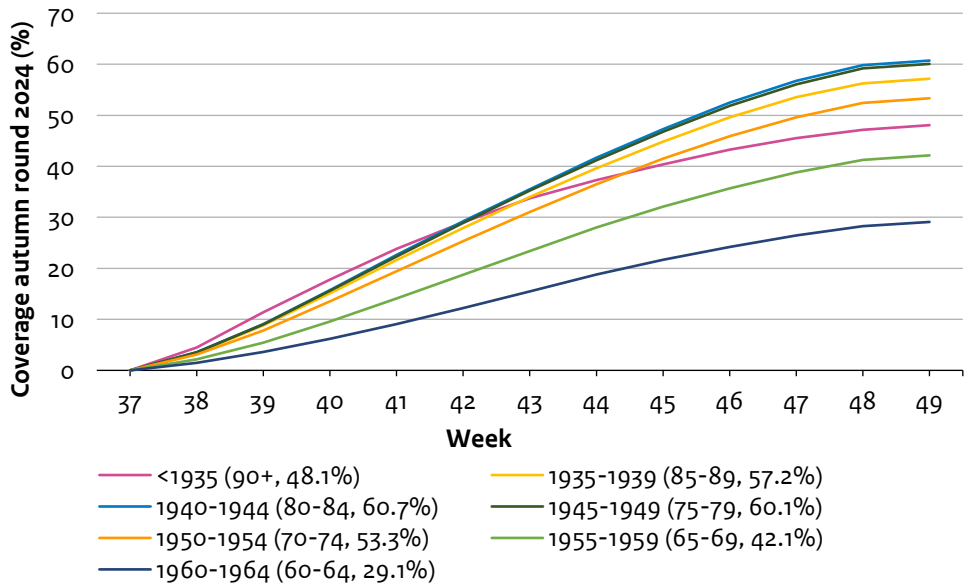
4 Vaccine coverage and determinants of vaccination

4.1 Vaccination coverage of the autumn 2024 vaccination round

In the autumn round of 2024, a total of 2,513,671 COVID-19 vaccinations were registered by RIVM. Vaccination coverage for people over 60 is 46.6%[47]. Vaccination coverage varied by age group and region. Until 6 December 2024, the COVID-19 vaccination was available and advised for people aged 60 and older, people between the age of 18 and 59 who receive an annual invitation to have the flu vaccine, children and adults with a high medical risk for severe COVID-19 (such as severely immunocompromised persons and healthcare workers who are directly in contact with vulnerable patients.

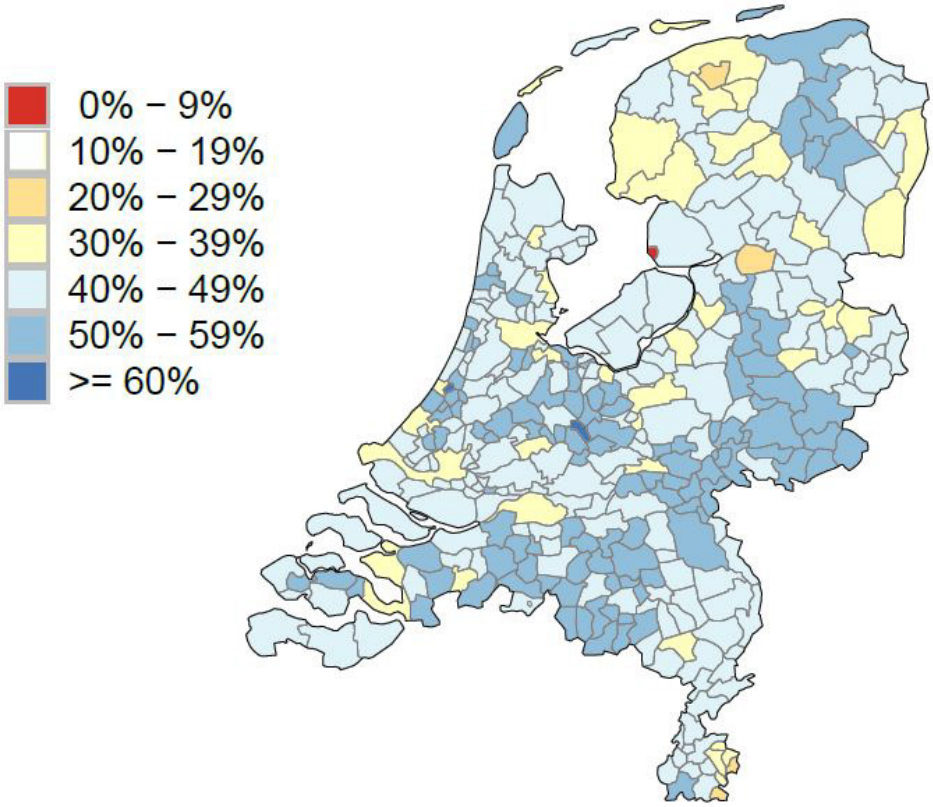
Vaccination coverage among over-60s was lowest for people aged 60–64 (29.1%) and highest for people aged 80–84 (60.7%) (Figure 4.1). Vaccination coverage was slightly lower than average in the three largest cities (Amsterdam, Rotterdam and The Hague). In some municipalities in the provinces of Friesland and Overijssel, in the 'Bible belt' and along the eastern border of the Netherlands, vaccination coverage was also lower than the national average (Figure 4.2).

Figure 4.1 Vaccination coverage of the autumn round 2024 per birth cohort, per week, week 38 until week 49, 2024. [1-2]



[1] Data source: CIMS
[2] COVID-19 vaccination was available for people aged 60 years and older, people between the age of 18 and 59 who receive an annual invitation to have the flu vaccine, children and adults with a high medical risk for severe COVID-19 (such as severely immunocompromised persons and healthcare workers who are directly in contact with vulnerable patients).

Figure 4.2 Vaccination coverage of the autumn round 2024 per municipality, birth years 1964 and before, week 38 until week 49, 2024.[1]



[1] Datasource: CIMS

4.2 Vaccine coverage of the autumn 2023 vaccination round

Detailed information on vaccine coverage for the general population aged 60 years and older, specific groups such as health care workers and medical high-risk groups, based on the national registration system CIMS, CBS data and the VASCO study cohort is available in the previous evidence update, published on 20 March 2024.

In January 2025, RIVM published a report in which the COVID-19 uptake among pregnant women was studied [48]. At the end of 2021, the uptake for at least one COVID-19 vaccine among women who delivered in 2021 and/or 2022 was 62%, whilst for all women in fertile age (born in 1976-2001) it was 73%.

A recent study from the University Medical Centre Utrecht assessed the coverage for several vaccines, including COVID-19, among immunocompromised patients. In contract to the other relevant vaccines, the coverage for COVID-19 vaccine was relatively high (92%) [49].

4.3 Acceptance and determinants of vaccination: RIVM research

In 2024, RIVM continued to study determinants of COVID-19-vaccination in several research projects. One of these is the Co-Detervax

study, which is carried out in a research platform within the CBS research environment. Findings have been reported in the scientific literature, the annual National Immunisation Programme (NIP) reports and the previous evidence update. Recently, Co-Detervax research focussed on determinants of COVID-19-vaccination among two key populations: those with an underlying medical risk for severe COVID-19, and those of non-Dutch origin. Results considering medical risk groups indicate that their vaccine coverage in 2023 was lower than in 2022, both in those over and below 60 years of age [50]. In the study among people of non-Dutch origin, determinants of COVID-19 vaccine uptake among those aged 60 years and older in the primary vaccination and 2022 autumn booster round were assessed. Results indicate that those less likely to be vaccinated were: Younger persons, migrants with two parents born abroad, inhabitants of highly or extremely urban areas and persons with low medical risk, lower income and lower education level. The effect of origin was only partially mediated by socio-economic status [51].

Other recent RIVM research included an exploratory interview study in 2022 among people of Moroccan origin in the Netherlands, aimed at gaining a better understanding of the factors at play in this population's vaccination decision-making [51]. Based on the interviews, the following eight themes were identified: (1) Over time, attitudes towards COVID-19-vaccination changed and vaccination decisions were postponed, (2) the decision whether or not to get vaccinated resulted from an individual risk-benefit assessment (3) decisional or anticipated regret influenced the vaccination decision, (4) Several information sources were used, including those of RIVM and municipal health services (5) perceived lack of trustworthiness of the information had a negative influence on the decision (6) Social environment could both support and burden the decision-making process (7) Religious beliefs and values could hamper and encourage getting vaccinated, and (8) Few practical barriers to vaccination uptake were encountered. Further information will become available in the NIP report 2024 and the scientific publication.

Mid-2023 another study was performed by RIVM into willingness to get COVID-19 vaccinated among the general population, consisting of a literature study, qualitative interviews and a questionnaire study (see Insights from behavioural research for the COVID-19 vaccination campaign in autumn 2023 | RIVM). Determinants of a positive attitude towards COVID-19 vaccination included: higher age, having received the previous COVID-19 vaccination; the estimated chance of getting severe COVID-19, being convinced that the vaccine is protective, being convinced that vaccination helps to prevent overburdening of healthcare, and vaccination choices of people's social environment. Participants who indicated they (probably) did not want to get vaccinated gave three main reasons: trusting their own immune system, not wanting to keep getting vaccinated every year, or not considering the COVID-19 situation seriously enough. Pregnant women were uncertain about why they were invited for COVID-19 vaccination, about the risks of COVID-19 and the safety of COVID-19 vaccination. Further information about this study is available in the NIP report of 2024.

In mid-June 2024, the RIVM behavioural unit has conducted a survey to investigate participants' willingness to get vaccinated against corona (see Compliance with and support for the basic rules of conduct | RIVM). At that time, 45% of participants who think they will be eligible for the influenza vaccination in the fall of 2024 indicated that they will probably or definitely get the COVID-19 vaccination. At the time of the survey, the willingness to get the influenza vaccination was higher than that to get the COVID-19 vaccination (67% and 45% respectively). Vaccination willingness among this target group is related to age and belief about the safety of the vaccine, but less to education type.
Almost half of all participants (both below and above 60 years old) who indicate that they do not want a COVID-19 vaccination during autumn 2024 are worried about side effects or unknown long-term consequences. A quarter of the participants who are hesitant about the COVID-19 vaccination would like to have more information about the effectiveness of the vaccine, and a fifth wants more information about the safety.

5 Epidemiological update COVID-19 and SARS-CoV-2 virology

5.1 Epidemiological update

5.1.1 Incidence of SARS-CoV-2 over time

Current indicators for the incidence of SARS-CoV-2 in the Netherlands are the number of virus particles in wastewater and the proportion of participants in 'Infectieradar' reporting a positive SARS-CoV-2 test. SARS-CoV-2 circulation does not have a stable seasonal pattern yet and increases are also observed outside the respiratory season. The optimal timing of booster vaccinations depends on the seasonality and on the waning of protection after booster vaccination.

The National Coordination Center for Patient Distribution (LCPS) stopped reporting the number of COVID-19 hospitalisations as of June 2024, but still receives data from around 50 hospitals. COVID-19 mortality via the cause of death statistics from CBS is currently available up to and including March 2024. It must be noted that COVID-19 as the cause of death may be missed as testing reduced over time. For example the general advise for self-testing was discontinued in March 2023, and COVID-19 guidelines for nursing homes updated in August 2023 indicate that after two residents have tested positive for COVID-19 in a department/living group, other residents of the same group suspected of having COVID-19 no longer need to be tested. See the latest figures on causes of death of deceased persons on the website of the Dutch Central Bureau of Statistics. More recent figures on total mortality are available (see further).

The figures as presented in the previous evidence update by RIVM have been updated here to include data from the period January 2022-January 2025 when available. After the peak in the winter of 2023/2024 described in the previous evidence update, the circulation of SARS-CoV-2 declined and stayed at low levels in the spring of 2024. In June circulation increased and a summer wave was observed with a peak in the second half of July. The average number of SARS-CoV-2 virus particles in wastewater in week 29 was 1,192 average virus particles (x100 billion) per 100,000 inhabitants, which was much lower compared to the peak average of 4,406 in week 51 of 2023. The percentage of Infectieradar participants with a positive SARS-CoV-2 test result was 1.7% in week 30 2024, compared to 3.6% at the peak of the winter wave in 2023. In week 39, 2024 there was an autumn peak, with on average 1,387 virus particles (x100 billion) per 100,000 inhabitants in waste water. The percentage of Infectieradar participants with a positive test was 1.4% in week 39, 2024. After this peak, the circulation of SARS-CoV-2 declined and stayed at low levels during winter 2024. The number of hospital admissions (LCPS data) at the peaks of the waves in 2024 was low (less than half) compared to the peaks in 2022 and 2023, even when adjusting for the reduced number of hospitals reporting. While excess mortality was observed during SARS-CoV-2 waves in 2023, weekly mortality remained within the expected range during the summer 2024 wave.

Figure 5.1 shows the viral load in wastewater (available at Weekly figures coronavirus SARS-CoV-2 | RIVM) and the percentage of Infectieradar participants with a positive test (available at Infectieradar) from 2022 up to and including 16 January 2025, and the number of hospital admissions per day in wards (available at Datafeed - LCPS) up to and including May 2024.

Figures 5.2 and 5.3 are provided by LCPS, whereby data for all time points is based on data from those hospitals that continued reporting after June 2024.

Figure 5.4 shows the number of deaths with COVID-19 as the cause of death per month for the period January 2022 up to and including August 2024 reported by CBS.

Figure 5.5 shows total mortality by age group up to 2 February 2025 (see Monitoring mortality rates Netherlands | RIVM).

Figure 5.1 Viral load in wastewater (7-day moving average) and proportion of participants in Infectieradar reporting a positive test per week (2020-16 January 2025), and the average daily number of hospital admissions (2020-May 2024).

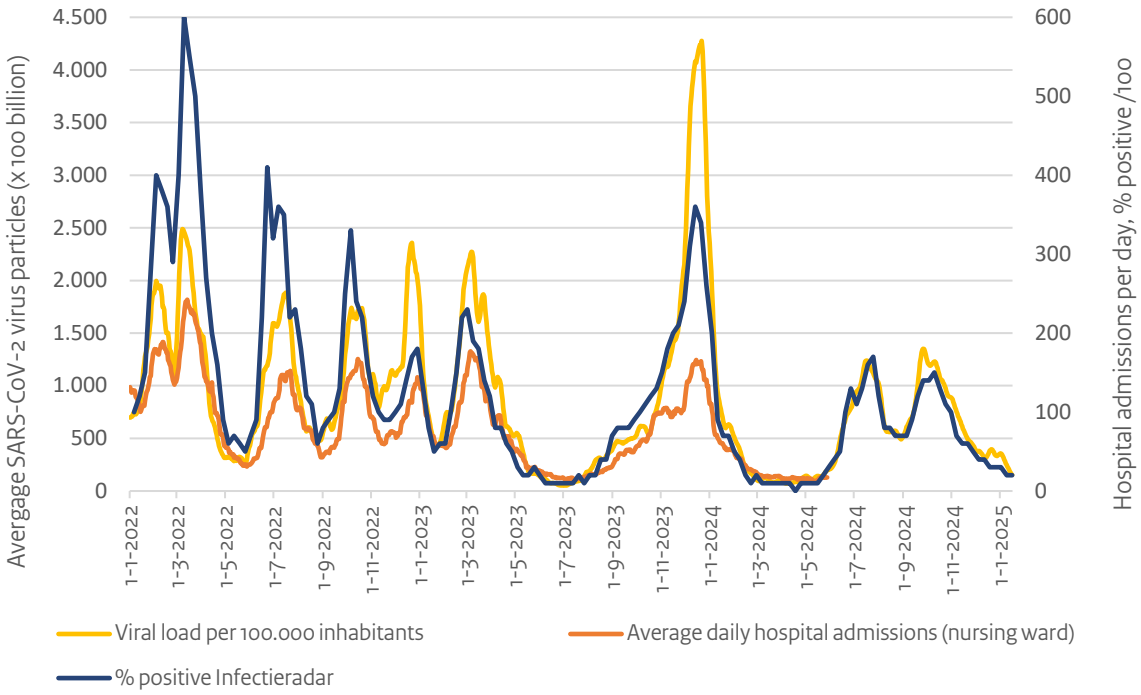
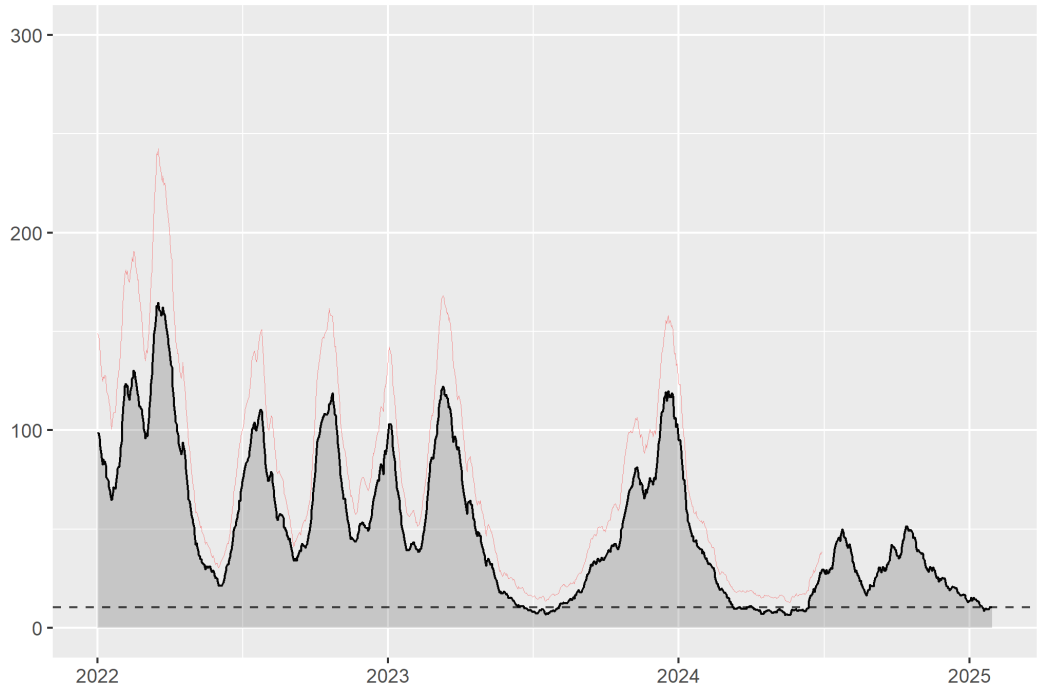
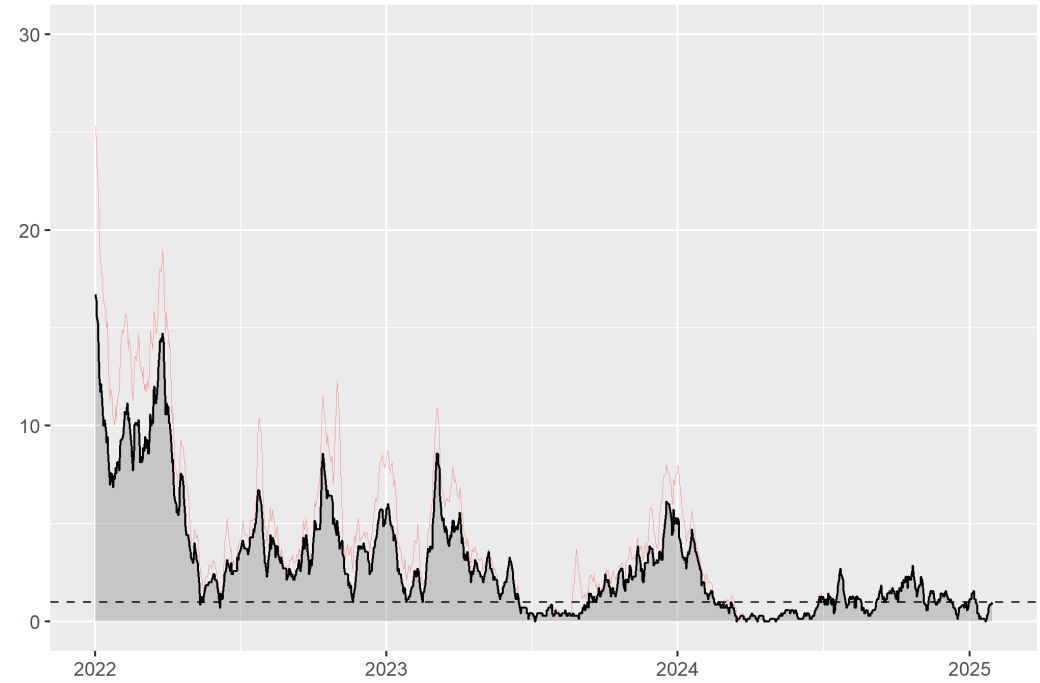


Figure 5.2 Daily number of nursing unit admissions of patients with SARS-CoV-2 infection (7-day moving average), reported to LCPS until 28 January 2025.



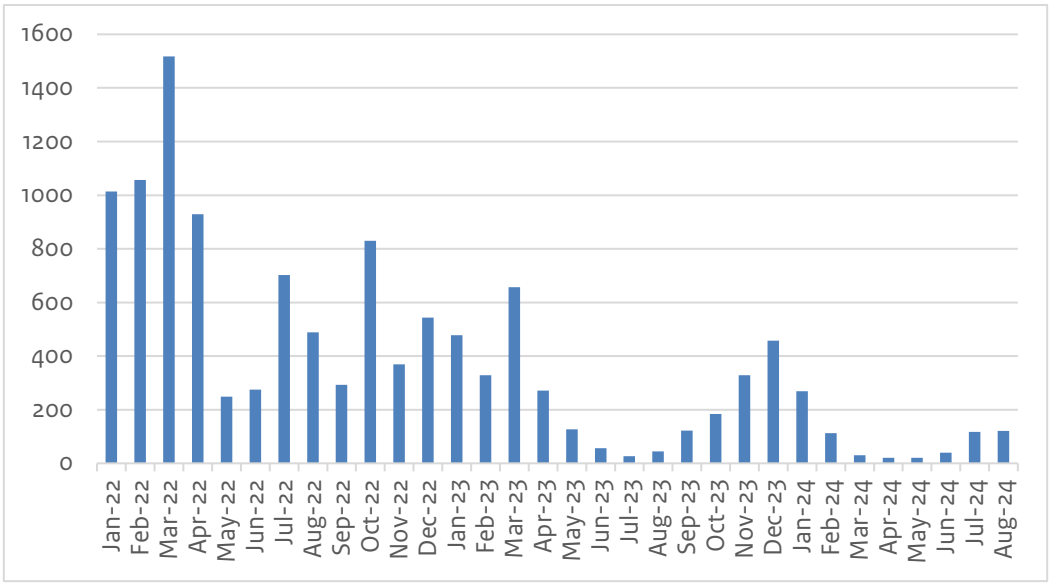
The red dashed line is based on the period up to 1 June 2024 when all hospitals provided data, the black line is based on data from around 50 hospitals that provided data after 1 June 2024. The dashed horizontal line corresponds to the average daily number 28 January 2025.

Figure 5.3 Daily number of intensive care unit admissions of patients with SARS-CoV-2 infection (7-day moving average), reported to LCPS until 28 January 2025.



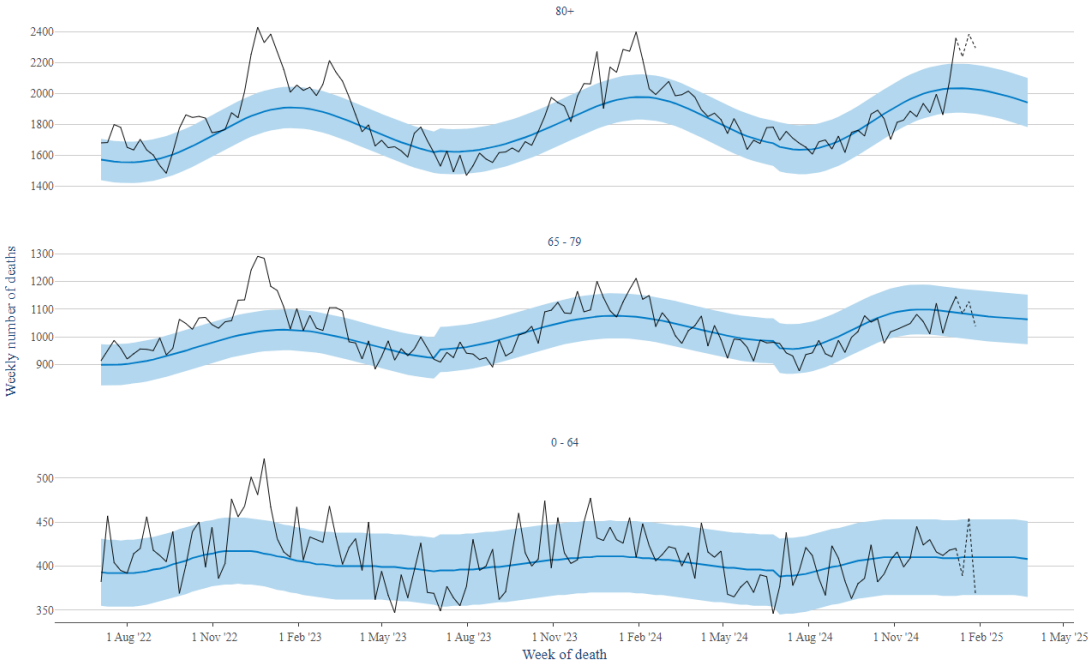
The red dashed line is based on the period up to 1 June 2024 when all hospitals provided data, the black line is based on data from around 50 hospitals that provided data after 1 June 2024. The dashed horizontal line corresponds to the average daily number on 28 January 2025.

Figure 5.4 Monthly mortality with COVID-19 as primary cause of death (Jan 2022-Aug 2024).



Note: Data source: CBS (see *the website of the Dutch Central Bureau of Statistics*).

Figure 5.5 Total mortality in the Netherlands by age group 0-64 years, 65-79 years and 80+ years (4-7-2022 until 2-2-2025).



Legend:
Black line: Reported mortality to CBS.
Blue line: expected mortality based on mortality rates of last years.
Band: upper and lower limit of the expected mortality.
Dashed line: estimates for the most recent 4 weeks.

5.1.2 *Severe COVID-19*

The incidence of hospital admissions and deaths due to COVID-19 are indicators of severe COVID-19. In the previous evidence update by RIVM (March 2024), detailed analyses of COVID-19 hospitalisations were presented. Since the beginning of 2024, however, data on hospitalisations from National Intensive Care Evaluation Foundation (NICE) is no longer available.

Table 5.1 presents re-analyses of NICE data from 2023, whereby the incidence by age-group is presented. Since April 2023, the NICE registration of COVID-19 hospital admissions has been increasingly incomplete. For illustration: between September 2023 and December 2023 only ~55% of COVID-19 hospital admissions were recorded in NICE. No correction has been made for this underreporting. The stratification by age group shows that hospitalisation incidence was relatively low among children >1 year of age and adults below age 50 years and notably higher among younger and older persons. The highest incidence was found among elderly aged ≥80 years, followed by the youngest age group <6 months. The high incidence among infants aged <6 months is discussed further in Chapter 3.2.

Table 5.1 Incidence of COVID-19 hospitalisation registered in NICE in 2023 by age group.[1-2]

	COVID-19 hospitalisation in 2023	
Age group	**Number**	**Incidence per 100,000 population**
<6 months	276	308.2
6 months - 1 year	77	86.0
1-4	79	11.5
5-9	29	3.2
10-19	65	3.3
20-39	467	10.4
40-49	369	17.3
50-59	1003	39.4
60-69	2389	109.8
70-79	4821	291.3
≥80	5624	659.2

[1] In 2023, NICE registration for COVID-19 hospitalisation was known to be incomplete.
[2] Not included in the estimates are hospitalisations for which it is mentioned that admission was due to non-COVID-19 reasons. However, hospitalisations for which information on the cause was missing (for about half of the hospitalisations this is the case) are included. Hence, for a considerable part of the included hospitalisations, it is unclear whether it was with or due to COVID-19.

5.2 Virology: update about the SARS-CoV-2-variants

During the COVID-19 pandemic, in the period before Omicron, SARS-CoV-2 evolved with new variants being dominant in cycles of about 6 to 10 months. New dominant variants had an evolutionary advantage compared to their predecessors in that they were more transmissible and could faster spread. This was due to factors including for example high virus excretion, stability of the virus, changes in binding properties and/or changes in Spike-protein cleavage during the infection process. In addition, immune escape played a role.
Those variants with an evolutionary advantage that potentially form a risk to public health are called Variants-of-Concern (VOCs), as such defined by WHO. Also within variants, changes occur leading to subvariants.

The pattern in the pre-Omicron period reflected adaption of the zoonotic SARS-CoV-2 to humans. Since Omicron emerged, immune escape is the most important driver of the emergence of new variants [53,54]. Omicron turned out to be a variant with relatively much immune escape (in a population with high levels of immunity), however generally causing less serious disease compared to Delta variants. Since Omicron emerged, the evolutionary pattern gradually changed. Omicron BA.1 became dominant quickly, within months succeeded by BA.2 and BA.5. After of the occurrence of BA.2, many subvariants emerged [55].

Since the end of 2023, however, a single Omicron sub-variant (JN.1), which is genetically very different from all previous variants, became dominant (source: RIVM). Based on this, WHO advised in April 2024 to use the JN.1 variant as the vaccine antigen. However, (sub)variants,

such as KP.2, KP.3, and XEC, a recombinant of two JN.1 subvariant, [56] keep emerging. The FDA decided, based on this, to recommend KP.2 based vaccines. In the Netherlands, KP.3 and XEC are the most common variants (January 2025). To date there are no indications that the subvariants of the Omicron JN.1 variant cause more severe disease in populations with high levels of immunity (see Variants of the coronavirus SARS-CoV-2 | RIVM). This observation was also made by WHO and ECDC (see SARS-CoV-2 variants of concern at ECDC).

Omicron subvariants have many changes in the S-protein. These probably play a role in the reduced neutralisation by existing vaccine induced and natural immunity, and also in transmissibility. Several studies confirm that antibodies induced by prior VOCs or Omicron subvariants are less able to neutralise new Omicron subvariants [57]. This is also the case for the currently dominant JN.1 variant [58,59]. Recent data confirm this picture. Serum samples that were taken after bivalent booster vaccination with BA.1 and XBB.1.5 vaccines neutralised JN.1 viruses less efficiently than they neutralised earlier variants [60]. Serum samples of XBB.1.5. vaccinated individuals, or those with XBB.1.5., EG.5, HK.1 or JN.1 break through infected individuals, neutralised KP.2 less than JN.1 [61]. These findings are confirmed by Roederer et al 2024 [62] and Jian et al, 2024 [63] (of note: these manuscripts are not yet peer reviewed). However, in addition to neutralising antibodies, other mechanisms, such as T-cell immunity, play an important role in the protection against severe disease.

Research into protective immunity of vaccines based on both previous and more recent Omicron variants is now available. Ma et al [64] (2024, not yet peer reviewed) found that XBB.1.5. vaccination was associated with less protection against hospitalisation due to JN.1 infection than against hospitalisation due to XBB.1.5 infection, but that some protection was still present. The severity of disease did not differ between the two subvariants in the studied populations. These observations were confirmed by Moustsen-Helms (2024) [65], whereas Lewnard et al 2024 [66] did find an indication that JN.1 caused less severe disease.

In summary, antibodies induced by previous Omicron variants are less able, in vitro, to neutralise more recent Omicron variants, although some neutralisation capacity remains. This is confirmed by vaccine effectiveness studies. The mismatch between the XBB.1.5. based vaccine and the JN.1 subvariant was larger than the relatively small mismatch between the JN.1 vaccine and the currently circulating KP.3 and XEC subvariants [67]. Of course, in spring 2025, different subvariants may circulate. Due to ongoing viral evolution, vaccines will always lag behind the circulating variants. However, to date, protection against severe disease due to more recent variants remains partly intact.

6 Immunogenicity, vaccine effectiveness and seroprevalence

6.1 Immunogenicity

6.1.1 Introduction

The RIVM Corona Vaccination studies monitor and evaluate the immunological responses induced by the vaccines delivered as part of the national COVID-19 vaccination programme in healthy participants of all ages eligible for vaccination. Here we report results that were obtained since the publication of the previous evidence update. These results include amplitude and kinetics of SARS-CoV-2 Spike S1-specific total binding antibody (IgG) concentrations which were measured in serum and mucosal lining fluid from the nose collected before and at 1, and 12 months after vaccination in healthy individuals of 60 years-old (y.o.) and older who were vaccinated with the monovalent Omicron variant XBB.1.5 based mRNA vaccine (Comirnaty® (BioNTech/Pfizer)) in the autumn of 2023. In addition, neutralizing capacity of these antibodies as well as T-cell memory responses against both the original Wuhan virus strain and the Omicron variant XBB.1.5 vaccine strain were determined.

Presented data are from people aged 60 years and older who were vaccinated according to the regular vaccination program. Results were stratified by three older adult age groups (60-69, 70-79 and 80-100 years of age; age groups were defined based on the age at the first primary vaccination). An overview of doses and vaccines used is provided in Table 6.1 below. In Appendix 10.2 the number of participants per assay, stratified by age group and SARS-CoV-2 infection status is presented (Table 10.2). Also the number of samples per assay, with multiple samples for different timepoints per participant, stratified by age group and SARS-CoV-2 infection status are presented in Appendix 10 (Table 10.3).

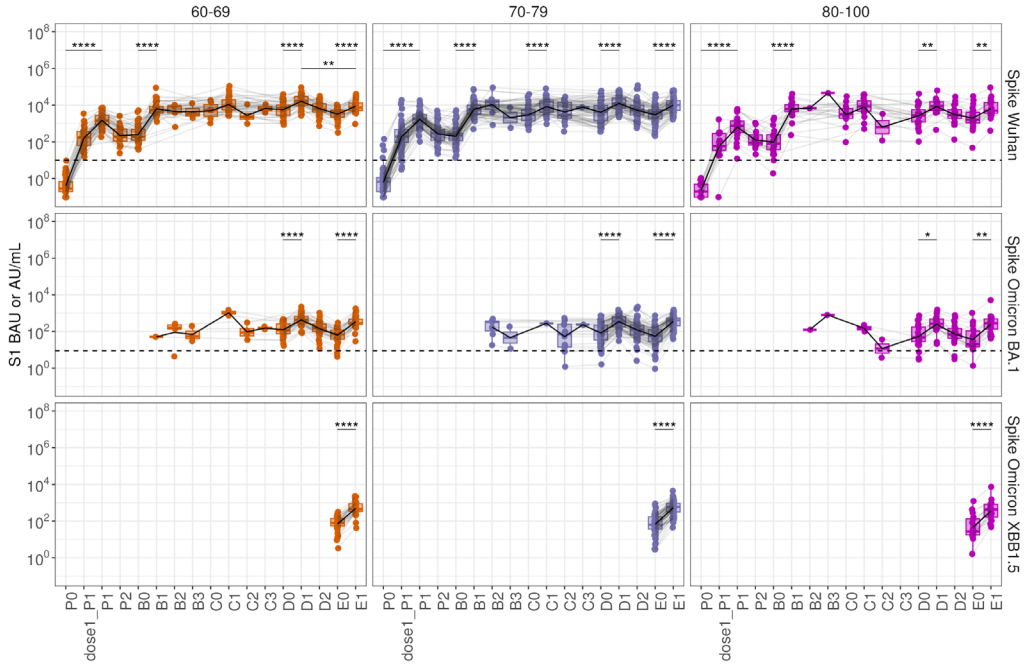
Table 6.1 Vaccination round, dose and type vaccine(s) used.

Vaccination	**Dose**	**Vaccine(s) used**
Primary series	1 & 2	monovalent mRNA vaccines (Comirnaty (BioNTech/Pfizer) or Spikevax (Moderna))
1st booster	3	monovalent mRNA vaccines (Comirnaty (BioNTech/Pfizer) or Spikevax (Moderna))
2nd booster (Spring 2022)	4	monovalent mRNA vaccines (Comirnaty (BioNTech/Pfizer) or Spikevax (Moderna))
Autumn 2022 booster	5	bivalent Wuhan-Omicron BA.1 based mRNA vaccine
Autumn 2023 booster	6	monovalent Omicron XBB.1.5 based mRNA vaccine (Comirnaty XBB.1.5 (BioNTech/Pfizer))

6.1.2 *Solid immune response after COVID-19 booster vaccinations in all older age groups*

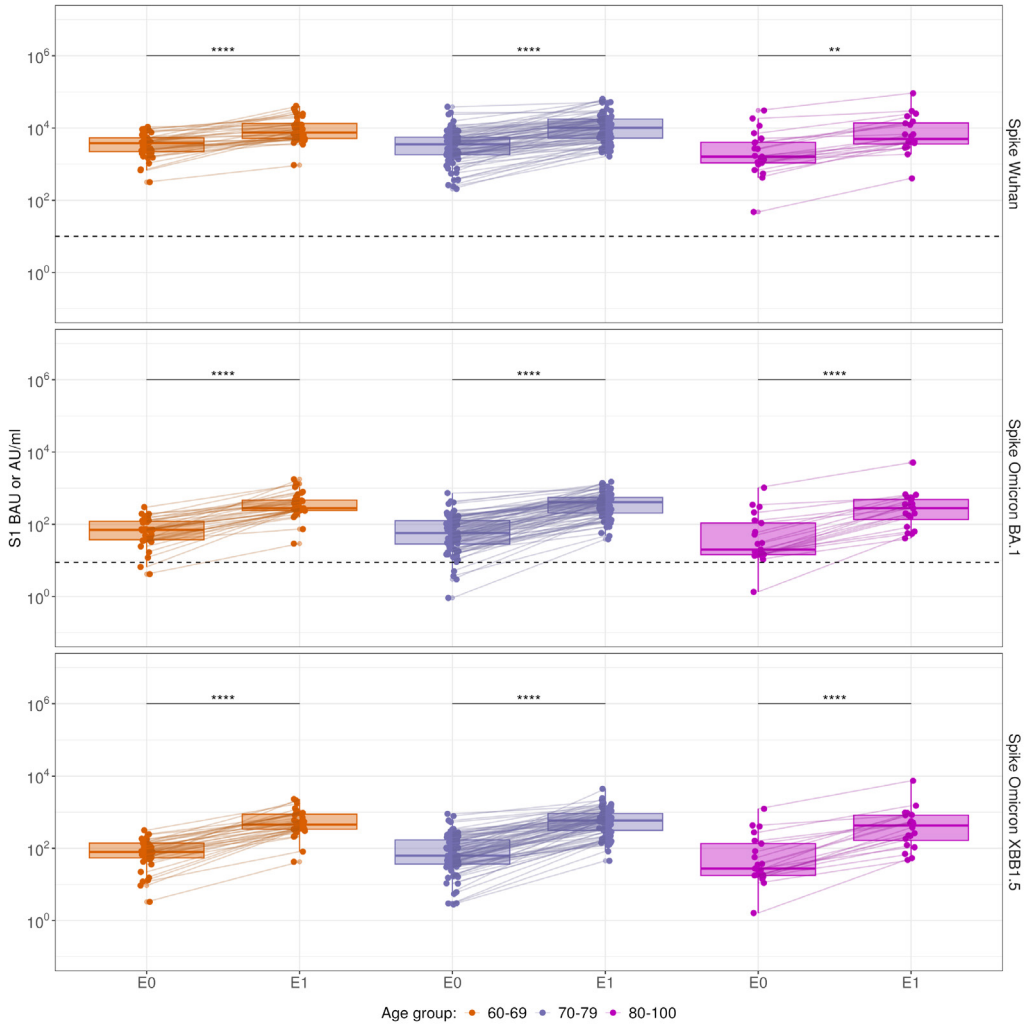
All older adult age groups show an increase in SARS-CoV-2 specific IgG total binding antibody concentrations after the autumn 2023 monovalent Omicron variant XBB.1.5 based booster vaccination. This is observed for IgG antibodies directed against the S-protein of the vaccine strain but also against the Omicron variant BA.1 and the original Wuhan strain that were part of the bivalent and previous monovalent vaccines (Figure 6.1). In addition, the IgG antibody levels induced by the XBB.1.5 booster vaccination were similar to those detected after the previous booster (D1 vs E1 IgG comparisons are not significantly different) except for Wuhan-specific IgG in the 60-69 age group where levels were lower. Moreover, the Omicron-based booster vaccines were able to induce Omicron BA.1-specific IgG antibodies in participants that were seronegative before vaccination (D0 and E0: before bivalent or XBB.1.5 booster (5th and 6th dose) respectively; Figures 6.1 and 6.2). Fold changes in vaccine-induced antibody concentrations were higher against both Omicron strains compared to against the original Wuhan virus (Figure 6.3).

Figure 6.1 Kinetics of Spike S1-specific antibody concentrations (IgG) following COVID-19 vaccinations for Wuhan (BAU/ml) and Omicron BA.1 and XBB.1.5 virus variants in community dwelling older adults by age group regardless of their health status.



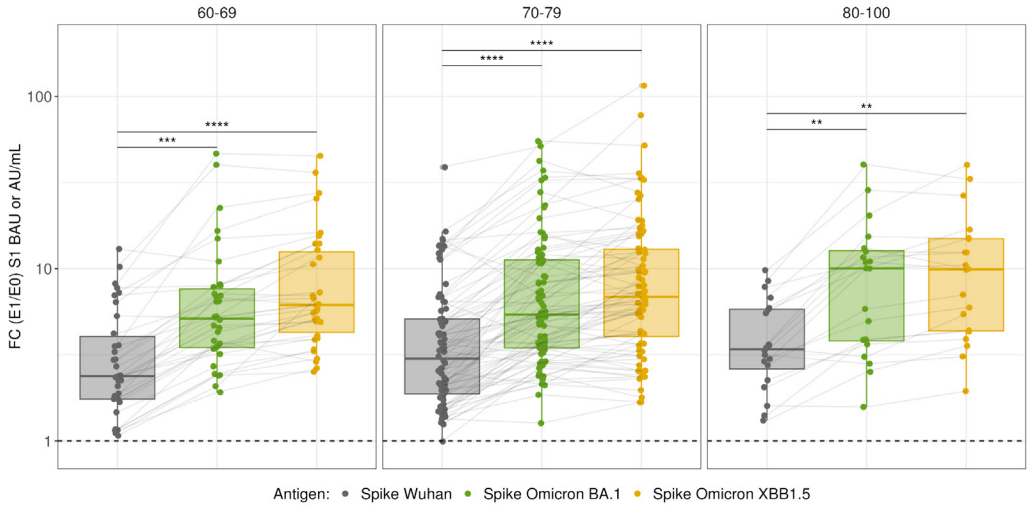
The dashed horizontal lines represent the threshold for seropositivity. The threshold for seropositivity for Omicron XBB.1.5 remains to be established. P/B/C/D/E-0 vs 1 and D1 vs E1 comparisons made with paired Wilcoxon signed ranked test (**** p-value (p)<0.0001; *** p<0.001; ** p<0.01; * p<0.05). Black line connects GMCs (Geometric Mean Concentrations). BAU: Binding Antibody Units; AU: Arbitrary Units. P: primary series (1st and 2nd dose); B: first booster (3rd dose); C: second booster (4th dose); D: bivalent booster (5th dose), E: Omicron XBB.1.5 booster (6th dose). 0: 1 pre-vaccination, 1: 1 month post-vaccination; 2: 6 months post-vaccination. E0, pre XBB.1.5 booster is a year post 5th dose.

Figure 6.2 Spike S1-specific IgG binding antibody concentrations pre- vs post-XBB.1.5 booster vaccination for Wuhan (BAU/ml) and Omicron variants BA.1 and XBB.1.5 (AU/ml) across age groups.



The dashed horizontal lines represent the threshold for seropositivity. The cut-off for Omicron XBB1.5 remains to be established. E0 vs E1 comparisons made with paired Wilcoxon signed ranked test (**** p-value (p)<0.0001; *** p<0.001; ** p<0.01). Age group comparisons made with Kruskal-Wallis test and Dunn's multiple tests with Benjamini-Hochberg (BH) correction for multiple comparisons (not statistically significant). BAU: Binding Antibody Units; AU: Arbitrary Units. E: Omicron XBB.1.5 booster (6th dose). 0: pre XBB.1.5 booster is a year post 5th dose, 1: 1 month post-vaccination.

Figure 6.3 Comparison of fold change (FC) post- to pre- Omicron XBB.1.5 booster vaccine-induced Spike-S1 IgG binding concentrations for Wuhan (BAU/ml) and Omicron BA.1 and XBB.1.5 variants (AU/ml) by age groups.



Paired Wilcoxon signed ranked test with Benjamini-Hochberg (BH) correction for multiple comparisons (**** p-value (p)<0.0001; *** p<0.001; ** p<0.01; *p<0.05). Dashed line represents no change between E0 and E1 response. E: Omicron XBB.1.5 booster (6th dose). 0: pre XBB.1.5 booster is a year post 5th dose. 1: 1 month post-vaccination.

Older adults with an infection history have slightly higher antibody titers compared with infection naive participants (data not shown).
Overall, antibody responses after booster vaccinations, including after the Omicron XBB.1.5 variant based vaccine, are similar for all older adult age groups and for male and female participants (data not shown). However, the age groups with participants of 70 years and older show more variation in responses compared with the 60-69 year old age group (Figures 6.1 and 6.2). Data from nursing home residents 52-100 years of age show similar antibody profiles (data not shown).

6.1.3 *Increase in Wuhan and Omicron variant XBB.1.5 specific virus neutralizing antibody titers after vaccination with XBB.1.5 based vaccine*

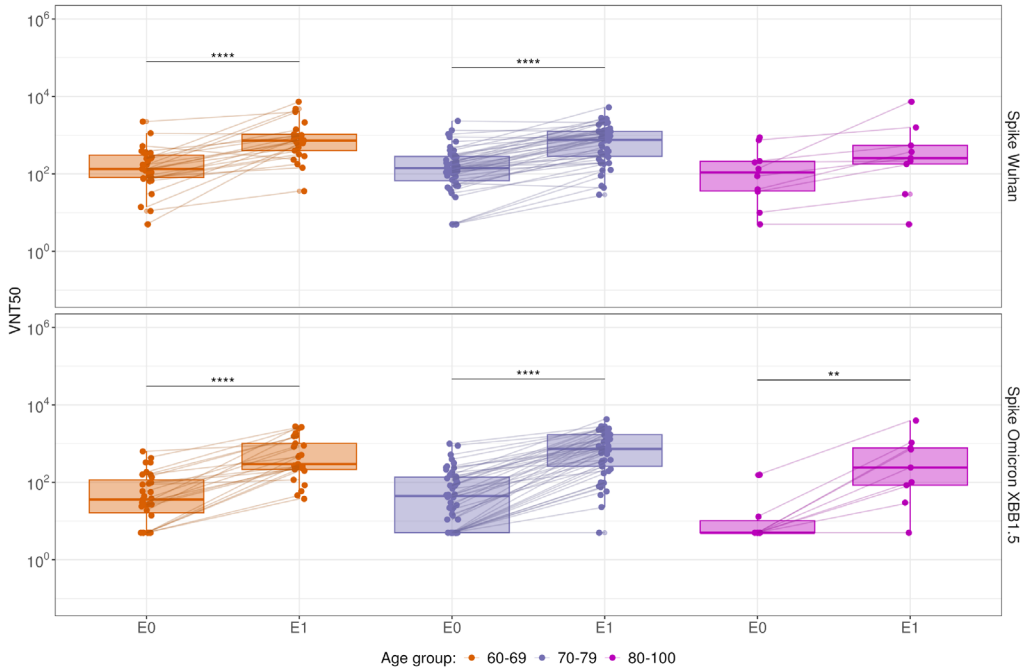
In addition to binding antibody levels virus neutralization titers (VNTs) have been assessed in subgroups of participants of all older age groups. VNTs against the original Wuhan strain and the XBB.1.5 variant strain have been measured in sera collected before and after vaccination, 6th dose for older adults (60+ years), of a subgroup of CVT study participants of 64-90 years of age (n=65). The VNTs specific for the Omicron XBB.1.5 strain, on which the 2023 vaccine was based, showed a clear increase at 1 month post vaccination for all older age groups (Figure 6.4). VNTs against the original Wuhan strain also increased after vaccination with the Omicron XBB.1.5 based vaccine. Roughly three quarters of the participants already had detectable antibodies that were able to neutralize XBB.1.5 virus before vaccination (data not shown).

6.1.4 *Local immunity in upper respiratory tract*

SARS-CoV-2 infection can induce S1-specific IgG and IgA antibodies within the nasal epithelium [68], but these local antibodies can also be derived from the circulation [68,69]. Mucosal IgG and IgA have virus neutralizing capacity that can protect against future infections and can

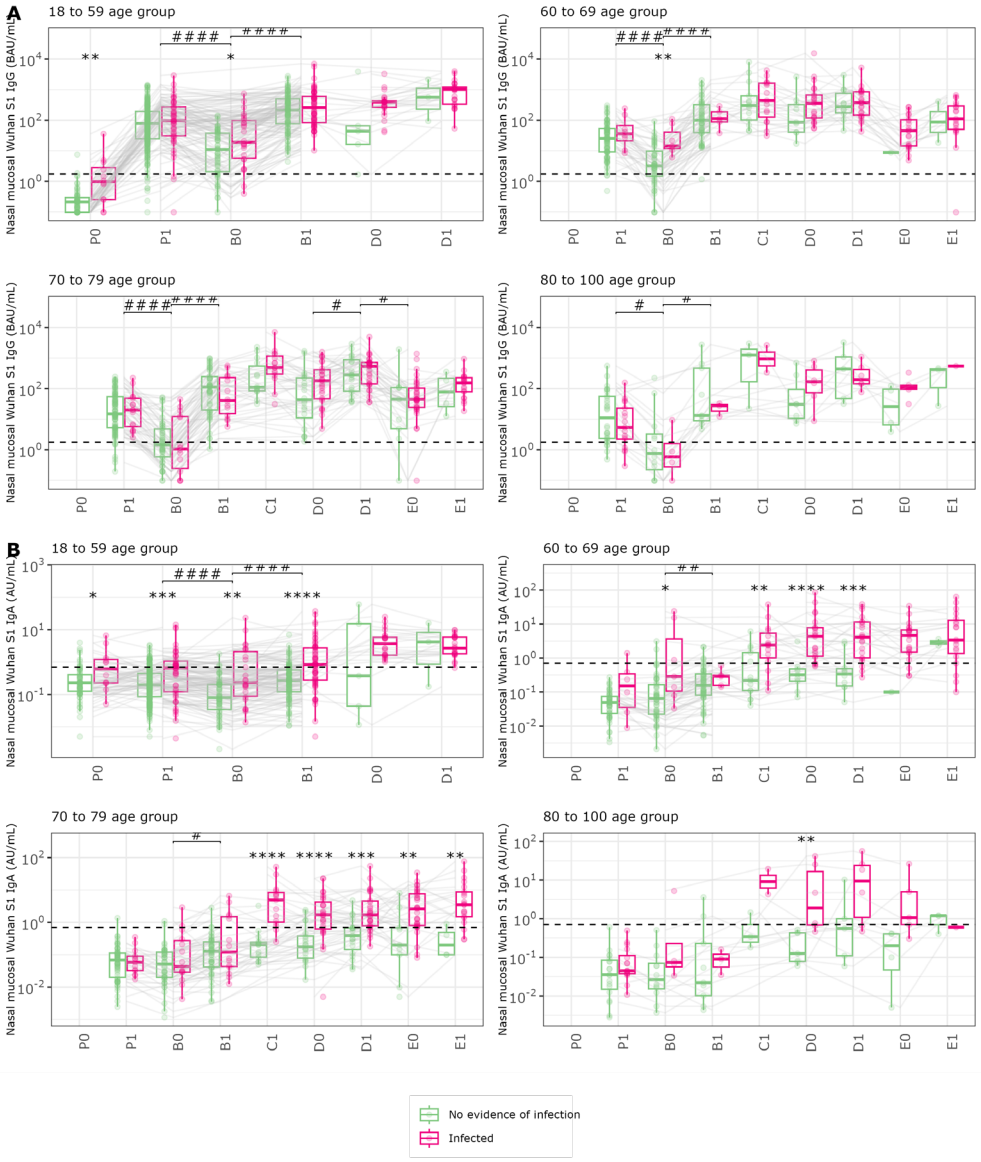
possibly also reduce transmission of the virus to others [70,71]. In the Corona Vaccination Studies both SARS-CoV-2 S1-specific IgG and IgA have been measured in nasal lining fluid samples. Since age differences were observed for systemic antibody responses of these participants (Figure 6.1), the mucosal antibody dataset has been stratified into four age groups (18 to 59; 60 to 69; 70 to 79; 80 to 100 years of age). Both Wuhan S1 specific IgG and, to a lesser extent, IgA, showed an increase in concentration in mucosal fluid after subsequent vaccinations (Figure 6.5 and 6.6)

Figure 6.4 The 50% virus neutralization titers (VNT50) against the SARS-CoV-2 original Wuhan strain and Omicron XBB.1.5 virus variants.



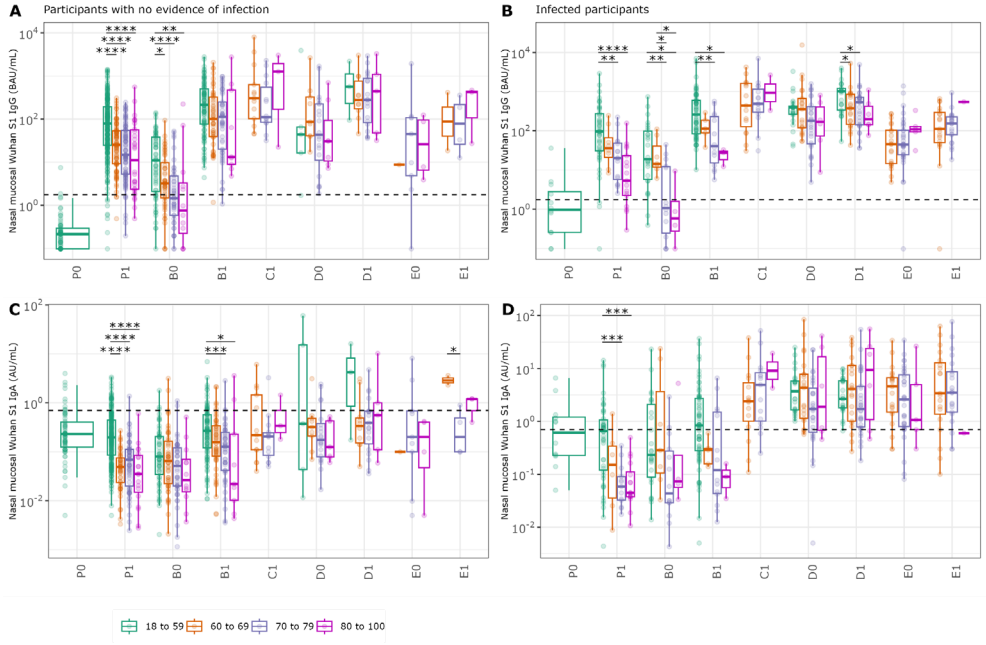
Pre- versus post- Omicron XBB.1.5 booster vaccination. Paired Wilcoxon signed ranked test (**** p-value (p)<0.0001; ** p<0.01). E: Omicron XBB.1.5 booster (6th dose). 0: pre XBB.1.5 booster is a year post 5th dose., 1: 1 month post-vaccination.

Figure 6.5 The effect of vaccination and SARS-CoV-2 infection on Wuhan S1 protein specific IgG (A) and IgA (B) antibody responses in nasal mucosa in four age groups (18 to 59, 60 to 69, 70 to 79 and 80 to 100 years).



Comparisons between infected and not infected are made with Wilcoxon signed ranked test (**** p-value (p)<0.0001; *** p<0.001; ** p<0.01; * p<0.05). Comparisons between the timepoints in not infected participants (i.e. the effect of vaccination or waning after vaccination) are made with paired Wilcoxon signed rank test (#### p<0.0001; ### p<0.001; ## p <0.01; # p<0.05). Both tests were corrected for multiple comparisons by means of Benjamini-Hochberg (BH) correction. BAU: Binding antibody Units; AU: Arbitrary Units. The dashed horizontal lines represent the threshold for seropositivity. P: primary series (1st and 2nd dose); B: first booster (3rd dose); C: second booster (4th dose); D: bivalent booster (5th dose), E: Omicron XBB.1.5 booster (6th dose). 0: 1 pre-vaccination, 1: 1 month post-vaccination; 2: 6 months post-vaccination. E0, pre XBB.1.5 booster is a year post 5th dose.

Figure 6.6 Comparison of nasal mucosal lining fluid Wuhan S1-protein specific IgG (A, B) and IgA (C, D) antibody concentrations in different age groups – 18-59, 60-69, 70-79 and 80-100 years. Mucosal Wuhan S1 IgG (A and B) and IgA (C and D) in persons with no evidence of infection (A and C); and in previously infected persons (B and D).



Age group comparisons were performed with Kruskal-Wallis test (significant for all panels), followed by Dunn's multiple test with Benjamini-Hochberg (BH) correction for multiple comparisons (**** p-value (p)<0.0001; *** p<0.001; ** p<0.01; * p<0.05). BAU: Biological Arbitrary Units; AU: Arbitrary Units. The dashed horizontal lines represent the threshold for seropositivity. P: primary series (1st and 2nd dose); B: first booster (3rd dose); C: second booster (4th dose); D: bivalent booster (5th dose), E: Omicron XBB.1.5 booster (6th dose). 0: 1 pre-vaccination, 1: 1 month post-vaccination; 2: 6 months post-vaccination. E0, pre XBB.1.5 booster is a year post 5th dose.

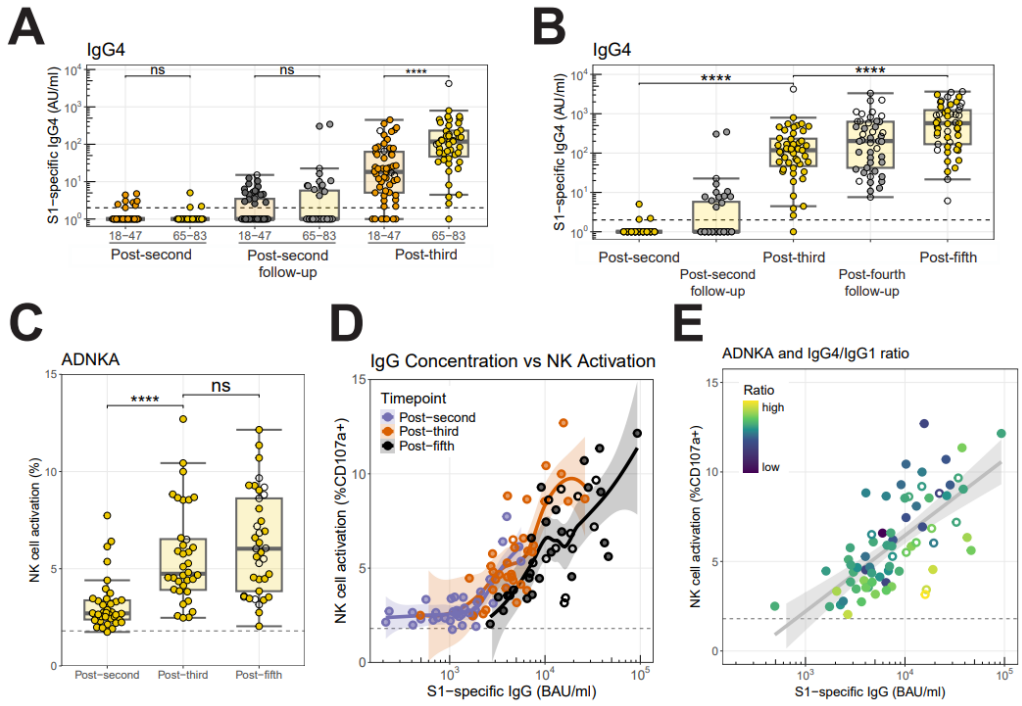
Overall mucosal IgA levels are very low specifically in infection naive participants. Kinetics of the S1 specific mucosal IgG antibody response is similar to the response measured in serum (Figure 6.1), suggesting an interplay between the systemic and mucosal compartment and a potential serum origin of mucosal IgGs.
Infected individuals had higher mucosal antibody concentrations compared to individuals with no evidence of a SARS-CoV-2 infection (Figure 6.5). The differences between these two groups were specifically visible for IgA, as most infection-naïve participants had antibody concentrations under the threshold for seropositivity [70]. Local S1 IgA in the nose is mainly boosted by recent SARS-CoV-2 infections; but the fact that mucosal S1 IgA concentrations also increase in infection-naïve participants after booster vaccination indicates that vaccinations increase local immunity (B0 and B1 timepoint, respectively; Figure 6.5 A).
Vaccination induced a significant increase in mucosal S1 specific IgG concentrations in all adult age groups (Figure 6.6). After the first vaccination adults of 70 years and older showed significantly lower nasal mucosal IgG and IgA concentrations compared with younger adults (18-59 yrs), with the lowest concentrations in the oldest age group. After second and subsequent boosters mucosal antibody concentrations in

older adults were similar to concentrations measured in younger adults regardless of the infection status (Figure 6.6). Indicating that older adults require an additional vaccination to mount a similar mucosal antibody response compared to younger adults. This was also observed for serum antibodies. As has been shown for serum antibodies levels mucosal antibody levels wane over time after vaccination even after having received five vaccinations.

6.1.5 SARS-CoV-2 specific IgG4 subclass concentrations and antibody effector functions in older adults

Antibodies can bind to and neutralize the SARS-CoV-2 virus with their virus-specific head but they also play a role in immune cell and complement activation through their Fc-tail. More data have become available that show that these Fc-effector functions play an important role in protection against disease caused by respiratory viruses, including SARS-CoV-2. There are 4 different IgG antibody subclasses (IgG1-IgG4) that differ in their constant region (Fc-tail) that can bind to Fc-receptors on immune cells. IgG1 and IgG3 antibodies are relatively good in activation of antibody-dependent immune effector functions, whereas IgG4 antibodies in contrast are much less effective and are thought to play a role in attenuating inflammation. Primary series vaccinations mainly induce IgG1 and IgG3 responses, while some individuals also show IgG2. Recent research has shown that repeated (booster) vaccination with COVID-19 mRNA vaccines in adults results in an increase in IgG4 antibody levels [72]. Data from our Corona vaccination studies confirm that repeated vaccination results in IgG4 antibody production (Figure 6.7. A). Furthermore, older adults (65 years and older) produced more IgG4 after the first booster vaccination (third dose) than younger adults, although other factors than age might play a role in this difference (e.g. timing of vaccination and vaccine type). IgG4 levels increase further with subsequent booster doses as was shown in older adults (B). In contrast, Fc-mediated functionality, such as natural killer cell activation, of the virus-specific antibodies only shows a marginal increase with subsequent booster vaccinations (C). This could be related to the decrease in capacity of S1-specific serum antibodies to mediate NK cell activation relative to S1-specific total binding IgG concentrations upon repeated vaccination (D). This decrease was associated with an increased IgG4/IgG1 ratio (E).
In summary, following repeated vaccination, adults start to produce increasing amounts of IgG4, an antibody subclass that is less capable of activating immune cells involved in killing of virus-infected cells. Although this might reflect an immune regulation process, further research is necessary to assess whether the induction of IgG4 after repeated vaccination affects vaccine effectiveness.

Figure 6.7 SARS-CoV-2 S1-specific IgG4 subclass concentrations in adults (18-47 years) and older adults (65+ years) one month after the second vaccination, 5-7 months after the second vaccination and one month after the third vaccination (A) and for older adults in addition to the timepoints included in (A) 5 months after the fourth vaccination and one month after the fifth vaccination (B). Antibody-dependent Natural Killer cell activation (ADNKA) capacity one month after primary series and third and fifth vaccine doses (C), correlation between virus-specific total IgG concentration and ADNKA (D) and association between relative ADNKA and IgG4/IgG1 ratio (E).



6.1.6 *T-cell immunity against the original Wuhan, Omicron-BA.1 and Omicron XBB.1.5 virus variant strains in older age groups*

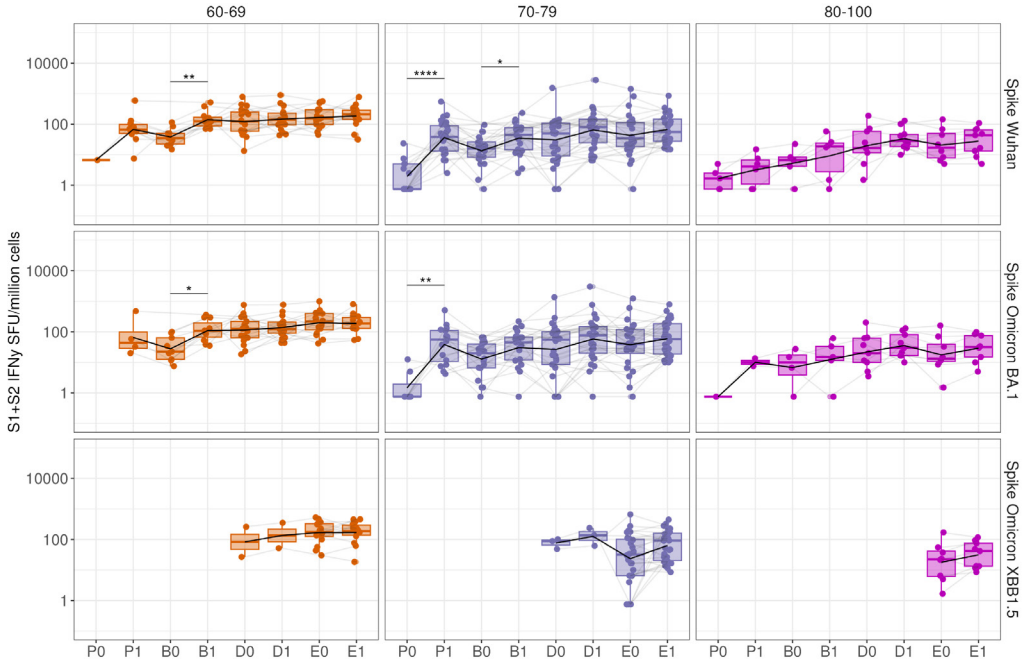
In older adults, SARS-CoV-2 Spike-protein specific T-cell immunity against the original Wuhan virus, Omicron-BA.1 and Omicron XBB.1.5 virus variant strains have been measured with an IFNγ ELISpot assay. Memory T-cells, important for protection against severe disease, are directed against a large number (around 30) of spike epitopes. Epitopes are specific regions within antigens that T-cells and B-cells can recognize and bind to. The large number of T-cells-recognized Spike epitopes, including many conserved regions of the Spike protein, assures protection against a broad spectrum of virus variants and renders T cell immunity less sensitive for escape of immunity by new virus variants.

Our data show a stable IFNγ T-cell response over time for all SARS-CoV-2 Spike protein variants after an initial significant increase after primary series vaccinations and for the 60-69 age group also after the first booster (3rd dose); Figure 6.8). Only a small (not significant) increase followed by a marginal decrease in T-cell frequencies has been observed after bivalent (Wuhan-OmicronBA.1) and Omicron XBB.1.5 booster vaccinations in all older age groups. However, a greater variation in T-cell responses was shown in participants older than 70 years than in the

60-69 year age group which can be partly explained by a higher number of individuals who did not respond to (primary) vaccination (<1 SFUs/million cells) in the 70+ group. Interestingly, these initially non responding participants highly benefit from further booster doses since 1 month after the 6th (2023) vaccination (E1), they all showed an IFNγ T-cell response >5 SFUs/million cells for Wuhan and Omicron BA.1 and >8.5 SFUs/million cells for Omicron XBB1.5.

Older adults with an infection history, (56% of the older adult participants of the T-cell analyses subset of our study) have slightly higher T-cell responses compared with infection naive participants (data not shown). In contrast to IgG levels, the IFNγ T-cell response drops with aging, with the 80-89 y.o. group showing a significantly lower IFNγ T-cell response than 60-69 y.o. participants pre- and post- Omicron XBB1.5 vaccination towards the Spike protein of all virus variants (Figure 6.9 right plot). Persons 70-79 y.o. participants only show a lower Omicron BA.1- and Omicron XBB1.5-specific IFNγ T-cell response prior Omicron XBB1.5 vaccination.
Interestingly, T-cell responses against the Omicron BA.1 and XBB.1.5 variants have been measured in almost all participants of all older age groups even before they were vaccinated with vaccines based on these Omicron variants. This indicates that the T-cell receptors can indeed recognize a wider range of epitope variants compared to the highly specific antibody response. Upon XBB.1.5 vaccination, the similar antigen-specific IFNγ T-cell response might be attributed to a synergistic effect of cross-reactive T-cells and de-novo Omicron-XB.B1.5 vaccine-induced T-cells (Figure 6.10).

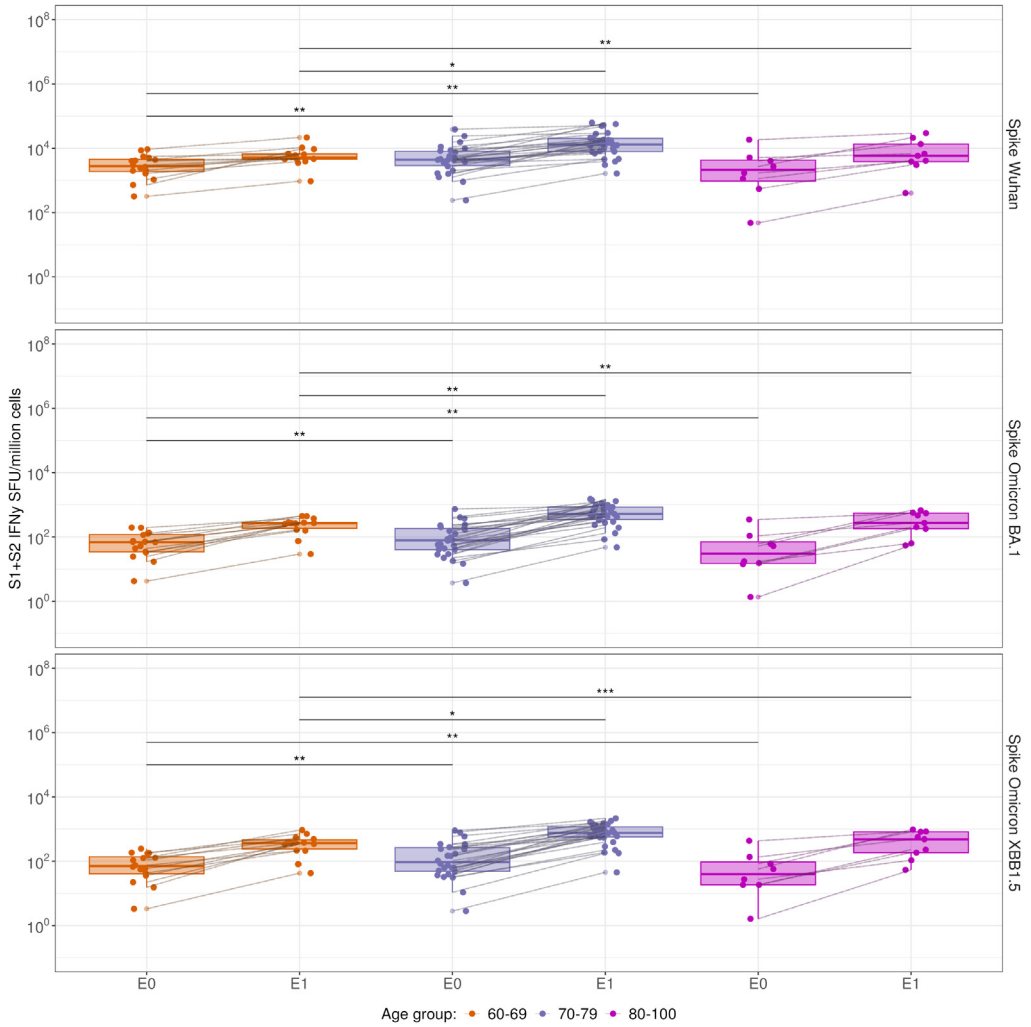
Figure 6.8 Kinetics of Spike S1+S2-specific IFNγ T-cell responses specific to Wuhan and Omicron BA.1 and XBB.1.5 virus variants in community dwelling older adults by age groups following COVID-19 vaccinations.



P/B/D/E-0 vs -1 and D1 vs E1 comparisons made with paired Wilcoxon signed ranked test (**** p-value (p)<0.0001; ** p<0.01; * p<0.05). Black line connects GMCs (Geometric

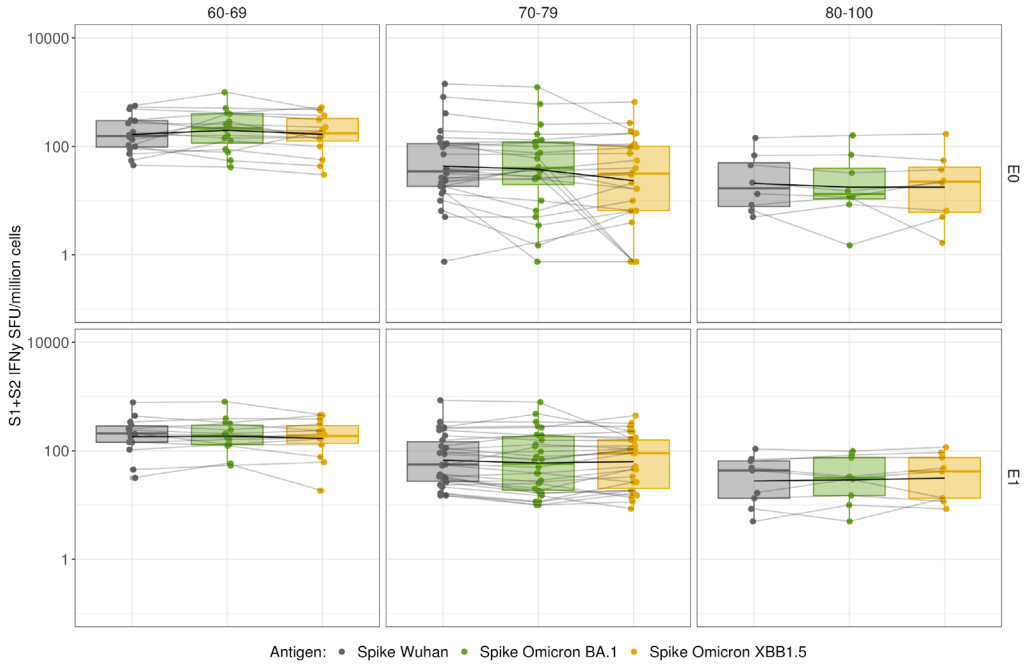
Mean Concentrations). P: primary series (1st and 2nd dose); B: first booster (3rd dose); C: second booster (4th dose); D: bivalent booster (5th dose), E: Omicron XBB.1.5 booster (6th dose). 0: 1 pre-vaccination, 1: 1 month post-vaccination;. E0, pre XBB.1.5 booster is a year post 5th dose.

Figure 6.9 Comparison of IFNγ ELISpot T-cell responses pre- vs post-XBB.1.5 booster vaccination to Wuhan and Omicron virus variants across age groups.



E0 vs E1 comparisons made with paired Wilcoxon signed ranked test (not statistically significant). Age group comparisons made with Kruskal-Wallis test and Dunn's multiple test with Benjamini-Hochberg (BH) correction for multiple comparisons (*** p<0.001; ** p<0.01; *p<0.05). E: Omicron XBB.1.5 booster (6th dose). 0: pre XBB.1.5 booster is a year post 5th dose., 1: 1 month post-vaccination.

Figure 6.10 Comparison of Wuhan, Omicron BA.1 and Omicron XBB.1-specific IFNγ ELISpot T-cell responses pre- (E0; top row) and post- (E1; bottom row) XBB.1.5 booster vaccination by age groups.



Paired Wilcoxon signed ranked test with Benjamini-Hochberg (BH) correction for multiple comparisons (not significant differences). E: Omicron XBB.1.5 booster (6th dose). 0: pre XBB.1.5 booster is a year post 5th dose., 1: 1 month post-vaccination.

6.2 Vaccine effectiveness (VE)

6.2.1 VE against death

VE estimates of the COVID-19 boosters offered in 2021 and 2022 against death by COVID-19, all-cause mortality and death from primary causes other than COVID-19 in the first 8 weeks after vaccination have been published in an RIVM report and summarised in the previous COVID-19-vaccination evidence update. It was concluded that the risk of death decreased after every booster dose, but that the protection offered by vaccination reduces over time. It was not possible to assess if the VE reduced faster over time in (some of the) medical risk groups, because in 2022 these groups were offered vaccination twice (see previous update).

Effectiveness of the XBB.1.5 vaccine used in the 2023 autumn booster campaign against death by COVID-19 has been estimated in international studies, although most estimates are quite uncertain. A study in three Scandinavian countries during both XBB and JN.1-dominated periods found high VE against death of 78% at 12 weeks of follow-up [74]. Similarly to VE against hospitalisation, VE was estimated to be lower during JN.1 dominance compared to during XBB dominance [75,76,77]. Pooling data from several European countries, the two aforementioned VEBIS studies estimated VE against death was 67% among persons aged 65 to 79 years and 72% among persons aged 80 years older during XBB.1.5 predominance and 59% and 51%, respectively, during JN.1 dominance, with the maximum time since vaccination around 3 months [76,77]. (NB: The XBB.1.5 period analyses

were based on data from only three countries [76].) Such a difference in VE against death between XBB and JN.1-dominated periods was also observed in a US study [75].

6.2.2 *VE against hospitalisation*

The most recent vaccine effectiveness (VE) estimates from the Netherlands concern the 2023 autumn booster campaign and are described in the previous evidence update by RIVM (March 2024). Estimated vaccine effectiveness of the XBB.1.5 vaccine was 70.7% (95%CI: 66.6-74.3) against hospitalisation and 73.3% (95%CI: 42.2-87.6) against ICU admission between October 9th and December 5th 2023 [78]. Repeating these analyses for a prolonged study period from October 9th to December 31st 2023 stratified by medical risk group (no increased risk, eligible for influenza vaccination, high medical risk) indicated that VE did not differ much between medical risk groups (see previous evidence update). In the Netherlands and elsewhere, nearly all administered vaccines since autumn 2023 are mRNA vaccines and VE studies either exclude vaccinations with other (protein-based) vaccines or do not distinguish between mRNA and other vaccines.

International studies also show that the XBB.1.5 vaccine protected against hospitalisation during the autumn and winter of 2023-2024 [74, 75,79,80,81]. As reported in the 2023-2024 National Immunisation Programme surveillance report, VE estimates among persons aged 65 years and older by the United Kingdom Health Security Agency (UKHSA) were somewhat lower than the aforementioned estimates from the Netherlands and decreased over time since vaccination [79], while VE estimates from other European countries were comparable to the Dutch estimates (VE between 60 and 76%) [74, 81]. According to UKHSA, VE of the XBB.1.5 vaccine was 55% at 2-4 weeks, 48% at 5-9 weeks and 42% at 10-14 weeks, with persons who received ≥2 COVID-19 vaccine doses at least 12 weeks prior but not the XBB.1.5 vaccine as the reference group [79]. The lower VE may be partially explained by higher overall immunity at the start of the campaign, as the United Kingdom also offered vaccination in spring 2024 [79]. Studies in the United States (US) and Canada also generally found lower VE against hospitalisation than Dutch estimates (between 38% and 61% at up to about 8 weeks after vaccination) [75,82,83,84,85], in part because these studies included adults aged 12 or 18 years and older, with one study among immunocompromised adults [84].

Different Omicron (sub-)lineages circulated in autumn and winter 2023-2024 (see chapter 6.3 of this document). XBB sub-lineages (e.g. XBB.1.5 and EG.5.1) were predominant in autumn, but from December 2023 - January 2024 onwards the BA.2.86 lineage and its descendant JN.1 dominated [76,79,82]. As the JN.1 sub-lineage differs antigenically and phylogenetically from the XBB.1.5 sub-lineage targeted by the XBB.1.5 vaccine [82], multiple international studies analysed VE against hospitalisation by an XBB variant / in an XBB-dominated period and by JN.1 / in an JN.1-dominated period separately [64,75,76,77,79,82,83,86]. These studies find that VE against hospitalisation by JN.1 / when JN.1 predominated was lower than VE against hospitalisation by an XBB variant / when an XBB variant predominated, but that vaccination also offered protection against

hospitalisation (likely) by the JN.1 variant. Using whole genome sequencing, the UKHSA estimated variant-specific VE against hospitalisation among persons aged 65 and older at 2-4 weeks after vaccination at 37% for JN.1, 45% for EG.5.1 and 74% for other XBB sub-lineages. VE decreased to 26% for JN.1, 43% for EG.5.1 and 68% for other XBB sub-lineages at 5-9 weeks [79]. Two European multi-country studies using similar methods (part of the Vaccine Effectiveness Burden and Impact Studies (VEBIS) project) estimated VE against hospitalisation in periods when XBB.1.5 and JN.1 predominated, respectively. In the XBB.1.5-dominated period, VE at 2 weeks to 3 months after vaccination was 67% among 65-79-year olds and 66% among persons aged 80 years and older, compared to 51% and 41%, respectively, in the JN.1-dominated period [76,77]. A similar trend was observed in four US studies, although VE estimates were lower [64,75,82,83]. Despite this trend, another multi-country European study confirms that the XBB.1.5 vaccine did protect against hospitalisation related to the JN.1 variant and provides VE estimates stratified by age, time since vaccination and (number of) chronic conditions [86].

6.2.3 VE against SARS-CoV-2 infection

In VASCO, a large Dutch prospective cohort study, VE of Omicron XBB.1.5 vaccination against self-reported SARS-CoV-2 infection between October 2023 and July 2024 was estimated in XBB.1.5 vaccine-eligible adults who previously received primary vaccination series and at least one booster [87]. In participants aged 60 years and older, VE against infection was 38% (95%CI: 33-43). The VE estimates were higher up to 6 weeks after vaccination compared with 7-12 weeks after vaccination (46% vs 31%). Protection against infection was highest after a prior infection in the past year either with (78%) or without (71%) previous XBB.1.5 vaccination. In participants aged 18-59 years, who were eligible to receive the XBB.1.5 vaccine because they were healthcare worker or belonged to a medical risk group, VE was 35% (95%CI: 25-45). Also in this age group VE was higher up to 6 weeks after vaccination compared with 7-12 weeks after vaccination (45% vs 29%), but CIs were wide. A prior infection in the past year provided relatively good protection against a new infection too, either with (82%) or without (63%) XBB.1.5 vaccination.

During the first three months of the study period, there was a transition from Omicron XBB variants (including EG.5) to BA.2.86 and its descendant JN.1. VASCO participants were asked to submit positive SARS-CoV-2 self-tests for sequencing. Of 593 infections during this transition period a sequencing result was known, of which 173 (29%) were caused by Omicron XBB and 407 (69%) by BA.2.86/JN.1. Among infected participants with sequencing data, those who had received the XBB.1.5 vaccine had slightly (though non-significantly) higher odds of their infection being caused by BA.2.86 and JN.1 sub-variants rather than XBB variants (OR: 1.5; 95%CI: 0.8-2.6). This analysis was adjusted for age, sex, educational level, medical risk condition, prior infection and calendar time. This suggests the XBB.1.5 vaccine might be less effective against infection with the JN.1 variant.

Similar to the VE estimation of Omicron XBB.1.5 vaccination, we estimated VE of Omicron JN.1 vaccination against self-reported infection

between 23 September 2024 and 5 January 2025. Vaccination data for this analysis was only available from self-report and was not yet cross-referenced with data from the vaccination registry CIMS. This might have underestimated our vaccine effectiveness estimates. In participants aged 60 years and older, VE against infection was 21% (95%CI: 6-33). VE was higher against symptomatic infection (34%; 95%CI: 18-47) and among participants who reported to (almost) always test in case of COVID-19 related symptoms (27%; 95%CI: 13-38). Protection against infection was highest after a prior infection in the past year either with (61%) or without (35%) JN.1 vaccination. In participants aged 18-59 years VE against infection was 41% (95%CI: 7-62). Because of low numbers we were not able estimate VE within healthcare workers or those with a medical risk condition separately. A prior infection in the past year provided relatively good protection against a new infection too, either with (79%) or without (69%) JN.1 vaccination.

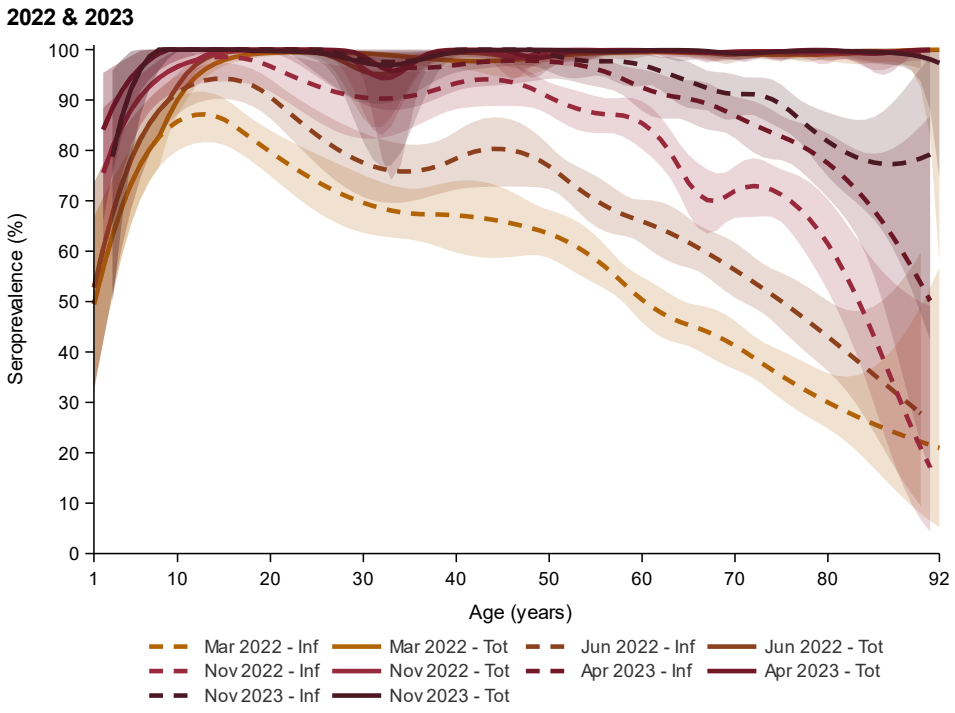
6.3 Seroprevalence

In the PIENTER-Corona (PICO) study, a prospective seroepidemiological study across all age groups and regions in the Netherlands, participants have consecutively been donating blood samples to assess SARS-CoV-2 antibodies and filling out questionnaires since the start of the pandemic in 2020.

As previously reported, the total SARS-CoV-2 seroprevalence (i.e., due to infection and/or vaccination) was above 95% in the general Dutch population already in the beginning of 2022, and remained high hereafter. Following the emergence of the Omicron variant in early-2022 and lifting of restrictions, infection rates have increased greatly across the population and became more similar between regions and sociodemographic groups [88]. The overall infection-induced seroprevalence (i.e., having had an infection at least once) in the general population increased from 74% (95% CI 70–77) in mid-2022, to 86% (95% CI 83–90) in late-2022, and 95% (95% CI 91–98) in spring 2023. The majority (over 90%) of persons below 60 years of age had already been infected at least once at the end of 2022 (Figure 6.11). The increase in infection-induced seroprevalence during winter 2022/2023 was particularly noticeable among older age groups, e.g., from 70% to nearly 90% in 70-year-olds, and from 60% to nearly 80% in 80-year-olds. Correspondingly, this was also reflected in a high proportion of breakthrough infections during that period (32% of vaccinated persons) – which generally has increased sharply since Omicron dominance. Incidence was lower among those with comorbidities (28%, vs. 33% without). For the older vaccinated age groups this was predominantly a primary infection, whereas for those in the younger age groups it was more often a re-infection. Although most of the vaccinated individuals had acquired hybrid immunity by spring 2023 (94%; to note, 96% of unvaccinated persons had proof of infection), still a fraction of groups at-risk had not, which supported targeted vaccination in autumn to maintain vaccine-induced immunity.

The most recent data from late 2023 indicates that the overall infection-induced seroprevalence increased further to 97% in the general Dutch population, and 97% of the vaccinated individuals had acquired hybrid immunity. Ninety percent of persons with comorbidities had evidence of (at least one) infection and practically all of those without comorbidities (99%). This was also illustrated by the rise in infection-induced seroprevalence at older age, with estimates above 90% in 70-year-olds and above 80% among 80-year-olds (Figure 6.11). The proportion of breakthrough infections among vaccinated individuals since spring 2023 was lower (19%) than during the previous (winter) period (33%). Incidence did not differ substantially between age groups or those with and without comorbidities, and for over 80% – regardless of age – it was a re-infection.

Figure 6.11 Weighted SARS-CoV-2 infection-induced ('Inf', dashed lines) and total ('Tot', i.e. infection and/or vaccination, solid lines) seroprevalence (with 95% confidence intervals) in the general population of the Netherlands in 2022 (March, June & November) & 2023 (April & November) (following the PIENTER Corona study rounds 7-11), by age (smoothed in years).



7 Disease burden of acute COVID-19 and cost-effectiveness of COVID-19 vaccination

7.1 Introduction

The burden of disease from acute COVID-19 in the Netherlands has previously been estimated and presented for the calendar years 2020, 2021, and 2022 in the previous evidence update. Here, we present an initial estimate of the burden of disease in the Netherlands for the calendar year 2023. The burden of post-acute sequelae of COVID-19 (PASC) is not included in any of these estimates. In 2023, following the pandemic phase, a COVID-19 vaccination programme was introduced for people aged 60 and older, medical risk groups, and healthcare workers, with a single vaccination in the autumn. We provide an order of magnitude estimate of the prevented burden of disease due to vaccination in 2023. Based on this, we provide an initial estimate of the cost-effectiveness of COVID-19 vaccination for those aged 60 and older.

7.2 Objective

The primary objective is to estimate the burden of acute disease from COVID-19 in the entire Dutch population in 2023. The secondary objective is to provide an order of magnitude estimate of the burden of severe acute COVID-19 that is prevented by vaccination. The tertiary objective is to compare the prevented burden of disease and related medical treatment costs against the costs of COVID-19 vaccination. The secondary and tertiary objectives are calculated only for those aged 60 and older. For medical risk groups under 60 years old, no burden of disease estimate is possible due to the lack of personal data on medical indications. For healthcare workers, the method used is not suitable because it only looks at direct protection for the vaccinated individuals themselves, while the goal of vaccination in this group also includes the protection of vulnerable patients with whom they have professional contact.

7.3 Methods

To express the burden of disease from various health outcomes in a single measure, the disability-adjusted life year (DALY) is used. This measure encompasses both the loss of quality of life due to illness and the years of life lost due to premature mortality. The method for DALY estimates of COVID-19 has been described in the literature for previous years [89,90]. We define severe COVID-19 as infections leading to hospitalisation, intensive care unit (ICU) admission, and/or death.

The numbers of COVID-19-related hospitalisations and ICU admissions by age and per calendar week in 2023 come from the National Intensive Care Evaluation Foundation (NICE) [91]. Since not all hospitals report to NICE, these numbers have been corrected for underreporting based on a comparison with the total number of reported COVID-19-related admissions by the National Coordination Center for Patient Distribution (LCPS) in 2023 [92]. The number of COVID-19 deaths by age in 2023 is

derived from cause-of-death data on deaths suspected or confirmed to be due to COVID-19 from Statistics Netherlands (CBS) [93].

An adjustment compared to previous burden of disease estimates, based on observations, is that for an ICU admission, a shorter length of stay of 7 days is now applied, and a longer length of stay on the general ward around this ICU admission of 13 days [94]. The prevented burden of disease due to the vaccination Programme for those aged 60 and older is estimated by calculating the expected number of deaths, ICU admissions, and hospitalisations in the actual situation with COVID-19 vaccination in the calendar year 2023 back to a hypothetical situation without COVID-19 vaccination in 2023. The expected cases of severe COVID-19 without vaccination are calculated using the formula: Number of cases with vaccination / (1 – vaccination rate * vaccine effectiveness).

The vaccination rate among those aged 60 and older in the COVID-19 autumn programme of 2023 was approximately 30% in the age group 60-64 years, 50% in 65-74 years, and 65% in those 75 and older [95]. The vaccine effectiveness against COVID-19-related hospitalisations and ICU admissions of the autumn dose of 2023 was estimated at about 70% for those aged 60 and older in the period from October 9 to December 31, 2023 (see previous evidence update). In the Netherlands, since early 2024, fewer data have been available on hospitalisations due to COVID-19, making such vaccine effectiveness analyses no longer possible. International data show that vaccine effectiveness decreases over time and disappears completely after 6 months [96]. Therefore, we limit the effectiveness of vaccination to the months of October through December and January through March. In 2023, approximately 80% of the total number of hospitalisations occurred during this period, and this percentage is also used for ICU admissions and deaths.

Given the uncertainty about vaccine effectiveness over time, three simplified scenarios are calculated: a constant vaccine effectiveness of 50% during this period (most realistic scenario), a lower effectiveness of 30%, and a higher effectiveness of 70%. The vaccine effectiveness is used against both hospitalisations and ICU admissions as well as against deaths.

The costs of hospital care are based on the length of stay and standard rates per day [97], adjusted to the price year 2023 [98]. A regular hospital admission costs €5,350, while an admission with ICU stay costs €28,500. The total vaccination costs consist of vaccine costs, administration costs, and Programme costs. For the fall campaigns of 2023 and 2024, the administration and Programme costs are not separately described in the national finances [99]. For the fall campaign of 2025, approximately €150 million has been reserved in the spring memorandum of 2024 for Programme costs for the RIVM, GGD GHOR, and the GGDs. Assuming 2.7 million vaccinations, as in 2023, this amounts to €55 per vaccinated person. The costs per vaccine are not public. We have calculated two scenarios: €20 and €45 per vaccine, resulting in total costs of €75 and €100 per vaccinated person, respectively.

In cost-effectiveness studies of other vaccines, programme costs are usually not included. Moreover, both administration costs and vaccine costs could decrease if the COVID-19 vaccination Programme becomes structural. Therefore, we also calculate total vaccination costs of €50 (€30 administration plus €20 vaccine) and €25 (comparable to influenza vaccination) per vaccinated person.

7.4 Results: Burden of Disease in 2023

The total burden of disease from COVID-19, including mild infections, in the entire Dutch population in 2023 is estimated at 37,800 DALYs (Appendix Table 10.1), which translates to a loss of 37,800 years of life in good health. This presented burden of disease is estimated based on the actual situation, thus in the presence of the existing vaccination program.

When looking solely at the burden of severe COVID-19 among those aged 60 and older, the estimated burden is 28,300 DALYs (Table 7.1). This burden arises from 22,150 hospitalisations, 1,050 ICU admissions, and 2,983 deaths. More than 80% of the hospitalisations and 97% of the deaths due to COVID-19 occurred among those aged 60 and older (Appendix Figure 10.1).

Table 7.1 Number of COVID-19-Related Hospitalisations and ICU Admissions (Corrected for Underreporting), Deaths, and DALYs Among Those Aged 60 and Older in the Netherlands in the Calendar Year 2023

Outcome	**Number of Cases**
Hospitalisations	22,150
ICU Admissions	1,050
Deaths	2,983
DALYs	28,300

7.5 Results: Burden of Disease Prevented by Vaccination

The estimate of the burden of disease prevented by vaccination depends on the assumed vaccine effectiveness (Table 7.2). In a scenario with a vaccine effectiveness of 50% during the periods January to March 2023 and October to December 2023, vaccination would have prevented 7,400 hospitalisations, 320 ICU admissions, and 1,100 deaths. This results in a prevented burden of disease of approximately 9,500 DALYs. In other words, vaccination has gained 9,500 years of life in good health.
With a vaccine effectiveness of 70%, the number of averted DALYs is estimated at 16,000, and with a vaccine effectiveness of 30%, at 4,900. The associated hospital costs prevented are estimated at €47 million with a vaccine effectiveness of 50%. With a vaccine effectiveness of 70%, the prevented hospital costs would be €80 million, and with a vaccine effectiveness of 30%, €24 million (Table 7.2).

Table 7.2 Estimated number of COVID-19-related hospitalisations, ICU admissions, deaths, DALYs, and hospital costs prevented by vaccination among those aged 60 and older per vaccine effectiveness scenario and based on an average vaccination rate of 50%.

Outcome	**70% Vaccine Effectiveness**	**50% Vaccine Effectiveness**	**30% Vaccine Effectiveness**
Hospitalisations	12,700	7,400	3,800
ICU Admissions	530	320	160
Deaths	1,900	1,100	550
DALYs	16,000	9,500	4,900
Hospital Costs (€ million)	80	47	24

DALY: Disability-adjusted life year, IC: Intensive care.

7.6 Results: Net Costs versus Effects

The prevented hospital costs can be compared against the incurred costs for vaccination. For example, with vaccination costs of €75 per vaccinated person, the vaccination Programme costs would be €180 million. When subtracting the hospital costs from this, the net costs at a vaccine effectiveness of 50% would be €133 million. With 9,500 averted DALYs, the net costs are then estimated at €14,000 per DALY averted (Table 7.4).
At vaccination costs of €50 per vaccinated person, the net costs decrease to €7,600 per DALY averted, and at vaccination costs of €100 per vaccinated person, they increase to €20,000 per DALY averted. If the vaccine effectiveness is 70% and the vaccination costs are €25 per vaccinated person, net costs would even be saved. In the case of low vaccine effectiveness of 30% and high costs of €100 per vaccinated person, the net costs would rise to €44,000 per DALY averted.

Table 7.3 Gross costs of the vaccination programme and net costs (after subtracting prevented hospital costs) by vaccination cost scenario.

Vaccination Cost per Person (€)	**Gross Costs of Vaccination Programme (€ million)**	**Net Costs (€ million), per Vaccine Effectiveness Scenario**		
		70%	50%	30%
25	60	-20 (Cost-saving)	13	36
50	120	40	73	96
75	180	100	133	156
100	240	160	193	216

Table 7.4 Net Costs per DALY averted based on different vaccine effectiveness and vaccination costs.

	Scenario: Net Costs (€) per Gained Year of Life in Good Health (DALY averted), per Vaccine Effectiveness Scenario		
Vaccination Cost per Person (€)	**70% Vaccine Effectiveness**	**50% Vaccine Effectiveness**	**30% Vaccine Effectiveness**
25	Cost-saving[1]	1,300[2]	7,400[2]
50	2,500[2]	7,600[2]	20,000[3]
75	6,200[2]	14,000[2]	32,000[4]
100	9,800[2]	20,000[3]	44,000[4]

DALY: Disability-adjusted life year. Colour Code:
1. Dark green: Cost-saving;
2. Light Green: Favourable (Net costs per DALY averted are below the reference value of €20,000);
3. Light pink: Neutral (Net costs per DALY averted are equal to the reference value of €20,000);
4. Dark pink: Unfavourable (Net costs per DALY averted are above the reference value of €20,000)

7.7 Discussion

Since the beginning of the COVID-19 pandemic in 2020, the annual burden of disease from COVID-19 within the Dutch population has decreased from approximately 200,000 DALYs in 2020 and 2021 to 94,000 DALYs in 2022. For 2023, the number of DALYs is estimated at 37,800, of which 28,300 are due to severe COVID-19 among those aged 60 and older. The burden of disease from COVID-19 in 2023 is still significantly higher than that of an average influenza season in the entire population (~9,000 DALYs [89]).

The cost-effectiveness of the COVID-19 vaccination programme for those aged 60 and older was investigated based on burden of disease data from 2023. In a realistic scenario of 50% vaccine effectiveness during the periods October to December and January to March, and with vaccination costs between €50-75 per vaccinated person, the net costs per DALY averted are estimated between €7,600 and €14,000. For preventive interventions such as vaccinations, a reference value of €20,000 per gained year of life in good health is often cited [100]. In other words, if the net costs are lower than €20,000 per DALY averted, the intervention is considered efficient.

This analysis shows that, with a realistic vaccine effectiveness of 50% during the period October to March, the net costs per DALY averted of the COVID-19 vaccination programme remain below this threshold value, unless the vaccination costs exceed €100 per vaccinated person. In a less realistic scenario of 30% vaccine effectiveness, the vaccination costs should not exceed €50 per vaccinated person to stay below this threshold value.

This analysis is a highly simplified representation of reality and includes only the essential aspects to calculate the cost-effectiveness of a vaccination programme. The results regarding costs and effects should be interpreted as an order of magnitude. Therefore, no confidence

intervals are presented. The Department of Health and Social Care in the United Kingdom also used a simplified impact analysis of vaccination on severe COVID-19 for advising on the autumn booster in 2023, instead of a full cost-effectiveness analysis [101].

In the Netherlands, a full cost-effectiveness analysis would also need to consider the impact of vaccination on the burden of COVID-19 infections outside the hospital and societal costs such as sick leave. This analysis also does not account for the loss of health due to long-term complaints after infection or hospitalisation (post-COVID syndrome). Including these additional aspects would improve the cost-effectiveness of vaccination. The analysis also does not consider the discounting of gained years of life (a gained year of life weighs less the further it lies in the future), which results in higher costs per DALY averted and thus lower efficiency. However, the assumed remaining life expectancy of an avoided death among those aged 60 and older is on average 9 years, so the influence of discounting on the results would be limited.

This calculation is mainly based on data from the calendar year 2023. Only for the administration and Programme costs, a budgeted amount for 2025 is used; it is assumed that this budget is based on real costs from previous years. The cost-effectiveness of a vaccination Programme is preferably evaluated over multiple years, as the burden of disease and vaccine effectiveness can vary over time. Since in previous years with COVID-19, many other measures besides vaccination were also in effect, we cannot use these years. It is difficult to predict how the burden of disease will change in the coming years. The protection from vaccination against COVID-19, for example, depends on the emergence of new virus variants and the duration of protection from vaccination. Values close to the burden of disease as estimated for 2023 seem more plausible than values as estimated for 2020-2022. The declining trend in the burden of disease between 2020 and 2023 may not continue if COVID-19 has reached an endemic situation in 2023.

7.8 Conclusion

The burden of disease caused by acute COVID-19 in 2023 is still significant compared to other infectious diseases. The prevented burden of disease due to vaccination is also substantial. A comparison of the prevented burden of disease, the prevented treatment costs of severe acute COVID-19, and the incurred vaccination costs shows that, with a realistic vaccine effectiveness of 50%, the net costs of COVID-19 vaccination for those aged 60 and older are lower than a reference value of €20,000 per DALY averted, provided the vaccination costs are lower than €100 per vaccinated person. If there are indications that the vaccine effectiveness would drop to 30% and the vaccination costs are higher than €50 per vaccinated person, the vaccination Programme may become more expensive than the reference value of €20,000 per DALY averted.

8 COVID-19-vaccination and post-COVID

8.1 Background

A subset of individuals continue to experience persistent, or develop new-onset, symptoms in the months to years after a SARS-CoV-2-infection. This is defined as post-acute sequelae of COVID-19 (PASC), or colloquially as post-COVID. The WHO defines PASC as the persistence or development of symptoms 3 months after SARS-CoV-2 infection for at least 2 months without an alternative explanation for the diagnosis [102]. Symptoms can fluctuate and relapse over time and generally have an impact on daily functioning. PASC can follow after asymptomatic, mild, or severe SARS-CoV-2 infection and affect one or more organ systems. A 2024 definition from the National Academies of Sciences, Engineering and Medicine (NASEM) from the United States omits the necessity for laboratory-confirmed SARS-CoV-2 diagnosis and the alternative explanation for the diagnosis, as in practice infections may go unrecognized as well as the presence of any overlapping medical condition does not preclude PASC [103]. Without a laboratory-confirmed SARS-CoV-2 diagnosis, it remains very difficult to say with certainty whether complaints are due to post-COVID. The PASC population prevalence can be assessed by asking people whether they think they experience persistent symptoms after laboratory-confirmed SARS-CoV-2 diagnosis. An incidence study relies primarily on good control data; the definition used for PASC is less important.
PASC is a heterogenous disease with many associated symptoms, most notably post-exertional malaise (PEM), fatigue, cognitive dysfunction such as brainfog and concentration problems, myalgia, and postural orthostatic tachycardia syndrome (POTS) [104]. Generally, it is considered that there are a few discernible phenotypes for PASC: muscle pain, fatigue, cardiorespiratory and ageusia/anosmia [105]. There are multiple proposed pathophysiological mechanisms to explain PASC phenotypes, to a certain extent corresponding to the phenotypes [106]. These include: immune dysregulation including viral persistence, microbiota dysbiosis, autoimmunity and immune priming, blood clotting and endothelial abnormalities, and dysfunctional neurological signaling.

8.2 Incidence and prevalence

In the prospective Lifelines study, 76,978 participants were periodically asked to score their symptomology pre- and post-SARS-CoV-2 infection [107]. In a pre-Omicron analysis it was shown that 12.7% of SARS-CoV-2 infected participants had long-term somatic symptoms 90-150 days following SARS-CoV-2 diagnosis as indicated by a higher post-infection score compared to pre-infection and unexposed controls. In the RIVM LongCOVID study, for Delta infected cases the initial prevalence of PASC was high, but decreased from 31.4% to 21.7% between 3 to 12 months [108]. Available literature shows that reinfections give an additional risk to develop PASC [109,110,111], with some studies suggesting an increased additional risk for each new infection [109] and others finding a lower additional risk after a second infection, compared to the first infection [111].

In the UK and Netherlands, nationwide surveys assessed the self-reported cross-sectional prevalence of PASC using a variation of the NASEM definition. Firstly, up to March 2023 the Office for National Statistics (ONS) in the UK, reported that 2.9% of adult respondents indicated that they would describe themselves as having PASC of which 20.2% suffered severe limitations in daily functioning (0.59% of total population) [112]. In the Netherlands, in the *Gezondheidsonderzoek COVID-19* study up to December 2023, 3% of adult respondents self-reported PASC-related symptoms of which a quarter indicated severe limitations in daily life (see Results quarterly survey | RIVM). Consequently, an extrapolated 80.000 – 127.000 adults are estimated to have a severe form of PASC in the Netherlands.

8.3 Risk factors

Currently, no clear biomarkers exist as a determinant of PASC, though several factors are associated with increased risk of developing PASC after SARS-CoV-2 infection. These include the female sex, higher age, higher BMI and smoking [113]. The severity of the acute phase of the infection is thought to be a risk factor as hospitalized patients have a higher PASC prevalence than the non-hospitalized counterparts, though PASC can develop even in mild or asymptomatic cases [114].
Impact of PASC over time: A 2024 study of 135,161 US veterans with SARS-CoV-2 showed that amongst non-hospitalized individuals the impact of *incident* PASC declined over three years with sequalae per 1000 persons with acute SARS-CoV-2 infection decreasing from 212.3, 125.0 to 41.2 with each year [115]. This represents that 59.6% of sequalae over the three years emanates in the first year, 29.9% in the second and 10.5% in the third year.

8.4 Prognosis

A two-year follow-up of the US Veteran cohort showed that the risk of most post-acute sequalae declined with time since infection though less pronounced amongst those who were hospitalized in the acute phase of the infection [116]. For most symptoms the risk became non-significant after two years, although this was not so for all 80 assessed symptoms. For example, the relative risk for fatigue declined from 2.27 to 1.55, 1.27 and 1.21 at 90, 180, 360 and 720 days after infection for non-hospitalized and from 12.52 to 2.67, 1.97 and 1.88 in the same time span for hospitalized patients. Moreover, most of the DALYs emanated from the first year following infection.

A second population-based study estimated excess symptom risk for unvaccinated at time of infection between 6 August 2020 en 19 January 2021 from 6 to 24 months after infection [117]. It was reported that 22.9% of SARS-CoV-2-infected individuals did not fully recover in the first six months. After respectively 12 and 24 months the PASC prevalence was 18.5% and 17.2% with excess symptom risk (compared to general population) highest for taste or smell alterations (9.8%), PEM (9.4%), concentration difficulties (8.3%), memory problems (5.7%) and fatigue (5.4%). The study was conceived and implemented during the early stages of the pandemic when a large part of the population had not yet been vaccinated or had an infection.

In fact, most studies report that the most significant reduction in post-COVID symptom in individuals with post-COVID, and with it the highest recovery, happens within the first half year following infection [118]. After this period, symptoms persist, in essence, as a chronic condition. The RIVM LongCOVID study has submitted a paper that corroborates these findings [119]. In Delta infected cases the initial prevalence of PASC was high, but decreased from 31.4% to 21.7% between 3 to 12 months. Whereas for Omicron infected cases the decrease was much less, though initially lower: 18.7% to 16.7% between 3 to 12 months. Altogether it may be that post-infectious symptomology from the first six months persist partly due to prolonged effects of SARS-CoV-2 infection and immune activation and partly due to (proposed pathophysiological) PASC mechanisms.

8.5 Vaccination for the prevention of PASC

Vaccine effectiveness (VE) against PASC can be defined as the potential protective effect of vaccination prior to infection against development of long-term symptoms after infection or as the therapeutic effect of vaccination after infection and development of long-term symptoms on symptom resolution. Regarding the effect of pre-infection COVID-19 vaccination, a meta-analysis of 6 observational studies indicated a protective effect of two doses on the incidence of long COVID symptoms including fatigue (OR, 0.62; 95% CI, 0.41-0.93) and pulmonary disorder (OR, 0.50; 95% CI, 0.47-0.52) compared to no vaccination (98). These findings are corroborated by a second systematic review assessing the effect of vaccination against any PASC symptom (OR, 0.57; 95% CI, 0.43-0.76) (92). A large population-based cohort study from Sweden investigated the effectiveness of one dose, two doses and three or more doses against the clinical diagnosis of PASC using ICD-10 codes [120]. In this study a VE of 21%, 59% and 73% compared to no vaccination was found, suggesting an increased protective effect with each successive dose, though the additional benefit was smallest between three or more doses compared to two doses. Individuals with COVID-19 in this cohort study were registered between 27 December 2020 and 9 February 2022. Moreover, studies have found a lower prevalence of PASC following Omicron compared to Delta and pre-Delta variants [108, 121], though one multicentre study found after correction for vaccination in a multivariable analysis, that these differences were no longer significant suggesting vaccination status as the determinant of the diminished risk [122].

This was corroborated by a study that was performed on the health records of the Department of Veterans Affairs consisting of 441,583 veterans with a SARS-CoV-2 infection between March 1, 2020, and January 31, 2022, and 4,748,504 noninfected contemporaneous controls [123]. Persons in the study were followed for 1 year to estimate the risk and burden of PASC during the pre-Delta, Delta, and Omicron eras. Vaccinated persons had a lower cumulative incidence of PASC at 1 year than unvaccinated persons (difference during the delta era, −4.18 events per 100 persons ; difference during the omicron era, −4.26 events per 100 persons. In a decomposition analyses it was shown that there were 5.23 fewer PASC events per 100 persons at 1 year during the omicron era than during the pre-delta and delta eras combined;

28.11% of the decrease was attributable to era-related effects (changes in the virus and other temporal effects), and 71.89% (95% CI, 69.50 to 74.43) was attributable to vaccines. Thus suggesting natural and vaccine-induced immunity rather than temporal effects have resulted in a decreased PASC incidence.
Nearly all observational studies have assessed the effect of vaccination against PASC in infected individuals, so not including VE against infection itself. In one study, staggered cohorts from the UK, Estonia and Spain were pooled using random effects to assess VE against PASC including the effect of vaccination against SARS-CoV-2 infection in the pathway to long COVID [123]. This resulted in a VE against COVID-19 and PASC ranging from 29% to 52%, reflecting a broader population-level VE.

8.6 Vaccination for PASC patients

Regarding the potential therapeutic effect of vaccination after infection in PASC patients, a systematic review of 5 studies found odds ratios for maintaining PASC of 0.38-0.91 though a meaningful meta-analysis was not possible due to high heterogeneity between the studies [124]. Another systematic review and meta-analysis concluded that vaccination did not affect the symptom trajectory of pre-existing PASC, and a greater number of individuals experienced improvement versus deterioration of pre-existing post-COVID symptoms after vaccination. Furthermore, there was a lack of evidence to suggest that vaccination exacerbated pre-existing PASC symptoms [125].

8.7 Fatigue pre- and post-SARS-CoV-2 infection in the Vaccine Study COVID-19 (VASCO)

In VASCO, fatigue was assessed during and after a SARS-CoV-2 infection by age, sex, presence of a medical risk condition, SARS-CoV-2 variant and vaccination status, accounting for pre-infection fatigue and compared with uninfected individuals. Fatigue was measured at inclusion and every three months during follow-up by the fatigue subscale of the Checklist Individual Strength (CIS; range 8-56). First (n=22,705) and repeat (n=6,414) SARS-CoV-2 infections reported by VASCO participants with CIS-fatigue scores 1-90 days pre-infection and 0-300 days post-infection were included.

Adjusted mean pre- vs post-infection CIS-fatigue scores showed a large increase during the acute phase of the infection, declined rapidly in the first 90 days after infection, but remained elevated until at least 270 days for Delta infections and 120 days for Omicron infections. Prevalence of severe fatigue (CIS-fatigue score ≥35) was 18.5% before first infection. It increased to 24.4% and 22.5% during the acute phase of the infection and then decreased to 21.2% and 18.9% at 90 days and 18.8% and 18.6% at 180 days after Delta and Omicron infection, respectively. No differences in mean post- vs pre-infection CIS-fatigue scores at 90-270 days post-infection were observed by vaccination status or between first and repeat Omicron infections. Matched uninfected participants showed a slight increase in mean CIS-fatigue score over time.

In this well-controlled prospective cohort study increased levels of mean fatigue scores after Omicron infection had resolved from 120 days post-infection, unlike after Delta infection. We did not find evidence of an effect of vaccination on mean long-term fatigue scores among infected individuals at population level. Analyses of VASCO data with more symptoms than just fatigue are ongoing.

8.8 Conclusion

The risk of post-COVID per infection is presently lower than early pandemic estimates. Vaccination is thought to have a contributing role in this risk-reduction as well as natural immunity, viral adaptations and other time variable factors. Notwithstanding, the additional protection against post-COVID of each subsequent vaccination dose was found to be incrementally lower. In the VASCO study, no protective effect of vaccination prior to infection was observed. No consensus for effects of vaccination after post-COVID onset were found in literature.

9 References

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10 Appendix

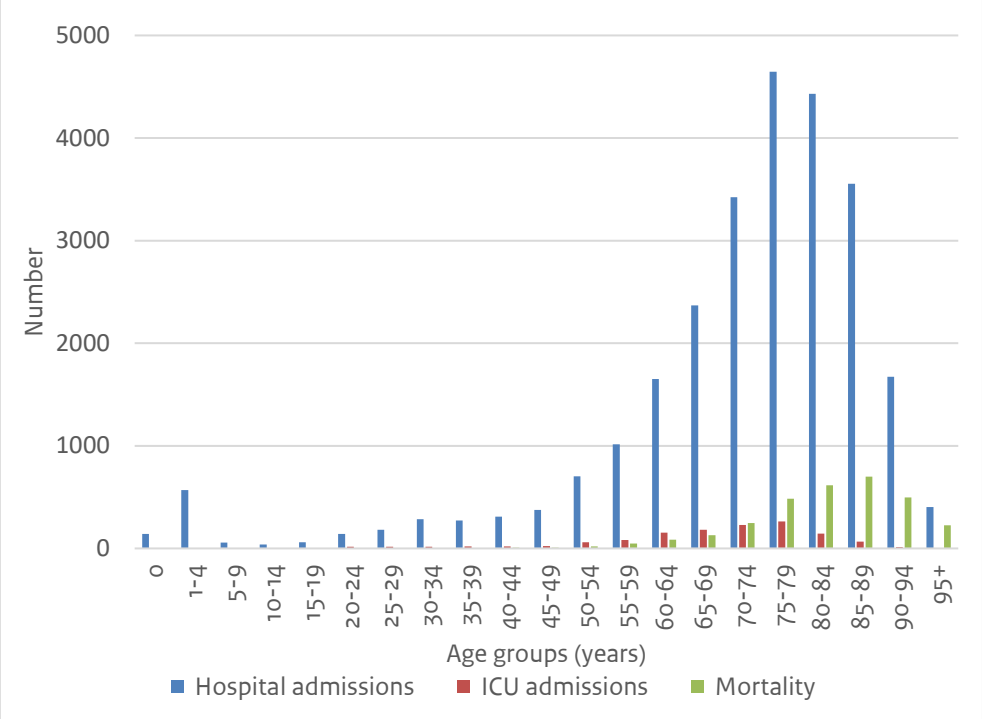
10.1 Supplementary Tables chapter 7

Table 10.1 Estimated numbers of COVID-19 episodes by disease outcome and disease burden expressed in disability-adjusted life years (DALYs) in the entire population in calendar year 2023.

Disease status	Numbers (95% BI)	DALY's (95% BI)
Mild symptomatic$	7.220.000 (7.120.000-7.330.000)	6.050 (5.970-6.140)
Severe, regular ward	26.300 (25.900-26.800)	79 (78-80)
Severe, ICU ward	1.311 (1.230-1.399)	16 (15-18)
Death	3.076*	31.600 (30.300-33.000)
Total†		37.800 (36.500-39.200)

95% CI: 95% confidence interval. †Due to rounding, totals may not correspond with the sum of the separate results. $ Mildly symptomatic also includes people who eventually became seriously ill or died. * Number of deaths is from unadjusted national data; therefore, no 95% confidence interval has been determined.

Figure 10.1 Number of hospital admissions and ICU admissions and number of deaths by age group in calendar year 2023. The number of hospital admissions has been corrected for underreporting by a factor of 1.45, and the number of ICU admissions has been corrected for underreporting by a factor of 1.1.



10.2 Supplementary Tables paragraph 6.1

*Table 10.2 Number of participants per assay, stratified by age group and SARS-CoV-2 infection status. The percentage of participants with absence or evidence of SARS-CoV-2 infection are given between brackets. The total number of participants are highlighted in bold. Only data from participants vaccinated with the OmicronXBB1.5 based vaccine are included in this table, except for mucosal antibodies, for which all participants who donated mucosal samples are included. The presented data reflects samples collected during the following vaccination series per assay (*P, B, C, D, E; **E; ***P, B, D, E).*

Antibodies (IgG)*	**Age group (years)**	**Participant with no evidence of infection**	**Infected participants**	**Total**
	60-69	16 (29%)	40 (71%)	56
	70-79	38 (39%)	60 (61%)	98
	80-100	15 (50%)	15 (50%)	30
	Total	69 (38%)	115 (63%)	**184**
Antibody virus-neutralization capacity**	**Age group**	**Participant with no evidence of infection**	**Infected participants**	**Total**
	60-69	12 (36%)	21 (64%)	33
	70-79	16 (33%)	33 (67%)	49
	80-100	5 (50%)	5 (50%)	10
	Total	33 (36%)	59 (64%)	**92**
Mucosal antibodies (IgG and IgA)*	**Age group**	**Participant with no evidence of infection**	**Infected participants**	**Total**
	18-59	208 (66%)	105 (34%)	313
	60-69	63 (63%)	37 (37%)	100
	70-79	74 (61%)	47 (39%)	120
	80-100	26 (55%)	21 (45%)	47
	Total	370 (64%)	210 (36%)	580
T-cell response (IFNγ ELISpot)***	**Age group**	**Participant with no evidence of infection**	**Infected participants**	**Total**
	60-69	2 (11%)	16 (89%)	18
	70-79	8 (27%)	22 (73%)	30
	80-100	4 (44%)	5 (56%)	9
	Total	36 (44%)	45 (56%)	**57**

P: primary series (1st and 2nd dose); B: first booster (3rd dose); C: second booster (4th dose); D: bivalent booster (5th dose), E: Omicron XBB.1.5 booster (6th dose).

*Table 10.3 Number of samples per assay, with multiple samples for different timepoints per participant, stratified by age group and SARS-CoV-2 infection status. The percentage of participants with absence or evidence of SARS-CoV-2 infection are given between brackets. The total number of samples are highlighted in bold. Only data from participants vaccinated with the OmicronXBB1.5 based vaccine are included in this table, except for mucosal antibodies, for which all samples are included. The presented data reflects samples collected during the following vaccination series per assay (*P, B, C, D, E; **E; ***P, B, D, E).*

Table of samples				
Antibodies (IgG)*	Age group (years)	Participant with no evidence of infection	Infected participants	Total
	60-69	554 (66%)	281 (34%)	835
	70-79	914 (67%)	445 (33%)	1359
	80-100	293 (72%)	116 (28%)	409
	Total	1761 (68%)	842 (32%)	**2603**
Antibody virus-neutralization capacity**	Age group	Participant with no evidence of infection	Infected participants	Total
	60-69	21 (38%)	35 (63%)	56
	70-79	32 (34%)	62 (66%)	94
	80-100	10 (53%)	9 (47%)	19
	Total	63 (37%)	106 (63%)	**169**
Mucosal antibodies (IgG and IgA)*	Age group	Participant with no evidence of infection	Infected participants	Total
	18-59	481 (70%)	203 (30%)	684
	60-69	278 (68%)	131 (32%)	409
	70-79	298 (63%)	177 (37%)	475
	80-100	74 (62%)	45 (38%)	119
	Total	1131	556	**1697**
T-cell response (IFNγ ELISpot)***	Age group	Participant with no evidence of infection	Infected participants	Total
	60-69	39 (41%)	56 (59%)	95
	70-79	103 (54%)	89 (46%)	192
	80-100	36 (63%)	21 (37%)	57
	Total	250 (61%)	159 (39%)	**344**

P: primary series (1st and 2nd dose); B: first booster (3rd dose); C: second booster (4th dose); D: bivalent booster (5th dose), E: Omicron XBB.1.5 booster (6th dose).

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