

Lilliput

Can a combination of vaccination and face mask wearing contain the COVID-19 pandemic?

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Summary

The COVID-19 pandemic is going into its third year with Europe again being the focus of major epidemic activity. The present review tries to answer the question whether one can come to grip with the pandemic by a combination of vaccinations and non-pharmaceutical interventions (NPIs). Several COVID-19 vaccines are of remarkable efficacy and achieve high protection rates against symptomatic disease, especially severe disease, but mathematical models suggest that the current vaccination coverage in many countries is insufficient to achieve pandemic control. NPIs are needed as complementary measures because recent research has also revealed the limits of vaccination alone. Here, we review the evidence for efficacy of face mask wearing in various settings. Overall pooled analysis showed significant reduction in COVID-19 incidence with mask wearing, although heterogeneity between studies was substantial. Controlled trials of mask wearing are difficult to conduct, separating mask wearing effects in population studies from the impact of other NPIs is challenging and the efficacy of masks depend on mask material and mask fit. The combination of vaccination and mask wearing is potentially synergistic since vaccination protects so far well from disease development (the omicron variant is currently an unknown) but immunity from infection wanes over few months after vaccination. In comparison, masks

interfere with the virus transmission process at a level of a physical barrier independent of coronavirus variant. Vaccination and masks are much less costly to apply than other NPI measures which are associated with high economic and social costs, but paradoxically both measures are the target of a vocal opposition by a sizable minority of the society. In parallel with biomedical research, we need more social science research into this opposition to guide political decisions on how to end the pandemic.

Introduction

The COVID-19 pandemic is now going into its third year and does not show signs of abating. A few months ago, there was hope that we were in a final phase of the pandemic and forecasts from health politicians and from well-informed newspapers predicted an end of the pandemic for Spring 2022. A major argument was the 2-year course of the last great pandemic, the Spanish flu from 1918/1919. However, a coronavirus pandemic may not follow the time-course of an influenza virus pandemic. In fact, if historical records from the Russian flu pandemic, indicating that it might have been a coronavirus pandemic, are trustworthy, we might have to count with a pandemic extending over several years (Brüssow and Brüssow, 2021; Brüssow, 2021b). Currently, the optimism for a forthcoming end of the pandemic is gone. Europe is again the focus of major epidemic activity and the appearance of a new variant of concern, omicron, first described in South Africa, is filling the headlines of newspapers and fuelling the political discussions. During the first wave of the COVID-19 pandemic, many governments imposed various containment measures and scientists explored their efficacy. Non-pharmaceutical interventions (NPIs) imposed by different governments included test and trace, isolation and quarantine strategies, stay-at-home orders, travel restrictions, closure of non-essential businesses and schools, physical distancing, limiting of social interactions, face mask wearing and amelioration of indoor ventilation. Some of the NPIs are socially very disruptive and impose a heavy economic burden on our societies. In the long run, some of

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the more drastic NPIs might not be economically sustainable and lead to a political split of our societies. Very efficient vaccines were developed in the first year of the pandemic, authorized in the late phase of the first wave and mass vaccination campaigns started during and after the second pandemic wave. The roll-out of national vaccination campaigns was seen as a complementary even synergistic measure to NPIs to cope with the pandemic (Doroshenko, 2021). While NPIs decrease transmission rates, vaccination decreases primarily symptomatic disease, hospitalization and death from infection and to a lesser extent infection rates. The burning question is why we have not yet come to grip with the pandemic by a combination of vaccination and NPIs. The present review tries an answer by analysing the efficacy of vaccination and face mask use, a low-cost NPI. Since national vaccination campaigns were initiated early in the UK which also has one of the best national health data capture systems to follow the epidemic trajectory, we start our literature review with publications on the descriptive pandemic epidemiology in the UK, followed by mathematical models exploring the impact of combining vaccination with NPIs. We then explore why vaccination alone is unlikely to stop the epidemic and explore the efficacy of mask wearing. Looking at the effect of other individual NPIs would be highly relevant, but data on the efficacy of individual NPIs from field trials are still scarce and beyond the scope of this review.

The UK approach: mass vaccination with relaxation of NPIs

Some governments reasoned that achieving a satisfactory vaccination coverage in the population could justify relaxing restrictions imposed by NPIs, which are considered by a small, but vocal minority of the Western societies as dictatorial and unconstitutional governmental measures and these groups are also frequently opposed to vaccination. To solve this dilemma, the UK Government designed a four-step COVID-19 roadmap for the lifting of NPIs during 2021 in parallel with the vaccination roll-out (UK Government, 2021a,b): (1) school reopening; (2) outdoor hospitality and non-essential retail reopening; (3) indoor hospitality reopening and (4) lifting of all remaining restrictions ('freedom day'). Freedom day was declared on 19 July 2021. Many epidemiologists doubted the wisdom of this decision since it occurred at a moment when daily case counts were nearly as high (61'000 on 15 July 2021) as in December 2020 at the height of the second wave (81 000 on 29 December 2020). To the surprise of many epidemiologists, the daily case numbers decreased to 20'000 at the end of July. The 70% full vaccination coverage seen in the adult population at that time was considered well below the herd immunity threshold

for the dominant delta variant circulating in the population. Many schools in England closed around 23 July for summer vacations and some epidemiologists suspected that this effect might have caused the dip in case numbers (Ball, 2021). However, the decrease in case numbers was not maintained, cases were in mid-October as high as in mid-July, death rates tripled between July and October 2021, but are with currently about 150 daily deaths substantially lower than during the peak of the first wave (1000 daily deaths in April 2020) and at the height of the second wave (1300 daily deaths in January 2021). Daily hospitalizations were at 1000 in October 2021 while they had reached peak values of 3100 during the first and 4500 daily hospitalizations during the second wave, which came close to overburden the health system (all data quoted from UK Government, 2021c). At the moment and with only few exceptions, case increases are seen across the whole of Europe and WHO has declared Europe the current focus of the COVID-19 pandemic and predicted up to 700 000 fatalities until March 2022. On 6 November 2021, the vaccination coverage in the UK was 87.2% for the first dose, 79.6% for the second dose and 16.3% for the third 'booster' dose as calculated for the population older than 12 years (UK Government, 2021c). Despite this high vaccination coverage, the UK government reintroduced face mask wearing in shops and public transport at the end of November. This renewed surge of the pandemic clearly shows that we need a better understanding of the effect of combining vaccination with NPIs in the fight against the pandemic.

Mathematical models

Raw epidemiological data published by governments are important to take health political decisions, but not enough to understand the underlying dynamics of the epidemic. Mathematical modelling studies are needed that analyse the impact of each of the four steps of the UK roadmap on the trajectory of the pandemic in the UK and to predict future developments. A consortium of researchers from London developed a mathematical model that integrated surveillance data, including hospital admissions, hospital occupancy, seroprevalence data and population-level PCR testing data using a Bayesian evidence synthesis framework for predicting the trajectory of the epidemic when relaxing certain NPIs. The Christmas school holidays 2020 and physical distancing in December 2020, followed by the third national lockdown in January 2021, successfully brought the reproduction number R of the coronavirus below the critical threshold of 1 (the R value describes how many people each infected person will infect on average, it is not a fixed value, but depends on a number of factors; it must drop below 1 to contain and then suppress an epidemic).

Educational institutions reopened on 8 March 2021, and cases continued to decrease. When non-essential retail opened on 12 April 2021, the R value remained below 1, possibly helped by Easter school vacations and increasing vaccine coverage. With step 3 reopening on 17 May 2021, the R value grew, however, above 1 which the authors attributed to the increase in prevalence of the more transmissible delta virus variant. Step 4 of the reopening ('freedom day') was postponed from 21 June to 19 July 2021, with the aim to further increase the vaccine coverage before total suppression of all NPIs. According to the model calculations, this delay helped to cut the rate of projected hospitalizations by a factor of 3. The model attributed the sharp increase in the R value seen in mid-July to an increased contact rate during the UEFA European Football Championship. Freedom day was followed by a transient decrease in cases, but subsequently infection rates increased again building up a broad third infection wave in the UK despite a high vaccination coverage in the population. The model predicts substantial future deaths – somewhat counterintuitively predominantly in fully vaccinated individuals aged 75 years or older – and the scientists concluded that vaccination alone in the absence of NPIs might not be sufficient to control the current epidemic with the delta variant (Sonabend *et al.*, 2021).

An earlier model from another group of UK scientists also concluded that vaccination alone will be insufficient to contain the outbreak. Taking their most optimistic assumption that the vaccine will prevent 85% of infections, they calculated an R value of 1.58 if no NPI measures were taken. Under the 85% infection protection hypothesis by a vaccine, removal of all NPIs after completing the vaccination programme will still lead to 21 400 deaths in the UK. With a vaccine that prevents only 60% of the infections, the number of deaths could raise up to 100 000 victims. In this scenario, 48% and 16% of all COVID-19-associated deaths would occur in recipients of one and two vaccine doses respectively. In their model, these researchers assumed a default vaccine uptake of 95% in people aged 80 years and older, 85% in those aged 50–79 years and 75% in those aged 18–49 years, which is a higher coverage than currently seen in many Western societies. An abrupt change from a high to lower strength of NPI control is predicted to precipitate an epidemic wave. Delaying the relaxation of NPIs will generate a smaller subsequent wave. If one would wait until January 2022 to completely lift all NPI restrictions, which in their model corresponds to the entire adult population having been offered (or received?) two doses of vaccine, the model still predicts a substantial outbreak upon relaxation of NPIs (Moore *et al.*, 2021).

Computer simulations with data from a US state also suggested that removing NPIs while vaccines are

distributed may result in substantial increases in infections. The calculations also suggested that vaccines of lesser efficacy used by a higher number of people gives better results than vaccines of higher efficacy used by a lower number of people, underlining the importance to motivate as many people as possible to get immunized (Patel, 2021).

The limits of vaccination against symptomatic and severe disease

Phase 3 clinical trials

The predictions from mathematical models and the current surge of the pandemic raise the question why highly efficient vaccines have not succeeded in stopping the epidemic in countries where mass vaccination campaigns have been launched. Indeed, some COVID-19 vaccines showed very high protection rates. In phase 3 clinical trials, the Moderna mRNA vaccine demonstrated a vaccine efficacy (VE) of 93% against symptomatic COVID-19 illness and 98% against severe disease. The efficacy in preventing asymptomatic infection starting 14 days after the second injection was 63% (El Sahly *et al.*, 2021). Similar data were published for the mRNA vaccine of Pfizer-BioNTech, which showed a VE of 91% against symptomatic COVID-19 (Polack *et al.*, 2020). After a longer follow-up of 6 months, the researchers observed a time-dependent decrease in VE. From its peak VE after the second dose of 96.2% against symptomatic disease at < 2 months, VE decreased to 90.1% at 2–4 months and then to 83.7% at > 4 months after vaccination. Against severe COVID-19 VE was still 96.7% (Thomas *et al.*, 2021).

Promising data were also reported for vaccines developed from other technology platforms. The recombinant nanoparticle protein vaccine from Novavax showed a VE of 90% against symptomatic infections (Heath *et al.*, 2021). The single-shot recombinant adenovirus-vectored vaccine from Johnson & Johnson achieved a VE of 66.1% against symptomatic infections and 85% against severe disease. VE against asymptomatic infection as diagnosed serologically was 65.5% (Sadoff *et al.*, 2021). An interim analysis of the first phase 3 trials in UK and Brazil with the adenovirus-vectored vaccine from Oxford-Astra Zeneca reported VE of 70% for symptomatic disease (91% in UK, 66% in Brazil) and a VE of 59% in UK against asymptomatic infection diagnosed by detection of viral RNA (Voysey *et al.*, 2021).

In an interim analysis of a smaller phase 3 trial with the Chinese whole inactivated virus vaccine CoronaVac in Turkey, which enrolled 10'000 adults younger than 60 years, a VE of 84% was observed against symptomatic COVID-19 after a median follow-up period of 43 days. With a 1-month longer survey period, VE seemed to decrease to about 60% (Tanriover *et al.*,

2021). Two inactivated virus vaccines from Sinopharm were tested in 40 000 adults from the United Arab Emirates and Bahrain in a placebo-controlled phase 3 clinical trial. An interim analysis after a median follow-up of 77 days showed a VE of 73% and 78% for the two vaccines against symptomatic COVID-19. Hospitalizations were rare and occurred only in placebo recipients (Al Kaabi *et al.*, 2021).

Real-world studies

Comparable protection rates were reported in a case-control study with healthcare workers (HCW) from 25 US states. The study investigated the vaccination status in COVID-19 cases (confirmed by PCR or antigen tests) with that in matched uninfected controls. VE against symptomatic disease with the Pfizer and the Moderna vaccine was calculated to 89% and 96%, respectively, after two injections. Over a 14-week period, the researchers observed a waning of VE to 80% (Pilishvili *et al.*, 2021).

In another study from the Southern US, HCW were tested weekly for SARS-CoV-2 by RT-PCR. In parallel a vaccination campaign was conducted. VE against infection was 81% after the first vaccination and 91% after the second vaccination. Only a marginal difference was observed between the Pfizer and Moderna mRNA vaccines. Among the subjects with a positive test, 63% of the unvaccinated and 25% of the vaccinated subjects showed fever symptoms. Compared with the infected unvaccinated subjects, the vaccinated subjects with breakthrough infection showed less fever days and days in bed (Thompson *et al.*, 2021).

The observations from phase 3 clinical trials with adenovirus and inactivated vaccines were also confirmed in real-world studies. For example, 81% of the 0.6 million citizens from Buenos Aires/Argentina older than 60 years who were vaccinated with the Russian Sputnik V adenovirus-vectored vaccine, the AstraZeneca adenovirus-vectored vaccine or the Chinese inactivated whole-virus vaccine from Sinopharm showed in comparison with unvaccinated citizens an 88% decrease in cases for the people who received one of the adenovirus vaccines, while the Chinese vaccine had a lower VE against infection and death (Macchia *et al.*, 2021). Notably, the two Chinese inactivated whole-virus vaccines represent together with the Pfizer mRNA and AstraZeneca adenovirus vaccine the most widely distributed vaccines with 1.5 billion doses delivered for each of them by October 2021 (Mallapaty, 2021).

Population studies

An 'ecological' analysis of national surveillance data in the US revealed that by March 2021, 50% of the citizen

older than 65 years were vaccinated, while only 10% of the age group between 50 and 64 years had received the vaccine. After March 2021, case incidence ratio showed a 60% decrease in cases, a 70% decrease in emergency department visits and a 69% decline in hospitalization for the more vaccinated older compared with the less vaccinated younger adults (McNamara *et al.*, 2021).

Public health scientists analysed VE data for infection and death in 780 000 US veterans between February and October 2021, when the US experienced a surge in the prevalence of the delta variant. Over this time period, VE against infection decreased from 88% to 48%. The decline was less important for the mRNA vaccines (VE of 58% for Moderna and 43% for Pfizer vaccine) but substantial for the adenovirus-vectored vaccine from Johnson & Johnson (VE of 13%). VE against death remained high for all three vaccines approved in the US: 73% for the adenovirus vaccine and 82–84% for the two mRNA vaccines. Breakthrough infections increased in parallel with the surge of the delta variant and they were not benign, since the risk of death was significantly higher in infected vaccinated people than in vaccinated subjects who remained uninfected. Nevertheless, infected vaccinated subjects showed a significantly greater survival than infected, unvaccinated subjects. Based on these data, the authors propose that even for vaccinated subjects NPIs should be maintained such as masking, physical distancing and hand washing (Cohn *et al.*, 2021).

Differentiating declining VE as a function of time-from-vaccination ('waning immunity') from lesser protection against variant viruses ('immune escape') is challenging. The vaccination campaign in Israel was conducted when the delta variant became dominant. Researchers explored the health register of an organization insuring 1.3 million Israelis. They compared an early (January and February) with a late (March and April) vaccination group for infections occurring in June and July 2021. They matched 330 000 vaccinees in each group and noted a significant twofold higher infection risk in the early vs. the late vaccination group. Breakthrough infections showed 37 cases per 10 000 for those vaccinated in January compared to 17 cases in those vaccinated in April. Longer distance from vaccination was also associated, albeit non-significantly, with an increased hospitalization rate (Mizrahi *et al.*, 2021).

In a study from the US, 16% of the hospitalized COVID-19 patients were vaccinated compared to 55% of controls hospitalized for other reasons. Breakthrough infections were associated with being older, being White and immunocompromised. The physicians asked whether people who develop COVID-19 despite vaccination had lower disease severity. Indeed, vaccine

breakthrough cases received less commonly ICU-level care (25%) than unvaccinated COVID-19 patients (40%) or invasive mechanical ventilation (8% vs. 23%). Unvaccinated patients accounted for 94% of fatal COVID-19 cases (Tenforde *et al.*, 2021).

In 3.2 million fully vaccinated Scottish citizens, only 236 COVID-19 deaths were reported (0.007%), with a comparable percentage between AZ and Pfizer vaccine recipients. Vaccinated compared with unvaccinated persons had a 4-fold, 15-fold and 30-fold lower death rate in the age groups 18–64, 65–79 and > 80 years. Fatal cases occurred mostly in older males with comorbidities (Grange *et al.*, 2021).

The limits of vaccination against infection and transmission

VE against infection

For the individual vaccinee, protection from disease is the most important vaccination effect, but for public health the interruption of infection chains by vaccination is of equal importance. The REACT-1 study in England evaluated RT-PCR results in swabs from 100 000 randomly chosen people, tested 2 to 3 times per month. The prevalence of positive tests increased from 0.15% to 0.63% when comparing the period May/June with June/July 2021, despite the vaccine roll-out. The increase was explained by the fact that the delta variant completely replaced the alpha variant in England. In mid-summer, the epidemic was driven by infections in the 5- to 24-years-old subjects, representing 50% of all infections. Vaccination with the Pfizer or the AstraZeneca vaccine reduced the risk of infection by threefold. The shift of infection to young age groups was explained by their much lower vaccination coverage. VE against infection decreased from 64% to 49% in the investigated time interval while VE against symptomatic disease decreased from 83% to 59%. Fully vaccinated subjects contributed 29% of the infections in the first interval, but 44% in the second interval, which the researchers explained by the increased social mixing, lesser vaccine protection against the delta variant and the waning of vaccine protection. Notably, 2.8% of fully vaccinated individuals tested swab positive after a reported contact with a known COVID-19 case as compared to 6.7% of unvaccinated subjects. In RT-PCR assays, vaccinated people who got infected showed a significantly lower viral load which may suggest a lower infectiousness. When plotting the time development of positive PCR tests, COVID-19-associated hospitalizations and deaths followed the PCR peak by 20 and 26 days, respectively, for the whole population. From early February 2021, when the alpha variant became dominant, the researchers observed in time series a decoupling of PCR positivity

from death rates with less deaths than expected from the number of infections. However, with the arrival of the delta variant in mid-April 2021, they observed a re-convergence of these key figures, but mortality remained still much lower than during the second wave (Elliott *et al.*, 2021).

Researchers analysed the infection rates in vaccinated and unvaccinated subjects from PCR-positive test results reported to the multistate Mayo Clinic Health System in the US. They used high-throughput, machine-augmented curation of electronic health record data. Tests were done on symptomatic and asymptomatic subjects. They compared the rates for 35 000 recipients of the Pfizer-BioNTech mRNA vaccine with 35 000 matched, but unvaccinated controls. Starting 7 days after the second dose they observed 82 vs. 563 infections in the two groups, corresponding to a VE against infection of 86%. The corresponding figures for a cohort of 11 000 recipients of the Moderna mRNA vaccine compared to 11 000 matched controls were 7 and 101, yielding a VE of 93%. After the first dose, the VE against infection was 46% and 52% for the Pfizer and the Moderna vaccine respectively. Overall, breakthrough infections in fully vaccinated subjects led to hospitalization in 17% of the subjects but death was not observed, while 3.4% of the hospitalized unvaccinated controls died (Pawlowski *et al.*, 2021). The same researchers investigated the impact of the adenovirus-vectored vaccine from Johnson & Johnson in 8900 recipients compared to 89 000 unvaccinated matched controls. Two weeks after this single-dose vaccination VE against infection was 73% when the alpha variant dominated in the US (Corchado-Garcia *et al.*, 2021).

Variants

Researchers from London sequenced 19 000 viral samples from COVID-19 cases in the UK when the delta virus variant started to replace the previously dominant alpha virus variant and connected the sequence database to an epidemiological database, which included information on the vaccination status. VE after the first shot was 49% against the alpha and 31% against the delta virus variant, with no difference between Pfizer or AstraZeneca (AZ) vaccines. After the second injection, VE against symptomatic infection with the alpha and the delta virus variants was 94% and 88%, respectively, for the Pfizer vaccine. The corresponding figures for the AstraZeneca vaccine were 75% and 67% respectively. The researchers observed a trend for waning protection with time for all vaccines (Lopez Bernal *et al.*, 2021).

In 2021, Qatar experienced three sequential infection waves during which the alpha variant was first replaced with the beta variant and then with the delta variant. Vaccination campaigns were conducted with the mRNA

vaccines from Pfizer and Moderna which allowed a determination of their VE against variant viruses. VE after the second injection against symptomatic or asymptomatic delta infection was 52% (Pfizer) and 73% (Moderna), while VE after the second injection against delta virus-induced severe, critical or fatal disease was 93% (Pfizer) and 96% (Moderna). VE against asymptomatic delta virus infection was 46% (Pfizer) and 54% (Moderna) (Tang *et al.*, 2021).

In a case-control study with 60 000 elderly participants in São Paulo State/Brazil, researchers determined the VE of the AZ vaccine during a period of dominant infections with the gamma variant virus. VE was 78% against symptomatic COVID-19, 88% against hospitalization and 94% against death associated with SARS-CoV-2 (Hitchings *et al.*, 2021).

Viral load

In a study conducted between January and February 2021 in Israel, scientists analysed the viral load deduced from RT-PCR tests in vaccinated (Pfizer) and unvaccinated infected subjects. From 12 days after the first immunization, they observed a threefold decrease in viral load compared with non-vaccinated subjects (Levine-Tiefenbrun *et al.*, 2021a), supporting hopes that vaccination would lower virus transmission. Indeed, with the roll-out of the national vaccination campaign, very few new COVID-19 cases were registered between April and June 2021. Then, a new surge of cases occurred concomitant with the appearance of the delta variant, suggesting that the delta variant is less susceptible to vaccine immunity. However, disproving this hypothesis, newly infected vaccinated subjects showed a 16-fold reduced viral load for the delta variant compared with infected unvaccinated controls. Viral load difference between vaccinated and unvaccinated people decreased to fourfold and disappeared after 2 and 4 months, respectively, following vaccination, indicating a rapid waning of VE against infection with the delta variant over time. Notably, a booster vaccination with the Pfizer vaccine again induced a reduction in viral load (Levine-Tiefenbrun *et al.*, 2021b) and a significant reduction in cases when compared with fully vaccinated subjects who did not receive a booster injection (Barda *et al.*, 2021; Bar-On *et al.*, 2021).

A British study investigated 1.9 million RT-PCR tests from randomly selected households for vaccine effects and reported 0.8% positive tests. VE against infection was 56% 3 weeks after the first dose and increased to 80% after the second dose. VE was very high against infections with self-reported symptoms (95%), high against infections with high viral load (91%), but lower against infections with low viral load (75%). Thirty-seven

per cent of subjects with high viral load reported symptoms compared to 17% of subjects with low viral load. There was no difference for VE against infection between subjects who received the Pfizer or the Astra-Zeneca vaccine (Pritchard *et al.*, 2021).

A British dataset from early 2021 with nearly 1 million household contact data of unvaccinated index cases showed a 10% secondary attack rate (SAR). SAR was only 5% when the index case had received either the AZ or the Pfizer vaccine (Harris *et al.*, 2021). A later British transmission study described that fully vaccinated index cases with delta virus breakthrough infections have peak viral loads similar to unvaccinated index cases. Vaccinated and unvaccinated index cases transmitted infections with comparable frequency to 24% of their contacts. SAR was 38% in unvaccinated and 25% in vaccinated contacts (Singanayagam *et al.*, 2021). All breakthrough infections were mild, and no hospitalizations and deaths were observed. An editorial noted that the vaccine effect on reducing transmission is minimal in the context of delta variant circulation, necessitating both a higher vaccine coverage and maintenance of NPIs to curtail transmission (Wilder-Smith, 2021).

The limits of vaccination – interpretation

Several COVID-19 vaccines are of remarkable efficacy and achieve up to 95% protection of the vaccinees against symptomatic disease after the second injection. However, this figure means that 1 in 20 vaccine recipients will experience COVID-19 symptoms, albeit with attenuated severity when compared with unvaccinated controls. Over the months following vaccination, this protection rate might fall to 80% by waning immunity, meaning that one in five vaccinees will experience a breakthrough infection (BTI). Protection against severe disease is decreasing more slowly and appears to be more durable, but BTI is not always benign in vaccinees. With longer time after vaccination, VE against infection decreases to 20% in epidemic conditions marked by a succession of more transmissible virus variants as seen in Qatar, however, VE against severe disease was maintained at high level (Chemaitelly *et al.*, 2021). The waning immunity can be reversed by booster immunization currently proposed 6 months after the second injection for mRNA vaccines. It is currently unknown whether further repeat immunizations will be needed as practiced by yearly re-vaccinations against influenza virus.

The VE against infection is less potent than the VE against disease, particularly against severe disease. While the vaccinated individual seems to be well protected against severe disease, vaccination has a lesser impact on the interruption of infection chains to curb the epidemic. This means that as long as a sizable

percentage of unvaccinated subjects remain, the pandemic will represent a burden to the health system and claim many lives.

The difference between protection from infection and protection from disease should not be surprising. Current vaccines are injected intramuscularly and are likely to induce a better systemic immune response which protects the lungs and other organs against viral attack than a local immune response on the nasal and oral mucosa which protects against an upper respiratory tract infection. Local immune responses are known to be of lesser durability than systemic immune responses. The lesser induction and probably quicker decrease in secretory antibodies on mucosal surfaces may again allow the replication of the virus in nose and pharynx, causing viral transmission by droplets and aerosols from vaccinated, but infected people to unvaccinated by-standers. Potential remedies are at hand, since nasal application of adenovirus-vectored vaccines, either as initial vaccination or as a booster vaccination after intramuscular injection, induced high levels of local antibodies that prevent viral replication in the upper respiratory tract of both mice (Lapiente *et al.*, 2021) and monkeys (Hassan *et al.*, 2020). From such a mixed intramuscular/intranasal vaccination strategy, one might expect a better interruption of viral transmission chains and decreased infection rates in the population, allowing to end the pandemic. Safety and efficacy of mRNA vaccines have been demonstrated in children older than 5 years and these vaccines start to be authorized for use in this age class, which also might help to curtail the circulation of infectious virus in the population (Walter *et al.*, 2021).

Newly emerging variants with increased transmission potential and escape from immune protection mediated by previous infection and/or vaccination remain a threat. SARS-CoV-2 has already evolved a number of viral variants that challenged vaccination efforts, and the current nervousness around the omicron variant detected in South Africa in November 2021 is a lively reminder of this danger. The large number of mutations in immunologically critical sites of the spike protein from the omicron variant and the unknown pathway how these multiple mutations were acquired (Kupferschmidt, 2021) raise the concern that the infection- and vaccination-acquired immunity might be less protective against this new variant. The situation is not yet clear, but a number of preprints and data from vaccine companies indicate that serum antibodies from infected and vaccinated subjects poorly neutralize the omicron virus variant. A press release from BioNTech/Pfizer indicates that the 20- to 30-fold decline in neutralizing antibody activity against omicron of fully vaccinated subjects can be corrected by a third 'booster' vaccination (Callaway, 2021). Since omicron spreads rapidly, many countries conduct now

booster vaccination campaigns. The protection achieved against omicron by the vaccine-induced cellular immunity cannot yet be assessed but widespread mask wearing also for the fully vaccinated subjects seems to be an urgent additional countermeasure by the precautionary principle.

As long as viral transmission chains are not effectively controlled and this is also a question of worldwide vaccine distribution, viral evolution is inevitable. Viral evolution might necessitate modifications of the vaccines: with the mRNA technology Moderna and Pfizer BioNTech think that they might have omicron-adapted vaccines ready in March 2022. Currently it is unknown whether omicron will outside of South Africa replace the delta variant due to an intrinsic greater infectiousness (or whether local factors favoured its spread in southern Africa). It is currently also unknown whether the omicron variant is of lesser or greater pathogenicity than the delta variant (Callaway and Ledford, 2021). Viral variants that are highly transmissible but display an attenuated pathogenic potential might pave the way from an epidemic to endemic infection which many virologists predict as future scenario for SARS-CoV-2 evolution and the end of the COVID-19 pandemic. The argument goes that viruses are selected for higher transmission, not for higher pathogenicity; however, it is unclear what time is required for this transition to endemicity.

However, the greatest factor prolonging the pandemic is human behaviour. In affluent societies where the governments offered efficient and safe vaccines to their population, only about 70% of the adult population got vaccinated in many countries. In view of the above-mentioned limitations of vaccination and the infection pressure of the delta variant (not to mention the threat by the omicron variant), this coverage is insufficient to expect a decline in the epidemic. If roughly a third of the population remains fully susceptible, we will see health systems reaching the breaking point in pandemic hot-spots, such as currently in Europe, with a number of people in need of intensive care beyond available capacity and dying from the disease. Vaccine hesitancy if not frank opposition to vaccination will limit the overall efficacy of vaccines, and some Western parliaments and governments discuss vaccine mandates to protect the life of citizens where the legal basis for compulsory vaccination is provided by the constitutions. Economic and logistic problems further compound the issue when it comes to the distribution of efficient vaccines to middle- and low-income countries.

In view of these problems, NPIs are needed as complementary measures to vaccination in the current epidemic situation. However, many NPIs infringe civic rights and might be challenged in courts if their efficacy has not been proven. Therefore, it is important to collect data

on the efficacy of individual NPI measures. We start here with an NPI that inflicts the least restrictions on civic rights, namely face mask wearing and ask about proof of its efficacy.

The benefits of wearing face masks

Initial controversy

In March 2020, WHO communicated that there was not enough evidence to prove that wearing a surgical mask significantly reduces a healthy person's risk of becoming infected at a personal or at a population level. Editorials in major medical journals insisted that evidence that face masks are of no use was likewise lacking (Feng *et al.*, 2020). In the absence of randomized mask trials, they recommended face mask use by the precautionary principle and argued that the costs of masks is low and that harm from wearing masks is not to be expected (Cheng *et al.*, 2020; Greenhalgh *et al.*, 2020). Before the COVID-19 pandemic, researchers from Hong Kong studied the effect of face masks on viral shedding in droplets and in aerosols from the exhaled breath and coughs of children and adults suffering from common cold. The subjects were naturally infected with seasonal coronavirus, influenza virus and rhinovirus. Wearing a surgical face mask reduced coronavirus titres determined by RT-PCR tests in droplets and in aerosols compared with unprotected exhalations and coughs. For influenza virus, masks decreased only viral titres in droplets, while for rhinovirus masks had no effect on virus excretion in either droplets or aerosols (Leung *et al.*, 2020). Additionally, epidemiologists insisted that face mask use must be widespread to be an effective public health measure. They calculated from data of the Wuhan outbreak that a 95% face mask wearing was needed to lead to an elimination of infections (Zhang *et al.*, 2020a). Based on these and other observations, the European Centers for Disease Control (ECDC) stated in April 2020 that the use of face masks in public may serve as source control by minimizing the excretion of coronaviruses from infected individuals who have not yet developed symptoms or who remained asymptomatic (ECDC, 2020).

Current recommendations

Like WHO, CDC advised first against mask use by the public, but subsequently changed to recommending even makeshift cloth masks, including children older than 2 years, for indoor public places (CDC, 2021c). Similarly, WHO changed position and advised that the general public should wear mask in all indoor settings and in outdoor settings where physical distancing of at least 1 m cannot be maintained (WHO, 2021b). CDC stated that masks are primarily intended to reduce the emission of

virus-laden droplets ('source control') by asymptomatic or pre-symptomatic infected wearers, who account for more than 50% of transmissions. Masks also help reduce inhalation of fine droplets by 70% in the mask wearer ('filtration for personal protection') as suggested by some 'real-world' observations. CDC quoted case studies such as 2 symptomatically ill hair stylists who interacted for an average of 15 min with 139 clients when both stylists and clients wore masks. None of the 67 clients who consented to testing developed infection. In a study of 124 Beijing households with a confirmed index case, mask use by the index patient and family contacts reduced transmission in the households by 79%. Use of face coverings on-board of a US aircraft carrier was also associated with a 70% reduced infection risk (CDC, 2021b).

Observational studies

Indirect evidence for the value of masks was suggested by the observation that countries which most effectively reduced the spread of the first COVID-19 pandemic wave implemented universal masking, including Taiwan, Hong Kong, Singapore and South Korea (Prather *et al.*, 2020). Supportive evidence also came from the US where guidelines for social distancing, quarantine and isolation were issued by the federal government on 16 March 2020. In New York, wearing face masks in public became mandatory in early April 2020 with the result that infection rate decreased in New York by 3% per day, while in those parts of the US without mask mandates infections continued to rise by 0.3% per day (Zhang *et al.*, 2020b).

Further evidence for the value of masks was derived from literature surveys. Canadian researchers conducted a meta-analysis of 172 observational studies investigating the effect of physical distancing, face masks and eye protection on person-to-person transmission of infections using data from SARS, MERS and COVID-19 coronavirus studies. Transmission of coronaviruses was lower with physical distancing of > 1 m (odds ratio 0.18). The absolute infection risk was 12.8% with shorter distance vs. 2.6% with a > 1 m distance. Face mask use also resulted in a large reduction in risk of infection (odds ratio 0.15, infection risk was 3.1% with mask vs. 17.4% without mask). The protective effect with N95 masks was higher than with disposable surgical masks. The face mask protection effect was greater in hospital settings than in the community. Eye protection by face shield or goggles reduced the infection risk by a factor of 3 (Chu *et al.*, 2020). More importantly, correct mask wearing was shown to be critical. Observations from Singapore, where N95 masks were distributed, indicated that only 13% of recipients managed to use the masks

properly. The most common mistake was a visible gap between the mask and the skin (Yeung *et al.*, 2020).

Technical aspects

During the initial shortage of medical masks, technical issues around face mask materials were widely discussed. Material scientists observed that two or three layers of highly permeable fabric, such as T-shirt cloth, may block droplets with an efficacy similar to that of medical masks, while still maintaining breathability (Aydin *et al.*, 2020). Physiological changes induced by face mask wearing were indeed small, often too small to be detected, even during very heavy exercise (Hopkins *et al.*, 2020). Filtration efficiencies of N95 masks and of surgical masks were 97% and 95% respectively. As masks were initially in short supply, reuse of masks was frequent. After one round of sterilization with hydrogen peroxide, the filtration efficiency of masks was maintained while chlorine dioxide sterilization decreased filtration efficiency (Cai and Floyd, 2020). US engineers tested commercial surgical masks which had mean particle removal efficiencies of 50–75% when worn as designed but up to 90% when snugged to the face. Cone-shaped masks had a better fit and a higher particle removal efficiency (Mueller *et al.*, 2020). CDC conducted experiments to assess whether fitting a cloth mask over a medical mask or knotting the ear loops of a medical mask and then tucking them to achieve a tighter face fit achieved a better air particle control. Unknotted medical mask or cloth masks alone blocked 43% of the particles from a simulated cough. When the source and receiver were both fitted with double masks or knotted and tucked masks, the cumulative exposure of the receiver was reduced by 96%, underlining the importance of a good fit to maximize mask performance (CDC, 2021a). Despite lower filtration efficiency of surgical masks compared with N95 respirators, observational studies showed no significant benefit of N95 masks over surgical masks for prevention of SARS (odds ratio, 0.86) and no documented SARS-CoV-2 outbreaks have been linked to settings in which surgical masks were assiduously used instead of N95 masks (Dugdale and Walensky, 2020; Lynch *et al.*, 2020). German scientists calculated the exposure and infection risk by using a comprehensive database on respiratory particle size distribution and exhalation flow physics under variable conditions of physical distancing and mask wearing. Their data indicated that social distancing alone between two speaking individuals is associated with a high risk of infection after a few minutes. When only the susceptible person wears a face mask and keeps a 1.5 m distance, the infection risk drops significantly, particularly if wearing an FFP2 mask. When both persons wear a surgical

mask and the infectious person is speaking, the risk is below 30% after 1 h, but when both wear a well-fitting FFP2 mask, the infection risk decreases to 0.4%. The authors concluded that wearing fitting FFP2 masks in the community provides excellent protection for others and oneself and makes social distancing less important (Bagheri *et al.*, 2021).

Animal tests

Animal experiments also supported the value of face masks. Classical virological observations in animals showed that the severity of disease is in general proportionate to the viral inoculum received, as documented in the concept of LD₅₀, the lethal dose 50, indicating at what dose 50% of the infected animals die. Reduction in a viral dose, not necessarily elimination of a virus, is crucial in practical terms. This point is illustrated in a clever animal test. Hamsters were housed in cages within an insulator. On one side, SARS-CoV-2-infected index hamsters were placed. Naive uninfected hamsters were placed on the other side. The cages were separated by an air porous partition with unidirectional airflow from infected to naive animals. Non-contact virus transmission by air was found in 67% of exposed naive hamsters. When surgical masks were placed over the air inflow to the cages of the naive hamsters, only 17% of the naive hamsters were infected, conferring a significant albeit not absolute protection (Imai *et al.*, 2020).

Face masks: epidemiological studies

Healthcare settings

Evidence supporting face mask use was also derived from epidemiological surveys. Mass General Brigham (MGB) is the largest healthcare system in Massachusetts with more than 75 000 employees. In March 2020, MGB implemented a multipronged infection reduction strategy involving first systematic testing of symptomatic HCWs, followed by universal masking of all HCWs and subsequently masking of all patients with surgical masks. During a pre-intervention period HCWs positivity rate steadily increased to 21%. After masking of HCW was introduced, the positivity rate remained constant. After masking of patients was introduced, the rate of positivity in HCW decreased gradually and this was in contrast to the increase in case number among the general population of Massachusetts (Wang *et al.*, 2020).

Another study also showed that ending mask mandates can contribute to the resurgence of cases. At a large health centre in California with 19 000 workers, the vaccination coverage with mRNA vaccines raised from 76% to 87% between March and July 2021. Despite that positive development the centre experienced a 20-fold

increase in attack rate in July 2021 which led to a concomitant decrease in vaccine effectiveness from 94% to 66%. The physicians associated the surge of cases with the emergence of the delta virus variant representing 95% of all isolates in July 2021 and the end of California's mask mandate in mid-June. The physicians requested the rapid re-instatement of non-pharmaceutical interventions, including indoor masking, to cope with a highly transmissible new virus variant (Keehner *et al.*, 2021).

Community settings

Many studies in community settings also suggested efficacy of mask wearing. Perhaps the most striking is a study from Germany. Regions with early introduction of face mask mandates were compared with control regions in which masks had not yet become compulsory. The city of Jena was the first to introduce obligatory face mask use and shortly after implementation the rate of new infections fell substantially in Jena. This was not the case in surrounding regions without mask mandate where the infection rate continued to increase. Before intervention, the infection trajectory was similar in Jena and its surroundings. Three weeks after introduction of the mask mandate, Jena had experienced a 23% decrease in cumulative COVID-19 cases compared with adjacent regions. The effect was even greater than 50% in the age group > 60 years. Jena passed a number of public health measures before the obligatory wearing of masks which included the closing of bars, cafés and restaurants or quarantine rules for travellers returning home and these measures were used as a placebo in-time test. None of these interventions suppressed the number of COVID-19 cases in Jena as did face mask wearing. In a follow-up analysis for other regions in Germany, an even greater effect of mask wearing mandates was achieved in larger cities with a 30% reduction compared to a 7% reduction in mixed urban and rural areas, probably explained by the greater contact rates and thus greater chances of viral transmission in urban centres (Mitze *et al.*, 2020a,b).

In another study, US scientists conducted a cross-sectional survey among 380 000 individuals on self-reported face mask wearing via a web platform. The survey responses were combined with instantaneous reproductive number estimates. A logistic model controlling for physical distancing, population demographics and other variables found that a 10% increase in self-reported mask wearing was associated with threefold better transmission control (Rader *et al.*, 2021). Similarly, between June and July 2020, a large prospective cohort study of 134 000 US participants was conducted, using a smartphone-based application that collected self-

reported, individual-level information on COVID-19-like symptoms, face mask use and other personal risk factors including social distancing data. Self-reported 'always' use of face mask was associated with a 62% reduced risk of reported COVID-19 events even after adjusting for living in a community with poor social distancing. In comparison, individuals living in communities with the greatest social distancing had a 31% lower risk of predicted COVID-19 compared with those living in communities with poor social distancing (Kwon *et al.*, 2020). Another group of US epidemiologists compiled data on the timing of state-level NPIs policies and evaluated the association with reduced viral transmission based on local R value estimates. Attributing individual NPI measures with R value reduction was difficult because many measures were implemented together. An exception was face mask order which followed other NPI measures with a 2-month delay and allowed thus a less confounded impact estimate. Face mask orders were associated with an 18% reduction in R value (Yang *et al.*, 2020).

An international group of scientists analysed the COVID-19 mortality reports from the first epidemic wave for 200 countries as a function of age, gender, obesity prevalence, temperature, urbanization, smoking, duration of the outbreak, lockdowns, viral testing, contact-tracing policies and public mask wearing norms and policies. In a multivariable analysis, the duration of the outbreak in the country, and the proportion of the population aged 60 years or older were positively associated with per-capita mortality, whereas mask wearing by the public was negatively associated with the observed mortality. They observed a striking mortality difference if mask wearing was introduced within 30 days after reporting the first cases compared with no mask wearing or mask wearing starting 30 days after epidemic onset (Leffler *et al.*, 2020).

Not all epidemiological studies provided evidence for face mask efficacy. During the first infection wave, 314 patients with mild COVID-19 from Barcelona had 753 contacts defining 282 clusters. A third of these clusters had at least one transmission event. The major risk factor for a secondary attack was the viral load of the index case while self-reported mask use did not affect the risk of transmission in this Spanish study (Marks *et al.*, 2021).

Mask wearing in schools also showed effects: A survey in 169 elementary schools in Georgia/USA showed that schools with requirements for teachers and staff to wear masks had 37% fewer COVID-19 cases than schools without a mask requirement (Gettings *et al.*, 2021). Children can also transmit infections to family members and in this context face masks can be protective: Children and adolescent who got infected in a

vacation camp transmitted the infection to 18% of the households when returning home, 10% of the infected household members were hospitalized. In households in which transmission occurred, half the household contacts were infected. Transmission of infection was reduced by a factor of 3 when physical distance was kept and by a factor of 5 when wearing a mask was practiced (Chu *et al.*, 2021).

An international consortium of computer scientists and public health experts analysed the impact of individual NPI measures on the development of the epidemic in a large number of countries. The impact was expressed as a per cent reduction in the R value. During the first wave, a mask wearing mandate in public spaces only contributed a 2% reduction in R value (Brauner *et al.*, 2020, 2021). When analysing data from the second infection wave, the same group calculated that the introduction of mask wearing in most public spaces reduced transmission of infection by 12% (Sharma *et al.*, 2021). During the first infection wave, mask wearing was introduced much later than the other NPIs due to lacking mask supplies and delayed mask recommendations from WHO and CDC, explaining the artificially small effect of masks estimated during the first wave. As observed in other studies, an early introduction of mask wearing during an epidemic wave is of critical importance (Leffler *et al.*, 2020).

Intervention studies

Intervention trials with face masks are difficult to conduct and to control explaining why they are not numerous. The benefit of mask wearing was tested at a mass-gathering event. For an indoor live music event in Barcelona with good ventilation, the organizers requested same-day screening with an antigen test and face mask wearing. A total of 520 test persons participated in the event and 490 matched persons did not enter the concert and continued with their ordinary life. Eight days later, two controls and none of the concert participants tested positive for SARS-CoV-2, indicating that such events can be safely performed under comprehensive preventive intervention (Revollo *et al.*, 2021). However, with this protocol, the authors were not able to easily separate mask effects from antigen testing effects.

In another trial protocol called DANMASK-19 study, 6000 Danish adults were encouraged to follow social distancing, half of them received surgical masks for wearing when outside of the home. Primary end-point was SARS-CoV-2 infection over a 1-month observation period in Spring 2020 as assessed by antibody tests. Infection rate did not differ significantly between the masked and the control group (1.8% vs. 2.1%). The secondary end-point was infection with other respiratory

viruses, which did not differ either (0.5% vs. 0.6%). The authors suggest that masks might be effective as source control but not effective in protecting the masked person. Social distancing might also have diluted a mask effect (Bundgaard *et al.*, 2021).

The efficacy of mask wearing was recently demonstrated under real-world conditions of a field trial in a developing country. A cluster-randomized trial was conducted in Bangladesh between November 2020 and April 2021. Researchers measured the effect of community-level face mask distribution and promotion among 342 000 adult test participants. At baseline, the 300 control and 300 intervention villages were similar. Mask wearing was 13% in control villages and 42% in intervention villages, indicating a 29% increase in mask wearing in villages where masks were distributed and the wearing encouraged by field workers and local authorities. Overall, 8.1% of participants reported experiencing COVID-19-like illnesses over a 9-week observation period. For control villages, this figure was 8.6% and for intervention villages it was with 7.6% significantly lower. Symptomatic seroprevalence (i.e. persons having COVID-19 like symptoms and being positive for SARS-CoV-2 IgG antibodies) was 0.76% in control villages and 0.68% in the intervention villages, indicating a 9% decline in proven infection. The decrease was significant for surgical masks, but not for cloth masks. When using WHO criteria for COVID-19 symptom definition, an 11.6% symptom reduction was seen. No attenuation of mask wearing was observed over the 9 weeks of surveillance; 4 months later, mask wearing waned, but remained 10 percentage point higher than in control regions. The impact of the intervention was most pronounced among older individuals. The researchers observed a 22.8% decline in symptomatic seroprevalence among individuals aged 50–60 years and a 35.3% decline among individuals aged > 60 years. The intervention had a cost of \$1.50 per person, most of it was linked to field work and not mask cost. The researchers noted that their data should not be taken to imply that mask wearing can prevent only 10% of COVID-19 cases – this is only the value for a 29% increase in mask use. Greater effects might be expected by mandatory mask wearing in the public enforced by local authorities (Abaluck *et al.*, 2021).

The benefits of wearing face masks – interpretation

Overall, the effect of mask wearing might appear small. The observed small effects sometimes reflect a discrepancy between self-reported and observed mask use. For example, a study assessing mask use in Kenya by phone survey versus direct observation revealed a vast gap between the two assessments (Jakubowski *et al.*,

2021). While only 12% of people admitted in phone interviews to not wearing a mask in public, 90% of people did not wear a mask when observed. In this respect, literature reviews and meta-analyses can provide further indications. An international group of epidemiologists identified 72 studies that investigated the effect of NPIs; 35 of them evaluated individual public health measures, and 6 of them (with a total of 2627 COVID-19 cases) analysed the effect of wearing masks. Pooled analysis showed a 53% reduction in COVID-19 incidence (relative risk RR 0.47, confidence interval CI 0.29–0.75) with mask wearing, although heterogeneity between studies was substantial. In comparison, a pooled analysis of five studies on physical distancing indicated a 25% reduction in incidence of COVID-19 (RR 0.75, CI 0.59 to 0.95), while pooling of three studies on hand washing showed a 53%, but statistically non-significant reduction in COVID-19 incidence (RR 0.47, CI 0.19 to 1.12) (Talic *et al.*, 2021). Designing trials for public health measures such as wearing masks is difficult. For example, the above-mentioned DANMASK-19 study (Bundgaard *et al.*, 2021) was underpowered since it made the unrealistic anticipation that a simple recommendation of wearing a mask in the outside would half the risk of infection. The authors of this study clearly mentioned this limitation in their publication. The value of underpowered studies is controversially discussed among epidemiologists. Some scientists argue that underpowered trials are better than no trials at all; meta-analyses of small trials might still help to contribute some knowledge (Fretheim, 2021). In contrast, other scientists argue that weakly designed and/or underpowered trials may be uninformative or worse even misleading (Haber *et al.*, 2021). The issue is sensitive since the inconclusive outcome of underpowered trials can be used without mentioning the limitation of the studies to discredit the use of masks in public places.

In fact, the COVID-19 pandemic has also caused a parallel epidemic, dubbed an 'infodemic' by WHO, where groups with political interests spread deliberately misinformation to destabilize the democratic system and discredit 'elite' knowledge provided by science and medical research (Anonymous, 2020). The dangers of misinformation on social media during the COVID-19 pandemic are well established. A new aspect is software that allows individuals to generate automated content and share it via counterfeit accounts ('bots') to amplify misinformation with political motivation (Ayers *et al.*, 2021). In this context, scientists should be alerted when it comes to 'alternative truths'. Deciding on true and wrong, facts and fakes is a critical foundation of our societies (Dieguez, 2021), but science is also built on the concept of searching true assertion and elimination of wrong concepts. Deliberate fraud is severely sanctioned in science

while over the past 15 years, information technology, social media and shifting societal norms have removed many filters that were once used by journalists to verify the trustworthiness of their information source. Today the veracity of a communication tends to be less important than the number of followers. As a consequence of this development, the remarkable discoveries achieved in record time by scientists and health industries were paradoxically associated with a historical low for the estimation of science by part of the public (Kupferschmidt, 2020). This philosophical dispute matters also for the very foundation of our social life and the organization of political systems, leading to fact check sites for political statements, but also for misinformation about the current pandemic by WHO (WHO, 2021a).

Outlook

Vaccination against COVID-19 is a success story (Brüssow, 2021a), but despite remarkable efficacy vaccination as currently practiced is unlikely to end the pandemic. The efficacy of face mask wearing is less well documented which is partly due to the fact that controlled clinical trials are very difficult to conduct and that in epidemiological studies face mask wearing effects are difficult to separate from other concomitantly applied NPIs. Confounding factors are numerous in such studies which might explain variable outcomes or small benefits. However, the weight of the reviewed evidence as well as physical plausibility point to a relevant public health benefit of face mask wearing. The personal protection effect of face mask wearing is certainly less than that conferred by vaccination. Since the masks mainly provide a source control of virus dissemination wherein vaccines are less efficient, one might expect synergistic effects from combining both interventions. There is some hope that with this combination of two measures which both do not impose an economic burden on our societies one could contain the pandemic. However, such hopes are under current practice not realistic. After state-wide mask mandates, self-reported mask wearing did not increase significantly in the US, indicating a disconnect between rules, messaging and actions, and that socio-behavioural research is needed to reinforce mask wearing (Clapham and Cook, 2021). A discrepancy between self-reported and observed mask wearing was also observed in developing countries such as Bangladesh and Kenya (Abaluck *et al.*, 2021; Jakubowski *et al.*, 2021). Mask wearing became even more difficult to encourage when masks were associated with the expression of political opinions (Mello *et al.*, 2020) and led to refusal of masks by populist movements in several countries.

The same observation applies to vaccination where medical research and surveillance of adverse

vaccination effects has demonstrated that the risk of immunization is widely outweighed by the benefit of protection from disease. It is disturbing to see that sizable minorities, sometimes a third of the population, is concerned about a few dozen (if ever) fatalities associated with vaccination when the death toll of COVID-19 is now worldwide at 5 million deaths (US: 782 000; UK: 145 000; Germany: 102 000; even small countries like Belgium: 27 000 deaths) (<https://coronavirus.jhu.edu/map.html>). Frustrated by a stagnating vaccination rate, the German Ministry of Health has requested an opinion poll institute to ask 3000 adult persons who remained unvaccinated in October 2021 about their motivations (Forsa, 2021). Four personalities were identified in this group: people who doubt the existence of the coronavirus SARS-CoV-2; people who fear a dictatorial government; people who think that the restrictions on civic freedom are more dangerous than the viral infection; and people with unclear motivation. Overall, 34% of the unvaccinated think that the vaccines are not sufficiently tested; 18% fear adverse reactions; 15% do not trust official information and 10% do not fear the virus and therefore do not care about taking precautions against it. Social media use in unvaccinated persons did not differ from that of the entire population for What's app, YouTube and Facebook while Telegram (Wikipedia, 2021) use was significantly higher in unvaccinated persons (38%) compared with its use in the general German population (17%). The collapse of the hospitals is not an argument for this part of the population and 10% pretend that their doctors argued against vaccination. Only 5% of the interviewed people intended to get vaccinated soon; 23% think they are unlikely to get vaccinated and 65% are definitively decided not to get vaccinated. They tell that pressure from the majority will only reinforce their rejection of vaccination. However, they are not generally against vaccination (anti-vaxxer) and half of them have a more positive opinion about inactivated virus vaccines. The Max Planck Institute for Social Policy conducted a survey in 47 000 Europeans older than 50 years and asked for characteristics of unvaccinated people. More than 90% of the respondents from Denmark, Spain, Belgium, Sweden, Finland and Israel were vaccinated. In contrast, less than 30% of the respondents from Romania and Bulgaria were vaccinated and nearly 40% wanted to remain unvaccinated. Non-vaccinated people were more frequent in Eastern Europe and the Baltic countries. Respondents who were undecided or refusing vaccines were significantly younger, had a lower education level, were unemployed, were feeling more lonely and had difficulties to make ends meet (Max-Planck-Gesellschaft, 2021).

In view of this sizable part of the population that does not consider to get vaccinated and cannot easily be

reached by rational arguments, vaccination cannot contain the epidemic. Misinformation, disinformation and credulity in Internet spread of unverified or frankly invented information (Anonymous, 2020; Fleming, 2020) further compounds the problem. Sad as it might sound, vaccination and face mask mandates that are enforced by the authorities with fines are probably needed to contain the current pandemic in Europe without risking economic recessions by repeated lockdowns or separation of the societies into two increasingly opposing camps. Governments in Austria and Germany are currently discussing vaccine mandates for COVID-19. Vaccine mandates are not a novelty and are since 2020 law in Germany for measles vaccination in many settings (<https://www.bundesgesundheitsministerium.de/impfpflicht.html>). COVID-19 vaccine is required for HCW in France and Italy, for the elderly population (> 60 years) in Greece, and a new policy will take effect on 27 December 2021 in New York, stating that all workers including the private sector will need to be vaccinated (Hooker, 2021; Kissel, 2021).

Conflict of interest

None declared.

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