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## Corona pandemic: Future considerations from the point of view of epidemiological modelling

In the simplest case, mathematical modelling of epidemics uses so-called SIR models. Here, the three upper-case letters describe the conditions of the individuals or the population relevant to the infection process: S stands for susceptible to infection, I stands for being infected and infectious and R stands for resistance (immunity). As elsewhere, SIR models are frequently used at the Robert Koch Institute (an der Heiden 2020; Maier 2022). Without further modifications, SIR models are used for modelling infectious diseases that produce a lifelong immunity following recovery, as is the case with many “childhood diseases”. But this in particular does not seem to apply to an infection with SARS-CoV-2. Findings suggest that both infection with, and vaccination against the coronavirus produce only temporary immunity (Baraniuk 2021). In addition, the virus is able to circumvent an existing immunity by means of new virus variants (so-called escape variants), against which cross-immunity from previous infections is not available or insufficient (Starr 2021; Weisblum 2020). This article describes neither the course of the disease in society nor the burden on the health system. Instead, the aim is to use modelling to investigate how various factors may influence infection transmission. Here, infections must not be equated with illness, which is influenced by many other factors (age, pre-existing conditions, etc.); infections occurring after previous vaccinations or after previous infections are also associated with a different probability of illness, which is very likely lower. The present article focuses on the parameters relevant to infection epidemiology, in particular those concerning prevalence and immunity.

### The peculiarity: loss of immunity

If corona infections only generate temporary immunity, this implies a continuous loss of immunity in the population. Individuals who have already recovered from an infection with the virus can become susceptible again and subsequently contract the coronavirus again (once or more times) (Pulliam 2022). This is described by so-called SIRS models, which take into account the possible “relapse” from the immune to the susceptible state ( $R \rightarrow S$ ). Adding to this the fact that infected individuals do not become infectious immediately, but first go

### Summary

Since the emergence of the Corona pandemic, there has been a worldwide question as to when the pandemic would come to an end. In the meantime, such hopes have been displaced by the fear that the infectious disease cannot be eliminated and will become endemic. The article presented here describes two reasons that speak for this hypothesis: seasonal transmission and temporary immunity. Both factors strongly influence transmission dynamics, which will shape our future management of SARS-CoV-2 and policy decisions. Based on a mathematical model, this article provides predictions on the character of future endemicity of SARS-CoV-2 and its implications for vaccination campaigns, contact restrictions and other intervention measures, as well as for the current debate on the introduction of compulsory vaccination in Germany.

### Keywords

Transmission dynamics, Endemicity, SARS-CoV-2, Intervention measures, Vaccination campaign, Epidemiological modelling, SIR model

through a latent period, one obtains a SEIRS model (E stands for “exposed” in international usage and designates the latent period between the infection and the infectious period).

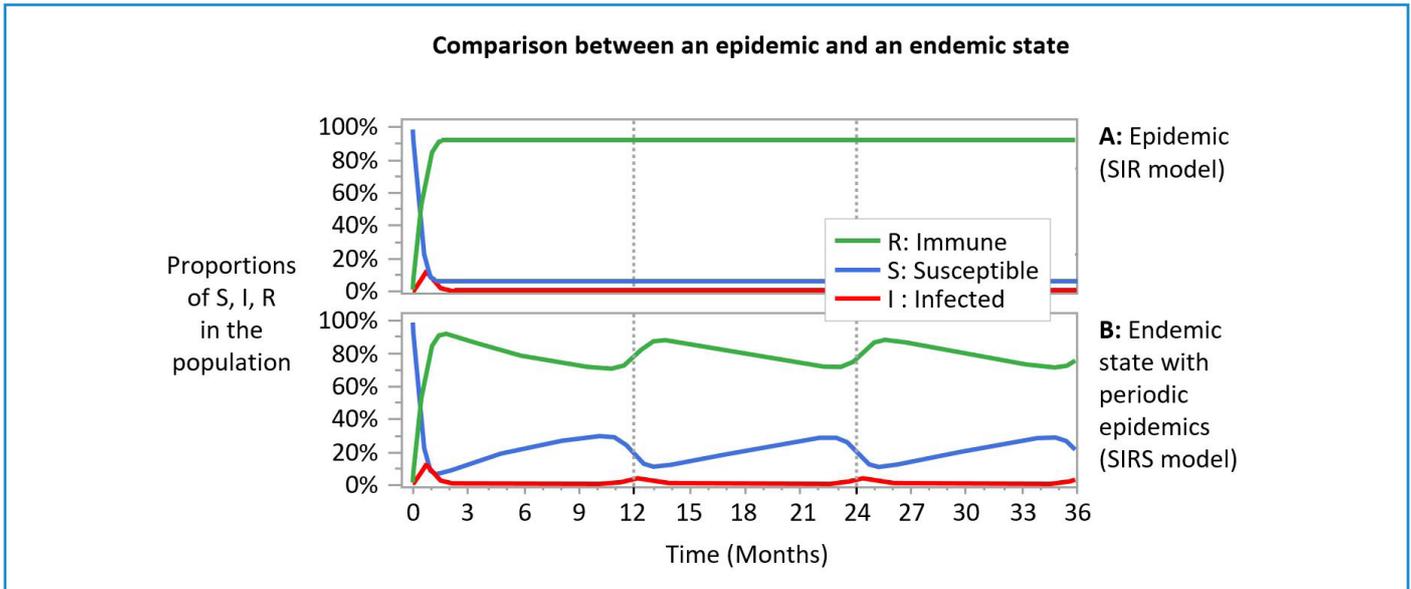
Model predictions of a SEIRS model compared to those of a SIR model are shown schematically in Fig. 1. The main difference lies in the fact that a SEIRS model leads to the endemic state fairly quickly, while a SIR model usually only creates a single epidemic that can only gain a foothold in the population again once many of the immune subjects have died and have been replaced by susceptible newborns. The most important difference between the two models is thus how and how quickly susceptible individuals emerge in the population. In the SIR model, susceptibility arises only through the birth of children; in the SEIRS model, it also arises through loss of immunity.

If immunity following infection is only temporary, the risk of an endemic condition, which can also produce recurrent epidemics, is inevitable. This risk increases in the case of a seasonally fluctuating transmission rate, as described, for example, for influenza (Goeyvaerts 2015; Vynnycky 2008). In northern latitudes, a higher transmission rate can be assumed during the winter months than during the summer (Kronfeld-Schor 2021). In the colder months of the year, this leads to increased contagion among the population, which in turn causes a temporarily increased immunisation of the population, which then, however, decreases again and again.

### Fatal coincidence: loss of immunity and seasonality

While a dynamic infection process leads to extensive immunisation of the population (strong “contagion”) during the winter semester, the opposite takes place in the warmer season. The decreasing transmission rate leads to fewer infections, and the concomitant loss of immunity prevails in the population. The growing number of susceptible individuals form the basis for a renewed severe outbreak of the epidemic in the autumn and winter months. The infection thereby becomes endemic, with a tendency to recurrent epidemics.

This article describes and discusses the consequences of this coincidence of immunity loss and the seasonally variable transmission rate. Some of the conclusions are trivial, such



**Fig. 1:** Schematic comparison between an epidemic (A) and an endemic condition (B), represented by the model predictions of a SIR model (A) and a SEIRS model (B) on the time-dependent proportions of infectious (I), immune (R) and susceptible (S) individuals. Because SIR models are based on the assumption of lifelong immunity, recurring epidemics do not occur - at least not in the short time intervals considered here. If an infection produces only temporary immunity, this leads to a loss of immunity in the population (drop of the green curve), which is why a new pool of susceptible individuals builds up in the population (rise of the blue curve). This pool then forms the basis for another epidemic.

as that the benefit of a vaccination campaign carried out, for example, in the spring is questionable if the protective immunity of a vaccination only lasts four to six months. In this case, the natural loss of immunity in the population cannot be offset by vaccination. On the other hand, the consequences can be complex and unexpected. This is shown in connection with a measure characteristic of epidemics, the so-called basic reproduction number  $R_0$  (Dietz 1993).

It turns out that the direct proportionality between  $R_0$  and the peak height of the epidemic known for the SIR model is reversed: a highly infectious disease (high  $R_0$ ) can produce large outbreaks in the SEIRS model, which with low peak values appear unexpectedly benign. On the other hand, infectious agents considered harmless due to a low  $R_0$  occur unexpectedly fulminant and with higher peak values in the SEIRS model. This publication is not intended to deal with the complex relationship between infection and disease, but it can be assumed that greater outbreaks of infection generally lead to a higher peak load on the healthcare system.

### The two sides of the endemic coin

These considerations show that some of the current epidemiological expectations need to be reconsidered when SARS-CoV-2 becomes endemic under the coincidence of immunity loss and seasonal transmission rate. It is also evident that the term “contagion”, which has predominantly negative connotations, can be viewed from a different perspective, as infections simultaneously lead to the immunisation of the population. Consequently, prevention of contagion among the population also means prevention of immunisation – the second side of the coin.

This points to the following new challenge to be overcome in the planning of prevention and intervention measures under

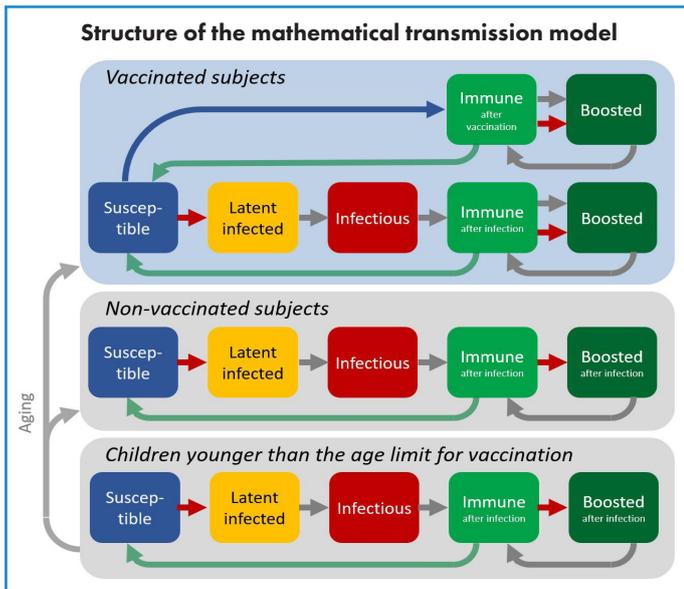
Corona, i.e. how can public health measures find the optimal balance between “harm from uncontrolled contagion” and “protection by immunisation”? Vaccination campaigns may not necessarily have only positive and protective effects, but can also produce negative epidemiological consequences at the population level. Likewise, measures to reduce contact that are not optimally timed can cause a loss of immunity greater than the containment of the infection process they produce. The implications for intervention decisions are discussed in this work.

### Methods

For our investigations, we use an extension of the basic SIR model, which is the basis for most infection transmission models. As in the basic model, we assume that humans are susceptible to infections at birth (susceptible: “S”) and can become infected. The duration of the infection is divided into two phases, the latent phase, in which the infected cannot yet infect others (“E”), and the subsequent infectious phase (“I”); infection is then followed by immunity (“R”). In contrast to the basic model, the immunity after a corona infection is only temporary and can be lost again (return to status “S”). However, upon contact with an infectious person, immune individuals may also “refresh” and prolong their immunity (immunity booster status “B”).

The model is extended by vaccinations, which is why three strata are distinguished:

1. children who are still too young to be vaccinated, and
2. older children, adolescents and adults who have chosen to be vaccinated, or
3. who have chosen not to be vaccinated. Those “willing” to be vaccinated are repeatedly vaccinated, but lose vaccine immunity over time, as is the case for natural immunity following infection.



**Fig. 2:** Structure of the mathematical model of the transmission dynamics of corona infections. The population is divided into three groups: 1) children who cannot yet be vaccinated, 2) older children, adolescents and adults who have chosen not to be vaccinated, or 3) those who have chosen to be vaccinated. Infections can occur within each group: Susceptible individuals can be infected, going first through a short phase of so-called latency, in which they are not yet contagious, then becoming contagious (infectious to others) and finally immune. Immunity is lost again, regardless whether generated by infection or by vaccination (the rate of immunity loss may, however, differ). The immunity of immune individuals is boosted (prolonged) upon contact with infected individuals. Individuals willing to receive a vaccination are vaccinated repeatedly. Vaccination does not always protect against infection (vaccination efficacy <100%). Red arrows: infections, green arrows: successful vaccinations, blue arrows: loss of immunity.

Individuals willing to receive a vaccination may also become infected, for example following contact with an infected person after the loss of sufficient immunity and before the next vaccination. However, their immunity may also be boosted by infection, not just vaccination. The model is shown in Fig. 2 and is described in the appendix in its mathematical form with the parameter values used here.

## Results

### Unexpected effect reversal

An invariable property of SIR models (which do not take loss of immunity into account) is that the peak value of an epidemic is proportional to the baseline reproduction number ( $R_0$ ) of the virus: the higher the  $R_0$ , the higher the epidemic peak and the faster it will be reached. Conversely, the following also applies: the smaller the  $R_0$ , the flatter and broader the course of the epidemic and the lower the peak.

This law is reversed in a SEIRS model with loss of immunity and seasonal transmission rate (Fig. 3; note: for seasonally fluctuating transmission,  $R_0$  quantifies the annual mean value of the time-varying  $R_0$  value.) The example shown in Fig. 3 of the dependence of the infection dynamics on the basic reproduction number  $R_0$  shows that conclusions from SIR models are no longer readily applicable when loss of immunity and a seasonal transmission rate apply.

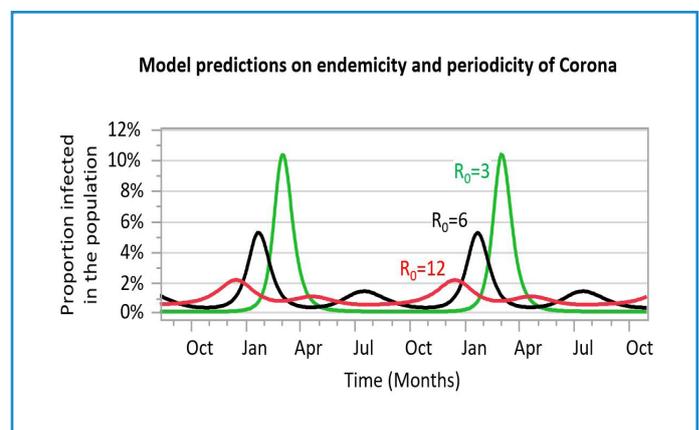
During the corona waves of the past two years, efforts were made to avoid an overload of hospital and intensive care

capacities, which would cause excess mortality due to the shortage in the care of the population. In this context, the peak value of the epidemic waves was particularly relevant because an overload is to be expected close to the peak of the epidemic. The inversely proportional relationship between the peak value and the basic reproduction number shown in Fig. 3 appears paradoxical at first glance. At second glance, however, it is obvious and only corresponds to what can be expected given the loss of immunity and the seasonal transmission rate (see below).

There is a simple reason for the apparent contradiction to the results of SIR models: a high rate of contagion leads to a persistently higher basic immunisation level of the population, and this prevents the later development of fulminant, high-amplitude epidemics. Conversely, it should be formulated accordingly that fulminant epidemics with a higher peak value are to be expected particularly from those virus variants that – measured by  $R_0$  – would rather be considered harmless.

Fig. 3 shows that for pathogens with loss of immunity and a seasonal transmission rate, the peak load on the healthcare system is greater for those virus variants that have a small baseline reproduction number, while virus variants with a large  $R_0$  maintain a high baseline immunisation of the population, resulting in the absence of high peak loads on the healthcare system.

The basic reproduction number  $R_0$  should not be confused with the effective reproduction number  $R_e$ , which is often reported as the “R value”. Values for  $R_e$  are smaller than  $R_0$  and are often close to 1.0 because they account for all current infection-reducing factors, while  $R_0$  in a sense reflects the maximum potential of the spread of an infection.



**Fig. 3:** Model predictions on the endemicity or periodicity of corona infections over a period of two years for three different assumptions regarding the basic reproduction number  $R_0$ . A SEIRS model with loss of immunity and seasonally fluctuating transmission rate is used as a basis. Black,  $R_0=6$ : A major winter epidemic and a minor summer epidemic occur, with peak prevalences of approximately 5.5% and 1.5%. Red,  $R_0=12$  (unrealistically high, shown for comparison purposes). At very high  $R_0$ , the curve flattens out and lower peaks occur, as a permanently elevated baseline endemicity (with a prevalence of about 1%) is maintained, generating a high level of immunisation in the population. This prevents the emergence of fulminant epidemics. Green,  $R_0=3$ : Epidemics only occur at annual intervals, but have very high peak values (>10% infected). The reason for the fulminant epidemic process is the combination of loss of immunity and a low transmission rate during the summer months, which causes a severe loss of immunity in the population. Starting with a high proportion of susceptible individuals at the end of the year, this results in very pronounced epidemics.

Since all factors that reduce the spread and change over time, such as immunity and contact restrictions, are taken into account separately in the model, various infectious agents can therefore be better characterised by  $R_0$ .

### Limited effects of vaccination campaigns

Effective vaccination campaigns need sufficiently high vaccination coverage and effective vaccines. In the case of corona vaccination campaigns in Germany, both are only given to a limited extent. The vaccination coverage in Germany is currently around 75% (RKI vaccination rate monitoring), and the efficacy of the available vaccines varies – depending on the virus variant and the vaccine under consideration – in a wide range, roughly estimated between 60% and 90% (Fiolet 2022). The effectiveness of a vaccination campaign results from the product of both percentages, which quickly brings the overall effectiveness of the vaccination campaign into the range of 50% or even below (e.g.  $0.75 \cdot 0.70 = 0.52 = 52\%$ ).

If a virus has a high contagion potential (high  $R_0$ ), then a low effectiveness of the vaccination campaign means that the population is mostly immunised by natural infection and no longer by vaccination, as intended. The infectious potential of the virus then compensates for any ineffectiveness of the vaccination campaign: under high  $R_0$ , the “leftover” susceptible subjects become infected very quickly and become immunised by infection. This relationship is shown in Fig. 4 for various vaccination rates and vaccine efficacy. The model used suggests the following assertions in this regard:

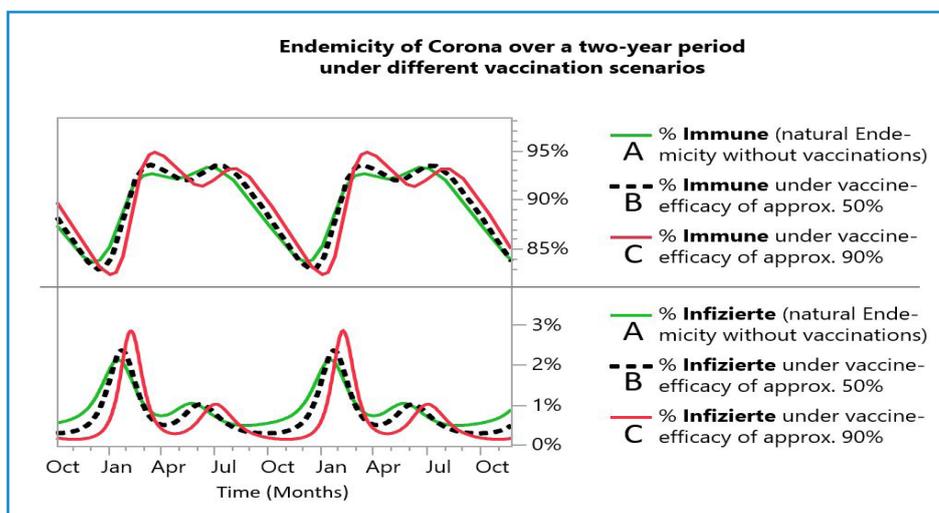
- 1. Immunisation of the population:** The vaccination campaign has hardly any additional influence on the immunity of the population if a highly contagious virus “exploits” or thwarts any form of non-immunity (i.e. susceptibility) by means of rapid infection. In this context, the origin of the susceptibility hardly matters, as it can have a variety of causes: low vaccination participation, low efficacy of the vaccines, unvaccinated population groups (children, non-vaccinable individuals), late vaccination, etc. Any existing susceptibility in the population is then converted into a (temporary) immunity by infection with the highly contagious virus. The additional immunisation by means of vaccinations thus lose much of its importance.

- 2. Endemicity:** When an infection has a high  $R_0$ , is seasonally transmitted, and exhibits a pronounced loss of immunity, vaccination can no longer prevent epidemics, and recurrent epidemics can be expected, with peak levels proportional to the proportion of the susceptible population before the outbreak. The results shown in Fig. 4 were generated using  $R_0=6$ , but are qualitatively also valid for smaller and larger values. Even in case of a 90% effective vaccination campaign (multiplication of vaccinated proportion and vaccination efficacy), the epidemic waves are hardly reduced in a noticeable manner. The reason for this is the continuous loss of immunity in the population, which leads to a permanently available pool of susceptible individuals as the starting point for the respective epidemic wave that follows. The greater the share of susceptible individuals in the population, the more pronounced a second outbreak will be later in the year. This depends on assumptions about the duration of immunity; in the case of very short-lived immunity, the model predicts smaller outbreaks in spring or even in summer.

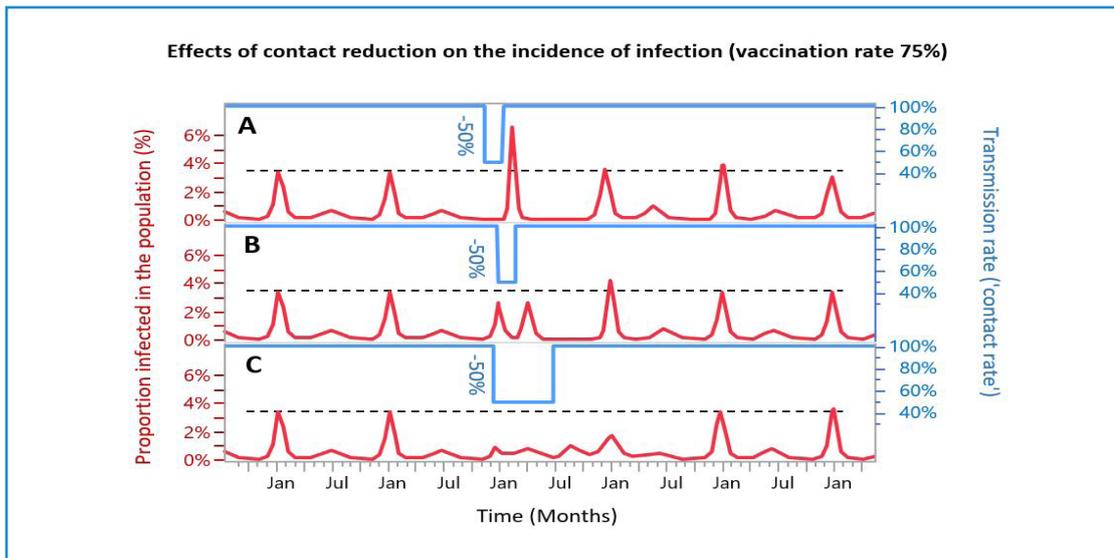
### Effects of vaccinations

The studies shown here do not consider the impact of interventions on the disease process, but only the infection process. To the extent that vaccinations prevent disease, they benefit both individuals and the health system. But even if the benefits of a vaccination for the vaccinated person are greater than his or her individual vaccination risk, the vaccination can have detrimental epidemiological side effects in the population average. This problem has been known since the 1980s (Dietz 1985) and was first documented during a rubella vaccination campaign (Panagiotopoulos 1999).

An undesirable side effect of a vaccination campaign against Covid-19 arises when the continuous loss of immunity in the population becomes greater due to the vaccination campaign than would be the case due to unhindered endemic immunisation (natural contagion). This constellation is to be expected if a vaccination campaign with limited effectiveness increases the degree of susceptibility of the population and does not reduce it as intended.



**Fig. 4:** Endemicity of Corona over a two-year period under different vaccination scenarios and using  $R_0=6$ . The prevalence of infected individuals is shown in the lower part of the graph and the proportion of immune individuals in the upper part. A: Green curves: Natural endemicity without any vaccination. The height of the epidemics is slightly smaller because they start with a higher percentage of immune individuals. B: Black, dashed curves (vaccination coverage 75% and vaccine efficacy 70%): At an effectiveness of the vaccination campaign of around 50%, the occurrence of the epidemic process hardly differs from the natural endemicity. C: Red curves (vaccination coverage 95% and vaccine efficacy 95%): This vaccination campaign with 90% effectiveness increases the amplitude of the winter epidemic, which starts from a smaller proportion of immunised individuals in the population. Even such a highly effective vaccination campaign cannot produce the same amount of immunity in the population as a virus with a high contagion or immunisation potential.



**Fig. 5:** Effects of contact restrictions on the infection process with a vaccination rate of 75% and a vaccination efficacy of 75% (= 56% effectiveness of the vaccination campaign). A: a 50% contact reduction over 60 days before the start of the winter epidemic increases the peak value of the subsequent epidemic. B: a 50% contact reduction over 60 days during the winter epidemic creates a “post” epidemic. C: a 50% contact reduction over 200 days creates endemic fluctuations that are hardly predictable anymore.

Figure 4 shows such a constellation in scenario C: a highly effective vaccination campaign leads to a situation in which the extent of the winter epidemic is slightly larger with vaccination. This is particularly the case

1. when booster vaccinations are sometimes only given after a significant loss of immunity has already occurred, i.e. “too late”;
2. when the immunity produced by vaccination is more short-lived than following natural infection (vaccination makes people susceptible again at an earlier point in time); and
3. if vaccination intervals are in an unfavourable relationship to the loss of immunity after vaccination (in extreme cases, vaccination in the spring after 6 months of immunity leads to new susceptibility in autumn and winter; precisely when a new epidemic develops).

Figure 4 can also be interpreted in two ways:

1. significantly different vaccination scenarios do not necessarily lead to a significant change in the infection process.
2. different vaccination scenarios can produce an unexpected reversal of effect, such that a desired intervention benefit is reversed, namely in an unexpected increase in the peak value of the seasonal epidemic.

Under these circumstances, the net effects resulting from various parameter assumptions (virus variant, effectiveness of the vaccination campaign, duration of immunity after infection and vaccination,  $R_0$  etc.) can hardly be predicted without a model.

This generally leads to the question of the extent to which the benefit of a vaccination campaign can be predicted in the presence of great uncertainties concerning indicators, in parameter estimates or in data (see discussion).

### Effect of contact restrictions

These considerations can be pursued for contact restrictions or, more generally, for all measures that reduce the transmission rate in the population. A reduction in the infection process (avoidance of contagion) necessarily leads to less immunisation

of the population (see above). This means that each period with a reduced transmission rate causes a loss of immunity in the population. Such a loss of immunity must be compensated at a later stage by a spread of infection until herd immunity is achieved (Randolph 2020).

The usual consequence is that the infection process accelerates after a reduction in contact, i.e. the incidence increases. Exemplary scenarios are shown in Fig. 5.

### Discussion

The article presented here discusses the predictions of a mathematical model on the future endemicity of Corona, with special consideration of the interaction between the loss of immunity and the seasonal rate of transmission. Both factors have been discussed in the scientific literature (Baraniuk 2021; Kronfeld-Schor 2021), but have hardly been taken into account in health policy and epidemiological decisions, or in the current debate on the introduction of compulsory vaccination either.

The results of the model shown here are limited to the epidemiological correlations of the infection and do not make any statements about clinical aspects, the disease process or the disease burden of corona infections. Since the focus of attention in Germany has so far been on counteracting an overload of the available hospital capacities, the epidemiological correlations of the infection have receded into the background. However, the future expected endemicity of Corona will mainly be determined by the infection process, while the disease process will follow it with a certain proportionality which will depend on both the virus variant and the immunity protection against infection (RKI 2022b).

The desired effect of vaccination is usually not only a reduction in the probability of illness, but also a reduction in the transmission of infection. In the case of SARS-CoV-2 infections, however, the reduction in the transmission of infection by means of previous vaccinations is proving to be problematic. In order to find an optimal compromise between these two opposing effects, extended models should be used to investigate whether vaccinations should perhaps be prioritised specifically for the particularly vulnerable population groups.



The obvious question is which strategies can best be used to combat such a new type of virus. Here, the first step will be to agree on a basic model structure and thus on the relevant influencing factors. Are immunity loss and the seasonal transmission rate critical factors?

If so, what does an adequate basic mathematical model look like, given this assumption? The next step will be to improve the quality of the input data and parameter estimates. The past two years of the pandemic have shown that not every available piece of data provides usable information; empirical research is needed here.

In addition, predictions and risk assessments should not be derived from single models, but from several independently developed models. The article presented here is therefore also intended to stimulate the notion that the same research questions on the endemicity of corona should be investigated independently by several working groups in the future. This is the only way to produce evidence that allows us to make good decisions for the future. This also applies to the current debate on the introduction of compulsory vaccination.

### Note

In addition to the bibliography, reference is made to independent networks and platforms for further scientific information on the topic (e.g. <https://corona-netzwerk.info>, <https://covid-strategie.de>)

### Addendum

An extended method part is available in the online version ([www.m-vf.de](http://www.m-vf.de)).

### Authors' statement

The authors have no conflicts of interest to declare.

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