



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

COVID-19 / SARS-CoV-2

Background information for the Health Council

RIVM letter report 2020-0151
Centre for Infectious Disease Control



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Colophon

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Centrum Infectieziektebestrijding (CIb) (author), RIVM
(Centre for Infectious Disease Control)

Contact:

Centrum Infectieziektebestrijding (CIb)

secretariaat.cib@rivm.nl

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P.O. box 1 | 3720 BA Bilthoven

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Synopsis

COVID-19 / SARS-CoV-2

Background information for the Health Council

COVID-19 is a disease caused by infection with the SARS-CoV-2 virus. This new coronavirus was first discovered in China at the end of 2019. It has since spread around the world and caused a pandemic. In the Netherlands, the first patient was officially reported in February 2020.

Many different vaccines against COVID-19 are currently being developed. The Ministry of Health, Welfare and Sport (VWS) has asked the Health Council of the Netherlands to provide advice on who can qualify for COVID-19 vaccination. Then preparations can be made for the moment the vaccine is available in the Netherlands.

To support the Health Council in this regard, RIVM has collected background information on vaccination against COVID-19. This overview contains all the information there is about COVID-19. This includes the pathogen, how it is transmitted, which symptoms people can get from it, and which factors increase the risk of infection. It also describes which vaccines are under development, how they protect humans, how the vaccine registration process works, public acceptance of vaccination, and considerations about vaccination costs versus effectiveness.

The symptoms of COVID-19 range from very mild to severe. Respiratory symptoms can be mild and cause non-specific symptoms, as well as a persistent dry cough and breathing problems. Serious pneumonia can also develop requiring people to be ventilated.

Fever, dry cough, shortness of breath, fatigue and nausea are the most common symptoms. Loss of taste and smell is also common. Complications such as thrombosis and a lack of oxygen may also occur. Other organs can also be affected, such as the heart, kidneys and liver. People who already have another chronic illness and those over 70 have a higher risk of becoming seriously ill or dying.

Keywords: COVID-19, SARS-CoV-2, epidemiology, immunology, vaccination, cost-effectiveness, acceptance.

Publiekssamenvatting

COVID-19 / SARS-CoV-2

Achtergrondinformatie voor de Gezondheidsraad

COVID-19 is een ziekte die wordt veroorzaakt door een infectie met het SARS-CoV-2-virus. Dit nieuwe coronavirus is eind 2019 voor het eerst ontdekt in China. Sindsdien heeft het zich verspreid over de wereld en een pandemie veroorzaakt. In Nederland is de eerste patiënt officieel in februari 2020 gemeld.

Op dit moment wordt er aan veel verschillende vaccins tegen COVID-19 gewerkt. Het ministerie van Volksgezondheid, Welzijn en Sport (VWS) heeft de Gezondheidsraad gevraagd een advies te geven wie voor de COVID-19-vaccinatie in aanmerking kan komen. Dan kunnen voorbereidingen getroffen worden voor het moment dat het vaccin er in Nederland is.

Om de Gezondheidsraad hierbij te ondersteunen heeft het RIVM achtergrondinformatie over vaccinatie tegen COVID-19 verzameld. In dit overzicht staat alle informatie die er over COVID-19 is. Het gaat onder andere over de ziekteverwekker, hoe hij wordt overgebracht, welke klachten mensen ervan kunnen krijgen, en welke factoren het risico op een besmetting vergroten. Daarnaast staat erin welke vaccins in ontwikkeling zijn en hoe zij mensen beschermen, hoe het registratieproces voor vaccins werkt, de acceptatie van het publiek van vaccinatie, en overwegingen over de kosten van vaccinatie ten opzichte van de effectiviteit.

De symptomen van COVID-19 variëren van zeer mild tot ernstig. Klachten aan de luchtwegen kunnen mild zijn en niet-specifieke klachten geven, maar ook een aanhoudende droge hoest en ademhalingsproblemen. Er kan ook een ernstige longontsteking ontstaan waarbij mensen moeten worden beademd.

Koorts, droge hoest, kortademigheid, moeheid, en misselijkheid zijn de meest voorkomende klachten. Verlies van smaak en geur komt ook veel voor. Complicaties kunnen trombose en een tekort aan zuurstof zijn. Ook kunnen andere organen worden aangetast, zoals het hart, de nieren en de lever. Mensen die al een andere chronische ziekte hebben en mensen die ouder zijn dan 70 jaar, hebben een groter risico om ernstig ziek te worden of te overlijden.

Kernwoorden: COVID-19, SARS-CoV-2, epidemiologie, immunologie, vaccinatie, kosteneffectiviteit, acceptatie.

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Background

COVID-19 is caused by the SARS-CoV-2, a corona virus that emerged for the first time at the end of 2019 in China. In the subsequent months the virus spread worldwide causing a pandemic. Since the outbreak, more and more information regarding the severity and disease burden of COVID-19 has become available, as well as information about various potential vaccines.

The Ministry requested the Health Council of the Netherlands to advise on COVID-19 vaccination to prepare for the situation once a vaccine becomes available. This background document aims to summarize the recent scientific information on SARS-CoV-2. It is thereby important to note that 1) new scientific information about SARS-CoV-2 becomes available at high speed, meaning that some information quickly becomes outdated and 2) some of the literature used in this document, has not been peer-reviewed at the moment of writing this document. Due to the large amount of literature available, the main focus of this document is on the situation in the Netherlands. The epidemiological situation is [dynamic](#), as is the vaccine [development](#). Both are closely monitored by the CIb, RIVM.

1 Pathogen SARS-CoV-2 virus

In December 2019, a novel human pathogenic coronavirus emerged in Wuhan, China [1]. Initially referred to as “2019 novel coronavirus” (2019-nCoV), it was later officially named “Severe acute respiratory syndrome-related coronavirus 2” (SARS-CoV-2) by the International Committee on Taxonomy of Viruses [2]. SARS-CoV-2 is a RNA virus classified in the Severe acute respiratory syndrome-related coronavirus (SARS-CoV) species, Sarbecovirus subgenus, Betacoronavirus genus, Coronaviridae family, Cornidovirineae suborder, Nidovirales order, Pisoniviricetes class, Pisuviricota phylum, Orthornavirae kingdom, Riboviria realm [2-4] (Figure 1.1). Human isolates of SARS-CoV from the same species caused an outbreak in 2002-2003, while the Middle East respiratory syndrome-related coronavirus (MERS-CoV) from the same genus has been causing outbreaks since 2012 [3, 5]. However, as can be seen in Figure 1.1 [4], Betacoronavirus genus also includes the widely circulating human coronavirus HKU1 (HCoV-HKU1) and human coronavirus OC43 (HCoV-OC43), part of the respiratory viruses responsible for the “common cold”, along with human coronavirus 229E (HCoV-229E) and human coronavirus NL63 (HCoV-NL63) from the Alphacoronavirus genus [3, 5].

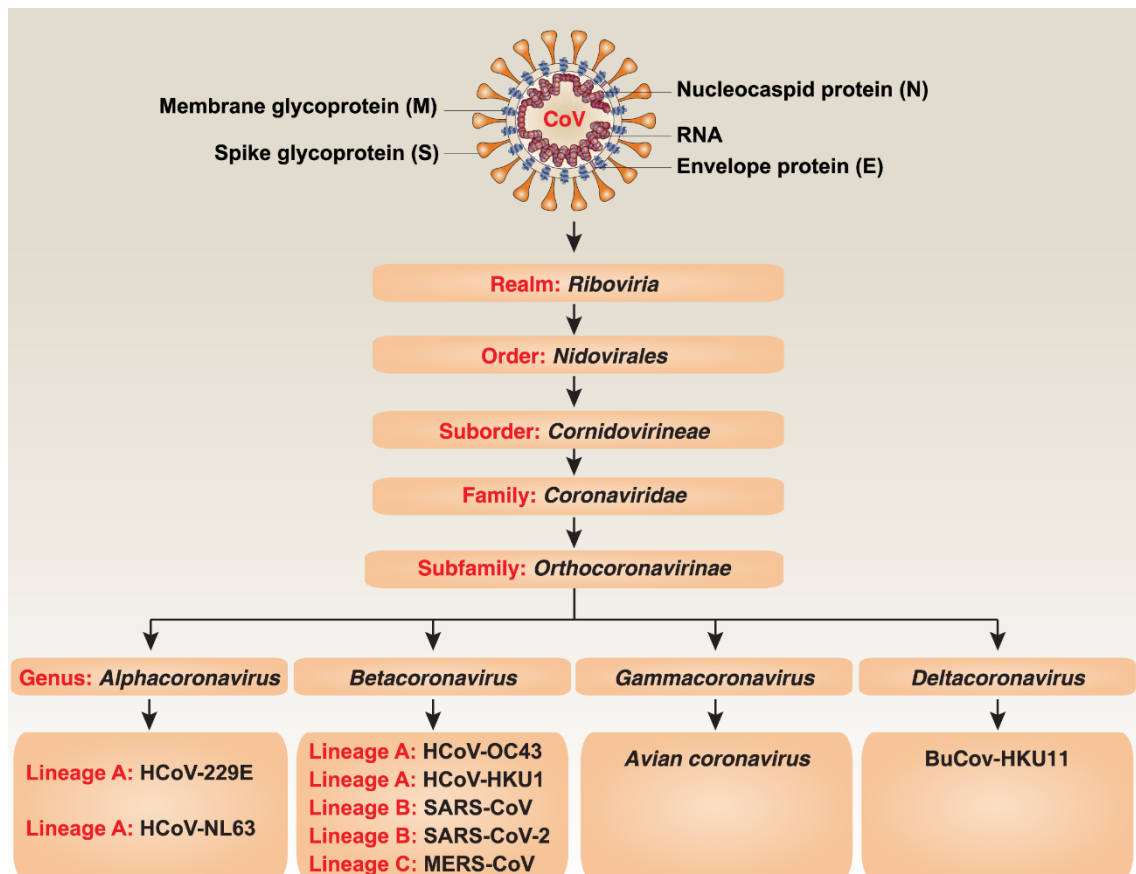


Figure 1.1 From Schematic representation of the taxonomy of Coronaviridae. From “The hallmarks of COVID-19 disease” by Tang D. et al.

Similarly to other human pathogenic coronaviruses [6], SARS-CoV-2 originated from an animal reservoir with zoonotic transmission to humans, though the exact origin and transmission events are still being investigated: bats are suggested as the most probable primary reservoir [7, 8] with other species (pangolins for example) as intermediate hosts or even secondary reservoir [9].

SARS-CoV-2 is a positive-stranded RNA virus. Its structure is shown in Figure 1.2 [10]. The virions are spherical with “spikes” projected outwards from the envelope resembling a solar corona, inspiring the name “coronaviruses”. The Spike protein plays a key role in binding of the virus to host cells. The viral RNA is situated in a helical nucleocapsid, protected by the thick envelope [5]. Current molecular diagnostics include PCR assays targeting different parts of the viral genome, for example sequences from the envelope (E gene) and RNA-dependent RNA polymerase (RdRp gene) are used in European assays [11], while the nucleocapsid (N gene and ORF genes) and spikes (S gene) are used in Asian and US assays. As with any novel virus, sequencing and drift monitoring of SARS-CoV-2 isolates are a vital part of the surveillance. They are needed to assure the annealing of primer-probe sets, and thus the reliability of the commonly-used assays [12-14]. More data is currently being gathered on the sequences and stability of the circulating SARS-CoV-2, its’ mutation rates and variants and how these affect the infectivity [12, 15, 16]. Initial analyses suggest that different SARS-CoV-2 strains (often referred to by regions: Asian, European, North American, etc.) co-exist and might be evolving with a different mutation pattern and even at a significantly different mutation rate [12, 16]. The latter would also have implications on the efficacy of vaccines and thus the need to maintain the surveillance of circulating SARS-CoV-2 via sequencing techniques.

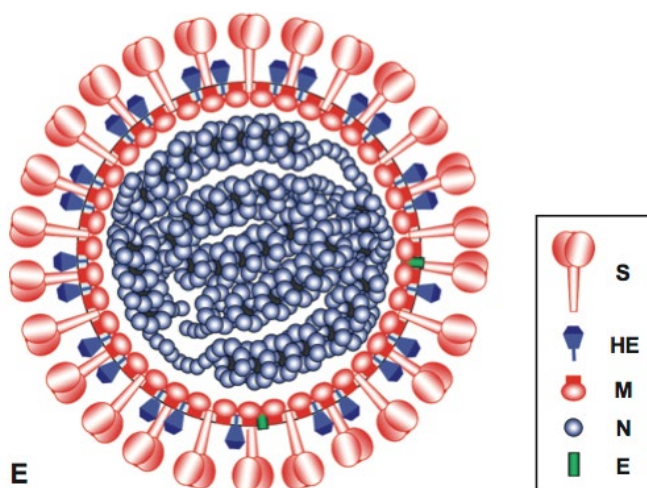


Figure 1.2 Schematic representation of a betacoronavirus virion. From ICTV 9th Report (2011) by the International Committee on Taxonomy of Viruses (ICTV)
E - envelope protein, HE - hemagglutinin-esterase, M - membrane glycoprotein, N - nucleocapsid protein, S - spike protein.

2 Transmission routes SARS-CoV-2 virus

(Adapted from "Scientific brief: transmission of SARS-CoV-2: implications for Infection prevention precautions-WHO 9 July 2020")

2.1 Contact and droplet transmission

Transmission of SARS-CoV-2 can occur through direct or indirect, close contact with infected people through infected secretions such as saliva and respiratory secretions like respiratory droplets, which are expelled when an infected person coughs, sneezes, talks or sings [17-25]. There are two types of droplets, respiratory droplets are $>5-10\ \mu\text{m}$ in diameter whereas droplets $<5\ \mu\text{m}$ in diameter are referred to as droplet nuclei or aerosols [26].

Respiratory droplet transmission can occur when a person is in close contact (within 1-2 meters) with an infected person who has respiratory symptoms (e.g. coughing or sneezing) or who is talking or singing [27]; in these circumstances, respiratory droplets that include virus can reach the mouth, nose or eyes of a susceptible person and can result in infection. Indirect contact transmission involving contact of a susceptible host with a contaminated object or surface (fomite transmission) may also be possible (see paragraph 2.3).

See the next paragraph for a discussion on aerosol-based airborne transmission.

2.2 Airborne transmission

Airborne transmission is defined as the spread of an infectious agent caused by the dissemination of droplet nuclei (aerosols) that remain infectious when suspended in air over long distances and time [26]. Airborne transmission of SARS-CoV-2 can occur during medical procedures that generate aerosols ("aerosol generating procedures") [28]. The WHO together with the scientific community, has been actively discussing and evaluating whether SARS-CoV-2 may also spread through aerosols in the absence of aerosol generating procedures, particularly in indoor settings with poor ventilation.

Aerosols persist in air for much longer than the larger droplets ($>5\ \mu\text{m}$) typically produced by coughing and sneezing, which settle on surfaces within minutes. Virus containing aerosols can induce infection in the respiratory tract when inhaled by a susceptible person. Both higher concentrations of infected aerosols in the inhaled air and prolonged exposure increase the risk of infection. Importantly, transmission by aerosols can have a much larger radius than the typical 1.5 meters cut-off for droplet transmission, making it particularly relevant in crowded settings.

The physics of exhaled air and flow physics have generated hypotheses about possible mechanisms of SARS-CoV-2 transmission through aerosols [29-32]. These theories suggest that 1) a number of respiratory droplets generate microscopic aerosols ($<5\ \mu\text{m}$) by

evaporating, and 2) normal breathing and speaking results in exhaled aerosols. Thus, a susceptible person could inhale aerosols, and could become infected if the aerosols contain the virus in sufficient quantity to cause infection within the recipient. However, the proportion of exhaled droplet nuclei or of respiratory droplets that evaporate to generate aerosols, as well as the infectious dose of viable SARS-CoV-2 required to cause infection in another person are not known.

Outside of medical facilities, some outbreak reports related to indoor crowded spaces [33] have suggested the possibility of aerosol transmission, combined with droplet transmission, for example, during choir practice [20], in restaurants [34] or in fitness classes [35]. In these situations, short-range aerosol transmission cannot be ruled out, particularly in specific indoor locations such as crowded and inadequately ventilated spaces, over a prolonged period of time with infected persons. However, the detailed investigations of these clusters suggest that droplet and fomite transmission could also explain human-to-human transmission within these clusters.

Airborne transmission has not been conclusively demonstrated to date, and its contribution to the overall transmission remains unclear, in particular in close setting with poor ventilation. More research is needed to gain insight in the role and the extend of this route of transmission.

2.3 Fomite transmission

Respiratory secretions or droplets expelled by infected individuals can contaminate surfaces and objects, creating contaminated surfaces (fomites). Viable SARS-CoV-2 virus and/or RNA detected by RT-PCR can be found on those surfaces for periods ranging from hours to days. This depends on the ambient environment (including temperature and humidity) and the type of surface, in particular in environments with high concentrations of virus, like in health care facilities where COVID-19 patients are being treated [36-46]. Therefore, transmission may also occur indirectly through touching surfaces in the immediate environment or objects contaminated with virus (e.g. stethoscope or thermometer), followed by touching the mouth, nose, or eyes.

Despite consistent evidence of SARS-CoV-2 contamination of surfaces and the survival of the virus on certain surfaces, there are no specific reports that directly demonstrate fomite transmission. People who come into contact with potentially infectious surfaces often also come into close contact with the infectious person, making it difficult to discern between respiratory droplet and fomite transmission. However, given consistent findings about environmental contamination in the vicinity of infected cases and the fact that other coronaviruses and respiratory viruses can also be transmitted this way, fomite transmission is considered a likely mode of transmission for SARS-CoV-2.

2.4 Other modes of transmission

SARS-CoV-2 RNA has also been detected in other biological samples, including the urine and faeces of some patients [47-51]. One study found viable SARS-CoV-2 in the urine of one patient [52]. Three studies have cultured SARS-CoV-2 from stool specimens [49, 53, 54]. To date

however, there have been no published reports of transmission of SARS-CoV-2 through faeces or urine.

Some studies have reported detection of SARS-CoV-2 RNA, in either plasma or serum, and the virus can replicate in blood cells. However, the role of bloodborne transmission remains uncertain; and low viral titres in plasma and serum suggest that the risk of transmission through this route may be low [49, 55]. Currently, there is no evidence for intrauterine transmission of SARS-CoV-2 from infected pregnant women to their foetuses, although data remain limited. Nevertheless, the receptors required for virus entrance into cells, ACE2 and CLEC4M, are also expressed in the placenta, along with the gastrointestinal tract (the alimentary system), heart, kidney, and lung.

The WHO has recently published a scientific brief on breastfeeding and COVID-19 [56]. This brief explains that viral RNA fragments have been found by RT-PCR in a few breast milk samples of mothers infected with SARS-CoV-2, but as of yet, studies investigating whether the virus could be isolated from breast milk have found no viable virus. Transmission of SARS-CoV-2 from mother to child would necessitate replicative and infectious virus in breast milk to be able to reach target sites in the infant as well as overcome the infant defence systems. WHO recommends that mothers with suspected or confirmed COVID-19 should be encouraged to initiate or continue to breastfeed [56].

While current evidence shows that SARS-CoV-2 is most closely related to known betacoronaviruses in bats, the role of an intermediate host in facilitating transmission in the earliest known human cases remains unclear [8, 57]. In addition to investigations on the possible intermediate host(s) of SARS-CoV-2, there are also a number of studies underway to better understand susceptibility of SARS-CoV-2 in different animal species. Current evidence suggests that humans infected with SARS-CoV-2 can infect other mammals, including dogs [58], cats [59], and farmed mink [60]. Research showed that it is considered highly likely that 2 workers at 2 different farms were infected by minks, showing these infected mammals pose a risk for transmission to humans [61].

2.5 When do people infected with SARS-CoV-2 infect others?

Knowing when an infected person can spread SARS-CoV-2 is just as important as understanding how the virus spreads (described above). The WHO has recently published a scientific brief outlining the current knowledge on when a person may be able to spread, based on the severity of their illness [62].

The available evidence suggests that SARS-CoV-2 RNA can be detected in people 1-3 days before symptom onset, with the highest viral loads, as measured by RT-PCR, observed around the day of symptom onset, followed by a gradual decline over time [48, 63-65]. The duration of RT-PCR positivity generally appears to be 1-2 weeks for asymptomatic persons, and up to 3 weeks or more for patients with mild to moderate disease [63, 66-69]. In patients with severe COVID-19 disease or

immunocompromised persons, RT-PCR positivity can last much longer, even during the recovery period [48].

Detection of viral RNA does not necessarily mean that a person is infectious and able to transmit the virus to another person. In asymptomatic cases, prolonged detection of viral RNA of up to 45 days is also reported [70], though it is still unclear for how long asymptomatic cases transmit the virus to others. Studies using viral culture of patient samples to assess the presence of infectious SARS-CoV-2 are currently limited [62]. Viable virus has been isolated from an asymptomatic case [71], from patients with mild to moderate disease up to 8-9 days after symptom onset, and for longer from severely ill patients [62]. Additional studies are needed to determine the duration of viable virus shedding among infected patients with and without clinical symptoms, also via faeces and urine.

2.6 SARS-CoV-2 infected persons who have symptoms infect others primarily through close contact

A study of the first patients in the Republic of Korea showed that 9 of 13 secondary cases occurred among household contacts [72]. Outside of the household setting, those who had close physical contact, shared meals, or shared enclosed spaces for approximately one hour or more with symptomatic cases (such as in places of worship, gyms, or the workplace) were also at increased risk of infection [20, 35, 73, 74]. Other reports have supported this with similar findings of secondary transmission within families and with other close contacts [75-77].

2.7 SARS-CoV-2 infected persons without symptoms can also infect others

Early data from China suggested that people without symptoms may also infect others [25]. To better understand the role of transmission from infected people without symptoms, it is important to distinguish between transmission from people who are infected but never develop clinical symptoms (asymptomatic transmission) [78] and transmission from people who are infected but have not yet developed clinical symptoms (pre-symptomatic transmission). This distinction is important when developing public health strategies to control transmission.

The extent of truly asymptomatic infection in the community remains unknown. The proportion of people whose infection is asymptomatic likely varies with age. This possibly results from the increasing prevalence of underlying conditions in older age groups (and thus increasing risk of developing severe disease with increasing age). Also, young children are seemingly less likely to show clinical symptoms compared to adults [79].

Early studies from the United States [80] and China [81] reported many cases as asymptomatic, based on the lack of symptoms at the time of testing. However, 75-100% of these people later developed symptoms. A recent systematic review estimated that the proportion of truly asymptomatic cases ranges from 4% to 41%, with a pooled estimate of 16% (12%-20%)[82]. However, all studies included in this systematic review have important limitations [82]. For example, some studies did

not clearly describe how and for what period researchers followed up with persons who were asymptomatic at the time of testing to ascertain if they ever developed symptoms. Other studies defined “asymptomatic” very narrowly as persons who never developed fever or respiratory symptoms, rather than as those who did not develop any symptoms at all [79, 83]. A recent study from China that clearly and appropriately defined asymptomatic infections, suggests that the proportion of infected people who never developed symptoms was 23% [84].

Multiple studies have shown that people infect others before they themselves became ill [23, 35, 71, 85, 86], which is supported by available viral shedding data (see above). One study on transmission in Singapore reported evidence for 6.4% of all secondary cases suggesting that these resulted from pre-symptomatic transmission[76]. Studies that inferred the date of transmission based on the estimated serial interval and incubation period, estimated that up to 40-80% of transmission may have occurred just before symptoms appeared [63, 87, 88].

It is difficult to study transmission from infected people without symptoms, both pre- or asymptomatic. However, information can be gathered from detailed contact tracing efforts, as well as epidemiologic investigations among cases and contacts. Information from contact tracing efforts reported to the WHO by member states, available transmission studies, and a recent pre-print systematic review, suggest that individuals without symptoms are less likely to transmit the virus than those who develop symptoms [23, 81, 89, 90]. Four individual studies from Brunei, Guangzhou China, Taiwan China, and the Republic of Korea found that between 0% and 2.2% of people with asymptomatic infection infected anyone else, compared to 0.8%-15.4% of people with symptoms [23, 74, 77, 91].

2.8 Remaining questions related to transmission

Many unanswered questions about transmission of SARS-CoV-2 remain; research seeking to answer those questions is ongoing and encouraged. More information on risk factors for transmission can be found in Chapter 4.3. Current evidence suggests that SARS-CoV-2 is primarily transmitted between people via respiratory droplets and direct contact routes, although the role of aerosols and other modes of transmission cannot be quantified yet. Transmission of COVID-19 mostly occurs by people who are presymptomatic or symptomatic to others in close contact¹, when not wearing appropriate PPE. However, transmission can also occur from people who are infected but remain asymptomatic, but the extent to which this occurs in the transmission chain is not fully understood and urgently requires further research on the transmissibility by these people. Currently, [a study from ZonMw](#) is looking into transmission via respiratory droplets. The role and extent of airborne transmission outside of health care facilities, and in particular in close settings with recirculation of air or poor ventilation also requires further study.

¹ Direct physical or face-to-face contact with a probable or confirmed case within one meter and for prolonged periods of time.

As research continues, we expect to gain a better understanding about:

- The relative importance of different transmission routes, including through
 - Droplets;
 - Physical contact, and;
 - Fomites;
- The role of airborne transmission via aerosols, also in the absence of aerosol generating procedures;
- The infectious dose of virus required for transmission to occur;
- The characteristics of people and situations that facilitate superspreading events such as those observed in various closed settings;
- The proportion of infected people who remain asymptomatic throughout the course of their infection;
- The proportion of truly asymptomatic persons who transmit the virus to others;
- The specific factors that drive asymptomatic and pre-symptomatic transmission, and;
- The proportion of all infections that are transmitted from asymptomatic and pre-symptomatic individuals.

3 COVID-19 disease symptoms and pathogenesis

The spectrum of the disease, caused by SARS-CoV-2, officially named COVID-19 on 11 February 2020 [92], is broad in its variety of clinical presentation. The mean incubation period for COVID-19 is 5 (interquartile range 2-7) days [93]. As reported above, asymptomatic infection is thought to occur in 4-41% of infected persons, but the incidence of true asymptomatic infection is yet to be clarified since mild symptoms may go unreported [82]. In a large Chinese cohort analysing the data from the national notification system until February 2020, 81% of symptomatic patients were classified as mild cases, 14% were severe cases and 5% of patients were critically ill, defined by respiratory failure, septic shock and/or multi-organ failure [94].

Respiratory symptoms vary from mild, non-specific complaints through persistent dry cough and breathing difficulties (dyspnoea), to severe pneumonia requiring mechanical ventilation and acute respiratory distress syndrome [8, 67, 95-98]. SARS-CoV-2 replicates both in the upper and lower respiratory tract and has been successfully isolated from the respective samples [1, 67, 96, 98-100]. In hospitalized patients, the most common reported symptoms are fever (up to 90% of patients), dry cough (60%-86%), shortness of breath (53%-80%), fatigue (38%), nausea/vomiting or diarrhoea (15%-39%), and myalgia (15%-44%) [93]. Anosmia and dysgeusia are reported in up to 80% of patients, but as a sole presenting symptoms these occur infrequently (3%) [93]. Gastrointestinal symptoms have been described in COVID-19 cases, which along with fever were some of the clinical signs strongly associated with a positive SARS-CoV-2 RNA test [101]. Viral RNA in gastrointestinal samples has been detected for prolonged periods in both mild and severe cases as well as convalescent patients [67, 97], and the virus was also isolated from stool samples [49, 54], though at this stage the specifics of the gastrointestinal infection are unclear.

Complications occur due to virus-mediated coagulopathy and endothelial damage. Subsequently, arterial and venous thrombosis is common, especially in the ICU thromboembolic events occurred in up to 31-59% of patients in Dutch hospitals [93, 102, 103]. Next to hypoxemic respiratory failure due to viral replication, vascular leakage and an exaggerated host-defence mechanism (referred to as cytokine storm or cytokine release syndrome) in the lungs, other organs may be involved in the systemic infection: myocarditis, cardiomyopathy, encephalitis, acute kidney injury and liver dysfunction [93, 104, 105]. Systemic infection with multi-organ involvement and viremia have also been described for severe cases [95]. SARS-CoV-2 RNA has been detected in other sites, signalling potential for COVID-19 related conjunctivitis [106-108], meningitis [109], Guillain-Barré syndrome [110, 111], and Kawasaki-like disease or multisystem inflammatory syndrome in children [112, 113]. The latter is a described yet rare post-infection disorder (2 in 100,000 persons <21 years) [112]. Due to as of yet unidentified factors, children with COVID-19 display milder symptoms, predominantly limited to the upper respiratory tract, with less than 7% of hospitalized children requiring mechanical ventilation [93, 114].

Patients with any comorbidity have poorer outcomes than those without, and two or more comorbidities are more often seen in severe cases according to a nationwide Chinese study [115]. Comorbidities that are reported frequently in hospitalized patients are diabetes (17-34%), hypertension (48-57%), cardiovascular disease (21-28%), chronic pulmonary disease (4-10%), chronic kidney disease (3-13%) [93], while an age over 65 years coinciding with these conditions increased the likelihood of requiring intensive care [116]. In Dutch elderly people living in nursing homes, COVID-19 symptoms like coughing (65%), fever (70%), shortness of breath (33%), sore throat (10%) and delirium/confusion/drowsiness (28%) linked to COVID-19 were difficult to distinguish from other acute illnesses. Almost half of the confirmed cases from these nursing homes died within 30 days [117].

Non-specific complaints like fatigue and headaches without respiratory symptoms have also been described in COVID-19 cases [49, 106]. The presence of any symptoms was reported by 57% of those testing positive for SARS-CoV-2 RNA in an overall population screening in Iceland, a country with a wide-spread screening and viral sequencing programme [118]. Even in patients who experienced mild symptoms related to the COVID-19 infection in the first period, prolonged fatigue and exercise intolerance for more than 4 weeks after the initial symptoms is reported [119]. An Italian study following up on 143 patients (73% with pneumonia, 13% admitted to ICU) post hospital discharge, reported worsened quality of life in 44% of patients, with symptoms like fatigue (53%), dyspnoea (43%), joint pain (27%) and chest pain (22%) persisting 60 days post illness onset [120]. Anecdotal evidence from the early days of the pandemic both suggest that some patients might experience myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) post-COVID-19 [121], but systematic reviews describing predisposition and outcomes are currently lacking. Data from prior epidemics and other viral diseases (for example influenza, Epstein-Barr virus and infectious mononucleosis, SARS, ebola) also suggest post-viral fatigue or ME/CFS [122-125].

4 Epidemiology of SARS-CoV2 and COVID-19

4.1 Burden of disease

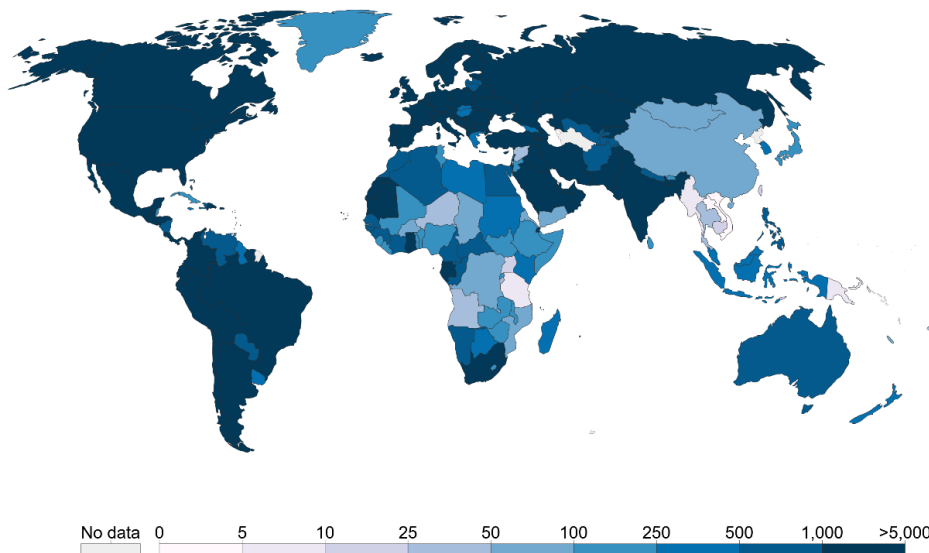
4.1.1 International

The Wuhan Municipal Health Commission of the city Wuhan communicated a cluster of pneumonia cases with unknown aetiology, with a link to a wholesale fish and live animal market, on December 31st, 2019. 10 Days later, the Chinese CDC reported that the causative agent within the cluster is a novel coronavirus. Subsequently, the virus quickly spread across the world and on March 11th, 2020, the WHO declared COVID-19 a global pandemic [126].

As of July 28th, 2020, 16,465,707 cases of COVID-19 have been reported, including 653,862 deaths [127]. Figure 4.1 shows the cumulative number of cases per million inhabitants per country as of July 28th, 2020 [128]. The United States are hit hard with a total of 4.21 million cases, followed by Brazil with 2.42 million cases, and India with 1.48 million cases at July 2020. The top three countries with the most confirmed deaths are the United States (146,331), Brazil (87,004), and the United Kingdom (45,759). The true number of cases and deaths will be higher due to limited testing and allocation of cause of death.

Cumulative confirmed COVID-19 cases per million people, Jul 28, 2020

The number of confirmed cases is lower than the number of actual cases; the main reason for that is limited testing.

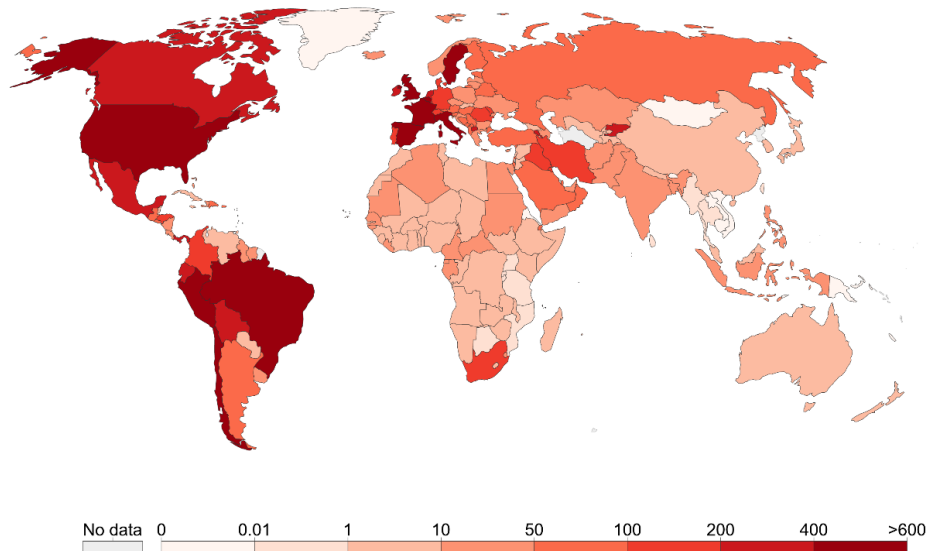


Source: European CDC – Situation Update Worldwide – Last updated 28 July, 11:07 (London time), Official data collated by Our World in Data CC BY

Figure 4.1 Cumulative confirmed COVID-19 cases per million inhabitants, 28 July 2020 [128]

Cumulative confirmed COVID-19 deaths per million people, Jul 28, 2020

Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.



Source: European CDC – Situation Update Worldwide – Last updated 28 July, 11:07 (London time), Our World In Data

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Figure 4.2 Cumulative confirmed COVID-19 deaths per million inhabitants, 28 July 2020 [128]

Within the EU/EEA and the United Kingdom a total of 1,688,757 cases have been reported as of July 28th, 2020, with the highest number of cases in the United Kingdom (300,111), Spain (278,782), and Italy (246,286) [129]. The number of deaths reaches up to 181,707, with the highest numbers in the United Kingdom (45,759), Italy (35,112), and France (30,209). As mentioned before, the true number of cases and deaths will be higher due to limited testing and allocation of cause of death.

4.1.2 *National*

The first COVID-19 case in the Netherlands was reported on February 27th, 2020. As of August 11th, 2020, a total of 59,973 cases have been reported, of which 11,994 were hospitalized and 6,149 died [130]. Again, the true number of cases and deaths are higher than reported. See Table 4.1 for an overview of the changes in testing policy in time. The excess all-cause mortality in the Netherlands was calculated to have been 9,768 deaths in the weeks 10-19 of 2020 (March 2nd - May 10th) [131]. Current number of cases can be found on <https://www.rivm.nl/coronavirus-covid-19/actueel>.

Figure 4.3 shows the number of COVID-19 cases, hospitalizations and deaths up to August 11th (see <https://www.rivm.nl/coronavirus-covid-19> for up-to-date information). The peak in cases was seen between March 24th and April 23rd with 178 cases per 100,000. The highest absolute number of reported cases on one day was on April 10th with 1,396 cases. After declining numbers of COVID-19 cases, a new increase in both numbers and percentage of tested persons positive for SARS-CoV-2 has been observed since early July. The increase was partly caused by the extension of the testing policy (Table 4.1). Nevertheless, the percentage of positive cases among the tested persons was low, around 1% in the first weeks after June 1st. This has increased up to 2.3% in the weeks of July 27th and 3.6% in the week of August 3rd.

Table 4.1 Overview of changes in testing policy

Start date	Who can be tested
27 Feb	<i>First infection was diagnosed</i>
12 Mar	Only persons belonging to a risk groups (aged above 70 years or with underlying medical conditions), persons with severe clinical picture, and health care workers in hospitals. Contact tracing is limited
6 Apr	Health care workers outside hospitals, with symptoms are added
30 Apr	Youth trainers are added
6 May	Educational staff and persons working in child day-care are added
11 May	Persons with professions with close contact to clients are added
18 May	Caregivers, persons working in public transportation, police, enforcers, military police are added
1 Jun	Everyone with symptoms

The peak in hospitalizations was seen on March 27th with 610 new admissions, but the number of hospitalizations has stayed below 25 per day since May 9th and has been below 10 between the end of May and the end of July; the number of hospitalizations has been increased slightly since the beginning of July. The curve of COVID-19 patients admitted to the ICU (Figure 4.4) was similar to the number of hospitalizations (Figure 4.3), although the peak was reached about a week later. The number of deaths peaked at the end of March/beginning of April, followed by a steady decrease and a stabilization since July (Figure 4.3).

4.2 Risk factors for COVID-19

4.2.1 Age and sex

Dutch data

Since the start of the surveillance of COVID-19 in the Netherlands a total of 59,973 cases have tested positive for SARS-CoV-2 (August 11th, 2020). Overall, more women (57%) than men (43%) have been reported to be SARS-CoV-2 positive. The sex distribution of reported cases was more skewed before June 1st (63% women vs. 37% men), when testing was focused on severely ill patients and on health care workers, than after June 1st (54% women vs. 46% men), when everyone with symptoms could be tested. A higher proportion of healthcare workers among female cases than male cases (42% vs. 12%) could explain the large sex difference before June 1st. In addition, differences in testing behaviour and age distribution in the general population between males and females could also influence the sex-distribution in reported cases. In all cases among non-healthcare workers reported on August 11th 2020 (n=41789), hospitalization was higher in men (35%) than in women (20%). Also death was more frequently reported in male cases (16% vs. 13%). In a preliminary analysis, the observed sex difference in hospitalization and mortality could not fully be explained by age and comorbidity, although limited data on comorbidity (excluding smoking and obesity) was available (manuscript in preparation).

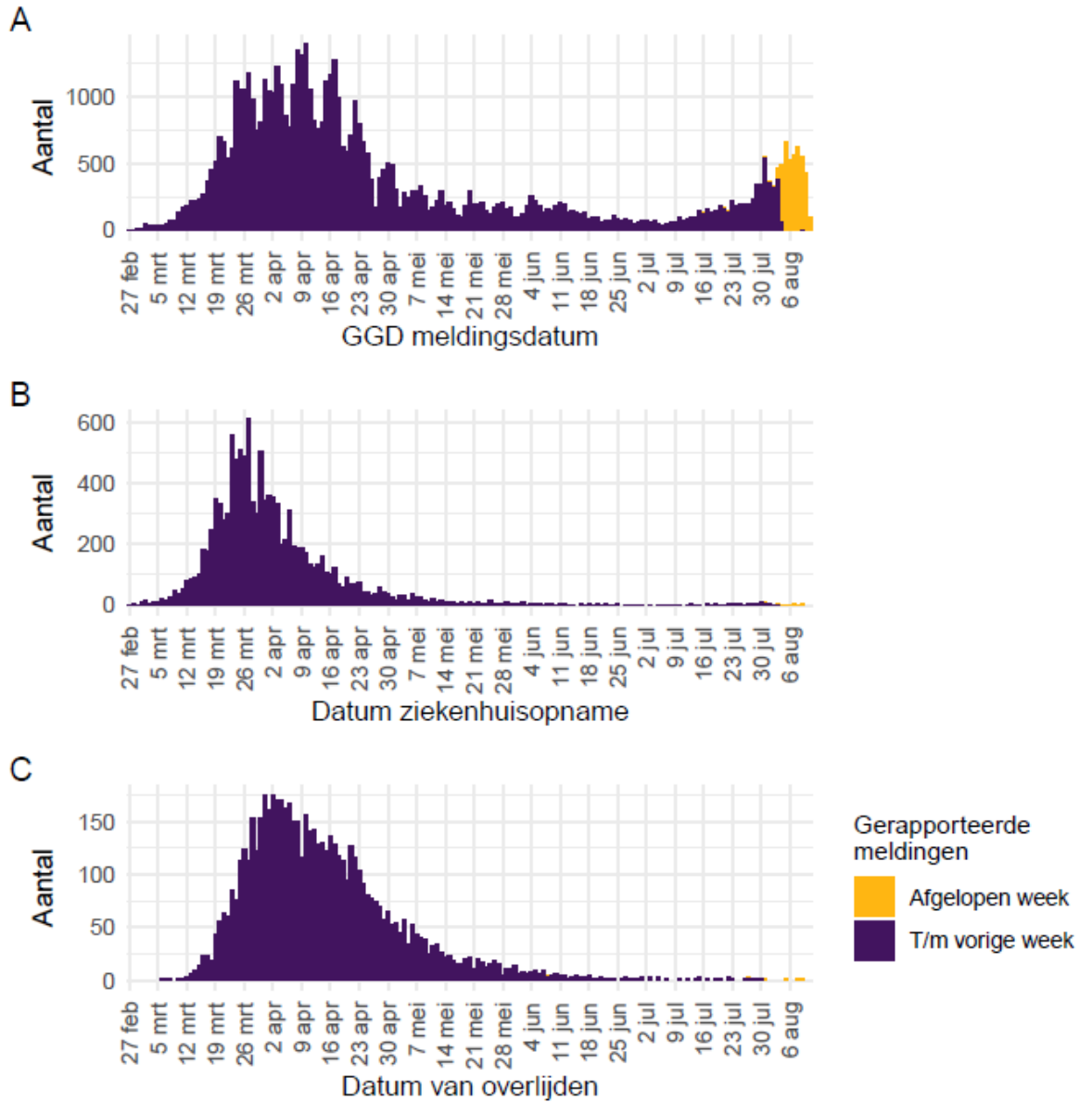


Figure 4.3 Reported COVID-19 cases, the Netherlands, August 11th 2020 [130]

(A) Number of reported COVID-19 cases, according to notification date.
 (B) Number of reported hospitalized COVID-19 cases, according to date of hospitalization.
 (C) Number of reported COVID-19 deaths, according to date of death.

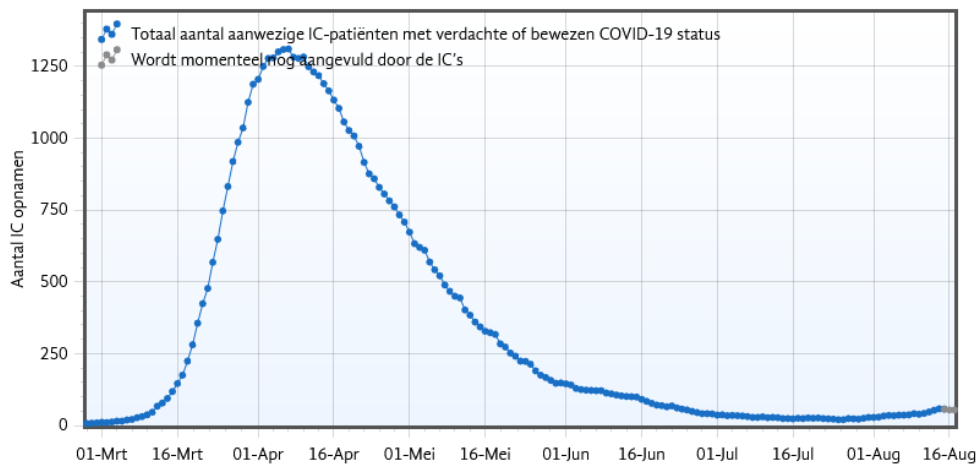


Figure 4.4 Total number of COVID-19 admitted to the ICU, the Netherlands, August 16th 2020 [132]

Due to the testing policy up to June 1st, not everyone was eligible for a SARS-CoV-2 test (see Table 4.1). In absolute numbers, 46,408 COVID-19 cases were reported before June 1st and 17,076 cases between June 1st and August 17th. Before June 1st, the age groups 50-54 (8.7%), 55-59 (9.6%), 80-84 (8.2%), and 85-89 (8.5%) years were the age groups with most cases. After June 1st, the younger age groups 20-24 (14.5%), 25-29 (12.3%), and 30-34 (9.9%) years were the most seen ages among notified cases. In the first period, the incidence of notified cases per 100,000 was highest among persons aged 75 years or older, and only small numbers were seen in children and young adults (Figure 4.5). After June 1st, everyone could be tested. At the moment, the highest incidence of notified cases is seen in young adults.

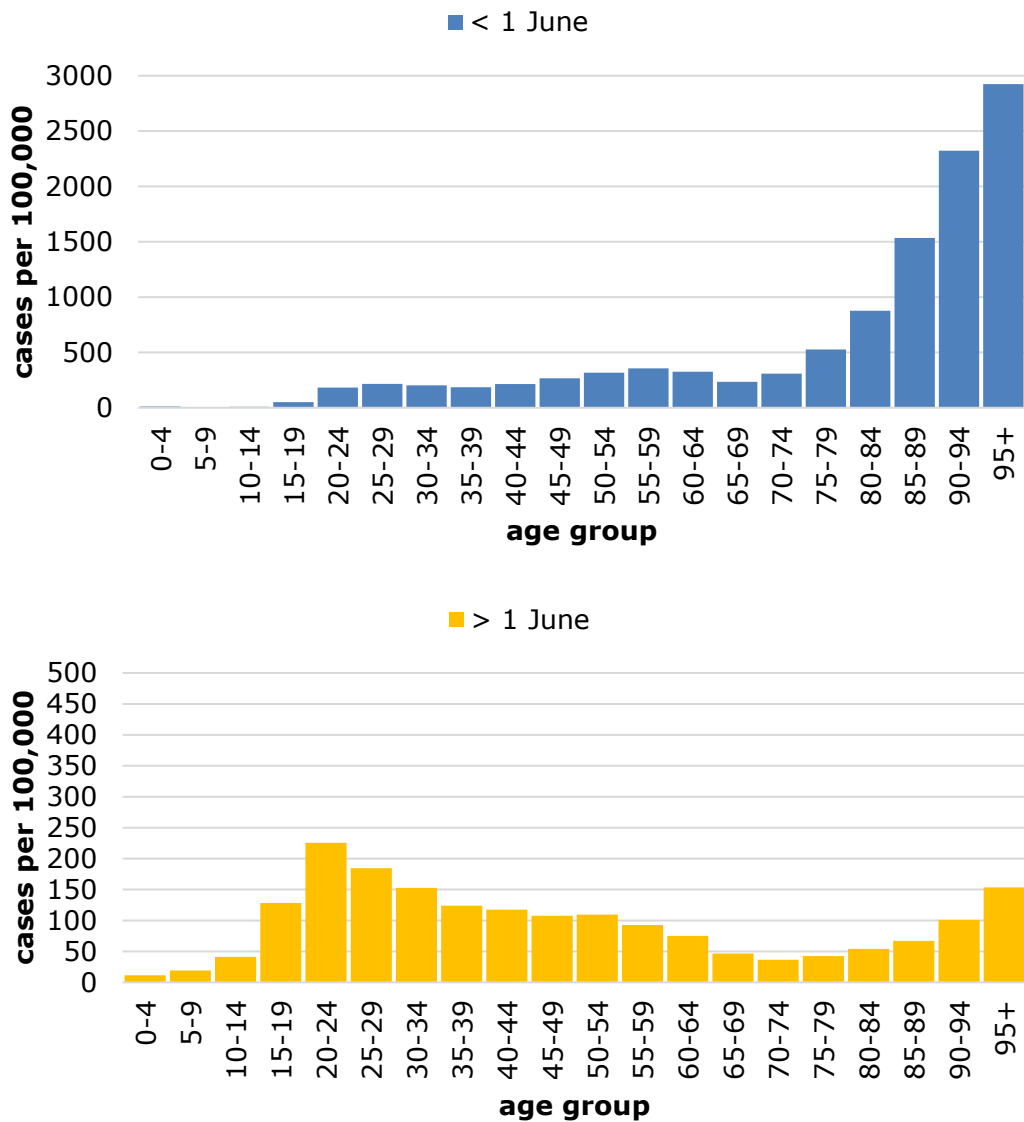


Figure 4.5 Incidence of notified SARS-CoV-2 infections in the Dutch population per age group, before June 1st (blue) and since June 1st (yellow), August 11th 2020

Since June 1st, everyone with symptoms can contact the regional public health agency to be tested for SARS-CoV-2 [133]. This can be on one's own initiative or in the context of contact tracing. Children in the age groups 0-6 and 7-12 years with respiratory symptoms, tested outside contact tracing, tested positive in 0.4-0.5% of the cases, and the 13-18 years old children in 1.6% of the tests (data up to August 11th). Adults with symptoms, not tested because of contact tracing and not noted as health care worker, educational staff/day-care, caregiver, or having a profession with direct contact with clients on the test form, tested positive in 1.5% of cases.

Half of the 11,994 COVID-19 cases that were hospitalized were aged 69 years or older. Of all reported COVID-19 positive cases, more than half of the reported cases in the age group 65-74 (53-55%) were hospitalized, followed by 47% in the age category 75-79 years, 32% in 80-84 years, and 31% in the youngest age group 0-4 years old children. The decrease in percentage hospitalizations with increase of age in the elderly is caused by the refer policy where the vulnerable elderly were less referred to a hospital [134]. The reported COVID-19 cases were in general hospitalized within 5-8 days after symptom onset, with exception of the youngest (0-4 years) and the oldest (85+ years) who were often hospitalized earlier. Around three quarter of the 2,894 cases who were admitted to the ICU were aged between 55 and 80 years [135]. The mean time spend on the ICU-ward was 20 days. 72% Of the ICU-cases was male, 77% were overweight (BMI>25), and around 20% had underlying diseases, such as chronic lung conditions.

Of the 6,149 cases who died, half were 83 years or older. Around 41% of the cases died in hospital, mostly after being hospitalized for 6-8 days. The case fatality rate is 0.0-0.1% up to the age group of 30-34 years and then increases to above 10% for the age group of 70-74 years, and up to 47% in the 95+ age group.

Literature

Acquiring infection

Results on the age and sex distribution of acquiring SARS-CoV-2 infection depends very much on policy and testing strategy. For infection acquisition, data from population screening are most informative to assess the distribution of SARS-CoV-2 in the population. In Iceland, population screening of active infection through PCR was performed in March/April 2020 and was open to all residents of Iceland who were either symptom-free or had mild symptoms [118]. Of all 13,080 participants tested, 100 tested positive for SARS-CoV-2 (0.8%). Persons who tested positive were on average older and more often male, with the lowest positivity rate in children <10 years (0%) and the highest in persons 40-50 years (1.4%). In the municipality of Vo', Italy, two population surveys were performed at the beginning of the lockdown at the end of February 2020 and at the end of the two-weeks lockdown at March 7th 2020 [136]. The prevalence of infection, measured by PCR, was 2.6% (73/2812) and 1.2% (29/2343) on the first and second survey respectively; note that during the second survey only eight new cases were found. No infections were detected in children from 0 to 10 years. The prevalence increased with age with the highest prevalence

among 70-80 year olds. The infection prevalence was higher in males than females (3.1% vs 2.1% in the first survey).

Studies generally show that children are less likely to acquire SARS-CoV-2 infection compared with adults. However, this is less apparent for secondary school aged children than for younger children [118, 136, 137].

Severe disease

The RIVM made a literature overview on risk factors for severe COVID-19 disease including 21 multicentre studies with >100 hospitalized patients and 6 studies on ICU patients [138]. Increasing age and male sex were more prevalent among patients admitted at the ICU and deceased patients compared with other hospitalized patients. This was in line with other several published meta-analyses. Also in most studies performing multivariable analyses, increasing age and male sex were independent risk factors for severe disease.

The Norwegian Institute of Public Health (NIPH) published a rapid review in May 2020 on risk factors for severe disease due to COVID-19 and included only results from multivariable analyses and studies with >400 participants [139]. This review concluded that increasing age stands out as the predominant individual risk factor for hospitalization, severe disease, and death due to COVID-19. Male sex also appears to be associated with increased risk, but results were more mixed.

Public Health England published a descriptive review of their surveillance data on risks and outcomes of COVID-19 in June 2020 [140]. These data showed that the risk of dying was much higher in people of older age and also higher in males than females. These analyses took into account socio-economic deprivation, region, and ethnicity, but not comorbidity, which is likely to explain some of the differences in outcomes.

A recently published article assessed risk factors associated with COVID-19 death by linking data from primary care records of 17 million adults in England to around 11,000 COVID-19 related deaths [141]. Male sex and older age were strong independent risk factors for death when adjusting for smoking, deprivation, obesity, and comorbidities.

Literature indicates that infections in children are generally milder than in adults [137]. Deaths in children have only been reported sporadically; mostly these are teenagers. Several countries reported a possible association between COVID-19 and a multisystem inflammatory syndrome in children (PIMS: paediatric inflammatory multisystem syndrome or like Kawasaki-like disease). A rapid risk assessment of ECDC (May 15th, 2020) described that about 230 suspected cases of PIMPS linked to SARS-CoV-2 have been reported in EU/EEA countries and the UK including two fatalities [142]. Based on available data, the association cannot be confirmed as of yet but seems plausible. The COPP study is a national registration study into COVID-19 in children who present at a hospital in the Netherlands (<https://www.covidkids.nl/>). Up to September 1st 2020, 36 children have been reported to this study of which 20% had an inflammatory syndrome.

4.2.2 *Pregnancy*

Dutch data

Up to April 10th, 150 pregnant women have been reported having COVID-19 of whom 38 were hospitalized. No deaths among pregnant women (data up to August 11th) were reported.

Literature

Several systematic reviews have been published on COVID-19 and pregnancy [143-148]. Also a multidisciplinary working group initiated by FMS (Federatie Medisch Specialisten) and the NVOG (Nederlandse Vereniging voor Obstetrie en Gynaecologie) have made recommendations based on the available literature [149]. These show that there are currently limited good-quality data about pregnancy outcome and COVID-19. Based on these limited data, there is currently no evidence that pregnant women themselves are at increased risk of acquiring SARS-CoV-2 infection or of severe disease following SARS-CoV-2 infection. There is currently also no evidence of an increased risk of adverse pregnancy outcomes in women with COVID-19. The risk of vertical transmission (transmission from mother to child during pregnancy or delivery) is considered low but cannot completely be ruled out. A very recent systematic review (published on 1 September 2020) including 77 studies however concluded that pregnant and recently pregnant women are potentially more likely to need intensive care treatment for COVID-19 than non-pregnant women of reproductive age, and that preterm birth rates are higher in pregnant women with COVID-19 than in pregnant women without the disease [150].

4.2.3 *Comorbidities*

Dutch data

Comorbidities of all reported cases were registered until April 10th 2020. Of the 23,072 registered cases, 51% had one or more underlying diseases (including pregnancies), 31% had no comorbidities, and for 19% comorbidity data was unknown. Of the hospitalized cases, 65% had underlying diseases, 22% had none, and for 13% comorbidity was unknown. In both total cases and hospitalized cases, cardiovascular diseases/hypertension was the most common underlying condition (48% and 52% respectively), followed by chronic lung conditions (25% and 27%) and diabetes (21% and 24%). Chronic neurological/neuromuscular diseases, malignancy, kidney diseases, immune deficiency, and liver diseases were mentioned in 1-11% of the cases with comorbidities.

A total of 70% of the cases under the age of 70 who died due to COVID-19 (data up to August 11th) had one or more underlying diseases, 10% had no reported comorbidities and for 20% this was unknown. Cardiovascular diseases/hypertension were the most reported underlying condition (43%), followed by diabetes (26%), and chronic lung conditions (24%). Malignancy and chronic neurological/neuromuscular diseases were both reported in around 15% of the deceased cases with comorbidities. Other diseases reported, in 1-10% of these cases, were kidney diseases, obesity, dementia/Alzheimer's disease, liver diseases, immune deficiency, and Parkinson disease. Of these, obesity, dementia/Alzheimer's disease, and Parkinson disease were not added to the standard asked comorbidities until April 11th, and thus were underestimated.

Literature

Risk of infection in case of comorbidity

There are limited data available on whether comorbidities are associated with acquiring infection. The population-based screening study in the municipality of Vo', Italy, showed no significant association between common comorbidities such as diabetes, hypertension, vascular disease and respiratory diseases and SARS-CoV-2 infection [136].

A study on risk factors for SARS-CoV-2 infections within a primary care network in the UK included 3802 tested individuals who attended the GP because of clinical symptoms of COVID-19, of which 587 (15%) tested positive [151]. There was no significant association between a positive tests and chronic conditions in multivariable analyses, except for chronic kidney disease. Increasing age, male sex, deprivation and obesity were independent risk factors for testing positive in this primary care cohort.

Severe disease

The RIVM literature overview on risk factors for COVID-19 showed that hypertension, diabetes, obesity, cardiovascular disease and lung disease were more prevalent in patients admitted at the ICU and deceased patients than in other hospitalized patients [138]. Studies using multivariable analyses could not always confirm these comorbidities as independent risk factors. For other diseases like cancer, renal disease, liver disease and immune deficiencies, no consistent association with severe COVID-19 disease was found.

The rapid review from the NIPH including only studies with multivariable analyses found that obesity and comorbidities appeared to be associated with increased risk of severe disease [139].

The study of Williamson et al. that linked primary care records of 17 million adults in England to approximately 11,000 COVID-19 related deaths found several comorbidities, including obesity, diabetes, severe asthma, respiratory disease, chronic heart disease, liver disease, stroke/dementia, other neurological diseases, reduced kidney function, autoimmune diseases and other immunosuppressive conditions to be independent risk factors for death [141].

4.2.4 *Socioeconomic status and ethnicity*

Dutch data

Recently, the 4 large cities have been particularly affected. Preliminary analyses by the municipal health services show large variation between neighbourhoods, suggesting that high rates of COVID-19 might be related to neighbourhood deprivation (personal communication). In the area of the regional public health agency GGD Rotterdam-Rijnmond, percentages of positive tests are available on district level. Figure 4.6 shows these percentages per district for June and July. Districts A up to D are neighbourhoods with overall a low socioeconomic status, as well as district E, but in this neighbourhood many students live as well. In general, the percentage of positive tests is higher in the districts A-E than in the other districts.

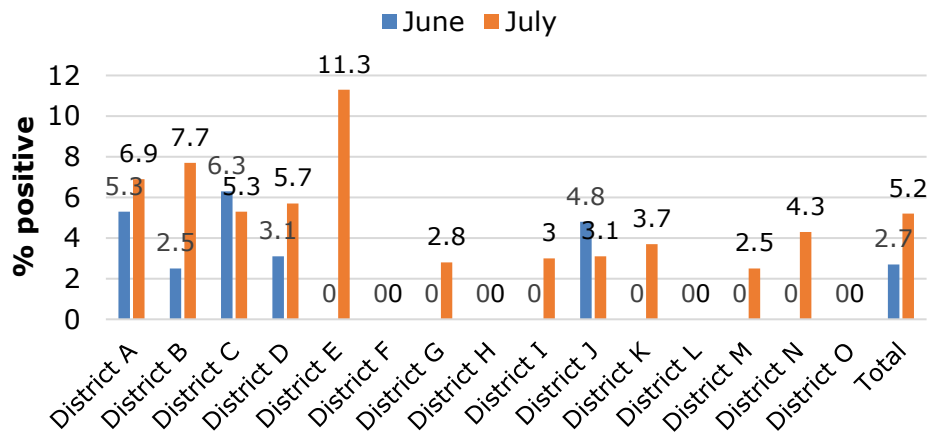


Figure 4.6 Percentages of positive COVID-19 tests in the different districts in the Rotterdam-Rijnmond area in June and July

Districts A-E are socio economic deprived neighbourhoods, district E also houses many students. Districts with less than 10 positive tests are not included.

Literature

The NIPH published a rapid literature review in June 2020 on social and economic vulnerable group during the COVID-19 pandemic [152]. Based on seven studies they suggest that low income, poverty, living in socio economic deprived areas and certain ethnic backgrounds are associated with an increased risk of COVID-19 related death compared to the general population.

Public Health England reported based on their surveillance data that people who live in deprived areas have higher diagnosis and death rates than those living in less deprived areas [140]. High diagnosis rates may be due to crowded living circumstances with geographic proximity to infections or a high proportion of workers in occupations leading to higher risk of exposure. Poor outcomes from COVID-19 infection in deprived areas remained after adjusting for age, sex, region and ethnicity, but the role of comorbidities requires further investigation. The same data from England showed that people from Black ethnic groups had the highest age standardised diagnose rates of COVID-19, and death rates from COVID-19 were highest among people of Black and Asian ethnic groups. Also after accounting for sex, age, deprivation and region, several ethnic groups had a higher risk of death from COVID-19 than White British people, although these analyses did not account for occupation and comorbidities which could explain part of the difference in risk of death.

4.2.5 Health care workers

Dutch data

A total of 18,046 health care workers have been reported with COVID-19 (data up to August 11th). Health care workers may have contracted the virus outside their work, as data about source of infection are not (always) available. This profession group represents 45% of the reported cases in the age group 18-69 years, caused by the testing policy up to 1 June. 539 (3%) of the reported health care workers were hospitalized, which is 9% of the hospitalizations in the age group 18-69 years. Thirteen health care workers (0.07%) died, all in the age between 40 and 69 years.

Since June 1st up to August 11th, 56,558 health care workers called their regional public health agency with symptoms and were tested; 0.9% was positive.

Literature

Health care workers could have a higher risk of acquiring SARS-CoV-2 infection because of their higher risk of exposure to a COVID-19 patient. However, the actual risk depends on the availability of protective equipment and protocols and adherence to these measures. Also detection of COVID-19 within health care workers is dependent on testing availability and prioritization of testing health care workers. A study in the UK and US estimated that frontline health care workers had a 3.4 fold higher risk than people living in the general community for reporting a positive test, after adjusting for the likelihood of receiving a test [153, 154]. Health care workers who reported reuse or inadequate use of personal protective equipment had a higher risk for a positive test compared with health care workers reporting adequate personal protective equipment.

The protection offered by good personal protective equipment in COVID-19 patient care was confirmed in a study from Wuhan which performed PCR and antibody testing in 420 'relief team' doctors and nurses who came from outside Wuhan [155]. None of them developed COVID-19. It should be noted that these teams were housed in dedicated hotels, transported in dedicated shuttles and ate meals brought to their rooms.

A living systematic review on epidemiology of and risk factors for infection in health care workers reported a prevalence of COVID-19 ranging from 1-23%, a prevalence of SARS-CoV-2 infection ranging from 0.4-50% and SARS-CoV-2 antibodies ranging from 2-24% [156-158]. SARS-CoV-2 infection seemed to be less severe in health care workers than in non-health care workers. Risk factors for infection were working in a high risk versus general department and suboptimal or improper use of personal protective measures.

4.2.6

Other professions

Dutch data

Since 1 June, everyone with symptoms can be tested at the regional public health agency. Up to August 11th, 224 of 40,129 (0.6%) of teaching staff and people working at day-care centres tested positive as well as 1255 of 86,747 (1.4%) persons with a profession with close contact to clients like hair dressers.

Also, clusters in the meat processing industry and the industry processing fruit, vegetables or fish, have been reported with relatively large numbers of affected employees (mainly labour migrants). These clusters were characterized by low viral loads and often absence of symptoms. Furthermore, SARS-CoV-2 has been detected in employees of mink farms as well as in the minks within those farms.

Literature

Public Health England reports that significantly higher rates of death from COVID-19 were reported in men working as security guards, taxi drivers and chauffeurs, bus and coach drivers, chefs, sales and retail

assistants, lower skilled workers in construction and processing plants, and men and women working in social care [140]. For many occupations, however, the number of deaths is too small to draw meaningful conclusions and further analysis will be required, though increased exposure is a likely explanation.

The ECDC published an overview of clusters of COVID-19 in different occupational settings as reported by EU/EEA countries and the UK (in total 16 countries reporting 1,376 clusters) [159]. Besides hospitals (241 clusters) and long-term care facilities (591 clusters), food packaging and processing industries reported most clusters (n=153), followed by factory/manufacturing settings (77 clusters) and offices (65 clusters).

The US report COVID-19 cases in 115 meat and poultry processing facilities with almost 5,000 cases [160]. They conclude that difficulties with workplace physical distancing and hygiene, and crowded living and transportation conditions potentially affect the risk for infection.

4.2.7 *Summary*

The data from the Netherlands and (inter)national literature show similar findings on risk factors for (severe) COVID-19. Increasing age and male sex are clearly risk factors for severe COVID-19 and also several comorbidities seem to be independent risk factors for severe COVID-19. Young children seem to be less likely to acquire SARS-CoV-2 infection compared with adults. Pregnancy may be a risk factor for severe COVID-19. Vertical transmission can occur but does not seem to be a large problem at this moment. There are indications that socioeconomic status and ethnicity are associated with an increased risk of SARS-CoV-2 infection. Several professions have been associated with an increased risk of SARS-CoV-2 infection, including health care workers (although this increased risk is dependent on the level of protective equipment) and workers in the (food) industry or factories.

4.3 **Risk factors for transmission**

4.3.1 *Dutch data*

Close contact and household transmission

4,464 household contacts of lab-confirmed cases were tested in a period of five weeks (week numbers 26-30, 2020) of which 13% (range per week: 9-18%) tested positive. This percentage is higher than the 5% (range per week: 3-7%) positives within 6,914 other close contacts of cases. Definitions of close contacts can be found in [133].

Transmission by age

Based on the national surveillance data up to May 11th, 732 transmission pairs were identified [137]. Transmission seemed to mainly occur between persons of similar age. In the period between March 23rd and April 16th, 54 households were included in a cohort study investigating transmission within the household. A positive health care worker was the index in 80% of the 54 households. A total of 174 family members were included of whom 67 adults and 107 children (1-16 years). On the inclusion day (day 1), 10% of the 19 and 16% of the 44 children aged 1-5 and 6-11 years, respectively, had a PCR-positive nose-throat swab

compared to 34% of the teenagers (n=44; 12-17 years), 28% of 18-45 years old (n=36) and 42% of the adults older than 45 years (n=31). Serology on day 1 was positive in 0% of the 1-11 year old, 9% of the 12-17 years old, 11% of the 18-45 years old and 19% of the aged 46+. Two to three weeks later, another 29 participants had seroconverted increasing the positivity rates. Lowest percentages were seen in the 6-11 years (13%; 4/31) and the 1-5 years (21%; 3/14) old. The percentages in the age groups 12-17 years (12/38) and 18-45 years (11/35) were comparable with 32% and 31%; highest percentage, 43%, was seen in the oldest age group (13/30). It should be noted that this study was performed during the partial lock down and school and day care closure, so the first identified cases were likely to be adult and a health care worker because of the testing policy. Currently, the epidemiological situation is closely monitored [161].

Transmission in health care settings

Setting is only reported for cases who indicate that there are related cases. Between May 4th and August 11th, the setting was reported for 9,540 (49%) of the cases. More than one setting can be reported per case. Several different types of health care have been registered as setting, of which nursing homes is the most commonly reported with 1,879 cases (20% of all cases with a reported setting), followed by residential care centres for the elderly (5%). Hospitals and other health care (not including general practices) are both mentioned as settings in 3% and 1% of the cases, respectively. General practitioners, other residential care centres, medical day-care and hospices are each mentioned in less than 1% of the settings.

Transmission in other settings

For most cases reporting related patients (data up to August 11th) household was mentioned as the most common setting of related cases (45%), followed by work (15%) and other family contacts (16%). The catering industry was added to the settings on July 1st, and was reported in 1.6% of the settings, and in 3.7% of the reported settings of the most recent week (4-11 August). Other settings were leisure activities (e.g. sports), school/day-care, church/religion related settings, fellow travellers and choirs. These were reported 1-81 times, representing 0.01-0.8% of the settings.

Transmission of SARS-CoV-2 in the meat processing industry and the industry processing fruit, vegetables or fish, could probably occur as a result of social circumstances, such as living and transportation circumstances of labour migrants, and the physical conditions of the work spaces, such as low temperature in combination with high humidity.

Besides the registration of settings for notified cases, the RIVM also asks regional public health agencies to report clusters. It is meant to get an overview of the settings in which clusters occur, including the number of related cases, and detect new settings or changes in settings.

4.3.2

*Literature***Close contact and household transmission**

Contact to a COVID-19 case is obviously a risk factor for transmission. Secondary attack rates highly depend on type of contact, setting and age. Close (unprotected) contact gives a higher risk than casual contact, as was shown in an outbreak investigation among 539 contacts of 7 cases in Zhejiang province in China [162]. The secondary attack rate was 29% among close contacts and 0.6% for casual contacts. Another study, in Taiwan, included 100 confirmed cases and 2,761 close contacts [77]. All 22 secondary cases were exposed to the index case within 5 days of symptom onset (attack rate 22/1,818: 1.0%). Household and non-household family contacts showed the highest attack rates with 4.6% and 5.3% respectively. Multiple studies have found higher secondary attack rates among household contacts versus non-household (close) contacts [17, 163-165], with secondary attack rates in households ranging from 10-17% and in non-household contacts from 0.5-7% (Table 4.2).

Table 4.2 Summary of four studies reporting secondary attack rates in household and non-household contacts

First author	Country	N index cases	N contacts	Secondary attack rate	
				Household	Non-household
Jing	China	215	2098	17%	7%
Park	South Korea	5706	59,073	12%	2%
Burke	US	10	445	10%	0.5%
Bi	China	391	1286	11%	1%

Transmission by age

A recent review (not peer-reviewed) assessed the age distribution of SARS-CoV-2 infection in contacts of COVID-19 cases [166]. Based on 10 studies that presented secondary attack rates by age groups, the authors concluded that there is evidence that susceptibility to infection in children under the age of 10 years is significantly lower compared to adults and that susceptibility to infection in older adults (over 60 years) is higher compared to younger/middle-age adults. Furthermore, they stated that there is limited evidence in the literature on age-related differences in infectivity. However, the limited data suggest that infectivity in children (particularly those aged <10 years) is somewhat lower than in teenagers and young/middle aged adults, while infectivity in older adults is somewhat higher compared to young/middle aged adults, which is also supported by studies of viral load and shedding.

Transmission in hospitals

As mentioned before, the risk of infection in health care workers and also nosocomial infection is dependent on preventive measures taken. Three studies that reported on infection in health care contacts (patients and workers) of confirmed cases found low secondary attack rates (0-5%) [17, 167, 168]. A study from the Netherlands in two hospitals in Noord-Brabant showed that 86 of 1353 health care workers who reported symptoms were positive for SARS-CoV-2 [169]. Only 3 positive health care workers (3%) reported having been exposed to an inpatient with COVID-19 before symptom onset. A study in three Dutch hospitals analysed genome sequences from 50 health care workers and 10 patients [170]. The genomic data were consistent with multiple

introductions into the hospitals through community-acquired infections and local amplification in the community. The authors concluded that although direct transmission in the hospitals could not be ruled out, their data did not support widespread nosocomial transmission as the source of infection in patients or health-care workers.

Transmission in elderly care

During the pandemic it became clear that nursing homes and elderly care facilities across Europe as well as worldwide have been severely affected by COVID-19 [153]. High morbidity and mortality in residents have been observed. In several EU countries, deaths among residents have accounted for over half of all COVID-19-related deaths [171]. Reasons for rapid and widespread transmission of SARS-CoV-2 in nursing homes may have included: 1) the difficulty of recognizing COVID-19, as typical symptoms may already be present or elderly may have non-specific or atypical symptoms; 2) high infectivity in the pre-symptomatic phase of the illness and a high prevalence of asymptomatic residents in this setting. This was shown in an outbreak investigation carried out in four nursing homes in London [172]. In this study, 40% of residents were positive for SARS-CoV-2; of these 43% were asymptomatic and 18% had only atypical symptoms. Also 4% of asymptomatic staff tested positive. In Belgium, 142,100 residents and 138,327 staff of long-term facilities were tested; 3.8% of the residents and 2.1% of the staff tested positive [173]. The symptom status at the time of testing was registered: 74.0% of the staff who tested positive hadn't reported symptoms as well as 75.3% of the residents. Also a limited testing policy and limited availability of tests and of personal protective equipment in the early phase of the pandemic likely contributed to widespread transmission in nursing homes.

Transmission in other settings

A review on what settings have been linked to SARS-CoV-2 clusters including both available literature and media reports, found clusters in a wide range of mostly indoor settings [33]. Many reports were for households and an increasing number were reported in elderly care settings across Europe. Also a relatively high number of events were reported in bar/restaurant settings, religious settings and work settings.

In a US study, 364 COVID-19 patients, who were diagnosed before implementation of stay-at-home orders, were asked about possible exposure to SARS-CoV-2 [174]. Among 265 participants without known contact with a laboratory-confirmed COVID-19 patient, the most commonly reported activities in the two weeks before symptom onset were attending gatherings of >10 persons (44%), traveling domestically (29%), working in a health care setting (28%), visiting a health care setting (23%) and using public transportation (22%).

4.4 SARS-CoV-2 population immunity

In most countries, the true number of SARS-CoV-2 infections are vastly underestimated due to (restrictive) testing policies as well as the high proportion of mild and asymptomatic infections that are not included in the case findings mostly. Therefore, populations-based serosurveys, measuring the levels of (IgG) antibodies targeted against specific viral

antigens indicating previous infection, can better estimate the true extent of the spread of the virus and its disease burden (e.g., assessing the infection-fatality ratio)[175-177]. Serology assays with high sensitivity and particularly high specificity (i.e., approaching near 100%) are vital given the low infection prevalence in this phase of the pandemic. Rigorous assay validation using pre-pandemic sera as well as a wide-range of PCR-confirmed COVID-19 cases (in terms of severity) are necessary to prevent false-positive and false-negative results from confounding the seroprevalence estimates. In addition, in assessing the true rate of infections, it should be noted that IgG antibodies are detected median 14 days after symptom onset, may be delayed in milder and asymptomatic cases, or even remain undetectable in a small subset of the latter, and possibly might wane below limits of seroconversion over time [70, 178-180].

Various seroprevalence studies are ongoing worldwide. Most of those published cover COVID-19 hotspots, specific regions, and/or have included specific subpopulations (e.g., only adults, healthy donors, healthcare workers, or used residual sera), such as in the US, China, Switzerland, Germany, Brazil, Italy, and the Netherlands, and were mainly performed between March and June, 2020 [181-190]. Up to date, large community-representative/nationwide population-based serosurveys are scarce. Two large studies from Brazil and Spain became available recently, and more will follow [191, 192]. The overall seroprevalence presented in the available studies range from below 1 to 11%, with highly affected regions, e.g., cities in Northern Brazil (Amazon), New York City, Geneva and Madrid, displaying the highest rates (hence, usually urban/rural differences). Sex differences were not observed and seroprevalence mostly was lowest in children. Dissimilarities between people from different ethnic backgrounds were also reported in some studies, and reflects the higher rates of confirmed COVID-19 cases and related deaths in ethnic minorities, e.g., in the US [193] and Brazil [194] and elsewhere [195]. The key overall finding from these studies is that the larger part of the population is suggested to be unexposed to the virus, i.e., did not show evidence of infection given the rather low seroprevalence, despite the healthcare system having been overwhelmed with severely ill patients.

In the Netherlands, the RIVM initiated a prospective nationwide population-based seroepidemiological study to be able to continuously monitor the spread of SARS-CoV-2 and assess risk factors for seropositivity over the course of the epidemic. The PIENTER-study [196], a serosurvey from 2016/17 primarily aimed to measure the protection against vaccine-preventable diseases, served as a baseline cohort for this PIENTER-Corona-study (PICO-study). In the first round of the PICO-study (PICO1) over 3,200 participants across the Netherlands donated a blood sample and filled out a questionnaire regarding risk factors in the beginning of April, 2020. PICO1 revealed that 2.8% (95% confidence interval 2.0 – 3.7) of the Dutch population had antibodies against SARS-CoV-2 (*paper under review*, [197]). No sex differences or dissimilarities between persons from various ethnic backgrounds were observed. Regional variations – equal to the number of cases, hospitalizations and deaths as reported by the RIVM [198] – were detected, with the Northern region having the lowest seroprevalence

(1.3%) and the other regions ranging between 2.7-4.0%. In line with the serosurveys abroad, seroprevalence was lowest in children (below 18 years of age), gradually increasing from 1% in 2 year-olds to 3% in 17 year-olds. Children seem to be less affected by the virus [199]. Highest estimates were seen in adults, particularly those aged 18-39 years (4.9%), which may be explained by increased social behaviour typical for this age, in addition to specific social activities in February, 2020 (skiing holidays, carnival festivities, etc.). Similar findings were reported by the Dutch blood donor study by Sanquin [185]. Additionally, PICO1 identified that persons taking immunosuppressants and those from the Orthodox-Reformed Protestant community had substantial higher odds of being seropositive as compared to others (both groups over four times). Moreover, anosmia/ageusia was the most discriminative symptom between seropositive and seronegative participants, and antibody concentrations were significantly higher in those with more severe symptoms (fever and dyspnoea). Preliminary analyses from PICO2 (covering PICO1 participants as well as an additional sample of approximately 4,500 persons throughout the Netherlands), conducted mid-June, 2020, show overall seroprevalence was 4.1% (95% CI 3.4-4.9) in PICO2 (June, 2020), and did not differ between sexes and ethnic background. Seropositivity was low in primary-school-aged children (slowly increasing from 0 to 2%, in line with previous estimates in April, 2020), however increased linearly in adolescents and peaked at around 10% in young adults (i.e., those in their early twenties). From there, seroprevalence decreased steeply to levels around 3% in persons 35 years of age and remain stable between 3-4% up till age 90 years. Further analyses are pending and additional PICO surveys will be performed, the next one in September 2020.

Taken together, detection of IgG antibodies does not necessarily correlate with immunity and protection from secondary infection, but provides information on previous exposure. Also, the fact that some recent studies [70, 200] showed that (neutralizing) antibodies tend to wane over time – as observed for circulating human non-SARS-CoV2-coronaviruses [201] – does not imply loss of immunity per se since other immune functions, such as cellular immunity, could confer protection. Like humoral immunity, infection probably results in T cell responses in the majority of people. There is evidence that this may also occur in the absence of detectable antibodies [202-206]. Still, the absence of antibodies might have important implications considering the durability of vaccine protection. Furthermore, since a small proportion of asymptomatic/mild cases had low antibody concentration or did not seem to seroconvert [70], true exposure rate might be slightly underestimated.

5 Immunological knowledge on SARS-COV2 infection

5.1 Immune responses to SARS-CoV-2

SARS-CoV-2 is a beta coronavirus, containing one of the largest genomes among RNA viruses (see also Chapter 1). The 5'-terminal two-thirds of the genome contains two open reading frames (ORFs) encoding two polyproteins, that are processed into 16 non-structural proteins (NSPs) [6, 7]. The 3'-one third of the genome encodes a series of structural proteins, including the Spike (S) glycoprotein, Envelope (E), Membrane (M) and Nucleocapsid (N) proteins as well as several smaller ORFs [207]. As seen for other enveloped viruses, the exposed and abundantly expressed structural SARS-CoV-2 S, E, and N proteins, internal to the envelope, are dominant human B-cell antigens after natural infection [64, 208-210]. Also expectedly, CD4+ and CD8+ T cell reactivity has been found against many peptide specificities of the SARS-CoV-2 structural and non-structural ORFs', not only S and N [202, 207, 211-215]. In this chapter, we discuss antibodies primarily directed against the Spike protein of SARS-CoV-2. Antibodies to the Spike protein that prevent the RBD from the protein from attaching to the ACE2 receptor on human cells have been shown protective in animal models [216, 217]. Spike protein epitopes are the antigen mostly applied in antibody detection assays.

A virus infection results in the induction of virus specific antibodies, neutralizing antibodies bind to the virus thus preventing infection of host cells with the virus. In addition the virus induces T cell responses. T-helper cells promote virus specific antibody production by B-cells and cytotoxic T cells reduce disease severity by killing virus infected host cells. The majority of immunological data for human immunity to SARS-CoV-2 is based on the development of specific serum antibodies to the S-protein after infection with SARS-CoV-2, although an increasing amount of studies now also report on the induction of helper T cells and virus-specific killer cells [202, 207, 211, 218-220] (see also Chapter 6). The detection of antibodies to SARS-CoV-2 might be an approach, to assess previous exposure to, and infection with SARS-CoV-2 and to assess seropositivity in the population [176, 179, 208, 221-225]. Multiple commercial assays to detect antibodies to SARS-CoV-2 are available that require little sample volume and include high-throughput multiplex immunoassays aimed at providing accurate estimations of the levels of immunity in the population [188, 192, 225]. The majority of assays detect antibodies to Spike subunit S1 or the Receptor Binding Domain (RBD). RBD directly interacts with the ACE2 receptor on human cells leading to infections. The detection of antibodies is a straightforward approach compared to cellular analysis of blood samples, which is more complex to conduct. In addition, at this stage, antibody-mediated neutralization of SARS-CoV-2 is proposed as the best benchmark to evaluate protective immunity, followed by assessment of numbers of SARS-CoV-2 virus-specific T cell response [217, 219, 226, 227].

A limitation is that not every person infected with SARS-CoV-2 develops sufficient anti SARS-CoV-2 antibody levels to be detected by available assays, partly related to the lower sensitivity of some of the applied immunoassays. However, another part of infected persons may not develop any antibodies at all, which is a remarkable observation. In particular this may be the case in children that have been exposed to the virus without developing disease [228]. It is not clear how, in the absence of the development of a humoral immune response, resistance to the virus occurs in these persons., A possibility is that resistance occurs through pro-inflammatory action as part of the innate immune response.

Like humoral immunity, infection probably results in T cell responses in the majority of people. There is evidence that that this may also occur in the absence of detectable antibodies [202-206]. In contrast to the positive correlation between the magnitude of antibody responses and an increased disease severity, the quantity of T cell responses may not be related to humoral antibody response titres, there may even be a negative correlation [229]. Consequently, antibody-based and T cell based assays are complementary in understanding immunity to SARS-CoV-2. This is e.g. confirmed in a small house-hold study showing evidence of cellular responses in the absence of evidence for the presence of antibodies [213].

In short, although determining the presence and level of antibodies is an efficient way to assess previous exposure to SARS-CoV-2, more research is needed to understand which cellular and humoral immune parameters confer protection against a novel infection (see also Chapter 6). In this context, the recent observations of the presence of pre-existing memory T cells from SARS recovered patients in 2003, which are cross-reactive with SARS-CoV-2, are of importance. They show that specific memory T cells generated in the past after human betacoronavirus infections, and possibly also from exposures to other 'common cold' corona viruses, may very well shape the susceptibility to, and clinical severity of, subsequent infections with SARS-CoV-2 [202, 207, 220].

The next paragraphs focus on antibody-mediated immunity, because current immunity data are primarily based on detection of SARS-CoV-2 specific antibodies and the Spike protein in particular as the most commonly used means to assess exposure in the population and degree of immunity. Levels and qualities of SARS-CoV-2 specific antibodies are therefore likely key endpoints and biomarkers for future immune assays and the evaluation of future vaccines.

5.2 Humoral immune protection against (severe) disease, immune pathogenesis

A primary criterium to assess the quality of immunity is the ability to prevent (severe) disease. At this stage, it is not known what concentration of antibodies associate with protection against disease in the majority of the population. The virus neutralizing capacity of antibodies has been associated with reduced virulence and viral shedding, this was less consistent during the acute phase of the disease [230-232]. Likewise, a correlation of virus neutralizing antibodies and

protection against both viral replication and disease has been established in nonhuman primate challenge models [233-236] and smaller animal models [216].

During the recovery phase, all Ig isotypes (IgA, IgM, IgG) can be detected in blood, all of which were shown to contribute to virus neutralization [190, 208, 221, 222, 230, 232, 237]. During the convalescent phase, antibodies are much more dominated by the IgG and IgA isotype, but which concentration of virus-neutralizing antibodies correlate with immune protection and its duration, needs to be established. Moreover, virus neutralization assays are technically demanding and require better standardization to compare results between different laboratories. There is also a need for a better understanding of the interaction between the receptor binding domain (RBD) of the spike protein of SARS-CoV-2 and other regions within the protein involved in host-cell interaction via the host receptor like ACE2 and genetic changes occurring in the virus (see also Chapter 6). Despite all these challenges, the presence of neutralizing antibodies in a person likely limits infection of host cells and thereby replication of the virus. The viral load likely contributes to disease progression, whereas the inflammatory response in COVID-19 contributes to the severity of disease. Therefore, limitation of viral load, even partial limitation of viral load, may reduce the pathological inflammation and cytokine storm observed in severe COVID-19. Promising results were obtained in patients who received convalescent plasma resulting in the reduction of viral load and improvement in their condition. This seemed to correlate positively with the concentration of antibodies, further supporting the hypothesis that antibodies could confer protection against SARS-CoV-2 [217, 226].

In severe COVID-19, SARS-CoV-2 can be detected in the blood of patients, not only indicating that the respiratory and gastro intestinal tract barrier function failed, it also likely increases the risk for complications. Although further research is needed to investigate this, the presence of neutralizing antibodies in serum may control systemic viral replication as it will block entry of the virus into new host cells. The downside could be that virus-antibody complexes may contribute the inflammation and cellular pathology, or antibody-mediated enhancement of disease (ADE), which has been documented for SARS [238-244]. ADE modulates the immune response and can elicit sustained inflammation, lymphopenia, and/or cytokine storm, one or all of which have been documented in severe cases and deaths. ADE also requires prior exposure to similar antigenic epitopes. To reduce the possibility of ADE to emerge, it has been suggested – in simple terms – that the virus neutralizing capacity of antibodies should outweigh the possible immunopathological effects of non-neutralizing antibodies that could be implicated in these phenomena. The implications of these findings are extremely important in COVID-19 vaccine development and the approach to optimise for safety and efficacy [245, 246].

5.3 Immune protection against (recurrent) infection and transmission

Infections with coronaviruses, including the new SARS-CoV-2, are not expected to induce lifelong immunity. In fact infection may re-occur already within several months after the first episode, as has been demonstrated on the basis of a detection of the virus in diagnostic specimens again, and by seroconversion [201, 247-249]. However, such recurrent infections, especially at such short notice during the current pandemic, are not expected to run a severe clinical course, in fact such infections are currently typed as very mild or even asymptomatic, and viral loads (based on PCR and culture) appear to be low. There are therefore also less likely contributing to new transmission.

The lower viral load and disease symptoms are expected to be related to the presence of immune memory, capable of providing a rapid secondary immune response to this recurrent infection and considered instrumental in rapid clearance of the virus, thereby reducing clinical severity and most likely also transmissibility. As exemplified for other respiratory virus infections like RSV, recurrent infections have been frequently described, even in the presence of high concentrations of antibodies. Such reinfections often occur in the absence of clinical symptoms, probably due to the fact that serum antibodies are also observed in the mucosal lung fluid of the respiratory tract and titres between serum and mucosal fluid correlate well. This indicates that humans may benefit from recurrent infections as a way to generate a more mature and sustained antibody response over time, characterized by IgG antibodies against SARS-CoV-2 of high avidity and functionality. Similarly, while (repeated) coronavirus infections may not provide sterile protection from SARS-CoV-2 re-infection, pre-existing immunity could provide sufficient protection against development of (severe) disease. Recent studies in rhesus macaques and small animal models confirm this protection by antibodies against secondary infections with SARS-CoV-2, and subsequent antibody boosting [216, 233]. Most recently, for the first time in humans the presence of neutralizing antibodies from prior SARS-CoV-2 infection were shown be associated with protection against re-infection [250]. This highlights the capacity to build up protective immunity but also the possible need for repeat application of future vaccines against COVID-19 to provide a more robust immunity, cellular and humoral, as described in Chapter 6.

How specific immune responses regulate virus transmission is largely unknown at this stage, though we know a negative correlation between the presence of virus neutralizing antibodies and viral shedding [231], and the ability of antibodies on mucosal surfaces to limit the ability of viral particles to infect cells via receptors. There are currently only few studies, but the presence of specific IgA antibodies against SARS-CoV-2 in saliva specimens is observed and also that these IgA antibodies have been associated with early virus neutralization [237, 251]. Neutralizing antibodies that prevent the interaction of the receptor binding domain (RBD) to receptors on human cells like the ACE2 receptor, are expected to prevent infection of host cells most effectively, likely to also limit the transmission from person to person. In addition, specific T cells of the helper phenotype as well as killer cells are expected to control viral

loads, especially during secondary immune response development. The viral load is strongly associated with the risk of virus transmission to other persons. In addition to immunity and immune-mediated reduction of viral load and neutralization of RBD, the clinical symptoms of the infected person leading to e.g. coughing and sneezing are important parameters. Consequently, children with a similar viral load compared to adults, may be less infective for other persons because of the absence of disease symptoms like coughing and sneezing and therefore less secretion of viral particles in droplets and aerosols.

5.4 Antibody dynamics, including waning

Following infection, specific serum antibodies against SARS-CoV-2 can be detected within 1-3 weeks. Recently, multiple reports on this topic have emerged, as outlined in paragraph 1.2, including published data from the RIVM which indicate that the level of antibodies produced in COVID-19 patients increases with increasing disease severity [197, 225]. In some COVID-19 cases, antibodies are observed within the first week of disease onset, whereas in other COVID-19 cases this could take over 2 weeks [178]. This is in part also related to symptomatic disease onset which varies from 2 days up to 10 days post initial exposure to the virus. The vast majority of COVID-19 patients with either moderate or severe disease, generate antibodies, but with a different kinetic profile and magnitude than observed in an often younger and healthier general population. In a general population setting the majority of persons exposed to the virus will develop mild symptoms, with a more delayed development of anti SARS-CoV-2 antibodies when compared to more severely diseased persons, but antibodies may also remain undetectable in blood serum. Also, SARS-CoV-2 antibody levels were shown to decline within months after primary infection, which phenomenon has been documented before for coronavirus infections in general [70, 200, 201, 252]. From preliminary data from the RIVM population survey (PICO2) and from longitudinal studies in COVID-19 patients, not all antibodies decay rapidly, and some higher avidity antibodies may persist longer, as currently suggested in the referred preprint studies (unpublished data), with remaining protective capacity. While this decline does not necessarily reflect the loss of functional (immune) protection (see also section 5.1), this decline will inevitably affect the analysis of the prevalence of anti SARS-CoV-2 antibodies in a large population survey (see also section 4.1).

6 Potential COVID-19 protective mechanism relevant for vaccines

Vaccine development against acute viral infections often focuses on recapitulating the type of protective immune response elicited by natural infection. However, at this point in time it is still unclear what immune response is required for protection against SARS-CoV-2 infection and against COVID-19 disease. Since SARS-CoV-2 is a new virus, insights into its complex interactions with the host and host responses of the innate and adaptive immune system have only emerged over the last six months. However, based on data from SARS-CoV-1 patients in 2003-2004 [253, 254], and based on the fact that over 95% of individuals infected with SARS-CoV-2 recover, convalescent immunity almost certainly comprises adaptive immune responses by specific B-cells, CD4+ T cells and CD8+ T cells, together resolving the infection [255]. These naturally acquired adaptive immune responses should therefore ideally be targeted by COVID-19 vaccines. Yet, it is becoming clear that natural infection is associated with a wide spectrum of immune manifestations, from undetectable, weak and significant responses to immunopathology like highly inflammatory responses and cytokine storms [256]. Many still to be established factors may play a role in this heterogeneity, including host-related factors such as age, genetics, sex, pre-existing immunity and the whole exposome [220, 241, 257, 258], as well as viral factors such as SARS-CoV-2 load and production of virulence factors that modulate early sensing of pathogen and danger signals by host innate immune cells [203, 241, 259]. Moreover, whether SARS-CoV-2 infections are good inducers of sustained protective immunological memory responses or are poor inducers, as was found for other human coronaviruses [201, 260], remains to be seen. These uncertainties warrant management of expectations when translating the current knowledge on the heterogeneous host immune responses to SARS-CoV-2 into the design of safe, efficacious COVID-19 vaccines.

6.1 Hallmarks of adaptive mechanisms of protection

Even though correlates of acquired protection against subsequent SARS-CoV-2 infections are unknown to date, based on earlier SARS-CoV and MERS-CoV models, it can be assumed that responses by all three adaptive lymphocyte classes, B-cells, CD4+ helper T cells and CD8+ cytotoxic T cells, are required for protection against SARS-CoV-2, as reviewed [259]. B cells mediate humoral immunity, especially by producing neutralizing antibodies preventing free virions from entering cells, while CD4+ T-helper and CD8+ cytotoxic T cells convey cell-mediated immunity, capable of clearing infected cells.

Safe and efficacious COVID-19 vaccines should therefore contain instructions for the immune system to mount effective adaptive B- and T cell responses together, associated with durable memory immunity while potential unwanted immune pathology or immune enhancement (see Chapter 5). The effectiveness of vaccine responses depends on two hallmarks: which and how many clonal B- and T cell specificities participate in the response and how well these clonal populations have

expanded and have acquired a function fit for purpose, i.e. preventing or clearing a future SARS-CoV-2 infection. *Antigen specificity* and *function* are therefore two crucial hallmarks of acquired vaccine responses and both are steered by the design of a vaccine. As outlined more fundamentally below, the antigen content and delivery of a vaccine drives the *specificity and breadth* of the adaptive immune response, whereas additional molecular cargo of the vaccine triggers non-specific innate immune factors and a cytokine milieu supporting *functional* maturation of the virus specific adaptive immune cells involved.

6.2 Antigen specificity; B and T cell receptor repertoires

The adaptive immune system generates an infinitely large number repertoire of different naïve B-and T cell clones, each expressing a unique B or T cell receptor molecule on their cell surface that may be capable of recognizing a particular foreign antigen, e.g. a viral antigen. Each naïve clone just contains a small number of cells. Structurally and functionally B and T cell receptors differ and represent complementary antigen detection systems, which is relevant for the working mechanisms of vaccines [261]. B-cell receptors are in fact membrane-attached Y-shaped antibody molecules, recognizing exposed native conformations on foreign antigens. Examples of antigens detected by B-cells are bacterial toxins secreted by micro-organisms or viral proteins decorating the outer surface of a virus particle, like the Spike protein as discussed in Chapter 5. What is actually recognized by B-cell receptors are smaller parts or subdomains of an antigen, so-called epitopes, that are linear peptide sequences or a conformational structure, e.g. an epitope in the RBD of the Spike protein. Antigens usually encode multiple epitopes and each epitope can potentially be recognized by multiple different B-cell clones in the naïve repertoire.

T cell receptors on the other hand recognize antigens indirectly, when they are proteolytically degraded inside antigen presenting cells and then exposed at the cell surface of these cells as small peptide fragments presented in the binding groove of so-called MHC molecules. There is a subtle but crucial difference between the source of antigens recognized by the two classes of T cells, CD4+ helper T cells or CD8+ cytotoxic T cells [262]. This is due to different classes of MHC molecules engaging with CD4+ or CD8 T cells, respectively, and the different processing pathways these MHC classes follow when picking up their antigen fragments. Typically, peptides presented to CD4+ T cells are derived from exogenous antigens, taken up by antigen presenting cells from their extracellular milieu and degraded in endo-lysosomal compartments into antigen fragments and then loaded on MHC molecules and presented at the cell surface. Alternatively, peptides presented to CD8+ T cells are derived from proteins that are internally produced by antigen presenting cells themselves and are then cytosolically degraded into fragments which are loaded on MHC molecules in the secretory pathway and presented at the cell surface. These pathways in principle, ensure broad tissue control and antigen detection by T cells in case of virus-infections. Which particular peptide fragments of an antigen are presented by MHC molecules is ruled by binding motifs, which are different for the large number of allelic MHC variants that exist in the population. So each individual will mount a T

cell response to each antigen but, depending on the inherited MHC molecules, with different T cell clones to different sets of presented peptides. Yet, whether both CD4+ and CD8+ T cells will take part in a response depends on the localization of the antigens. While CD4+ T cell responses are more ubiquitous because there will always be antigens available outside antigen presenting cells, responses of CD8+ T cells require antigens to be localized in the cytosol. This is typically the situation when e.g. viral messenger RNA transcripts are being translated in the cytosol of virally infected cells.

As eluded to in Chapter 5.1, dominant B-cell antigens of SARS-CoV-2 are the abundantly exposed structural native envelope proteins S, E, and N [66, 208, 220, 221] while CD4+ and CD8+ T cell reactivity, expectedly, can be found against many processed peptide epitopes of both SARS-CoV-2 structural and non-structural open reading frames (ORFs') [192, 219, 222-226].

With this B- and T cell biology in mind, to design an effective COVID-19 vaccine the overall antigen content is important, as it determines specificity and breadth of B- and T cell responses. Narrow antigen and epitope coverage may determine the risk of secondary vaccine failure through immune escape if antigen variants or knock-outs may arise. Yet also the formula of the antigen is important. Vaccines delivering antigens as 'exogenous whole' antigens may only be capable of mounting good B-cell and CD4+ T cell responses. Vaccines delivering the genetic code allowing intracellular production or delivery of antigens may mount CD8+ T cell responses as well.

6.3 Functional B and T cell responses: outgrowth, functional maturation and maintenance of selected clones

Naïve B or T cell repertoires may be able to tackle any foreign antigen or antigen fragment, but have no means to defend the body. This requires expansion of individual B or T cell clones into larger cell populations, followed by a process of functional maturation. This leads to the acquisition of new properties important for effector function, fitness and homing of B and T cells. This 'learning' process takes days to weeks and starts when naïve B or T cells are activated by their antigen, which alters their gene expression program [263]. How this program is altered and which functions are acquired is instructed by 'programming' signals received from the innate immune system. Such innate immune signals are triggered by host-pathogen interactions during natural infection, but in case of vaccination molecular cargo in the vaccine takes over this particular task. Functional maturation of antigen-specific B cells, including avidity maturation as referred to in Chapter 5, is a process taking place in typical lymphoid organ structures and requires help from specific CD4+ T cells, and implies various processes [261]. First, per responding B cell clone, the grip on the antigen by the B-cell receptor can be improved by ongoing DNA editing at the gene level. This optimizes the 'head' of the membrane-attached Y shaped antibody molecule, the variable antigen binding domain. Also, the constant 'tail' domain of the Y shaped molecule can switch from one particular functional class to another, such as from IgM to IgG or IgA, or it can become decorated by certain sugar molecules. Once this affinity

maturation and class switch of the antibody molecules have taken place, B-cells will start producing large quantities of their B-cell receptor molecules and secrete them as soluble antibodies. These are the basis of humoral anti-pathogen immunity via a variety of mechanisms. Depending on the affinity of their 'head' and the form of their 'tail', functions can include direct neutralization of a pathogen, prevention of adhesion of the pathogen to, or entry into cells, or, after interaction with receptors for the antibody tail domains on innate effector cells, opsonophagocytosis and killing of pathogen by phagocytes or antibody-dependent cellular cytotoxicity by NK cells [263]. Another part of the B-cells develops into memory B-cells, having the same 'head' and 'tail' maturation but keeping the B-cell receptor as a membrane-bound molecule. Memory B-cells have self-renewal potential, home to particular tissues and can rapidly expand and mature into antibody secreting plasma cells when encountering antigen later in life again. Similarly, when activated by their specific MHC-presented peptide epitope on antigen presenting cells, naïve CD4+ T cells or CD8+ T cells start changing their gene expression profile leading to clonal expansion, acquisition of effector function and memory [261]. This process is again dictated by the innate response to the surrounding circumstances. CD4+ T cells may differentiate into one of a variety of helper T cell lineages, so-called Th1, Th2, Th17, Tfh or Treg cells, producing different sets of effector cytokines. Which Th type dominates the response depends on the inflammatory conditions created during the infection or vaccination. CD4+ T cells helper functions are important for the maturation of B-cell and CD8+ T cell responses and for regulation of immunity. CD8+ T cells acquire cytotoxic effector function consisting of the capacity to release granules containing enzymes and cytokines toxic for the recognized antigen presenting cell. Like memory B-cells, memory CD4+ and CD8+ T cells have self-renewal capacity, acquire a particular homing preference and respond rapidly and effectively when encountering their specific antigen later in life again.

Natural infections with SARS-CoV-2 have been shown to drive functional maturation of B and T cell immunity. The development of class-switched, neutralizing antibodies to Spike protein (section 5.2) implies ongoing affinity and functional maturation of antibody 'heads' and 'tails'. To learn more about these specific antibody responses, a multitude of serological platforms are being set up rapidly, including dedicated tests to assess functional properties [263]. Also, maturation of CD4+ and CD8+ T cells has been found in patients with mild and severe COVID-19 [202, 212]. Current T cell test platforms are even more diverse and still under construction, to learn more about dominance of SARS-CoV-2 antigens and epitopes and functional hallmarks. The data indicate variable outcomes, with a slight dominance of Th1 differentiation, being regarded the 'more protective type, over Th2 differentiation, an issue that is key to understanding the potential role of T cell responses in immunopathology during disease, as well as to inform vaccine design and evaluation.

6.4 Requirements of COVID-19 vaccines to instruct effective B and T cell immunity

From the above it can be concluded that the effectiveness of a COVID-19 vaccine will relate to its antigenic content and molecular composition, together programming i) the breadth of antigen specificities, ii) the adaptive immune arms involved (B cell, CD4+ T cells, and or CD8+ T cells), and iii) the functional maturation and memory formation of the B and T cell clones. It is likely that memory from all three adaptive cell types to a broader antigen repertoire would contribute to a more effective protection from a new acute infection. The most favourable Th-type has been suggested to be Th1 helper T cell immunity, as the opposite Th2-type has been associated with suboptimal functional maturation of antibody responses and even antibody dependent enhancement of disease (see also section 5.2)[264]. Other features likely playing a role in the effectiveness or duration of the immunological protection are iv) properties of memory immunity to home to the respiratory mucosae and v) self-renewal capacity of memory B and T cell populations. It is known e.g. for other respiratory pathogens that local presence of functional antibodies at the respiratory mucosae, the 'port d'entrée' of the pathogen (see also section 5.3), as well as tissue residency of the memory B- and T cells in the upper or lower respiratory tract are crucial for effective rapid clearance of a challenge dose of a pathogen [265, 266].

In conclusion, vaccines targeting a broader SARS-CoV-2 antigen profile and steering a more optimal type, localisation and duration of adaptive response can be expected to confer a higher degree of immune protection. It is therefore difficult to speak about 'a' correlate of protection. Moreover this term needs careful definition of whether it concerns protection from infection, disease, or virus transmission. To predict protection from infection (sterile immunity), a high maintained neutralising antibody level and/or rapid memory B-cell response to SARS-CoV-2 Spike protein, inhibiting its binding to the host receptor ACE2, might be a good biomarker. This presumption was recently supported by a study describing an COVID-19 outbreak on a fishing vessel [250]. Notably, such antibody response requires CD4+ T cell help as well. To predict protection from disease or transmission, in case of leaky antibody immunity and virus production to some extent, it is likely that the presence of CD8+ T cell responses, to any of the dominant SARS-CoV-2 antigens, could be a proxy.

6.5 Reproduction number in the Netherlands

The vaccination coverage required to stop the transmission of SARS-CoV-2 depends on the reproduction number R , that signifies the number of secondary infections caused by one infectious person. When R is larger than one, the epidemic will grow, and when R is smaller than one the epidemic will die out. The basic reproduction number R_0 is the reproduction number in a fully susceptible population without any interventions. At the start of the epidemic, when no interventions were implemented, immunity was non-existent and no interventions were implemented, the basic reproduction number was estimated to be 2.2 – 4.7 [267-273], mainly based on outbreak data of China.

In the Netherlands the reproduction number was around 2 at the start of the epidemic, and declined when interventions such as increased hygiene and physical distancing were implemented in the beginning of March (Figure 6.1). Since May, after the first wave, physical distancing measures have slowly been relaxed (which could increase R) combined with more rigorous testing and contact tracing (which could reduce R). Current information can be found on <https://www.rivm.nl/coronavirus-covid-19/actueel>. When introducing vaccination, it should be taken into account that some physical distancing measures and the test and trace regime could be maintained, thereby lowering the reproduction number and thus the critical vaccination coverage.

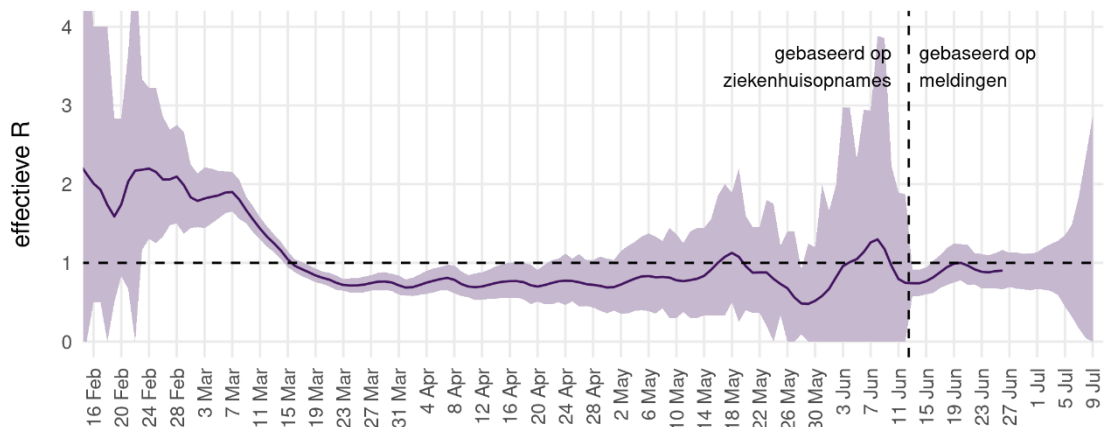


Figure 6.1 Effective reproduction number R in the Netherlands, estimated from reported hospital admissions (up to June 12th) and reported positive SARS-CoV-2 tests (from June 12th onwards). Point estimate (solid purple line) and 95% confidence interval (shaded purple area). Based on Osiris data of July 10th.

6.6 Control effort

In a population where everyone mixes at random, the required level of immune persons to achieve herd protection is $(1-1/R_0) \times 100\%$. For the estimated value of the reproduction number of COVID-19 in the Netherlands of approximately 2, this amounts to 50 % of the population being immune.

In the actual population, persons do not mix at random. They tend to make more contact with people who live in the same household, and with peers who are of a similar age. Accounting for these contacts, patterns tend to lower the level of immunes at which herd protection is achieved [274]. The actual percentage of immune persons in the population that is required to achieve herd protection may therefore be less than the 60% calculated above, and depends on the distribution of contact patterns within the population.

6.7 Stratification of the population by age, age-specific mixing

The Dutch population is a typically ageing population, where the youngest age groups are not the largest. The fraction of 50-59 year-olds is larger than any of the other 10-year age groups (Figure 6.2).

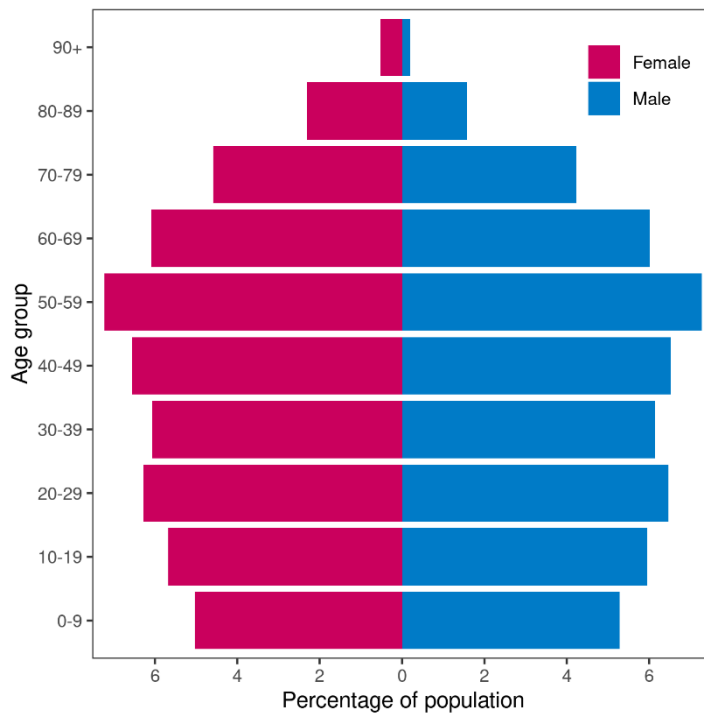


Figure 6.2 Population of the Netherlands on 1 January 2019, stratified by sex and 10-year age groups [237]

For virus transmission, it is also important to know the contact rate between persons of similar age as well as between different age groups. Conversational contacts have proven to be a good proxy for transmitting respiratory infections [275], and this type of contact can be easily measured using contact diary studies. Between February 2016 and October 2017, a cross-sectional study was conducted in a sample of the Dutch population from 0 to 89 years of age [196]. The study consisted of an extensive questionnaire, and included questions regarding the participants' age, sex and occupation, the age and sex of their household members, and the total number of unique persons they had contacted outside their household the previous day. This study was repeated in March – April 2020 after physical distancing measures were implemented as part of the PICO-study.

Comparison of the results of both studies reveals some similarities as well as differences. In both studies, the contacts are mainly age-assortative, i.e. people tend to mix mainly with people of the same age. In households however, many intergenerational contacts are observed between parents and children (not shown here). Physical distancing has decreased the number of contacts a person makes in the community from on average 12.5 (interquartile range: 2-17) to 3.7 (interquartile range: 0-4), a reduction of 71% (Figure 6.3) [276]. Preliminary results of a follow-up contact survey conducted after physical distancing measures were relaxed in June 2020 suggest that the number of contacts have increased but remain under precorona levels.

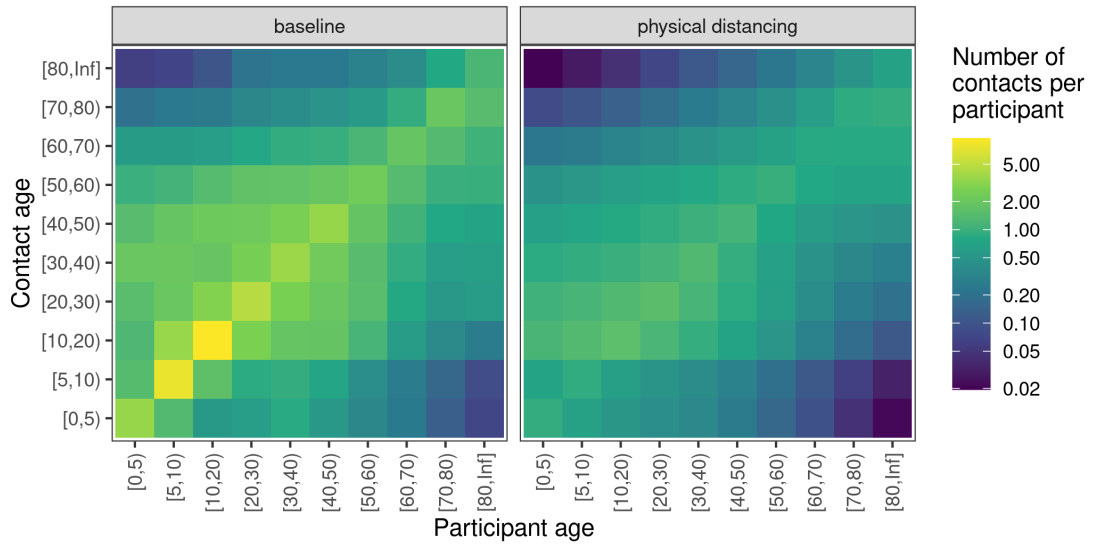


Figure 6.3 Contact pattern of age-specific mixing for the baseline (measured 2016/2017) and under physical distancing (measured March/April 2020)

6.8 Number of healthcare workers

According to Statistics Netherlands, the number of people working in the healthcare sector in 2019 was 1.26 million [277]. A stratification of the number of workers by branch is shown in Table 6.1. However, not all these workers necessarily have close contacts to patients, as these numbers also include overhead jobs that may well be performed from home. When it would be assumed that 15% of the workers have overhead jobs, the number of workers eligible for vaccination would decrease to 1.07 million.

Table 6.1 Number of people working in the healthcare sector by branch in 2019

Sector	Number of workers
Hospital	301,000
Mental healthcare services	100,000
General practitioner- and health centres	48,000
Nursing homes, residential care and home care	384,000
Disability care services	157,000
Youth care services	35,000
Social care	60,000
Other ¹	174,000
Total	1,259,000

¹ Practices of dentists, dental specialist, midwives, physiotherapists, other paramedical practices and alternative healers, working conditions guidance and reintegration, preventive healthcare and medical laboratories, thrombosis services and other treatment support, ambulance services and healthcare cooperation services.

6.9 Number of individuals at increased risk of severe COVID-19

The RIVM website reports that all adults aged ≥ 70 years and adults aged 18-69 year with certain chronic medical conditions (for instance, people with respiratory, cardiovascular, liver, or kidney diseases, diabetes, immune disorders, and obesity) are at increased risk of complications following COVID-19 infection [278]. To estimate the population size of the clinical risk groups, estimates of people indicated for influenza vaccination could be used, considering there is substantial overlap between these populations. Table 6.2 shows an overview of the population at risk of COVID-19 complications according to the RIVM website and the population indicated for influenza vaccination according to the advice of the Health council of the Netherlands [279]. Compared to influenza vaccination indications, the COVID-19 clinical risk groups for are based on a higher minimum age for being at risk regardless of a chronic medical condition (70 years versus 60 years), includes morbidly obese people, and excludes children with chronic diseases or specific medication use, people with intellectual disability, and those living in a nursing home but not falling under the other categories. Furthermore, clinical COVID-19 high-risk groups seem restricted to people with a worse disease status compared to an indication for influenza vaccination, for instance listing only poorly controlled diabetes patients or diabetes patients with complications, and respiratory ill patients that are under treatment of a pulmonologist.

Table 6.3 shows the population sizes at risk of complications from COVID-19. Using population data of 2019, there are 2.3 million people aged 70 years or older. According to the NIVEL registration data of 2018 [280], 26% of the people aged 18-59 years and 31% of the people aged 60-64 years had an indication for influenza vaccination due to a chronic illness. Applying this 31% risk rate also to the age-group 65-69 years, a total of 3.1 million people aged 18-69 years are at risk of COVID-19-related complications due to chronic illnesses. The RIVM website does not provide a definition of very high weight, but Public Health England and the US Centers for Disease Control and Prevention report a Body Mass Index (BMI) of 40 or higher as being high risk from COVID-19. In the Netherlands, 0.9% of the people aged 20-64 years were reported to be morbidly obese in 2017 [281]. Given that morbidly obese people also more often have chronic illnesses compared with non-obese people, a significant overlap between chronic ill people and obese people is expected. In 2012, 8% of the obese people (BMI ≥ 30) aged 12 years or older had a cardiovascular disease and 13% had diabetes type 2, and 35% high blood pressure [282]. When we conservatively assume that 50% of the morbidly obese people (BMI ≥ 40) already have an indication for influenza vaccination (twice as high as in the general adult population), the number of additional people at increased risk of COVID-19 complications is 52,000. The total number of people at increased risk of COVID-19 related complications would then be 5.44 million.

Table 6.2 Clinical risk groups for complications from COVID-19 infection according to the RIVM website and people indicated for influenza vaccination according to the advice of the Health Council of the Netherlands

Risk of complications from COVID-19 [278]	Indication for influenza vaccination [279]
People aged 70 years and older	People over 60 years
Adults ¹ with chronic respiratory or lung problems who are under the treatment of a pulmonologist.	People with lung diseases and respiratory diseases, such as asthma, chronic bronchitis, or emphysema
Adults ¹ with chronic heart patients who are therefore eligible for a flu shot.	People with heart diseases, such as people who have had a heart attack, people who have heart complaints such as cardiac arrhythmias, or people who have had heart surgery
Adults ¹ with diabetes that is poorly controlled by medication and/or with complications.	People with diabetes; not only people who inject insulin, but also people who take tablets with blood sugar lowering medicines or who follow a diabetes diet.
Adults ¹ with kidney disease who need to undergo dialysis or wait for a kidney transplant.	People with kidney disease; especially if the kidneys are not working properly due to an illness (i.e. not because of kidney stones).
Adults ¹ with reduced resistance to infections because they take medicines for an autoimmune disease, and people who have had an organ or stem cell transplant. People who do not have a spleen or a spleen that is not functioning, and people who have a blood disease. People with reduced resistance because they take resistance-reducing medicines. Cancer patients during or within three months after chemotherapy and/or radiation. People with severe immune disorders for which they need treatment from a doctor.	People with little resistance due to other diseases or medical treatment; for example, people who have recently had a bone marrow transplant, people who have had their spleen removed (asplenia), people with an autoimmune disease with reduced resistance, people with leukaemia (blood cancer), and people who undergo chemotherapy or radiation.
Adults ¹ with HIV infection who are not (yet) being treated by a doctor or who have an HIV infection with a CD4 cluster or differentiation 4 cluster or differentiation 4 number below <200 / mm ²	People who are infected with HIV.
Adults ¹ with severe liver disease.	People with a reduced resistance to infections, for example due to cirrhosis of the liver.
Adults ¹ who are very overweight.	People with an age from 6 months to 18 years who use salicylates for a long time (for example in chronic bowel diseases). People with an intellectual disability living in an institution.
	People with a home in a nursing home, which do not fall under the above categories.

¹ Adults aged 18-69 years

Table 6.3 Number of people that are at increased risk of complications due to COVID-19

Category	Number of persons
Adults aged ≥ 70 years	2,321,000
Adults aged 18-69 years with an indication for influenza vaccination	3,067,000
Adults aged 18-69 years with a BMI ≥ 40 , assuming that 50% of this group has no indication for influenza vaccination	52,000
Total	5,440,000

6.10 Effectiveness of imperfect vaccines

A perfect vaccine would block infection in all vaccinated, thus preventing disease and further transmission. With a perfect vaccine, all vaccinated persons are protected directly, and unvaccinated persons are indirectly protected by herd protection. If the vaccination degree is above the critical vaccination threshold, outbreaks cannot occur [283]. For illustration in this section, we use the critical vaccination threshold of $(1 - 1/R_0) * 100\% = 60\%$.

Most vaccines are not perfect. For individual protection, it is most important that a vaccine reduces the probability to get infected when exposed to the virus, and/or reduces severity of disease should you nevertheless get infected. For herd protection, a vaccine should reduce the probability to get infected and reduce excretion of the virus to prevent infecting others. If you are less likely to get infected, and if you are less likely to pass the infection on to others, virus transmission is reduced and herd protection may be reached. If a vaccine is imperfect, the critical vaccination threshold increases. Vaccine effectiveness is expressed as a proportion, e.g. $VE = 0.8$ means that there is 80% reduction in transmissibility (susceptibility and infectivity combined). The critical vaccination threshold for an imperfect vaccine is $(1 / VE) * (1 - 1/R_0) * 100\%$. In our example, with $VE = 0.8$, it would increase from 60% to 75% [284].

If the critical vaccination coverage is not reached, or cannot be reached because VE is too low and the calculated critical coverage is above 100%, SARS-CoV-2 cannot be eliminated by vaccination alone. If elimination is not possible, another aspect of vaccine effectiveness comes into play to understand what will happen: is the vaccine a leaky vaccine, or is it an all-or-nothing vaccine [284]? With $VE = 0.8$ and a leaky vaccine, everyone has 80% less chance to get infected with each contact; with $VE = 0.8$ and an all-or-nothing vaccine, 80% of the vaccinated are completely protected and 20% are not protected at all. If the virus keeps circulating in the population, people come into contact with the virus more than once. Because a leaky vaccine provides a per-contact reduction, such a vaccine results in more infected people than an all-or-nothing vaccine which protects against all contacts.

6.11 Optimal allocation of scarce resources to reduce transmission and offer indirect protection

Scarce and/or costly control measures such as vaccines and anti-infective drugs must be allocated while epidemiological characteristics of the disease remain uncertain. Wallinga, van Boven & Lipsitch [285] presented first the principles for allocating scarce resources with limited data: under a broad class of assumptions, the simple rule of targeting intervention measures at the group with the highest risk of infection per individual will achieve the largest reduction in the transmission potential of a novel infection. For vaccination of susceptible persons, the appropriate risk measure is force of infection in the initial phase of the emerging epidemic.

Suppose that we wish to target vaccination of susceptible individuals to minimize transmission of an infection. A measure of the transmission potential is the reproduction number R , defined as the number of secondary infections caused by a typical primary case. We find that the marginal benefit of allocating a dose of vaccine to a given age group i is approximately proportional to the product of the incidence rate per person, denoted by x_i/n_i , and the force of infection, denoted by x_i/s_i , where force of infection is defined as incidence rate per susceptible person. If contact reciprocity holds and all else is equal, this implies that the greatest reduction in transmission of the infection population-wide can be achieved by vaccinating a person in the group with the highest product of incidence and force of infection. More generally, this reduction depends on the efficacy of the vaccine in each group q_i , the per contact probability of becoming infected for each group a_i , and the per contact infectiousness of each group c_i :

$$\frac{1}{R} \frac{dR}{du_i} \approx -hq_i \frac{c_i x_i(t)}{a_i s_i(t)} \frac{x_i(t)}{n_i}$$

The relative change in transmission depends on the product of two measures for risk infection, which implies that small differences between groups in risk of infection could hint at substantial benefits for targeting specific groups.

The serological studies into SARS-CoV-2 infections in the Netherlands provide a clear indication on the potential for targeted vaccination (Figure 6.4) [185, 197]. The studies reveal substantial variation in risk of infection between groups, which means that there is a large benefit in targeting the groups with a high risk of infection. To get an idea about the order of magnitude, we applied these first principles to observation from the PICO-study, first wave [197]. We found that vaccinating a 20 to 40 year-old person is approximately more than three times as effective as vaccinating a 40 to 80 year old person. Note that these calculations are done assuming that vaccine efficacy is the same for these ages, and that the ratio of infectiousness over susceptibility is the same for these ages.

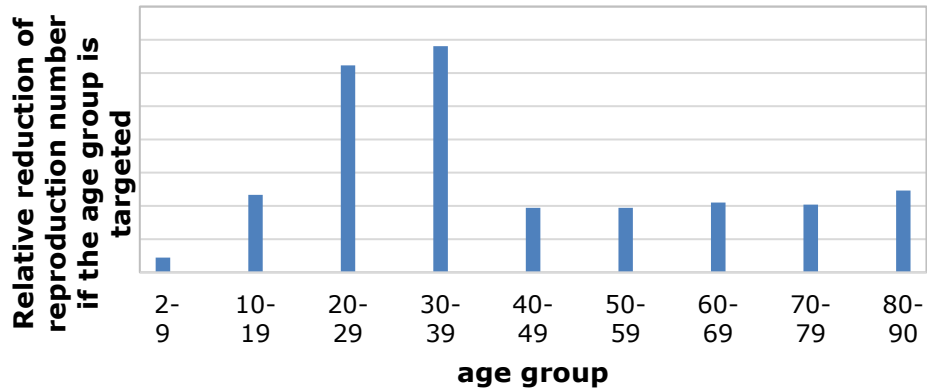


Figure 6.4 The impact on transmission by vaccinating a specific age group. The estimated values are relative, based on the measured incidence of infection in the PICO1-study in April 2020. Possible age-specific differences in vaccine efficacy are not accounted for. Possible age-specific differences in susceptibility and infectivity are also not accounted for; increased susceptibility relative to other ages decreases the impact; increased infectivity relative to other ages increases the impact.

6.12 Optimal allocation of scarce resources to offer direct protection

The allocation of vaccination such as to offer direct protection to those at highest risk of developing severe complications is straightforward when vaccine efficacy is constant: the groups at highest risk of complications should be vaccinated first. The groups with a high risk of complications are described in Table 6.2. It is important to realize that with a limited amount of vaccine, it is possible to protect those at highest risk directly by targeting them, or to offer indirect protection by targeting the groups that infect most others.








7 COVID-19 vaccines in development

7.1 Overview status of vaccines in development

The landscape of COVID-19 vaccines in development is rapidly growing since the outbreak of the SARS-CoV-2 pandemic. As of August 25th 2020, according to the WHO there are 173 candidates in development, 31 of which are being tested in clinical phase and 142 in preclinical phase [286]. Different platforms are being used to design the vaccines. These include traditional technologies for the production of vaccines, which we know from vaccines that are part of our current National Immunization Programme, such as inactivated whole virus (known from polio, hepatitis A and influenza vaccines), live attenuated virus (measles, mumps) and sub-unit or virus-like particle (VLP) protein-based vaccines (influenza, HPV). In addition there are more innovative technologies such as DNA or RNA, or vector-based platforms. Using such novel platforms, vaccines may be more rapidly developed and produced, but no vaccines based on these technologies have reached the (human) market yet. This applies e.g. for RNA-based vaccines. A summary of products according to their design and phase of development is given in Table 7.1.

Different vaccine platforms require different production facilities. For the production of whole virus-based vaccines (live attenuated or whole inactivated) large quantities of virus need to be cultured, which will strict regulation and require Bio Safety Containment Level (BSL) 2-3 facilities for safety reasons. In contrast RNA and DNA-based vaccines do not require reactor-based biomanufacturing of micro-organisms.

Table 7.1 Overview of COVID-19 vaccine candidates

Phase	Type				
	1. inactivated virus 	2. attenuated virus 	3. vector a. non replicating b. attenuated 	4. protein a. subunit b. VLP 	5. DNA/RNA a. RNA b. DNA 
Preclinical (n=139) 	12*	3	a. 19 b. 18	a. 50 b. 12	a. 16 b. 12
Clinical (n=27) 	5	0	a. 5 b. 1	a. 9 b. 1	a. 6 b. 4

* Number of candidates in pipeline (as of August 25th 2020).

Source:

<https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>

7.2 Impact of the design of COVID-19 vaccine candidates on the immune responses

Most COVID-19 vaccine candidates aim at inducing high levels of neutralising antibodies to the Spike protein (S-protein). The S-protein contains a receptor binding domain for attachment to the ACE2 receptor on host cells and is thus required for infection of human host cells. Antibodies to the S-protein that prevent the RBD of the S-protein from attaching to the ACE2 receptor have been shown to be protective in animal models [216]. Therefore, vaccines that target the S-protein are likely to confer protection. In most currently used vaccine concepts, except for whole virus vaccines, S-protein or its RBD-domain are indeed the major vaccine antigens. A minority of vaccine candidates encode next to S additional structural proteins, such as N or M. Additional antigens will enlarge the breadth of the adaptive response, which will be especially relevant for T cell immunity.

By another classification one can distinguish gene-based and protein-based vaccines, which differ in the cell types of the adaptive immune system they induce. The gene-based class consists of vaccines that contain the genetic code for a viral protein, e.g. the S-protein, which is delivered to the human body e.g. as RNA encapsulated in a lipid nanoparticle. This can enter host cells which will subsequently translate this genetic viral code and start producing S-protein intracellularly, thereby now resembling virus infected cells that trigger an immune response. This class of vaccines can trigger all B cell, CD4+ T cell and CD8+ T cell types (see section 6.2). The live-attenuated whole virus, the vector-based and the RNA/DNA-vaccines are included in this category. The other classes of vaccines contains the protein antigens themselves, such as the inactivated vaccines, and the sub-unit or VLP protein-based vaccines. By just delivering the antigens as foreign exogenous protein, most of these vaccines will 'only' trigger B cell and CD4+ T cell responses (see section 6.2). Exceptions are those 'protein delivery technologies' in which protein antigens are formulated in such a way that they can gain access to the cytosol of human cells, which could be the case for certain VLP-based vaccines or lipid nanoparticles. Presence in the cytosolic would then allow relevant processing and MHC presentation of peptides to CD8+ T cells as well.

Finally, vaccine design can steer effectiveness of the immune response. Depending on the vaccine platform, various innate signals might be incorporated. These in turn will give different instructions to the adaptive immune system through pro-inflammatory cytokine production, co-stimulatory molecules and antigen processing.

In summary, based on the wide variety of vaccine designs and antigenic cargos of the current COVID-19 vaccine landscape and basic B- and T cell biology, one can expect variability in breadth, induction of types of adaptive virus specific immune cells and effectiveness of immune responses induced, resulting in differences in vaccine effectiveness. This means that for different target groups (risk groups, such as elderly and people with comorbidities or healthy adults) different vaccine types can be optimal.

7.3 Preclinical and clinical data on several advanced products

Since the publication of the first SARS-CoV-2 genome on January 11th 2020, development of COVID-19 vaccine candidates have proceeded at an unprecedented pace [287]. Where on average bringing a human vaccine to the market, from concept to product, takes 10-15 years, the first COVID-19 vaccines may be expected to be ready to seek Emergency Use Authorization and subsequently regulatory approval by the end of 2020 or early 2021. This is extremely fast within 1-1.5 years after emergence of the pathogen. This is not achieved by cutting corners and omitting test phases, -the regular required steps in vaccine development will be followed-, but will be realised by changing paradigms altogether. Acceleration is being achieved by i) open access, exchange and use of innovative scientific knowledge and technologies e.g. on the 24th of January 2020 the complete SARS-CoV-2 genome sequence had already been published, ii) accelerated start of test phases such as starting clinical testing before preclinical R&D has completely finished, and prioritization and acceleration of regulatory procedures, iii) starting large-scale manufacturing of promising candidates during the clinical test phase (financial risks in the private sector being covered through international funds); and iv) strong international coordination (e.g. by the WHO) and collaboration in efficacy studies between scientific developers and manufacturing giants. Covid-19 vaccine developed and admitted to the market in this unprecedented speed way may have proven efficacy and safety in large Phase 3 trials, this does not mean that long term or rare side effects will come to the surface. This warrants extremely careful post-marketing surveillance in phase 4.

Clinical testing of vaccine candidates is now expanding rapidly, with several candidates moving into large global Phase III trials. Yet, published data is lagging behind. Weekly updates in COVID-19 vaccines in development are provided on the WHO-website, draft COVID-19 vaccine landscape [286], and on the website of the Dutch KNVM [287].

Of all COVID-19 vaccines that are currently front runners in the development process, some are more relevant for The Netherlands than others since there either is a deal between the EU commission and the vaccine manufacturer for delivery of vaccine doses or there are deal negotiations ongoing. These are the viral vector vaccines from Oxford/Astra Zeneca and Janssen, the mRNA vaccines of Moderna and BioNTech/Pfizer and the subunit protein vaccines from Sanofi/GSK and Novavax. Global dosing schedules, preclinical and clinical advancement of these vaccines are summarized in Table 7.2. One should keep in mind though that the COVID-19 vaccine development landscape is dynamic and with more data becoming available front runners may change [287].

Preclinical testing of COVID-19 vaccine candidates in general involves four different animal models, human ACE2 transgenic mice, Syrian hamsters, ferrets and non-human primates (NHP) [216, 235]. These animal models are used to test safety and immunogenicity but also to assess whether the vaccine provides protection against disease and/or infection of the nose and lungs. Animals are being vaccinated and a few weeks later exposed to a challenge with SARS-CoV-2. Available

protection data from rhesus monkeys, macaques and/or hamsters for mRNA and viral vector vaccines candidates show similar results. They show protective capacity in upper and lower respiratory tract: vaccinated animals became less ill and recovered faster and no virus could be detected in the lungs. Some of the vaccinated macaques had detectable levels of virus in the nose, although much less than in the unvaccinated animals. The NHP-model data thus suggest that vaccination with these vaccine candidates is unlikely to stop transmission of the virus in the community but could protect against severe disease. Clinical data are required to show whether this is also the case in humans.

Reported clinical phase 1/2 data for the mRNA (Moderna, BioNTech) and viral vector (Astra Zeneca) vaccines show that both vaccine types are reasonably well tolerated and produce neutralizing antibodies against the S-protein one month after vaccination and induce Th1-type CD4+ and CD8+ T cell immunity. However, available data are generated in relatively small groups of participants and direct comparison of the immunogenicity data obtained for the different vaccines is difficult because of incompleteness of preclinical and clinical data, differences in the design of the preclinical models used, and the absence of standardized COVID-19 specific antibody and T cell test platforms. There are currently no data available for any of the front runners on duration of long-term protection or safety, nor on immunogenicity profiles in older (or younger) age groups. Homologous booster regimes are being tested, but it is likely that heterologous prime-boost combinations will also be tested in the future.

Table 7.2 Overview of several front-runner COVID-19 vaccine candidates

COVID-19 Vaccine developer/ manufacturer	Design ○ Ag ○ # Product name	Preclinical NHP model ○ # animals ○ schedule ○ dose ○ challenge (pfu SARS-CoV-2)	Phase I/II ○ # subjects ○ age strata ○ dose ○ schedule	Phase II/IIb ○ # subjects ○ age strata ○ schedule ○ doses	Phase II/III ○ # subjects ○ age strata ○ schedule ○ doses ○ country	Reactogenicity & Immunogenicity profile	Lit.
NON_REPLICATING VIRAL VECTOR							
University of Oxford/ AstraZeneca	○ Adenovector (Chimpanzee) ChAdOx1 ○ S (full length) # AZD1222	○ n=6 ○ 2.5×10^{10} vaccine ○ single dose ○ 2.6×10^6 TCID50	○ n=1077 ○ 18-55 yrs; extension 55-71 yrs ○ 10, 25, 100, 250 µg ○ D0, D28	○ n=5000 ○ various ○ D0, D28 ○ 10, 30, 100 µg	○ N>35000 ○ various; ○ D0, D0 and D28 ○ 100 µg ○ Globally multiple sites (US, Brasil, S. Africa)	Phase I/II: Tolerable reactogenicity & good Immunogenicity (mAbs, Th1 CD4 T cells, CD8+ T cells) profiles, 2 doses strongest response	[236, 288]
CanSino Biological Inc./Beijing Institute of Biotechnology	○ Adenovector Ad5 ○ S	Undisclosed	○ n=108 ○ 18-60 yrs ○ 5×10^{10} , 1×10^{11} , 1.5×10^{11} ○ one dose	○ n=508 ○ ≥18 yrs ○ 5×10^{10} , 1×10^{11} ○ one dose	Planned	Tolerable reactogenicity but immunogenicity dependent on anti-vector immunity	[289, 290]
Janssen Pharmaceutical Companies	○ Adenovector Ad26 ○ S, full length stabilized pre-fusion # Ad26.COVS.S	○ n= 52 ○ single ○ 10^{11} vaccine ○ 1.0×10^5 TCID50 (at 6wks)	○ n=1045 ○ 18-55; ≥65 ○ Low or high ○ One or two		Planned September 2020	Protection in NHP	[291]

COVID-19 Vaccine developer/ manufacturer	<ul style="list-style-type: none"> ○ Design ○ Ag ○ # Product name 	Preclinical NHP model	Phase I/II	Phase II/IIb	Phase II/III	Reactogenicity & Immunogenicity profile	Lit.
	<ul style="list-style-type: none"> ○ # animals ○ schedule ○ dose ○ challenge (pfu SARS-CoV-2) 	<ul style="list-style-type: none"> ○ # subjects ○ age strata ○ dose ○ schedule 	<ul style="list-style-type: none"> ○ # subjects ○ age strata ○ schedule ○ doses 	<ul style="list-style-type: none"> ○ # subjects ○ age strata ○ schedule ○ doses ○ country 			
mRNA PLATFORM							
MODERNA	<ul style="list-style-type: none"> ○ lipid nanoparticle encapsulated mRNA ○ S, full length stabilized, pre-fusion # mRNA-1273 		<ul style="list-style-type: none"> ○ n=45 ○ 18-55 yrs; extension 55-71 yrs ○ D0, D28 ○ 10, 25, 100, 250 µg 	<ul style="list-style-type: none"> ○ n=5000 ○ various ○ D0, D28 100µg 	<ul style="list-style-type: none"> ○ N>30000 ○ various; ○ D0, D28 ○ 100 µg ○ Globally multiple sites (US) 	Phase I/II: Tolerable reactogenicity & good Immunogenicity profile (mAbs, Th1 CD4 T cells, CD8+ T cells)	[292, 293]
Pfizer/ BioNTech	<ul style="list-style-type: none"> ○ mRNA ○ S full length or RBD # BNT162b2 (and three other candidates) 	Undisclosed	<ul style="list-style-type: none"> ○ n=45 per candidate ○ 18-55 yrs; extension 18-85 yrs ○ D0, D28 ○ 10, 30, 100 µg 	<ul style="list-style-type: none"> ○ n=7600 ○ various ○ D0, D28 ○ 30, 100µg 	<ul style="list-style-type: none"> ○ n >30000 ○ various ○ D0, D28 ○ 30 µg ○ Globally multiple sites 	Lead candidate and dose selected based on best reactogenicity / immunogenicity (nAbs, Th1 CD4 T cells, CD8+ T cells) profiles	[294]
PROTEIN-BASED PLATFORM							
Novavax	<ul style="list-style-type: none"> ○ Trimer particle ○ S, stabilized, pre-fusion; adjuvanted with Matrix M # NVX-CoV-2373 	Undisclosed	<ul style="list-style-type: none"> ○ n=131 ○ 18-59 yrs; ○ D0 single or +D21 ○ 5, 25µg 	<ul style="list-style-type: none"> ○ n>2400 ○ various ○ D0, D21 ○ 5 or 25µg ○ Various sites 	<ul style="list-style-type: none"> Planned ○ n >35000 ○ various ○ D0, D21 ○ 5 or 25 µg ○ Globally multiple sites 		[295]
Sanofi/GSK	<ul style="list-style-type: none"> ○ Recombinant DNA technology based ○ Mutated S protein with GSKs AS03 adjuvant # - 	Undisclosed	<ul style="list-style-type: none"> ○ Planning start September 2020 		Planned end 2020	No data yet, pre-clinical data expected September 2020	

8 Passive immunization

As no antiviral therapies or vaccines are currently available for treatment or prevention of COVID-19, passive immunization (PI) through broadly neutralizing antibodies derived from plasma from previously SARS-CoV-2 infected persons that bind to the specific antigens of SARS-CoV-2, might be a potential solution to address the immediate health threat of COVID-19 pandemic while vaccines are being developed.

In two studies of respectively five and 10 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing anti SARS-CoV-2 antibodies was followed by improvement in their clinical status, including radiological resolution of chest X-ray inflammation, reduction in SARS-CoV-2 viral loads, and improved survival [217, 296]. The limited sample size and study design prevent a definitive statement about the potential effectiveness and clinical benefit of this type of treatment. These observations require further evaluation in clinical trials. Patients in both studies had shown clinical improvements, but the optimal dose, timing and duration of this passive immunization treatment still needs to be clarified [297]. Also, neither of the two studies described the severity of disease of the COVID-19 donors, from which plasma was derived relatively shortly after resolution of the clinical symptoms. Whether convalescent plasma of COVID-19 donors with different degrees of severity has different therapeutic effects remains to be further investigated [297].

Globally, blood centres have robust infrastructure for undertaking collections and constructing inventories of convalescent plasma to meet the growing demand. In the Netherlands, a number of initiatives have already started to use passive immunization in the treatment of COVID-19. For example, ConCoVid, a study from ErasmusMc Rotterdam in collaboration with 18 hospitals and Sanquin, in which patients receive plasma antibodies from ex-COVID patients [298]. Interim results show that for patients who developed specific antibodies themselves, additional antibody treatment did not contribute to a faster or better recovery.

Nonetheless, there are numerous challenges remaining, both regulatory and logistical, spanning donor eligibility, donor recruitment, collections, and transfusion itself. Data from rigorously controlled clinical trials of convalescent plasma are few, underscoring the need to evaluate its use objectively for a range of indications (e.g., prevention vs. treatment) and patient populations (e.g., age, comorbidities). An overview of use of convalescent plasma in case of SARS-CoV-2 infection, including evidence of benefit, regulatory considerations, logistical work flow, and proposed clinical trials has been recently published [299].

Promising results could also be obtained by a monoclonal approach, using human or humanized monoclonal antibodies that can neutralize SARS-CoV-2 (and SARS-CoV) as was shown in vitro in cell culture. Cross-neutralizing antibodies that target a communal epitope on these two SARS-CoV-2 viruses may also offer potential for prevention and treatment of COVID-19 [300].

9 Registration process in Europe and United States

9.1 European Medicine Agency

In relation to SARS-CoV-2, the European Medicines Agency (EMA) facilitates development and access to therapeutics and vaccines. The EMA interacts with developers of potential COVID-19 treatments and vaccines to enable promising medicines to reach patients as soon as possible. Furthermore, the EMA is responsible for the marketing authorization of these medicines and the monitoring of the safety of these medicines across their life cycle. In the interest of public health, applicants may be granted a [conditional marketing authorization](#) for such medicines where the benefit of immediate availability outweighs the risk of less comprehensive data than normally required, based on the scope and criteria defined in legislation and [guidelines](#).

At present, there are no effectiveness and efficacy data of COVID-19 vaccination available.

9.1.1 *Prelicensure period*

Endpoints of clinical trials and safety assessment

With respect to SARS-CoV-2 vaccines, in June 2020 the EMA, the FDA, and other regulatory authorities, participating in the International Coalition of Medicines Regulatory Authorities (ICMRA), discussed preclinical- and clinical data requirements to support proceeding to phase 3 clinical trials with SARS-CoV-2 vaccine candidates [301]. In addition, concepts of trial designs, e.g. regarding trial population, endpoints, and statistical considerations were discussed. Several key points were mentioned:

- Approval of proceeding into Phase 3 clinical trials will be determined on a case-by-case basis, depending on the specific SARS-CoV-2 vaccine construct, and the totality of preclinical and clinical data available for the concerning construct.
- To support general safety and immunogenicity of the respective vaccine candidate, initiation of Phase 3 clinical trials should be preceded by adequate characterization of safety and immunogenicity for each dose level and age group to be included in late stage trials.
- Nonclinical data characterizing the vaccine-induced immune response derived from studies in animal models vaccinated with clinically relevant doses of the SARS-CoV-2 vaccine candidate, should include an evaluation of immune markers of potential enhanced respiratory disease outcomes, e.g. assessments of functional immune responses (such as neutralizing antibodies) versus total antibody responses and Th1/Th2 balance.
- Phase 3 clinical trials aimed at demonstrating vaccine efficacy will need to enrol many thousands of participants, including those with medical comorbidities, to generate relevant data for the key target populations.
- The primary endpoint should be laboratory-confirmed COVID-19 of any severity. Other important endpoints include:

- SARS-CoV-2 infection monitored for and confirmed by either virologic methods or serologic methods evaluating antibodies to SARS-CoV-2 antigens not included in the vaccine, and;
- Severity of disease as measured by hospitalization, mechanical ventilation, or death.
- Efficacy point estimates should be specified in phase 3 trials and reflect the desired vaccine efficacy and specification of the lower bound of appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate.
- Vaccine safety and efficacy:
 - Need to be assessed in SARS-CoV-2 naïve individuals;
 - Should be powered to assess the overall vaccine efficacy across subgroups enrolled, and;
 - Should include adults over 55 years of age, including those with co-morbidities.
- Manufacturers should also assess safety and effectiveness for SARS-CoV-2 vaccines in children, given the epidemiology of COVID-19 in this population, and because safety and effectiveness of SARS-CoV-2 vaccines may differ between children and adults.
- Follow-up of study participants for COVID-19 outcomes should be long enough (i.e. 1 year or longer post-vaccination) to evaluate safety, duration of immune response, and risk of disease enhancement as antibody titres wane.
- Safety evaluation as part of Phase 3 clinical trials (including solicited local and systemic adverse events, unsolicited adverse events, serious or other medically attended adverse events), as well as the size of the safety data base and follow-up time, should be in the same range as for other preventive vaccines.

9.1.2 *Post licensure period*

The EMA requires manufacturers to have regular safety monitoring in place, including reporting of spontaneous reports of Adverse Events Following Immunization (AEFI) and information on the tolerability/reactogenicity of the vaccine.

To increase the knowledge on SARS-CoV-2 vaccine safety and effectiveness, the EMA aims to use real world observational data from clinical practice.

The ACCESS project (Vaccine Covid-19 monitoring Readiness) is a feasibility study to prepare for monitoring the safety and effectiveness of the novel coronavirus vaccines when they become available on the market [302, 303]. A Europe-wide network of data sources (including health records from general practitioners and hospitals) will be used to provide continuous monitoring of the coverage, safety, and effectiveness of COVID-19 vaccines, and to conduct specific studies on effects of COVID-19 vaccines. Furthermore, background rates of AEFIs (Adverse Events Following Immunization) and AESIs (Adverse Events of Special Interest) and other relevant conditions will be provided. Likewise, specific research questions can be studied through this network.

The ACCESS project is using the blueprint of a monitoring system that was developed by the European Centre for Disease Prevention and

Control and describes a vaccine monitoring infrastructure that is now implemented in the Vaccine monitoring Collaboration for Europe [304], an important partner of the ACCESS project. This infrastructure was designed and tested as part of the ADVANCE project [305] following the lessons learned from the 2009 H1N1 pandemic, which showed that European collaboration is needed to adequately and rapidly monitor benefits and risks of novel vaccines.

Likewise, a framework to conduct multi-centre cohort studies on the use of medicines for prevention or treatment of COVID-19 will be built [306].

The Coalition for Epidemic Preparedness Innovations (CEPI) and the Safety Platform for Emergency vACcines (SPEAC) composed a list of AEFI of special interest, see Table 9.1 [307, 308]. For these so called AESIs, the Brighton Collaboration will develop standardized case definitions that can be used in the post marketing safety surveillance of SARS-CoV-2 vaccines. To put these AESIs in context, literature reviews to describe background rates within the target populations are needed. The latter will be studied within the ACCESS project.

Table 9.1 Adverse events of special interest (AESI) applicable to COVID-19 vaccines

Body system	AESI type
<i>AESI relevant to vaccination in general</i>	
Neurologic	Generalized convulsion Guillain-Barré Syndrome (GBS) Acute disseminated encephalomyelitis (ADEM)
Hematologic	Thrombocytopenia
Immunologic	Anaphylaxis Vasculitides
Other	Serious local/systemic AEFI
<i>AESI relevant to specific vaccine platforms for COVID-19 vaccines</i>	
Neurologic	Aseptic meningitis Encephalitis/Encephalomyelitis
Immunologic	Arthritis
Other	Myocarditis
<i>AESI relevant to COVID-19</i>	
Immunologic	Enhanced disease following immunization Multisystem inflammatory syndrome in children
Respiratory	Acute respiratory distress syndrome (ARDS)
Cardiac	Acute cardiac injury including: <ul style="list-style-type: none"> •Microangiopathy •Heart failure and cardiogenic shock •Stress cardiomyopathy •Coronary artery disease •Arrhythmia •Myocarditis, pericarditis
Hematologic	Coagulation disorder <ul style="list-style-type: none"> •Deep vein thrombosis •Pulmonary embolus •Cerebrovascular stroke •Limb ischemia

Body system	AESI type
Renal	•Hemorrhagic disease Acute kidney injury
Gastrointestinal	Liver injury Guillain Barré Syndrome
Neurologic	Anosmia, ageusia Meningoencephalitis
Dermatologic	Chilblain-like lesions Single organ cutaneous vasculitis Erythema multiforme

9.2 FDA

The FDA issued a set of non-binding recommendations to assist sponsors in the clinical development and licensure of vaccines for the prevention of COVID-19 [309]. These recommendations for industry describe the FDA's current recommendations regarding the data needed to facilitate clinical development and licensure of COVID-19 vaccines. There are currently no FDA accepted surrogate endpoints that are reasonably likely to predict the clinical benefit of a COVID-19 vaccine. Thus, at this time, the goal of development programs should be to pursue traditional approval via direct evidence of vaccine safety and efficacy in protecting humans from SARS-CoV-2 infection and/or clinical disease.

9.2.1 *Prelicensure period*

Efficacy considerations

Similar to the EMA, the FDA also has guidelines for phase 3 clinical trials.

- Either laboratory-confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection is an acceptable primary endpoint for a COVID-19 vaccine efficacy trial.
- Acute cases of COVID-19 should be virologically confirmed (e.g., by RT-PCR).
- SARS-CoV-2 infection, including asymptomatic infection, can be monitored for and confirmed by either virologic- or serologic methods evaluating antibodies to SARS-CoV-2 antigens not included in the vaccine.
- Standardization of efficacy endpoints across clinical trials may facilitate comparative evaluation of vaccines for deployment programs, provided that such comparisons are not confounded by differences in trial design or study populations. To this end, the FDA recommends that either the primary endpoint or a secondary endpoint (with or without formal hypothesis testing) be defined as virologically confirmed SARS-CoV-2 infection with one or more of the following symptoms:
 - Fever or chills;
 - Cough;
 - Shortness of breath or difficulty breathing;
 - Fatigue;
 - Muscle- or body aches;
 - Headache;
 - New loss of taste or smell;
 - Sore throat;
 - Congestion or runny nose;
 - Nausea or vomiting, or;

- Diarrhoea.
- As it is possible that a COVID-19 vaccine might be much more effective in preventing severe than mild COVID-19, sponsors should consider powering efficacy trials for formal hypothesis testing on a severe COVID-19 endpoint. Regardless, severe COVID-19 should be evaluated as a secondary endpoint if not evaluated as a primary endpoint. FDA recommends that severe COVID-19 be defined as virologically confirmed SARS-CoV-2 infection with any of the following:
 - Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO₂ $\leq 93\%$ on room air at sea level or PaO₂/FiO₂ < 300 mm Hg);
 - Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO);
 - Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors);
 - Significant acute renal, hepatic, or neurologic dysfunction;
 - Admission to an ICU, or;
 - Death.
- SARS-CoV-2 infection (whether or not symptomatic) should be evaluated as a secondary or exploratory endpoint, if not evaluated as a primary endpoint.
- The above diagnostic criteria may need to be modified in certain populations, for example in paediatric patients and those with respiratory comorbidities. Sponsors should discuss their proposed case definitions with the FDA prior to initiating enrolment.

Statistical Considerations

- To ensure that a widely deployed COVID-19 vaccine is effective, the primary efficacy point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be set such that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is $> 30\%$.
- The same statistical success criterion should be used for any interim analysis designed for early detection of efficacy.
- A lower bound between $0 - \leq 30\%$ may be acceptable as a statistical success criterion for a secondary efficacy endpoint, provided that secondary endpoint hypothesis testing is dependent on success on the primary endpoint.
- For non-inferiority comparison to a COVID-19 vaccine of proven effectivity, the statistical success criterion should be: the lower bound of the appropriately alpha-adjusted confidence interval around the primary relative efficacy point estimate is $> -10\%$.

Safety Considerations

The general safety evaluation of COVID-19 vaccines, including the size of the safety database to support vaccine licensure, should be no different than for other preventive vaccines for infectious diseases.

Safety assessments throughout clinical development should be done for:

- Solicited local and systemic adverse events for at least 7 days after each vaccination in an adequate number of study

participants to characterize reactogenicity (including at least a subset of participants in late phase efficacy trials).

- Unsolicited adverse events in all study participants for at least 21–28 days after each vaccination.
- Serious and other medically attended adverse events in all study participants for at least 6 months after completion of all study vaccinations. Longer safety monitoring may be warranted for vaccine platforms that contain or are based on new technologies such as novel adjuvants.
- All pregnancies in study participants for which the date of conception is prior to vaccination or within 30 days after vaccination should be followed for pregnancy outcomes, including pregnancy loss, stillbirth, and congenital anomalies.

The pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure. The FDA anticipates that adequately powered efficacy trials for COVID-19 vaccines will be of sufficient size to provide an acceptable safety database for all populations, provided that no significant safety concerns arise during clinical development that would warrant further pre-licensure evaluation.

- COVID-19 vaccine trials should periodically monitor unfavourable imbalances between vaccine and control groups in COVID-19 disease outcomes, in particular for cases of severe COVID-19 that may be a signal for vaccine-associated Enhanced Respiratory Disease (ERD).
- Studies should include pre-specified criteria for halting based on signals of potential vaccine-associated ERD.
- FDA recommends use of an independent data safety monitoring board (DSMB) [310] for vaccine-associated ERD and other safety signal monitoring, especially during later stage development.

9.2.2 *Post licensure period*

General considerations

- As with all licensed vaccines, there can be limitations in the safety database accrued from the pre-licensure clinical studies of a COVID-19 vaccine. For example:
 - The number of subjects receiving a COVID-19 vaccine in pre-licensure clinical studies may not be adequate to detect adverse reactions that may occur infrequently.
 - Pre-licensure safety data in some subpopulations likely to receive a COVID-19 vaccine (e.g. pregnant individuals, individuals with medical comorbidities) may be limited at the time of licensure.
 - For some COVID-19 vaccines, the safety follow-up period to monitor for possible vaccine-associated ERD and other adverse reactions may not have been completed for all enrolled subjects in pre-licensure clinical studies before the vaccine is licensed.
- For COVID-19 vaccines, it is likely that during the early post marketing period, a large population might be vaccinated in a relatively short timeframe. Thus, the FDA recommends early planning of pharmacovigilance activities before licensure.

- To facilitate accurate recording and identification of vaccines in health records, manufacturers should consider establishment of individual Current Procedural Terminology (CPT) codes and the use of bar codes to label the immediate container.

Pharmacovigilance Activities for COVID-19 Vaccines

- Routine pharmacovigilance for licensed biological products includes expedited reporting of serious and unexpected adverse events as well as periodic safety.
- The FDA recommends that at the time of a Biologics License Application (BLA) submission for a COVID-19 vaccine, applicants submit a Pharmacovigilance Plan . The contents of a Pharmacovigilance Plan for a COVID-19 vaccine will depend on its safety profile and will be based on data, which includes the pre-licensure clinical safety database, preclinical data, and available safety information for related vaccines, among other considerations.
- The Pharmacovigilance Plan should include actions designed to address all important identified risks, important potential risks, and important missing information. Pharmacoepidemiologic studies or other actions to evaluate notable potential risks, such as vaccine-associated ERD, should be considered.

The FDA may recommend one or more of the following as components of a Pharmacovigilance Plan for a COVID-19 vaccine:

- Submission of reports of specific adverse events of interest in an expedited manner beyond routine required reporting;
- Submission of adverse event report summaries at more frequent intervals than specified for routine required reporting;
- Ongoing and/or extended safety follow-up (under an IND) for vaccine-associated ERD of subjects enrolled in pre-licensure clinical studies;
- A pharmacoepidemiologic study to further evaluate (an) important identified or potential risk(s) from the clinical development program, such as vaccine-associated ERD or other uncommon or delayed-onset adverse events of special interest, and/or;
- A pregnancy exposure registry that actively collects information on vaccination during pregnancy and associated pregnancy and infant outcomes.

Required Postmarketing Safety Studies

- The FDA can require studies or trials at the time of approval
 - To assess a known serious risk related to the use of the drug;
 - To assess signals of serious risk related to the use of the drug, or;
 - To identify an unexpected serious risk when available data indicate the potential for a serious risk.
- The FDA can also require studies or trials after approval if FDA becomes aware of new safety information.
- For COVID-19 vaccines, the FDA may require post marketing studies or trials to assess known or potential serious risks when such studies or trials are warranted.

10 Data on perception of the public towards COVID-19 vaccine

Although a vaccine against COVID-19 is not yet available, it is important to have insight in the willingness of people to be vaccinated against COVID-19. This is because herd protection through vaccination requires a sufficient proportion of the population to be vaccinated. It must be noted that the intention to vaccinate might differ from actual vaccine uptake (vaccination decision).

10.1 Acceptance of vaccination in the Netherlands

RIVM and GGD-GHOR (together with the Municipal Health Services (GGD)) are conducting a large study about people's behaviour, what they think of governmental measures and how they are doing physically, mentally, and socially in this era of corona [311]. Updates can be found on <https://www.rivm.nl/gedragsonderzoek>. In the third and fifth round of this study, the survey included a question about willingness to be vaccinated if a COVID-19 vaccine were available.

Figure 10.1 shows that approximately two-thirds of the participants were willing to be vaccinated, although part of them first wanted to know if they have already had corona. A considerable part of the participants did not know yet whether to be vaccinated. The size of this group increased from 18% in round 3 to 28% in round 5. The participants that did not want to get vaccinated, either because they already have had COVID-19 or because of other reasons, decreased from 11% to 8% between the two rounds.

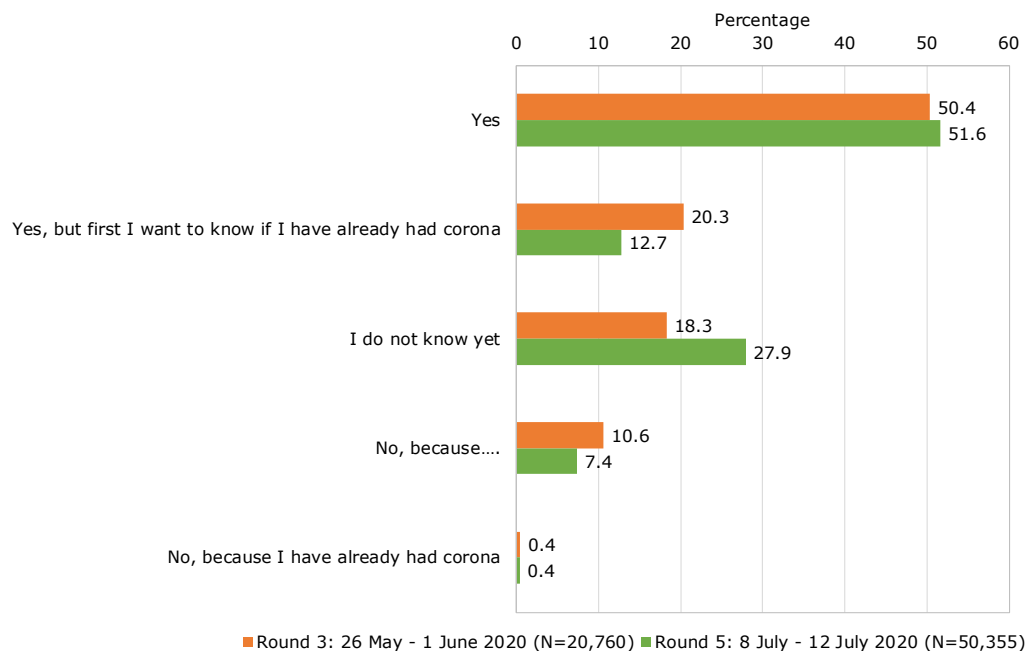


Figure 10.1 Response on the question: 'If there is a vaccine against coronavirus later, would you like to be vaccinated?'

The willingness to get vaccinated against COVID-19 was higher among males than among females, and lower among people aged between 25-54 compared to other age categories (Figure 10.2). Note that in the older age groups, men tended to be higher educated than women and people with a higher education were in general more positive towards vaccination.

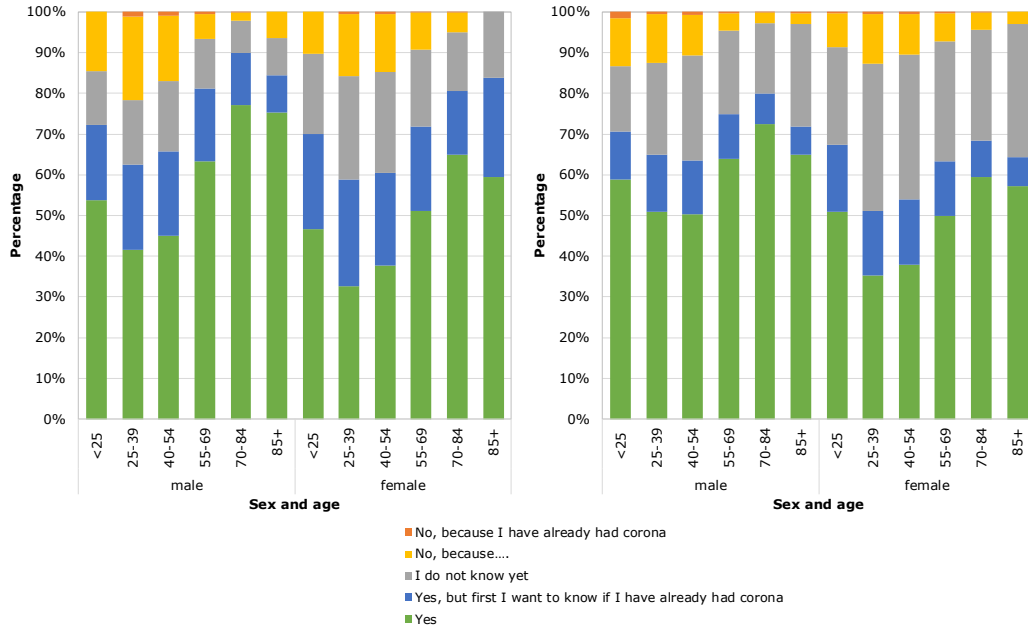


Figure 10.2 Response on the question: 'If there is a vaccine against coronavirus later, would you like to be vaccinated?' divided by sex and age (left: round 3 (May 26th – June 1st, 2020); right: round 5 (July 8th – 12th, 2020))

Among respondents who answered the question in rounds 3 and 5 (N=12,761), 32% did not reply with the same answer in both rounds. Most changed from 'yes' (regardless if they first wanted to know if they have already had COVID-19) to 'I do not know yet'.

Respondents who answered 'No, because....' were offered the option to elaborate on their reasoning for this. In round 3, this was the case for 10.6% of the respondents, which resulted in 2,104 open answers. These answers were labelled through open coding. Roughly two-thirds of the answers were coded with a single label and another quarter with two labels. The remaining ones were left blank (two cases) or coded with three or four labels. All labels were grouped into overarching categories. Figure 10.3 shows the reasons that were most often mentioned, based on these overarching categories.

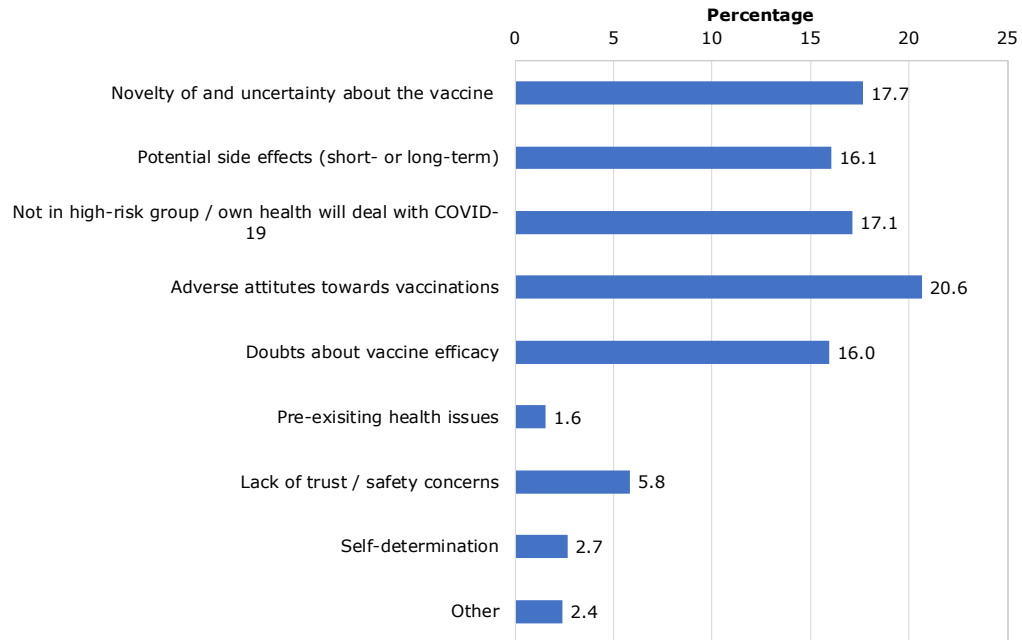


Figure 10.3 Reasons for not wanting a potential COVID-19 vaccination (round 3: May 26th – June 1st, 2020)

The reasons most often mentioned for not wanting to receive a potential COVID-19 vaccination were:

- Adverse attitudes towards vaccinations (20.6%);
- Issues surrounding the novelty and uncertainty of any potential COVID-19 vaccine to be introduced (17.7%);
- Not belonging to a high-risk population group combined with beliefs that someone's own health or immune system could adequately deal with COVID-19 (17.1%);
- Potential side effects of a COVID-19 vaccine (short- or long-term) (16.1%), and;
- Doubts about the efficacy of a potential COVID-19 vaccine (16.0%).

During round 5 of the study, vaccination acceptance was also covered in in-depth interviews with 27 respondents. Reasoning for acceptance centred largely around the vaccine offering protection to either themselves or others. Among those expressing doubts or possible refusal of a vaccine, reasoning focussed primarily on potential side-effects (both short- and long-term) and on the efficacy of a possible vaccine. All respondents expressed an understanding to first vaccinate people who they deemed high-risk groups (e.g. the elderly, people with health issues) and those working in health care and other vital sectors if a vaccine were to initially become available in insufficient quantities to cover everyone. Respondents were divided on the idea of paying a contribution to get vaccinated against COVID-19. Roughly one-third saw no issue with this, with some framing it akin to paying for a travel vaccination. Another one-third would possibly be open to a contribution provided they had received sufficient information on the efficacy and potential side-effects. The remaining respondents were opposed to the idea, stating that this might lead to conflicting priorities in less well-off households.

10.2 Acceptance of vaccination in other countries

A European survey, conducted between April 2nd and 15th, 2020, in seven countries including the Netherlands, on the willingness to be vaccinated against COVID-19, showed that 73.9% would be willing to be vaccinated against COVID-19 if a vaccine would be available. Another 18.9% were not sure and 7.2% did not want to get vaccinated. Compared to the abovementioned RIVM and GGD-GHOR survey conducted in July 2020, similar percentages (~7%) of participants did not want to get vaccinated. Approximately two-thirds (64.3%) of participants were willing to get vaccinated in the RIVM and GGD-GHOR survey, compared to 73.9% in the European survey. It should be noted that the answer options in both surveys were different. Furthermore, the most recent survey of RIVM and GGD-GHOR was held later in time (July 2020) than the European survey (April 2020), while opinions evolve over time and will probably be affected by the phase of the pandemic.

The willingness was highest in Denmark and the United Kingdom (approximately 80%) and lowest in France (62%), while the Netherlands scored in between with 73% (Figure 10.4). The willingness to get vaccinated was lower among women and persons below the age of 55. Respondents who were unsure about being vaccinated or did not want to get vaccinated were mainly concerned about potential side effects of the vaccine (55% and 38% respectively). A common concern is that a COVID-19 vaccine might be experimental, without any studies on side effects, and may not be safe for specific groups [312].

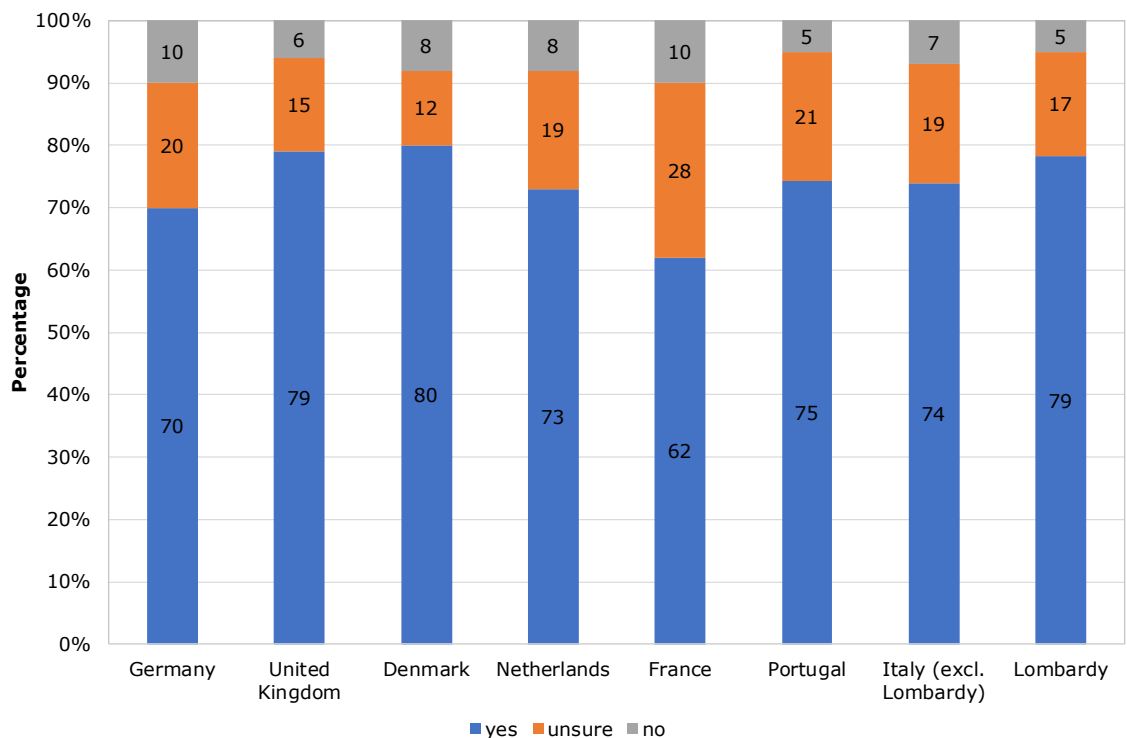
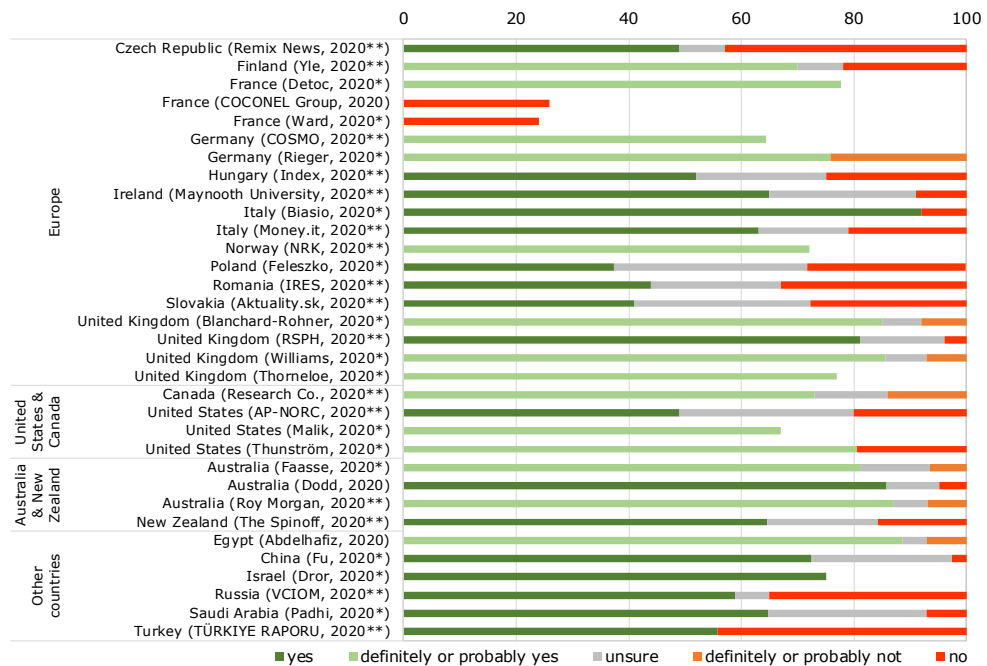


Figure 10.4 Willingness to be vaccinated against COVID-19 by country (2-15 April 2020) [312]

Different national surveys also estimated the willingness to get vaccinated against COVID-19 (Figure 10.5). Note that most of these data concern preliminary results that have not undergone peer review (preprints) or polls from websites. Furthermore, differences between results of national surveys are difficult to interpret because they depend amongst other things on the representativeness of the sample, the timing of the survey relative to the pandemic phase in the country, and the specific question used ('yes'/'unsure'/'no' or 'yes definitely'/'yes, probably'/'unsure'/'no, probably not'/'no, definitely not').

The willingness to vaccinate against COVID-19 in these national surveys ranged from relatively low, mainly in Eastern Europe (37% in Poland, 41% in Slovakia, 44% in Romania), to relatively high (92% in Italy, 89% in Egypt, 87% in Australia, 86% in the United Kingdom). The percentage of people who do not want to get vaccinated against COVID-19 ranged from very low (2.6% in China, 4% in the United Kingdom) to quite high (44% in Turkey, 43% in Czech Republic). In most of these national studies, males and older adults were more likely to accept a vaccine.



* preprint: preliminary report that has not undergone peer review ** poll/webpage

Figure 10.5 National surveys on willingness to be vaccinated against COVID-19 [313-345]

11 Cost effectiveness

11.1 Health economic arguments in a pandemic

Nowadays, health-economic evaluations play a prominent role in decision making on public health interventions in the Netherlands, and trade-offs between health and wealth are continuously made. Cost-effectiveness analyses relate the economic consequences of the intervention with the health consequences, the latter generally expressed in quality-adjusted life years (QALYs), a measure that comprises the impact on quantity as well as quality of life. Concerning costs, the guideline for health-economic evaluation in healthcare states that all relevant costs and benefits should be taken into account and that the societal perspective is recommended. This societal perspective includes costs within the healthcare sector (vaccination, medical resource use, and, since the update of the Dutch guideline in 2016, also healthcare costs unrelated to studied disease in life years gained) as well as costs outside the healthcare sector (non-medical resource use and indirect time loss or productivity losses).

For vaccination programmes against endemic infectious diseases, health economic analysis is generally practiced as a *partial equilibrium* analysis [346]. This means that the consequences of the vaccination programme is limited to a certain part of the healthcare sector or economy that is considered as 'relevant', while another part of the healthcare sector or economy is assumed to remain unaffected because the indirect impact of the intervention is assumed to be small. However, in the setting of the SARS-CoV-2 pandemic, the disease COVID-19 as well as the measures to control the spread of the virus have considerable impact on the health care sector and economy as a whole. Within the healthcare sector, for instance, the demand for hospital and ICU beds may exceed the available capacities and healthcare workers may get exposed and sick themselves. Therefore, the traditional approach of multiplying the estimated number of ICU cases by the cost per ICU visit could be misleading as capacity issues are ignored. Furthermore, treatments in regular care may have to be postponed to create capacity for COVID-19 treatments. Outside the healthcare sector, non-essential travel and non-vital consumption activities become affected, as the people's behaviour is influenced by the presence of a health threat. It is important to consider that in a 'do nothing' scenario, the pandemic will also affect the wider economy, as part of the population will change their behaviour themselves and stay at home to avoid the health threat. Furthermore, epidemiological conditions and mitigation measures in other countries also impact the Dutch economy. In case of a long duration of the health treat, behavioural or societal changes may even become permanent as society adapts to the new situation.

Table 11.1 contains a list of relevant items that could be considered when the health-economic consequences of a vaccination programme against a pandemic disease are studied. They are formulated so that the reference scenario is a setting in which measures against COVID-19 are taken in place. This list is not complete, and potentially many more

consequences of COVID-19 measures could be added. It is therefore important that there is consensus between the different stakeholders, including modelers, disease experts and decision makers, about the economic aspects that should be included in a health-economic analysis.

Table 11.1 Relevant aspects when considering the health-economic consequences of a vaccination programme against COVID-19 compared to the current Dutch setting in which mitigation measures need to be introduced and regular healthcare is down-scaled. The table is modified from Kim & Neumann, MDM 2020.

Healthcare sector perspective	
Healthcare outcomes	Positive impact: <ul style="list-style-type: none"> - Life-years gained due to averted COVID-19 cases - Health-related quality of life (HR-QoL) improvement due to averted COVID-19 cases (cases, caregiver, society) - Averted adverse consequences on life-years and HR-QoL when healthcare capacities are not exceeded - Averted adverse consequences on life-years and HR-QoL among non-COVID-19 patients as regular treatments are not postponed
	Negative impact: <ul style="list-style-type: none"> - Adverse consequences of vaccination on HR-QoL
	Unknown impact: <ul style="list-style-type: none"> - HR-QoL impact due to the removal of the pandemic health treat - HR-QoL impact due to the potential aversion/lifting of mitigation measures (short- and long-term of life style changes regarding physical activity, smoking and alcohol consumption, increased home violence, long-term effects of avoided missed schooldays) - Long-term macro-economic effects on healthcare budgets
Healthcare costs	Positive impact: <ul style="list-style-type: none"> - Averted screening and treatment costs of COVID-19 cases
	Negative impact: <ul style="list-style-type: none"> - Costs of the vaccination programme and its adverse events - Costs of non-COVID-19 related treatment costs in life years gained - Costs of recurring non-beneficial treatments from upscaled regular healthcare
	Unknown impact: <ul style="list-style-type: none"> - Impact of the shift to digital healthcare and back

Societal perspective	
Labor market	<p>Positive impact:</p> <ul style="list-style-type: none"> - Reduction of productivity loss due to averted COVID-19 cases (case and caregiver) - Reduction of productivity loss due to averted societal disruption or fear of contagion. - Averted unemployment due to business closures (non-health sectors, particularly in travel and non-vital consumptions) <hr/> <p>Negative impact:</p> <ul style="list-style-type: none"> - Averted expansion of employment in healthcare sector <hr/> <p>Unknown impact:</p> <ul style="list-style-type: none"> - Impact on productivity due to no longer working from home
Consumption	<p>Positive impact:</p> <ul style="list-style-type: none"> - Impact on non-health consumption due to removal of fear for contagion
Legal/criminal justice	<p>Negative impact:</p> <ul style="list-style-type: none"> - More traffic accidents due to lifting mitigation measures <hr/> <p>Unknown impact:</p> <ul style="list-style-type: none"> - Increase of crime rates due to lifting mitigation measures and increase of tourism
Education	<p>Unknown impact:</p> <ul style="list-style-type: none"> - Change from online education back to physical education
Environment	<p>Negative impact:</p> <ul style="list-style-type: none"> - Increase of air pollution and noise due to increased travel and factories

Furthermore, it is important to decide on optimization points. Traditionally, cost-effectiveness analyses explore the relation between the price of the vaccine and the societal impact. However, in the case of a pandemic cost-effectiveness analysis are more complex. The vaccine might already be bought, making the price less relevant, and the outstanding question will be reduced to whether it is worth it to provide the vaccine. On the other hand, estimating the possible costs of the pandemic on a societal level is an open-ended analysis, as there is no set methodology to estimate this. It is therefore important to pre-define the endpoints that have to be optimized in this decision making process. On top of this, the risk of vaccine side-effects is a very important consideration when vaccinating many people with a new vaccine. People perceive the risk of side-effect differently to normal disease. In standard cost-effectiveness analysis, side-effects are poorly included, and when they are included they are weighted similarly to prevented disease (thus 1 prevented QALY by vaccination is offset by 1 QALY due to induced side-effects) which is not how people think.

A final aspect to be discussed in health-economic evaluations of pandemics is the willingness-to-pay (WTP) for a QALY gained. The willingness-to-pay for a QALY gained that is obtained because hospital bed capacities are not overwhelmed might be considerably higher than a

€20,000 per QALY gained that is usually considered as a WTP threshold for vaccination programmes in the Netherlands. Generally, society is willing to spend much more for savings lives of identifiable groups of people (rule of rescue). This rule may very well apply to deaths that could have been averted when healthcare capacities would not have been overwhelmed, as this situation is deemed unacceptable.

11.2 Available evidence

The literature on health economic models that capture the full macro-economic impact of a pandemic is limited. A modelling study by Keogh-Brown *et al.* (unpublished work, personal communication) aimed to estimate the impact of COVID-19, associated behaviours and policies on the UK economy using a *general equilibrium* model.

However, this study did not account for the behavioral changes that will also occur during an unmitigated pandemic, the effects of overloaded intensive care units, and the monetary value of QALYs gained due to preventive interventions. This study estimated that the economic burden of an unmitigated COVID-19 scenario at 1.73% of the gross domestic product (GDP), a mitigation strategy consisting of household quarantine for 14 days when an individual within a household is affected, shielding of those over 70 years, social distancing of the entire population, and closure of schools and universities. Assuming these measures were applied over a period of 12 weeks, the economic burden would be 13.5% of GDP. The economic burden of a long-term suppression strategy, in which the mitigation measures were remained for 30 weeks, was estimated to result in an economic burden of 29.2% of GDP.

12 Other NITAG considerations

NITAGs (National Immunization Technical Advisory Groups) have a key role to play in helping their Ministry of Health during the pandemic and advising on how best to maintain immunization activities now and plan for tomorrow. Work groups from several countries have launched an *interim advice on priority groups for COVID-19 vaccination* to explain its current prioritization. These recommendations may need to be revised frequently as countries change strategies and more is known about the virus.

12.1 Considerations from NITAGs in neighbouring countries

12.1.1 SHC (*Superior Health Council, Belgium*)

The SHC recommends to prioritize the following groups for vaccination against Covid-19 based on the available data and statistical evidence [347]:

- All workers in the health care sector, to secure their health and a working health care sector during a potential next COVID-19 wave or pandemic;
- All people above 65 years of age, and;
- Patients between 45 and 65 years with the following comorbidities which are at risk for developing severe COVID-19: obesity, diabetes, hypertension, chronic cardiovascular, lung, kidney and liver diseases and haematological malignancies up to 5 years from diagnosis, and all recent solid cancers (or recent cancer treatments).

Further prioritization inside the above groups may be considered if a limited amount of vaccine is available.

This recommendation can be changed according to new data and information on immunogenicity of the type of vaccine(s) that will be available. For instance, data regarding pregnant woman or other immunocompromised patients, as well as the impact of socio-economical and ethnic background will be followed. Furthermore, the impact and the need of vaccination against Covid-19 to manage an outbreak will be evaluated when more information will be available on the new vaccine(s).

An estimation of around 4 million people are in the risk and priority groups for vaccination against Covid-19 in Belgium. It is assumed that at least 20% to 30% in the priority and risk groups will refuse vaccination.

12.1.2 JCVI (*Joint Committee on Vaccination and Immunization, UK*)

The JCVI developed an advise following a request from the Department of Health and Social Care and Public Health England, to facilitate planning for the deployment of any safe and effective vaccine(s) as soon as licensure is obtained for use in the UK [348, 349]. This advice forms a preliminary framework for refining future advice for the basis of a national COVID-19 vaccination strategy.

The committee advises priority vaccination of the following groups:

1. Frontline health and social care workers, and;
2. Those at increased risk of serious disease and death from COVID-19 infection, stratified according to age and risk factors.

ad 1. Frontline health and social care workers

This group is at increased personal risk of exposure to infection with COVID-19 and of transmitting that infection to susceptible and vulnerable patients in health and social care settings. Vaccination of frontline health and social care workers will also help to maintain resilience in the NHS and for health and social care providers.

ad 2. Those at increased risk of serious disease and death

Current evidence strongly indicates that the risk of serious disease and death increases with age and is increased in those with a number of underlying health conditions. Therefore, after health and social care workers, the committee advises the prioritization of vaccination using a mortality risk-based approach.

Currently available data from the UK indicate that those at greatest risk of severe illness and mortality from COVID-19 include:

- Adults over the age of 50, with the risk increasing with age, and;
- Those with underlying co-morbidities including chronic heart disease, chronic kidney disease, chronic pulmonary disease, malignancy, obesity and dementia.

Based on expert advice, the government has also defined a shielded population that it considers to be at greatest risk of severe illness, which includes:

- Solid organ transplant recipients;
- People with specific cancers;
- People who have had bone marrow or stem cell transplants in the last 6 months, or who are still taking immunosuppression drugs;
- People with severe respiratory conditions including all cystic fibrosis, severe asthma and severe chronic obstructive pulmonary disease (COPD);
- People with rare diseases and inborn errors of metabolism that significantly increase the risk of infections (such as severe combined immunodeficiency (SCID), homozygous sickle cell);
- People on immunosuppression therapies sufficient to significantly increase risk of infection, and;
- Women who are pregnant with significant heart disease, congenital or acquired.

This advice of the JCVI about vaccinating priority groups will be updated as more information becomes available on:

- Vaccine efficacy and/or immunogenicity in different age and risk groups;
- The safety of administration in different age and risk groups;
- The effect of the vaccine on acquisition of infection and transmission;
- The transmission dynamics of the SARS-CoV-2 virus in the UK population, and;
- The epidemiological, microbiological, and clinical characteristics of COVID-19.

12.1.3 *STIKO (Standing Committee on Vaccination), Germany [350]*

In Germany, the Standing Vaccination Commission (STIKO) developed recommendations on how the available Covid-19 vaccine stocks can be used with the best possible benefit for the population (prioritization) in the case of presumably limited vaccine quantities. Ethical aspects are of particular importance because the pandemic has a drastic effect in many areas of people's lives and there is therefore a special need for a fair distribution of vaccines with limited vaccine quantities. The aim of prioritization is primarily to contribute to the best possible avoidance of serious illnesses and deaths through targeted use where the availability of vaccines may be limited. In order to evaluate how a maximum benefit can be achieved with the vaccination, knowledge must be available on various aspects. These are i.e. the age- and job-specific risk of infection, the risk of serious illnesses, the vaccination protection that can be achieved for a specific age and risk group, the quality of the vaccination protection (e.g. with regard to the prevention of SARS-CoV-2 infection or severe disease as well as the number of vaccine doses required). The interaction of these parameters can best be assessed using mathematical transmission modeling, in which the influence of uncertainties regarding the parameters can also be checked. At the Robert Koch Institute (RKI), such a model is currently being developed in close cooperation with the STIKO. Further aspects of a COVID-19 vaccination prioritization are the protection of the functionality of the medical / nursing care system. It is also important to take into account the protection needs of people who are particularly exposed because of their work and who come into contact with many people.

If these aspects are relevant to the decision, they are explicitly explained in the context of ethical principles, such as those formulated, for example, in the guiding principles of the Competence Network Public Health COVID-19 on ethical aspects of COVID-19 vaccination [350].

Given the limited data on vaccines, an initial recommendation for prioritization will also have to be made on the basis of assumptions. Together with the RKI and other institutions, the STIKO will continuously process and evaluate the evidence from scientific examinations and clinical studies, whereby the safety and effectiveness of the vaccines will always be of central importance. The mathematical model is also continuously updated, taking new data into account. The STIKO recommendation will be adjusted further if, after weighing the risks and benefits, there is evidence that a change in the recommendation can achieve better vaccination protection for the population.

12.1.4 *HAS (High Authority for Health), France [351]*

At the request of the Ministry of Solidarity and Health, the High Authority for Health (HAS) made preliminary recommendations to anticipate the development of the vaccine strategy against COVID-19 with a view to the future arrival of one or more vaccines. The public health objectives of vaccination against Covid-19 are threefold:

- To protect against infection and thus reduce the risk of contracting the disease or limit its consequences;
- To slow down the transmission of the virus within the population in an epidemic control perspective;
- To allow the maintenance of activities vital to the functioning of the country.

To respond to this when one or more vaccines become available, the HAS developed different possible vaccination strategies through four scenarios based on the level of circulation of the virus in the territory: 1) viral circulation at the national level, 2) strong viral circulation localized in certain territories, 3) low noise viral circulation (outbreaks infection), 4) no indicator of viral circulation.

Each of these situations implies different choices on the populations to be targeted as a priority (age, state of health, profession, necessary doses, etc.) and appropriate implementation methods (professionals mobilized to vaccinate, follow-up of vaccinated persons, conditions of administration and storage). The characteristics of the vaccines available will also influence these choices. For each scenario, the HAS summarizes the priority target populations, the expected vaccine prerequisites and the dose requirements necessary to achieve the three vaccination objectives.

Overall, the HAS proposed as first priority for vaccination:

- Healthcare professionals, such as doctors, surgeons, dentists, pharmacists, midwives, nurses and carers and other professionals with contact with the general population (i.e. shop workers, school staff, transport staff and hospitality workers; those working in smaller spaces such as abattoir staff, taxi drivers, migrant workers and construction teams);
- People who could be considered vulnerable due to their age (over 65), or a chronic condition (cardiovascular illness, hypertension, diabetes) or obesity. Other people in a "precarious state" would also be considered as a priority.

The HAS also mentioned a list of people who would take "second priority". These would include people who live in departments - including in French overseas territories - at risk of a lack of intensive care beds, people living in closed, at-risk sites (such as prisons, disabled care units and psychiatric hospitals), and people with a "strategic" job, such as police, the military, and firefighters.

This strategy will be updated as the pandemic continues, ensuring the latest information is incorporated into the plan. In particular, the status and spread of the virus will be monitored.

12.2 Considerations of NITAGs in other countries

12.2.1

ACIP (Advisory Committee on Immunization Practices, US)

ACIP provides advice to the CDC director and the Secretary of the Health and Human Services on use of vaccines in the US civilian population in a transparent, evidence-based process. To help inform ACIP deliberations around use of COVID-19 vaccines, a work group is reviewing the epidemiology of COVID-19 to

- Ensure safety and effectiveness of COVID-19 vaccines;
- Reduce transmission, morbidity, and mortality in the population;
- Help minimize disruption to society and economy, including maintaining healthcare capacity, and;
- Ensure equity in vaccine allocation and disruption.

Based on this information and lessons learned from the H1N1 influenza pandemic, the work group developed a rough, five-tier priority scheme for vaccinating subgroups of the population in the US [352, 353].

Based on current knowledge, the work group has proposed that vaccine priority should be given to:

- Healthcare personnel and other essential workers, and;
- High risk populations:
 - Adults aged ≥ 65 years;
 - Long term care facility residents, and;
 - Persons with high-risk medical conditions.

Furthermore, the work group considered that among these target groups, a subset of critical healthcare and other workers should receive initial doses to protect healthcare infrastructure and other critical societal functions. This priority target group included highest risk medical workers, national security workers, and other essential workers. Further tiering of the targets groups may be necessary based on vaccine supply and program planning.

Next steps for the work group are refinement of priority groups based on ACIP feedback, and assignment of tiers to other groups such as children, pregnant women, and racial/ethnic groups at high risk. Other questions that need to be addressed, are:

- Who, exactly, is a high-risk medical worker?
- Should the poor be given preferences because they have less access to health care, live in more crowded conditions, and suffer more if they become sick and must take time off work?
- Should priority be given to young and healthy people who have a lower risk of a severe COVID-19 infection, but based on their profession or environment are at increased risk of getting infected (for example teachers, grocery store workers, prisoners)?

Prioritization will need to be refined as more information becomes available.

12.2.2 *CAVEI (Chile's National Advisory Committee on Immunization; in Spanish)*

CAVEI responds to the request of the Department of Immunizations on target groups that should receive the vaccine either for conditions that increase their risk of serious illness and/or to preserve the health system and/or other considerations that apply.

CAVEI preliminarily recommends that the target groups to vaccinate in Chile against COVID-19 will be as follows, and that their access to the vaccine will be prioritized in the order presented [354]:

1. Health care workers
 - a. Professionals and technicians in the health area;
 - b. Volunteers or students authorized by the director of the healthcare centre or whoever delegates the tasks inherent to their responsibility,
 - c. People who perform direct health care tasks for patients,

- d. People working in health facilities of the country's Health Services, experimental and Primary Municipal Health Care,
- e. People either in direct or close contact (within 1 meter distance) with patients;
- f. People in clinical support services (laboratories, blood banks, radiology, food, etc.);
- g. People at administrative units (files, allocation of hours, cleanliness, etc.) or logistical support, and;
- h. Personnel who work in the Ministry of Health and in the other organizations dependent on that Ministry and those who are related to it.

2a. Closed detention centres, SENAME (National Service for Minors) centres, long-stay centres (elderly people, rehabilitation, reception centres, etc.)

2b. Risk groups

Factors or risk conditions that make this person prone to have a serious condition (perspective protection of the individual and prevention of burden on the health system and mortality), such as:

- a. People over 65 years of age, and;
- b. People of any age with underlying disease, including:
 - Chronic lung disease (bronchial asthma, COPD, cystic fibrosis, pulmonary fibrosis of any cause);
 - Neurological disease (congenital or acquired neuromuscular, which includes swallowing or management disorders of respiratory secretions, epilepsy refractory to treatment);
 - Chronic kidney disease (stage 4 or greater kidney failure, dialysis);
 - Chronic liver disease (cirrhosis, chronic hepatitis, liver disease);
 - Metabolic diseases (diabetes mellitus, congenital diseases of metabolism);
 - Heart disease (congenital, rheumatic, ischemic and cardiomyopathies of any cause);
 - Arterial hypertension drug treatment, and;
 - Obesity (BMI \geq 30 in adults and adolescents).

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List of abbreviations

ACCESS	Vaccine Covid-19 Monitoring Readiness
ACE2	Angiotensin-Converting Enzyme 2
ACIP	Advisory Committee on Immunisation Practices (US NITAG)
ADE	Antibody Enhanced Disease
ADEM	Acute Disseminated Encephalomyelitis
ADVANCE	Accelerated development of vaccine benefit-risk collaboration in Europe
AEFI	Adverse Event Following Immunisation
AESI	Adverse Event of Special Interest
ARDS	Acute Respiratory Distress Syndrome
BLA	Biologics License Application
BMI	Body Mass Index
BSL	Bio Safety Containment Level
CAVEI	Chile's National Advisory Committee on Immunisation (Chile's NITAG)
CDC	Centers for Disease Control
CEPI	Coalition for Epidemic Preparedness Innovations
Chinese CDC	Chinese Centers for Disease Control
Cib	Centrum Infectieziektebestrijding (Centre for Infectious Disease Control)
CLEC4M	C-type Lectin Domain Family 4 Member M
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease 2019
CPT	Current Procedural Terminology
DNA	Deoxyribo Nucleic Acid
DSMB	Data Safety Monitoring Board
E	Envelope protein
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal Membrane Oxygenation
EMA	European Medicine Agency
ERD	Enhanced Respiratory Disease
EU/EEA	European Union/European Economic Area
FDA	Food and Drug Agency
FMS	Federatie Medisch Specialisten (Federation Medical Specialists)
GBS	Guillain-Barré Syndrome
GDP	Gross Domestic Product
GGD	Gemeentelijke Gezondheidsdienst (Municipal Health Service)
GGD-GHOR	Gemeentelijke Gezondheidsdiensten en Geneeskundige Hulpverleningsorganisaties in de Regio
HAS	High Authority for Health (French NITAG)
HPV	Human papillomavirus
HR-QoL	Health-Related Quality of Life
ICU	Intensive Care Unit
IgA	Immunoglobuline A (antibody type A)
IgG	Imunoglobuline G (antibody type G)
IgM	Immunoglobuline M (antibody type M)

JCVI	Joint Committee on Vaccination and Immunisation (UK NITAG)
KNVM	Koninklijke Nederlandse Vereniging voor Microbiologie (Royal Dutch Organisation for Microbiology)
M	Membrane protein
ME/CFS	Myalgic Encephalitis/Chronic Fatigue Syndrome
MERS-CoV	Middle East Respiratory Syndrome - Corona Virus
MHC	Major Histocompatibility Complex
mRNA	Messenger RNA
N	Nucleocapsid protein
NHP	Non-Human Primates
NHS	National Health Service
NIPH	Norwegian Institute of Public Health
NITAG	National Immunization Technical Advisory Group
NVOG	Nationale Vereniging voor Obstetrie en Gynaecologie (National Organisation for Obstetrics and Gynaecology)
ORF	Open Reading Frame
PCR	Polymerase Chain Reaction
PICO	PIENTER-Corona-Study
PIENTER	Peiling Immunisatie Effect Nederland Ter Evaluatie van het Rijksvaccinatieprogramma
PIMS	Paediatric Inflammatory Multisystem Syndrome
PPE	Personal Protection Equipment
QALY	Quality-adjusted Life Year
R	Reproduction number
RBD	Receptor Binding Domain
RdRp gene	RNA-Dependent RNA Polymerase gene
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (National Institute for Public Health and the Environment)
RKI	Robert Koch Institute
RNA	Ribonucleic Acid
RT-PCR	Real Time Polymerase Chain Reaction
S	Spike protein
SARS	Severe Acute Respiratory Syndrome
SARS-CoV(-1)	Severe Acute Respiratory Syndrome - Corona Virus
SARS-CoV-2	Severe Acute Respiratory Syndrome - Corona Virus - 2
SCID	Severe Combined Immunodeficiency
SENAME	National Service for Minors
SHC	Superior Health Council (Belgian NITAG)
SPEAC	Safety Platform for Emergency vACcines
STIKO	Standing Committee on Vaccination (German NITAG)
Tfh	Follicular (B-cell) helper T-cell
Th	Helper T-cell
Treg	Regulatory T-cell
UK	United Kingdom
VLP	Virus Like Particle
WHO	World Health Organisation
WTP	Willingness To Pay
µm	Micrometer

