National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

COVID-19 vaccine booster dose

Background information for the Health Council

RIVM letter report 2021-0181
Centre for Infectious Disease Control

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Synopsis

COVID-19 vaccine booster dose
Background information for the Health Council

Since January 2021, people in the Netherlands have been able to get vaccinated against COVID-19, the disease caused by the new coronavirus named SARS-CoV-2. The most important objective of this vaccination is to prevent severe disease and death. The question now is whether people who have been vaccinated would benefit from an extra vaccination. This so-called booster is intended to boost the effectiveness of the initial series of vaccinations. The Health Council of the Netherlands advises the Dutch Ministry of Health, Welfare and Sport on whether this booster is necessary and, if so, for whom, when, and with which vaccine.

RIVM has provided The Health Council of the Netherlands with a review of the scientific knowledge on the factors relevant for this advice. The use of a booster depends roughly on four factors: The current situation of the population (such as the number of sick persons and vaccinated persons), the vaccines (which vaccines are available, are they safe and effective, et cetera), the protection (such as the timing of the booster and the influence of natural infection), and the virus variants in circulation.

A booster can be necessary if the protection provided by the initial series of vaccines diminishes too much after a certain period of time. A booster can also be necessary if it turns out that the vaccinations provide less protection against new variants of the coronavirus. Until now, the current initial series of vaccinations provide effective protection against severe disease and death, including all the variants circulating in the Netherlands.

It is not yet clear if and when a booster can help reduce severe disease and death. Globally, there is still not much experience with a booster and there is still little scientific evidence for its use as of yet.

Keywords: COVID-19, booster, vaccination, breakthrough infections, immunity, humoral immune response, cellular immune response, vaccine effectiveness

Publiekssamenvatting

Boostervaccinatie tegen COVID-19
Achtergrondinformatie voor de Gezondheidsraad

Sinds januari 2021 kunnen mensen in Nederland zich laten vaccineren tegen COVID-19, de ziekte die door het nieuwe coronavirus SARS-CoV-2 wordt veroorzaakt. Het belangrijkste doel van deze vaccinatie is om ernstige ziekte en sterfte te voorkomen. De vraag is nu of mensen die gevaccineerd zijn baat hebben bij een extra vaccinatie. Deze 'booster' is bedoeld als oppepper, die de werking van de eerste serie vaccins kan verbeteren. De Gezondheidsraad adviseert het ministerie van VWS of deze booster nodig is, en zo ja voor wie, wanneer, en met welk vaccin.

Het RIVM heeft voor de Gezondheidsraad de wetenschappelijke kennis verzameld over factoren die relevant zijn voor dit advies. De inzet van een booster hangt grofweg van vier factoren af. Dat zijn: de situatie bij de bevolking (zoals het aantal zieken en gevaccineerden), de vaccins (onder andere: welke zijn er, zijn ze veilig, werken ze goed), de bescherming (zoals de timing van de booster, de invloed van natuurlijke infectie), en virusvarianten.

Een booster kan nodig zijn als de beschermende werking van de eerste serie vaccins na een tijd te veel afneemt. Een andere reden voor een booster is wanneer de vaccinaties minder goed blijken te beschermen tegen nieuwe varianten van het coronavirus. Tot nu toe beschermen de huidige vaccins goed tegen ziekte en sterfte, ook tegen de varianten die in Nederland voorkomen.

Het is nog niet duidelijk of en wanneer een booster kan helpen om ernstige ziekte en sterfte te verminderen. Wereldwijd is er nog weinig ervaring met een booster en er is nog weinig wetenschappelijk bewijs.

Kernwoorden: COVID-19, booster, vaccinatie, doorbraakinfecties, immuniteit, humorale immuunrespons, cellulaire immuunrespons, vaccineffectiviteit

Contents

Terms of reference

The Ministry requested the Health Council of the Netherlands to advise on COVID-19 vaccine boosters. To this aim, the Ministry asked the National Institute for Public Health and the Environment (*RIVM)* to provide a report to outline the various considerations for a COVID-19 vaccine booster programme.

The scope of this report is to provide available evidence up till August 14, 2021 on topics relevant for potential COVID-19 booster vaccination, based on international literature (peer reviewed and non-peer reviewed preprint) as well as (preliminary) data and research from the RIVM. It is important to note that this document will not provide an exhaustive overview of all available data, but rather focusses on the most important topics. Also, the RIVM will continue to review emerging scientific data, including data relating to the duration of immunity and effectiveness from the current vaccines and development of new SARS-CoV-2 Variants of Concern. New data may considerably change the current context over time.

Overall Summary

There are situations where additional doses of a COVID-19 vaccine in previously vaccinated individuals may be considered, e.g. in case of:

- evidence that primary vaccination never induced enough immunity to be protective, e.g. immunocompromised persons or recipients of vaccines with low or unproven efficacy;
- waning of vaccine-immunity to the point that previous vaccination is believed to be no longer adequately protective;
- new variants that escape vaccine-induced immunity, and previous vaccination is no longer believed to be adequately protective.

Insufficient protection after the primary vaccination series

Immunocompromised persons

Immunocompromised persons with a suboptimal vaccine response are outside the scope of the current review. Selected groups of (severely) immunocompromised patients will potentially be invited for an additional (extra) vaccination as part of their primary series, based on a separate advice of treating medical specialists. This advice of professionals treating immunocompromised patients will be based on current ZonMw studies in immunocompromised patients, literature and expert opinion.

Recipients of vaccines with low or unproven efficacy

With respect to low efficacy of primary vaccination series, this does not apply to the current vaccines used in the Netherlands. The four vaccines in use are the two adenoviral-vector vaccines Vaxzevria (AstraZeneca) and Janssen COVID-19 vaccine (Johnson & Johnson), and the two mRNA vaccines Comirnaty (Pfizer/BioNTech) and Spikevax (Moderna). All four vaccines have proven efficacy against COVID-19, as shown in large randomized controlled efficacy studies. Unless a person has had another COVID-19 vaccine outside the standard Dutch COVID-19 vaccination programme (i.e. abroad or in vaccine efficacy studies), that was found insufficiently effective, this is not a reason for additional vaccinations.

Waning immunity

To determine the point where previous vaccination no longer adequately protects, one needs to define what vaccine effectiveness outcomes are considered most critical. Vaccine efficacy has shown greater protection against severe disease > symptomatic illness > confirmed infection (including asymptomatic). Protection against severe disease may require lower antibody levels and may be less affected by waning immunity with time.

Severe disease vs. mild infection and boost by natural COVID-19 infection

Most people would agree that primary protection against severe disease is most important, while mild disease is tolerated for many other illnesses. Natural infection as a boost in vaccinated persons may even confer long-term protection advantages, since natural infection-induced boosting includes immunity against the Spike protein plus other non-structural viral proteins, with potentially longer presence of antigen.

Natural infection will generate broader systemic immunity, but also mucosal immunity. On the other hand, in case of SARS-CoV-2 breakthrough infection, increases in incidence in mild disease after vaccination may predict subsequent increases in incidence in severe disease. We do not know enough on outcomes like long COVID that occur after milder disease or the rare condition like Multi System Inflammatory Syndrome in Children (MIS-C).

Duration of protection
The duration of protection against COVID-19 following full vaccination and against severe COVID-19 still needs to be determined. Effectiveness of vaccines tends to drop over time but appears to remain high for at least the first 6 months after the last COVID-19 vaccination. For the Comirnaty vaccine, post-dose 2 vaccine efficacy in a large randomized controlled study against symptomatic COVID-19 confirmed with a positive test, was 96,2% (93.3-98.1) after 7 days to 2 months, 90.1% (86.6-92.9%) 2 to <4 months, and 83.7% (74.7-89.9) 4 to 6 months over time. This type of data is much less known for severe illness. For Spikevax, vaccine efficacy of 93% up through six months after full vaccination is mentioned (not peer reviewed). For Vaxzevria, vaccine effectiveness was 66.7% (95% CI: 57.4-74.0) after a median follow-up of 3.4 months (IQR 1.3-4.8). Data on vaccine effectiveness of different vaccines are hard to compare directly, due to many confounding factors. While data on long term effectiveness are still limited, long-term protection against severe illness by antigenically similar strain may be maintained for a longer time, even if one becomes susceptible to mild infection. Combined impact of waning immunity and circulating Variants of Concern with reduced antibody neutralization may lead to lower vaccine effectiveness.

Antibody neutralization levels with time post vaccination
In serosurveillance studies, there is a small but linear decline in (neutralizing) antibody levels with time after vaccination, though it is unknown whether a fall in (neutralizing) antibodies necessarily means a loss of protection against *severe* disease. Most currently used vaccines induce strong CD4 and somewhat lower CD8 T-cell responses, but the role of cellular immunity and the role of immune memory in long term protection against COVID-19 is not known. The fact that a booster dose at six months after the primary vaccination series, induces strong booster responses, and that a third homologous mRNA vaccine induces antibody levels that exceed several folds the antibody levels achieved after the second dose, point at good long term memory induction. This was also the case for elderly. In case of Vaxzevria, first data on a (third) booster dose show that the third booster vaccination restores antibody levels to at least the antibody levels after the second dose or higher. There are only limited data from the Janssen COVID-19 vaccine, though a small study showed only minimal decline in antibody levels 8 months after the first dose, and improved protection against VOCs vs. one month postvaccine. It is not known whether very high antibody levels following the booster mRNA vaccination contribute to extra or longer protection, and whether fractional booster doses (i.e. half or one quarter of the standard dose) would be preferred over full booster doses, also in view of safety.

Waning immunity in elderly and older adults
Vaccine-induced protection may be less durable in elderly. Frail elderly but also older adults 50-65 years and over, are known to have lower primary immune responses upon vaccination and somewhat faster waning of antibody levels with time. Current data are insufficient to determine whether the observed trend in decline in antibody levels in older adults leads to clinically significant loss in vaccine effectiveness, though a trend towards lower effectiveness estimates against SARS-CoV-2 infections with time is reported. However, we currently have very scarce data whether lower antibody levels will result in a significant decline in vaccine effectiveness against *severe* clinical illness, beyond 6 months after vaccination.

Breakthrough infections
Breakthrough infections do occur, primarily in elderly that were vaccinated first, but are reported in other age groups as well. In the vast majority of breakthrough infections, symptoms were relatively mild. Breakthrough infections increase with age and elapsed time since last primary series. In case of severe illness/hospitalization, breakthrough infections often concern individuals with multiple comorbidities and persons with immunosuppression. Coming autumn and winter months will teach us more about severe COVID-19 illness in vaccinated persons. Since age is the most important risk factor for severe COVID-19 in the unvaccinated, some countries like the United Kingdom, France and Germany however already intend to start booster vaccinations in older age groups of 50 or 60 years and over as a precautionary measure.

Different vaccines and waning immunity
With respect to different vaccines and vaccine platforms, we know not enough about difference in vaccine induced mechanisms of protection to firmly decide who needs a booster vaccination. Antibody levels, as shown by recent serosurveillance studies in the general population in the Netherlands, point at lower anti-Spike IgG levels after the single Janssen COVID-19 vaccine as compared to two doses of Vaxzevria. The mRNA vaccines Comirnaty and Spikevax show the highest antibody levels. A strong advantage of these Dutch studies is that vaccine-induced immunity between groups can be directly compared, since samples from different studies are measured with the same assay and by the same laboratory, in contrast to the many studies in literature. Based on these Dutch studies, antibody levels are the lowest in case of a single Janssen COVID-19 vaccine. Based on antibody levels alone, adults of 50 years and over after the Janssen COVID-19 vaccine may need to be prioritized to optimize neutralizing antibody levels. The next group would be older adults of 60 years and over vaccinated with a homologous series of two doses of Vaxzevria. For elderly and long-term care facility residents, data from Dutch studies on antibody and cellular immune data will become available within the next months. There is a trend for lower antibody levels with age and frailty of elderly.

Prevention of transmission as reason for booster vaccination
At present, transmission is mainly driven by the unvaccinated younger age groups. In case prevention of transmission would be the goal of booster vaccination, we do not yet have direct evidence about the impact of vaccines in use today on transmission (e.g. now Delta variant

circulating) and on the longer term. Dutch data collected during the Alpha variant period, show considerable reduction in transmission after complete vaccination, but may no longer be the case now the Delta variant is dominant. We need to realize that herd immunity and long-term protection against transmission may be impossible to achieve with current vaccines and currently circulating virus variants. Booster vaccination may be considered for certain groups like health care personnel, some of whom are vaccinated early in the COVID-19 vaccine roll-out and have continued exposure to SARs-CoV-2. Booster vaccinations of health care personnel may support continuity of essentials health care services but also may reduce viral transmission to vulnerable patients. Is remains however essential to achieve high coverage of primary vaccination among health care and social care workers in the first place. The same is true for household contacts of vulnerable persons.

Other considerations are that in case of health care or social care workers, those vaccinated with Janssen COVID-19 vaccine may be prioritized for a booster vaccination, to optimize anti-Spike antibody levels that may potentially help to prevent transmission. We are however not sufficiently informed about differences in immunity between vaccines and in particular cellular immunity differences between vaccines and platforms, and consequences for long-term protection against disease and transmission based on immune memory. So, decisions based on antibody levels also may underestimate overall immunity. For estimation of real-world vaccine effectiveness, the follow-up time after the Janssen COVID-19 vaccine introduction is still short. Also, in the Netherlands, vaccination with the Janssen COVID-19 vaccine is mainly administered to younger and healthy adults above 18 years, which makes the differences in vaccine effectiveness hard to assess.

Vaccine induced protection against variants of SARS-CoV-2 variants of concern

Neutralizing antibodies and Variants of Concern

Booster vaccination may be required to protect against illness when new variants arrive, that escape vaccine-induced immunity. Factors that may negatively impact vaccine-induced protection from illness by variants are: partial escape from neutralizing antibodies through mutation that decreases antibody affinity for the Spike-protein, mutations that increase affinity of the Spike-protein for ACE2 or increase fusogenicity, partial escape from T-cell responses, higher replication capacity and exposure to higher viral loads as well as waning of vaccine induced IgG levels on mucosal surfaces (protection from infection), and waning of immune responses in general. Across all in vitro laboratory assays, and of all known VOC’s, the Beta variant had the greatest impact on antibody recognition and the Alfa variant the least. Gamma and Delta were intermediate. In contrast, variants may not or to a lesser extent escape vaccine induced T-cell response, and neutralizing antibodies may fall faster than vaccine efficacy. Efficacy and effectiveness against severe disease may be also less dependent on neutralizing antibodies alone.

Vaccine effectiveness and Variant of Concern
The Delta variant has the highest estimated transmissibility of all current SARS-CoV-2 variants of concern (VOC) and is outcompeting all variants in countries where the Delta variant has presented and is expected to become dominant worldwide in the coming months if trends continue. With up to 75% higher transmissibility compared with the Alpha variant and high viral load in the upper respiratory tract, and with reduction of vaccine induced neutralizing antibody activity, there may be more infection and transmission even by vaccinated persons as compared to the Alpha variant, though likely less than by unvaccinated individuals and vaccines may transmit the Delta variant for a shorter period of time. The Delta variant may however potentially also result in increased risk of hospitalization, also for vaccinated persons.

Real world evidence suggests lower vaccine efficacy and effectiveness against the Delta variant compared with the Alpha variant. This is reported after only a single first vaccination with Comirnaty and Vaxzevria, while after two doses, effectiveness against the Delta variant improves, effectiveness of Vaxzevria remains below that of Comirnaty, and in case of the Delta variant are below effectiveness estimated against the Alpha variant. A lower efficacy was also shown in randomized trials with the Janssen COVID-19 vaccine against the Delta variant, but real-world effectiveness data in case of Janssen COVID-19 vaccine and the Delta variant are still largely lacking. First data from the Netherlands on the Janssen COVID-19 vaccine effectiveness points to a lower vaccine effectiveness compared with the other three vaccines used in the Netherlands in the (relatively short) period dominated by the Delta variant.

To limit emergence of new and more severe escape variants of concern in the near future, worldwide vaccination is more important than booster vaccination in a limited number of high-income countries.

Data need for policy
Safety of booster vaccination
It is generally accepted that vaccine benefits need to exceed the risks. Risk of boosting may include currently unknown immediate reactogenicity (safety) concerns, but also unknown long-term consequences of boosting, for young adolescents and young adults, and public health outcomes. There are also still many open questions about optimal timing of booster, standard doses or fractional doses of booster vaccination and best combinations of vaccine platforms. Data of first studies on antibody levels and safety after booster vaccination are only just emerging. Israel began offering Comirnaty booster vaccination beginning of August 2021 to people over age 60, as part of efforts to slow the spread of the highly contagious Delta variant. First and preliminary data showed that 88% of participants receiving the 3rd dose felt similar to how they felt after the 2nd dose, with 31% that reported side effects (like soreness at the injection site) and 1% that sought medical treatment. First data on a third dose of Comirnaty and of Spikevax showed similar side effects as after the second dose. We do not know yet whether we can use less vaccine as a booster dose (fractional doses), as was suggested for recent studies on Spikevax with a one half or quarter dose. Data on side effects after fractional doses are

underway. A third booster dose of Vaxzevria resulted in higher antibody levels than after the second dose, though cellular immunity did not change. Reactogenicity was similar after the 2nd and 3rd dose and lower than after the first dose.

Vaccines for booster vaccination
Data on vaccines that are adapted to variants of concern have also started to be reported, but these vaccines will not become available before 2022. New COVID-19 vaccines will be marketed in Europe in the near future and will become available in the Netherlands. Five (candidate) vaccines are currently under rolling review by EMA: NVX-CoV2372 developed by Novavax (in review since 3rd Feb 2021), CVnCoV developed by Curevac (12th Feb 2021), Sputnik-V developed by Gamaleya Research Institute (4th March 2021), the protein subunit candidate developed by Sanofi Pasteur (since 20th July 2021), and CoronaVac developed by Sinovac Biotech (since 4th May 2021). In particular the protein subunit vaccines from Sanofi and Novavax may be of interest for the Netherlands also for booster vaccination but expected to become available not before January 2022.

A heterologous booster vaccination may offer advantages over homologous boosting, as was shown by first single viral vector vaccination followed by a second dose with mRNA vaccines, resulting in higher anti Spike antibody levels and improved cellular immunity. Results on booster dose studies in the Cov-Boost study from the UK which 7 different COVID-19 vaccines in adults, with a booster dose 84 days post second dose vaccination, will become available coming months. Also, half dose for 3 vaccines to assess efficacy and reduction of side effects are included in the Cov-Boost study. The use of fractional doses has implications not only for reactogenicity and safety issues, but also and more important for vaccine availability and global vaccination equity.

Other questions also remain. If heterologous boosting is targeted, specific studies to address different types of priming and boosting need to be conducted and more data on boosting with fractional doses. There is a need for safety/reactogenicity investigation for rare reactions after homologous and heterologous boost, timing and safety of heterologous boost vaccinations, but also timing and safety of booster vaccination in subjects naturally infected and vaccinated at different time points. Safety of additional doses in special groups like pregnant and immunocompromised persons and younger persons are also required. Data on coadministration of other vaccines like influenza vaccine are expected to become available soon.

Population groups for booster vaccination
Altogether, introduction of booster doses needs to be evidence-based and data driven, but many aspects are still unknown. The rationale for implementing booster vaccination needs to be guided by vaccine effectiveness data, of severe disease in persons at risk like in older adults or high-risk populations with underlying comorbidity. Long-term care facility residents, older adult age groups and younger people with comorbidity need to be considered. Special attention is required after a primary vaccination series with adenoviral vector vaccines, after a single

vaccination with the Covid-19 vaccine Janssen, in older adults. Special groups like health care and social care workers, and household contact of immunocompromised or frail people, also need to be considered.

Timing of booster vaccination
Booster vaccinations may not be indicated before 6 months after the last vaccination in the primary series. Modified vaccines targeted at VOC (Beta variant) are currently investigated but will not be available this autumn/winter 2021/22. At the moment, to protect risk groups and prevent emergence of VOC, optimal coverage of the primary series in the Netherlands, but more importantly, worldwide is mandatory. Vaccine equity during the period of extreme worldwide vaccine shortage is required for worldwide public health and the basis for economic stability and quality of life for everyone.

1 Introduction

In the current COVID-19-vaccination programme, the primary goal has been to prevent severe 'Corona Virus Disease 2019' (COVID-19) and mortality due to the 'Severe Acute Respiratory Syndrome Corona Virus 2' (SARS-CoV-2) infection. There is good evidence that a complete series of current COVID-19 vaccines in the Netherlands will provide good protection against severe disease and hospitalization for at least 6 months after the last COVID-19 vaccination, though less data is available for the Janssen COVID-19 vaccine and for the longer-term effectivity of all four vaccines. The present vaccination coverage in the Netherlands is high with 80% above 65 years of age and 93% above 90 years (week report 17 August), though lower among younger age groups. While severe COVID-19 and hospitalization rates may at the moment be contained, Variants of Concern (VOC) with high transmissibility and high viral load are circulating. Breakthrough infections in fully vaccinated persons are expected and will increase with time elapsed after the last vaccination and increasing age. COVID-19 vaccine booster doses may prevent loss of protection due to waning immunity and/or may optimize immunity to provide additional resilience against new VOCs. Various factors play a role in the decisions on timing and for whom a COVID-19 vaccine booster dose might be indicated (see Figure 1).

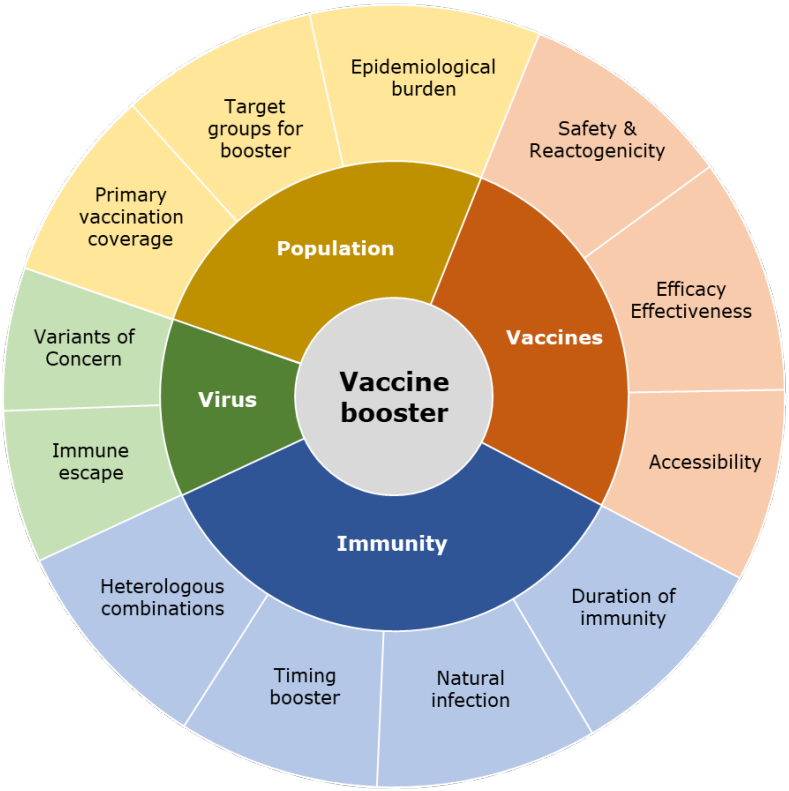

Figure 1 Overview of the various elements related to a COVID-19 vaccine booster programme.

Current evidence from international literature on the virus is presented in Chapter 2, COVID-19 vaccines and vaccine effectiveness are reviewed in Chapter 3. In Chapter 4, new and preliminary data from Dutch research are described. Chapter 5 addresses various scenarios that might be the outcome of considerations on including a booster shot or not. A summary of the review is provided in the overall summary.

1.1 Definition of a COVID-19 vaccine booster dose

The definition of a COVID-19 vaccine booster dose is an additional vaccine dose, for a person who has received a full primary vaccination series, intended to boost waning immunity and increase the level of immunity. Generally, a primary vaccine series consists of a single dose in case of the COVID-19 Janssen vaccine or one or two doses, depending on prior COVID-19-infection.

Please note: For certain severely immunocompromised patients the recommended primary series may consist of 3 instead of 2 primary doses in order to reach a desired level of initial immunity. The additional third dose in an extended primary series is not considered as an additional primary dose and not as a booster dose in this document. The evidence and considerations for an extended primary vaccination series will be addressed in a separate report based on the advice of representatives of the respective medical specialists who care for immunocompromised patients.

1.2 Groups to consider for a COVID-19 vaccine booster programme

In the situation where social distancing measures might be ceased and social contact may return towards pre-pandemic norms, the coming winter of 2021-2022 will be the first winter when SARS-CoV-2 will co-circulate alongside other respiratory viruses. The timing and magnitude of potential influenza and SARS-CoV2 infection waves for winter of 2021-2022 are currently unknown, but both may add substantially to the 'winter burden' for hospital and primary care, particularly if infection waves from both viruses coincide. Next to influenza vaccination, COVID-19 booster revaccination may lower the burden for health care. This may be an important reason to implement a booster COVID-19 revaccination for groups at risk of *severe* COVID-19 i.e. long term care facility residents, elderly of 70, 75 or 80 years and over, or all older adults from age 50 to 65 years and over, and/or vulnerable younger teenagers and adults with defined comorbidities.

For other groups, like frontline healthcare and social care workers in contact with vulnerable persons, an additional COVID-19 booster dose may reduce infection, with potential illness and transmission, and promote continuation of essential healthcare, similar to recommended seasonal influenza vaccination for health care workers. COVID-19 booster vaccination may prevent illness and absence from work, and reduce SARS-CoV-2 transmission to vulnerable people.

With respect to the different COVID-19 vaccine platforms, difference in neutralizing antibody levels after a primary series of current COVID-19 vaccines exist, as well as indications of lower efficacy and effectiveness over time in case of COVID-19 adenoviral vector vaccines compared

with messenger ribonucleic acid (mRNA) vaccines. In particular for higher risk groups for COVID-19, this may be reason to prioritize COVID-19 vaccine booster vaccination for adults of 50 years and over after a single dose of the Janssen COVID-19 vaccine. In addition potentially also older adults aged 60 and over after a primary series of two doses of Vaxzevria.

Lastly, with the primary goal of reduction of transmission, COVID-19 booster vaccination of younger age groups in the population, including adolescents and people under 30 years of age with a limited risk of severe COVID-19, may help to avoid measures like school closures, physical and social distancing and other measures required to keep transmission at a low level. This in particular when new VOC's cause a high burden of disease in the population and require lock down measures or severe restrictions in social life.

2 SARS-CoV-2

2.1 Targets of current COVID-19 vaccines

The entry of SARS- CoV-2 into host cells is mediated by the transmembrane Spike (S) glycoprotein (S-protein) through binding to the angiotensin-converting enzyme 2 (ACE2) receptor on human cells at the onset of infection. The S-protein is the target of the current vaccines and consists of a membrane-proximal S2 domain containing the fusion peptide and a membrane-distal S1 domain containing the receptor binding domain (RBD) and the N-terminal domain (NTD). Neutralizing antibodies (NAbs) to the S-protein induced by vaccination or infection can reduce SARS-CoV-2 infection and as a consequence reduce disease burden and transmission/circulation of the virus.

2.2 Determinants of virulence. How has the virus changed up until now?

Although most mutations in the SARS- CoV-2 genome are expected to be either deleterious and swiftly purged or relatively neutral, a small proportion will affect functional properties and may alter infectivity, disease severity or interactions with host immunity. The emergence of SARS- CoV-2 in late 2019 was followed by a period of relative evolutionary stasis lasting about 11 months. Since late 2020, however, SARS- CoV-2 evolution has been characterized by the emergence of sets of mutations, in the context of VOCs, that impact virus characteristics, including transmissibility and antigenicity, probably in response to the changing immune profile of the human population [1]. The most important mutations in the VOCs include amino acid substitutions or deletions within the receptor binding domain (RBD) the N-terminal domain (NTD) and the S2 domain of the Spike protein. These mutations lead either to an enhanced interaction with the human ACE2 receptor resulting in increased infectivity and transmissibility. These substitutions can also result in alteration of binding to vaccination- or infection-induced NAbs. For example, B.1.1.7, B.1.351 and P.1 all share the N501Y RBD mutation, which contributes to an enhanced interaction with the ACE2 receptor [2, 3]. In addition, both B.1.351 and P.1 contain the E484K substitution and a substitution at position 417 (K417N in B.1.351 and K417T in P.1) both of which have been implicated in escape from NAbs [1, 4, 5]. Substitutions and deletions in the NTD also affect the response of such NAb responses. However, there is no clear evidence yet whether current VOC have been selected due to advances in transmissibility or that immune evasion did play a role in the rise and spread of these VOC.

Monitoring of SARS-CoV-2 variants causing break-through infections in fully vaccinated individuals do not reveal an enrichment of specific variants or mutations in the Netherlands as of yet, and do not suggest of positive selection of variants (see section 4.2.6). The data provided here will focus on the Alpha variant (B.1.1.7, first reported in the United Kingdom), the Beta variant (B.1.351, first reported in South Africa), the Gamma variant (P1, first reported in Brazil), and the Delta variant (B.1.617.2, first reported in India). Studies assessing the ability of sera

from vaccine recipients to neutralize SARS-CoV-2 variants, show reduced Spike binding and neutralization in vitro of VOCs: the largest reduction in neutralization is observed for the Beta variant (6-fold) followed by the Delta variant (5-fold), and relatively small reduction (2-fold) in neutralization against the Gamma variant and the Alpha variant [5, 6]. Overall, there does not seem to be a selection of specific variants among vaccinated individuals and vaccine-induced antibodies are able to neutralize all VOCs in vitro, albeit in some cases to a lower extend depending on the vaccine.

2.3 How do escape variants come into existence? Will waning immunity accelerate virus evolution?

Variants of Concern can arise in (and spread from) hosts with high viral replication. Vaccination is likely to slow down viral evolution since vaccination limits transmission. Whether waning immunity in a population accelerates the emergence of immune escape variants, due to suboptimal inhibition of viral replication, is under debate [7, 8]. The understanding of viral phylodynamics (the intersection of the epidemiological and evolutionary dynamics of pathogens) is still in its infancy, especially for novel pathogens like SARS-CoV-2. On the one hand, even partial immunity will likely reduce the number of infections and opportunity for new variants to emerge [8]. On the other hand, also partial immunity induced by vaccination or natural infection, may allow for ongoing viral replication and generation of immune escape variants due to selection pressure [7, 9]. Notwithstanding arguments either supporting or disputing that partial/waning immunity may accelerate the emergence of new SARS-CoV-2 variants, far more relevant is the global nature of the SARS-CoV-2 pandemic and continuing transfer of viral variants across continents. It is an illusion that the policy of any one country can have a large influence on the global evolution of the virus [8]. Therefore, from the virus escape point of view, there is an urgent need for global equity in vaccine distribution and deployment.

Future immune escape variants may require modified vaccine (rather than homologous booster vaccination with current vaccines). In what way the virus might change in the future is however difficult to predict [10, 11] and should be monitored by genomic surveillance programs.

3 COVID-19 vaccines

Based on their immunogenicity, efficacy and safety data obtained from phase 3 randomized controlled trials, four vaccines have received conditional marketing authorization in the European Union/European Economic Area (EU/EEA) following evaluation by the European Medicines Agency (EMA): Comirnaty (*BNT162b2*) developed by BioNTech/Pfizer [12], Spikevax (*mRNA-1273*) developed by Moderna [13], Vaxzevria (*AZD1222*) developed by the University of Oxford and AstraZeneca [14], and Janssen COVID-19 vaccine (*Ad26.COV2.S*) developed by Janssen (Johnsen & Johnsen) [15] (see Supplementary table 2) Vaxzevria and Ad26.COV 2.S are registered for use in people aged 18 years and older. Comirnaty and recently Spikevax obtained authorization for use in people aged 12 years and above. In the Netherlands all four vaccines have been used in the COVID-19 vaccination program which started January 6th, 2021.

3.1 Vaccine-induced immunity

To understand how COVID-19 vaccine-induced immune responses relate to the protective capacity of vaccines against SARS-CoV-2 infection, both asymptomatic and symptomatic infection (i.e. COVID-19), and to estimate the duration of immune protection, ongoing evaluation of immunity and infection data from vaccinees is required. During the clinical phase 1/2b and pivotal phase 3 trials of the EU/EEA authorized vaccines, immunogenicity data were gathered on the development and short-term maintenance of SARS-CoV-2 S-protein antibodies, including NAbs and on SARS-CoV-2 specific T-cell responses. For all four EU/EEA marketed vaccines and candidate vaccines under review by EMA, high responder rates of NAbs and Th1 type responses were found (see Supplementary table 2) [16]. For the current four registered vaccines, initial data are now being supplemented with long term follow-up data from phase 1/2b and 3 trials, next to additional randomized post-marketing trials and observational studies. It should be noted that different vaccine manufacturers and studies use different SARS_CoV-2 specific assays to analyze immune responses, such as NAbs and T-cell immunity data. Data from different manufacturers and studies can therefore not be directly compared. Over the next months, new immunological data in the vaccinated healthy population, including different age groups, and in groups at risk of poor vaccine responsiveness, will be obtained to support policy making.

3.1.1 Duration of vaccine-induced immune responses per vaccine

Comirnaty

Antibody levels following vaccination with Comirnaty were described up to 100 days after full two-dose vaccination in a study performed in Israel by Shapira *et al.* [17]. Antibody levels reached a stable plateau after 10-12 days in adults aged 18-44 years but declined later on in the older 50-86 years of age group, though antibody levels remained above the seropositivity detection threshold. Shrotri *et al*. also describe declining but detectable antibodies following Comirnaty (and Vaxzevria) vaccination at 10-22 weeks following 2nd dose [18]. Study participants

aged >65 years demonstrated lower initial antibody levels following vaccinations and also lower levels at the end of the follow up period. Long term immune responses may be supported by persistent human germinal center responses following vaccination [19]. Recently, preliminary and not yet peer reviewed data was released by the Pfizer company demonstrating neutralizing antibody titers 8 months after vaccination, that decline however during month follow up, especially in 65-85 years old (N=12) [20]. In the same preliminary data release, an increase in neutralizing titers against both wild type and the Delta variant was observed following a 3rd (booster) dose.

Spikevax
Antibody responses were reported by Widge *et al.* at 90 days after vaccination [21]. Recently, Doria-Rose *et al.* reported in a correspondence to the editor [22] that in all 33 participants who had received Spikevax during the Phase I trial, robust and high antibody levels were maintained for 6 months after full 2-dose vaccination, although antibody geometric mean titers (GMTs) declined with age [22]. In adults 18-55 years old, GMTs against SARS-CoV-2 spike RBD were 92.5 (95% CI: 57.1-149.6); in 56-70 years of age 62.4 (95% CI: 36.8-106.0); and in adults > 71 years old 49.3 (95% CI: 25.2-96.8). In various (pseudo) neutralization assays, similar age differences were noted, although nearly all study subjects demonstrated NAb activity.

Vaxzevria
As mentioned, Shrotri *et al.* [18] demonstrated declining but detectable antibodies following Vaxzevria (and Comirnaty) vaccination at 10-22 weeks following 2nd dose, with lower initial and long term immune responses in study participants aged >65 years. In a preprint by Flaxman *et al.* both antibody and T-cell responses were observed one year after a single dose of Vaxzevria and immune responses were boosted by a late second dose, or by a third dose given 263-266 days after an initial 2-dose schedule given at 8 week interval [23].

Janssen COVID-19 vaccine
Recently, Barouch *et al.* reported on data after 8 months follow up for the Janssen COVID-19 vaccine in a correspondence to the NEJM editor [24]: antibody responses were detected in vaccine recipients (N=20, of which some received two doses) on day 239, including a possible expansion of NAb breadth against variants with time. Also, cellular immune responses were demonstrated.

3.1.2 *Neutralizing antibodies against Variants of Concern, per vaccine*

SARS-CoV-2 continues to evolve and recently emerging variants with substitutions in the S-protein have led to growing concerns over increased transmissibility and disease severity as well as immune evasion. Variants of concern tested for NAb activity include the Alpha, Beta, Gamma and Delta variant.

Comirnaty
A study performed in the UK by Wall *et al.* in 250 participants (median age 42 years [IQR 33–52]) showed that two doses of Comirnaty elicited (ELISA-detected) anti-Wild-type Spike antibodies in at least 95% of participants, and NAb activity against all tested viral strains, including

three VOCs (Alpha, Beta and Delta variant) [25]. However, NAb titers against the Delta, Beta and Alpha variants were respectively 5.8-fold (95% CI: 5.0-6.9), 4.9-fold (95% CI: 4.2–5.7) and 2.6-fold (95% CI: 2.2–3.1) lower than in case of the wild-type strain. Across all variants, increased age was correlated with reduced NAb titers.

Spikevax
Sera from 8 participants immunized with 2 doses of Spikevax were tested for neutralizing activity against several SARS-CoV-2 variants [26]. Neutralization titers against the Alpha variant were only minimally affected (1.2-fold reduction compared with wild type), whereas in cases of other VOCs such as the Beta, Gamma and Delta variant neutralization antibody titers were reduced (6.9-8.4, 3.2 and 2.1-fold reductions, respectively) compared with the wild-type strain. However, all viral strains remained susceptible to Spikevax-elicited serum neutralization.

Vaxzevria
A UK study by Liu *et al.* showed a reduced neutralizing capacity of antibodies against two variants of the Delta variant in serum of individuals after two doses of Vaxzevria [27]. NAb titers against the two Delta variants were reduced 4.3-fold relative to the wild-type virus. In another study, reduction in Nab was most with Beta strains with less resistance against Alpha and Gamma variants [28]. Although significant reductions in Nab were measured, there was no evidence of complete escape from neutralization.

Janssen COVID-19 vaccine
Sera from recipients of a single dose of the Janssen COVID-19 vaccine were tested for neutralizing activity against several SARS-CoV-2 variants of concern. All tested variants demonstrated susceptibility to Janssen COVID-19 vaccine-induced serum neutralization, albeit reduced as compared with the wild type Wuhan strain (B.1 strain). Most pronounced reduction was observed for the Beta (3.6-fold) and Gamma (3.4-fold) variants, that contain similar mutations in the receptor-binding domain (RBD) while only a 1.6-fold reduction was observed for the widely spreading Delta variant. Different types of T cells responded similarly against the variants compared with the original virus.

3.1.3 *Immunogenicity after a heterologous primary series*

In the UK, a heterologous two-dose COVID-19 vaccination study was performed in individuals of 50 years and older, comparing all four combinations of Vaxzevria and Comirnaty at 28-day and 84-day intervals in participants of 50 years and over [29, 30]. Both heterologous vaccine series Vaxzevria/Comirnaty and Comirnaty/Vaxzevria induced greater systemic reactogenicity following the boost dose than their homologous counterparts. One month post-boost SARS-CoV-2 anti-spike IgG geometric mean concentration (GMC) in Vaxzevria/Comirnaty recipients was significantly higher (12,906 ELU/ml) compared with Vaxzevria/ Vaxzevria recipients (1,392 ELU/ml) with a geometric mean ratio (GMR) of 9.2 (one-sided 97.5% CI: 7.5, ∞). For Comirnaty primed participants, GMR of a heterologous Comirnaty/Vaxzevria (GMC 7,133 ELU/ml) versus a homologous Comirnaty/Comirnaty (GMC 14,080 ELU/ml) schedule was lower (0.51 (one-sided 97.5% CI: 0.43, ∞). Still, antibody levels were boosted by

Vaxzevria following Comirnaty, with significantly higher GMC as compared to Vaxzevria/Vaxzevria. Mixed series showed also the highest cellular response. Geometric mean of T cell response at 28 days post-boost was highest in the Vaxzevria/Comirnaty group; 185 SFC/10^6 spot forming cells/10^6 peripheral blood mononuclear cells) compared to 50, 80 and 99 SFC/10^6 PBMCs for Vaxzevria/Vaxzevria, Comirnaty/Comirnaty, and Comirnaty/Vaxzevria. Study results Another study from Spain confirmed that Comirnaty, given as a second dose 8–12 weeks after a first dose of Vaxzevria, induced a robust antibody response and with reactogenicity in an acceptable range [31]. A German study in 216 individuals compared S-protein specific antibody and CD4 and CD8 T-cell responses after a heterologous Vaxzevria/mRNA schedule with homologous schedules with Vaxzevria, Comirnaty and Spikevax [32]. In this study, antibody and neutralizing antibody titers and CD4 T-cells levels in the vector/vector vaccine group were significantly lower than in all other groups, and results of the heterologous group were similar to both mRNA homologous groups. CD8 T-cell levels where highest in the heterologous group and the two vector-primed groups had the highest percentage of polyfunctional CD4 T cells, irrespective of the boosting vaccine. Plasmablast numbers were comparable for all groups. Another smaller German study by Gross *et al.* in 26 younger adults (median age 30.5 years) 25−46 years (median: 30.5 years) who received Vaxzevria followed by Comirnaty, the neutralizing activity against the Beta variant was reduced two-fold compared to the (at the time of the study prevalent) Alpha variant, but similar for Delta variant [33]. In addition, for the prevalent Alpha variant, the neutralizing activity was 3.9-fold higher after the heterologous series compared with the homologous Comirnaty series. Data on the duration of the responses are still limited. A multi-center study comparing immune responses after a 2-dose homologous COVID-19 vaccine series with different combinations of heterologous schedules (Janssen COVID-19 vaccine/Comirnaty and Janssen COVID-19 vaccine/Spikevax) is currently ongoing in the Netherlands. Data on SARS-CoV-2 Spike-protein specific IgG antibody titers for the different groups are expected in September/October 2021).

3.1.4 *Immunogenicity after a homologous booster dose, per vaccine*

Comirnaty

Data from an ongoing booster study show that a third Comirnaty dose given 6 months after the second dose has a similar tolerability profile while eliciting high neutralization titers against the wild type and the Beta variant, which are 5 to 10 times higher than after two primary doses [34].

Spikevax

First data of an ongoing booster study on immune responses after a third dose of 50µg (half the standard dose) of the original Spikevax vaccine compared with the response after a booster with a modified mRNA-1273.351 vaccine (encoding for the S-protein found in the Beta variant) are now available [35]. Preliminary data show that two weeks after the third dose, given approximately 6 months after the second dose, titers against the wild-type original strain as well as the Beta and Gamma variants, increased to levels at least similar or higher than peak antibody levels after the primary series vaccinations. Although both

Spikevax and mRNA-1273.351 boosted NAbs in case of the wild-type original strain and Beta or Gamma variants, the modified mRNA-1273.351 booster appeared to be most effective at increasing neutralization of the Beta variant.

Vaxzevria
A study performed in 90 volunteers in the UK showed that a third dose of Vaxzevria given 30 weeks after the second dose resulted in an increase in antibody levels that was higher than after the second dose [23]. Antibody levels were significantly higher following a third dose when compared with the response 28 days after a second dose. Neutralizing antibody levels following a third dose were higher than those after second dose against Alpha, Beta and Delta variants. T-cell responses were also boosted after a third dose, but peak responses at day 28 after a third dose was not significantly different to the response after the second dose. Reactogenicity after a late second dose or a third dose was lower than reactogenicity after a first dose.

Janssen COVID-19 vaccine
The phase 3 trial included a group vaccinated with a two-dose schedule; data are expected in September.

3.1.5 *Immunogenicity after a heterologous booster dose*

Currently no data are available on immune responses after a booster vaccination with a heterologous COVID-19 vaccine. In the UK a large study has started including participants with primary series doses with Comirnaty, Vaxzevria or Spikevax that will receive a booster dose with one of the different COVID-19 vaccines available in the UK (see Supplementary table 1). Also, the National Institute of Health (NIH) in the US has started a booster trial. The first data of both studies are expected in September 2021. In theory, after a primary series with viral vector vaccines, Vaxzevria and Janssen COVID-19 vaccine, a booster with mRNA vaccine may seem the obvious choice to optimize in particular NAb levels, based on data of a mixed primary series. After a primary series with mRNA vaccines, heterologous boosting with another mRNA vaccine may also offer advantages but data are not yet available. Similarly, boosting with whole cell vaccine or protein vaccines may result in additional immunity stimulation, though impact on protection is unknown.

3.1.6 *Duration of antibody persistence and cellular immunity after natural SARS-CoV-2 infection*

Li *et al.* in Nature Comm [36] demonstrate low but detectable receptor binding domain -IgG levels at 12 months following infection in over 70% of COVID-19 convalescent plasma donors. Though antibodies decreased over the 12 months follow up, this seemed to stabilize around 9 months. In other recent studies, antibodies were detected up to 1 year after infection [37, 38], even if infection had been asymptomatic [37], though another study found that in 40% of asymptomatic patients, responses dropped already during the convalescent phase [39]. Antibody levels following infection are maintained by long lived bone marrow plasma cells, that have been demonstrated in patients up to 11 months after infection [40].

Neutralizing activity of antibodies was demonstrated and remained relatively stable during 6 to 12 months after infection [41]. Vaccination after prior SARS-CoV-2 infection increased the already broad post-natural infection response, as demonstrated by expansion of B cell clones that express broad antibodies after vaccination [41].

Infection also induces long lived memory T cells as recently demonstrated, by Jung *et al.* [42]: antigen-specific CD4+ and CD8+ T cell responses were detected in individuals 10 months after infection. Among activated T cells, stem cell-like memory T cells were found and memory T cell responses were maintained regardless of disease severity or symptomatic infection or not.

As previously reviewed, this is suggestive of a long term immune response following infection, that is expanded in amplitude and breadth of neutralizing activity by vaccination [43, 44].

3.1.7 COVID-19 booster vaccine versus natural infection

Boosting immunity can either be achieved by either vaccination or by a natural infection. Consequences of natural boosting by SARS-CoV-2 infection in vaccinated persons are unknown. On the one hand, natural infection may not lead to severe illness while providing broad immunity for the future. On the other hand, it may induce also severe COVID-19 in some individuals, as well as long COVID-19 but we have not no data on breakthrough infections and long-term consequences in fully vaccinated persons yet. It is also unknown whether SAR-CoV-2 infection in vaccinated persons may still lead to the rare presentation of multisystem inflammatory syndrome temporarily associated with COVID-19 in children, adolescents and adults. The currently dominant Delta variant is much more transmissible, reaching a higher viral load with potentially different consequences for breakthrough infections compared with for example the Alpha variant.

3.2 Vaccine efficacy and effectiveness estimates based on international literature

The effects of vaccination can be assessed by either the vaccine *efficacy* or vaccine *effectiveness (VE)*. Vaccine *efficacy* is measured in randomized controlled clinical trials. For drug authorization of the COVID-19 vaccines, interim analyses for vaccine efficacy are mostly performed after a pre-specified number of COVID-19 cases are diagnosed and/or after a median follow-up of two month. VE is estimated in observational studies. Follow-up times in studies that investigate COVID-19 VE are currently variable and depending on the time of vaccine introduction in a population.

Overall efficacy rates of COVID-19 vaccines deployed in EU/EEA pivotal phase 3 trials in Europe are required to fulfill criteria for the studies' primary efficacy endpoints. These are described in the guidance for industry entitled "Development and Licensure of Vaccines to Prevent COVID-19", and include a point estimate for a placebo-controlled efficacy trial of at least 50%, with a lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate of >30%). For the two mRNA vaccines Comirnaty and

Spikevax the efficacy rates against symptomatic infection after the full 2 dose-series were 95%. For the adenovector-based Vaxzevria and Janssen COVID-19 vaccine efficacy rates of 62-81% and 67% were obtained after their full 2 dose and 1 dose schedules, respectively (see Supplementary table 3 and Supplementary table 6). These rates reflect the potency and immunogenicity of the individual vaccines but also the diversity in study populations, local pandemic circumstances and case definitions in the phase 3 trials, and comparisons should be made with caution.

So far VE analyses have confirmed findings on vaccine efficacy from the phase 3 trials, suggesting high rates of protection of disease, especially against severe disease, hospitalization and death at all ages. Also evidence was found that COVID-19 vaccines reduce the incidence of asymptomatic infection and the viral load in individuals who become infected despite vaccination [45, 46]. These data were derived from the period before widespread circulation of the Delta Variant of Concern. Post-implementation analyses revealing the real-world effectiveness are addressed later in this chapter.

3.2.1 *Vaccine effectiveness against SARS-CoV-2 Variants of Concern*

The rise of SARS-CoV-2 VOCs, such as the Alpha and Delta variant with increased transmissibility has raised concerns about possible decreases in vaccine effectiveness (VE) due to mutations in the virus. Numerous studies have estimated VE against different variants of concern. A summary of available estimates is presented in Table 1 (VE against any infection) and Table 2 (VE against severe infection, hospitalization, and death). The limited time of follow up after full vaccination, differences in study designs, outcomes, study populations and circulating SARS-CoV-2 variants, challenges the comparability between studies and thereby a conclusion about the impact of potential waning of vaccine efficacy and VE overall and by age group [47].

Against any SARS-CoV-2 infection

For the Alpha variant, VE estimates against any SARS-CoV-2 infection ranged between 37% and 88.1% after a single dose and between 73% and 100.0% after the second dose of Comirnaty, Spikevax or Vaxzevria [49-56] (see Table 1). Comirnaty-specific VE estimates against any SARS-CoV-2 infection with the Alpha variant ranged between 38% and 66% after a single dose and between 88% and 93.7% after the second dose [48, 52, 56]. VEs of 88.1% (95% CI: 83.7—91.5) [54] and 83% (95% CI: 80-86) [56] were reported after a single dose of Spikevax. These VEs ranged between 91% and 100% after receival of the second Spikevax dose [54]. For Vaxzevria, VE estimates against any infection with the Alpha variant ranged between 37% and 64% after one dose and between 73% and 75% after two doses [48, 52, 56].

Table 1 Overview of vaccine effectiveness against any SARS-CoV-2 infection by Variant of Concern, by key literature.

		VE (95% CI), vaccine			
Reference	**Time interval**	**Alpha**	**Beta**	**Gamma**	**Delta**
Lopez Bernal *et al.* [52]	≥21 days after dose 1 – dose 2	47.5 (41.6-52.8), COM			35.6 (22.7-46.4), COM
		48.7 (45.2-51.9), VAX	-	-	30.0 (24.3-35.3), VAX
	≥14 days after dose 2	93.7 (91.6-95.3), COM	-	-	88.0 (85.3-90.1), COM
		74.5 (68.4-79.4), VAX	-	-	67.0 (61.3-71.8), VAX
Sheikh *et al.* [48]	≥28 days after dose 1	38 (29-45), COM	-	-	30 (17-41), COM
		37 (32-42), VAX	-	-	18 (9-25), VAX
	≥14 days after dose 2	92 (90-93), COM	-	-	79 (75-82), COM
		73 (66-78), VAX	-	-	60 (53-66), VAX
Pritchard *et al.* [49]	≥21 days after dose 1 – dose 2	68 (62-73), COM & VAX	-	-	-
	≥0 days after dose2	85 (79-89), COM & VAX	-	-	-
Chung *et al.* [53][a]	≥14 days after dose 1	61 (56-66), COM & SPX	-	-	-
	≥7 days after dose 2	90 (85-94), COM & SPX	-	-	-
Skowronski *et al.* [50]	≥21 days after dose 1	67 (57-75), COM & SPX	-	61 (45-72), COM & SPX	-
Chemaitelly *et al.* [54]	≥14 days after dose 1 – dose 2	88.1 (83.7-91.5), SPX	61.3 (56.5-65.5), SPX	-	-
	≥14 days after dose 2	100 (91.8-100.0), SPX	96.4 (91.9-98.7), SPX	-	-
Carazo *et al.* [51]	≥14 days after dose 1 – dose 2	60 (53.6-65.5), COM & SPX	-	-	-
	≥7 days after dose 2	92.6 (87.1-95.8), COM & SPX	-	-	-

		VE (95% CI), vaccine			
Reference	**Time interval**	**Alpha**	**Beta**	**Gamma**	**Delta**
Nasreen *et al.* [56][a]	≥14 days after dose 1	66 (64-68), COM 83 (80-86), SPX 64 (60-68), VAX	60 (52-67), COM 77 (63-86), SPX 48 (28-63), VAX	60 (52-67), COM 77 (63-86), SPX 48 (28-63), VAX	56 (45-64), COM 72 (57-82), SPX 67 (44-80), VAX
	≥14 days after dose 2	89 (87-91), COM 91 (84-95), SPX 75 (-98-97), VAX	85 (70-93), COM - -	 - -	85 (59-94), COM - -
Tang *et al. [57]*	≥14 days after dose 1 – dose 2	- -	- -	- -	64.2 (38.1-80.1), COM 79.0 (58.9-90.1), SPX
	≥14 days after dose 2	- -	- -	- -	53.5 (43.9-61.4). COM 84.8 (75.9-90.8), SPX
Tang *et al.* [57][a]	≥14 days after dose 1 – dose 2	- -	- -	- -	76.3 (46.7-90.7), COM 85.7 (62.7-95.7), SPX
	≥14 days after dose 2	- -	- -	- -	56.1 (41.4-67.2), COM 85.8 (70.6-93.9), SPX
Elliot *et al. [59]*		-	-	-	62 (38-77), COM & VAX[b]
Puranik *et al. [55]*	≥14 days after dose 2	88 (77-94.1), COM[c] 91.5 (82-96.7), SPX[c]	- -	- -	42 (13-62), COM 76 (58-87), SPX

a Symptomatic SARS-CoV-2 infection; b COVID-19 vaccine type is not mentioned in publication but the listed COVID-19 vaccines where authorized in the country of study conduction; c VEs of the month April are presented, the Alpha variant was the dominantly circulating variant in this month; COM Comirnaty; SPX Spikevax; VAX Vaxzevria.

Table 2 Overview of vaccine effectiveness against severe COVID-19, hospitalization, and death per Variant of Concern, by key literature.

		VE (95% CI), vaccine			
Reference, outcome	**Time interval**	**Alpha**	**Beta**	**Gamma**	**Delta**
Chung *et al.* [53], Hos & Mor	≥14 days after dose 1	59 (39-73), COM & SPX	-	-	-
	≥7 days after dose 2	94 (59-99), COM & SPX	-	-	-
Tenforde *et al.* [60], Hos	≥14 days after dose 2	92.8 (83.0-96.9), COM & SPX	-	-	-
Stowe *et al.* [58], Hos	≥1 days after dose 1	83 (62-93), COM	-	-	94 (46-99), COM
		76 (61-85), VAX	-	-	71 (51-83), VAX
	≥1 days after dose 2	95 (78-99), COM	-	-	96 (86-99), COM
		86 (53-96), VAX	-	-	92 (75-97), VAX
Nasreen *et al.* [56], Hos & Mor	≥14 days after dose 1	80 (78-82), COM 79 (74-83), SPX 85 (81-88), VAX	77 (69-83), COM 89 (73-95), SPX 83 (66-92), VAX	77 (69-83), COM 89 (73-95), SPX 83 (66-92), VAX	78 (65-86), COM 96 (72-99), SPX 88 (60-96), VAX
	≥7 days after dose 2	95 (92-97), COM 94 (89-97), SPX 67 (-155-96), VAX	98 (82-100), COM - -	98 (82-100), COM - -	- - -
Tang *et al. [57],* Sev, Hos & Mor	≥14 days after dose 1 – dose 2	-	-	-	100.0 (8.2-100.0). COM
		-	-	-	100.0 (28.1-100.0), SPX
	≥14 days after dose 2	- -	- -	- -	89.7 (61.0-98.1), COM 100.0 (41.2-100.0), SPX
Puranik *et al.* [55], Hos	≥14 days after dose 2	90 (57-98.8), COM[a]	-	-	75 (24-93.9), COM
		94.3 (64-99.9), SPX[a]	-	-	81 (33-96.3), SPX

a VEs of the month April are presented, the Alpha variant was the dominantly circulating variant in this month; COM Comirnaty; Hos hospitalization; Mor mortality; Sev severe COVID-19 disease; SPX Spikevax; VAX Vaxzevria.

For the Delta variant, VE estimates against any infection ranged between 30% and 76% after a single dose of Comirnaty and between 42% and 88% after the second Comirnaty-dose [48, 52, 55-57]. VE estimates against any SARS-CoV-2 infection with the Delta variant ranged between 72% and 85% after a single dose of Spikevax [56]. After two doses of Spikevax, corresponding VEs ranged between 76% and 85.5% [55, 57]. For Vaxzevria, corresponding VEs against any SARS-CoV-2 infection with the Delta variant ranged between 18% and 67% after a single dose [48, 52, 56] and were 67% (95% CI: 61.3-71.8) and 60% (95% CI: 53-66) after the second dose [48, 52].

Against severe COVID-19 outcomes
VE estimates were high against severe outcomes of COVID-19 (e.g., hospitalization and/or death) for all COVID-19 vaccines, particularly after 2 doses (see Table 2) [55, 57]. Additionally, the difference in effectiveness against severe outcomes against the Alpha and Delta variants were rather small after 2 doses. Specifically, VE against hospitalization after infection with the Alpha variant was 83% (95%CI 62-93) after one and 90% (95% CI 57-98.8) [55] and 95% (95%CI 78-99) [58] after two doses of Comirnaty, and 76% (95%CI 61-85) after one and 86% (95%CI 53-96) [58] after two doses of Vaxzevria, respectively [58]. After infection with the Delta variant, VE against hospitalization was 94% (95%CI 46-99) after one and 75% (95% CI 24-94.6) [55] and 96% (95%CI 86-99) [58] after two doses of Comirnaty, and 71% (95%CI 51-83) after one and 92% (95%CI 75-97) after two doses with Vaxzevria [58].

3.2.2 *Vaccine effectiveness over time*

Information about VE over time is limited since COVID-19 vaccines have been in use outside clinical trials for less than 9 months. A first pre-print about waning vaccine efficacy of Comirnaty is available [61]. Below, results of this study are described. An overview is given of the literature in which vaccine-specific effectiveness against symptomatic infection, hospitalization and death is estimated after full vaccination (i.e. two doses for Comirnaty, Spikevax or Vaxzevria and one dose for the Janssen COVID-19 vaccine).Of all identified pre-preprints and peer reviewed articles of observational studies, only the one with the longest time since vaccination is mentioned.

Comirnaty
Symptomatic infection: A first study on long term efficacy from the randomized controlled study on Comirnaty was recently published [61]. Symptomatic SARS-CoV-2 infection (COVID-19) occurring at least 14 days after full vaccination was observed in 8 of the 18,175 individuals who received Comirnaty and 139 of the 18,261 individuals who received a placebo. This resulted in a vaccine efficacy of 94.2% (95% CI: 88.7-97.2) (see Supplementary table 3) [62]. Individuals were followed for a median of two months. A recent efficacy update after two doses of Comirnaty given 21 days apart with longer follow-up was provided by Thomas *et al.* [61]. COVID-19 occurrence at least 7 days after full vaccination was observed in 81 of 21,642 participants who received Comirnaty and 873 of the 21,689 participants who received a placebo. Corresponding vaccine efficacy was 91.1% (95% CI: 88.8- 93.0) with a peak in efficacy of 96.2% (95% CI: 93.3-98.1) for COVID-19 occurring

between 7 days and 2 months after vaccination (see Supplementary table 3). An average decline in vaccine efficacy of ~6% every 2 months was observed with vaccine efficacy estimates of 90.1% (95% CI: 86.6-92.9) and 83.7% (95% CI: 74.7-89.9) for COVID-19 occurring between 2 and 4 months, and ≥4 months after full vaccination, respectively. Saciuk *et al.* reported a VE of 93.0% (95% CI: 92.6-93.4) against a SARS-CoV-2 infection occurring >14 days after full vaccination (see Supplementary table 3) [63].

Hospitalisation: Comirnaty vaccine efficacy against hospitalization is not always separately estimated in clinical trials. Pawlowski *et al.* reported a VE against hospitalization at least 14 days after full vaccination of 88.3% (95% CI: 72.6-95.9) (see Supplementary table 7) [64]. In the same study, a VE against admission to the intensive care unit was estimated at 100.0% (95% CI: 18.7-100.0). The longest time since full vaccination was 120 days with a median of 58 (IQR 27-78) days in this study.

Case fatality: After a maximum of 98 days since full vaccination, Saciuk *et al.* reported a VE against death occurring more than 14 days after vaccination of 91.1% (95% CI: 87.0-94.0) (see Supplementary table 8) [63].

Spikevax
Symptomatic infection: Baden *et al.* investigated the vaccine efficacy of Spikevax against COVID-19 [65]. COVID-19 was confirmed in 11 of the 15,210 individuals who were fully vaccinated with Spikevax and in 185 of the 15,210 individuals who received a placebo after a median follow-up of 64 days (range 0-97). The corresponding vaccine efficacy against COVID-19 occurring at least 14 days after full vaccination was 94.1% (95% CI: 89.3-96.8) (see Supplementary table 4). In the second quarter fiscal report of Moderna, a vaccine efficacy of 93% up through six months after full vaccination is mentioned [66]. Within a retrospective cohort in adults, VE against COVID-19 occurring at least 14 days after full vaccination of 92.3% (95% CI: 82.4-97.3) was observed after a median follow-up time of 58 days (range 0-120 days) [64].

Hospitalisation: Vaccine efficacy estimates against hospitalization were not estimated in clinical trials. Pawlowksi *et al.* reported a VE against hospitalization at least 14 days after full vaccination of 90.6% (95% CI: 76.5-97.1) after a median and maximum time since full vaccination of 58 and 120 days, respectively (see Supplementary table 7) [64]. The corresponding VE against intensive care unit admission was 100.0% (95% CI: 17.9-100.0).

Case fatality: No publication was found in which the vaccine efficacy against death for Spikevax is estimated. Flacco *et al.* aimed to estimate Spikevax VE against death [67]. However, too few deaths were observed after full vaccination to provide such estimate.

Vaxzevria
Symptomatic infection: COVID-19 was diagnosed at least 15 days after full vaccination in 84 of the 8597 individuals who received Vaxzevria and

248 of the 8581 individuals who received a placebo [68]. This resulted in a vaccine efficacy against COVID-19 of 66.7% (95% CI: 57.4-74.0) after a median follow-up of 3.4 months (IQR 1.3-4.8) (see Supplementary table 5). Vaxzevria VE against COVID-19 occurring at least 14 days after full vaccination was 66.1% (95% CI: 51.0- 75.0) for the Alpha variant and 59.8% (95% CI: 28.9-77.3) for the Delta variant in a young population in which the majority was aged 16-39 years [52]. Corresponding VE against COVID-19 with the Gamma variant as the dominant circulating VOC, was 77.9% (95% CI: 69.2-84.2) in adults aged ≥60 years [69]. The median follow-up time in this study was limited to 13 (IQR 8-24) days for cases and 20 (IQR 10-34) for controls.

Hospitalization: After a median follow-up time of 78 days (range 17-127), eight participants in the placebo group and none in the Vaxzevria group (standard dosing/standard dosing) were hospitalised due to COVID-19 at least 15 days after full vaccination [70]. This resulted in a vaccine efficacy against hospitalization of 100% (95% CI: 42.7, NE). VE against hospitalization occurring at least 14 days after full vaccination of 87.6% (95% CI: 78.2-92.6) was estimated in adults aged ≥60 years by Hitchings *et al.* [69]. The median time since full vaccination was limited with 13 days (IQR 8-24) for cases and 20 days (IQR 10-34) for controls.

Case fatality: No publication was identified in which vaccine efficacy against death for Vaxzevria was estimated. VE against death occurring at least 14 days after full vaccination was 93.6% (95% CI: 81.9-97.7) [69]. Cases were followed for a median of 20 (IQR 10-34) days and controls for a median of 13 (IQR 8-24) days in this study.

Janssen COVID-19 vaccine
Symptomatic infection: After a median follow-up time of 58 days (range 1 to 124 days), moderate to severe-critical COVID-19 occurring at least 28 days after full vaccination was observed in 66 of the 19,306 persons who received the Janssen COVID-19 vaccine and 193 of the 19,178 persons who received a placebo. Corresponding vaccine efficacy was 66.1% (95% CI: 55.0-74.8) (see Supplementary table 6) [71]. Vaccine efficacy increased steadily from 14 days after vaccination to plateau around 56 days after full vaccination (see Supplementary figure 1). The uncertainty in vaccine efficacy estimates beyond 56 days increased due to the decrease in number of participants with a follow-up beyond this time. In a retrospective cohort study, VE against a SARS-CoV-2 infection occurring ≥15 days after full vaccination was estimated at 76.7% (95% CI: 30.0-95.3) [72]. The longest time since vaccination was approximately 45 days in this study.

Hospitalization: A vaccine efficacy against COVID-19 requiring hospitalization at least 14 days after full vaccination of 81.8% (95% CI: 16.7-98.0) was reported in the Janssen COVID-19 Vaccine Emergency Use Authorization for an Unapproved Product Review Memorandum of the US Food and Drug Administration [73]. Corresponding vaccine efficacy at least 28 days after full vaccination was 100% (95% CI: 15.7-100.0). Moreover, projected vaccine efficacy estimates against severe-critical COVID-19, i.e. including hospitalization and death, seemed to steadily increase between 14 and 56 days after full vaccination (see Supplementary figure 2) [71]. The uncertainty in these estimates is

larger beyond 56 days due to the limited number of participants with a longer follow-up. VE estimates of the Janssen COVID-19 vaccine are only provided in the publication by Corchado-Garcia *et al.* [72]. However, the number of hospital admissions was too low to provide VE against hospitalization.

Case fatality: A vaccine efficacy against all-cause mortality of 81.3% (95% CI 34.6, 96.5), 80.0% (95% CI 29.4, 96.3) and 75% (95% CI -25.2, 97.4) was reported for deaths occurring at least 1, at least 14 and at least 28 days after full vaccination (Supplementary table 8) [73]. In absolute number of deaths, 19 participants died of any cause of which 6 deaths were related to COVID-19, all in the placebo group.

3.2.3 *Breakthrough infections after full vaccination*

In a study among 1,497 healthcare workers from Israel that were fully vaccinated with Comirnaty, 39 breakthrough infections were reported during the four-month period after the second vaccine dose [74]. Most of the breakthrough infections were mild with few symptoms, although persistent symptoms (>6 weeks) did occur in 19%. The median age of the infected healthcare workers was 42 years (range 24-66), and the median interval between the second vaccine dose and SARS-CoV-2 detection was 39 days (range 11-102). One of the infected persons had immunosuppression. Another study from Israel also found that severe COVID-19 developed in a minority of fully vaccinated individuals (Comirnaty), especially in patients of older age and with multiple comorbidities or immunosuppression [75]. About 40% of the Israeli breakthrough patients were immunocompromised, which is in line with the proportion of 44% found in a US study [60]. Dutch hospitals reported that in week 28 (12-18 July) of 2021 approximately 75% of COVID-19 hospital admissions concerned unvaccinated or not fully vaccinated individuals; 9% of hospitalized patients were fully vaccinated individuals who were not immunocompromised; 5% were fully vaccinated immunocompromised individuals, and for the remaining 11% there was insufficient data to determine their status [76].

3.2.4 *Vaccine effectiveness of vaccine boosters*

There are no data on vaccine efficacy or VE after booster vaccination available. Only data on immunogenicity have been reported (see section 3.1.4 and 3.1.5).

3.2.5 *Vaccine effectiveness over time by age*

No studies have been published in which age-specific waning of vaccine efficacy or effectiveness is investigated. Instead, an overview of age- and vaccine-specific efficacy and effectiveness is provided below. For VE, publications with the longest follow-up or longest time since vaccination are mentioned.

Comirnaty

Symptomatic infection: Vaccine efficacy against COVID-19 occurring ≥7 days after full vaccination was consistent across several age groups in the clinical trial of Polack *et al.* [77]. In the trial no decline in efficacy was observed with older age. Corresponding vaccine efficacy estimates were 95.6% (95% CI: 89.4-98.6), 93.7% (95% CI: 80.6-98.8), 94.7% (95% CI: 66.7-99.9) and 100.0% (95% CI: -13.1-100.0) for individuals

aged 16-55, >55, ≥65 and ≥75 years, respectively. In contrast, Saciuk *et al.* reported an 11% higher VE against a SARS-CoV-2 infection occurring >14 days after full vaccination for those aged 16-44 years compared with individuals aged ≥75 years [63]. The VE estimate were 94.7% (95% CI: not provided), 89.1% (95% CI: 83.0-93.0) and 84% (95% CI: not reported) for those aged 16-44 years, ≥70 years and ≥75 years, respectively. Within this retrospective study, the maximum follow-up time was 98 days with a median of 64 days for vaccinated and 28 days for unvaccinated individuals. Haas *et al.* stratified VE by age in a prospective cohort study [78]. After a median follow-up time of 48 (IQR 30-60) days, VE against a SARS-CoV-2 infection ≥14 days after full vaccination was 97.1% (95% CI: 96.7-97.3), 96.5% (95% CI: 96.3-96.7) and 95.9% (95% CI: 95.5-96.3) for individuals aged 15-44 years, 45-64 years and ≥65 years, respectively. For symptomatic SARS-CoV-2 infections, i.e. COVID-19, corresponding VE estimates were higher with 97.8% (95% CI: 97.5-98.1), 97.7% (95% CI: 97.4-97.9) and 97.5% (95% CI: 97.2-97.8), respectively. VE against asymptomatic PCR-confirmed SARS-CoV-2 infections were 95.2% (95% CI: 94.6-95.8), 94.0% (95% CI: 93.4-94.4) and 91.5% (95% CI: 90.4-92.5) for those aged 15-44 years, 45-64 years and ≥65 years, respectively.

Hospitalization: Stratified VE estimates against hospitalization by age group are provided by Haas *et al.* [78]. After a median follow-up time of 48 (IQR 30-60) days, VE against hospitalization due to COVID-19 ≥14 days after full vaccination remained well above 95% with 98.1% (95% CI: 97.1-98.7), 98.2% (95% CI: 97.7-98.6) and 97.9% (95% CI: 97.6-98.1) for individuals aged 15-44 years, 45-64 years and ≥65 years, respectively. Corresponding VE estimates against severe and critical hospitalization were in the same range with 99.0% (95% CI: 97.5-98.9), 98.5% (95% CI: 97.9-98.9) and 98.3% (95% CI: 98.0-98.6), respectively.

Case fatality: Haas *et al.* reported a VE against COIVD-19 related death occurring ≥14 days after full vaccination of 96.5% (95% CI: 93.2-98.2) and 98.2% (95% CI: 97.7-98.7) for individuals aged 45-64 and ≥65 years, respectively [78]. For individuals aged 15-44 years, 36 COVID-19 related deaths were observed in the unvaccinated individuals against none in the vaccinated individuals resulting in a VE against COVID-19 related death of 100.0% (95% CI: not estimated).

Spikevax
Symptomatic infection: Vaccine efficacy against COVID-19 occurring ≥14 days after full vaccination was 95.6% (95% CI: 90.6-97.9) for individuals aged 18 to 65 years against 86.4% (95% CI: 61.4-95.2) for individuals aged ≥65 years [65]. No publication could be identified in which Spikevax-specific VE against COVID-19 or a SARS-CoV-2 infection after full vaccination are stratified by age.

Hospitalization and case fatality: Baden *et al.* [65] aimed to investigate Spikevax vaccine efficacy against severe COVID-19, which included both hospitalization and death. Severe COVID-19 was observed in 30 individuals of the placebo group and none of the individuals who received Spikevax. Corresponding vaccine efficacy could therefore not

be estimated. Age- and Spikevax-specific VE estimates against hospitalization and death after full vaccination are lacking.

Vaxzevria
Symptomatic infection: Clinical trial results showed a vaccine efficacy against COVID-19 occurring ≥15 days after full vaccination of 60.0% (95% CI: 46.0-70.4) for individuals aged 18-64 years and 44.8% (95% CI: -88.8-83.9) for individuals aged ≥65 years [70] with a dosing interval between 4 and 12 weeks. The maximum follow-up time was approximately 11 weeks. A VE against symptomatic SARS-CoV-2 infections occurring ≥14 days after full vaccination of 77.9% (95% CI: 69.2-84.2) was reported in individuals aged ≥60 years [69]. With a dosing interval of 65-84 days, VE against a SARS-CoV-2 infection was 77% (95% CI: 74-79), 74% (95% CI: 69-79) and 82% (95% CI: 68-89) for individuals aged 50-64, 65-79 and ≥80 years, respectively [79]. The median time since full vaccination in those age groups was 54, 70 and 84 days, respectively.

Hospitalization and case fatality: Vaxzevria vaccine efficacy estimates against hospitalization or death stratified by age group have not been found. Hitchings *et al.* estimated the VE against hospitalization, intensive care unit admission and death occurring ≥14 days after full vaccination for individuals aged ≥60 years [69]. After a median time since full vaccination of 13 (IQR 8-24) days for cases and 20 (IQR 10-34) days for controls, corresponding VE estimates were 87.6% (95% CI: 78.2-92.9), 89.9% (95% CI: 70.9-96.5) and 93.6% (95% CI: 81.9-97.7), respectively.

Janssen COVID-19 vaccine
Symptomatic infection: Vaccine efficacy against moderate to severe-critical COVID-19 with onset ≥14 and ≥28 days after full vaccination was 63.7% (95% CI: 53.9-71.6) and 66.1% (95% CI: 53.3-75.8), respectively, for individuals aged 18-59 years [71]. Corresponding vaccine efficacy estimates for individuals aged ≥60 years were similar with 76.3% (95% CI: 61.6-86.0) and 66.2% (95% CI: 36.7-83.0), respectively. Vaccine efficacies against moderate to severe-critical COVID-19 occurring ≥14 days after full vaccination of 64.2% (95% CI: 55.3-71.6), 82.4% (95% CI: 63.9-92.4) and 100% (95% CI: 45.9-100.0) for individuals aged 18-64, ≥65 and ≥75 years, respectively, were reported as well [80]. With a disease onset ≥28 days after full vaccination, the vaccine efficacy point estimates were 66.2%, 66.3%, 62.1%, 79.6%, in individuals aged 18-39, 40-59, 60-69 and 70-79 years (there were no cases aged ≥80 years). Efficacy was 74.0% (95% CI: 34.4-91.4) in individuals ≥65 years.

Hospitalization and case fatality: No publications were found in which age- and vaccine-specific efficacy or effectiveness estimates against hospitalization and/or death were reported.

4 The Dutch population

4.1 Vaccine acquired Immunity in the Dutch population (PiCo study)

4.1.1 The Pienter Corona (PiCo) Study

The PiCo study is a nationwide prospective population-based study on immunity against SARS-CoV-2. Participants aged 1-91 years across the Netherlands are randomly selected from the Dutch population registry, proportional to municipality size and age-stratified [81, 82]. The study is without exclusion criteria, since the aim is to obtain repetitive blood (and other) samples from a large group of individuals representative of the Dutch population. The first sampling round was in April 2020 and four sampling rounds followed: 2nd: June 2020; 3rd: September 2020; 4th: February 2021, with the last 5th round in June 2021. For the present report, we focus on the first data from the 5th round, with special attention to the development and duration of specific antibodies against SARS-Cov-2 by the different vaccines introduced in the Dutch population. Sampling started at 18 June and samples up to 20 July were included for the analysis (median inclusion date 24 June, with 90% samples collected before 5 July). In preliminary analyses of this 5th round, overall weighted seroprevalence (this includes humoral immunity derived from both infection and/or vaccination) in the general Dutch population was estimated at 63% (95% CI 62-65%). In accordance with prioritization of elderly in the vaccination programme, seroprevalence increased significantly with age from 40% in young adults to over 90% in those 55 years and older.

COVID-19 vaccination data from participants are retrieved via self-collected (online) questionnaires and include vaccination dates, and the vaccine type. Documented data from the questionnaires are linked to laboratory measurements of IgG antibodies to the SARS-CoV-2 Spike protein in sera obtained from self-sampled fingerstick blood, and measured by the bead-based multiplex immunoassay (MIA) developed at RIVM [83]. Antibody concentrations are presented in BAU/mL according to the World Health Organization international standard NIBSC, 20/136. Self-reported PCR- or antigen test results on SARS-CoV-2 infection and/or serological evidence of infection prior to vaccination data based on laboratory results from the participant in previous study rounds, are used to identify participants with and without infection history. In the Dutch COVID-19 vaccination programme that started in January 2021, the oldest and most vulnerable groups were prioritized and therefore their time since vaccination is longest. Vaccination of younger age groups followed later in time.

4.1.2 Vaccinations in participants of the PiCo cohort

Participants of PiCo received their vaccinations according to availability and scheduling of priority groups, which results in different follow-up time post-vaccination, vaccine interval time between vaccine doses, and number of people vaccinated per vaccine type/brand. When possible, this is accounted for in the data analyses, e.g., by sub-setting age groups. The mean interval between the two doses of the mRNA-based vaccines was 34 days for Comirnaty and 32 days for Spikevax, and for

the viral vector vaccine Vaxzevria 71 days. Most vaccinated participants received Comirnaty vaccination: >95% of all participants aged 70 and over, and 56-69% among those aged 18-60 years. Within the age group 60-69 years, half of the participants were vaccinated with Vaxzevria. In the age groups 18-60 years, vaccination with Spikevax was mostly reported after Comirnaty, followed by Janssen COVID-19 vaccine and Vaxzevria. Overall, most participants had received an mRNA-based vaccine (see Table 3).

Table 3 Applied vaccines among the different age groups in participants from PiCo-5.

	Age group															
	18-24		**25-29**		**30-39**		**40-49**		**50-59**		**60-69**		**70-79**		**80+**	
Vaccine	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Comirnaty	45	56.3	58	59.8	192	61.0	437	68.7	582	63.4	493	48.6	777	97.1	143	98.6
Spikevax	8	10.0	19	19.6	74	23.5	114	17.9	127	13.8	21	2.1	10	1.3	2	1.4
Vaxzevria	13	16.3	8	8.2	25	7.9	40	6.3	81	8,8	499	49.2	10	1.3	0	0.0
Janssen	14	17.5	11	11.3	24	7.6	44	6.9	127	13.8	2	0.2	1	0.1	0	0.0

4.1.3 Seroconversion following vaccination in participants without prior infection

The mRNA vaccines Comirnaty and Spikevax administered twice are highly immunogenic. In participants without prior evidence of infection, nearly all those vaccinated (180/182, 99%) showed seroconversion with positive SARS-CoV-2 IgG levels after the first vaccination for both mRNA vaccines. Likewise, nearly all participants (1193/1203, 99%) were seropositive two weeks after the second vaccination.

Likewise, in those without prior infection after the first dose with Vaxzevria and after the single vaccination with Janssen, 91% (253/279) and 99% (75/76), respectively, seroconverted after 4 weeks. Nearly all, (194/195) presented with SARS-CoV-2 IgG antibodies after the second dose with Vaxzevria.

4.1.4 SARS-CoV-2 infection and vaccine response

All participants with a history of infection (based on either a positive test (PCR or antigen) or antibodies prior to vaccination) showed high SARS-CoV-2 Spike S1-specific IgG antibodies after a first vaccination with any COVID-19 vaccine (Figure 2), most notably in the mRNA vaccines, followed by Janssen. In general, after a first dose of any of the COVID-19 vaccines used in the Netherlands, participants with a history of infection showed substantially higher SARS-CoV-2 Spike S1-specific IgG antibody concentrations than participants without prior infections after two doses of the same vaccine (Figure 2).

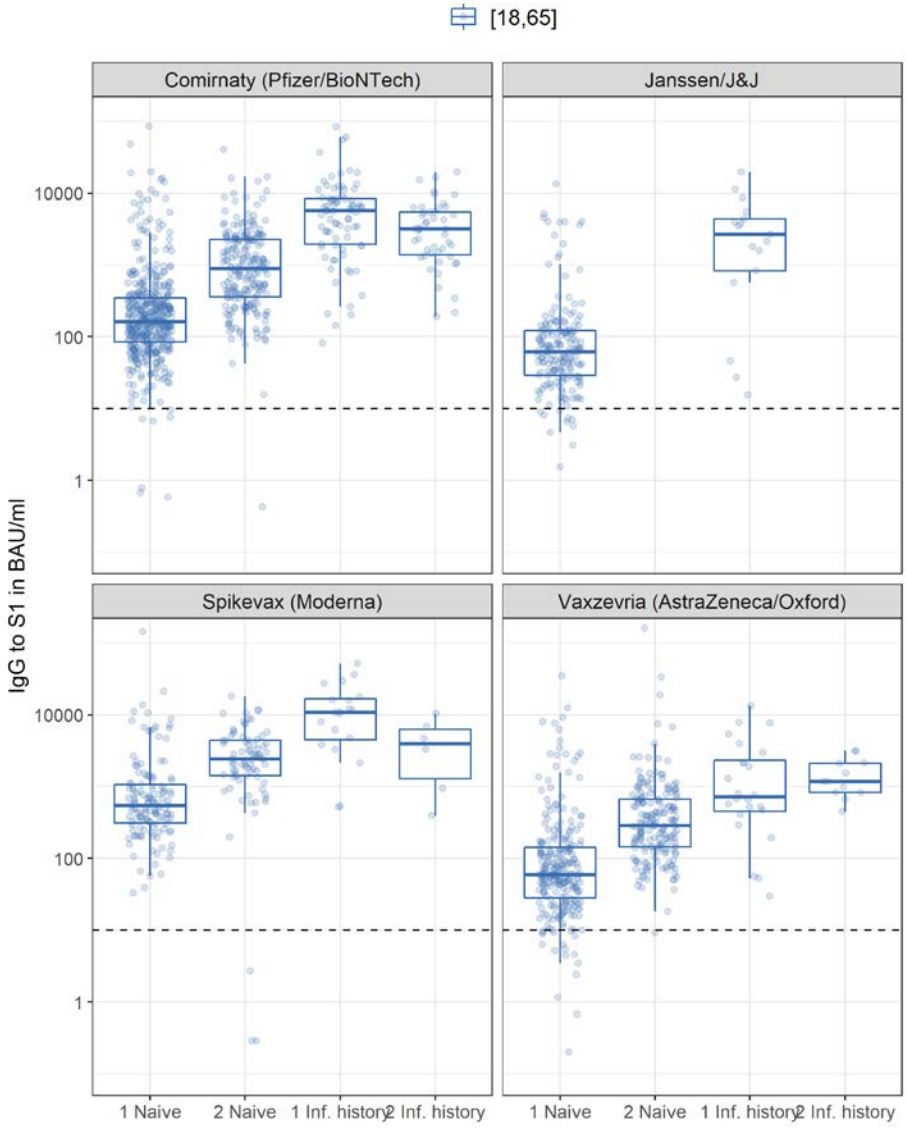

Figure 2 Antibody responses (IgG) to Spike S1 according to infection history, number of doses and vaccine brand in participants aged 18 to 65 years old. IgG measurements were taken >14 days after the indicated dose.

Since with increasing age, dates of vaccinations were a longer time ago, no direct comparisons between age groups and antibody levels can be made. A more accurate representation of the effect of age on the vaccine response for participants > 60 years of age is presented in the VIDO study, for which first data are included in this report.

4.1.5 *Concentrations of antibodies induced by different vaccines*

For evaluation of SARS-CoV-2 Spike S1-specific IgG concentrations in participants without prior infection after one or two doses of the different COVID-19 vaccines, only participants 18-65 years of age were selected to minimize the potential effects of age and time since vaccination (see also Figure 3). After the first dose, concentrations induced by the vector-based vaccines Vaxzevria and Janssen COVID-19 vaccine are similar, but both lower than the levels after mRNA-based

vaccines Comirnaty and Spikevax (see left part of Figure 3). Concentrations increase significantly after the second dose with a mRNA-based vaccine (see right part of Figure 3). Following the second vaccination with Vaxzevria, concentrations are also higher than after the first dose, and higher than after a single vaccination with Janssen COVID-19 vaccine, but lower than after two doses with the mRNA-based vaccines. Note that Janssen COVID-19 vaccine is shown in the right part of the figure, as full vaccination involves one dose only.

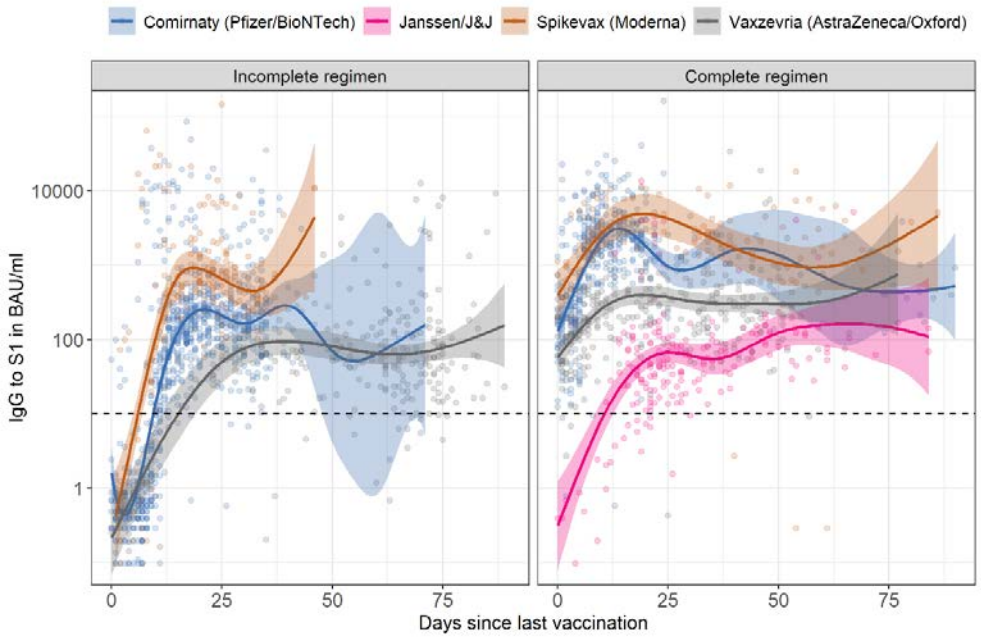

Figure 3 Antibody responses (IgG) to Spike S1 following vaccination in participants aged 18 to 65 years old without a history of SARS-CoV-2 infection prior to vaccination.

The dashed horizontal line reflects the cut-off for seropositivity of the MIA assay (10 BAU/mL). Smoothed fit and 95% confidence interval from Generalized Additive Model using penalized splines.

4.1.6 *Duration of vaccine-induced immunity*

For the discussions on waning immunity and in view of a potential booster dose, level and duration of SARS-CoV-2 Spike S1-specific IgG antibodies, as one of several parameters of immunity, is valuable. Of all participants aged 18-65 years with available data on SARS-CoV-2 infection history, 241 participants had received Comirnaty in the February/March 2021 study round of PiCo. Of these, 224 also participated in the PiCo 5 round of June/July 2021, and from 124 participants, samples from both study rounds were available for analysis. In Table 4 and Figure 4, the change over time in IgG concentration and seroprevalence to Spike S1 is shown for those participants after two doses of Comirnaty. Only one participant did not seroconvert, whereas all others remained seropositive over time, including those with a sample up to 3-5 months after their 2nd Comirnaty vaccination (n=112). As expected, participants with a history of infection show substantial higher SARS-CoV-2 Spike S1-specific IgG levels directly after vaccination, which remain present for the period

studied. The rate of antibody decay, however, did not differ between those with and without prior infection (up to 150 days after the second dose, i.e. interaction term between time and infection history not statistically significant). The estimated half-life of SARS-CoV-2 Spike S1-specific IgG is 87 (95% CI: 68-122) days (following Generalized Estimating Equations adjusted for infection history; insufficient numbers available to also adjust for sex). This is shorter than a previous estimate of IgG half-life after SARS-CoV-2 following infection without vaccination, which accounted to 158 (95% CI: 136-189) days [84].

Table 4 The presence of SARS-CoV-2 Spike S1-specific IgG (seroprevalence) at different time intervals post complete vaccination.

Time since second dose	N	%
14 to 28 days	88/89	99%
29 days to 3 months	23/23	100%
3 to 5 months	112/112	100%

* Individuals aged 18-65 years, vaccinated with Comirnaty

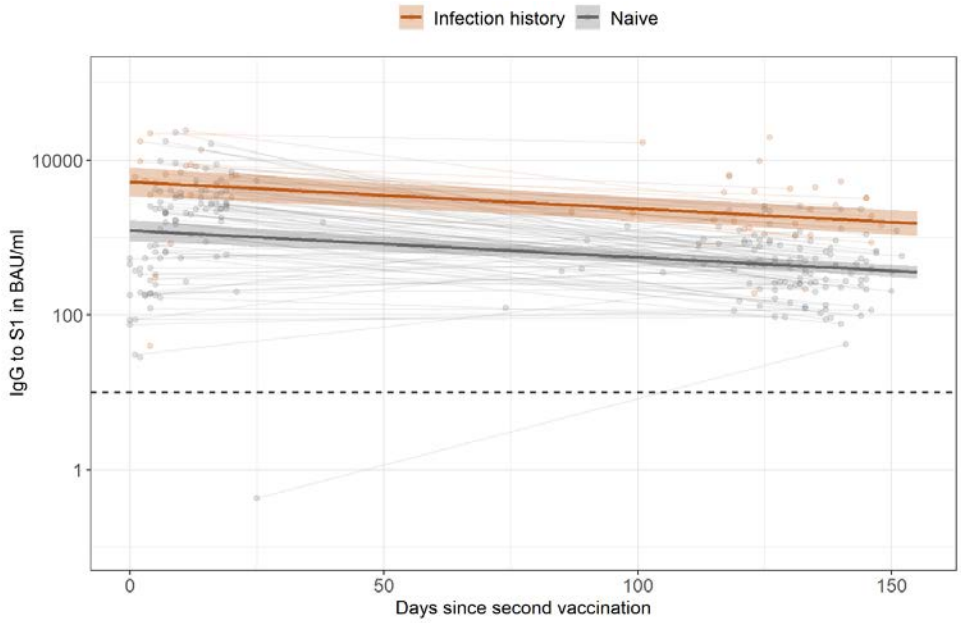

Figure 4 Kinetics of antibody responses (IgG) to Spike S1 according to infection history in Comirnaty-vaccinated participants aged 18 to 65 years old who received two doses.

Linear fits with 95% confidence interval from Generalized Estimating Equations to adjust for repeated sampling.

4.1.7 *Discussion on data of the PiCo study*

All adults aged 18-65 years showed SARS-CoV-2 Spike S1-specific IgG antibodies 3-5 months after completing vaccination. The COVID-19 vaccine Comirnaty used in older age groups with two doses, also effectively induced humoral immunity in all participants up to 91 years of age. It needs to be noted that decay typically is relatively fast after the first few months when short-lived plasma cells disappear. After a few months the effect of dwindling numbers of antibody-secreting short-lived plasma cells is decreasing and a steadier decay rate is established usually resulting in longer duration of circulating antibody estimates

later after the immunization event (reflection from Pico-5 report for OMT, 4-8-2021).

Due to the availability of vaccines and priorities for specific groups in the vaccination programme, direct comparison of antibody levels between different vaccines and age groups is confounded. However, by stratifying for age groups, we are able to compare the four vaccines used in the Netherlands for adults aged 18-65 years. The mRNA vaccines Comirnaty and Spikevax induce the highest concentrations of SARS-CoV-2 Spike S1-specific IgG antibodies. After full vaccination, the lowest levels of SARS-CoV-2 Spike S1-specific IgG are observed after the Janssen COVID-19 vaccine.

A history of SARS-CoV-2 infection prior to vaccination results in substantial immune-boosting after a single vaccination for all 4 vaccines used in the Netherlands. Previously we observed high antibody levels after the first vaccination with Comirnaty in participants with a history of infection. This is now confirmed also for adults aged 65 years and over and for the vaccines Spikevax, Vaxzevria and Janssen COVID-19 vaccine as well after a single vaccination, though levels after Vaxzevria remain below those of mRNA vaccines in infection naïve participants. Only humoral data are presented, comparison between vaccines may look different when evaluating also cellular immunity.

Data of vaccinated and convalescent participants show a strong correlation between Spike S1 antibody concentrations and virus neutralization (also directly compared between our RIVM assay and PRNT50 of eg Viroscience dept, ErasmusMC, [85]), indicating that higher concentrations of antibodies do contribute to protection against disease (from Pico-5 report for OMT, 4-8-2021).

4.1.8 *Monitoring immunogenicity of SARS-Cov-2 vaccination in Dutch middle-aged and older individuals (VIDO study)*

The primary objective of the *Vaccin Immunogeniciteit Doetinchem Onderzoek (*VIDO) study, which is a specific part of the ongoing Doetinchem Cohort Study [86], is to assess antibody responses against the SARS-CoV-2 vaccines in blood of individuals of 52-90 years of age at several timepoints (1, 3, 6 and 12 months) post vaccination, with respect to age, sex and frailty index. The secondary aim is to address which specific pre-vaccination frailty characteristics and metabolic and immunological biomarkers are related to SARS-Cov-2 (VE).

About 1400 persons are participating in this study since March 2021. Serum is obtained mostly from fingerstick blood. Longitudinal antibody determinations were carried out with the bead-based multiplex immunoassay (MIA) at RIVM. Preliminary first results confer anti Spike S1 antibody concentrations - expressed as international BAU/ml units of specific IgG –in 4 different age groups (50-59, 60-69, 70-79 and 80+), measured at 1 month after the first vaccination, and 1 month after full (second) vaccination. The first data at 3 months after the second vaccination are available only for 80+ persons. Longitudinal data for the other groups will follow during the coming months. All data are indicated in the Table 5. Persons who have been infected prior to vaccination

(based on the presence of SARS-Cov-2 anti-nucleoprotein specific antibodies by MIA) are excluded from this analysis.

Table 5 S1 antibodies levels in persons above 50 years of age measured in de VIDO study.

Comirnaty Pfizer				
Age:	**80+**	**70-79**	**60-69**	**50-59**
1 month post 1st	43 (30-64) N=57	76 (64-90) N=197	105 (92-120) N=247	147 (125-173) N=73
1 month post 2nd	680 (529-875) N=61	716 (618-829) N=207	642 (538-766) N=209	859 (572-1289) N=35
3 months post 2nd	191 (148-245) N=46		284 N=11	418 N=6
Vaxzevria Astra Zeneca				
1 month post 1st			48 (38-58) N=191	42 (22-79) N=29
1 month post 2nd			101 (81-127) N=129	209 (132-331) N=22

Binding antibody levels (BAI) in geomean +/- 95% C

Most participants have received Comirnaty. The 50+ and 60+ age groups include a representative group of participants who have received 2 vaccinations with Vaxzevria, and are presented separately from the Comirnaty vaccinated age groups in Table 5.

Figure 5 and Figure 6 represent a graphical representation of participant 50 and 60 years and over that have received Vaxzevria and persons above 80 and 70 years of age that received Comirnaty.

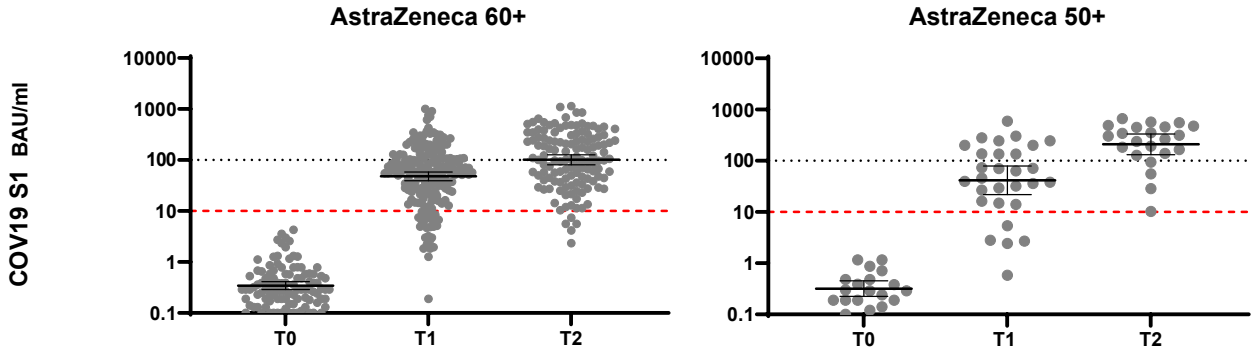

Figure 5 BAI antibody levels per person with geomean +/- 95% CI in groups of persons 60-69 and 50-59 years of age.

T1 1 month post 1st vaccination; T2 1 month post 2nd vaccination. The red dotted line depicts the cut-off of seropositivity.

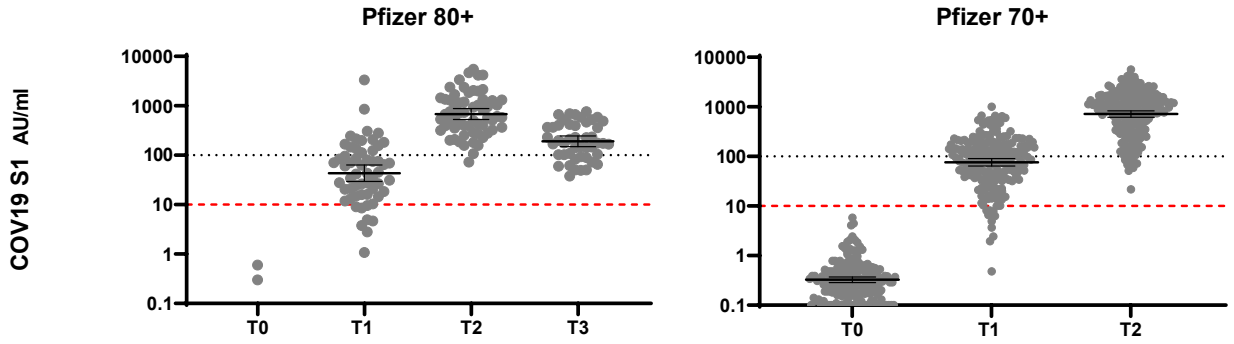

Figure 6 BAI antibody levels per person with geomean +/- 95% CI in groups of persons 80+ and 70-79 years of age.

T1 1 month post 1st vaccination; T2 1 month post 2nd vaccination. For persons above 80+: T3 3 months post 2nd vaccination.

With a few exceptions, all participants over 50 years respond adequately to the (Pfizer) vaccine, with a positive anti Spike S1 IgG titer/response rate of (almost) 100% after 2 vaccinations, irrespective of age. There is a slight decline in anti-Spike S1 antibody IgG concentration with age as measured at 1 month after completion of the vaccination series.

At 3 months post last vaccination, antibody concentrations had dropped significantly for the 80+ age group, when compared to the decay in antibody concentrations in another study in the general population (PiCo data). At the moment, sufficient data to support this can only be presented for the 80+ vaccination group, sampling and analysis for the other age groups are still pending. Vaccination with the viral vector vaccine Vaxzevria clearly results in lower concentrations of anti-Spike S1 IgG antibodies after completion of the series (2x) when compared to mRNA vaccine Comirnaty. In fact, in case of Vaxzevria, a small proportion of participants have antibody levels below the cut-off level of antibody detection. Also, the second dose Vaxzevria showed limited boosting effect with only about half of the participants showing at least two-fold higher antibody levels.

4.2 Vaccine effectiveness in the Netherlands

Several methods and data sources are employed by RIVM to assess VE against positive SARS-CoV-2 tests in the Netherlands. The three methods which are presently able to provide VE estimates are the screening method, the test-negative design (TND) hospital study VECTOR and a household-contact study based on source and contact tracing (BCO) data. The screening method provides VE estimates based on SARS-CoV-2 testing and against COVID-19 hospitalizations; the VECTOR study provides VE estimates against COVID-19 hospitalization; the BCO study provides VE estimates against a SARS-CoV-2 positive test result and against infectiousness. Ongoing studies not yet providing estimates are summarised at the end of this section.

4.2.1 *Vaccine effectiveness against a SARS-CoV-2 positive test and against hospitalization, by age group and variant, estimated by the screening method*

The screening method is a relatively crude method for estimating VE, based on the proportion of notified cases vaccinated compared to the vaccine coverage in the population the cases are derived from [87]. This method can be used to provide VE estimates per COVID-19 vaccine and per age group. As the vaccine coverage is constantly changing, the proportion vaccinated among cases and the population coverage are estimated by week, and an overall VE is estimated across weeks. For more information on the methods and data, see De Gier *et al.* [88]. The source of data for the proportion of notified cases that are vaccinated, is Osiris. The source of data for the population vaccination coverage is CoronIT (anonymous data on all vaccinations given by the *Gemeentelijke Gezondheidsdienst (*GGD)), supplemented by CIMS data for all non-GGD vaccinations in people who have given consent for registration in CIMS.

Table 6 VE (95% CI) for full vaccination with any vaccine (at least 2 weeks after second dose, or at least 4 weeks after Janssen COVID-19 vaccine) against positive SARS-CoV-2 test, by age group, vaccine, and period.

		Alpha period	**Delta period**
Age group (years)		**VE (%) (95% CI)**	**VE (%) (95% CI)**
15-29	Overall	81 (79-83)	69 (68-70)
	Comirnaty	80 (77-82)	72 (71-74)
	Spikevax	95 (90-98)	86 (84-87)
	Vaxzevria	80 (67-88)	59 (57-62)
	Janssen COVID-19 vaccine	NA	18 (10-25)
30-49	Overall	76 (75-78)	72 (71-73)
	Comirnaty	74 (72-76)	76 (75-77)
	Spikevax	89 (85-92)	84 (82-86)
	Vaxzevria	73 (62-81)	61 (57-65)
	Janssen COVID-19 vaccine	NA	27 (19-34)
50-69	Overall	83 (81-84)	66 (65-67)
	Comirnaty	80 (79-82)	74 (72-75)
	Spikevax	92 (90-94)	86 (83-87)
	Vaxzevria	87 (82-90)	62 (59-65)
	Janssen COVID-19 vaccine	NA	31 (26-36)
70+	Overall	90 (89-91)	62 (58-66)
	Comirnaty	90 (89-91)	64 (60-68)
	Spikevax	92 (88-95)	47 (26-62)
	Vaxzevria	NA	45 (19-62)
	Janssen COVID-19 vaccine	NA	NA

Data sources: Osiris-AIZ, CoronIT, CIMS, as of 4 August 2021. NA: not applicable.

To explore a possible change in VE after the surge of the Delta variant, VE estimates were stratified by period, crudely designating a period dominated by the Alpha variant (April-May 2021) and a "Delta period" (July 2021).

Higher estimates of the VE against a positive SARS-CoV-2 test after full vaccination were found in April-May ("Alpha period") compared to July ("Delta period"), most notable and significant in age groups above 50 years (see Table 6). When notified hospitalizations from Osiris (which is an incomplete data source for hospitalizations) are analysed with the screening method, the VE against COVID-19 hospitalization remained was very high in both time periods (data not shown). Please note that this latter observation is uncertain; estimates of VE against hospitalization based on NICE hospital registration data, combined with CIMS vaccination status data, are expected in September 2021.

Of note, the one-dose Janssen COVID-19 vaccine schedule seems to result in a low VE in the period dominated by the Delta variant. Vaxzevria shows a moderate VE against a positive SARS-CoV-2 test in the Delta period. In the Delta period, a low VE against hospitalization is observed for Vaxzevria and Spikevax in the age group above 70 years. Note that these estimates are based on very low numbers.

4.2.2 *Vaccine effectiveness against a SARS-CoV-2 positive test and against hospitalization by age group and variant, over time since vaccination, estimated by the screening method*

VE against a positive SARS-CoV-2 tests was estimated for different post-second-dose time intervals: 1-6 weeks, 6-10 weeks, 10-14 weeks, 14-18 weeks and 18 or more weeks post-second-dose. Because the Comirnaty vaccine (Pfizer/BioNTech) was implemented earlier in the year, we can estimate VE after more than 10 weeks post-vaccination only for this vaccine. To disentangle any decreases in VE from the emergence of the Delta-variant, this analysis was stratified by the "Alpha period" (April-May 2021) and the "Delta period" (July 2021).

The VE against a SARS-CoV-2 positive test declined by time since vaccination (see Table 7). These results are consistent with recently published trial data. Preliminary estimates of VE against hospitalization due to COVID-19, based on notified hospitalizations in Osiris (NB OSIRIS is incomplete regarding hospitalisation and selection bias might have occurred), show a consistently high VE in the first 6 months after completing the Comirnaty schedule (data not shown). This observation needs to be verified using the NICE registry data, results are expected early September 2021.

4.2.3 *Vaccine effectiveness against COVID-19 related hospital admission estimated by the VECTOR study in Alpha period*

The VECTOR study estimates VE against COVID-19 related hospitalization by comparing the vaccination status in hospitalized persons testing positive for COVID-19 and hospitalized persons testing negative for COVID-19. This test negative design (TND) is a variation of a case-control design and is frequently used for to estimate influenza VE against seasonal influenza viral infections.

Table 7 Estimated VE (95% confidence interval) against positive SARS-CoV-2 test due to COVID-19 for Comirnaty vaccine, by age group, time since second dose, and period.

		Alpha period	**Delta period**
Age group (years)	**Time since vaccination (weeks)**	**VE (%) (95% CI)**	**VE (%) (95% CI)**
15-29	1-6	88 (78-94)	81 (80-82)
	6-10	78 (73-82)	68 (61-74)
	10-14	80 (76-83)	NA
	14-18	81 (75-86)	48 (27-63)
	18+	100 (-)	53 (50-56)
30-49	1-6	78 (59-88)	81 (80-83)
	6-10	74 (70-78)	74 (68-79)
	10-14	74 (70-77)	NA
	14-18	77 (71-81)	28 (-21-58)
	18+	79 (17-95)	62 (58-66)
50-69	1-6	86 (82-89)	75 (74-77)
	6-10	80 (77-83)	83 (81-86)
	10-14	77 (75-80)	48 (21-65)
	14-18	86 (82-89)	36 (16-51)
	18+	100 (-)	52 (47-57)
70+	1-6	90 (89-91)	36 (19-49)
	6-10	88 (86-89)	64 (58-69)
	10-14	89 (86-92)	67 (61-72)
	14-18	88 (52-97)	60 (52-67)
	18+	NA	58 (48-66)

Data sources: Osiris-AIZ, CoronIT, CIMS

Within the VECTOR study, the study population consists of adults admitted to the hospital for suspected respiratory infection and eligible for COVID-19 vaccination at the time of admission. We defined the study population as cases suspected respiratory infection as 1) hospitalization for respiratory complaints including cough and/or shortness of breath with an onset within 10 days before hospitalization, and 2) a respiratory specimen tested for SARS-CoV2 at admission or in the 14 days prior to admission at the municipal health services. Data is retrospectively collected from electronic patient records from 6 hospitals. Inclusion was divided in 3 age-groups based on vaccine eligibility at the time. The following groups of patients were included: those aged 75 years and older (born before 1946) admitted between March 1st and May 10th; those born between 1960 to 1946 admitted between April 12th and June 7th; and those born between 1961 to 2003 admitted between May 3rd and July 4th.

COVID-19 cases were defined as patients with a respiratory sample positive for SARS-CoV-2, tested within 48 hours after hospital admission, or at the municipal health services no more than 14 days preceding hospital admission. Controls (test-negatives) were defined as patients testing negative for SARS-CoV-2 on all respiratory samples

taken during the first 48 hours of admission or in the 14 days preceding hospital admission. VE was estimated for both full vaccination (having received both doses of a two-dose vaccine schedule, or one dose of a single-dose vaccine schedule at least 14 days before symptom onset) and partial vaccination (having received one dose of a two-dose vaccine at least 14 days before symptom onset). All patients who did not receive a COVID-19 vaccine or were vaccinated within 14 days prior to symptom onset were considered unvaccinated. We did not take into account previous COVID-19 infection. The VE for respectively full and partial vaccination as preventive factor for COVID-19 hospitalization is calculated by 1 minus the odds ratio of vaccination. In this preliminary analysis, we adjusted for age, sex and week of hospital admission.

Preliminary results of the VECTOR study
At time of analysis (June 28) a total of 450 patients were included among whom 253 COVID-19 patients and 197 test-negatives. Of these 450 inclusions, only 177 inclusions had complete data on vaccination status and were included in the analysis. Of the age category above 75 years, inclusion was complete. Of the other two age categories inclusion was still ongoing. These current results consist of VE estimates for all inclusions in total, with a sub analysis of inclusions aged 75 years and older.

Of all COVID-19 cases, 15% was partially vaccinated and 2% was fully vaccinated. Of the controls, percentages were respectively 21% for partial and 14% for full vaccination. Among elderly aged above 75, 2% of COVID-19 cases was fully vaccinated compared to 12% of controls. Of the COVID-19 cases, 11 % was partially vaccinated compared to 22% of controls. VE-estimates are shown in Table 8.

Table 8 Vaccine effectiveness among people of 75 years and older, estimated with the VECTOR study, as of June 28, 2021.

	Controls (test-negatives)	**COVID-19 cases**	**VE partial series (%) (95% CI)**	**VE complete series (%) (95% CI)**
Total	69	108	58 (3-83)	87 (41-98)
Age 75+	42	59	54 (-38-85)	95 (64-100)

Discussion VECTOR study
The preliminary results suggest the VE against COVID-19 related hospitalization for full vaccination is high and estimated to be 87% (95% CI: 41-98%) for all groups and 95% (95% CI; 64-100%) for individuals of 75 years and over. For partial vaccination the VE is moderate. For both estimates, confidence intervals are wide due to incomplete data, which will improve as data collection is ongoing.

Data was collected between March 1st and July 4th with most inclusions in the months March-May. Therefore, we expect the prevalence of the Delta variant to be minimal among cases. For this reason, current estimates represent the estimated VE against the Alpha variant and are not representative for the Delta variant.

A limitation of this analysis is that it is only based on participants with a known vaccination status as documented in the patient dossier. Cases with an unknown vaccination status were equally distributed among COVID-19 cases and test-negatives, and a sensitivity analysis (considering unknown vaccination status as non-vaccinated) resulted in comparable estimates. We expect a potential bias due to missing information to be minimal. More robust estimates will be available after linking study-data to the national vaccination registry.

4.2.4 *Vaccine effectiveness against transmission from household contact data*

Based on routine contact monitoring data, we estimated the vaccine effectiveness against transmission (VET) and the VE against infection among household and other close contacts of confirmed cases of SARS-CoV-2) infection [89]. We used data between 1 February and 27 May 2021, a period when the Alpha variant was the dominant variant.

The VET was calculated by comparing the secondary attack rate among household and other close contacts of vaccinated and unvaccinated index cases. The VE among contacts of positive cases was calculated by comparing the risk of SARS-CoV-2 infection in vaccinated and unvaccinated contacts. In the analysis we adjusted for age group of the index case and contact, and for month of notification of the index case.

Partly vaccinated was defined as having received the first dose of a two-dose coronavirus disease (COVID-19) vaccine, with a time since vaccination of at least 14 days. Fully vaccinated was defined as having completed a two-dose schedule with a time since vaccination of at least 7 days, or the one-dose Janssen COVID-19 vaccine schedule with a time since vaccination of at least 14 days.

The final dataset contained 253,168 contacts of 113,582 index cases. Of the index cases, 622 (0.5%) were fully vaccinated and 2,088 (1.8%) were partly vaccinated. Of the contacts, 5,397 (2.1%) were fully vaccinated and 4,411 were partly vaccinated (1.7%). The secondary attack rate was 31% among household contacts of unvaccinated index cases and 11% among household contacts of fully vaccinated index cases. The adjusted VET to household contacts after full vaccination was 71% (95% CI: 63-77). The VET to other close contacts was much lower (22%; 95% CI: −5 to 43), probably because of the larger risk of the contact being infected through another source. The adjusted VET after one dose was considerably lower than after two doses (21%; 95% VI: 12 to 28). The adjusted VE among contacts of confirmed cases was 75% (95% CI: 72 to 78) for fully vaccinated household contacts and 79% (95% CI: 74 to 83) for fully vaccinated other close contacts.

The data used in this study was not primarily collected for research purposes, therefore it has some limitations. For example, if some contacts of vaccinated index cases were infected through other sources, the VET will be an underestimation. Also, if vaccines are more likely to be asymptomatic, this source of misclassification may result in an overestimation of the VET.

Together, results showed that the COVID-19 vaccines not only protect the vaccinee against SARS-CoV-2 infection, but also offer protection

against transmission to close contacts after completing the full schedule. This finding underscores the importance of full vaccination of close contacts of vulnerable persons.

4.2.5 *Ongoing studies to estimate vaccine effectiveness*

The CONTEST study is an ongoing study asking persons that get tested at a GGD test location to fill out a questionnaire on demographics, vaccination status and potential risk factors for acquiring COVID-19 (see www.rivm.nl/contest-onderzoek). By comparing the vaccination status in persons testing positive and testing negative, we are able to calculate VE. Currently, 18.457 persons are included in the CONTEST study of which 1.203 tested positive. Of all included persons who were eligible for vaccination at the time of their test (N= 4.842), 26% was unvaccinated, 21% was partly vaccinated and 22% was fully vaccinated. The numbers are still too low to calculate VE. As data collection continues, we hope to be able to do this in the near future.

The VAccination Study COrona (VASCO) is a large cohort study aimed at estimating VE on the long term (see www.rivm.nl/vasco). Vaccinated and unvaccinated participants are followed up with monthly questionnaires to obtain data on SARS-CoV-2 testing results. In addition, blood samples at baseline, at 6 months, at 12 months, and 1 month after full vaccination are obtained to measure antibody levels against SARS-CoV-2. In this way we can detect (asymptomatic) SARS-CoV-2 infections that occurred before and during the study. In addition, we can measure response to vaccination in vaccinated participants. As of July 2021, more than 20,000 participants are included in the study. First VE estimates are expected at the beginning of 2022.

Ongoing efforts are put into linkage of different registries to estimate VE. These registries include the vaccination register CIMS, the notification data of OSIRIS, the test data of the GGDs (CoronIT), the hospital and intensive care admission data of NICE, and other health care related registries. The linkage has not been established yet as this is a long process due to legal and privacy regulations. Including data from CIMS in NICE is prioritised; VE estimates from this are expected in September 2021.

Lastly, data from the 'GGD testing streets', containing tests performed by the GGD, can be used to study VE. The 'test-negative design' for VE estimation can be applied to these data, as the vaccination status is asked to persons requesting a test. An advantage of this method is that differences in testing behaviour between vaccinated and unvaccinated people will be a less likely source of bias. This data has only very recently been made available to RIVM; therefore, no results are available yet.

4.2.6 *Effectiveness by SARS-CoV-2 variants of concerns*

The observed decline in VE against positive tests in July 2021 compared to May-June suggest that the COVID-19 vaccines may provide a lower level of protection against the Delta variant. Another way to confirm this is to compare the proportion of the Delta variant relative to the other variants (mainly Alpha variant) in vaccine breakthrough cases. This was done in a preliminary analysis of the SARS-CoV-2 isolates sequenced

from unvaccinated and vaccinated individuals, in the period when both Alpha and Delta variants circulated in the Netherlands.

Adjusted for time of sampling (in ISO weeks), and 10-year age group, the proportion observed in the data (Figure 7) and odds of being infected by the Delta variant (Figure 8) were significantly higher for fully vaccinated individuals compared to unvaccinated people. This measure does not provide a VE estimate against Delta, but it confirms the notion that the VE against the Delta variant is lower compared to the Alpha variant.

We analyse the variant typed samples using a logistic regression in a generalized linear model. The logistic regression expresses the Delta variant status (Delta or not Delta variant) as a function of iso week sampling date, 10-year age group, and type of vaccine. Sequenced cases are at an increased risk (OR) of Delta variant (data not shown). Stratified by vaccine a significant risk is found for Janssen COVID-19 vaccine (see Figure 8), in agreement with the VEs found in the Alpha and Delta period.

Figure 7 Top panels: Bar (weeks) chart of the number of isolates for (left) unvaccinated individuals, (middle) partly vaccinated individuals (>=14 days first dose or second dose <14 days), fully vaccinated individuals (>= 14 days second dose or >= 14 days first dose of the Janssen COVID-19 vaccine) from 01-01-2021. Bottom panels: The proportion of the respective groups shown if the sample count is equal to or above 10.

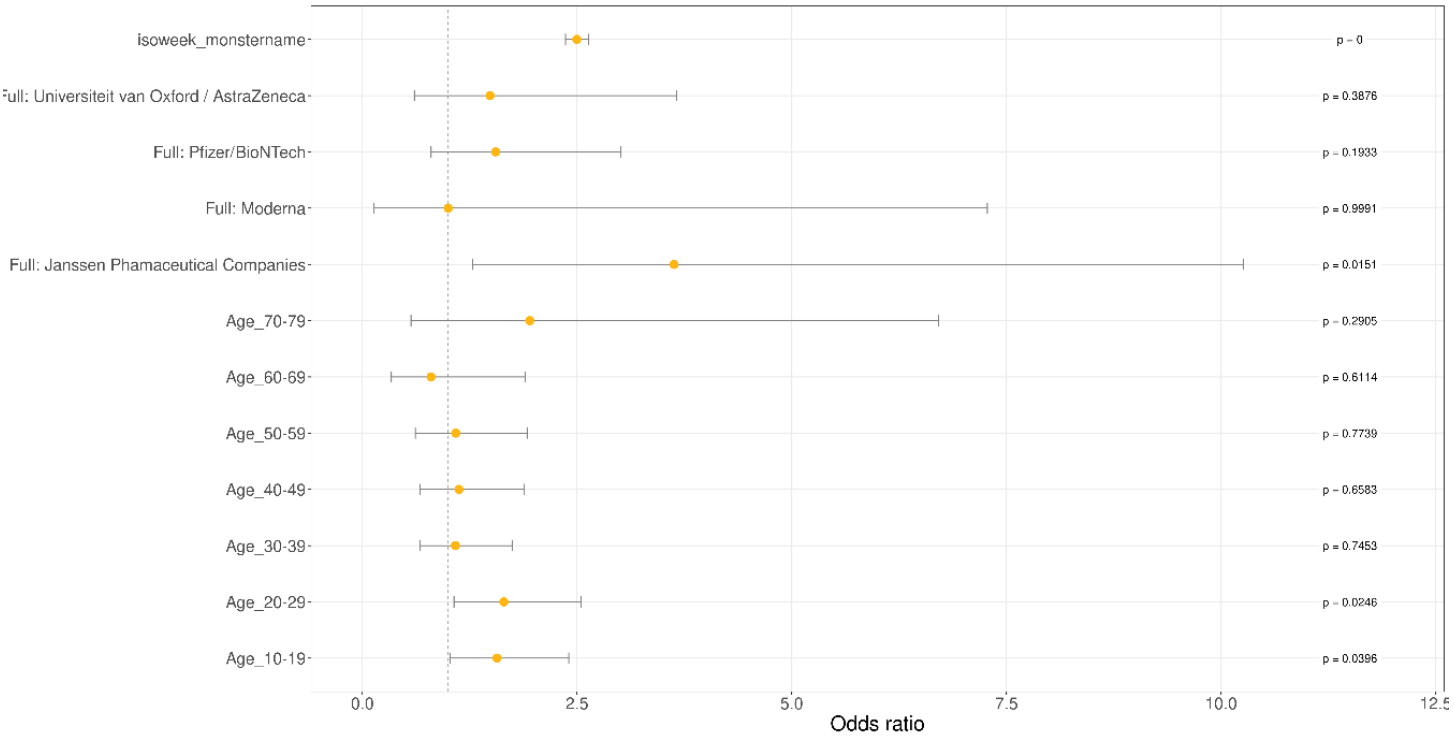

Figure 8 Odds ratios of the logistic regression model adjusted for age (group) and sampling week for different vaccines. Error bars correspond to the 95% confidence intervals.

4.2.7 *Considerations regarding Vaccine effectiveness estimates in the Netherlands*

So far, VE estimates obtained during the period of high prevalence of the Delta variant are limited and based only on the screening method. This method can lead to biased results due to several reasons. First, it uses data from Osiris, which is lacking positive results from self-tests which are not confirmed by a laboratory. Differential testing behaviour between vaccinated and unvaccinated individuals may bias VE estimates. Second, differential exposure of vaccinated and unvaccinated individuals due to differences in behaviour, could also bias VE estimates. If vaccinated individuals take more risks, this would underestimate VE. Further, incompleteness of the vaccination registry may somewhat reduce VE estimates.

An observed decline in VE over time may not necessarily indicate waning immunity. It can also result from a change in the prevalence of VOCs over time (i.e. the emergence of the Delta variant), changes in the incidence of SARS-CoV-2 infection (which in combination with a leaky vaccine leads to relatively more breakthrough infections in vaccinated individuals) and from changes in risk and testing behaviour.

The VE against a positive SARS-CoV-2 test and infectiousness was high during the period when the Alpha variant was prevalent. However, the VE against a positive SARS-CoV-2 test was lower in July, when the Delta variant was most prevalent, most notable and significant in age groups above 50 years. This is consistent with the observation that

breakthrough infections are more likely to be caused by the Delta rather than the Alpha variant, when adjusting for age and week of sampling.

The VE of, in particular, the single-dose Janssen COVID-19 vaccine against a positive SARS-CoV-2 test was low in the Delta period, while the viral vector vaccine Vaxzevria showed a moderate VE against a positive test in the Delta period.

The VE against a SARS-CoV-2 positive test declined by time since vaccination, since July 2021. This may not necessarily indicate waning of vaccine induced immunity, but more with VOC circulating as explained above.

VE against hospitalization will be obtained from NICE data and are expected in September and might be used to confirm current relatively high estimates on VE using incomplete hospitalisation data from OSIRIS.

5 Considerations for a booster program

The following scenarios may be subject to substantial changes when we have learned more about waning immunity and/or the emergence of SARS-CoV-2 variants of concern over time.

The COVID-19 vaccination programme in the Netherlands started in January 2021, with the oldest age groups and with the primary goal to prevent severe COVID-19 disease, hospitalization and mortality due SARS-CoV-2-infection. The present vaccination status among the Dutch population is high for those 65 and over (87-91% for those 65-90 years, 80% for 90 years and over) and declines with age (78-81% for age group 50-64 years; 62-73% for age group 36-40 years; 49-55% for age group 18-40 years); 14% for age group 12-17 years (vaccination started recently in teenagers and is still ongoing) (for actual data see Annex COVID-19 Vaccination Coverage in The Netherlands).

There is some evidence that a full course of current COVID-19 vaccines in the Netherlands will provide protection against **severe COVID-19 and hospitalization** for at least the first 6 months following the last vaccination, for all vaccines, though data are limited in particular for the COVID-19 Janssen vaccine mainly used in younger adults. Variants of Concern may alter vaccine effectiveness. Breakthrough infections are reported in all age groups with higher risk with increasing age and with more time elapsed after the last vaccination. The currently dominant Delta as the highest estimated transmissibility of all current SARS-CoV-2 variants of concern (VOC) and is outcompeting all variants in countries where the Delta variant has presented. With up to 75% higher transmissibility compared with the Alpha variant and high viral load in the upper respiratory tract, transmission to others by both vaccinated as unvaccinated individuals may occur. Apart from the risk for severe disease in case of waning immunity and VOC, which is still unsure, it is also unknown whether vaccination protects against long COVID or Multisystem Inflammatory Syndrome in children, teenagers and young adults in case of breakthrough infection. Although (some) protection may seem likely, currently there is no data.

COVID-19 booster revaccination as a precautionary measure may ensure that loss of protection due to waning immunity is prevented and/or that immunity is optimized to provide additional resilience against new SARS-CoV2 variants of concern. This may be of particular importance for vulnerable older age groups and younger persons with comorbidities.

Apart from certain groups of who are recommended an additional primary dose after an initial 2-dose primary series at least 28 days after the last vaccination, based on advice of professional who provide health care to immunocompromised people, groups to be considered for a booster dose are elderly in long term care facilities, community dwelling elderly of 70-80 plus and older adults (50-60 plus) and vulnerable groups due to comorbidities.

Other groups to be considered for booster vaccination may be adults aged 50 years and over, who have had with a single Janssen COVID-19 vaccination, or after a homologous series with Vaxzevria due to somewhat lower vaccine effectiveness estimates compared with mRNA vaccines. The highest stable VE is reported for Spikevax at the moment, followed by Comirnaty. However, long term data for all vaccines are still scarce and comparison between vaccines based on studies in literature is hard to due to many confounding factors and in particular due to differences in circulating virus variants at the time of the studies. Dutch preliminary data point at the lowest VE for the COVID 19 vaccine Janssen. This is in line with the lowest anti-spike antibody levels as measured in RIVM studies.

Special considerations include continuity of health care systems, and health care personnel may also be considered for booster vaccination. Frontline workers in health care and social care, some of whom are vaccinated early in the COVID-19 vaccine roll-out, may have continued exposure to SARS-CoV-2. Booster vaccination of health care personnel may reduce viral transmission to vulnerable patients. The same is true for household close contacts of vulnerable persons.

In the situation where social distancing may stop and social contact may return towards pre-pandemic norms, winter 2021 to 2022 will be the first winter when SARS-CoV-2 will co-circulate alongside other respiratory viruses. The timing and magnitude of potential influenza and SARS-CoV2 infection waves for winter 2021 to 2022 are currently unknown, but both may add substantially to the 'winter burden' for hospital and primary care [90]. This in particular if infection waves from both viruses coincide. Next to COVID-19 booster revaccination, high coverage of influenza vaccination may lower the overall burden for health care.

Lastly, in case prevention of transmission is an important aim, COVID-19 booster vaccination of larger groups in the population, including adolescents and people under 30 years of age with low risk of severe disease may be considered. In case of highly transmissible VOC, booster vaccination also in younger age groups may help to avoid measures like school closures and other measures required to keep transmission at a low level. The primary aim here would however be to achieve a high coverage of the primary series before considering a booster re-vaccination.

5.1 Timing of COVID-19 booster dose

All currently available booster immune response data with a third COVID-19 vaccine dose are from studies with homologous booster vaccines that have been given 5-9 months after completion of the primary series. Overall, post booster SARS-CoV-2 spike-protein specific NAb titers against the wild-type strain were higher than post second dose. Since COVID-19 vaccination may protect for at least six months, a minimal interval of six months or longer between completion of the primary series and the booster dose is plausible. However, vaccine effectiveness data against the currently circulating VOC's may alter the optimal interval.

5.2 Safety and reactogenicity after the booster dose

Data on safety and reactogenicity of a COVID-19 vaccine booster dose are still limited. After the third booster dose of the same vaccine in studies with Comirnaty and Spikevax, reactogenicity was in the same range as after the second dose. After a third Vaxzevria dose, reactogenicity was most outspoken after the first dose and less after the second and third dose. Data on very rare but serious adverse events like myocarditis, or thrombotic thrombocytopenic syndrome and potential long-term events are not available yet. This is particularly relevant for children and younger adults.

5.3 Potential target populations

The following groups might be offered a third dose COVID-19 booster vaccine. Where practicable, those with the longest interval since the second dose of their primary course of vaccination should be called first.

- **Those living in residential care homes for older adults**
  These are the most frail people, expected to have the least high immune response upon vaccination and the fastest waning of immunity. At the moment, despite breakthrough infections, hospitalization because of COVID-19, have remained limited, even in case of the Delta variant, though we need to await developments coming autumn. This group of was among the first to be vaccinated, mainly with Pfizer, starting early 2021. Also, health care personnel working here may be offered a booster vaccination.
- **All adults aged 80 years or over**
  This groups built up the lowest immune response upon vaccination and was among the first vaccinated (mainly with mRNA vaccines). In case of waning immunity, they will be first to contract COVID-19, though it is unknow whether this will lead to hospitalization and death.
- **Severe immunocompromised persons aged 12 years and over who are considered clinically extremely vulnerable**
  At the moment, medical specialist advice on select subgroups of immunocompromised patients who failed to respond sufficiently upon the primary series with mRNA vaccines and who they consider for an additional third vaccination in September/October 2021.
- **Frontline health and social care workers**
  An additional booster COVID-19 vaccination may potentially contribute to less SARS-CoV-2 infection and illness in healthcare workers and social care workers, in particular in case of highly transmissible known or newly emerging VOCs. Booster vaccination of health- and social care workers may also help to avoid quarantine periods with absence from work in case of contact with infected persons and reduce SARS-CoV-2 transmission to vulnerable people in care.
- **All adults aged 50 or 60 years and over**
  Older adults are high risk groups for severe COVID-19 and death. In particular adults age 50 years and over, vaccinated with a single Janssen COVID-19 vaccine or a primary series with 2 doses of Vaxzevria, may be prioritized for an early booster vaccination with mRNA vaccine because of lower NAb levels and

potentially associated with less protection against infection with VOCs.

- **Adults aged 16 to 49/50 years who are in an influenza or COVID-19 at-risk group**
  These persons are more vulnerable for severe COVID-19 when unvaccinated and may be at higher risk in case of VOC.
- **Morbid obese persons and persons with Down syndrome after 40 years of age**
  In particular after 40-50 years of age, these persons may be at a higher risk for severe COVID-19 when unvaccinated.
- **Adult household contacts after 12 years of age (Comirnaty) of immunosuppressed individuals**
  This to prevent transmission of SARS-CoV-2 or VOC to immunosuppressed persons.

5.4 Accessibility of COVID-19 vaccines

5.4.1 Future COVID-19 vaccines

Worldwide 21 COVID-19 vaccines have obtained conditional marketing or emergency use authorization [91] and more than 100 candidate vaccines are in clinical trials [92]. Five (candidate) vaccines are under rolling review of EMA: NVX- CoV2372 developed by Novavax (in review since 3rd Feb 2021), CVnCoV developed by Curevac (12th Feb 2021), Sputnik-V developed by Gamaleya Research Institute (4th March 2021), the protein subunit candidate developed by Sanofi Pasteur (since 20th July 2021), and CoronaVac developed by Sinovac Biotech (since 4th May 2021).

The COVID-19 vaccines authorized (n=4) and under review (n=5) for the EU/EEA market represent different platform technologies and molecular designs, including mRNA (Comirnaty, Spikevax, CVnCoV), viral vector (Vaxzevria, Janssen COVID-19 vaccine), protein subunit (NVX- CoV2372, and the Sanofi Pasteur candidate) and whole inactivated SARS-CoV-2 virus (CoronaVac) type of vaccines, respectively (see Supplementary table 2). The designs of all vaccines, except CoronaVac which contains the whole inactivated virion, are based on the Spike protein of SARS-CoV-2 (S) to evoke protective immune responses.

Apart from the current four COVID-19 vaccines available up until now, the Netherlands has ordered other COVID-19 vaccines that may become available for use in a booster programme in the coming period (see Supplementary figure 3). Vaccines designed specifically against VOCs will not be available in time for booster revaccination this autumn. New vaccines may be added. The various options for vaccination series will be discussed, once data from studies is available.

The discussion around homologous versus heterologous COVID-19 booster revaccination will continue, with new data expected in the coming months, in particular on mixed primary series but also on homologous booster series.

5.4.2 Transnational considerations

Several countries in Europe like Germany and France and countries like the United Kingdom have already decided to implement COVID-19

booster vaccination as a precautionary measure for another COVID-19 wave coming autumn/winter season, for adults aged 50 or 60 years or over, and adults aged 16 years and over who are considered clinically extremely vulnerable. Also, frontline health and social care workers are recommended to have a COVID-19 booster vaccination. As the COVID-19 pandemic is a global crisis, the effects of measures related to booster vaccination are not limited to national borders, but are situated in an international context. The degree to which the global population is vaccinated has an important impact on the emergence of new virus variants that will inevitably also reach The Netherlands.

In addition to these public health and economic considerations, there is a moral aspect to the implementation of a booster programme in a limited number of high-income countries as well. The majority of countries have not reached a sufficient vaccination coverage in their populations due to an unequitable distribution of available vaccines. In the current context of global vaccine scarcity, it means that the decision to use vaccines for boosters will consequentially limit the availability of vaccines for other countries to use for primary series [93].

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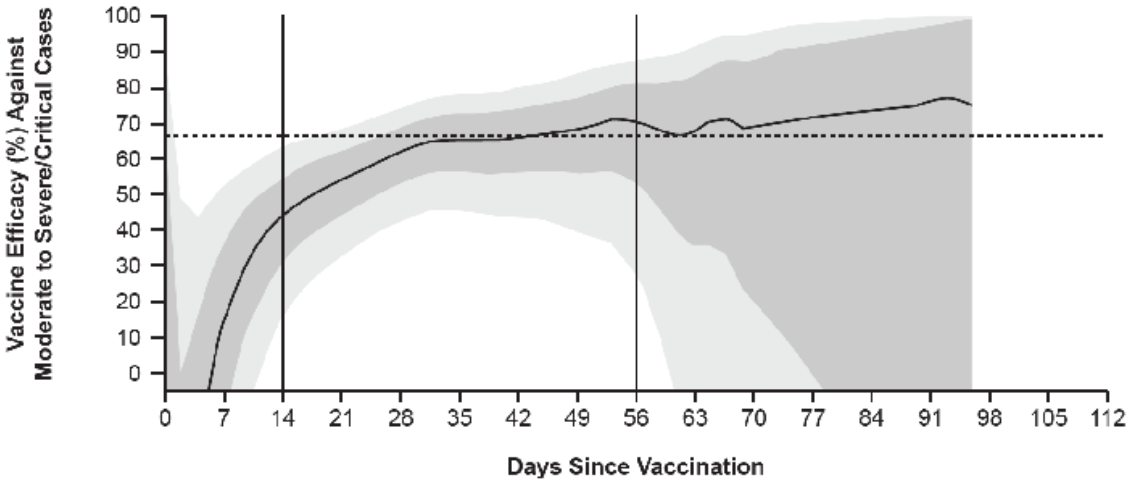
List of abbreviations

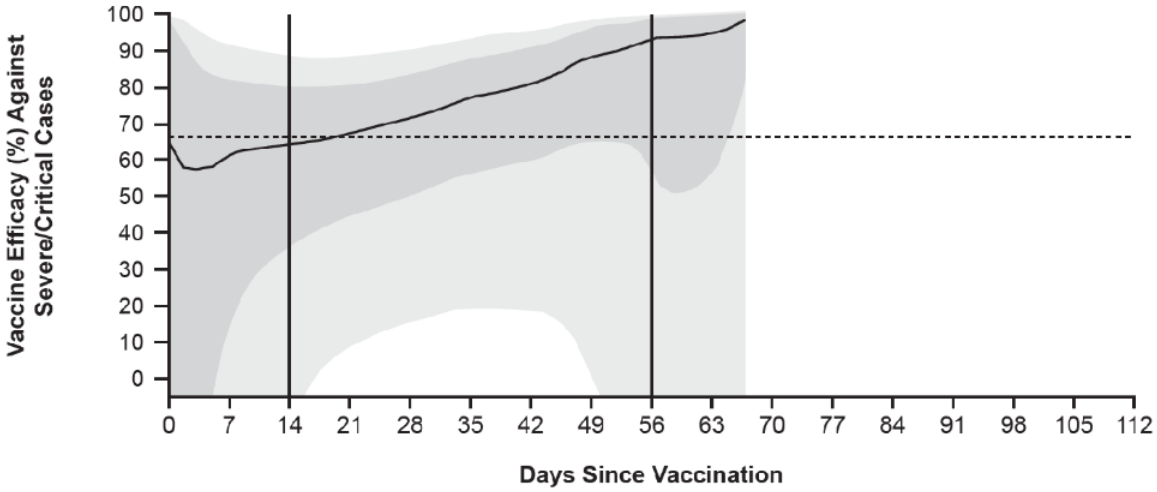
BCO	Bron- en contactonderzoek (Source and contact tracing)
COVID-19	Corona Virus Disease 2019
EMA	European Medicine's Agency
EU/EEA	European Union / European Economic Area
GGD	Gemeentelijke Gezondheidsdienst (Community Health Services)
GMT	Geometric mean titers
NAb	Neutralizing antibody
MIA	Multiplex immunoassay
mRNA	messenger ribonucleic acid
NIH	National Institute of Health
NTD	N-terminal domain
PBMC	Peripheral Blood Mononuclear Cell
PiCo	Pienter Corona study
RBD	Receptor Binding Domain
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
S-protein	Spike glycoprotein
TND	Test Negative Design
UK	United Kingdom
US	United States
VE	Vaccine effectiveness
VET	Vaccine effectiveness against transmission
VIDO	Vaccin Immunogeniciteit Doetinchem Onderzoek

Supplementary figures



Supplementary figure 1 Projected vaccine efficacy against moderate to severe-critical COVID-19 over time.

Projected vaccine efficacy against moderate to severe-critical COVID-19 over time [71]. The dark grey shading reflects the 95% pointwise confidence interval and the light grey shading shows the 95% simultaneous confidence interval.



Supplementary figure 2 Projected vaccine efficacy against severe-critical COVID-19 over time.

Projected vaccine efficacy against severe-critical COVID-19 over time [71]. The dark grey shading reflects the 95% pointwise confidence interval and the light grey shading shows the 95% simultaneous confidence interval.

					Q4			Q1			Q2		
			Aug	Sept	Okt	Nov	Dec	Jan	Feb	Mrt	Apr	Mei	Jun
Pfizer	Levering per maand	mRNA	3.136.699	3.136.699	1.035.000	1.035.000	1.035.000	1.458.333	1.458.333	1.458.333	1.458.333	1.458.333	1.458.333
Pfizer	Levering cumulatief		3.136.699	6.273.397	7.308.397	8.343.397	9.378.397	10.836.730	12.295.064	13.753.397	15.211.730	16.670.064	18.128.397
Moderna	Levering per maand	mRNA	1.151.667	1.151.667	2.466.667	2.466.667	2.466.667	783.333	783.333	783.333	783.333	783.333	783.333
Moderna	Levering cumulatief		1.151.667	2.303.333	4.770.000	7.236.667	9.703.333	10.486.667	11.270.000	12.053.333	12.836.667	13.620.000	14.403.333
Janssen	Levering per maand	Janssen	828.308	828.308	383.333	383.333	383.333	83.333	83.333	83.333	83.333	83.333	83.333
Janssen	Levering cumulatief		828.308	1.656.615	2.039.949	2.423.282	2.806.615	2.889.949	2.973.282	3.056.615	3.139.949	3.223.282	3.306.615
Novavax/Sanofi	Levering per maand	Novavax/Sanofi	-	-	-	-	-	-	175.000	175.000	175.000	175.000	175.000
Novavax/Sanofi	Levering cumulatief		-	-	-	-	-	-	175.000	350.000	525.000	700.000	875.000

- Toeleveringen 2021 vanuit forecast LCC VWS 2021
- Toeleveringen 2022 op basis van VWS website

Supplementary figure 3. Expected delivery of COVID-19 vaccines for Q4 of 2021 and Q1, Q2 of 2022, The Netherlands.

Supplementary figures 4-6 can be found in Annex COVID-19 Vaccination Coverage in The Netherlands*.*

Supplementary tables

Supplementary table 1 Overview of the ongoing studies on the immunogenicity of heterologous COVID-19 vaccine booster doses.

	Primary vaccine	**Booster vaccine**	**Interval prim-boost**	**Participants**	**Start**	**Time points**
UK CoV-Boost	Comirnary Spikevax Vaxzevria	Comirnary Spikevax Vaxzevria Janssen COVID-19 vaccine Novavax Valneva Curvac Sanofi/GSK	10-12 weeks	N=2886 >=30 years	June 2021, first data September 2021	Safety and immunogenicity at 28, 84, 309 and 365 days post booster
US, NIH, Baylor colloge of medicine, URMC	Comirnary Spikevax Janssen COVID-19 vaccine	Spikevax	12-20 weeks	N=150-500 18-55 yrs 56+ yrs	First data end of summer 2021	Safety and immunogenicity up to 1 year

Supplementary table 2 Overview of COVID- 1Su9 vaccines, formulation, and antibody and T-cell immune responses in humans.

Vaccine (Developer, Dosing, Regimen)	**Formulation**	**Antibody responses in humans**	**T-cell responses in humans**
mRNA			
Comirnaty BNT162b2 [77] • BioNTech/Pfizer • 30 µg mRNA • 2 doses, 21 days apart *Authorized in EU since 21-12-2020*	mRNA- lipid nanoparticle encoding full- length S protein, modified by two proline mutations to lock protein in the pre- fusion conformation [94-96]	S1- binding antibody present after 1 dose, responses increased following 2nd dose [97]; significant NAb was only present after 2nd dose [97]. Neutralizing titer was age dependent at 14 days after vaccination [98]	Increases in antigen- specific IFNγ+ CD4+ and CD8+ T cells after 2nd dose; predominance of IFNγ and IL-2 secretion, compared with IL-4, suggesting TH1 cell polarization [99]
Spikevax mRNA-1273 [65] • Moderna • 100 µg mRNA • 2 doses, 28 days apart *Authorized in EU since 06-01-2021*	mRNA- lipid nanoparticle encoding full- length S protein, modified by two proline mutations to lock protein in the pre- fusion conformation [100]	S- binding antibody detected 14 days after first dose, levels increased slightly by 28 days, with marked increase after 2nd dose [100]; minimal Nab present after 1st dose, peak at 14 days after 2nd dose [21]	Significant increases in CD4+ T cells secreting TH1 type cytokines (TNF > IL-2 > IFNγ) after 2nd dose, small increases in TNF- and IL-2- secreting cells after 1st dose; minimal change in TH2 cell responses; low levels of CD8+ responses [99]
Viral vector			
Vaxzevria ChAdOx1 nCoV-19 [101] • University of Oxford/Astra-Zeneca • 2.5–5 × 10^{10} viral particles • 2 doses, ≥28 days apart *Authorized in EU since 29-01-2021*	Recombinant, replication-deficient simian adenovirus vector expressing the full-length S protein with a tPA leader sequence [102]	S- binding antibody present 14 days after first dose, levels increased by 28 days [102]; marked increase after second dose, peak at 14 days after second dose; predominantly IgG3 and IgG1 ([103]); significant NAb detected after first dose, increased by 14 days after second dose; IgG avidity increased 28–56 days after single dose [103]; peak IgM and IgA responses at day 14 or 28	Peak T cell responses 14 days after 1st dose, but slightly higher responses measured 28 days after second dose [102, 103]; increase in TNF and IFNγ production by CD4+ T cells at day 14

Vaccine (Developer, Dosing, Regimen)	Formulation	Antibody responses in humans	T-cell responses in humans
Janssen COVID-19 vaccine Ad26.COV2.S [71] • Janssen (Johnsen & Johnsen) • 5 × 10^{10} viral particles • 1 dose *Authorized in EU since 11-03-2021*	Recombinant, replication-deficient human adeno-virus 26 expressing full length S-protein with two amino acid changes in S1/S2 junction that delete furin cleavage site and two proline substitutions in hinge region that lock protein in the pre-fusion conformation [104]	S- binding and neutralizing antibody present by 28 days after vaccination in 99% of individuals and antibody levels sustained until at least 84 days post vaccination [104] [24, 71, 104-106]	CD4+ and CD8+ T cell responses present at 14 and 28 days post vaccination, based on presence of CD4+ and CD8+ T cells secreting IFNγ and/or IL-2 and not IL-4 or IL-3, suggesting TH1 cell polarization of the CD4+ T cell response [24, 71, 104-106]
Under review			
mRNA			
CureVac COVID-19 vaccine CVnCoV [107, 108] • Curevac AG • 12 µg mRNA • 2 doses, 28 days apart *Rolling review since 12-02-2021*	mRNA-lipid nanoparticle, containing natural, non-modified, nucleotides, encoding full- length S protein, with intact S1/S2 cleavage site sequence-modified by two proline mutations (K986P and V987P, S-2P). to lock protein in the pre-fusion conformation (adjuvanticity through controlled interaction with TLR7/8)	S- binding IgG antibodies by ELISA, and SARS-CoV-2-virus neutralizing antibodies measured by micro-neutralization, displayed dose-dependent increases, four-fold increase in all participants who received 12 µg doses [109]	Significant increases in CD8 and CD4+ T cells secreting TH1 type cytokines (IFNa > IFNγ > IL-5) after 2nd dose in rodents and NHP [108, 110]

Vaccine (Developer, Dosing, Regimen)	Formulation	Antibody responses in humans	T-cell responses in humans
Viral vector			
Sputnik V Gam-COVID-Vac [111] • Gamaleya Research Institute • 10^{11} viral particles • 2 doses, 21 days apart *Rolling review since 04-03-2021*	Recombinant, replication-deficient human adenovirus 26 (dose 1) and human adenovirus 5 (dose 2) expressing full- length S protein [112]	S- binding antibody detected in 85–89% and NAb in 61% of individuals 14 days after first dose [112]; S antibody levels (binding and neutralizing) boosted by 2nd dose, with binding antibody in 98% and neutralizing antibody in 95% of individuals 14 days after 2nd dose [111]	CD4+ and CD8+ T cell responses observed by 14 days after first dose (based on proliferation assays and antigen- specific IFNγ secretion) [112]; all individuals had S- specific IFNγ responses 7 days after 2nd dose based on in vitro stimulation of PBMCs
Protein subunit			
Novavax COVID-19 vaccine NVX-CoV2373 [113] • Novavax • µg protein • 2 doses,21 days apart *Rolling review since 03-02-2021*	Recombinant nanoparticle of full- length S-protein with mutations at the S1/S2 cleavage sites to confer protease resistance and two proline substitutions to stabilize protein in a pre-fusion conformation, with saponin- based adjuvant (Matrix- M1) [114]	S- binding antibody detected 21 days after first dose, with a marked increase after the 2nd dose; some nAb present after the 1st dose, with a significant increase by 7 days after 2nd dose [115]	CD4+ T cell responses present by 7 days after 2nd dose, based on IFNγ, IL-2 and TNF production in response to S-protein stimulation, with a strong bias towards a TH1 cell phenotype; minimal TH2 cell responses (as measured by IL-5 and IL-13) [114]

Vaccine (Developer, Dosing, Regimen)	Formulation	Antibody responses in humans	T-cell responses in humans
Protein-based candidate • Sanofi Pasteur • monovalent 10 µg D614 (wt) Protein + AS03, • 2 doses, 21 days apart • bivalent 5+5 µg D614 (wt) +B1.351 (β, S-Afr) Protein + AS03 • 2 doses, 21 days apart *Rolling review since 20-07-2021*	Recombinant SARS-CoV-2 Spike protein without transmembrane or intracytoplasmic domains with mutations at the S1/S2 cleavage sites to confer protease resistance and two proline substitutions to stabilize protein in a pre-fusion conformation, with squalene-containing adjuvant (GSK, AS03)	In study with substantially lower antigen doses than planned: S- binding antibody detected 14 days after the second dose; some NAb present after the first dose, with a significant increase by 14 days after second dose [116]. After product improvement strong rates of neutralizing antibody responses in all adult age groups in a Phase 2 study with 722 volunteers [117]	In study with substantially lower antigen doses than planned: CD4+ T cell responses assessed 14 days after second dose, indicated increases of IFN-γ, IL-2, and TNFα cytokines to be more robust than increases for IL-4, IL-5, and IL-13, especially in the AS03-adjuvanted groups, suggesting no Th2 cell bias in the cell-mediated responses [116]
Whole inactivated SARS-CoV-2 virus			
CoronaVac • SinovacBiotech • 3 µg protein • 2 doses, 14–28 days apart [118, 119] *Rolling review since 04-05-2021*	SARS- CoV-2 grown in Vero cells, inactivated with β-propiolactone and adsorbed onto aluminium hydroxide [118]	By day 28 day after second dose, RBD-specific binding antibody detected in 88–97% of participants with a 14- day dosing interval and 99–100% with a 28- day interval; NAb present in 94–100% of individuals 28 days after second dose [118, 119]	

ELISpot enzyme-linked immunosorbent spot; GMT geometric mean titer; IFNγ interferon-γ; IL-2 interleukin-2; Nab neutralizing antibody; PBMC peripheral blood mononuclear cell; RBD receptor-binding domain; S spike; TH1 cell T helper 1 cell; TLR toll-like receptor; TNF tumour necrosis factor. Table adapted from Sadarangani et al. [16]

Supplementary table 2 Vaccine efficacy and effectiveness against COVID-19 of Comirnaty (2 dose schedule).

Vaccine efficacy

First author	Time interval[c]	Vaccine efficacy - % (95%CI)	Longest time since full vaccination	Study design	Country	Age - yr, mean ± SD or median [range]	Dominantly circulating VOC
EMA [62]	≥14 days after dose 2	94.2 (88.7-87.2)	Median of 2 months	Clinical trial	USA, Argentina, Brazil	50.6 ± 15.7 (intervention) 50.4 ± 15.8 (placebo)	NR
Press release by Pfizer & BioNTech [120]	≥7 days – 6 months after dose 2	91.3 (89.0-93.2)	6 months	Clinical trial	NR	NR	NR
Thomas *et al*. [61]	≥7 days – 2 months after dose 2	96.2 (93.3, 98.1)	51% of the participants aged ≥16 yr had 4 to <6 months of follow up. 58 % of the participants aged 12-15 yr had a follow-up of ≥2 months.	Clinical trial[a]	USA, Argentina, Brazil, South Africa, Germany, Turkey	[12 - 91]	South Africa: beta NR for the other countries
	≥2 months – 4 months after dose 2	90.1 (86.6, 92.9)					
	≥4 months after dose 2	83.7 (74.7, 89.9)					
	≥7 days – 6 months after dose 2	91.1 (88.8, 93.2)					ccc

VE

First author	Time interval[c]	VE - % (95%CI)	Longest time since full vaccination	Study design	Country	Age - yr, mean ± SD or median [IQR]	Dominantly circulating VOC
Saciuk[b] [63]	>14 days after dose 2	93.0 (92.6, 93.4)	98 days	Retrospective cohort	Israel	>50% is aged 16-44	Alpha

a Blinded period only; b VE against a SARS-CoV-2 infection, irrespective of symptoms; c Either the longest time interval with a vaccine efficacy or effectiveness estimate is mentioned or several time intervals are mentioned if waning is considered; IQR interquartile range; NR not reported; SD standard deviation; USA United States of America; VOC Variant of Concern; yr years.

Supplementary table 3 Vaccine efficacy and effectiveness against COVID-19 of Spikevax (2 dose schedule).

Vaccine efficacy

First author	Longest time interval reported	Vaccine efficacy - % (95%CI)	Longest time since full vaccination	Study design	Country	Age - yr, mean ± SD or median [IQR] or mean (range)	Dominantly circulating VOC
Baden *et al.* [65]	≥14 days after dose 2	94.1 (89.3-96.8)	97 days (median 64 days)	Clinical trial	USA	51.4 (18-95)	NR
Moderna [66]	NR	93% (NR)	6 months	Clinical trial	NR	NR	NR

Vaccine effectiveness

First author	Longest time interval reported	VE - % (95%CI)	Longest time since full vaccination	Study design	Country	Age - yr, mean ± SD or median [IQR]	Dominantly circulating VOC
Pawlowski *et al.* [64]	≥14 days after dose 2	92.3 (82.4-97.3)	120 days (median of 58 days)	Retrospective cohort	USA	63.0 ± 16.1 (vaccinated) 62.2 ± 16.7 (unvaccinated)	NR

IQR interquartile range; NR not reported; SD standard deviation; USA United States of America; VOC variant of concern; yr years.

Supplementary table 4 Vaccine efficacy and effectiveness against COVID-19 of Vaxzevria (2 dose schedule).

Vaccine efficacy							
First author	**Longest time interval reported**	**Vaccine efficacy - % (95%CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD or median [IQR] or mean (range)**	**Dominantly circulating VOC**
Voysey [68]	≥15 days after dose 2	66.7 (57.4-74.0)	Median of 3.4 months (IQR 1.3-4.8)	Clinical trial	UK, Brazil, South Africa	About 90% is aged 18-55	NR
Vaccine Effectiveness							
First author	**Longest time interval reported**	**VE - % (95%CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD or median [IQR] or mean (range)**	**Dominantly circulating VOC**
Lopez Bernal [52]	≥14 days after dose 2	66.1 (54.0-75.0; Alpha VOC) 59.8 (28.9-77.3; Delta VOC)	≥14 days	Test-negative case control	England	62.7% is aged 16-39	Alpha & Delta
Hitchings [69]	≥14 days after dose 2	77.9 (69.2, 84.2)	Median of 20 (IQR 10, 34) days for controls and 13 (IQR 8, 24) for cases	Test-negative case control	Brazil	66.5 ± 6.5	Gamma

IQR interquartile range; NR not reported; SD standard deviation; UK United Kingdom; VOC variant of concern; yr years.

Supplementary table 5 Vaccine efficacy and effectiveness against a SARS-CoV-2 infection of Janssen COVID-19 vaccine (1 dose schedule).

Vaccine efficacy							
First author	**Longest time interval reported**	**Vaccine efficacy - % (95%CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, median [range]**	**Dominantly circulating VOC**
Sadoff[a] [71]	≥28 days after vaccination	66.1 (55.0-74.8)	124 days (median of 58 days)	Clinical trial	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA	52 [18-100]	Beta in South Africa. No dominant circulating VOC in other countries.
VE							
First author	**Longest time interval reported**	**VE - % (95%CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr**	**Dominantly circulating VOC**
Corchado-Garcia[b] [72]	≥15 days after vaccination	76.7 (30.3-95.3)	27 Feb – 14 Apr -> 45 days	Retrospective cohort	USA	50% was aged <65	NR

a Vaccine efficacy against moderate to severe-critical Covid-19. b VE against a SARS-CoV-2 infection, irrespective of symptoms. NR, not reported; USA, United States of America; yr, years.

Supplementary table 6 Vaccine efficacy and effectiveness against hospitalization after vaccination, by vaccine.

Comirnaty							
First author	**Longest time interval reported**	**VE - % (95% CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD or median [IQR]**	**Dominantly circulating VOC**
Pawlowski *et al.* [64]	≥14 days after dose 2	88.3 (72.6-95.9)	120 days (median of 58 days)	Retrospective cohort	USA	53.5 ± 18.0	NR
Pawlowski[a] *et al.* [64]	≥14 days after dose 2	100 (18.7-100)	120 days (median of 58 days)	Retrospective cohort	USA	53.5 ± 18.0	NR
Spikevax							
First author	**Longest time interval reported**	**VE - % (95% CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD or median [IQR]**	**Dominantly circulating VOC**
Pawlowski *et al.* [64]	≥14 days after dose 2	90.6 (76.5-97.1)	120 days (median of 58 days)	Retrospective cohort	USA	53.5 ± 18.0	NR
Pawlowski[a] *et al.* [64]	≥14 days after dose 2	100 (17.9-100)	120 days (median of 58 days)	Retrospective cohort	USA	53.5 ± 18.0	NR
Vaxzevria							
First author	**Longest time interval reported**	**VE - % (95% CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD or median [IQR]**	**Dominantly circulating VOC**
EMA assessment report[b] [70]	≥15 days after dose 2	100 (42.7-NE)	127 days (median of 78 days)	Clinical trial	UK, Brazil	44.0 [NR] (UK), 37 [NR] (Brazil)	NR
Hitchings *et al.* [69]	≥14 days after dose 2	87.6 (78.2-92.9)	Median of 20 (IQR 10-34) days for controls and 13 (IQR 8-24) days for cases	Test-negative case control	Brazil	66.5 ± 6.5	Gamma

Janssen COVID-19 vaccine							
First author	**Longest time interval reported**	**VE - % (95% CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD or median [IQR]**	**Dominantly circulating VOC**
FDA [73]	≥15 days after vaccination	81.8 (16.7, 98.0)	Median of 61 days (aged 18-59 yr) and 52 days (aged ≥60 yr)	Clinical trial	Brazil, Chile, Argentina, Colombia, Peru, Mexico, USA, South Africa	51.1 ± 15.0	Beta in South Africa. No dominant circulating VOC in other countries.
	≥28 days after vaccination	100 (15.7, 100)					

a intensive care unit admission; b vaccine efficacy against hospitalization; c either the longest time interval with a vaccine efficacy or effectiveness estimate is mentioned or several time intervals are mentioned if waning is considered; IQR interquartile range; NR not reported; SD standard deviation; USA United States of America; VOC variant of concern; yr years.

Supplementary table 7 Vaccine efficacy and effectiveness against case-fatality, by vaccine.

Comirnaty							
First author	**Longest time interval reported**	**VE - % (95%CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD**	**Dominantly circulating VOC**
Saciuk *et al.* [63]	>14 days after dose 2	91.1 (87.0-94.0)	98 days	Retrospective cohort	Israel	>50% 16-44	Alpha
Spikevax							
First author	**Longest time interval reported**	**VE - % (95%CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD or median [IQR]**	**Dominantly circulating VOC**
-	-	-	-	-	-	-	-
Vaxzevria							
First author	**Longest time interval reported**	**VE - % (95%CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD or median [IQR]**	**Dominantly circulating VOC**
Hitchings *et al.* [69]	≥14 days after dose 2	93.6 (81.9-97.7)	Median of 20 (IQR 10-34) days for controls and 13 (IQR 8-24) days for cases	Test-negative case control	Brazil	66.5 ± 6.5	Gamma

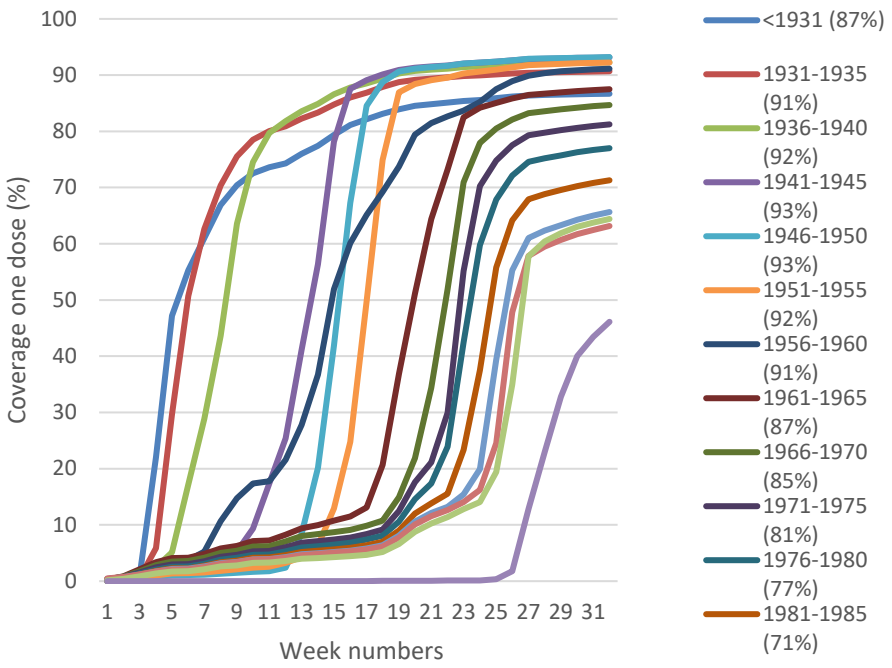
Janssen COVID-19 vaccine							
First author	**Longest time interval reported**	**VE - % (95%CI)**	**Longest time since full vaccination**	**Study design**	**Country**	**Age - yr, mean ± SD or median [IQR]**	**Dominantly circulating VOC**
FDA [73]	≥1 days after vaccination	81.3 (34.6-96.5)	Median of 61 days (aged 18-59 yr) and 52 days (aged ≥60 yr)	Clinical trial	Brazil, Chile, Argentina, Colombia, Peru, Mexico, USA, South Africa	51.1 ± 15.0	Beta in South Africa. No dominant circulating VOC in other countries.
	≥14 days after vaccination	80.0 (29.4-96.3)					
	≥28 days after vaccination	75.0 (-25.2-97.4)					

IQR, interquartile range; NR, not reported; SD, standard deviation; USA, United States of America; VOC, variant of concern; yr, years.

Annex: COVID-19 Vaccination Coverage in The Netherlands

Key points:

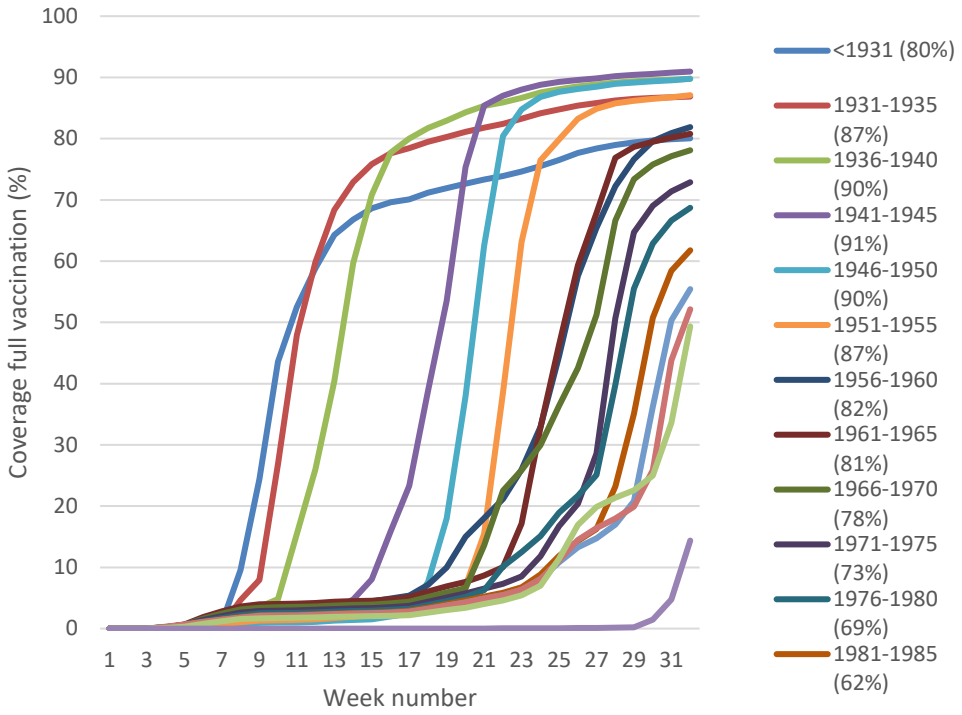
- By week 32 the coverage for at least one dose COVID-19 vaccination and full COVID-19 vaccination for persons born in 2003 or before was between 80-85% and 72-75% respectively. For persons born in 2009 and before these coverages were between 78-82% and 67-70% respectively, taken into account that only the persons born in 2009 who already turned 12 years old, were included in the denominator.
- High coverages (87-93%) for at least one dose COVID-19 vaccination are observed in persons born in 1955 or before by the end of week 32. In younger birth years however, with exception of 2004-2009, a plateau becomes visible by week 28, which stabilizes by week 32, indicating that comparable coverages as the older birth years might not be reached in future weeks.
- Regarding persons born in 2003 or before, high coverages (>75%) for at least one dose COVID-19 vaccination are observed in most municipalities, with exception of a few large cities and municipalities in the Bible Belt. The highest coverages (>85%) are observed in municipalities in the south-east of the country and the lowest coverage is observed in Urk (20-39%).
- Up-to-date and more extensive information about the COVID-19 vaccination coverage can be found in the weekly report which is published every Tuesday here. In this report also information on (limitations in) the data sources used for the figures in this chapter can be found.
- A lower vaccination coverage is observed in Amsterdam, Rotterdam and The Hague too. At a more detailed level, the lower vaccination coverage in these cities is mainly observed in deprived neighborhoods and among persons with a migration background. Research by the RIVM shows that persons with a migration background and/or a low Social Economic Status (SES) are less willing to be vaccinated against COVID-19 [121, 122]. In Amsterdam, Rotterdam and The Hague the population relatively includes many people with a low SES and/or a migration background. This is also in line with results for participation in the NIP [123].



Supplementary figure 4 Cumulative coverage at least one dose COVID-19 vaccination, stratified by birth year and for week 1-32, 2021.

The coverage of at least one dose COVID-19 vaccination is shown, by five-year birth cohorts, and for week 1-32.

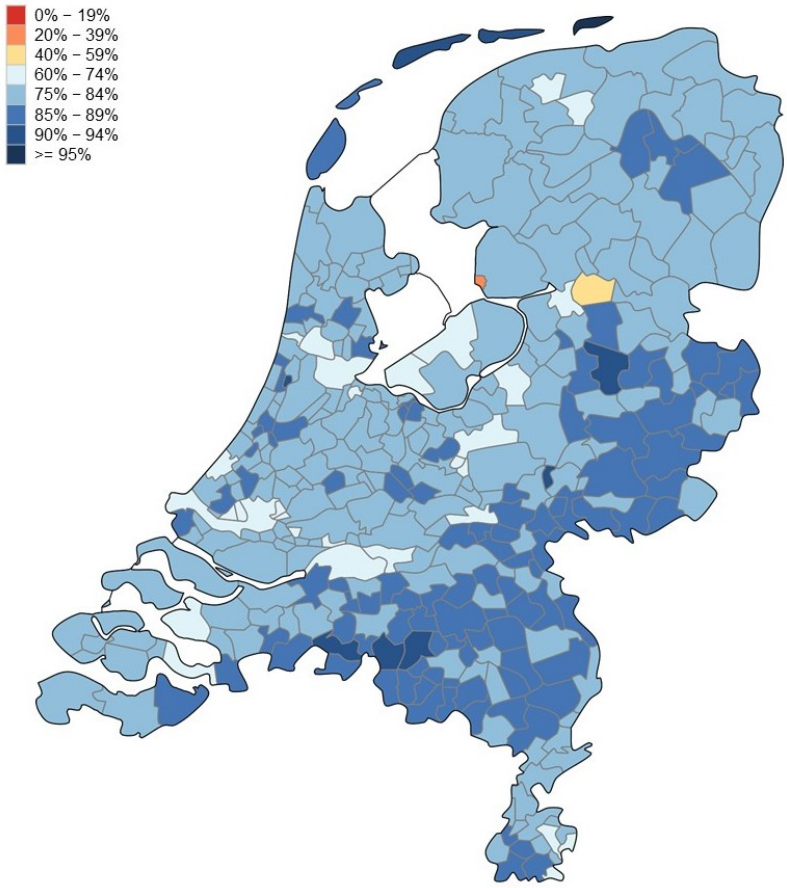
By the end of week 32 the coverages were 87% (<1931), 91% (1931-1935), 92% (1936-1940), 93% (1941-1945), 93% (1946-1950), 92% (1951-1955), 91% (1956-1960), 87% (1961-1965), 85% (1966-1970), 81% (1971-1975), 77% (1976-1980), 71% (1981-1985), 66% (1986-1990), 63% (1991-1995), 64% (1996-2003), 46% (2004-2009). In younger birth years, with exception of 2004-2009, a plateau becomes visible by week 28, which stabilizes by week 32, indicating that comparable coverages as the older birth years might not be reached in future weeks.



Supplementary figure 5 Cumulative coverage full COVID-19 vaccination, stratified by birth year and for week 1-32, 2021.

The coverage of full COVID-19 vaccination is shown, by five-year birth cohorts, and for week 1-32.

By the end of week 32 the coverages were 80% (<1931), 87% (1931-1935), 90% (1936-1940), 91% (1941-1945), 90% (1946-1950), 87% (1951-1955), 82% (1956-1960), 81% (1961-1965), 78% (1966-1970), 73% (1971-1975), 69% (1976-1980), 62% (1981-1985), 55% (1986-1990), 52% (1991-1995), 49% (1996-2003), 14% (2004-2009).



Supplementary figure 6 Cumulative coverage at least one dose COVID-19 vaccination, birth years 2003 and before, week 1-32, 2021

The cumulative coverage of at least one dose COVID-19 vaccination is shown for persons born in 2003 or before by municipality, up to and including week 32, 2021.

A coverage >75% is observed in most municipalities, with exception of a few large cities and municipalities in the Bible Belt. The highest coverages (>85%) are observed in municipalities in the south-east of the country and the lowest coverage is observed in Urk (20-39%). A high coverage (> 85%) is also observed on the Wadden Islands, since younger age groups were invited for vaccination there during similar weeks as higher age groups.

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