microbial biotechnology

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Special Issue Article

mRNA vaccines against COVID-19: a showcase for the importance of microbial biotechnology

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Summary

Pfizer-BioNTech and Moderna developed in record time mRNA vaccines against COVID-19 of high efficacy. The modest protection achieved with a similarly designed mRNA from CureVac underlines the importance of biotechnological details in formulation such as replacement of uridine by pseudouridine in the mRNA encoding the SARS-CoV-2 spike protein or the lipid composition of the nanoparticle coating the mRNA. Phase 3 vaccine trials and vaccine studies in special subject groups as well observational studies in whole populations confirmed the real-world vaccine efficacy against symptomatic disease, particularly against severe COVID-19 cases and to a lesser extent against mild SARS-CoV-2 infections. mRNA vaccine protection extended also to the alpha and beta variant viruses. The surge of delta variants led to an increase of infections and cases even in populations which achieved high vaccine coverage. This efficacy decline resulted to a lesser extent from a weaker neutralization of the delta variant but mostly from a waning vaccine protection over time. Data from Israel documented the efficacy of a third 'booster' injection 5 months after the second injection in older segments of the population. Adverse reactions consisted of transient injection site pain, headache, muscle pain, fatigue, fever and chills. Extensive surveillance studies documented a good safety profile revealing only a non-significant increase in transient facial nerve paralysis and a significant, but modest increase in myocarditis in vaccinated young males that was lower than the myocarditis risk induced by SARS-CoV-2 infection.

Received 1 November, 2021; accepted 3 November, 2021.
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Microbial Biotechnology (2022) **15**(1), 135–148
doi:10.1111/1751-7915.13974
Funding Information
No funding information provided.

Introduction

For the author of these lines, the most remarkable event of the last year with respect to microbial biotechnology was the rapid ('light speed' and 'warp speed') development of very efficient and safe mRNA vaccines against COVID-19. Mass vaccination campaigns started less than one year after the sequence of the viral pathogen became available. In the past, viral vaccines took 10 years or more of development – the shortest was mumps vaccine with a 4 year development time. In highlighting the importance of the mRNA vaccines for microbial biotechnology, the author is not alone. An editorial in *The New England Journal of Medicine* titled 'In Gratitude for mRNA Vaccines' ends with the sentence 'we owe them an unfathomable debt of gratitude' (Stuart, 2021). A news item in *Nature* wonders why mRNA vaccines did not won this year's Nobel Prize in chemistry or medicine (Callaway, 2021). Reasons quoted were time lags between discovery and awards of Nobel Prizes, and another argument was that many people contributed to the success of mRNA vaccines.

Basic aspects

The mRNA vaccine biotechnology

Short history. The idea with nucleic acid-based vaccines started with DNA which is more stable than RNA, but must be targeted to the nucleus of the cell for transcription to allow subsequent antigenic protein expression in the cytosol. In the past, DNA vaccines yielded only few veterinary vaccines (but they are back on the scene with an Indian DNA vaccine against COVID-19). In contrast, mRNA vaccines 'only' need targeting to the cytosol for protein expression. However, they face problems of chemical instability due to the omnipresent RNase activity and of toxicity due to the induction of immune reactions when detected as foreign RNA by the cell. In 1993, researchers from the French biotech company Transgène showed that mRNA in a liposome could elicit a specific antiviral immune

response in mice. Work of tumour biologists who introduced synthetic DNA into extracorporeal blood cells, which they then injected back into the body, inspired the founders of the German firms CureVac and BioNTech, two of the largest current mRNA companies, to take up this work. Direct injection of mRNA into mice causes however an unacceptable immune reaction (Dolgin, 2021b).

Key discoveries. Two key developments were needed to lead to the current mRNA vaccines. Foreign mRNA is recognized by the innate immune system (Toll-like receptors) and the RIG-I pathway, which induce an inflammatory response and cell death. Therefore, injection of mRNA in animals leads to shock. A key to avoid this problem was made at the University of Pennsylvania showing that modification of mRNA by replacing uridine with pseudouridine attenuated immune activation, but retained the ability to encode proteins. Another key discovery were lipid nanoparticles and the discovery of an ionizable lipid that becomes neutral under physiological conditions in the cell, thus limiting toxic effects of the lipid packaging. A special apparatus was then developed that mixed lipids dissolved in alcohol and RNA dissolved in acidic buffer. Another important contribution to the success was a modification of the spike protein configuration that made it more immunogenic (Chaudhary *et al*., 2021; Dolgin, 2021). All fundamental discoveries combined led to the expedient development of highly efficient and very safe mRNA vaccines by both Moderna and BioNTech.

mRNA synthesis. The procedure is also industrially scalable since one million doses of mRNA vaccine can be produced in a 5 liter bioreactor. The mRNA approach uses synthetic mRNA transcribed *in vitro* from a DNA plasmid by using the bacteriophage T7 RNA polymerase. The mRNA is co-transcriptionally capped with a 2′-O-methylated cap to prevent mRNA degradation by exonucleases, and the cap prevents the mRNA to be recognized by cytosolic sensors as viral RNA. A poly(A) tail of 100 nucleotides is encoded on the DNA plasmid for efficient translation. Since this length of the poly(A) tract destabilizes the DNA plasmid, BioNTech introduced a 10 bp UGC linker into the plasmid. With this procedure, mRNA is produced in a one-step process followed by purification from contaminating double-stranded RNA and aborted transcripts (Chaudhary *et al*., 2021).

Lipids. Moderna and BioNTech use a similar lipid composition in the lipid-based nanoparticles for delivery of the mRNA drug. A crucial element is the ionizable, cationic lipid since its positively charged amines facilitate the encapsulation of negatively charged RNA. Using combinatorial chemistry, numerous ionizable lipids were created that differed in physiological properties and could confer some specificity to the delivery system. Moderna and BioNTech use both a tertiary amine with two long and one short side-chain, differing in small chemical details (SM-102 vs. ALC-0315). Cholesterol, the second compound of the nanoparticles, fills the gaps between the lipids and aids in fusion with cell membranes. The third component is helper lipids that modulate the nanoparticle fluidity and confers target organ specificity. Moderna and BioNTech use the same helper lipid DSCP. The fourth component of the nanoparticles is PEGylated lipids, which regulate nanoparticle size and circulation time. Moderna and BioNTech use two different PEGylated lipids (Chaudhary *et al*., 2021).

Spike protein. Both Moderna and Pfizer-BioNTech (as well as CureVac) vaccines use mRNA for the nanoparticles encoding the full-length SARS-CoV-2 spike glycoprotein with two proline substitutions in the S2 subunit, which lock the protein in its prefusion conformation. In the mRNA from Moderna and BioNTech, all uridines were replaced by N1-methylpseudouridine to enhance mRNA translation. Pfizer-BioNTech had also developed a mRNA encoding a trimerized, secreted version of the spike protein's receptor-binding domain as alternative. Due to stronger adverse reactions in early tests, this mRNA vaccine did not enter phase 3 vaccine trials.

CureVac's failure. How important it was to follow the key discoveries is demonstrated by the failure of the mRNA vaccine encoding the same SARS-CoV-2 spike glycoprotein construct by CureVac. Instead of replacing uridine by pseudouridine, CureVac altered the genetic sequence of the mRNA to minimize the amount of uridine in its vaccines. CureVac patented an approach where A and U at the third codon position is replaced by G and C to mimic human mRNA codon use. 245 healthy adults received the CureVac mRNA vaccine with a dose escalation from 2 to 12 μg mRNA in lipid nanoparticles. Adverse events were dose dependent, but mild. The 12 μg mRNA dose elicited an antibody response against the spike protein that overlapped that observed in convalescent sera from SARS-CoV-2 infected subjects (Kremsner *et al*., 2021). In collaboration with Bayer, Curevac launched a phase 2b/3 clinical trial enrolling 40 000 participants from Latin America and Europe in a placebo-controlled vaccine trial. An interim analysis after observing 134 symptomatic COVID-19 cases revealed a vaccine efficacy (VE) of only 47%. In a press release, the company suspected that the high percentage of variant viruses of concern (57% of the sequenced viruses) and the relatively low antibody titre observed in phase 1 trials led to the low protection rate. A second generation of COVID-19 mRNA is under development in

a collaboration with the pharmaceutical company GSK (press release: CureVac Provides Update on Phase 2b/3 Trial of First-Generation COVID-19 Vaccine Candidate, CVnCoV – CureVac) and differs from the first generation by further changes in the 5' and 3'-untranslated regions of the mRNA conferring a twofold higher *in vitro* protein expression and by induction of a 10-fold higher antibody titre (Hoffmann *et al*., 2021). Some scientists suspect, however, that the lack of chemical modification of the uridine residues in the mRNA contributed to the modest outcome of the trial (Dolgin, 2021a).

In countries able to afford mRNA vaccines or alternative vaccines developed from different platforms, vaccination campaigns changed the trajectory of the pandemic. Paradoxically, the speed of the development of mRNA vaccines and its novelty are for some parts of the population a cause for vaccine hesitancy, which prevented the development of herd immunity even in countries that started early with mass vaccinations. Since vaccine hesitancy is now a major obstacle to stop the pandemic, I will summarize the available data about the immunogenicity, efficacy and safety of mRNA vaccines.

Immunity studies

Moderna. In an effort of dose sparing compared with the 100 μg dose given to more than 100 million US adults, Californian researchers studied the immune response to a 25 μg dose of Moderna vaccine in 35 adults. Neutralizing antibodies were detected in 29% and 100% of the vaccinees after one and two injections, respectively, and were detected for at least 7 months, albeit with a 10-fold lower titre than the peak titre reached two weeks after the second vaccine dose. The 7 month neutralizing antibody titres were comparable to those achieved after natural infection with SARS-CoV-2 and twofold lower than titres achieved with the 100 μg mRNA vaccine doses. Spike-specific CD4+ T cell responses were observed after the first vaccination in 97% of subjects and maintained for at least 6 months. T follicular helper (T_{FH}) a specialized subset of CD4+ T cells providing B cell help and critical for the generation of neutralizing antibodies were induced in 75% of the vaccinees. CD4+ responses were twofold lower than in subjects receiving the 100 μg dose. CD8+ T cells were seen in 34% and 53% of the subjects after the first and second dose, respectively, their number was comparable to those in COVID-19 cases and remained detectable for > 6 months. Half of the subjects showed preexisting cross-reactive memory T cells; in this subgroup, spike-specific memory CD4+ T cell frequencies were also higher after vaccination. Older vaccinees showed a comparable cellular immunity response (Mateus *et al*., 2021).

An important question is the development of cross-neutralizing antibodies against variant viruses by vaccination and their decay over time, which was addressed in a recent study (Pegu *et al*., 2021). 24 subjects immunized with the Moderna vaccine were followed over 7 months. Satisfying peak titres were observed 2 weeks after the second dose against a wide range of variant viruses, namely B.1.1.7 (alpha), P.1 (gamma), B.1.429 (epsilon), B.1.526 (iota) and B.1.617.2 (delta), while titres against B.1.351 (beta) were significantly lower. Titres declined against all viruses over time, but even after 7 months 58% of the sera from the vaccinees showed detectable neutralizing antibodies even against B.1.351 (beta). The researchers suspected that individuals who demonstrate waning immune responses over time are likely to have memory B cells capable of delivering an anamnestic response to those variants in the event of exposure to virus.

For vaccine developers, knowledge about immune correlates of protection is important to get surrogate endpoints for vaccine efficacy without repeating large clinical trials. Scientists explored the effect of immunizing primates with 0.3–100 μg Moderna vaccine, followed by a subsequent viral challenge. Vaccination induced circulating and mucosal antibody responses in a dose-dependent manner. Viral replication in the lung and the nose was inversely correlated with spike-specific and neutralizing antibody titre. Higher antibody titres were needed to suppress the nasal compared with the lung viral replication. Passive transfer of vaccination-induced immunoglobulin G from monkeys to naïve hamsters was sufficient to confer protection against virus challenge (Corbett *et al*., 2021).

Australian scientists analyzed data on neutralizing antibody titres and clinical protection rates achieved with seven different COVID-19 vaccines from published studies and compared them with neutralizing antibody titres in convalescent sera. The comparison of data across the studies is not easy since different neutralization tests, different case definition and different clinical trial protocols were used and a standardized convalescent serum sample is not yet available as international standard. With these caveats in mind, the researchers developed a graph plotting the observed vaccine efficacy (VE) / protection rate in per cent against the neutralizing activity of the sera of the vaccinees expressed as a fraction or multiple of that of convalescent sera. The resulting curve is linear for vaccines achieving neutralizing titre below that of convalescent sera (inactivated whole virus vaccines and adenovirus-vectored vaccines), but deviates from linearity and approaches a plateau of about 90% protection for vaccines that achieve neutralization titres twofold higher than convalescent sera (mRNA vaccines and protein nanoparticle vaccine). The researchers estimated that it needs a 20% convalescent antibody level to achieve a 50% protection against infection while only

a 3% convalescent antibody level is needed for a 50% protection level against severe disease. Modelling of the decay of the neutralization titre over the first 250 days after immunization predicted that a significant loss in protection from infection will occur, while protection from severe disease should be largely retained by mRNA vaccines (Khoury *et al*., 2021).

BioNTech (BNT). Another group of US immunologists studied the immune response to BNT vaccine in adults using blood samples and fine needle aspirates of the draining axillary lymph nodes. Serum neutralizing antibody titres increased from 58 after the first to 570 after the second injection of 30 μg BNT mRNA vaccine when tested against the earlier dominant D614G variant virus. These titres were 370 and 140 against the B.1.1.7 (alpha) and B.1.351 (beta) variants respectively. Subjects who had experienced a natural SARS-CoV-2 infection showed neutralizing antibody titres of 240, 200 and 140 against these viruses. Spike-specific IgG- and IgA-secreting plasmablasts peaked 5 weeks after the booster injection, followed by a decline over time. In the lymph nodes, germinal centre B cells reactive with the spike protein were detected in all subjects and remained at their peak frequency at least 15 weeks after immunization. Monoclonal antibodies generated from these germinal centre cells reacted mostly with the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, but some recognized the spike protein from seasonal beta-coronaviruses. The researchers detected robust plasmablast responses in the draining lymph nodes of all subjects which might be an indicator for induction of long-lived plasma cell responses by vaccination (Turner *et al*., 2021).

Cellular immune response to SARS-CoV-2 after BNT vaccination is the focus of a report from German researchers. They asked what immune reaction might underlie the partial early clinical protection against infection and disease already observed about 10 days after the first vaccine dose. At that time point, neutralizing antibodies induced by the vaccination are hardly detectable. They described a stable and fully functional CD8+ T cell response one week after prime vaccination with BNT. At that time point, circulating CD4+ T cells and antiviral antibodies are only weakly detectable. After the second vaccine dose, they observed a robust expansion of highly differentiated effector CD8+ T cells that are stably maintained over several months (Oberhardt *et al*., 2021). Antiviral immune response after mRNA vaccination might thus be mediated by both the humoral and cellular immune system. These fundamental observations are important for the discussion around waning immunity and the need for a third 'booster' vaccination in the clinical vaccination trials reported in the following section.

Clinical vaccination trial

Efficacy in phase 3 clinical trials

Moderna. Fifteen thousand two hundred subjects from across the United States received the Moderna mRNA vaccine mRNA-1273 (100 μg, threefold higher than the BNT dose, by two intramuscular injections, separated by 28 days), while 15 200 other subjects received a placebo in an observer-blinded manner. Observer-blinded means that the medical staff caring for patients and the researcher evaluating the test are blinded to treatment allocation of the patients. The cut-off date for the evaluation was end of March 2021 when the delta virus variant was not yet dominant in the United States. The median follow-up was 5.3 months after vaccination allowing a medium-term evaluation of VE. When assessed two weeks after the second injection, VE was 93.2% for COVID-19 cases (55 in vaccine and 744 in the placebo group). Efficacy in preventing severe COVID-19 was 98.2% (2 vs. 106 cases and 1 vs. 3 deaths respectively). The VE was similar across subgroups differing in race, sex and age (including participants older than 75 years) and occupations (with a trend for lower VE in health-care personnel) and comorbidities (with a trend for lower VE in people with liver disease). Adverse events related to the injections were reported by 8.5% of placebo and 13.9% of the vaccine recipients and consisted mainly of erythema at the injection site; serious injection-related adverse events occurred in four placebo and 12 vaccine recipients (< 0.1%) including anaphylaxis in two participants in each group. Thromboembolic events were seen in 43 and 47 individuals of each group, Bell's palsy in three and eight subjects but both conditions were not considered to be linked to the vaccine. The efficacy in preventing infection was 63% with 214 vs. 498 asymptomatic infections detected in the vaccine and the placebo group, respectively, over a 5 month observation period. (El Sahly *et al*., 2021).

BNT. Pfizer-BioNTech reported data from an ongoing, placebo-controlled, observer-blinded, multinational phase 3 trial conducted in the United States, Argentina, Brazil, South Africa, Germany and Turkey. Half of the 44 000 adult participants had more than 6 months of follow-up. Adverse events were reported in 30% of vaccine and 14% of placebo recipients; severe adverse events occurred in 1.2% vs. 0.7% respectively. No new safety signals were reported than those already reported after 2 months of follow-up (Polack *et al*., 2020), indicating that this mRNA vaccine continued to be safe. 77 of 22 000 vaccine compared with 850 of 22 000 placebo recipients experienced a symptomatic COVID-19 infection, corresponding to a VE of 91.3%. From its peak after the second dose, the observed VE declined from

96.2% (< 2 months), to 90.1% (2–4 months) and 83.7% (> 4 months). Severe COVID-19 after the first injection was seen in 31 subjects; 30 were placebo recipients indicating a VE of 96.7%. Subgroups defined by different age, sex, race, comorbidity and country showed comparable VE. This was also the case for South Africa where 9 COVID-19 cases with the prevalent B.1.351 (beta) variant virus were observed, which all occurred in placebo recipients (Thomas *et al*., 2021).

Vaccine efficiency in special groups

Adolescents. Severe infection can occur in adolescents, and vaccination would allow a higher in-presence school education. Without vaccinating adolescents and later school children, achieving herd immunity will remain an unrealistic goal. In the United States, 2260 adolescents 12–15 years of age received either the BNT vaccine or placebo. Vaccine safety was comparable to that observed in 1000 young adults (16–25 years), and complaints consisted of injection pain, fatigue, headache, chills, muscle pain and fever, mostly of mild degree and of short duration. One vaccinee developed 40.4°C fever for one day. No cases of thrombosis or anaphylaxis were observed. The BNT-vaccinated adolescents developed a better neutralizing antibody response than young adults, and VE was 100% (16 COVID-19 cases in placebo and none in the BNT vaccine group counted from 7 days after the second injection) (Frenck *et al*., 2021).

The Moderna vaccine was tested in 3700 12–17 years old adolescents in a randomized, placebo-controlled trial. Vaccinees showed more adverse events after the second than after the first vaccine dose. Adverse reactions consisted mainly of injection site pain, headache, fatigue and muscle pain. A serological response to the vaccine was seen in 99% of the adolescents, and neutralizing antibody titres were comparable to those of young adults. During a 3 month follow-up, four symptomatic COVID-19 cases were seen in the 1200 placebo recipients and none in the 2400 vaccinees. Vaccination prevented about half of the SARS-CoV-2 infections detected by PCR tests (Ali *et al*., 2021).

Pregnant women. During pregnancy, women undergo changes in the immune system and show decreased levels of lymphocytes and cytokines and thus were initially excluded from phase 3 trials for safety reasons. In an observational cohort study from Israel, 10 861 pregnant women vaccinated with BNT were compared with matched 10 861 unvaccinated women. Both groups were followed for a median of 77 days. In total, 131 and 235 documented infections occurred in the vaccinated and unvaccinated women respectively. The cumulative incidence curves started to differ at 14 days after the first injection. VE effectiveness for symptomatic infections was 66% in the third week and 76% in the fourth week after the first injection and increased to 97% one week after the second injection. VE against hospitalization was 89% (Dagan *et al*., 2021a).

Health-care workers (HCW). HCW are frequently exposed to COVID-19 patients and, therefore, at higher risk of infection. At hospitals across 25 sites in the United States, 110 000 HCW were tested for SARS-CoV-2 by PCR or antigen test. 8365 (7.6%) tested positive, and 1482 of them showed at least one COVID-19 symptom – the latter constituted cases. Cases were matched to 3450 control HCW who tested negative in PCR or antigen test. VE was calculated from this case-control study. VE differed for time after vaccination rising from 25% shortly after first dose to 90% for completely vaccinated subjects (BNT: 89%, Moderna: 96%). Peak protection was achieved 3–4 weeks after the second dose, and thereafter VE gradually decreased (but with large overlap of confidence intervals) to 80% at 3 months after vaccination (Pilishvili *et al*., 2021).

In a study from the Southern US, 3975 health-care and frontline workers were tested weekly for SARS-CoV-2 by RT-PCR assay; 80% of the participants were vaccinated once at least. Overall, 204 infections were detected (5%): five in twice vaccinated, 11 in once vaccinated and 156 infections in unvaccinated participants resulting in a VE against infection of 81% and 91% after one and two doses respectively. VE was similar for BNT and Moderna vaccines. Infected vaccinated participants showed fewer fever reactions (25% vs. 63%), less fever days and less days in bed (1.5 vs. 4 days) than infected unvaccinated participants. In addition, mean viral RNA load was significantly lower than in infected vaccinated participants (2.3 $\log_{10}$ vs. 3.8 $\log_{10}$ copies per millilitre) and the duration of RNA detection was significantly shorter (3 vs. 9 days) than in infected unvaccinated participants (Thompson *et al*., 2021a).

Hospitalized patients. US physicians investigated 41 000 hospitalizations and 21 000 emergency department visits (ED) in > 50 year old patients during the first half of 2021 and compared the odds of a positive test for SARS-CoV-2 infection among vaccinated patients with those among unvaccinated patients. VE counted from two weeks after the second dose was 89% against SARS-CoV-2 confirmed hospitalization; 90% against intensive care unit (ICU) admission and 91% against ED visit. VE was similar for BNT and Moderna vaccine (87% vs. 91% for hospitalization). VE was also high in patients older than 85 years (83%), Hispanics and subjects with chronic disease. VE higher than 86% was maintained for at least 4 months with no significant downtrend (Thompson *et al*., 2021b).

Nursing homes. Eighteen thousand residents of US nursing homes were regularly tested for infection. Breakthrough infections occurred in 1% and 0.3% of single-vaccinated residents before and after 2 weeks following the second dose of mRNA vaccine compared with 4.3% in unvaccinated residents. Most infections in the vaccinated residents were asymptomatic (White *et al*., 2021).

Population studies

Israel. Data were retrieved from Israel's largest health-care organization insuring 1.5 million persons; 600 000 persons vaccinated with BNT during January 2021 were matched to 600 000 unvaccinated controls. During the first month of follow-up, 10 000 infections were documented by PCR; 6000 of them were symptomatic COVID-19 disease leading to 369 hospitalizations. Among the hospitalized patients, 229 were severe cases resulting in 41 deaths. In the third week after the first vaccination, VE against infection was 46%, against symptomatic disease 57%, against hospitalization 74% and against severe disease 62%. One week after the second injection, the VE for the corresponding groups was with 92%, 94%, 87% and 92%, respectively, substantially increased and 72% of the deaths were prevented. Vaccine protection was similar across different age groups and slightly lower in persons with multiple comorbidities (Dagan *et al*., 2021b).

Another study from Israel used national surveillance data from the first 4 months of the nationwide vaccination campaign which took place from February to March 2021. At the beginning of April, 5.2 million citizens had been vaccinated with BNT. The vaccine coverage was high in old people (90% in those > 65 years) who were vaccinated with priority, 72% in the whole population older than 16 years, but lower in Arabs (55%) and ultraorthodox Jews (43%). During a 2 month follow-up, 155 000 SARS-CoV-2 infections were registered; 55 000 of them were symptomatic cases. 7700 citizens were hospitalized, 4480 showed severe disease and 1113 died from COVID-19. VE was 91% against asymptomatic infection and 97% against all forms of symptomatic disease including death in older people (> 75 years). As cumulative vaccination coverage increased, the 7 day moving average of SARS-CoV-2 infections decreased in Israel. Since this decrease occurred earlier in the older age groups which were also vaccinated earlier, the researchers attributed this decline to the vaccination campaign and not lockdowns imposed at end of December 2020 which were lifted early in February 2021 (Haas *et al*., 2021a).

With a somewhat greater data set, researchers from Israel conducted a retrospective study using the national surveillance data gathered during the first 4 months of the vaccination campaign with BNT. They estimated that the campaign averted 159 000 infections, 24 600 hospitalizations, 17 400 severe or critical diseases and 5500 deaths, mostly in citizens older than 65 years. Without the vaccination campaign, Israel would have experienced the triple of the actual hospitalizations which would have overwhelmed the health system (Haas *et al*., 2021b).

A nationwide retrospective cohort study from Israel showed in BNT-vaccinated subjects older than 16 years a VE of 54% against infection, but a VE of 98% against death and severe or critical disease. In breakthrough cases, vaccination reduced complications and death (Glatman-Freedman *et al*., 2021).

US. US physicians conducted a retrospective cohort study between December 2020 and August 2021 involving 3.4 million members of a Californian health-care organization. A third of them had received the BNT vaccine, a third the Moderna vaccine and a third remained unvaccinated. Outcomes were evaluated with positive SARS-CoV-2 PCR tests and COVID-19-related hospital admissions. The insurance provided access to cost-free testing. During the study period, 184 000 (5.4% of the participants) were infected with SARS-CoV-2, and for 9000 PCR samples virus genome sequencing was done. 12 000 participants (6.6% of the infected individuals) were admitted to hospital for COVID-19. For fully vaccinated individuals, VE against SARS-CoV-2 infections was 73%. Effectiveness against infections declined from 88% directly after full vaccination to 47% 5 months later. VE against infection with the delta variant whose prevalence increased from 0.6% in April to 87% in July was 93% directly after full vaccination (which speaks against immune escape of this variant) and decreased to 53% after 4 months when protection had decreased from 97% to 67% for non-delta variants (arguing for a waning immunity against infection independent of variant virus type). In contrast, VE against COVID-19-related hospital admissions was initially 90% and was maintained even against the surge of the delta variant with a VE of 93% 6 months after vaccination. Immune parameters were not measured or discussed in this report, but the data could be explained by waning local immunity in the nasopharynx leading to an increasing number of infections (but frequently with low viral load as indicated by failure of sequencing of PCR-positive samples). A maintained systemic immune response could explain the continued protection against hospitalization (Tartof *et al*., 2021).

England. British researchers conducted a prospective cohort study (SIREN) among 23 000 HCW working at 100 sites. Participants were on average 46 years old, predominantly (> 84%) female and White. At baseline,

35% had evidence for a prior SARS-CoV-2 infection. Vaccine coverage, mostly with BNT, was 89%. Every 2 weeks participants had a PCR test for detection of asymptomatic infections, they regularly answered a questionnaire for COVID-19 symptoms and had an antibody test every month. VE against infection 21 days after the first dose of BNT was 70% and increased to 85% one week after the second dose. Vaccinees had a reduced risk of infection within 3 days after their first vaccine dose; protection from infection increased with time and reached a plateau after 21 days (Hall *et al*., 2021).

Scotland. A prospective cohort study was done with the EAVE II database which links vaccination, primary care, PCR testing and hospital admission data for 5.4 million people in Scotland. The researchers investigated VE against COVID-19 hospital admission by BNT. Four weeks after first vaccination, VE against hospitalization was overall 91%, even 93% in the 65–79 year age group but dropped moderately to 83% in subjects older than 80 years (Vasileiou *et al*., 2021).

Between December 2020 and April 2021, 2.5 million people in Scotland received their first vaccine dose (33% the BNT vaccine and 67% the AstraZeneca recombinant adenovirus vaccine ChAdOx1). Less than 0.1% of the vaccinated people were hospitalized or died when counted 14 days after receiving the first vaccine dose. The rate of severe breakthrough disease was similar between the two vaccine groups, and only half of that for the substantially younger (and thus at much lower risk of severe outcome) unvaccinated population. The risk factors for severe breakthrough infection in vaccinated people were similar to those observed in the unvaccinated population and showed the following ranking: age > 80 years (relative risk RR = 4.7); multiple comorbidities (RR = 4.2), prior hospitalization (RR = 3.0) and care home residence (RR = 1.6) (Agrawal *et al*., 2021).

Vaccine efficacy against variant viruses

UK. Researchers from London sequenced 19 000 viral samples from COVID-19 cases in 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. Infection with the delta virus variant was associated with travel history and Indian or Pakistani background of cases. VE after the first shot was 49% against the alpha and 31% against the delta virus variant with no difference between BNT mRNA and AstraZeneca adenovirus vaccines. After the second injection, VE against the alpha and delta variants was 94% and 88%, respectively, for the BNT vaccine. After two vaccinations, the AstraZeneca vaccine was with 75% and 67% protection against alpha and delta virus variants, respectively, substantially lower. The researchers observed a trend for waning protection over time (Lopez Bernal *et al*., 2021).

The BNT vaccine was effective in reducing the risk of infection and COVID-19 hospitalization in people infected with the delta variant, but VE against infection with delta was lower than against the alpha variant (Sheikh *et al*., 2021).

Israel. In Israel, the lower age limit for mass vaccination with BTN was extended to adolescents at a time period when the delta variant became dominant (June to September 2021). VE against SARS-CoV-2 infection in 94 000 vaccinated adolescents compared with an identical number of unvaccinated adolescents was 93% after the second dose (based on 10 PCR tests per 100 persons per week and 900 observed infections). VE efficacy against symptomatic disease was 93% after the second dose based on 162 documented COVID-19 cases. This protection rate is thus similar to that against the alpha variant during preceding tests in the general population of Israel (Reis *et al*., 2021).

US. An outbreak with the delta variant was seen in a Californian prison where the virus infected 15% of the inmates. When 470 inmates vaccinated with the Moderna vaccine were compared with 360 unvaccinated inmate controls, a VE of 57% was seen against infections (n = 122) and a VE of 84% against disease (n = 28) in this congregate setting (Chin *et al*., 2021).

Qatar. Qatar launched a mass immunization campaign when the virus epidemiology changed from the dominance of B.1.7.7 (alpha) to the B.1.351 (beta) variant in spring 2021 which allowed VE estimates of the BNT vaccine against these two variant viruses. Two weeks after the second dose, VE against infection with variant B.1.7.7 was 90% but only 75% against B.1.351. VE against severe, critical or fatal disease with these variant viruses was 97%. However, among 385 000 vaccinated Qataris, 6600 (2%) breakthrough infections occurred in once vaccinated and 1600 (0.4%) in twice vaccinated persons, resulting in seven deaths (Abu-Raddad *et al*., 2021).

181 000 Qataris were vaccinated with the Moderna vaccine. One week after the second dose, VE against the alpha and beta variants was 99% and 96%, respectively, and protection against severe disease was 100%. A protection rate of 82% and 48% against infections with these two variant viruses was already observed in the third week after the first dose; protection from severe disease was 70%. Since the vaccination campaign with Moderna started later than that with BNT vaccine, the authors explain the better results seen with the Moderna

vaccine by the fact that older people at greater risk were in majority vaccinated with BNT (Chemaitelly *et al*., 2021a).

Waning immunity

Despite high vaccine coverage and effectiveness, the incidence of symptomatic infections with SARS-CoV-2 has been increasing in Israel. To test whether this increase of infection is associated with waning immunity from BNT vaccination, physicians tested 3800 HCW monthly for IgG antibodies to the viral spike protein and neutralizing antibodies in a 6 month longitudinal prospective study. They observed a constant decrease in antiviral IgG with time, resulting in a decrease by a factor of 18 after 6 months. They also observed a decrease in neutralizing antibodies over the first 3 months by a factor of 4, but between 3 to 6 months after vaccination the neutralizing antibody titre remained constant. When looking into subgroups, they noted a lower antibody titre in male, older and immunosuppressed HCW, while titres were higher in obese subjects (Levin *et al*., 2021). Waning anti-spike IgG antibody titres after vaccination with BNT were also observed in vaccinees from England, and remaining titres were lower in males and older subjects (Shrotri *et al*., 2021).

Follow-up data from US vaccinees who received mRNA vaccines also showed declines for virus-neutralizing antibodies from peak titres after the second dose. Eight months after vaccination, antibodies decreased by a factor of 34 for BNT and 44 for Moderna vaccine. In contrast, antiviral T cell responses were maintained (Collier *et al*., 2021).

Immunologists noted that the decline of neutralizing serum antibody over time does not necessarily mean that immune protection against SARS-CoV-2 is short-lived. The initial high antibody response is transient because plasma cells that secrete antibodies are short-lived. They are replaced by long-lived memory plasma cells that persist in the bone marrow and maintain an IgG antibody level of 10–20% of the acute phase and increase when re-encountering the virus or a vaccine. Whether immune protection against SARS-CoV-2 is long-lived without a need for booster vaccination (Radbruch and Chang, 2021) is currently under discussion.

Scientists from Israel addressed this caveat by analysing the waning efficacy of protection after time of second vaccination. The rate of confirmed SARS-CoV-2 infection showed a clear increase as a function of time from vaccination. For the > 60 year age group, it increased from 1.7 over 2.2 to 3.3 infections per 1000 persons with respect to one month steps of time interval from vaccination. A similar pattern was observed for severe COVID-19 in this age group which showed a monotonic increase from 0.12 to 0.34 cases per 1000 persons with increasing distance from vaccination. The same trend for an eroding protection rate was seen for the 40–59 years age group with time from vaccination (Goldberg *et al*., 2021).

Breakthrough infections

1500 vaccinated HCW from a hospital in Israel were surveyed by RT-PCR tests: 39 breakthrough infections were observed (5%). The source of infection was frequently unvaccinated fellow workers. A third of breakthrough infections were asymptomatic, and the remainder showed initially mild symptoms. However, a fifth of them developed long COVID (loss of smell and fatigue), none were hospitalized, but one did not return to work. 74% had a C_t value less than 30, indicating substantial virus excretion, but none transmitted an infection. In a case-control study with 104 matched vaccinated controls who did not experience an infection, subjects with breakthrough infections had lower neutralizing antibody titres than those without infection. Antibody titres were inversely related with viral load (Bergwerk *et al*., 2021).

In a study from the Southern US, 3975 HCW with exposure to COVID-19 patients were tested weekly for SARS-CoV-2 by RT-PCR assay. In parallel, a vaccination campaign was conducted such that in the same time period unvaccinated, simply and doubly vaccinated subjects were available for analysis. VE against infection was 81% after the first vaccination and 91% after the second vaccination. Only a marginal difference was observed between BNT and Moderna mRNA vaccines. Among the subjects with a positive PCR test, 63% of the unvaccinated and 25% of the vaccinated subjects showed fever (Thompson *et al*., 2021a).

A study from Qatar used the matched test-negative, case–control study design to calculate VE. In the test-negative design, the case patients were those who tested positive for SARS-CoV-2 (or according to the individual study design were represented by COVID-19 cases, hospitalization and deaths), and the control patients were those who tested negative for the chosen parameter. VE is estimated by comparing the odds of vaccination between cases and controls. These observational studies can assess VE for rare, but clinically relevant outcomes for which randomized controlled trials tend to be underpowered. This study design was initially developed for the evaluation of influenza vaccines but has now also become popular for the evaluation of COVID-19 vaccines (Dean *et al*., 2021). In Qatar, health authorities conducted a vaccination campaign mostly with the BNT vaccine. By September 2021, 80% of the population was fully vaccinated. During the vaccination campaign (summer 2021), an epidemiological change of

virus dominance from variants B.1.7.7 (alpha) and B.1.351 (beta) to variant B.1.617.2 (delta) was observed. While in February 2021 only 2% of the observed infections were breakthrough infections in vaccinated subjects, the percentage of breakthrough infections increased to 15% at the peak of the beta variant wave and to 30% when the delta variant became dominant. The researchers tested whether the increased breakthrough infections were due to immune escape by variant viruses or by waning vaccination immunity. They first plotted VE against any SARS-CoV-2 infection with respect to time from vaccination. Two weeks after the first dose, VE was 37%; VE increased to a peak of 78% one month after the second dose and declined then first modestly and then more rapidly such that VE was about 50% four months and 20% six months after vaccination. The decay of VE with time was observed in the different age groups and notably also with different virus variants, again suggesting waning immunity and not immune escape as reason for the observed declining VE. A decline was seen both for asymptomatic and for symptomatic infections, but VE against symptomatic infection was consistently higher. Reassuringly, VE against severe (hospitalization), critical (ICU) and fatal COVID-19 reached 96% one month after complete vaccination, and this level of protection was maintained over the 6 months observation period (Chemaitelly *et al*., 2021b).

Third Booster injection

The vaccination campaign in Israel was initially associated with a reduction of both viral transmission and disease burden: incidence of COVID-19 dropped from approximately 900 cases per million inhabitants per day in mid-January 2021 to fewer than two cases per million per day by June 2021. However, by end of August 2021 a resurge of infections was observed: 600 hospitalizations of severe cases per day were registered. It was unclear whether this resurge reflected the higher transmission potential of the delta variant, its immune evasion from the vaccine-induced immunity or a waning of vaccine-induced immunity in the population over time. To cope with the situation, Israeli authorities approved a third dose of the BNT vaccine ('booster') in 1.1 million persons older than 60 years who were fully vaccinated more than 5 months ago. Epidemiologists compared the rate of confirmed cases and severe illnesses which occurred in re-vaccinated citizens 12 days after receiving the booster vaccination with matched controls who did not receive this booster, but had two BNT injections from the initial vaccination campaign. In the boosted group, the infection rate was by a factor of 11 lower than in the matched controls, and severe illnesses were even lower by a factor of 20. As this difference was observed when the delta variant was dominant, BNT vaccination protects also against variant delta virus (Bar-On *et al*., 2021). This study from the Health Ministry was complemented by an analysis of the Clalit Health Services data, which provides health-care coverage for over half of the Israeli population. Here, the researchers matched 728 000 persons (mean age 52 years) who received the third dose of BNT vaccine 5 months after the second dose to 728 000 controls who did not receive a third dose but had received the two initial vaccine doses. VE was evaluated starting 7 days after the booster injection: for documented SARS-CoV-2 infection VE was 88%; against symptomatic infection 91%; against COVID-19 associated hospitalization 93%; against severe COVID-19 disease 92% and against COVID-19 associated death 81%. The third injection was sequentially offered to groups of decreasing age shifting successively from > 60 year to > 30 year old citizens. An analysis of the positive PCR tests per age group demonstrated that shortly after the introduction of the booster injection the SARS-CoV-2 infection numbers decreased in each age group (Barda *et al*., 2021b).

Booster injections in US adults who had already received two doses 8 months ago ($n = 11$) resulted in antiviral antibody titres that were five times higher than after the second dose and neutralized beta and delta variant viruses as efficiently as the wildtype virus (Falsey *et al*., 2021).

Safety aspects

The speed with which mRNA vaccines were approved for use by major health authorities such as FDA and EMA was cited by many people as a major argument for vaccine hesitancy. This leads to the public health dilemma that the most efficient vaccine is of limited use if it is not taken up by a sufficient large part of the population to achieve herd immunity and thereby cannot contribute as efficiently as theoretically possible to end the pandemic. To address this aspect of vaccine hesitancy, it is important to disseminate in an unbiased form the results of safety studies and provide general information about the vaccine safety assessment process in Western countries.

Risk assessments

Safety is a numerical figure, and understanding safety issues needs some numerical skills. Research has shown that even in industrialized countries numerical skills are less developed in the population than literary skills. The basic dilemma and a popular misunderstanding of part of the public is the fact that a no-risk situation does not exist in life and certainly not for medical interventions. Pharmacologists stated that a drug which has no side-effects is unlikely to have a primary therapeutical

effect either. This applies specifically to vaccines that have to arouse a strong immune response for future protection against an infection and which will also lead to side-effects. Biotechnologists and pharmacologists thus have to steer between the Scylla of inacceptable side-effects of the vaccine (too high reactogenicity) and the Charybdis of a too low immunogenicity and thereby low VE. The situation is complicated by the fact that this risk assessment is different for different groups in a population. Older people are at higher risk than younger people to develop severe disease after infection; consequently, the vaccination risk assessment is different for these two age groups. The situation is again different for children, who rarely develop severe COVID-19 after infection. However, the vaccination issue cannot only be addressed with a personal health risk assessment since vaccination could support children in attending kindergartens and schools without interruptions and restrictions. Infectious diseases make it necessary to factor aspects into the risk assessment that go beyond the individual because the disease is transmissible to others. Ending the pandemic might need to include children into vaccination programs even if their individual risk to suffer severe disease as a consequence of SARS-CoV-2 infection is low. Prolonging the pandemic by vaccine hesitancy could have economic and societal consequences that could become a burden for our societies.

Safety signals from phase 3 trials

The basic need for a rational risk assessment of vaccination is numbers. The initial phase 3 trial with the BNT mRNA vaccine compared adverse events in 21 000 vaccine and 21 000 placebo recipients. It revealed in addition to fatigue, headache, muscle and joint pain, fever and chills, which are commonly observed with many vaccines, one safety signal: it described 64 cases of lymphadenopathy in the vaccine but only six cases in the placebo recipients (Polack *et al*., 2020). The initial phase 3 trial with the Moderna mRNA vaccine revealed in addition to the same common side reactions as for the BNT vaccine two safety signals: hypersensitivity reactions in 1.5% of vaccine and 1.1% of placebo recipients and three and one cases of facial nerve (Bell's) palsy in the vaccine and placebo group respectively (Baden *et al*., 2021). The hypersensitivity reaction risk was confirmed during the initial roll-out of the mRNA vaccine campaigns with 17 million doses in the United States when 66 persons developed an anaphylactic shock within less than an hour after vaccine injection amounting to 2.5 cases/million doses administered, the rate was twofold higher with BNT. This potentially lethal condition can, however, be treated: 92% of the shock patients received epinephrine, seven patients required endotracheal intubation, and none died (Shimabukuro *et al*., 2021a). This risk led to recommendation that persons with previous anaphylactic shock conditions should use non-mRNA vaccines and that vaccinees should after injection remain in vaccination centres under surveillance for prompt intervention.

However, phase 3 trials have inherent limitations in evaluating vaccine safety since they enrol a relatively small number of participants (several ten thousands) who are, in addition, generally healthier than the average population. Hence, they are often underpowered to identify less common adverse events. Surveillance is, therefore, also required during the roll-out of national vaccination campaigns. A seminal study from Israel provides here a set of important data for the safety issue.

Safety signals from population surveys

Scientists used the data from the largest health-care organization in Israel to evaluate the safety of the BNT vaccine. They collected health data from 885 000 vaccinees covering a period of 42 days after the injection (a time frame considered by FDA and CDC for the assessment of acute adverse vaccine effects) and compared it with data from 885 000 non-vaccinated matched controls. This analysis revealed an association of vaccination with an elevated risk of myocarditis (risk ratio (RR) 3.2), lymphadenopathy (RR 2.4), appendicitis (RR 1.4) and herpes zoster infection (RR 1.4). The myocarditis risk translates into three additional events among 100 000 vaccinees. The authors provided another comparator for putting this risk in perspective. A person avoiding an immunization for fear of the risk of vaccination is exposed to a greater risk of infection. 233 000 SARS-CoV-2 infections analysed by the researchers in Israel were associated with an 18-fold increased risk of myocarditis – translating into 11 additional events per 100 000 infected persons. Additional serious adverse events associated with SARS-CoV-2 infection included pericarditis, arrhythmia, deep vein thrombosis, pulmonary embolism, myocardial infarction and thrombocytopenia. Due to its large sample size, this study also noted beneficial effects of the vaccine beyond protection from COVID-19; the researchers identified protective effects against anaemia and intracranial haemorrhage (Barda *et al*., 2021a,b).

Myocarditis

The surveillance procedure in Israel was as follows. At the beginning of the vaccination campaign, a program of passive surveillance was initiated. Health-care providers reported the data about events directly (< 1 month) following the vaccination to the Ministry of Health, as required by Israeli law. After receipt of reports about

myocarditis, the Ministry of Health subsequently initiated active surveillance beginning in February 2021 by requesting that all hospitals report cases of myocarditis since December 2020. Among 304 persons with symptoms of myocarditis, 142 occurred after receipt of the BNT vaccine. The clinical presentation was judged to be mild in 95% of the cases, but one fatal case was noted. Most vaccine-associated cases of myocarditis occurred during days 2–4 after the second dose, and mostly young males were affected (Mevorach *et al*., 2021).

These observations were confirmed by another research group which based their analysis on the health reports collected by the largest Israeli health system (Clalit). Among the 2.5 million vaccinated members, 54 cases of possible vaccine-associated myocarditis were identified, amounting to two cases per 100 000 vaccinees. The highest incidence of myocarditis (10 cases per 100 000) was reported in male patients between the ages of 16 and 29 years; 76% of cases of myocarditis were described as mild and 22% as intermediate; 1 case had a cardiogenic shock. After a median follow-up of 3 months, one patient had been readmitted to the hospital, and one had died of an unknown cause (Witberg *et al*., 2021). One fatal case of myocarditis was also reported in the United States in a 45 year old man who presented fever and chills 2 weeks after the second injection with the Moderna vaccine. A cardiogenic shock led to death, and the autopsy showed an endomyocardial inflammatory cell infiltrate (Verma *et al*., 2021).

Bell's palsy

Bell's palsy (BP) describes a sudden onset of unilateral facial paralysis. It is usually transient, with 70% of patients recovering within 6 months without treatment. Corticosteroid treatment is associated with a 90% recovery. Physicians from Hong Kong studied the occurrence of BP in 0.5 million of BNT vaccine recipients within a window of 42 days after vaccination. They noted 16 BP cases after BNT vaccination. Compared with the background population incidence of BP for Hong Kong, this number corresponds to two additional cases per 100 000 in BNT vaccinees. In a nested case-control analysis, they compared 300 BP patients that were hospitalized during the vaccination campaign in Hong Kong with 1100 matched controls; the odd ratio for BP after BNT vaccination was with 1.7 not significantly increased (Wan *et al*., 2021). During the vaccination campaign in Israel, 37 cases of BP were observed and no excess of vaccinated subjects was observed. The number of admissions for BP during the same period in preceding years (2015–2020) revealed a stable number, and the authors concluded that there was no association between BP and BNT vaccination (Shemer *et al*., 2021).

Abortion

As the vaccination is being extended to further population segments that were previously excluded for safety considerations, researchers looked for safety signals in these groups. The extension of vaccination trials to pregnant women raised the question whether vaccination increases the risk of spontaneous abortion. Analysis of the US CDC v-safe COVID-19 vaccine pregnancy registry revealed 165 spontaneous abortion among 2450 pregnant women vaccinated with BNT. This rate is within the range reported before the pandemic in pregnant US women (Zauche *et al*., 2021). A larger US study investigating 36 000 vaccinated pregnant women and identified no safety concern with respect to spontaneous abortion or other health risks. Overall reactogenicity profile was similar among pregnant and non-pregnant women. While injection site pain was reported more frequently in the pregnant group, systemic reactions were reported more frequent in the non-pregnant women (Shimabukuro *et al*., 2021b). No increased pregnancy loss or other increased health risks were also reported from Norway (Magnus *et al*., 2021).

Outlook

The available data indicate that the mRNA vaccines developed by Pfizer-BioNTech and Moderna against COVID-19 are both highly efficient and safe. These vaccines (together with those developed by other organizations and companies based on other vaccine platforms) have the potential to influence the trajectory of the pandemic provided that they get into the arms of the populations. One problem for achieving this goal is vaccine hesitancy – unbiased and understandable information about data documenting the efficacy and safety of mRNA vaccines should help to alleviate the concerns of a substantial part of the not-yet vaccinated population. Scientists have here a role to play, but it needs also trust of the public in authorities, namely scientific, medical and political authorities which are currently eroded by populist movements and unchecked (mis)information circulating on the Internet. To find the right arguments, it needs sociologists to understand the current sources of distrust in authorities. The problem gets even more complex when it comes to anti-vaxxer who oppose vaccination for fundamental emotional reasons and fight actively against vaccination campaigns with the aim to discourage the vaccine hesitant from immunization. The phenomenon is old and goes back to the early days of vaccination introduced by Jenner in the late 18th century. Why one of the medical inventions that has saved perhaps the largest numbers of human lives is the target of such an aggressive and fundamental opposition needs to be studied by psychologists supported by a

multi-disciplinary team of scientists. Since the enemies of vaccination are more vocal than its supporters and are predicted to soon outnumber vaccine supporters, this research has a great medical and political impact.

Apart from these psychological problems, there are also a number of practical problems that limit the impact of mRNA vaccines. There are economic issues: mRNA vaccines are too expensive for purchase by low-income countries. As long as the world population is not sufficiently vaccinated, the transmission of SARS-CoV-2 will continue, and new variants with still higher transmission potential or the ability to evade the vaccine-induced immunity might emerge and thus even jeopardize the protection by current vaccines in industrialized countries. How to settle this economic problem is a political question, and microbial biotechnology cannot contribute much to its resolution. Finally, vaccines particularly two-shot vaccines need a substantial infrastructure to get to the recipients, an infrastructure that does not exist in countries with a fragile infrastructure, especially when it needs to vaccinate billions of people. Even international organizations only have experience with mass vaccination of children under these conditions. Thermostability is here an important requirement, and it is a sad story that the mRNA vaccine from CureVac which has greater thermostability than the mRNA vaccines from Moderna and Pfizer-BioNTech failed in an efficacy trial to achieve a protection rate defined by WHO as a lower level for a useful vaccine. Here microbial biotechnologists might again come into play, perhaps more with COVID-19 vaccines produced from other platforms. For developing countries, less efficient vaccines that are easier to distribute in low- and middle-income countries might have a greater overall impact. Some experts expect an end of the pandemic for the spring/ summer 2022, which would solve these problems. However, this expectation is more based on the two-year spontaneous duration of the Spanish flu pandemic than on data-based predictions for the COVID-19 pandemic. Data from the Russian flu pandemic from 1889 seem to indicate that a pandemic could also take up to nine years to disappear (Brüssow, 2021) and even if we can get rid of the COVID-19 pandemic in the next year, the next zoonotic spillover infections are already lurking somewhere and microbial biotechnology might again be a crucial tool to limit its destructive impact.

Acknowledgements

I thank Sophie Zuber and Kenneth Timmis for critical reading of the manuscript.

Conflict of interest

None declared.

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