Epidemiological impact and effectiveness of COVID-19 measures

RIVM/CIb/EPI/MOD

Version 23 January 2024

Contents

Verzoek van VWS aan RIVM

Naar aanleiding van het tweede rapport van de OVV d.d. woensdag 12 oktober 2022 heeft VWS het RIVM gevraagd te bezien op welke wijze de effectiviteit van (combinaties van) maatregelen inzichtelijk gemaakt kunnen worden, zodat deze kennis beschikbaar is t.b.v. advisering en besluitvorming in een volgende besmettingsgolf of pandemie. Het doel van deze opdracht is om voorbereid te zijn op de toekomst. RIVM heeft hierin als kennisinstituut - zowel vanuit de wettelijk taak van het RIVM gerelateerd aan de Wet publieke gezondheid (op het terrein van infectieziektebestrijding, gezondheidsadvisering en psychosociale hulpverlening) als op basis van het gezondheidsonderzoek bij crisis en rampen – een belangrijke rol waar het gezondheids- en maatschappelijke (welzijns-) effecten en gedrag betreft in de vorm van advisering aan VWS, OMT en MIT. De wens is om hierbij ook internationaal beschikbaar onderzoek te betrekken en waar mogelijk de Nederlandse situatie te vergelijken met andere vergelijkbare landen.

Het gaat hierbij primair om het versterken van het inzicht in directe epidemiologische gevolgen van maatregelen (effectiviteit). Dit levert kennis en inzichten op, die vooruitkijkend bruikbaar zijn voor advisering en beleidsvorming t.b.v. COVID-19 en pandemische paraatheid.

Samenvatting

We leveren bewijs voor de effectiviteit van de genomen COVID-19 maatregelen in Nederland. We schatten de effectiviteit van de pakketten van niet-farmaceutische interventies in het tegengaan van transmissie van infectie. We laten zien dat eenzelfde effectiviteit tegen transmissie tot heel andere uitkomsten van de pandemie zou hebben geleid als de interventies één of drie dagen later zouden zijn ingegaan, en we vergelijken de effecten van de maatregelpakketten zoals gekwantificeerd voor Nederland met die zoals gekwantificeerd voor andere landen (België, Duitsland, Denemarken, Zweden, Verenigd Koninkrijk). We laten zien dat de effectiviteit van maatregelen toeneemt met toenemende stringentie van de maatregelpakketten. Deze associatie wordt aangevuld met de waarneming dat met toenemende stringentie van de maatregelpakketten het aantal gerapporteerde contacten in contactonderzoeken afnam, en dat de transmissie afnam van andere infectieziekten met dezelfde transmissieroute als SARS-CoV-2. In een literatuuroverzicht identificeren we wat er bekend is over de bijdrage van individuele interventies aan de effectiviteit van maatregelpakketten, en wat er bekend is over de effectiviteit van COVID-19 vaccins. We bespreken methoden om de effectiviteit van maatregelpakketten te ontleden in bijdragen van individuele interventies met behulp van gegevens uit meerdere landen, we verwijzen naar de huidige beste schattingen, en identificeren de beperkingen van het gebruik van deze schattingen voor toekomstige infectieziektebestrijding. We bevelen aan de complementariteit van interventies te onderzoeken en een structuur voor gegevensstromen op te zetten zodat informatie geleverd kan worden voor infectieziektebestrijding bij toekomstige pandemie.

Summary

We provide evidence for the effectiveness of COVID-19 measures in the Netherlands. We estimate the effectiveness of the bundles of non-pharmaceutical interventions (NPIs) against transmission. We show that the effectiveness against transmission would have resulted in a very different outcome on the pandemic if the interventions would have been delayed by one or three days, and we compare the effects of the bundles of interventions as quantified for the Netherlands with the bundles of interventions as quantified for other countries (Belgium, Germany, Denmark, Sweden, UK). We show that the effectiveness increases with increasing stringency of the control measures. This association is complemented by an association with a decreasing number of contacts as reported in contact surveys, and a reduction in transmission of other infectious diseases that have the same transmission route as SARS-CoV-2. In a literature review we identify what is known about the contribution of individual interventions and the vaccine effectiveness. We report on approaches to disentangle the contribution of individual interventions to the overall effectiveness in reducing transmission, using information from multiple countries, we point to current best estimates and identify the limitations to using these estimates for future infection control. We recommend looking into complementarity of interventions, and setting up data streams that inform infection control in a future pandemic.

Introduction

Pandemics are a threat to society. At the peak of a pandemic wave there is a substantial risk of increased absenteeism and problems might arise with, for example, supply chains to supermarkets, garbage collection, and traffic control. This can lead to societal unrest and even to collapse of the critical societal infrastructure. The healthcare demand can exceed the available healthcare capacity, which can result in a collapse of the healthcare infrastructure. Critical healthcare personnel can become infected, which reduces the available capacity, which increases the risk of collapse of the healthcare infrastructure. A collapse of healthcare infrastructure, or societal infrastructure, could result in withholding essential care from those who need it most, resulting in higher mortality rates. The costs of such a collapse are huge.

The healthcare demand per day due to an infectious disease is determined by several factors. These factors are the number of new infections per day, the probability of a severe outcome per infection, and the number of days that healthcare is needed for a severe outcome of the disease. For SARS-CoV-2, the virus that causes the disease COVID-19, the transmission potential was sufficiently high to spreadamong a large number of individuals who were susceptible in the beginning of 2020, which could cause a large number of new infections per day in absence of control. This, combined with a relatively high probability of severe outcome and relatively long duration of required healthcare for those with a severe outcome, provided COVID-19 the potential to cause a collapse of the healthcare infrastructure in absence of control. In the Netherlands, the approach to control during the first phase of the COVID-19 pandemic has been guided by monitoring the spread of the virus, ensuring that healthcare demand does not exceed the available capacity, and protecting the vulnerable risk groups in the population. Later, in 2021, weighing the economic and societal consequences was also explicitly mentioned.

Infection control reduces the probability of infection per unit of time of being exposed to infection. One way of interpreting this, is that infection control results in postponing the time of infection and spreading the risk of infection over a longer period. By postponing and spreading the time of infection, a wave of healthcare demand that would exceed the capacity can become a steady trickle of demand that can be dealt with in the healthcare infrastructure. Infection control can also reduce the transmissibility of infection. When infection control measures reduce transmissibility, they will decrease the growth rate of the number of daily infections, hospitalizations, IC admissions, deaths. The level of control required to stop this growth is determined by the reproduction number, defined as the number of infections that are caused on average by a typical single infectious person. For example, if an infection is transmissible such that each infectious person would on average infect five others, we say the reproduction number is 5, and that the critical level of control is achieved when 4 out of 5 (80%) of the secondary infections are prevented. If we prevent fewer secondary cases, the number of daily new cases will increase. If we prevent more, the number of daily new cases will decrease.

In a pandemic, policy makers have to base their decisions on incoming information from infectious disease surveillance and monitoring. Decision making is a dynamic problem in the sense that, when control is insufficient, the risk of collapse of the healthcare infrastructure increases exponentially fast over time, whereas the costs of control tend to remain constant. When the objective is to avoid healthcare collapse, the question is when to start control and how to achieve the required level of control. Given the situational assessment, policy makers decide when to control, where to control, and how targeted control measures are. The required level of control is determined by the characteristics of the infection and the population. A key question for policy makers is which bundles of interventions can achieve the required effectiveness. A secondary question is which sufficiently effective bundles meet additional requirements of sufficient support, sufficiently high compliance, at proportional and acceptable societal costs.

Here we address the following questions: How effective were bundles of COVID-19 measures in reducing SARS-CoV-2 transmission in the Netherlands? How does this translate into effectiveness against other outcome measures, such as hospitalisations and deaths? How did individual measures contribute to this effectiveness? It is important to know whether measures were effective. It is also important to understand the contribution of individual measures to the overall effectiveness to support the application of similar measures in a future pandemic.

This report summarizes information from the international literature and from various studies that focus on the COVID-19 pandemic in the Netherlands. These studies have been published in international peer-reviewed journals, or they are being prepared for publication. The list with these publications, manuscripts, and a review of the international literature, are provided as appendices to this report. As these publications, manuscripts and review contain a detailed overview of the national and international literature, we have chosen to provide only essential references in this summary. We will make a distinction in the control measures and treat vaccines separately from non-pharmaceutical interventions (NPIs) such as distancing and working from home.

We organize the text into chapters that each address a specific question. We will first indicate where one can find information on vaccine coverage in the Netherlands and information on the timeline of implemented NPIs. Second, we assess the effectiveness of bundles of NPIs and vaccination against transmission of SARS-CoV-2 in the Netherlands. Third, we translate the effectiveness against transmission into effectiveness of control strategies against severe outcomes such as death and hospitalisations. We compare strategies from different neighbouring countries and highlight the importance of timing of interventions in determining the effectiveness against severe outcomes. Fourth, we check whether bundles of NPIs also resulted in lower number of contacts in the population, and whether a lower number of contacts in the population resulted in less transmission of pathogens that spread along the transmission route of SARS-CoV-2. Fifth, we describe a strategy to decompose the effectiveness against transmission into individual contributions of measures and highlight the underlying assumptions; we summarize results for individual measures from peer-reviewed scientific publications. Sixth, we pull the different lines of argument together to indicate what this means for the limitations on what we can do with the outcomes for a future pandemic. Last, we recommend specific further steps for preparing for infection control in future pandemics.

COVID-19 measures in the Netherlands

Non-pharmaceutical interventions

An overview of the non-pharmaceutical interventions in the Netherlands is provided online (https://www.rivm.nl/gedragsonderzoek/tijdlijn-van-coronamaatregelen-2020). As there are many individual measures, we score the stringency of the entire bundle of individual measures at any day. We use the Stringency Index, defined by the Oxford Coronavirus Government Response Tracker (OxCGRT) project. This is a composite measure of nine of the response metrics: school closures; workplace closures; cancellation of public events; restrictions on public gatherings; closures of public transport; stay-at-home requirements; public information campaigns; restrictions on internal movements; and international travel controls, see https://github.com/OxCGRT/covid-policy-tracker/blob/master/documentation/index_methodology.md. An increasing score implies that a country's government response is becoming more stringent, a decreasing score implies that the response becomes less stringent. The absolute value of the stringency index is hard to interpret or compare but changes in value are useful to indicate the periods when control becomes more stringent, and the periods when control is relaxed. The stringency of the Dutch government response as measured by the Oxford Stringency Index shows gradual build-up towards local peaks followed by gradual relaxation, with localized peaks occurring by the end of March 2020; the end of January 2021; and the start of January 2022 (Figure 1).

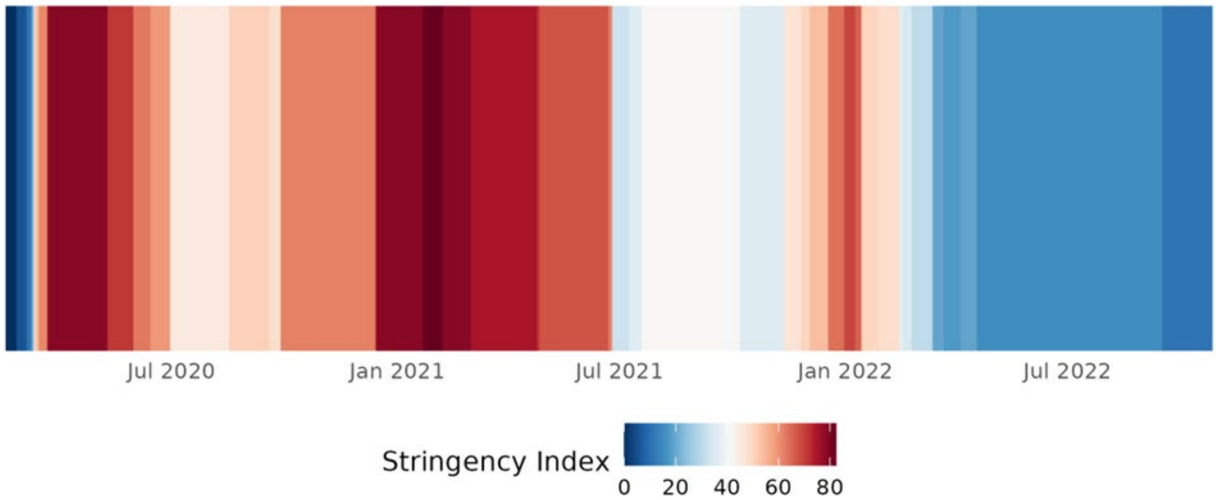

Figure 1: Stringency Index for the Dutch government response to the COVID-19 pandemic (1 January 2020 - 31 December 2021)

Vaccination coverage

An overview of vaccination coverage in the Dutch population is available by age-group/birth cohort and by type of vaccine. RIVM routinely update their estimate of the current national-level vaccination coverage (both aggregated over age, and by 5- or 10-year age-group). These estimates are available online (https://coronadashboard.rijksoverheid.nl/landelijk/vaccinaties). For instance, according to data as of 12 April 2023, 80.2% of persons aged 12 years or older had completed their primary series of vaccinations (1 or 2 doses, depending on vaccine type and whether the person already has confirmed SARS-CoV-2 infection). The per age-group coverage for the primary series varied from 3% (5-11 year olds) to 93% (70-79 year olds).

Effectiveness of COVID-19 measures in reducing transmission

Effectiveness in reducing transmission

Effect of interventions can be quantified using various outcome measures, such as the reproduction number, or numbers of cases, hospitalizations, or deaths. Of these, the effectiveness in reducing reproduction numbers is an instantaneous effect, whereas other outcome measures are affected by earlier interventions with large lag times and have to be defined over a specific time interval. The primary rationale of non-pharmaceutical interventions (NPIs) is to reduce person-to-person transmission by altering contact rates and contact patterns and by reducing the probability of infection upon contact. This in turn will reduce the probability of infection per day of those who are at risk of developing severe disease (hospitalization or death). This rationale motivates our choice to focus first on the effectiveness of NPIs to reduce transmission and quantify reduced transmission by the reduction in the effective reproduction number.

Effective reproduction number R_t in the Netherlands

The effective reproduction number R_t is defined as the average number of secondary cases infected by a primary case. The epidemic grows when the value is larger than one, and the epidemic declines when the value is smaller than one. The value of the reproduction number provides information on the required control effort to prevent the epidemic from growing. Here, we use the reproduction number for SARS-CoV-2 infections to assess the effect of various bundles of interventions. The reproduction numbers for the Netherlands were calculated weekly or twice per week from March 2020 onwards, and the results are published in the open RIVM data (https://data.rivm.nl/covid-19/) and on the COVID-19 dashboard (https://coronadashboard.rijksoverheid.nl/). The effective reproduction number is calculated from the time series of reported symptom onset dates and the distribution of the generation interval (i.e., the time between successive infections). The mean generation interval was 4 days for all SARS-CoV-2 variants other than Omicron, and 3.5 days for Omicron variants (Figure 2).

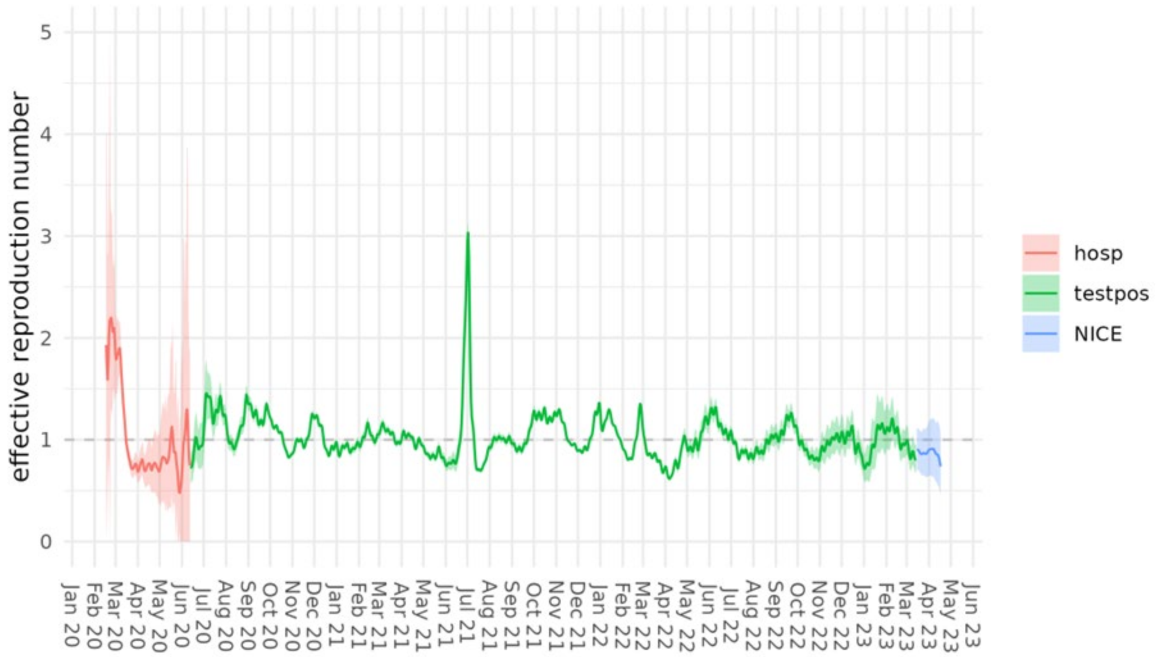

Figure 2 Time series of effective reproduction number R_t in the Netherlands (mean and 95% confidence interval), based on data of 2 May 2023. The reproduction number was based on the hospitalisations reported in Osiris from 17 Feb 2020 until 12 Jun 2020, on the test-positive cases

reported in Osiris from 13 Jun 2020 until 14 Mar 2023 and on the hospitalisations reported in NICE from 15 Mar 2023 onwards. Of these, we consider the reproduction number based on test-positive cases as the most accurate. As test-positive cases were not available at the start of the pandemic, we use test-positive hospitalizations in the initial phase, as recorded in Osiris. As test-positive cases were no longer available at the end, we use hospitalizations which were tested positive by NICE in the most recent phase.

Effectiveness of non-pharmaceutical interventions in reducing transmission in the Netherlands

We use the time series of the effective reproduction number R_t to explore the effectiveness of non-pharmaceutical interventions (NPIs). We use the basic reproduction number, $R_0(t)$, to express how many secondary cases would have been infected on average by a primary case in a fully susceptible population without any control measures. This coincides with the observed value of R_t at the very start of an epidemic before interventions were implemented. We would like to quantify to what extent the R_t is reduced from this value $R_0(t)$ due to interventions, and not due to a build-up of immunity due to natural infection and vaccination. To this end we estimate the effective susceptible fraction of the population (S^{eff}). This leads to an estimator of the effectiveness of the NPIs:

$$\text{effectiveness}(t) = 1 - \frac{R(t)}{S^{eff}(t)R_0(t)}.$$

In this definition, the effectiveness of NPIs includes compliance.

The basic reproduction number $R_0(t)$ can change over time. Seasonal effects can increase R_0 in winter due to meteorological conditions that are favorable for virus survival and crowding. For SARS-CoV-2 the basic reproduction number has also increased over time due to the emergence of new, more transmissible variants. Here, we assume that the growth advantages of the Alpha and Delta variants were completely attributable to a higher transmissibility (that is, to a higher R_0). The calculations do not account for the immune escape that allowed the Omicron variants to supersede the previously circulating variants. Therefore, we limit the analysis to the period before the Omicron variants became dominant.

Over the course of the pandemic, the proportion of immunes increased in the population by infection and from early 2021 onwards by vaccination. We estimate the proportion immunes by infection from the Pienter Corona serosurveys that were conducted two or three times per year. For each age group, we impute the cumulative infection incidence for the days between consecutive serosurveys from the reported case data. The proportion of immunes due to vaccination is calculated from the vaccination uptake per age group, multiplied with the vaccine effectiveness. We account for the waning of immunity over time, i.e., the loss of protection against infection, both after infection and after vaccination. The effective susceptible fraction is calculated as a population weighted average of the proportion susceptibles (those who are not immune or infected). In an additional sensitivity study, we also accounted for the dynamic effect of heterogeneities in infection attack rate between age groups (results not shown), but this did not change the results.

The results (Figure 3) indicate that effectiveness of NPIs in reducing transmission in the Netherlands was high during the first wave (March – May 2020) and during the winter of 2021 when the Alpha variant emerged. The negative values for effectiveness around July 2021 (‘dansen met Janssen’) suggest that the number of at-risk contacts for transmission was higher than before implementation of interventions. In the autumn of 2021, the effectiveness of NPIs in reducing transmission decreased due to high vaccination levels, and the extent of this decrease strongly depends on the assumed rate of waning. Localized peaks in effectiveness correspond to localized peaks the stringency index.

In interpreting these results, it is important to acknowledge the assumptions made. For instance, immunity is considered as an all-or-nothing response, where an individual whose immunity waned is assumed to be as susceptible to infection as a naïve individual, and – when infected again – as infectious as a naïve individual. Second, the calculations accounted for the uncertainty with respect to the effective reproduction number, the serological survey results, and the waning rates, but not for uncertainty with respect to the seasonality effect and the transmissibility of new variants.

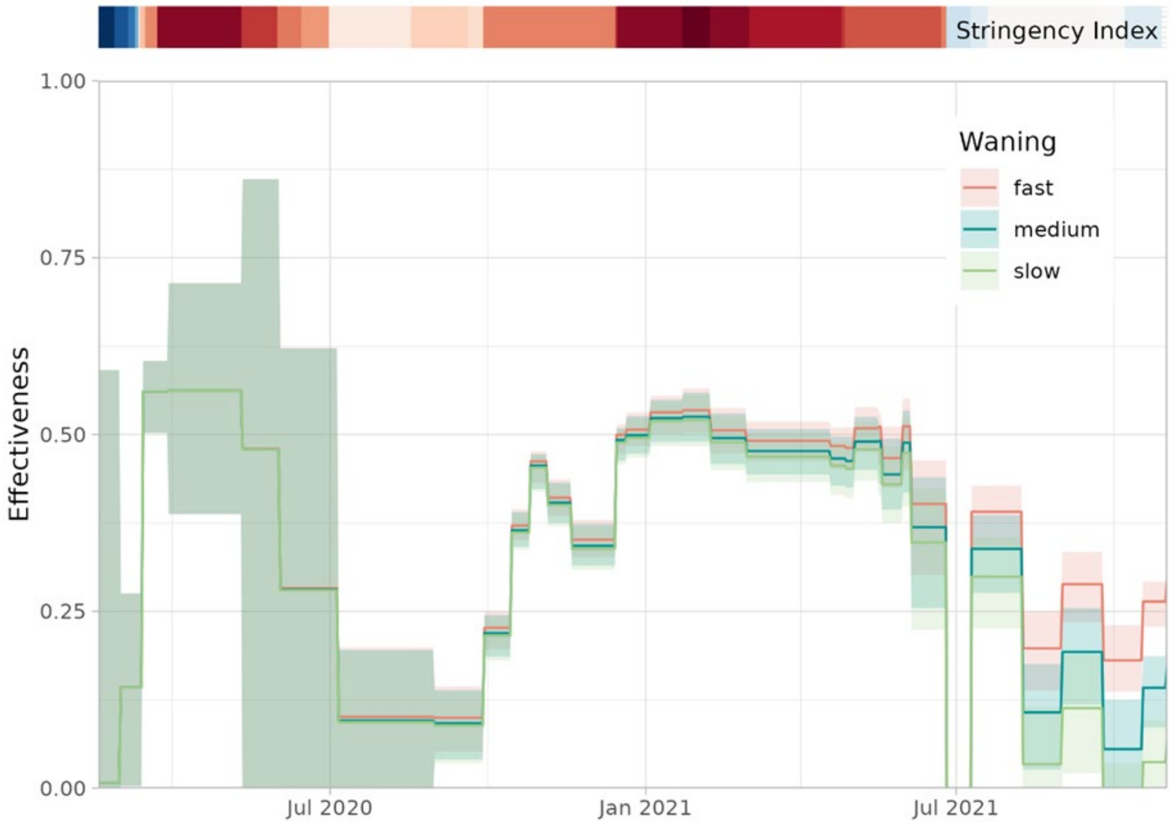

Figure 3 Effectiveness of NPIs in reducing transmission from the start of the COVID-19 pandemic up to the emergence of the Omicron variant in the Netherlands, for three different scenarios of waning of immunity over time after infection and vaccination (mean and 95% confidence interval). For comparison, we indicate the stringency index of the Dutch COVID-19 policy. Localized peaks of stringency (dark red) correspond with localized peaks in effectiveness, and conversely, localized throughs in stringency (blue) correspond with localized throughs in effectiveness. (10 February 2020 – 1 November 2021

Effectiveness of control strategies in reducing severe outcomes

Whereas implementing a bundle of interventions has an almost instantaneous effect on reducing transmission, the effect of on other outcome measures, such as number of infections, or number of cases, number of hospital admissions and mortality, will depend also on the timing of the interventions. Here we illustrate how different interventions with different timing could have led to alternative outcomes in the Netherlands. We focus on interventions as taken by other Western-European countries, as these countries were in a comparable situation to the Netherlands at the start of the COVID-19 pandemic. We focus on mortality as an outcome measure for the practical reason that time series with mortality are available for multiple countries. We choose to use a method and code that has been developed and published by another research team outside the Netherlands, and that has not been previously applied to data on the Netherlands. We focus on the first pandemic wave, specifically the period from February 2020 to July 2020, to highlight the impact of timing of intervention measures; in subsequent waves the impact of timing of interventions relative to the timing of the wave would suffer from interference with earlier measures.

What if we had implemented COVID-19 control strategies as in Belgium, Denmark, Germany, Sweden, or the UK?

We explore how the impact of the first COVID-19 wave in the Netherlands may have differed if it had adopted response strategies from other Western-European countries. We build upon a prior modelling study by Mishra et al. (2020) and compare response strategies of six countries: the Netherlands, Belgium, Denmark, Germany, Sweden, and the United Kingdom (UK). The time-dependent reproduction number (R_t) during the first pandemic wave (February 2020 up to and including June 2020) was estimated for each country using time-series of daily laboratory-confirmed COVID-19 deaths by date of death. In this study, we use different data and a different method to estimate the effective reproduction number R_t as compared to the previous section. Here, the basic reproduction number R_0 is obtained by fitting the model to the first week of time-series of deaths after a country had observed a total of 10 cumulative death cases.

Time series of laboratory-confirmed COVID-19 mortality by date of death for the Netherlands were extracted from the OSIRIS database, the national registry for laboratory-confirmed COVID-19 cases of the RIVM. For Belgium, similar time series data were obtained from Sciensano, and for Germany from the Robert Koch Institute (personal communication, M. an der Heiden, 1 December 2022). A detailed description of the mortality time series for the other countries and on how R_t was computed can be found in Mishra et al (2020). Infection-to-death delay distributions were assumed to be the same between countries. We described the distribution of generation interval by a gamma distribution with a mean of 4 days and a standard deviation of 2 days to maintain consistency with the observed duration of the serial interval for SARS-CoV-2 transmission in the Netherlands and the calculations in the previous section. For the counterfactual assessment, we simulated a growing epidemic for the Netherlands with the reproduction number R_t equal to R_0 until 13 March 2020. From 13 March 2020 to 1 July 1 2020 we substituted the relative reduction in the reproduction number (i.e., the ratio of the effective and the basic reproduction numbers R_t/R_0) for the Netherlands by that of another country (e.g. Belgium) on the same calendar day. This approach allowed us to adopt the calendar time and reduction in transmission as observed in another country.

The median basic reproduction number R_0 was highest for Belgium, the Netherlands, and the UK, and lowest for Sweden and Denmark. Following the implementation of strict control measures after 13 March, the reproduction number R_t decreased rapidly in all countries, eventually dropping below 1, indicating the suppression of the epidemic. The pace of this decline in R_t during March varied among countries. The Netherlands and Denmark were the first countries achieving an R_t below 1. Sweden showed a less rapid decline in the reproduction number R_t as compared to the other countries. In all countries, there was an increase in the reproduction number R_t in the second half of April.

We obtain alternative, counterfactual control strategies for the Netherlands by transferring the relative reduction in reproduction number from other countries to the Netherlands from 13 March onwards. The subtle differences in the reproduction number R_t between countries lead to substantial differences in absolute numbers of deaths (Figure 7 and Table 1). If R_t were to drop below 1 only a few days later, as seen in the time series of reproduction numbers as observed in Denmark, Belgium, Germany and the UK, the peak number of deaths in the Netherlands during the first wave would have increased from approximately 170 per day to a range of 300 to 600 per day (Figure 4, based on median estimates). In case of a response strategy from Sweden, the peak number of daily deaths in the Netherlands would have reached almost a thousand deaths per day. With any other response strategy, the total number of deaths throughout the first wave would have significantly increased in the Netherlands (Table 1). Transferring the response strategies of Belgium and Denmark to the Netherlands would have resulted in a two-fold increase in number of deaths compared to the observed amount. The response strategies of Germany and UK would have led to three-fold increase in deaths, and the response strategy of Sweden was even associated with a seven-fold increase in deaths.

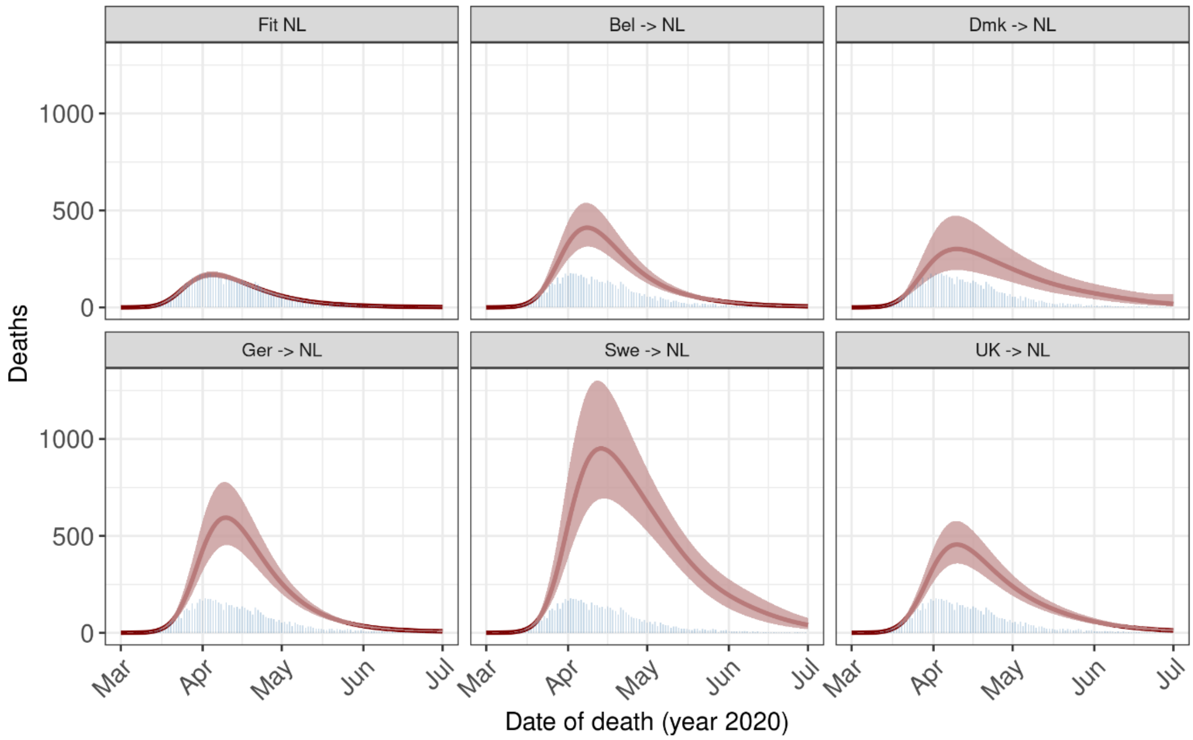

Figure 4: Estimated median number of daily deaths with 95% credible intervals for the Netherlands, showing the fit to observed data (blue bars) and the counterfactual analyses, involving the transfer of the relative reduction in reproduction number from Belgium (Bel), Denmark (Dmk), Germany (Ger), Sweden (Swe), and the United Kingdom (UK) to the Netherlands (NL) in the period March 13, 2020, to July 1, 2020.

Table 1: Estimated relative differences in cumulative deaths during the first COVID-19 wave, compared to observed number of deaths, when the response strategy from another country would have been transferred to the Netherlands. The analysis covers the period February 2020, up to and including June 2020, with counterfactual scenarios involving the transfer of the relative reduction in reproduction number from different countries to the Netherlands from March 13, 2020, onwards. If the multiplication factor is above 1, the number of deaths of the Netherlands would have increased with the counterfactual response strategy, and if below 1, the number of deaths would have decreased.

Response strategy	Multiplication factor of cumulative deaths, median (95% credible interval)
The Netherlands	Reference (=1)
Belgium	2.4 (1.8-3.0)
Denmark	2.5 (1.7-3.5)
Germany	3.4 (2.6-4.3)
Sweden	7.1 (5.6-8.9)
United Kingdom	3.0 (2.4-3.7)

What if the Dutch control strategy would have started a few days later?

To assess whether the outcomes might be due to differences in timing of implementation of the strategies, rather than the difference in strategies per se, we also assessed how the impact of the first COVID-19 wave may have differed if the response strategy of the Netherlands had been delayed by one day or by three days. To assess the consequences of delaying the Dutch response strategy, we shifted the time-series of deaths used for computing the reproduction number R_t to one day or three days later and interchanged the values of the relative reduction in the reproduction number (R_t/R_0) as explained for the international comparison.

Slight changes in the reproduction number R_t lead to substantial differences in absolute deaths. A one-day delay in response measures would increase the peak number deaths to more than 200 per day (Figure 5), while a three-day delay would have more than doubled the peak number of daily deaths to 400. The number of deaths throughout the first wave was estimated to increase by a factor 1.2 (95% credible interval [CrI]: 0.9-1.6) for a one-day delay (Table 2). For a three-day delay, the number of deaths throughout the first wave significantly increased by factor 2.3 (95% CrI: 1.7-3.1).

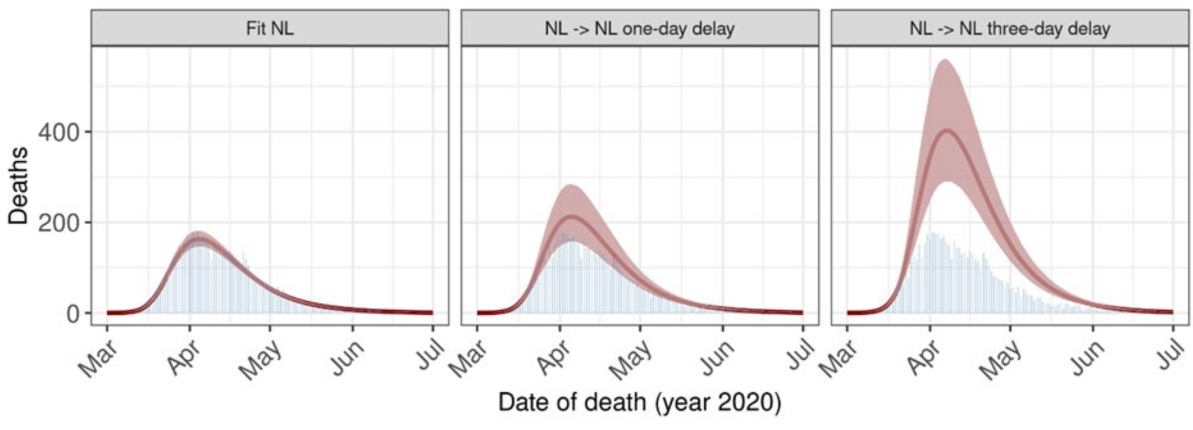

Figure 5: Estimated median number of daily deaths with 95% credible intervals for the Netherlands, showing the fit to observed data (blue bars) and the counterfactual analyses involving response measures taken one day later or three days later in the period March 13, 2020, to July 1, 2020

Table 2: Estimated relative differences in cumulative deaths during the first COVID-19 wave, compared to observed number of deaths, if the response strategy of the Netherlands would have been delayed by one day or by three days. The analysis covers the period February 2020, up to and including June 2020, with counterfactual scenarios involving the transfer of the relative reduction in reproduction number from different countries to the Netherlands from March 13, 2020, onwards. If the multiplication factor is above 1, the number of deaths of the Netherlands would have increased

with the counterfactual response strategy, and if below 1, the number of deaths would have decreased.

Response strategy	Multiplication factor of cumulative deaths, median (95% credible interval)
The Netherlands	Reference (=1)
The Netherlands, one-day delay of response	1.2 (0.9-1.6)
The Netherlands, three-day delay of response	2.3 (1.7-3.1)

This analysis provides a quantitative understanding of the possible impact that alternative COVID-19 response strategies would have had on mortality in the Netherlands during the first pandemic wave in the period February 2020, up to and including June 2020. The analysis illustrates that in a rapidly growing epidemic, relatively slight differences in timing of measures can result in large differences in absolute number of deaths. In the initial phase of the epidemic, without control measures, the incidence of new infections doubled every 2-3 days. Delaying the response strategy by three days could therefore lead to more than a doubling in mortality during a single epidemic wave. As the Netherlands was slightly earlier to suppress the epidemic wave (in the sense of bringing the reproduction number Rt below the critical value of 1), compared the Belgium, Denmark, Germany, Sweden and the UK, adopting the response strategies from these other countries would have led to at least a doubling in mortality in the Netherlands. As the response strategy from Sweden was also less strict, such an approach would have led to a seven-fold increase in mortality in the Netherlands.

The question is whether this outcome is specific to the choice of mortality as outcome measure, and whether a similar ordering of strategies would result if we would have taken time series of hospitalization. When comparing weekly hospitalizations rates by admission date during the first wave between the Netherlands and Belgium, the Netherlands was also slightly earlier in scaling the peak and decreasing the incidence of hospitalizations. Even though there are variations in admission criteria and hospital bed capacities, which might complicate the interpretation of incidence of hospitalizations, the order for strategies in which they achieved the peak incidence of new hospitalizations aligns with the order for strategies in which they achieved the peak incidence of mortality. This suggests the outcome of the counterfactual assessment using mortality time series would have been similar the outcome of a counterfactual assessment with hospitalizations time series.

Great care must be taken in distinguishing the counterfactual assessment where the time series of relative reduction in reproduction numbers are transferred from one country to another from the actual implementation a different strategy in another country. For example, a high incidence of infection may trigger policy makers to increase stringency of the measures, the perceived severity of infection and fear may affect compliance; also, trust in the government may play a role in determining compliance and thus affect the outcome. Public support for more stringent measures might be higher in a country when neighboring countries are introducing or have already introduced stringent measures, as compared to a situation where a country is the first to impose stringent measures. The six countries differed with respect to the incidence of infection when more information became available about the SARS-CoV-2, the required control effort, and the severity of infection. Countries with a higher level of incidence of infection at the start date of this study will have, all other aspects remaining equal, a higher number of infections and severe outcomes over the entire study period.

The effect of interventions in reducing number of contacts per day

When we assess the effectiveness of interventions on transmission, this implicitly suggests that the intervention is a cause, and that the reduced transmission is an effect. For vaccines, the randomized clinical trials provide evidence that there is a causal relation. For non-pharmaceutical interventions there are no randomized clinical trials; a trial with a NPI during a pandemic might be considered unethical. Because the effectiveness of a bundle of NPIs is achieved in part by reducing contacts, we can see if there is evidence for an association between the intervention and the reduction of contacts, and between the reduction of contacts and the reduction of transmission.

Non-pharmaceutical interventions (NPIs)

Unlike vaccines, NPIs do not go through randomized controlled trials (RCTs) to prove their effectiveness before they are implemented. The estimates of their effectiveness are derived from observational studies. The primary rationale of NPIs is to reduce transmission through reducing contacts between individuals and reducing the probability of transmission upon contact. It is essential to test whether they have achieved the reduction in contacts and reduction in probability of transmission upon contact. In this setting, the contacts per day are termed 'mediating variables,' as they mediate between the cause and effect. The RIVM has set up studies to observe the effects of interventions on contacts for different age groups, as mediating variables, and we report the results here. If the reduction in contacts affects the transmission of SARS-CoV-2 we should also expect it would affect the transmission of other infections that have a similar transmission route as SARS-CoV-2; we report here on the surveillance of such infections.

Contact surveys reveal that contacts were reduced

Pienter Corona contact survey

The effect of intervention bundles on contact patterns in the Dutch population was monitored in regular intervals. The RIVM conducted the Pienter Corona studies in which a representative sample of several thousand persons from the Dutch population indicated how many contacts were made on the previous day. Intervals between successive survey rounds were a few months, with the first round in April 2020 and at the time of writing the most recent round in autumn 2023.

The results of this study show that the intervention bundles affected the age groups differently. During the initial stages of the first wave, contacts of all age groups were drastically reduced (on average 76%, Backer et al. 2020), but whereas the youngest children quickly reverted to their prepandemic behaviour, adults have remained below their prepandemic levels by the autumn 2023. In the survey rounds of November 2022 and May 2023 the weighted average number of contacts in the general population is well below the prepandemic level. This indicates a 'new normal' behaviour may have established, which could affect the transmission potential of not only COVID-19 but all respiratory infections (Figure 6).

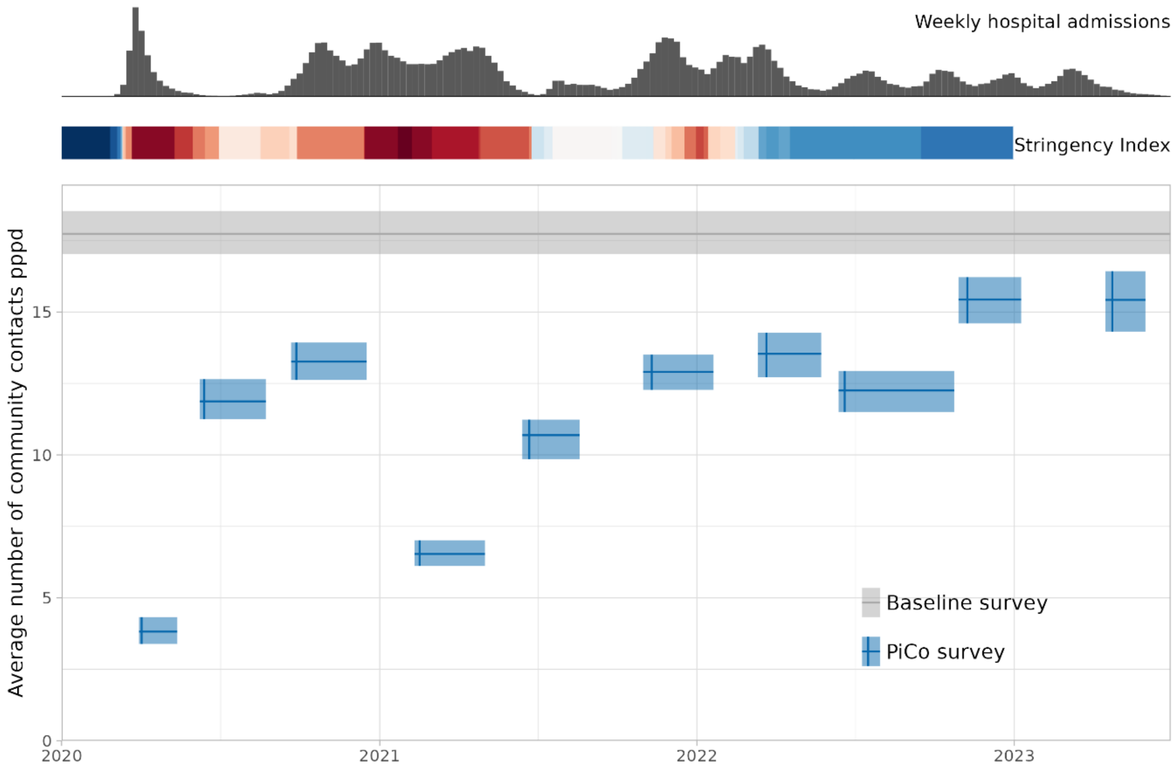

Figure 6 Number of community contacts (i.e., with persons outside the household) per participant per day (weighted by age, sex, and week/weekend) over the course of the COVID-19 pandemic, compared to the prepandemic baseline (Pienter3, 2016/2017). Shown is the average number of contacts (horizontal line) and 95% bias-corrected bootstrap interval (shaded area). Study rounds are shown from the minimum to maximum survey date, with the median survey date (vertical line). As a reference the weekly number of hospital admissions and the Oxford Stringency Index are depicted on top with the same timeline. Localized peaks of stringency (dark red) correspond with localized dips in the number of contacts in the community per capita, and conversely, localized throughs in stringency (blue) correspond with localized peaks in the number of contacts in the community per capita. (1 January 2020 – 30 June 2023).

COMIX contact survey

The CoMix study was conducted as part of the EU Horizon project EpiPose, with the aim of monitoring contact patterns using the same methodology in various European countries. A panel of Dutch people reported how many contacts were made with an interval between consecutive reporting moments of two weeks.

The survey included 1659 participants from April to August 2020 and 2514 participants from December 2020 to September 2021. We categorized the number of unique contacted persons excluding household members, reported per participant per day into six activity levels, defined as 0, 1, 2, 3-4, 5-9 and 10 or more reported contacts. After correcting for age, vaccination status, risk status for severe outcome of infection, and frequency of participation, activity levels increased over time, coinciding with relaxation of COVID-19 control measures.

Because of the European design of the CoMix study, we can make an international comparison of contact patterns. The same protocol and questionnaire were used in 20 European countries, with the longest time series of contact patterns for England, Belgium, and the Netherlands. A final survey round was conducted in these three countries November and December 2022 with 7,477 participants. Despite the number of contacts being higher compared to pandemic levels, they were not back to the levels seen prior to the pandemic (Figure 7).

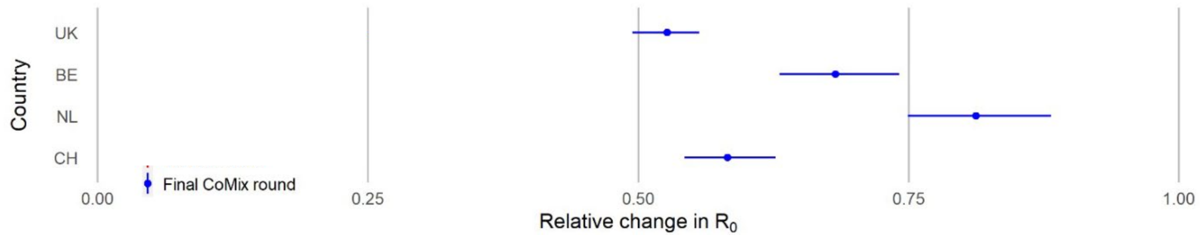

Figure 7. Relative change in typical number of contacts per person in the CoMIx survey in 2022 compared to a baseline contact survey in 2007, Polymod study, which measured contacts in Western European countries, using the dominant eigenvalues of contact matrices to estimate a relative change in R_0 (after Jarvis et al. 2023). If there would have been no change in contacts per person since 2007, the value would have been one, the observed values lower than one indicate a decreased number of contacts in 2022 relative to 2007.

SCONE contact survey

Another survey monitoring contact patterns was specifically focused on contacts of the elderly. The SCONE study, a ZonMw project conducted by RIVM, looked at how frailty affected the number of contacts of persons aged 70 years and older, in two periods in 2021. During the first period in April 2021 when stringent measures were in place, frail and non-frail participants had significantly lower numbers of contacts compared to the second survey period in October 2021 with moderate measures. During this second survey period, non-frail participants had significantly more contacts outside their household than frail participants. The change in number of contacts between the first and second survey period was largest for the eldest non-frail participants. As these eldest non-frail individuals may interact closely with highly aged and highly frail persons, a reduction in the number of their contacts might offer indirect protection of frail elderly from SARS-CoV-2 exposure (Figure 8).

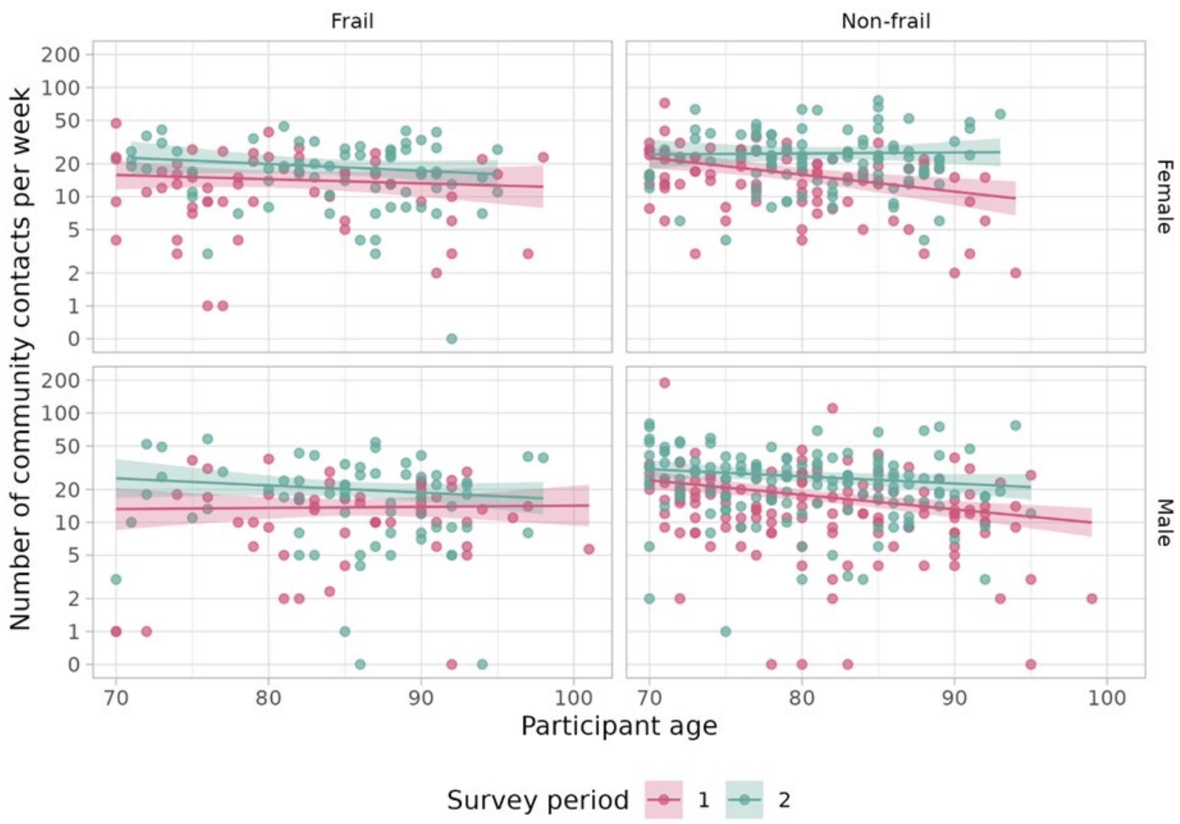

Figure 8: Weekly number of community contacts (i.e., persons contacted outside the household) per participant by age in survey periods 1 (April 2021) and 2 (October 2021). Plots show the data (one point for each participant) and model results (mean as solid line and 95% confidence interval as shaded area) by frailty (columns) and gender (rows).

Side-effect of COVID-19 NPIs: a decline in transmission of other respiratory infections

Circumstantial evidence for the effectiveness of NPIs is provided by a drop in reported infections with other seasonal respiratory viruses while measures were in place during the COVID-19 pandemic (Middeldorp et al. 2020; Annual report Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2021/2022 https://www.rivm.nl/bibliotheek/rapporten/2022-0098.pdf). If the NPIs are effective in reducing transmission of SARS-CoV-2, they should be effective in reducing transmission of any other pathogen that has a similar transmission route as SARS-CoV-2. Substantive reductions in transmission are expected for pathogens with a transmission potential that is lower than SARS-CoV-2. Moreover, the typical seasonal dynamics of such pathogens might be shifted in presence of NPIs. Examples of other respiratory pathogens with a lower reported incidence of cases, and with altered seasonal dynamics include influenza virus, RSV and metapneumovirus. The incidence of cases with invasive pneumococcal infections was also lower. There is hardly any underreporting of cases with an invasive pneumococcal infection since the infection is severe and results in hospitalization. The drop in reported incidence cannot be attributed to a changing health-seeking behaviour during the pandemic and reflects reduced transmission. This was not only the case in the Netherlands. Many countries around the world reported much less influenza and RSV during the winters of 2020-2021 and 2021-2022 than in previous years. It is difficult to demonstrate that interventions did not affect infections with other transmission routes, as interventions could also have affected other transmission routes and health-seeking behaviour.

Contribution of individual interventions to overall effectiveness

Non-pharmaceutical interventions (NPI): evidence from literature

We reviewed literature to evaluate the empirical effectiveness of COVID-19 measures. Even though there are thousands of articles on the topic, there are only a handful of reviews with acceptable to high quality, which indicates a lack of synthesis of results. The evidence in this literature review suggests that COVID-19 measures did in fact reduce the risk of transmission and the risk of acquisition of infection. A precise quantification of the reduction in risk is methodologically complicated. Most NPIs were implemented around the same time, bundled in packages, making it difficult to disentangle the effect of the different interventions, as interventions influence each other. Furthermore, the effect of the different NPIs is dependent on the timing of implementation regarding the COVID-19 epidemiology, as well as contextual factors such as the demographic composition of the population (e.g., age structure, but also household size and population density), the social and political-economic situation, and cultural factors, including trust in the government and compliance.

We found the following results for the different NPIs:

- Hand hygiene: Most included studies showed a protective effect of handwashing. However, when and how frequently hand hygiene should be performed was not clear.
- Social distancing: Measures such as physical distancing, stay at home measures, restrictions on (mass) gatherings, and lockdown were found to be effective in reducing transmission.
- School closure: This was predominantly effective in reducing transmission and disease, but effectiveness varied.
- Travel restrictions: The literature provides mixed evidence. If it is effective, it is in delaying an epidemic in the country receiving infections from another country that has an outbreak or a large epidemic. Symptom-based or exposure-based screening was likely not effective.
- Face masks: Multiple studies found a protective effect of wearing face masks, while other studies show a less pronounced effect to no effect of wearing face masks in the community on COVID-19 incidence. Studies, mainly in the healthcare setting, suggest that higher-quality masks (e.g., N95 masks) were more effective than surgical masks.
- (Digital) Contact tracing: Some studies point towards a decreasing effect of contract tracing apps on transmission (quantified by R_t), incidence and mortality, while others found no effect on COVID-19 epidemic control.

Appendix B gives the full text of the review.

Decomposing total effectiveness into contributions by individual measures: international evaluation reports

Reports from various national and international organizations that evaluated the COVID-19 response mention the methodological difficulties and state that evaluation of the individual effects of measures may not be possible. The UK Chief Medical Officers write in their Technical Report (Whitty et al, 2022) in Chapter 8: “It may never be possible fully to disentangle some of the effects of individual NPIs in this pandemic as many were used together”. The German Sachverständigenausschuss states on page 12 and 13 of their report (2022) “Die genaue Wirksamkeit von Schulschließungen auf die Eindämmung der Ausbreitung des Coronavirus ist trotz biologischer Plausibilität und zahlreicher Studien weiterhin offen, auch, weil im schulischen Bereich eine Reihe von Maßnahmen gleichzeitig eingesetzt wurden und damit der Effekt von Einzelmaßnahmen nicht evaluiert werden kann.” The OECD report (2023) states on page 130: “Understanding the relative impact of different NPIs is of great interest to policy makers, as it provides a basis for calibrating the public health response throughout different stages of a shock such as a pandemic. Studies use advanced modelling and statistical techniques to evaluate the relative contribution of NPIs to containing the spread of COVID-19. However, such analyses are difficult for technical reasons – for example, the simultaneous implementation of multiple measures makes it difficult to disentangle the relative contribution of each." Below we look into a study that presents an approach to disentangling the effects of individual NPIs and focus on the technical difficulties in more detail.

Decomposing total effectiveness into contributions by individual measures: estimates derived from combined data from different countries

Many control measures were introduced and lifted at the same time, which results in poor identifiability of effectiveness of individual control measures. Combining information from different countries where different bundles of interventions were used alleviates this identifiability problem but requires measures to be grouped into categories across countries. Effectiveness of categorized individual interventions in reducing the reproduction number can then be estimated using a regression approach. For example, Brauner et al. 2021 provide estimates of effectiveness for the first pandemic wave, and Sharma et al. 2021 provide estimates of effectiveness for the second pandemic wave. The latter publication uses a set of European countries that includes the Netherlands, at a regional level (for the Netherlands, these are the safety regions). Comparing the estimates over different period reveals that the estimated effectiveness of individual measures is dynamic, in the sense that estimated values change over time as the context change. Especially the estimated effectiveness of school closure was higher in the first wave than in the second wave; the high effectiveness in the first wave is considered an artefact rather than a real effect. We present the estimates of effectiveness obtained in the second pandemic wave by Sharma et al. (2021) in Table 3. These estimates of effectiveness obtained in the second wave performed better in predicting the effectiveness of measures in the third wave, as compared to estimates obtained in the first wave, but as argued by the authors who report these estimates, these estimates cannot be generalized for future use. As lessons learned from this approach, the authors state that the practical value of the existing evidence is limited due to methodological issues and absence of a standardized assessment practice (Lison et al. 2023).

Table 3. Intervention effectiveness in a multinational dataset that includes the Netherlands, as percentage reduction in the reproduction number R_t, after Sharma et al 2021, Figure 2A. Effectiveness has been estimated of NPIs in 114 regions of 7 European countries, including the Netherlands (in Safety regions) over the period 1 August 2020 – 9 January 2021. Uses daily public data on daily reported cases and deaths at low geographical resolution. Note that estimates differ from earlier estimates using a similar method for a different set of countries over the period between January 2020 and the end of May 2020 (Brauner et al 2021). The authors stress that these estimates outperformed earlier, different estimates in predicting the effectiveness in the third wave, and that the results on NPI effectiveness are dynamic in time. This implies that to inform crucial policy decision should depend on real-time modelling of evolving NPI effects.

Intervention	**Reduction in R_t (%)**	**Uncertainty range (95% credible interval)**
All non-essential business closed	35	29 - 41
All gatherings banned	26	18 - 32
All educational institutions closed	7	4 - 10

Nighttime curfew	13	6 - 20
Stricter mask wearing policy	12	7 - 17

The effectiveness attributed to individual interventions, as in Table 3, is obtained using a regression approach. The main assumptions in this regression approach are that the effect of each intervention is multiplicative, that there are no interaction effects between the interventions, and that all relevant factors that would affect the reproduction number are accounted for. However, the regression model does not include effects of compliance and the stringency of an intervention, it does not include effects of contact tracing or seasonal variation in transmission. The regression framework does account for mediating variables such as the daily number of contacts or a proxy measure such as observed mobility. The regression approach assumes that the interventions are independent (there is no multi-collinearity). In the subsequent sections we assess to what extent violation of these assumptions would affect the estimated effectiveness of individual control measures.

The effect of compliance on effectiveness

The regression approach that was used to obtain the estimates of effectiveness of individual interventions as in Table 3 does not account for the compliance or the intensity of the measures. In this section we analyse how compliance could affect the resulting estimates of effectiveness. We focus on “stay-at-home requirements” as an NPI, specifically those that restrict the number of visitors per household. We study the impact of introducing the stay-at-home measure on the effective reproduction number and the proportion of the population that becomes infected during an epidemic wave (infection attack rate) at various intensities of the measure. We use a mathematical transmission model that allows for differences in compliance: a part of the population will comply to the measures and another part of the population will continue its contact behaviour irrespective of the measure. A reduction in contacts for the compliant sub-population always results in reduced average number of contacts in the entire population. As expected, an intervention of a moderate intensity is more effective in reducing the reproduction number than no intervention. However, counterintuitively, an intervention of high intensity can be less effective in reducing the reproduction number than an intervention of a moderate intensity (Figure 9, left panel). This reduced effectiveness at high intensity arises because non-compliant individuals will visit non-compliant households, such that most infections are transmitted among the individuals who do not comply. Similar outcomes for the reproduction number are expected for other NPIs where contacts between complying and non-complying change at increasing intensity. We observe a similar but less pronounced for the proportion of the population that becomes infected (Figure 9, right panel). Throughout, the compliant sub-population is relatively unaffected by the behaviour of the non-compliant sub-population. The results also reveal that the effectiveness of a measure in reducing the number of infections in an epidemic wave can be much higher than the effectiveness in reducing reproduction numbers. These findings highlight the importance of monitoring the actual compliance to measures and including it into the regression analysis, as compliance has a modulating effect on the epidemiological outcomes of interest.

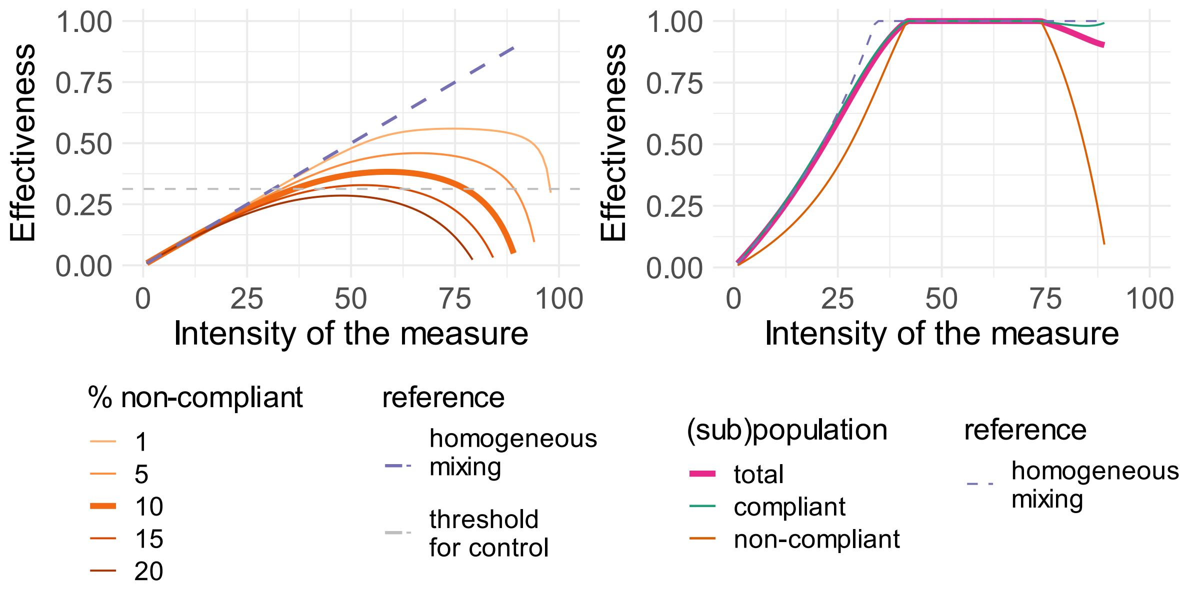

Figure 9: Effectiveness of intensity of the stay-at-home measure on the reproduction number (left) and the proportion of the population that becomes infected during an epidemic wave (right). Results are obtained with an epidemic transmission model where individuals belong to a household, and all the households are compliant or not. The effectiveness of intensity of the stay-at-home measure is evaluated at various levels of compliance.

The effect of seasonality on estimates of effectiveness

The regression approach that was used to obtain the estimates of effectiveness of individual interventions as in Table 3 did not account for a seasonal fluctuation of the reproduction number. The effect of these seasonal fluctuations was not firmly established at the time of the analysis in 2020-2021. Since then, a sufficient number of publications have appeared that allows us to establish the effect size. We express the seasonal effect as the reduction in the reproduction number in Summer compared to Winter. Early in the pandemic, Xu et al (2020) studied the relation between R_t and meteorological factors by comparing many regions in the world, resulting in an estimate of about 20% reduction in Summer in London and Paris as compared to Winter. Later studies looked at observations throughout a complete year. Gavenciak et al (2021) took data from 143 locations in Europe and estimated a 42% reduction in R_t in Summer compared to Winter. Johnsen et al (2022) estimated the relation between R_t and temperature in Denmark and estimated that R_t was reduced by 27%. For the Netherlands, we estimated a 26% reduction in the effective reproduction number R_t in Summer compared to Winter. The magnitude of this effect of seasonality on the reproduction number R_t is large in comparison to the attributed effectiveness of individual interventions. This implies that seasonality should be accounted for in a statistical regression approach to estimate effectiveness, and that ignoring the effect of seasonality could result in substantially biased results.

The effectiveness of contact tracing

The regression approach that was used to obtain the estimates of effectiveness of individual interventions as in Table 3 did not account for contact tracing. We estimate the effectiveness of contact tracing by making a mathematical model that describes the control measure in detail. For instance, we estimated the effectiveness of the contact tracing app CoronaMelder by a detailed simulation model that combined all available knowledge and data on epidemiology and behaviour. For instance, the model included epidemiological details on infectivity, incubation period, contact frequencies, behavioural details on willingness to test, go into quarantine, or use the tracing app, and technical details on the logistics of testing and tracing such as the time between making a test appointment and receiving the test results. The effectiveness of CoronaMelder was measured as a reduction in the reproduction number R_t, which is the mean number of secondary infections per primary infected. It is the mean reduction, measured in a population where some people strictly adhere to all measures and others not at all. According to this model, the CoronaMelder app resulted in a 0.3% reduction in the reproduction number, up to 0.8% in subgroups with many app users. Contact tracing, in the baseline scenario, resulted in a 6.5% reduction in the reproduction number. The small magnitude of this effect of contact tracing, relative to the attributed effectiveness of individual interventions, implies that not accounting for contact tracing in statistical regression analysis could results in limited bias of the results.

The complementarity of interventions

The regression approach that was used to obtain the estimates of effectiveness of individual interventions as in Table 3 did not account for interactions between effects of interventions. As such interactions are to be expected, estimating the magnitude of these interactions would be helpful for assembling individual interventions into effective bundles. However, it is statistically challenging to estimate both the effectiveness and the interactions of individual interventions. The interactions provide a way to quantify how the effectiveness of interventions is determined by the context (the other interventions that are implemented at the same time). The variation over time in estimated magnitude of effectiveness of individual interventions suggests that such interactions do exist, and that their effect is relevant. That quantification is hard does mean that interactions are unimportant or that context is irrelevant.

Mediating variables

The regression approach that was used to obtain the estimates of effectiveness of individual interventions as in Table 3 did not account for the number of reported contacts per day. A statistical approach that may be appropriate for assessing the impact of public health measures while accounting for this variable could be along the lines of a method known as path analysis. This is a regression-based approach that can be used to statistically separate explained variation and to examine the causal chain between public health interventions, measured mediating variables (e.g., number of contacts per day), and the effective reproduction number, while adjusting for potential confounding factors (e.g., seasonality or temperature). The working assumption of this approach is that the impact of intervention measures on the course of the epidemic can be observed in the effective reproduction number (as calculated from the time-series of reported positive tests and/or hospital admissions for COVID-19). A major difficulty with this (and related modelling approaches) remains the disentangling of the effects of measures that had been introduced simultaneously. In other words, attribution of the potential impact on transmissibility from overlapping potential causes remains highly challenging. This kind of analysis is only viable for analysis of time periods before the launch of the vaccination programme, as effective vaccination can have large and prolonged direct and indirect effects on the course of the epidemic, and before the arrival of virus variants that (partially) escape natural immunity.

Vaccines: evidence from literature

Vaccines go through an extensive process of testing, including randomized controlled trials (RCTs) to prove that protective effects are actually caused by the vaccine. For personal protection, the effectiveness of vaccination can be quantified as effectiveness against infection, COVID-19 disease, hospitalization, or death due to COVID-19. The rationale of vaccination in infection control is to reduce person-to-person transmission by reducing the risk of infection and subsequent transmission upon exposure. Estimates of the effectiveness of vaccination against infection and transmission tend to be higher than effects of NPIs, and the effectiveness lasts for considerable duration (e.g., Wu et al 2023).

We reviewed evidence for vaccine effectiveness, and briefly sketch the qualitative patterns that emerged from this review. Vaccine effectiveness (VE) estimates are different for the different virus variants, vaccine types, populations, and outcomes assessed. In general, a very high VE (> 95%) was found against severe disease, especially shortly after vaccination, for all variants, vaccines and populations. Against mild disease or infection, the VE was a bit lower but still high (> 80%), although the estimate for the Omicron variant was substantially lower (around 50%). The estimated VE against transmission for non-Omicron variants was a bit lower than the VE against severe or mild disease (50-70%). For all outcomes, the VE decreased within weeks or months after vaccination; waning was slower for VE against severe disease as compared to VE against the other outcomes. The estimates of VE were high again shortly after booster vaccination. Appendix B gives the full text of the review.

Discussion

We address the following questions: How effective were bundles of COVID-19 measures in reducing SARS-CoV-2 transmission? How did individual measures contribute to this effectiveness? How does this translate into effectiveness against severe measures, such as hospitalisations or deaths? We assessed the effectiveness and established increasing effectiveness against transmission was associated with increasing stringency of control measures, and conversely, decreasing effectiveness against transmission was associated with decreasing stringency of control measures. We established that the effectiveness against severe outcomes such as death is determined by effectiveness against transmission as well as the timing of measures: delaying the bundle of control measures in March 2020 would have resulted in more severe outcomes. We have shown that the total effectiveness against transmission can be decomposed into contributions of individual control measures under specific assumptions, but that these assumptions are not always met, which means that the estimates are biased and can change over time.

We briefly discuss the effectiveness of measures against COVID-19.

- Vaccination. This is the control measure for which we have randomized controlled trials (RCTs) and good estimates of effectiveness, independent of other measures. Of these estimates, the best documented is the effectiveness against severe outcomes such as death and hospitalization; the effectiveness against transmission of SARS-COV-2 is harder to measure in RCTs but seems reasonably high.
- NPIs. We do not have RCTs but there are observational studies that reveal associations between implementation of interventions and increased effectiveness in reducing transmission. We verify that the interventions have affected the contact behaviour in the population as intended, and reduced transmission of infections with a similar transmission route as SARS-COV-2.

We have abstained from balancing effectiveness of measures versus unintended societal consequences of these measures. The Royal Society report on the effectiveness of NPIs (2023) asserts that balancing effectiveness versus unintended societal consequences is a political question, not a scientific one. Science can assist in clarifying which decisions are to be made: If the objective is to keep numbers of infection below a given threshold value set by a policy maker, science can provide the average effectiveness that a bundle of measures should attain, as determined by properties of the pathogen and the population. The policy question is how to compose the package of measures such that the unintended consequences remain limited. Scientific expert groups (such as the Health Council, the MIT (Maatschappelijk Impact Team) and the Outbreak Management Team in the Netherlands) could assist in identifying tradeoffs and bringing consequences of measures to the attention of policy makers. We agree with the Royal Society in the sense that scientists should bring relevant expertise and evidence to the table and be careful to avoid being cast into a role of weighing values that is up to policy makers.

We have not discussed the effectiveness of interventions in specific settings, including nursing homes, hospitals, restaurants, pubs, night clubs, concert venues and shops. Here we faced an absence of data to provide evidence for effectiveness. This does not imply absence of effectiveness of those measures.

We have presented results of observational studies on effectiveness of bundles of control measures in reducing transmission, the effectiveness in reducing contacts, and the breakdown by individual measures. The take-home message of all of these, taken together over many different countries, is that there is clear evidence that the bundles of NPIs and the combined effect of vaccination and NPIs were effective in reducing SARS-CoV-2 transmission. The observational studies also show that individual NPIs were effective in reducing transmission. The question how effective individual NPIs were, and how effective they were in combination with others, is difficult to answer as the effectiveness is determined by the context in which they were applied, such as their timing relative to epidemic, the intensity of the measure, the compliance in the population, and the complementarity to other interventions. Irrespective of such difficulties, the comprehensive literature review and individual studies presented here provides additional information about the effectiveness of individual measures that were taken in the COVID-19 pandemic.

We have stressed several methodological issues that limit the usefulness of existing estimates of effectiveness of individuals interventions in a future pandemic. This is in line with the studies that use multi-country data and regression approaches to obtain the existing estimates; most of these studies are accompanied by extensive investigations into the substantial uncertainty surrounding estimates of individual interventions, and sensitivity analyses form an essential part of these studies (although often reported in supplementary information). Information of effectiveness in subgroups in the population, based on ethnicity or socio-economic status or religion, is not available.

In summary, we provide evidence that the applied measures, both vaccines and bundles of NPIs, were effective in reducing the transmission of SARS-CoV-2. How this reduction in transmission translates into reduction of numbers of cases, hospitalizations and deaths will depend on the timing of the intervention and the period over which the effectiveness is evaluated. The effectiveness of individual interventions depends on the specific context in which they are implemented. Attributing effectiveness to individual interventions, when possible, has limitations for future use.

Recommendations

Composing effective bundles of interventions

In trying to label an intervention with a single effectiveness estimate, one misses several other important aspects of the interventions: communication about the interventions, complementarity of interventions, and the objective of an intervention. We will highlight briefly three recommendations that follow from this.

- Communication about interventions is a relevant element of effectiveness that deserves further attention. Clear messaging is essential to ensure proper compliance with NPIs. Consistency in messaging may clash with the continuous updating of information based on ongoing scientific research into a novel pathogen. An example is case isolation and contact tracing: this generates information on the incubation period, which is an integral part of the isolation procedure such that updated values for the incubation period can easily cause confusion. Clear and consistent messaging should allow for updates in the information that is communicated.
- Complementarity of interventions deserves more attention. A first start at quantifying complementarity of interventions would be to test for interactions between interventions in the regression analysis for attributing effectiveness to individual interventions. Another approach would be to map out the different at-risk contacts in a population by age groups and settings and reconstruct from contact surveys, after introduction of a control measure, which of the contacts were prevented or replaced by other contacts. Understanding the complementarity is essential to composing effective bundles of interventions.
- The objective of individual interventions deserves further attention. Interventions can be designed for specific sub-populations or risk-groups and can target distinct parts of the transmission chain. They could aim to reduce the risk of introduction of infection into a population, reduce the risk of transmission of infection in that population toward individuals who are at increased risk of a severe outcome, and to reduce the risk of infection of individuals who are at increased risk of a severe outcome during a potential exposure. Interventions such as screening and triage are relevant for preventing introduction, the use of personal protection is relevant for reducing risk of exposure. Composing effective bundles of interventions, aimed at specific populations, could benefit from recognizing the specific role and objective of individual interventions.

Preparedness of data streams

Monitoring and surveillance of infectious disease in the Dutch population is needed in real time to underpin effective responses and adaptations to changing conditions during a pandemic. Here it is essential to collect information for different sub-populations (based on, for example, age, gender, ethnicity). During the COVID-19 pandemic data on ICU admissions was used in the Netherlands because all admitted patients were tested for SARS-CoV-2, surveillance was timely, and the number of occupied ICU beds were perceived to be a bottleneck in healthcare. But such surveillance is not standard, and for a different infection the surveillance could be focused on other groups.

- Data for establishing the incubation period and the time scale of transmission of the new pathogen are essential to assess the reproduction number and to determine the required control effort in a new pandemic. Suitable data for estimating the incubation period requires reporting for the same case the approximate moment of infection and symptom onset date. Suitable data for estimating the time scales requires reporting for the same case the most likely infector, the moment of infection or symptom onset date. During the COVID-19 pandemic these variables could be inferred from well-documented outbreaks, from contact tracing reports and the OSIRIS registration system. This should be routinely built into surveillance and monitoring systems for other pathogens.

- Contact surveys in the population proved essential during the COVID-19 outbreak in the Netherlands to check how NPIs worked out and were critical to inform policy decisions. We need a baseline assessment how many at-risk contacts there are in the population, preferably broken down by demographics of those involved in the contacts, the setting of the contact, the duration of the contact, the location of the contact. This is helpful in finding out which of these contacts can be prevented, or which of these contacts has a lower risk of transmission, when a control measure would be implemented. Such contact surveys should be structurally funded to provide a baseline measurement when a new pandemic starts.
- Mobility, as measured by aggregated and anonymized mobile phone data, has been identified as a useful proxy for the response of the population to NPIs in many European countries. In the Netherlands, it has not been possible to collect and use this information. If the concerns about possible infringement of privacy sensitive data of the anonymized mobile phone data outweigh the expected societal benefits in the Netherlands, there should be room for an alternative approach (for example, mobility as monitored in the National Mobility Panel with an app such that a participant consents to sharing information). Such monitoring instruments are not structurally available for infectious disease surveillance, this should be ready before a new pandemic starts.

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Appendix A studies on which this report is based

Publications in peer-reviewed scientific journals

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Manuscripts in preparation

Jantien A Backer, Cheyenne C. E. van Hagen, Eric R. A. Vos, Hester E. de Melker, Fiona R. M. van der Klis, Jacco Wallinga. Contact behaviour before, during and after the COVID-19 pandemic in the Netherlands. Manuscript in preparation.

Pieter de Boer, Fuminari Miura, Jacco Wallinga. Counterfactual modelling of COVID-19 Response Strategies: A comparison between the Netherlands and Five European Countries. Manuscript in preparation.

Jantien A Backer. Effectiveness of non-pharmaceutical measures in reducing SARS-CoV-2 reproduction numbers in the Netherlands, 2020-2022. Manuscript in preparation.

Ka Yin Leung, Jacco Wallinga. Unintended outcomes of non-pharmaceutical interventions for pandemic control: how they may arise, and how they can be prevented. Manuscript in preparation.

Appendix B Evaluation of the epidemiological effectiveness of COVID measures: a literature review

RIVM/CIb/EPI

Version 19 December 2023

Literature search

Non-pharmaceutical interventions

An extensive amount of papers are published since the start of the COVID-19 pandemic. When searching scientific medical literature for COVID-19 and non-pharmaceutical interventions (NPIs), approximately 8,500 articles were found. When adding the pharmaceutical intervention 'vaccination' to the search terms, about 60,000 extra articles were found. To obtain an overview of this immense field, our search was restricted to reviews and meta-analyses on NPIs, in English and Dutch, focusing on Northern, Western and Southern European countries. NPIs and outcomes included in the search can be found in the appendix C. A literature search was conducted in Embase by an experienced library information specialist on June 8, 2023. The complete search is available on request. Using strict search terms for the measures and outcomes to include, 140 review articles on NPIs implemented during the COVID-19 pandemic in the Netherlands were identified. An updated search on October 11, 2023 resulted in 7 extra review articles on NPIs. Next to that, the Cochrane library was searched using the keyword 'COVID', resulting in 96 papers. Additionally, the six review articles that formed the basis of the report on the effectiveness of NPIs of The Royal Society in the UK[1] were assessed. Selection criteria included the use of empirical data on COVID-19 and reporting of quantitative results. No formal quality assessment was done, but quality of the retrieved articles was deemed variable. After careful review of titles, abstracts and full texts of these 249 articles, 16 were included in the final selection, assessed to be of moderate to high quality and fulfilling the selection criteria. Three more articles were added after reference checking, for a total of 19 review articles (Table 1).

Vaccination

Vaccination is a pharmaceutical intervention. The vaccine effectiveness (VE) of COVID-19 vaccination is extensively researched by the RIVM for the Dutch situation. VE is a measure indicating the protection provided by vaccination; by comparing the occurrence of, e.g., infection, hospitalization or death from COVID-19 in a vaccinated group to an unvaccinated group. RIVM uses vaccination coverage data, surveillance data, and dedicated studies to monitor vaccine effectiveness against SARS-CoV-2 infection, transmission, and severe COVID-19 (i.e., hospitalization and intensive care unit (ICU) admission, and death).[2, 3] The RIVM also structurally keeps track of the scientific literature regarding VE of COVID-19 vaccination. An ongoing weekly systematic search by the International Vaccine Access Center of the Johns Hopkins Bloomberg School of Public Health, the World Health Organization and the Coalition for Epidemic Preparedness Innovations was checked and summarized for internal use.[4] Furthermore, online resources such as LitCovid (containing articles from PubMed categorized by research topic)[5], EPPIcentre (a living map of research articles on COVID-19)[6] and the COVID-19 rapid reviews conducted by the UK Health Security Agency (UKHSA)[7] were monitored on a regular basis in the beginning of the pandemic. Next to that, Embase was searched weekly by experienced library information specialists of the RIVM. A summary of the results of studies on VE in the Netherlands, combined with results from international literature, is presented in this review.

Results

NPIs

Hand hygiene

When pooling results from 3 observational studies on the effectiveness of hand washing using a random effects model and adjusting for heterogeneity, Talic et al. [8] found an non-statistically significant reduction of 53% on incidence of SARS-CoV-2 infection (relative risk (RR) 0.47, 95% CI 0.19;1.12).[i] The unadjusted model showed a similar, but significant reduction (0.49, 95% CI 0.33;0.72). The included studies differed in study design (two case-control studies and one cross-sectional survey) and definition of hand washing (often vs. sometimes, yes vs. no, hand washing after specific activities), making it difficult to combine results. Risk of bias of the included studies ranged from moderate to serious or critical. For example, other (risk) behaviour of included individuals should be taken into account to avoid confounding. A review by Gozdzielewska et al. [9], summarizing results from eight observational studies (mostly from the year 2020) on hand washing and COVID-19, is in line with this, with most included studies showing a (statistically significant) protective effect. However, similar limitations as described above hold, and all studies were assessed to have an unclear or high risk of bias. Also, when and how frequently hand hygiene should be performed was not clear. Nevertheless, the protective effect of hand washing in the community setting is well established for other respiratory and gastrointestinal infectious diseases. [9-12]

Social distancing

Social distancing is a term used to describe multiple measures. All measures that aim to limit contacts between people fall under this definition, e.g., physical distancing, stay-at-home requirements, lockdown, school closure, workplace closure, restrictions on gathering size, etc. Some of the included studies focus on individual measures, while others evaluated social distancing in the broad sense.

Murphy et al. [13] conclude in their review that social distancing measures were the most effective of all NPIs, with more stringent measures having greater effects. Although no pooled measure is available, Sun et al. [14] report a lower transmission risk related to physical distancing and prohibition of mass gatherings by combining results from seven observational studies. Liu et al. [15] analysed data from seven observational studies using contact patterns before and during initial mitigation (defined as national and/or regional declaration of lockdown and the most stringent measures in spring 2020) to extrapolate to changes in the effective reproduction number (Rt)[ii]. They found a 62-83% reduction in Rt due to changed contact patterns. It should be noted that contact patterns used for the pre-COVID period in several cases were from many years earlier.

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[i] Relative risk (RR): ratio of the probability of an outcome (e.g., SARS-CoV-2 infection) in an exposed group (e.g., those who wash their hands according to the guidelines) to the probability of an outcome in an unexposed group (e.g., those who do not wash their hands according to the guideline). A RR below 1 indicates a protective effect of the ‘exposure’ or NPI. Thus, a RR of 0.47 means that the intervention (handwashing) reduces the risk of SARS-CoV-2 infection with ((1 - 0.47) * 100%) 53%.

[ii] Effective reproduction number (Rt): average number of secondary cases per index case on a given timepoint, i.e., how many people are on average infected by someone who is infected with SARS-CoV-2.

Physical distancing

In the review and meta-analyses of Talic et al. [8], physical distancing was found to be effective in reducing incidence of SARS-CoV-2 infection, with a pooled RR of 0.75 (95% CI 0.59;0.95) based on five observational studies. It is not mentioned what physical distances were studied. Three studies not included in the meta-analysis all reported a decreasing effect on either transmission, Rt and mortality. Chu et al. [16] pooled data from 5 observational studies on physical distance and risk of COVID-19 infection using a random effects model and found a RR of 0.15 (95% CI 0.03;0.73). Distances differed between the different studies, ranging from 0 to 1.8 metres. In a further analysis by Chu et al., also including papers on other pathogens (MERS, SARS, and COVID-19), protection was increased as distance was increased. Murphy et al. [13] included 34 papers in their review on physical distancing (of which 19 were observational), and all but one found it effective. However, no pooled quantitative measure was available.

Restrictions on mass gatherings

Twenty-eight studies were included in Murphy et al. [13] that focused on mass gathering restrictions, of which all but two reported a substantial reduction in the impact of COVID-19. The smaller the maximum gathering size, the greater the reduction in transmission. Furthermore, the effectiveness of the measure seemed to increase over time. However, the time period considered was relatively short (first half of 2020), thus not taking into account that adherence could have waned if the restrictions were implemented for longer periods, e.g., in subsequent waves.

Stay-at-home requirements

Stay at home or isolation measures were assessed in the review of Talic et al. [8] All four observational studies included in the review reported reductions in transmission of SARS-CoV-2. For example, in an observational study in the US these measures were found to have contributed to a 51% reduction in Rt (95% CI 46;57). In a observational study in the UK Rt pre-intervention was 3.6, and decrease to 0.6 (95% CI 0.37;0.89) post-intervention. In Iran, similar results were found: 2.70 and 1.13 (95% CI 1.03;1.25), respectively. The effect of quarantine on incidence and transmission was assessed in two included studies. [8] A 4.9% decrease in the incidence of COVID-19 eight weeks after the implementation was reported in an observational study from Saudi Arabia. An observational study from India reported a 14 times higher risk of SARS-CoV-2 transmission associated with no quarantine compared with strict quarantine.

Lockdown

A universal lockdown was found to have a decreasing effect on incidence of COVID-19 in three observational studies included in the review of Talic et al. [8] with reductions ranging from 11% to 14%. Three observational studies assessed the effect on mortality, all reporting a decrease, although one was not statistically significant. In four observational studies looking at the effect on transmission, the (absolute) decrease in Rt ranged from 1.27 to 3.97 in three studies, and a relative decrease in Rt of 11% was found in the fourth. Sun et al. [14] give an overview of articles on the effectiveness of lockdown and report similar reductions in Rt and incidence, but no pooled measure is available. The same holds for Vardavas et al. [17]. Murphy et al. [13] included 151 studies, of which 119 found a substantial reduction in Rt, incidence of SARS-CoV-2 and mortality of stay-at-home orders or lockdowns. The included studies differed in design, population and definitions and stringency of stay-at-home orders. Reductions in Rt were estimated around 50%, however, the range was wide (6% to 81%). Also, several studies found that the additional effect of lockdown on top of other measures (such as school and business closures, and restrictions on gathering size) was small, with one study estimating Rt to drop by 13% (95% prediction interval 5;31). The effectiveness of stay-at-home orders on incidence and mortality were more mixed, with over one third of the included studies reporting no significant association.

Closure of schools, businesses and workplaces

School closure as an individual measure was assessed in only one paper from Sweden included in the Cochrane review by Krishnaratne et al. [18] They found exposure to open rather than closed schools resulted in a small to moderate increase in the number of infections among parents and teachers, and their partners. Quantitative results are not reported in the review. Sun et al. [14] describe an predominantly decreasing effect of school closure and workspace measures on COVID-19 incidence and mortality. School closure was also assessed in five observational studies included in the review of Talic et al. [8] A US study reported a 62% decrease on incidence of COVID-19 infections and a 58% decrease in COVID-19 mortality after state-wide closure of primary and secondary schools, while in a study in Japan no effect of school closure on incidence was seen. Two other studies in the US found a 10-13% reduction in Rt after school closure. Murphy et al. [13] included 104 studies on school closure, and over half of these studies showed evidence for the effectiveness. However, the impact varied due to differences in study populations, study period, the timing of implementation and the interaction with other NPIs. Thirteen studies examined the impact of reopening schools, of which nine showed an increasing trend in the number of daily new confirmed COVID-19 cases, growth rate or Rt. The other four studies observed no substantial increase in transmission when other measures were in place.

Business closure was assessed in two observational studies from the US included in the review of Talic et al. [8] and they observed a 12-16% reduction in transmission after business closure. Thirty-seven studies were included in the review by Murphy et al. [13] on workspace closure. Most studies (92%) observed a beneficial effect of workplace closures alone or in combination with other interventions to reduce incidence. However, the sizes of these effects are not reported.

Travel restrictions

Travel restrictions were studied in a Cochrane review by Burns et al. [19] Symptom/exposure-based screening at borders was likely not effective, with eight out of nine observational studies reporting that the proportion of cases detected would be less than 54%. Five studies observed that the proportion of cases detected through test-based screening varied from 58% to 90%. One observational study included in the review of Talic et al. [8] came to a similar conclusion that screening for fever lacked sensitivity (ranging from 18% to 24%) in detecting people with SARS-CoV-2 infection. Four observational studies assessed the impact of quarantine and screening at borders, and found that the proportion of cases detected ranged from 68% to 92%.[19] Another Cochrane review[20] indicated that evidence of empirical studies is scarce, but the included (empirical and modelling) studies point towards a reduction of incidence and mortality of COVID-19 due to travel restrictions, especially for quarantine of individuals travelling from a country with a declared COVID-19 outbreak. However, the magnitude of the effect is uncertain. Similar conclusions were drawn by Grepin et al. [21] Although no quantitative measures were mentioned, they conclude that symptom/exposure based screening had no had no significant effect on reducing importation or transmission. Targeted restrictions such as banning entry from specific countries likely had a moderate effect on transmission, especially in the beginning of the pandemic, while quarantine at entry borders was assessed to be the most effective.

Two observational studies included in the review of Talic et al.[8] had opposing results regarding the impact of border closures on Rt: in African countries border closures had minimal effect on the incidence of COVID-19, while in the US restrictions on travel between states were estimated to reduce SARS-CoV-2 transmission by about 11%. Bou-Karroum et al.[22] included 15 observational studies on effectiveness of travel restrictions. Travel restrictions included amongst others border closure, screening of travellers, quarantine of travellers, and restriction on international or regional movement. Although quantitative outcomes were hardly reported and it was unclear which results were derived from empirical studies (as opposed to modelling studies), travel measures seemed predominantly effective in controlling the COVID-19 pandemic. Overall, there is mixed evidence and it will most likely be effective only in delaying the onset of an epidemic in the country receiving infections from another country where the pathogen already is spread. The effect of travel restrictions is influenced by many factors and depends on, amongst others, levels of community transmission, travel volumes and duration, other public health measures in place, and the timing of the measures.

Face masks

The effectiveness of wearing face masks in the community was assessed in the Cochrane review of Jefferson et al.[12] Based on results from 9 randomized controlled trials (of which one was conducted during the COVID-19 pandemic) they conclude that wearing medical/surgical masks in the community probably makes little or no difference of the outcome of influenza-like illness/COVID-19 like illness compared to not wearing masks (RR 0.95, 95% CI 0.84;1.09). Also, little to no result was seen for the outcome of laboratory-confirmed influenza/SARS-CoV-2 (RR 1.01, 95% CI 0.72;1.42) when combining results from 6 RCTs (of which one was conducted during the COVID-19 pandemic).

Boulos et al.[23] included 24 studies on the effectiveness of masks versus no masks on SARS-CoV-2 transmission in community settings, of which two were RCTs and 22 were observational. Furthermore, 23 observational studies in healthcare settings were included. Due to widely varying study designs and timing during the pandemic no pooling was done, but of the observational studies, 39 (87%) studies found that mask wearing was significantly associated with a reduction in transmission, with effect sizes (OR) ranging from 0.08 to 0.80. Five (11%) studies found no significant association, and one (2%) study performed in the community setting favoured the control group. One RCT found that mask wearing was significantly associated with a reduction in transmission (OR 0.88; 95% CI 0.85;0.90), while the other found no effect (OR 0.82, 95% CI 0.54;1.23). Of note, multiple studies were also included in the other reviews included here. Using mostly the same studies, a living review by Chou et al.[24] which had its final update in 2023, came to a similar conclusion that in community settings mask use may be associated with a small reduced risk for SARS-CoV-2 infection versus no mask use. Furthermore, Boulos et al.[23] found that wearing higher quality compared to lower quality masks was favourable in those studies where a significant effect was found, in line with Chu et al.[16] Also, the majority of included studies found that mask mandates (compared to voluntary mask wearing) reduced transmission of SARS-CoV-2.[23] However, critical risks of bias were present in most studies.

Talic et al.[8] combined data from 6 studies to estimate the effectiveness of face masks in the community on incidence of SARS-CoV-2. The studies had different designs, including a randomized controlled trial as well as observational studies. The pooled RR was estimated to be 0.47 (95% CI 0.29;0.75), indicating a protective effect. The type of mask was not specified. The estimate is in line with the review of Chu et al.[16] who found a protective effect of face masks on infection, with a pooled unadjusted RR of 0.34 (95% CI 0.26;0.45, 29 observational studies), and an adjusted RR of

0.18 (95% CI 0.08;0.38, 10 observational studies). They also found that there were stronger associations with N95 or similar respirators compared with disposable surgical masks or similar. However, most of the studies included the latter review were done in the healthcare setting and it must be noted that studies on MERS and SARS were also included, next to COVID-19. Five other observational studies included in the review of Talic et al. [8] (but not included in the meta-analysis) all show a reduction in incidence, transmission, and/or mortality after mandatory mask wearing or when comparing countries or regions with and without mandatory mask wearing. The two observational studies included in the review of Vardavas et al. [17], both in the community setting, show a less pronounced to no effect on COVID-19 incidence. However, they conclude that the timing of implementation may have played a crucial role.

Digital contact tracing

Five observational studies included in a living review by Jenniskens et al. [25, 26] point towards a decreasing effect of contract tracing apps on Rt, incidence of COVID-19 infections and mortality. However, data were limited and risk of bias was judged to be unclear or high. Pozo-Martin et al. [27] provide an overview of twelve observational studies, of which two report results of contact tracing combined with another NPI. Two studies were also included in Jenniskens et al. [26] Of the remaining two studies focusing exclusively on contact tracing, one found a decreasing effect of contact tracing on mortality, while the other study found no effect on the attack rate. The other six articles explored the effectiveness of contact tracing in the context of the implementation of other NPIs and found a marginal weak (1 study) or no effect (5 studies) on COVID-19 epidemic control. The review by Littlecott et al. [28] included seven papers on the impact of contact tracing, of which three were also included in Jenniskens et al. [26] Of the remainder, three studies concluded that contact tracing led to a significant decline in incidence, Rt or mortality, with reductions in mortality of 48 to 68%, while one study found no relationship.

Corona certificate; Self testing

No reviews of sufficient quality on these subjects were found in our search.

Vaccination

Here, we describe the vaccine effectiveness (VE)[iii] of COVID-19 vaccination for different outcomes. First, an overview of results from the Netherlands is given, and at the end of each paragraph a comparison is made with results from international literature. The text below is a summary of the chapters on VE in the yearly reports on the National Immunization Program in the Netherlands. [2, 3] A more detailed overview can be found there.

Vaccine effectiveness against hospitalization and ICU admission

By enriching the hospital register data from the Netherlands (NICE) with data from the central COVID-19 vaccination Information and Monitoring System (CIMS), VE of COVID-19 vaccines against hospital and ICU admission could be estimated. Estimates of VE of full primary vaccination against hospitalization and ICU admission were very high during the period when the Delta variant

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[iii] Vaccine effectiveness (VE) is expressed as (1-RR) * 100%. Thus a VE of 93% against hospitalization means that vaccination reduces the risk of hospitalization after SARS-CoV-2 infection with 93%.

dominated (July-November 2021): 93% (95% CI 93;94) and 97% (95% CI 96;97), respectively.[29, 30] After November 2021 a decrease in VE against hospitalization and ICU admission was seen with increasing time since vaccination.[31]

Omicron BA.1 and BA.2 dominated from February 2022 onwards, and VE was much lower for these variants. VE of full primary vaccination against hospitalization was 35% (95% CI 30;39) in the period February-March 2022, while it was 45% (95% CI 34;55) against ICU admission. However, VE increased considerably after booster vaccination to 81% (95% CI 80;82) against hospitalization and 90% (95% CI 88;92) against ICU admission. Waning of VE by time since vaccination was also observed after booster vaccination.[32] Therefore, a second booster dose was offered to vulnerable groups (e.g., persons aged 60 years and older, and persons below the age of 60 with chronic diseases) since the end of February 2022. After this booster, VE increased to 88% (95% CI 73;92) against hospitalization in persons aged 70 years and over.[33]

During the course of the pandemic, infection-induced immunity and hybrid immunity (due to both infection and vaccination) became more important factors in determining the risk of severe outcomes. VE estimates were increasingly impacted by previous infections. Therefore, since August 2022 the RIVM does not report on VE against hospitalization anymore, but on the RRD (relative risk difference). During June-July 2022, when Omicron BA.5 dominated, the RRD for the first booster vs. primary vaccination was -51% (95% CI -56;-46), e.g., persons who received the first booster had a 51% lower risk for hospitalization compared to persons who received the full primary series vaccination only.[34] Persons aged 60 years and older who received a second booster, had a 25% lower risk for hospitalization compared to persons who received the first booster only (RRD -25%, 95% CI -32;-18). The RRDs dropped to -47% (95% CI -53;-39) and -22% (95% CI -30;-12), respectively, during July-September 2022.[35]

Since September 2022 bivalent booster vaccinations have been offered. During October-November 2022 the RRD for a bivalent booster vaccination compared with receipt of at least one COVID-19 vaccination but not a bivalent vaccination for persons aged 60 years or over was -63% (95% CI -68;-58) against hospitalization and -55% (95 CI -76;-14) against ICU admission, which reduced to -42% (95% CI -46;-37) and -45% (95% CI -61;-22), respectively, during March-May 2023.[36]

The above findings of the RIVM for the Dutch situation are in line with results from international research, which also show that VE was lower during the period where Omicron variants were dominant, compared to the period where the Delta variant dominated.[37, 38] Furthermore, waning of VE with increasing time since vaccination was also observed. A booster vaccination increased VE to 80-90%, but again waning was visible after approximately four months.[37-39] International studies showed that receiving a fourth monovalent COVID-19 vaccine dose restored the effectiveness against hospitalization during the Omicron predominant period.[40-50] Studies on VE of a bivalent booster against severe disease showed a protective effect, with estimates ranging from 50% to 81%.[50-57] Waning of the effectiveness was shown 10+ weeks after receiving the bivalent booster.[58]

Vaccine effectiveness against death

Through linkage of the CIMS vaccination registry to causes of death and other registry data of Statistics Netherlands (CBS), VE against COVID-19 mortality was estimated for the period January 2021-January 2022.[59] A summary measure was calculated for all circulating SARS-CoV-2 variants that year (wild type, Alpha, Delta, Omicron), as stratification into variant periods did not result in informative estimates due to small numbers. VE against COVID-19 mortality – adjusted for amongst others medical risk group, sex, year of birth and country of origin – was >90% for all age groups two months after completion of the primary series. VE gradually decreased thereafter, to around 80% at 7-8 months post-primary series for most groups, and around 60% for elderly receiving a high level of long-term care and for people aged 90+ years. Following a first booster dose, the VE increased to >85% in all groups. [59]

Similar results were found in international literature, with high VE against COVID-19 mortality after completion of the primary series (>90%, although lower in the highest age groups) [60-62], but waning was seen over time. [61-65] VE after booster vaccination was estimated to be around 90%.[66, 67] In a study by the WHO using data from 33 European counties, it was estimated that 51% of the expected deaths in persons aged 60 years and older were averted by vaccination from December 2020 to November 2021. The impact of vaccination on mortality by country ranged from 6% to 93%, with the largest impact in countries with high early uptake. [68] It should be noted that no data from the Netherlands were included in this study.

Vaccine effectiveness against mild disease/infection

VE against infections was estimated using community testing data in a test-negative case-control design. During the Delta-dominant period, VE against infection was high (>80%), with lower VE among elderly, close contacts of confirmed cases, and people having received vector vaccines. Protection of primary vaccination against Omicron variants was much lower (35% at >=7 months after vaccination). Booster vaccination increased VE against Omicron infection to around 65% at one month post-vaccination. [69]

In the VAccine Study COvid-19 (VASCO) cohort it was found that during the Delta period, VE decreased from 80% (95% CI 69;87) <6 weeks after completing the primary series to 71% (95% CI 65;77) 18-23 weeks after completion of the primary series, and increased to 96% (95% CI 86;99) <6 weeks after booster vaccination. In the Omicron period, these estimates were 46% (95% CI 22;63), 25% (95% CI 8;39) and 57% (95% CI 52;62), respectively; VE decreased to 31% (95% CI 17;44) 18-23 weeks after booster vaccination. VE was lower among persons belonging to medical risk groups. [70] Furthermore, it was found that hybrid immunity was more protective against infection with SARS-CoV-2 Omicron than vaccine-induced immunity. [71]

Effectiveness of bivalent original/Omicron BA.1 vaccination relative to receiving the primary vaccination series and one or two monovalent booster vaccinations was 31% (95% CI 18;42) in 18-59-year-olds and 14% (95% CI 3;24) in 60-85-year-olds during September-December 2022. In both age groups, relative protection from a prior Omicron infection with or without bivalent vaccination was substantially higher (80-83%).[72]

Similar results were found in international literature. VE against infection with the Omicron BA.1 and BA.2 variant appeared to be lower compared to previous variants and protection waned over time. [73] Comparable results were found for VE against infection with the Omicron BA.4 and BA.5 variant. [58] The UK Health Security Agency provides VE consensus estimates by taking estimates from the UK as well as international data into account. They found that 0-3 months after the first booster dose, VE estimates against infection with Omicron BA.1 or BA.2 were around 50% (95% CI 40;60%). After 4-6 months, this was approximately 30% (95% CI 20;40%).[74] VE estimates against infection with Omicron BA.4, BA.5, BQ.1 and CH1.1 0-1 month after a monovalent or bivalent booster dose were around 30% (95% CI 20;40). After 2-3 months, the VE estimates decreased to around 20% (95% CI 10;30) and after 4-6 months to approximately 10% (95% CI 0;20).[58] When specifically looking at bivalent booster vaccines, VE estimates ranged between 8% and 29% 7 days or more after vaccination.[75-78]

Vaccine effectiveness against transmission in case of infection

Estimation of VE against transmission in case of infection in the Dutch situation was possible due to comprehensive source and contract tracing data. During the period that the Alpha variant dominated (February-May 2021), VE against transmission was estimated to be 71% (95% CI 63;77).[79] During August and September 2021, when the Delta variant dominated, VE against transmission to unvaccinated household contacts was 63% (95% CI 46;75), while VE against transmission to fully vaccinated household contacts was 40% (95% CI 20;54).[80] With an alternative method, comparable to the screening method, researchers at the RIVM found similar results: in all age groups, VE against transmission dropped from 59-72% in April-June 2021 to 32% in October 2021.

In the VASCO cohort, the VE of primary vaccination against transmission was 64% (95% CI 15;84) in the Delta-dominant period and 49% (95% CI -4;75) in the Omicron-dominant period. In the Omicron period, VE against transmission was higher with each additional booster: 64% (95% CI 32-81) for the first booster, 67% (95% CI 35;84) for the second booster and 70% (95% CI 33-86) for the third booster. VE of the booster vaccination in the Delta-dominant period was very uncertain due to low numbers.[70-72]

In international literature, VE against transmission of the Alpha variant has been estimated between 35% and 88%.[79, 81-84] VE estimates against transmission of the Delta variant vary between 24% and 82%.[80-82, 85-87] Available data indicates a small, but significant effect of a booster vaccination against Omicron-transmission, with VE estimates ranging from 1-12% for transmission to household contacts[85, 88], and 24-44% to close contacts in a non-household setting.[88-91] However, the UK Health Security Agency stated in their COVID-19 vaccine surveillance report from January 2023 that there is insufficient data for a consensus VE estimate against transmission for a booster dose.[52]

Discussion

Most measures during the COVID-19 pandemic were suggested, advised and implemented because of their biological or epidemiological plausibility to decrease the risk of transmission from one individual to another. This literature study indicates that indeed the evidence suggests that these measures reduced the risk of transmission or acquisition of infection. In this sense, they were effective. The precise quantification of this reduction is methodologically much more complicated. Most NPIs were implemented in bundles, making it methodologically difficult to disentangle the effect of individual interventions. Interaction between effects of individual measures, missingness of factors affecting outcomes (such as seasonality), and difficulties in including mediating variables (such as mobility statistics) make it difficult to pinpoint a precise effectiveness for individual measures. Countries surrounding the Netherlands, such as Germany[92] and the UK[1, 93] come to similar conclusions in their reports evaluating the COVID-19 pandemic, stating that “It may never be possible fully to disentangle some of the effects of individual NPIs in this pandemic as many were used together”.[93] Similar conclusions were drawn by the OECD.[94]

Furthermore, the effect of the different NPIs is dependent on the timing of implementation regarding the COVID-19 epidemiological situation, as well as contextual factors such as the demographic composition of the population (e.g., age structure, but also household size and population density), the social and political-economic situation, and cultural factors, including trust in the government and compliance or adherence. [1, 95] Similar limitations hold for the implementation of COVID-19 vaccination.

Cross-country comparisons of the effectiveness of NPIs are even more difficult as differences in the effectiveness of NPIs can be attributed to multiple factors. Combinations of NPIs implemented in different countries can lead to different effect estimates. Next to the abovementioned aspects, factors such as resilience of the healthcare system, health system characteristics, national per capita expenditures for health, and prior experiences with novel epidemics influence the effectiveness. [1, 94] Therefore, the (diversity of) effect sizes mentioned in the paragraphs before for different countries should be interpreted with caution and cannot be directly translated to other situations (e.g., the Dutch situation in the same time period, or effects size in future waves of COVID-19, or effect size in a future pandemic caused by a different pathogen).

Our initial (unrestricted) literature search showed that an enormous amount of scientific articles has been published related to COVID-19. However, even with our restricted search, we ended up with a large number of which many articles were of low quality. Only a handful of reviews with acceptable to high quality were found, indicating a lack of synthesis of results. Next to the aforementioned limitations regarding the quantification of the effect of NPIs and vaccination, there are other methodological challenges, further complicating a review on effects of NPIs. [96] Many of the reviews that we found and included were an inventory of individual studies, without a pooled measure or meta-analysis. This is not always possible due to, for example, the low number of (good quality) studies, or heterogeneity in populations included, outcomes studied, definition of NPIs or study designs. [8, 96] However, many reviews still provide pooled measures, despite methodological barriers. Their validity may, in some cases, be questionable. An innovative way to circumvent these issues was used in the review of Mendez-Brito et al. [97] who display the results of the different included studies using heatmaps by the ranking the NPIs on impact and not pooling quantitative measures, because of the corresponding limitations. Multiple reviews state that there was a lack of empirical, real-world data, e.g., there were very little data on the actual implementation of interventions. [18-20] Nevertheless, it is to be expected that more reviews will come available in the coming years.

Several issues should be kept in mind when assessing the included reviews. Publication bias could have played a role, as it is likely that mostly studies that found an (statistically significant) effect were published, while studies that found no effect were not. Furthermore, the definition of the included NPIs differed per study. For example, ‘social distancing’ is interpreted in many different ways. While for some the physical distance between persons was the main focus of interest, i.e., a single intervention[8, 16]; in other studies multiple measures could fall under this definition. In those studies ‘social distancing’ is actually studied as a package of interventions. [14, 15] It should also be noted that most studies took place during the first year of the COVID-19 pandemic. This could be the result of the delay in publication of reviews, but it is also likely that disentangling the effect of the different interventions gets even more methodologically challenging later on in the pandemic. Effects of NPIs are getting increasingly intertwined, including the effect of vaccination that started in the end of 2020/beginning of 2021.

Vaccine effectiveness of COVID-19 vaccination could be studied relatively well for the Dutch situation, as this is extensively researched by the RIVM for the Dutch situation. It is one of the few interventions where it has been possible to quantify the effectiveness in a reliable way with small bias. The results of this review show that COVID-19 vaccination is very effective in preventing SARS-CoV-2 infection, transmission, and severe COVID-19. International literature is in line with this. The VE estimates differ for the different virus variants, vaccine types, populations, and outcomes assessed. Studies on the VE in the Dutch situation were complicated by the fact that consent from the vaccinee is needed for registration in the Dutch national COVID-19 vaccination register (CIMS). This causes misclassification of vaccinated persons that did not give consent as being unvaccinated. An analysis by the RIVM shows that a modest non-consent for registration of vaccination records could result in substantial bias in the VE (e.g., underestimating the VE), especially when there is a high vaccination uptake.[98] These results stress the importance of vaccination registers with national coverage and adequate privacy assurance that are complete and do not suffer from non-consent bias, to facilitate adequate monitoring and evaluation of current and future vaccination programmes.

Given the large number of publications already published and the rate at which new publications appear, one cannot claim that a literature search is complete. The restrictions we applied to our literature search may have left some relevant studies out, as our search terms may not have captured all articles discussing relevant NPIs and outcomes. Furthermore, we only included reviews and no individual studies. This led to some individual studies being included in multiple reviews. We have tried to filter this out as much as possible. Also, it must be noted that some of the included papers are pre-prints and are not yet peer-reviewed. Their results should be interpreted with caution. New techniques, such as artificial intelligence and machine learning, can make the process of conducting a systematic literature review much more efficient and transparent.[99] As a pilot we imported the 8,500 articles on COVID-19 and NPIs that we found with our broad search into ASReview.[100] We did not redo the complete selection process of the articles, but we experienced that already soon after starting, mostly relevant-looking articles were presented to us by the algorithm. These algorithms are promising tools for future literature reviews; not only by speeding up the process but also by making it possible to include more papers (i.e., less restrictions) in the initial search.

The focus of the review was on the effectiveness of measures, not on the costs. Most NPIs can have a negative impact on the general well-being of people, the functioning of society, and the economy.[1, 94, 101, 102] In the future, based on lessons from the COVID-19 pandemic, the effectiveness of NPIs should be carefully balanced with the costs for society.

Conclusion

We conclude that vaccination is an important and effective intervention to protect the population from SARS-CoV-2 infection and sequelae, but vaccine effectiveness estimates are different for the different virus variants, vaccine types, populations, and outcomes assessed. NPIs were also effective in reducing transmission and (severe) disease, but effectiveness varied. Most included studies on hand washing showed a protective effect. Yet, when and how frequently hand hygiene should be performed was not clear. Social distancing measures such as physical distancing, stay at home measures, restrictions on (mass) gatherings, and lockdown were found to be effective in reducing transmission. School closure was predominantly effective on reducing transmission and disease, but effectiveness varied. The literature provides mixed evidence on the effect of travel restrictions. If it is effective, it is in delaying an epidemic in the country receiving infections from another country that has an outbreak or a large epidemic, not in preventing it. This would require quarantine upon entry. Symptom/exposure-based screening was likely not effective. Multiple studies found a protective effect of wearing face masks, while other studies show a less pronounced to no effect of wearing face masks in the community on COVID-19 incidence. Studies, mainly in the healthcare setting, suggest that higher-quality masks (e.g., N95 masks) were more effective than surgical masks. Results of some studies point towards a small reduction of contract tracing apps on Rt, incidence and mortality, while others found no effect on COVID-19 epidemic control. Whereas precise quantification of the effects is methodologically complicated, if not impossible, and caution is warranted when translating the effects from one context to another, it is clear in retrospect that the bundled interventions were effective in reducing SARS-Cov-2 transmission Also, high quality reviews on the effectiveness of NPIs are scarce. Better synthesis of results is warranted.

Table 1. Included reviews

Author	Journal	Publication year	End date literature search	NPI studied	Number of studies included
Bou-Karroum et al. [22]	Journal of Infection	2021	December, 2020	Travel restrictions	69 of which 19 observational
Boulos et al. [23]	Philosophical Transactions of the Royal Society A	2023	January 27, 2023	Face masks	75 of which 35 in the community setting (3 RCTs and 32 observational)
Burns et al. [19]	Cochrane Database of Systematic Reviews	2021	November 13, 2020	Travel restrictions	62 of which 13 observational
Chou et al. [24]	Annals of Internal Medicine	2023	June 2, 2022	Face masks	24 of which 13 in the community setting (2 RCTs and 11 observational)
Chu et al. [16]	Lancet	2020	March 26, 2020	Physical distancing Face masks	172 observational, of which 44 included in meta-analysis*
Gozdzielewska et al. [9]	BMC Public Health	2022	February 2022	Hand hygiene	22 (6 RCTs and 16 observational)*
Grepin et al. [21]	Philosophical Transactions of the Royal Society A	2023	Early 2023	Travel restrictions	5 reviews containing 43 observational studies
Jefferson et al. [12]	Cochrane Database of Systematic Reviews	2023	October, 2022	Face masks Hand hygiene	78 RCTs*
Jenniskens et al. [25, 26^]	F1000Research (previous version: BMJ Open)	2022	June 9, 2021	Contact tracing	27 of which 5 observational
Krishnaratne et al. [18]	Cochrane Database of Systematic Reviews	2022	December 9, 2020	School closure	38 of which 4 observational
Littlecott et al. [28]	Philosophical Transactions of the Royal Society A	2023	January 6, 2023	Contact tracing	25 observational
Liu et al. [15]	Epidemiology	2021	February 15, 2021	Physical distancing	12 observational
Murphy et al. [13]	Philosophical Transactions of the Royal Society A	2023	December 1, 2022	Social distancing	338 (mostly observational)

Nussbaumer-Streit et al. [20]	Cochrane Database of Systematic Reviews	2020	June 23, 2020	Quarantine	51 of which 8 observational*
Pozo-Martin et al. [27]	European Journal of Epidemiology	2023	July 7, 2021	Contact tracing	78 of which 12 observational
Sun et al. [14]	BMJ Open	2022	September 30, 2020	Social distancing	41 (observational and modelling, all based on empirical data)
Talic et al. [8]	BMJ	2021	June 7, 2021	Hand washing Face masks Physical distancing Stay at home/Isolation Quarantine School closure Business closure Lockdown Travel restrictions	72 observational
Vardavas et al. [17]	medRxiv	2021	April 15, 2021	Lockdown Face masks	45 of which 15 observational

* also including other respiratory illnesses (e.g., SARS, MERS, influenza)

^ two versions of the paper (one peer reviewed, one updated preprint)

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Appendix C

NPIs included in the literature search

Hand hygiene

Social distancing

- Physical distancing
- Stay at home requirements
  - Isolation
  - Quarantine
  - Working from home
- Closure of non-essential businesses
  - Closure of hospitality industry
  - Work ban for non-medical contact-based professions/Closure of close contact service
  - Closure of non-essential shops/retail
  - Closure of night clubs
- Closure of schools and child care
- Restricting visitors per household
- Restrictions on gatherings
  - Restrictions on the number of visitors
  - Closure of publicly accessible locations/public events
- Night time curfew
- Sport restrictions

Travel restrictions

Face mask

(Digital) Contact tracing

Corona certificate

- Proof of vaccination
- Proof of recovery
- Negative test result

Self-testing

Outcomes included in the literature search

- Reproduction number/Rt
- Infection rate
- Virus transmission
- Mortality
- Intensive care unit admission
- Hospital admission
- Life expectancy

Additional (broad) search terms:

- Mathematical model
- Quantitative analysis