



9th ad hoc statement – 10 November 2021

Antivirals against SARS-CoV-2: current situation and approaches to improved preparation for future pandemics

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Preliminary remarks by the President

Since the novel coronavirus first emerged around two years ago, our knowledge about this pathogen as well as the medical, economic and social consequences of the pandemic has grown fundamentally. Currently available infection prevention measures and the swiftly developed vaccines are effective tools targeting the further spread of the coronavirus when applied extensively and consistently.

The successful containment of the pandemic essentially hinges on three pillars:

1. Hygiene measures such as social distancing, wearing a face mask in certain situations and sufficient ventilation in indoor environments;
2. Vaccines and antiviral agents (antivirals);
3. Provision of care to infected patients.

It is also essential to ensure that persons suffering from other acute or chronic diseases receive the medical treatment they need.

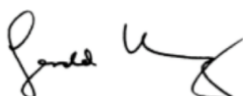
The publication of this ad hoc statement on antivirals coincides with the fourth wave of the COVID-19 pandemic, which has gained considerable momentum again, including in Germany. Unlike a year ago, we are now in a situation in which many anti-infection measures have been scaled back despite increasing case numbers. While vaccines authorised and available in Germany are resulting in lower rates of infection and high protection against severe disease and thus a fatal outcome in vaccinated individuals, the vaccines do not offer one hundred percent protection against an infection. In addition, the protection provided by vaccines starts to decline in all vaccinated individuals after around six months, with older individuals starting out with a lower level of protection than younger individuals. Furthermore, the emergence of more transmissible variants of the virus means that community protection is harder to achieve through vaccination. The insufficient vaccination uptake rate – approx. 16 million adults in Germany are currently not vaccinated – is a major challenge given the increasing rates of severe courses of illness, some of which involving long hospital stays. This poses considerable challenges for the healthcare system and, if the situation does not change, will overwhelm it. We are already seeing a high burden on nursing staff and doctors as well as a decline in the intensive care capacities of hospitals.

In view of this, the following measures in particular are now essential:

- a) Wearing a face mask in indoor environments, especially when the immune status (“2G rule” in Germany: completely vaccinated (geimpft) or recovered (genesen)) is uncertain and it is not possible to ensure social distancing or ventilation;
- b) Significantly increasing vaccination uptake rates and offering booster vaccinations to all persons who are already fully vaccinated;
- c) Consistently testing persons who are not immune if they wish to participate in indoor community activities;
- d) Adapting intensive medical care by providing appropriate capacities, but generally keeping the need for intensive care low through infection control.

Longer-term measures also include promoting research on antivirals, as described in this ad hoc statement.

For Germany, this winter will pose a societal and medical challenge owing to a lack of prevention, clear rules and stringency. However, there are still opportunities to improve our tools for curbing the pandemic: a more appropriate regulation on disclosing vaccine status in the Occupational Health and Safety Regulation, broader application of the “2G rule” and compulsory vaccination for multiplier groups. Viral and other pandemics should also be expected in the future. To ensure a timely and effective response, it is therefore vital to now draw conclusions from experience gained over the past two years and – as part of internationally concerted efforts – improve existing structures as well as create new ones to address the significant shortcomings brought to light by the pandemic.



Gerald Haug

1. Summary and recommendations

Current data suggests that the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) will become endemic in the long term; as such, it will continue to circulate among parts of the population, meaning that even after the pandemic has subsided, infections will continue to occur which may result in severe cases of COVID-19 and fatal outcomes. As a result, in addition to available vaccines, comprehensive diagnostics enabling the early detection of infected persons and available symptomatic therapies, there is a need for antiviral agents (antivirals) which are suitable for use in the treatment of specific groups of persons. This applies, for example, to those who have not been vaccinated at all or only partially, and to those who have not built up sufficient immunity even after multiple vaccine doses. In addition, new variants of the virus could develop, against which the vaccines might provide reduced protection. At global level in particular, antivirals could – provided they can be administered orally or by inhalation and are available in sufficient quantities – make a significant contribution, as large parts of the global population do not have sufficient access to vaccines or medical infrastructure. Antivirals to treat SARS-CoV-2 available to date have either had limited effectiveness or significant adverse side effects or have been too time-consuming and costly to manufacture and administer. These factors have considerably limited their widespread application.

However, the current pandemic has also highlighted an insufficient level of preparedness for newly emerging pathogens. In this connection, fundamental research, clinical development and stockpiling of broad-spectrum antivirals will play a major role in enhancing our ability to better respond to emerging pandemics in the future.

Against this background, the German National Academy of Sciences Leopoldina recommends the following:

1.1 Development of therapies against SARS-CoV-2

The further development of antivirals specifically targeting SARS-CoV-2 is urgently needed as a complementary measure to vaccination. The desired outcome are highly effective antiviral agents which block those viral or cellular factors required by the virus to replicate. Furthermore, drugs need to be developed which put the immune system on high alert, enabling the body to detect invading viruses at an early stage and fend them off more effectively.

Such antivirals should have few side effects, be widely available and easy to administer, ideally in oral form or by inhalation. They should also counteract the emergence of resistant variants of the virus. The agents should be used as soon as possible after the infection or the onset of symptoms – and also as a preventative measure under certain circumstances – to stop viral replication within the first few days and thus prevent both transmission of the virus to others and severe, sometimes life-threatening, disease. In the late stages of COVID-19, current data indicates that in most cases only symptomatic therapy makes sense, since viral replication has ceased in the majority of patients by this time, rendering direct-acting antivirals largely ineffective.

1.2 Development of broad-spectrum antivirals

There is an urgent need to develop broad-spectrum antivirals which are effective against as many different variants of a virus family as possible in preparation for pandemics expected in the future. A corresponding list of possible pandemic pathogens has been made available and is maintained by the World Health Organization. The development of such agents is still largely in its infancy, however, and will require significant efforts. The intended broad-spectrum effect might reduce antiviral activity

against individual variants of a given virus group, though this is likely to be overcome by the combination of several antiviral agents.

Market-based incentive structures for pharmaceutical and biotechnology companies are hard to reconcile with the development of such active substances for preventative purposes. Consequently, relevant financial incentives should be created so that the development of antivirals against a certain group of pathogens is worthwhile even if this group of pathogens does not lead to a pandemic in the following years or decades. In the academic sector, structures should be created which enable the development of active substances up to the completion of a detailed clinical phase I characterisation so that, should a new pathogen emerge, these substances can be developed further together with partners from industry and approved swiftly. Alternatively, government funding could be granted to companies in order to finance such developments up to the completion of a detailed clinical phase I characterisation and production of a supply of the new substances by such companies as well.

1.3 Strengthening infrastructures for fundamental and translational research

Extensive fundamental research will continue to be crucial in identifying new cellular and viral targets for antivirals and developing new therapeutic approaches. Since work with highly contagious pathogens is associated with particular challenges in terms of infrastructure and expertise, support provided in this regard should also ensure access to high-security laboratories, the necessary cell systems or animal models and funding for appropriately trained staff. In order to successfully translate fundamental scientific research into medical practice, researchers also require access to infrastructures which actively and continuously support processes leading to clinical application – such as medical and pharmaceutical chemistry facilities but also associated structures facilitating clinical research such as biobanks, patient registries and medical information infrastructures. Researchers also require information and support with regard to the conditions laid down in guidelines for the manufacture and testing of substances in the context of clinical studies, as well as with regard to statistics, business development, patent applications, regulatory issues and contract management. Funding instruments must allow for appropriate further training measures and enable individual tasks and development steps to be outsourced to suitable service providers, including provision of the required budgets.

In this connection, it is also important to have an organisational structure in place which connects the infrastructures and expertise needed for research into the most important pathogen groups. An association of or cooperation between academic institutions (at both the national and international level) and biotechnology and pharmaceutical companies should be established for this purpose. This network should also include representatives from regulatory bodies – as well as the policy makers responsible in an emergency situation – with the objective of advancing necessary research and development of therapies up to the first clinical studies in order to make effective therapies available much more rapidly.

1.4 Particular requirements for clinical studies dealing with highly contagious respiratory viruses

Owing to the course of infection with highly contagious respiratory viruses such as SARS-CoV-2 and influenza viruses, designing appropriate clinical studies is subject to special requirements. With regard to the clinical development of antivirals in the academic context, however, there are virtually no structures in Germany for implementing, in a swift and coordinated manner, early-stage pilot and feasibility studies or phase III studies on an outpatient and pre-admission basis. To enable qualified study staff to identify patients with newly diagnosed viral infections on site and, provided they meet

the relevant criteria, include them in clinical studies at university hospitals, networks should be formed by test centres, outpatient care, public healthcare services, care facilities and university outpatient departments as part of a coordinated study infrastructure.

Studies should be designed such that infected individuals are identified at an early stage, enabling them to be included in studies in compliance with infection control measures. This means that hospitals and central study sites carrying out such studies must be specialised in patients with highly contagious infections and have available the necessary infrastructure. It should also be kept in mind that, for patients with severe courses of illness, swift measures may need to be taken to treat their symptoms, including transfer to an intensive care unit by the study centre.

1.5 Improved monitoring of circulating virus strains

To obtain a comprehensive overview of circulating viruses and their pandemic potential, as well as the effectiveness of available vaccines and antivirals against these pathogens, it is important to promote continuous epidemiological monitoring, including genomic sequencing and propagation of viral pathogens in patient and animal samples. To this end, public healthcare services need to have access to sequencing capacity and sequence databases in order to be able to detect emerging virus variants quickly and monitor their spread. Special attention must be paid to the selection of samples to ensure a representative and comprehensive analysis. This requires employees of public healthcare services (health authorities) to undergo further epidemiological training and cooperate with experienced epidemiologists, as well as a structured international network.

2. Background information: SARS-CoV-2 and the COVID-19 disease

2.1 Current situation

Following its detection at the end of 2019, SARS-CoV-2 caused a pandemic within just a few months. Building on more than ten years of preparatory work with a wide range of vaccine technologies and experience with the first SARS coronavirus, which was responsible for the SARS epidemic of 2002/2003, several effective vaccines were developed in less than a year, including novel mRNA vaccines. This outstanding achievement was the result of years of scientific groundwork. Vaccinating large parts of the global population as quickly as possible will now be a deciding factor in how quickly and successfully the pandemic can be combated. Immunity requires both B cells, which produce neutralising antibodies, and a robust cellular basis, such as T cells. B cells and T cells also remain in the body in the long term in the form of memory cells.¹ Current data shows that the majority of those who have been vaccinated are protected from severe courses of illness (*Coronavirus Disease 2019*; COVID-19).² The same applies to persons who have recovered from an infection.³

The genetic variability of SARS-CoV-2 poses a challenge. Since the beginning of the pandemic, variants of the virus have emerged which differ in some of the biological properties found in the original virus (see table 1). Some of these variants replicate more effectively in the upper respiratory

¹ Radbruch, A., & Chang, H. D. (2021). A long-term perspective on immunity to COVID. *Nature* 595, 359-360.

² Regev-Yochay, G., Amit, S., Bergwerk, M., Lipsitch, M., Leshem, E., Kahn, R., ... & Kreiss, Y. (2021). Decreased infectivity following BNT162b2 vaccination: A prospective cohort study in Israel. *The Lancet Regional Health-Europe*, 7, 100150. Elliott, P., Haw, D., Wang, H., Eales, O., Walters, C., Ainslie, K., ... & Riley, S. REACT-1 round 13 final report: exponential growth, high prevalence of SARS-CoV-2 and vaccine effectiveness associated with Delta variant in England during May to July 2021.

³ Wheatley, A. K., Juno, J. A., Wang, J. J., Selva, K. J., Reynaldi, A., Tan, H. X., ... & Kent, S. J. (2021). Evolution of immune responses to SARS-CoV-2 in mild-moderate COVID-19. *Nature communications*, 12(1), 1-11. Updated statement by the German Society of Virology on the immunity of persons who have recovered from an infection, available at: <https://g-f-v.org/2021/09/30/4411/> (last accessed on: 9 November 2021).

tract and are shed by infected individuals for longer, rendering the pathogen more transmissible and therefore accelerating the spread of the virus. Immune-evasive variants have also emerged in which the genetic code for the spike protein of the virus has altered, making it more difficult for neutralising antibodies to bind to the virus and thus facilitating its spread among immunologically protected populations (persons who have been vaccinated and persons who have recovered). Some of these Variants of Concern (VoC) thus entail reduced protection against infection, whereas findings to date show that protection from severe courses of illness is largely maintained.⁴ The Delta variant in particular has spread rapidly around the globe and has become the dominant form. Even in countries with high vaccination rates, such as Israel and the United Kingdom, it has led to increasing case numbers, hospitalisations and death numbers. However, the various vaccines available have largely proven effective in terms of preventing severe illness,⁵ though levels of neutralising antibodies in the body decline significantly over time.⁶ Infections with the Delta variant in particular occur even in fully vaccinated individuals, with the viral loads in some of these persons found to correspond to those observed in infected unvaccinated persons in the first days of the infection.⁷

⁴ Jalkanen, P., Kolehmainen, P., Häkkinen, H. K., Huttunen, M., Tähtinen, P. A., Lundberg, R., ... & Julkunen, I. (2021). COVID-19 mRNA vaccine induced antibody responses against three SARS-CoV-2 variants. *Nature communications*, 12(1), 1-11. Liu, C., Ginn, H. M., Dejnirattisai, W., Supasa, P., Wang, B., Tuekprakhon, A., ... & Screaton, G. R. (2021). Reduced neutralization of SARS-CoV-2 B. 1.617 by vaccine and convalescent serum. *Cell*, 184(16), 4220-4236. Planas, D., Veyer, D., Baidaliuk, A., Staropoli, I., Guivel-Benhassine, F., Rajah, M. M., ... & Schwartz, O. (2021). Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature* 596, 276–280. Updated statement by the German Society of Virology on the immunity of persons who have recovered from an infection, available at: <https://g-f-v.org/2021/09/30/4411/> (last accessed: 9 November 2021).

⁵ Dagan, N., Barda, N., Kepten, E., Miron, O., Perchik, S., Katz, M. A., ... & Balicer, R. D. (2021). BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *New England Journal of Medicine*, 384(15), 1412-1423. Haas, E. J., Angulo, F. J., McLaughlin, J. M., Anis, E., Singer, S. R., Khan, F., ... & Alroy-Preis, S. (2021). Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *The Lancet*, 397(10287), 1819-1829. Amit, S., Regev-Yochay, G., Afek, A., Kreiss, Y., & Leshem, E. (2021). Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *The Lancet*, 397(10277), 875-877. Lopez Bernal, J., Andrews, N., Gower, C., Gallagher, E., Simmons, R., Thelwall, S., ... & Ramsay, M. (2021). Effectiveness of Covid-19 vaccines against the B.1.617.2 (delta) variant. *New England Journal of Medicine*.

⁶ Levin, E. G., Lustig, Y., Cohen, C., Fluss, R., Indenbaum, V., Amit, S., ... & Regev-Yochay, G. (2021). Waning immune humoral response to BNT162b2 covid-19 vaccine over 6 months. *New England Journal of Medicine*. Chemaitelly, H., Tang, P., Hasan, M. R., AlMukdad, S., Yassine, H. M., Benslimane, F. M., ... & Abu-Raddad, L. J. (2021). Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *New England Journal of Medicine*.

⁷ Brown, C. M. (2021). Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings—Barnstable County, Massachusetts, July 2021. *MMWR. Morbidity and Mortality Weekly Report*, 70. Twohig, K. A., Nyberg, T., Zaidi, A., Thelwall, S., Sinnathamby, M. A., Aliabadi, S., ... & Bashton, M. (2021). Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B. 1.617. 2) compared with alpha (B. 1.1. 7) variants of concern: a cohort study. *The Lancet Infectious Diseases*, DOI: 10.1016/S1473-3099(21)00475-8.

⁸ Barda, N., Dagan, N., Cohen, C., Hernán, M. A., Lipsitch, M., Kohane, I. S., ... & Balicer, R. D. (2021). Effectiveness of a third dose of the 0-6736(21)02249-2. Kamar, N., Abravanel, F., Marion, O., Couat, C., Izopet, J., & Del Bello, A. (2021). Three doses of an mRNA COVID-19 vaccine in solid-organ transplant recipients. *New England Journal of Medicine*. Benotmane, I., Gautier, G., Perrin BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *The Lancet*. DOI: 10.1016/S014, P., Olagne, J., Cognard, N., Fafi-Kremer, S., & Caillaud, S. (2021). Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients With Minimal Serologic Response to 2 Doses. *JAMA*, 326(11), 1063-1065.

In response to these developments, Israel, for example, began offering double vaccinated individuals a third vaccine some time ago; current studies underline the effectiveness of this measure in preventing severe courses of illness.⁸ In Germany, booster vaccines are now also being administered, currently primarily to fully vaccinated individuals with risk factors and medical staff coming into contact with patients.⁹

Table 1. Properties of SARS-CoV-2 Variants of Concern¹⁰

WHO classification	Classification by lineage (Pango lineage)	Earliest documented sample	Altered properties
Alpha	B.1.1.7 All Q lineages	United Kingdom, September 2020	Increased transmissibility
Beta	B.1.351 B.1.351.2 B.1.351.3	South Africa, May 2020	Reduced susceptibility to adaptive immune response
Gamma	P.1 P.1.1 P.1.2	Brazil, November 2020	Slightly increased transmissibility, reduced susceptibility to adaptive immune response
Delta	B.1.617.2 All AY lineages	India, October 2020	Increased transmissibility and virulence, reduced susceptibility to adaptive immune response; likelihood of increased hospitalisation rate ¹¹

As outlined, vaccinations primarily prevent severe courses of illness, but only partially protect individuals from infection and infectivity. Furthermore, the emergence of new virus variants, including those against which available vaccines do not offer sufficient protection, poses a potential threat. Owing to this, and to the declining level of protection offered by vaccination over time, the development of antivirals as a complementary measure to vaccination is extremely urgent. This also serves to protect persons with weakened immune systems and those who have not (yet) been vaccinated or have only been partially vaccinated. These antivirals must be able to be used early in the course of infection and should prevent the virus from spreading in the body – thus preventing severe courses of illness – as well as reduce further transmission of the virus and therefore slow the spread of infection in the population.

⁸ Barda, N., Dagan, N., Cohen, C., Hernán, M. A., Lipsitch, M., Kohane, I. S., ... & Balicer, R. D. (2021). Effectiveness of a third dose of the 0-6736(21)02249-2. Kamar, N., Abravanel, F., Marion, O., Couat, C., Izopet, J., & Del Bello, A. (2021). Three doses of an mRNA COVID-19 vaccine in solid-organ transplant recipients. *New England Journal of Medicine*. Benotmane, I., Gautier, G., Perrin BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. *The Lancet*. DOI: 10.1016/S014, P., Olagne, J., Cognard, N., Fafi-Kremer, S., & Caillard, S. (2021). Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients With Minimal Serologic Response to 2 Doses. *JAMA*, 326(11), 1063-1065.

⁹ For information on recommendations concerning booster vaccinations in Germany, see, for example, www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/Ausgaben/43_21.pdf?__blob=publicationFile and www.rki.de/SharedDocs/FAQ/COVID-Impfen/FAQ_Genesene_Impfdosis.html (last accessed: 9 November 2021).

¹⁰ As at 14 October 2021; for the current overview see www.who.int/en/activities/tracking-SARS-CoV-2-variants (last accessed: 9 November 2021).

¹¹ Twohig, K. A., Nyberg, T., Zaidi, A., Thelwall, S., Sinnathamby, M. A., Aliabadi, S., ... & Bashton, M. (2021). Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B. 1.617. 2) compared with alpha (B. 1.1. 7) variants of concern: a cohort study. *The Lancet Infectious Diseases*, DOI: 10.1016/S1473-3099(21)00475-8.

Like many other epidemic and pandemic viruses (e.g. other coronaviruses, influenza viruses, Ebola viruses and Zika viruses), SARS-CoV-2 can cause severe disease in two ways.¹² Firstly, these viruses are cytotoxic and lead to the rapid death of infected cells. This process occurs primarily in the early phase of infection and can be considerably reduced through antiviral treatment, provided it is administered at an early stage. Secondly, infections with these viruses can trigger an excessive immune response dominated by inflammation. This response is characterised by high concentrations of inflammatory messengers between cells (cytokines), uncontrolled activation of immune cells like T cells, and an insufficient antibody response which does not effectively control the viral infection. These processes play a role in the later phase of infection in particular and are sometimes decoupled from viral replication. While these responses are triggered by the latter, they occur largely independently from the virus in their further course. Treatment with antivirals must therefore be administered in the early stage of infection, while symptomatic therapy to alleviate the symptoms of the disease is required in the late stages (see box 1).

Box 1. Approaches to the symptomatic treatment of COVID-19 in severe courses of illness

Symptoms: high fever, pneumonia with dyspnoea, possible respiratory failure and/or multiple organ failure (for further symptoms see Chapter 2.2)

Measures and objectives:

- Close monitoring of vital signs
- Administration of oxygen, if necessary including artificial ventilation and extracorporeal membrane oxygenation
- Monitoring of inflammatory markers, as well as liver and kidney function and coagulation
- Treatment / optimisation of comorbidity treatment
- Imaging depending on the clinical course
- Positioning therapy¹³
- Prevention of lung damage and promotion of lung regeneration¹⁴
- Precautionary and therapeutic treatment of blood coagulation disorders¹⁵
- Treatment of excessive immune response (hyperinflammation), for example with steroids¹⁶

¹² Nelemans, T., & Kikkert, M. (2019). Viral innate immune evasion and the pathogenesis of emerging RNA virus infections. *Viruses*, 11(10), 961. Krammer, F., Smith, G. J. D., Fouchier, R. A. M., Peiris, M., Kedzierska, K., Doherty, P. C., & Palese, P. 546 Shaw ML, Treanor J, Webster RG, García-Sastre A. 2018. Influenza. *Nat Rev Dis Primers*, 547(4), 3.¹³ Camporota, L., Sanderson, B., Chiumello, D., Terzi, N., Argaud, L., Rimmelé, T., ... & Guérin, C. (2021). Prone Position in Coronavirus Disease 2019 and Noncoronavirus Disease 2019 Acute Respiratory Distress Syndrome: An International Multicenter Observational Comparative Study. *Critical care medicine*. Advance online publication. <https://doi.org/10.1097/CCM.0000000000005354> (last accessed: 9 November 2021).

¹³ Camporota, L., Sanderson, B., Chiumello, D., Terzi, N., Argaud, L., Rimmelé, T., ... & Guérin, C. (2021). Prone Position in Coronavirus Disease 2019 and Noncoronavirus Disease 2019 Acute Respiratory Distress Syndrome: An International Multicenter Observational Comparative Study. *Critical care medicine*. Advance online publication. <https://doi.org/10.1097/CCM.0000000000005354> (last accessed: 9 November 2021).

¹⁴ In clinical phase II/III studies, e.g. through administration of lung tissue protective vasoactive intestinal peptide (VIP) or granulocyte-macrophage colony stimulating factor (GM-CSF) for improving host defence function and lung repair.

¹⁵ See also the therapy overview of specialist group COVRIIN, available at: www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Therapieuebersicht.pdf?blob=publicationFile and S3 guideline on the inpatient therapy of COVID-19, available at: www.awmf.org/uploads/tx_szleitlinien/113-001LGI_S3_Empfehlungen-zur-stationaeren-Therapie-von-Patienten-mit-COVID-19_2021-10_1.pdf (both last accessed: 9 November 2021).

¹⁶ RECOVERY Collaborative Group. (2021). Dexamethasone in hospitalized patients with Covid-19. *New England Journal of Medicine*, 384(8), 693-704. Angus, D. C., Derde, L., Al-Beidh, F., Annane, D., Arabi, Y., Beane, A., ... & Writing Committee for the REMAP-CAP Investigators. (2020). Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *Jama*, 324(13), 1317-1329. Abani, O., Abbas, A., Abbas, F., Abbas, M., Abbasi, S., Abbass, H., ... & Ali, M. (2021). Tocilizumab in patients admitted to hospital with

2.2 Properties and replication cycle of the virus as well as the target sites of antivirals

SARS-CoV-2 is a member of the *Coronaviridae* family and is genetically closely related to the SARS pathogen (SARS-CoV, *severe acute respiratory syndrome coronavirus*), which emerged primarily in China in 2002/2003 and belongs to the same virus species within the betacoronaviruses group.¹⁷ Other viruses which are closely related to SARS-CoV-2 and SARS-CoV have been detected in various species of bats over the last two decades, and it is therefore considered very likely that SARS-CoV-2 originated from a betacoronavirus naturally occurring in bats and adapted to humans as a new host through spontaneously occurring mutations in its genome (genetic makeup).¹⁸ Similarly to what has been demonstrated for the SARS pathogen, certain animals could have acted as intermediate hosts in the transmission of a SARS-CoV-2 precursor virus from bats to humans, facilitating its transmission and adaptation to humans. However, there is currently no conclusive evidence for this hypothesis, or for other possible factors which could have enabled the transmission of a bat coronavirus similar to SARS-CoV-2 to humans via an intermediate host.

Coronaviruses are enveloped and have a single-stranded RNA genome spanning the length of approximately 30,000 nucleotides. The virus envelope contains numerous spike protein molecules which are responsible for binding the virus to the cellular receptor of the host (see figure 1). The main cellular receptor is the ACE2 protein, but the virus is also able to use other receptors on the cell surface, at least in cell culture systems; however, the biological relevance of these receptors is not yet understood.¹⁹ Target cells of SARS-CoV-2 include in particular epithelial cells of the respiratory tract, but also other cells expressing ACE2,²⁰ such as cardiac muscle cells, cells lining the walls of blood vessels and, indirectly, cells of the central nervous system, which likely plays an important role in the significant heterogeneity of clinical symptoms observed.

COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *The Lancet*, 397(10285), 1637-1645. REMAP-CAP Investigators. (2021). Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *New England Journal of Medicine*, 384(16), 1491-1502.

¹⁷ Gorbalenya, A.E., Baker, S.C., Baric, R.S., de Groot, R.J., Drosten, C., Gulyaeva, A.A., ... & Ziebuhr, J. (2020). The species *Severe acute respiratory syndrome-related coronavirus*: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 5, 536-544.

¹⁸ Holmes, E. C., Goldstein, S. A., Rasmussen, A. L., Robertson, D. L., Crits-Christoph, A., Wertheim, J. O., ... & Rambaut, A. (2021). The origins of SARS-CoV-2: a critical review. *Cell*. Zhou, H., Ji, J., Chen, X., Bi, Y., Li, J., Wang, Q., ... & Shi, W. (2021). Identification of novel bat coronaviruses sheds light on the evolutionary origins of SARS-CoV-2 and related viruses. *Cell* 184, 4380-4391.

¹⁹ Baggen, J., Vanstreels, E., Jansen, S. et al. (2021). Cellular host factors for SARS-CoV-2 infection. *Nat Microbiol* 6, 1219–1232.

²⁰ Iwasaki, M., Saito, J., Zhao, H., Sakamoto, A., Hirota, K., & Ma, D. (2021). Inflammation triggered by SARS-CoV-2 and ACE2 augments multiple organ failure of severe COVID-19: molecular mechanisms and implications. *Inflammation*, 44(1), 13-34.

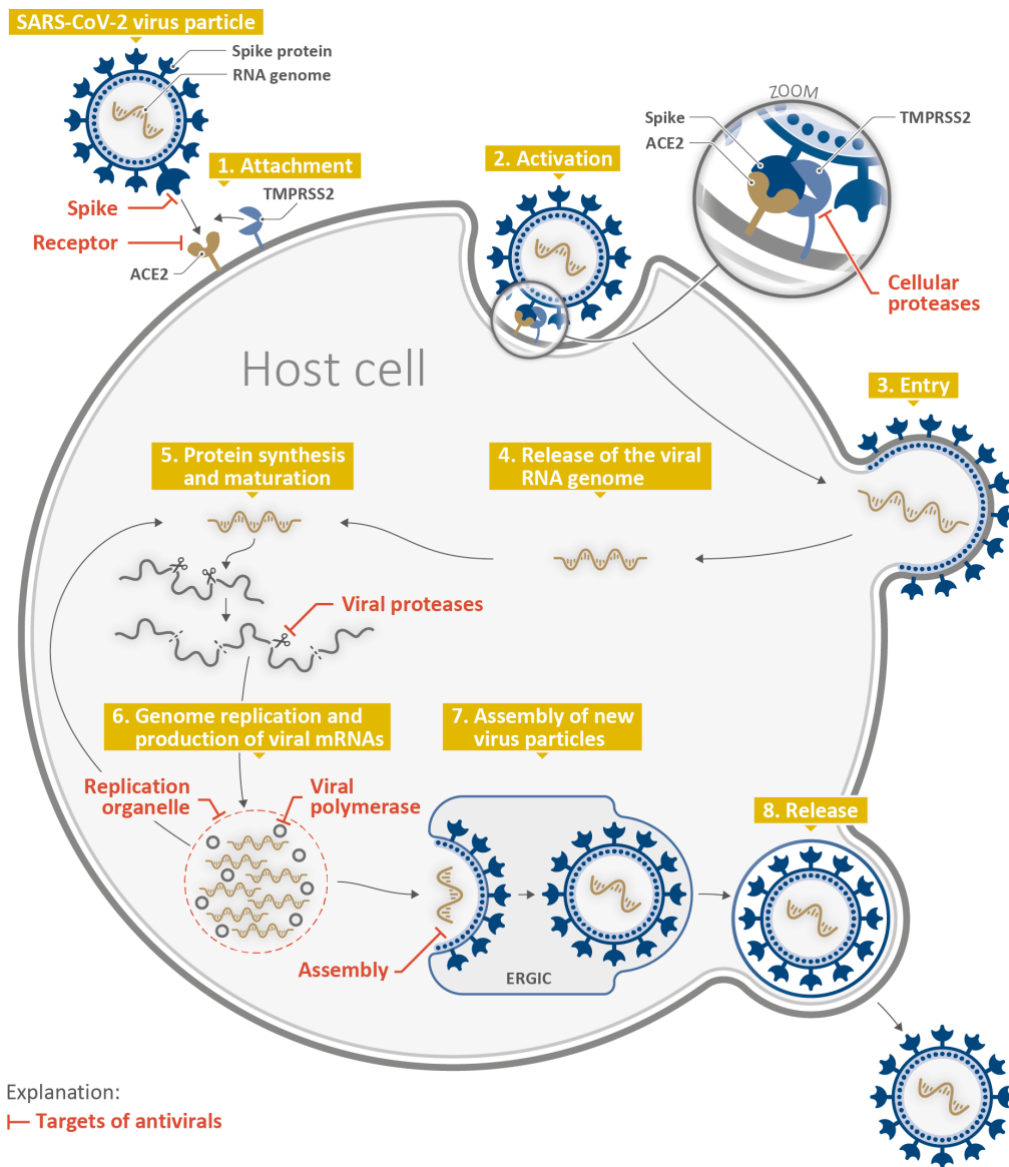


Figure 1: Simplified representation of the replication cycle of SARS-CoV-2 and possible target sites of antivirals. The virus possesses numerous copies of the spike protein on its surface, which it uses to bind to the main receptor of the cell, ACE2 (1). During virus entry, the spike protein is cleaved by cellular enzymes, particularly the protease TMPRSS2. This activation (2) is one of the prerequisites for the fusion of the virus envelope with the cellular membrane (3). Alternatively, the virus can also enter the cell through endocytosis (after binding to the receptor and bypassing the need for TMPRSS2) (not shown). In both cases, the viral RNA genome is deposited into the cytoplasm of the cell (4) and subsequently serves as a template for the synthesis of the viral proteins (5). These are initially produced as protein precursors, which need to be cleaved into the active components by two viral proteases. The viral proteins induce the formation of replication organelles in the cytoplasm, which are specialised structures enclosed by cellular membranes, in which amplification of the viral genome and synthesis of additional viral mRNAs occur with the help of the viral polymerase (6). These mRNAs are needed, for example, to produce the structural proteins of the virus, such as the spike protein, which accumulates in special cellular membranes (ERGIC = endoplasmic-reticulum–Golgi intermediate compartment) and allows the assembly of new virus particles there (7). During this process, membrane invagination occurs, causing the virus envelope to form and resulting simultaneously in engulfment of a complex of nucleocapsid proteins and the viral RNA genome. Numerous virus particles are created in this way (only one shown) that are released from the cell (8) to infect other cells. The selected target sites of antivirals are shown in red. These may be viral factors, such as viral proteases or polymerase, or cellular factors required for virus entry, for example.

SARS-CoV-2 is a pathogen primarily transmitted via respiratory air (aerosols) and can cause a rather wide spectrum of symptoms and clinical presentations. Known as COVID-19, the infection can result in few to no symptoms, but in some cases can also lead to severe pneumonia with acute respiratory distress syndrome (ARDS), which requires ventilation, and multiple organ failure with a fatal outcome. Since the cellular main receptor for SARS-CoV-2, ACE2, is present not only in the respiratory tract, but also in other organs, COVID-19 can also manifest in other organs, such as the gastrointestinal tract, in a variety of ways. This may lead directly or indirectly to other symptoms, such as nausea and diarrhoea. Other symptoms may include: difficulty of concentrating, mental health problems, loss of taste and smell, fatigue, cardiovascular symptoms even including heart failure, as well as kidney function disorders, as is also typical for other severe illnesses, for example after intensive care treatment. Some of these severe consequences seem to be caused by damage to the inner wall of the blood vessels with disturbances of the coagulation system and resulting thromboses (known as microcirculatory disorders).²¹

There is still an insufficient understanding of the molecular and immunological foundations underlying development of the disease. SARS-CoV-2 is highly effective at evading early detection by the innate immune system, since it produces multiple viral proteins which block or destroy individual components of the immune system's defensive mechanisms.²² Furthermore, the virus also induces signalling pathways which result in a misdirected immune response.²³

Various factors may increase the risk of a severe course of COVID-19. These factors include in particular older age, male sex and certain pre-existing health conditions, such as a weakened immune system, obesity, diabetes, and pre-existing respiratory, respiratory tract and cardiovascular system disorders. Initial studies show that defects in the innate immune response, particularly the interferon system, can significantly increase the risk of severe forms of progression in some patients.²⁴ The relevance of the interferon system in gaining early control of the infection – and thus in preventing severe symptoms – is also underlined by the fact that children exhibit a significantly more rapid interferon response to the infection than older persons.²⁵

In addition to the acute symptoms of a SARS-CoV-2 infection, some affected individuals develop what has been termed as long COVID. Symptoms of long COVID include extreme fatigue, coughing and headaches, long-lasting taste and smell disturbances, poor concentration and thought disorders and, in some hospitalised patients, severe lung damage and changes to various organs. Treatment of these long-term effects of a SARS-CoV-2 infection will not be elaborated on in this statement, since

²¹ Bonaventura, A., Vecchié, A., Dagna, L., Martinod, K., Dixon, D. L., Van Tassel, B. W., ... & Abbate, A. (2021). Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19. *Nature Reviews Immunology*, 21(5), 319-329. Varga, Z., Flammer, A. J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A. S., ... & Moch, H. (2020). Endothelial cell infection and endotheliitis in COVID-19. *The Lancet*, 395(10234), 1417-1418. Levi, M., & Coppens, M. (2021). Vascular mechanisms and manifestations of COVID-19. *The Lancet Respiratory Medicine*, 9(6), 551-553.

²² Zheng, Y., Zhuang, M. W., Han, L., Zhang, J., Nan, M. L., Zhan, P., ... & Wang, P. H. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) membrane (M) protein inhibits type I and III interferon production by targeting RIG-I/MDA-5 signaling. *Signal transduction and targeted therapy*, 5(1), 1-13.

²³ Ferreira-Gomes, M., Kruglov, A., Durek, P., Heinrich, F., Tizian, C., Heinz, G. A., ... & Mashreghi, M. F. (2021). SARS-CoV-2 in severe COVID-19 induces a TGF- β -dominated chronic immune response that does not target itself. *Nature Communications*, 12(1), 1-14.

²⁴ Zhang, Q., Bastard, P., Liu, Z., Le Pen, J., Moncada-Velez, M., Chen, J., ... & Casanova, J. L. (2020). Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science*, 370(6515). Bastard, P., Rosen, L. B., Zhang, Q., Michailidis, E., Hoffmann, H. H., Zhang, Y., ... & Casanova, J. L. (2020). Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science*, 370(6515).

²⁵ Loske, J., Röhm, J., Lukassen, S., Stricker, S., Magalhães, V. G., Liebig, J., ... & Lehmann, I. (2021). Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. *Nature Biotechnology*, 1-6.

the specific causes of these effects are not well understood and have not yet been clearly linked to active viral replication.²⁶ Nevertheless, long COVID is a possible consequence of a SARS-CoV-2 infection which should be taken seriously.

3. Necessity of antivirals in the treatment of a SARS-CoV-2 infection

Despite the success of vaccination efforts to date, vaccines, diagnostics for the early detection of infected persons and the symptomatic therapies available up to now are not sufficient: There are groups of persons who fail to build up sufficient immunity even after vaccination, for instance those receiving immunosuppressants. Furthermore, there are groups of persons in whom protection against infection and illness wanes after a certain amount of time (see above)²⁷ or who are not vaccinated for various reasons.

The development of antivirals is also a matter of urgency in light of possible novel virus variants against which vaccines offer insufficient protection as well as in preparation for possible novel pandemic viruses.

It is also predictable that the worldwide vaccination rate will remain insufficient for achieving permanently low case numbers for some time to come. As such, the assumption is that the virus will become endemic and circulate continually amongst parts of the population.²⁸ This means that, even once the pandemic has subsided, SARS-CoV-2 infections will continue to occur, including those leading to severe courses of illness and fatal outcomes.

Against this background, the development and administration of medication specifically targeting SARS-CoV-2 are urgently needed. Substances which put the innate immune system on high alert will also be very valuable,²⁹ which would enable the body to better detect and fend off viruses, as seems to be the case in children infected with SARS-CoV-2.³⁰ Another approach is the development of broad-spectrum antivirals which, for example, are effective against different types of viruses in a virus family. Such medications would also be of crucial importance for future virus pandemics, for which there are no effective vaccines yet.

The focus of this statement is primarily on direct antiviral therapy, which interferes with and inhibits the mechanisms of viral replication. This therapy must be administered in the early stage of infection, known as the replication phase, ideally before the point of maximum viral replication. Since viral load levels in patients are usually no longer significant in the late stage of the infection, direct antiviral therapy is no longer effective at this point.

²⁶ Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C. et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 11, 16144 (2021).

²⁷ Levin, E. G., Lustig, Y., Cohen, C., Fluss, R., Indenbaum, V., Amit, S., ... & Regev-Yochay, G. (2021). Waning immune humoral response to BNT162b2 covid-19 vaccine over 6 months. *New England Journal of Medicine*.
Chemaitelly, H., Tang, P., Hasan, M. R., AlMukdad, S., Yassine, H. M., Benslimane, F. M., ... & Abu-Raddad, L. J. (2021). Waning of BNT162b2 vaccine protection against SARS-CoV-2 infection in Qatar. *New England Journal of Medicine*.

²⁸ Riley, Ainslie, Eales et al. (2021). Resurgence of SARS-CoV-2: Detection by community viral surveillance. *Science*, 372(6545), 990–995.

²⁹ Coch, C., Stümpel, J. P., Lilien-Waldau, V., Wohlleber, D., Kümmerer, B. M., Bekeredjian-Ding, I., ... & Hartmann, E. (2017). RIG-I activation protects and rescues from lethal influenza virus infection and bacterial superinfection. *Molecular Therapy*, 25(9), 2093-2103. Bartok, E., & Hartmann, G. (2020). Immune sensing mechanisms that discriminate self from altered self and foreign nucleic acids. *Immunity*, 53(1), 54-77.

³⁰ Loske, J., Röhm, J., Lukassen, S., Stricker, S., Magalhães, V. G., Liebig, J., ... & Lehmann, I. (2021). Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. *Nature Biotechnology*, 1-6.

3.1 Examples of established antiviral therapies

The last few years have seen significant advancements in the treatment of predominantly chronic virus diseases, i.e. infections after which the virus remains in the body permanently. The best-known example is the infection with the human immunodeficiency virus (HIV), a retrovirus which triggers the disease AIDS (acquired immunodeficiency syndrome). This virus was discovered in 1983 and also triggered a global pandemic. Thanks to intensive research and development, we now have an arsenal of different active substances to choose from which target different steps of the HIV replication cycle, halt the disease process and counteract the development of resistant HI viruses. The current therapy, a targeted combination of different antivirals,³¹ suppresses HIV replication to such an extent that severe immune deficiency is prevented and patients can have a virtually normal life. Today, this therapy is recommended for all infected individuals, regardless of whether they already have a weakened immune system.³² The United Nations has established the objective of ensuring global access to these medications to ensure that AIDS no longer develops in infected individuals.³³ Reducing transmission of HIV is another goal of treatment.³⁴ Despite enormous efforts around the globe, there is still no effective HIV vaccine, meaning that treatment of the virus is simultaneously the most effective means of preventing transmission.³⁵

A similar situation is observed in the treatment of an infection with the hepatitis B virus (HBV), which similarly to the hepatitis C virus (HCV) causes a chronic infection of the liver, often leading to liver cirrhosis and liver cancer. Similarly to the HIV situation, antiviral therapy can reduce viral replication in an HBV infection to such an extent that hepatitis recedes and severe liver damage is avoided. However, the virus remains in the body persistently, meaning that the therapy has to be administered to the patients for the rest of their life. This reduces the risk of liver cancer. In the case of HCV, however, administration of a combination of two to three antivirals is now able to completely eliminate the virus from the body and thus even cure this chronic infection.

One example of therapy for an acute viral infection is influenza therapy. Both SARS-CoV-2 and influenza A viruses primarily infect the respiratory tract and can cause pneumonia of varying severity. Four antivirals are currently approved for the treatment of influenza.³⁶ Here, one of the challenges lies in the fact that the virus has an immense ability to acquire mutations, which confer resistance to these antivirals. As a result, owing primarily to the rapid development of resistance, administration of the first antivirals developed against influenza is no longer recommended.³⁷ Another challenge is

³¹ Lengauer, T., Sander, O., Sierra, S., Thielen, A., & Kaiser, R. (2007). Bioinformatics prediction of HIV coreceptor usage. *Nature biotechnology*, 25(12), 1407-1410.

³² Insight Start Study Group. (2015). Initiation of antiretroviral therapy in early asymptomatic HIV infection. *New England Journal of Medicine*, 373(9), 795-807.

³³ Nosyk, B., Min, J. E., Lima, V. D., Yip, B., Hogg, R. S., & Montaner, J. S. (2013). HIV-1 disease progression during highly active antiretroviral therapy: an application using population-level data in British Columbia: 1996–2011. *Journal of acquired immune deficiency syndromes (1999)*, 63(5), 653. Joint United Nations Programme on HIV/AIDS (UNAIDS). (2017). Ending AIDS: Progress towards the 90-90-90 targets. *Global AIDS update*.

³⁴ Vernazza P., Hirschel B., Bernasconi E., Flepp M. HIV-infizierte Menschen ohne andere STD sind unter wirksamer antiretroviraler Therapie sexuell nicht infektiös. *Bull Med Suisses* 2008; 89:165-69.

³⁵ Cohen, M. S., Chen, Y. Q., McCauley, M., Gamble, T., Hosseinipour, M. C., Kumarasamy, N., ... & Fleming, T. R. (2011). Prevention of HIV-1 infection with early antiretroviral therapy. *New England journal of medicine*, 365(6), 493-505.

³⁶ Three of these four medications (oseltamivir, zanamivir and peramivir) target and block the viral surface protein neuraminidase (NA). Since the NA protein is responsible for the release of the virus, NA inhibitors do not stop virus production, but rather halt the further spread of viruses. The fourth medication (baloxavir) blocks a subunit of the viral polymerase (the cap-dependent endonuclease), which is required for the production of viral mRNA. This directly prevents viral replication in the infected cell.

³⁷ Lehnert, R., Pletz, M., Reuss, A., Schaberg, T. (2016) Antiviral medications in seasonal and pandemic influenza – a systematic review. *Deutsches Ärzteblatt International* 113: 799–807. DOI: 10.3238/arztebl.2016.0799

ensuring early administration of the therapy (and the resulting necessity to detect pathogens at an early stage), as the influenza virus, unlike the chronic infections mentioned above, only remains in the body for a relatively short time.

3.2 Requirements for antivirals against SARS-CoV-2

A key aspect of antiviral therapy to treat SARS-CoV-2 is the **time of its administration**, which crucially depends on the speed with which viral replication takes place (see figure 2). It has been established that significant replication of SARS-CoV-2 occurs even before the first symptoms appear,³⁸ whereas viral replication is barely detectable in individuals at an advanced stage of disease,³⁹ similarly to an infection with the influenza virus.⁴⁰ Antiviral therapy, i.e. treatment with substances which inhibit viral replication, must therefore be administered as soon as possible after the infection or, as a prophylactic measure, even prior to a possible infection. The latter applies in particular to non-immune persons with risk factors for a severe course of infection and who have been exposed to the virus.

Agents may be small chemical molecules which inhibit certain functions in viral replication (e.g. viral enzymes like proteases or RNA polymerase; see figure 1). Likewise, small protein fragments (peptides) which correspond, for example, to receptor-binding regions, or antibodies targeting the spike protein of the virus which prevent it from attaching to cells and thus spreading further in the organism, may be effective. Therapeutics which stimulate the innate immune response are also helpful at this stage. While there is always the risk of resistant variants of the virus developing when using targeted small chemical molecules and virus antigen-specific monoclonal antibodies – unless several substances are combined – this is not the case for therapeutics which stimulate the immune system.

³⁸ Ganyani, T., Kremer, C., Chen, D., Torneri, A., Faes, C., Wallinga, J., & Hens, N. (2020). Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Eurosurveillance*, 25(17), 2000257.

³⁹ He, X., Lau, E. H., Wu, P., Deng, X., Wang, J., Hao, X., ... & Leung, G. M. (2020). Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature Medicine*, 26(5), 672-675.

⁴⁰ Ip, D. K., Lau, L. L., Leung, N. H., Fang, V. J., Chan, K. H., Chu, D. K., ... & Cowling, B. J. (2017). Viral shedding and transmission potential of asymptomatic and paucisymptomatic influenza virus infections in the community. *Clinical infectious diseases*, 64(6), 736-742.

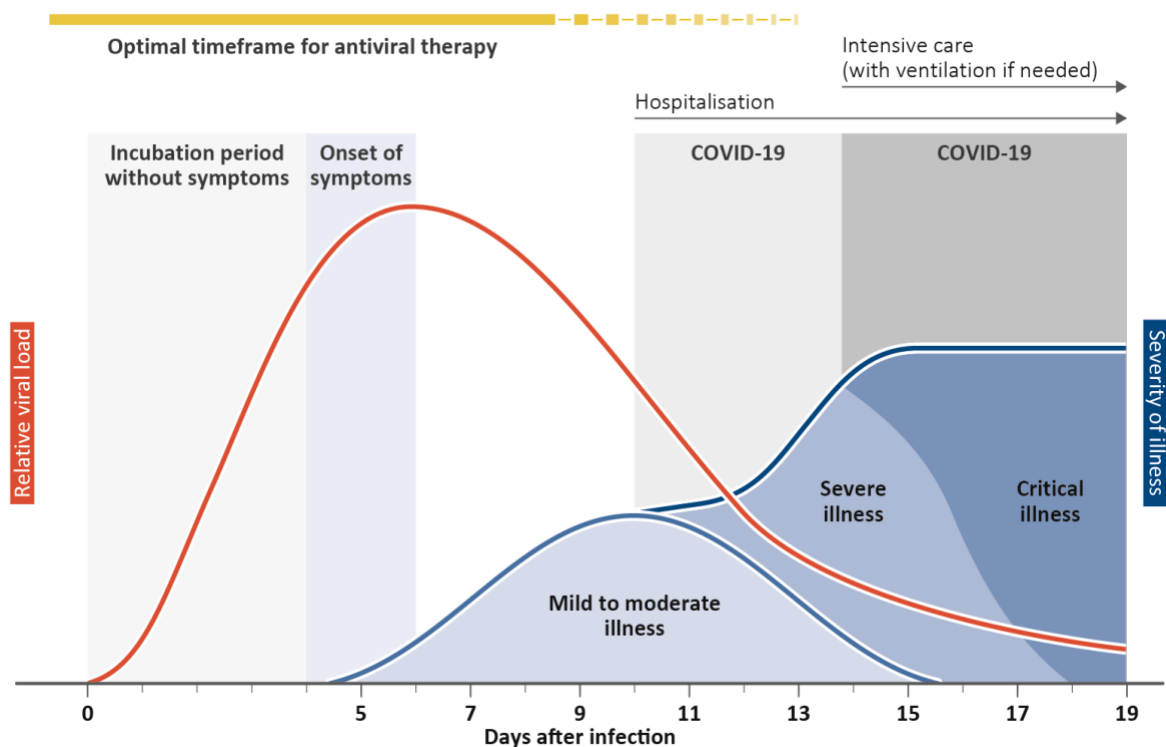


Figure 2: Typical course of a SARS-CoV-2 infection (simplified overview).⁴¹ Following an infection with SARS-CoV-2, onset of the first mild symptoms generally occurs only after four to five days (incubation period). However, infected individuals are often already contagious two days before experiencing the first symptoms and up to 10 to 14 days after the infection. The maximum viral load in the throat is generally found between the fourth and eighth day after the infection, by which point antiviral therapy should have begun. For individuals with a comparatively high risk of becoming infected and becoming ill, consideration may be given to prophylactic administration. Symptoms in persons without a restricted immune system are usually most severe 9 to 11 days after the infection. This is usually the point at which the symptoms either start to improve or transition into a severe illness with COVID-induced pneumonia occurs. The further course or speed with which the illness transitions to ARDS (acute respiratory distress syndrome, lung failure) and requires ventilation and/or extracorporeal membrane oxygenation is often dependent on the individual risk profile (figure adapted pursuant to Cevik et al. 2020⁴²).

For antiviral therapies to be initiated at a very early stage, they need to be **easily accessible and easy to administer** in an outpatient setting, ideally in an oral form, i.e. as a medication which can be swallowed or inhaled. This is also underlined by experience with administering monoclonal therapeutic antibodies targeting the spike protein of SARS-CoV-2. In this case, treatment was largely administered in an inpatient setting for logistical reasons, owing to a lack of structures for early outpatient administration. As a result, the majority of high-risk patients with an indication for early use of these agents could not be reached and stockpiled antibody doses could not be administered.⁴³

Depending on the safety profile, effectiveness and costs of antiviral therapies, the question arises as to whether every person with a confirmed infection should be treated or only persons with risk

⁴¹ He, X., Lau, E. H., Wu, P., Deng, X., Wang, J., Hao, X., ... & Leung, G. M. (2020). Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature medicine*, 26(5), 672-675 Sun, K., Wang, W., Gao, L., Wang, Y., Luo, K., Ren, L., ... & Yu, H. (2021). Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. *Science*, 371(6526).

⁴² Cevik, M., Kuppalli, K., Kindrachuk, J., & Peiris, M. (2020). Virology, transmission, and pathogenesis of SARS-CoV-2. *bmj*, 371.

⁴³ Currently, the administration of antibodies in the combinations bamlanivimab/etesevimab and casirivimab/imdevimab is primarily recommended for non-hospitalised patients in the early stage of the infection (maximum of three days after a positive PCR test or no later than seven days after symptom onset). A prophylactic (post-exposure) application is being discussed.

factors, such as older age, cardiovascular or coagulation system disorders, obesity or a weakened immune system. Given that severe cases of COVID-19 have also been observed in persons without any discernible risk factors on occasion, identifying and defining corresponding signatures or progression parameters as part of translational research projects is highly relevant to enabling accurate therapeutic decisions to be made in the early stage of the infection.

To ensure that they can be administered as widely as possible, and taking into account any symptoms which have already appeared, antivirals must also cause as **few side effects as possible** and must not have a negative impact on symptomatic treatment or the innate immune response. In addition, antiviral therapy should be as **widely available** as possible in terms of manufacture, storage and transport, which is highly important for developing countries with limited health system resources in particular.

The design and selection of antivirals must counteract the **development of resistance** to the extent possible. SARS-CoV-2 starts to replicate within a few hours after infection. However, genetic changes (mutations) occur at a significantly slower pace for coronaviruses than is the case for other RNA viruses, such as HIV or HCV.⁴⁴ Nevertheless, extensive replication, a short generation time and the capacity of different viruses to exchange pieces of their genome (recombination) are swiftly creating a number of variants.⁴⁵ Some mutations may be advantageous for the virus if they increase transmissibility and/or reduce sensitivity to neutralisation by antibodies as a result of vaccination or a former infection. Such variants of the virus, for example the Delta variant, subsequently supersede the original virus and certain mutations become dominant.

There are viral proteins that are crucial for viral replication and in which mutation-related changes are usually accompanied by a fitness disadvantage for the pathogen. This means that fewer changes occur in these highly conserved structures, making them particularly suitable as target sites for antivirals. An example of a strongly conserved element of SARS-CoV-2 is the viral main protease, which is responsible for cleaving the viral protein precursors (see figure 1, step 5). It mutates around 10 times less frequently than, for example, the spike protein (targeted by antibodies and vaccination).⁴⁶ In addition, substances targeting such highly conserved sites have the potential to achieve a certain broad-spectrum effect, meaning that they can also inhibit viruses related to SARS-CoV-2. Another strategy for counteracting resistance to therapy is the combination of antivirals, an approach already successfully applied to the even more variable HIV or HCV variants (see Chapter 3.1).

3.3 Mechanisms of action and examples of antivirals targeting SARS-CoV-2

Generally speaking, antivirals follow one of two strategies: The first strategy targets the virus itself and has a direct inhibitory effect on certain components of viruses. The second strategy targets the host organism, using one of two approaches: The first approach takes advantage of the fact that viruses require numerous factors to replicate, which they find in the infected cell. Therefore, by (temporarily) blocking these cellular factors which the virus needs, the virus is no longer able to replicate. The second approach uses the natural antiviral defence system found in all cells. This system is cleverly outsmarted by numerous viruses such as SARS-CoV-2, allowing them to evade this

⁴⁴ Rausch, J. W., Capoferri, A. A., Katusiime, M. G., Patro, S. C., & Kearney, M. F. (2020). Low genetic diversity may be an Achilles heel of SARS-CoV-2. *Proceedings of the National Academy of Sciences*, 117(40), 24614-24616.

⁴⁵ See also <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants> (last accessed: 9 November 2021).

⁴⁶ Harvey, W. T., Carabelli, A. M., Jackson, B., Gupta, R. K., Thomson, E. C., Harrison, E. M., ... & Robertson, D. L. (2021). SARS-CoV-2 variants, spike mutations and immune escape. *Nature Reviews Microbiology*, 19(7), 409-424.

defence mechanism. Speed is the decisive factor here: It is a race between how quickly the virus is detected by the cell triggering the defence mechanisms on the one hand, and how quickly the virus blocks these mechanisms on the other. If defensive action is taken quickly enough, the infection will be brought under control. If it is taken too late, the virus will have already developed a blockade system in the cell and be able to replicate. If the defence system has already been activated prior to infection, the cell will be largely resistant to the virus. This is exploited by therapeutically activating this natural antiviral defence mechanism at an early stage. The two fundamental strategies resting on this therapeutic approach are explained in further detail below.

Inhibitors which directly target the virus block, for example:

- The entry of the viruses into the cells (e.g. using recombinant antibodies or ACE2 fusion proteins which bind the spike protein; see figure 1, step 1);
- Viral protein maturation. This is caused by protease inhibitors which block the activity of viral proteases. These viral proteases create the necessary components of the viral replication machinery, such as polymerase (see figure 1, step 5);⁴⁷
- The viral machinery for replicating the RNA genome of the viruses (polymerase inhibitors); these either inhibit the RNA polymerase itself, which is the key enzyme for viral RNA synthesis, or target one of the numerous helper proteins (cofactors) of the viral polymerase, which requires them for certain functions (see figure 1, step 6)⁴⁸;
- Other viral target sites (e.g. structurally relevant virus components).

In the search for new antivirals targeting SARS-CoV-2, the first step was to test existing medications which are effective against highly conserved enzymes of other known viruses (an approach known as “drug repurposing”). The inhibitors of these enzymes indicate broad-spectrum effectiveness, as has been confirmed in a range of polymerase inhibitors which have been approved or are in the process of being approved. If used at a late stage of the infection, however, these antivirals are only found to have a low impact, or no impact at all.

Monoclonal antibodies which target the SARS-CoV-2 spike protein were developed early in the pandemic and are an effective approach to preventing COVID-19 or a severe course of illness.⁴⁹ To achieve a high level of effectiveness, the antibodies must be administered early after the infection. In the late stage of the illness or once patients have already built up antibodies to SARS-CoV-2 themselves, it is no longer beneficial to administer antibodies.⁵⁰ A disadvantage is that antibodies

⁴⁷ Báez-Santos, Y. M., St. John, E. S., & Mesecar, A. D. (2015). The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. *Antiviral Research*, 115, 21-38. Ullrich, S., & Nitsche, C. (2020). The SARS-CoV-2 main protease as drug target. *Bioorganic & Medicinal Chemistry Letters*, 127377. Citarella, A., Scala, A., Piperno, A., & Micale, N. (2021). SARS-CoV-2 Mpro: A Potential Target for Peptidomimetics and Small-Molecule Inhibitors. *Biomolecules*, 11(4), 607. Zhang, L., Lin, D., ... & Hilgenfeld, R. (2020). Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. *Science*, 368, 409-412.

⁴⁸ Williamson, B. N., Feldmann, F., Schwarz, B., Meade-White, K., Porter, D. P., Schulz, J., ... & De Wit, E. (2020). Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature*, 585(7824), 273-276.

⁴⁹ O'Brien, M. P., Neto, E. F., Musser, B. J., Isa, F., Chan, K. C., Sarkar, N., ... & Covid-19 Phase 3 Prevention Trial Team. (2021). Subcutaneous REGEN-COV Antibody Combination for Covid-19 Prevention. medRxiv. Dougan, M., Nirula, A., Azizad, M., Mocherla, B., Gottlieb, R. L., Chen, P., ... & Skovronsky, D. M. (2021). Bamlanivimab plus etesevimab in mild or moderate COVID-19. *New England Journal of Medicine*. Cohen, M. S., Nirula, A., Mulligan, M. J., Novak, R. M., Marovich, M., Yen, C., ... & BLAZE-2 Investigators. (2021). Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. *JAMA*, 326(1):46-55.

⁵⁰ ACTIV-3/TICO LY-CoV555 Study Group. (2021). A neutralizing monoclonal antibody for hospitalized patients with Covid-19. *New England Journal of Medicine*, 384(10), 905-914. Horby, P. W., Mafham, M., Peto, L., Campbell, M., Pessoa-Amorim, G., Spata, E., ... & Landray, M. J. (2021). Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv.

generally have to be administered intravenously, a problem which can be greatly reduced by developing formulations for subcutaneous injection. In addition, the antibody production process is relatively time-consuming and cost-intensive, which is why they only have limited suitability for widespread use. One advantage, however, is that certain properties of monoclonal antibodies, such as stability in the organism, are very easy to modify. High stability enables, for example, patients with a low immune response to receive prophylactic treatment with a single injection providing protection for several months.

The antibodies developed thus far bind to the spike protein, which is able to change as a result of immune selection pressure caused by vaccination and infections (see Chapter 3.2). Potential SARS-CoV-2 escape mutations may consequently also reduce or eliminate the effectiveness of antibodies.⁵¹ To ensure effectiveness against a large number of SARS-CoV-2 variants and prevent escape mutations, monoclonal antibodies are therefore often combined with one another.

No active substance has been authorised for the inhibition of the SARS-CoV-2 main protease to date, though substances for intravenous or oral administration are currently undergoing clinical trials. These medications are undergoing testing on non-hospitalised patients and are designed to be effective against all known human coronaviruses (including MERS-CoV and the first SARS-CoV).⁵² One of these substances has exhibited good results when administered at an early stage and could soon receive emergency use authorisation. Three substances targeting polymerase have already been authorised for use in some countries, while several others are in late-phase clinical testing.⁵³ These polymerase inhibitors were originally developed for use against other viruses, and it can be assumed that their effectiveness may be optimised further. One such substance was recently found to induce a significant reduction in the risk of illness and death when administered at an early stage, with emergency use authorisation currently in the process of being obtained.⁵³

For the second strategy, namely the **antiviral approach targeting the host organism**, the first step is to identify cellular molecules required by the virus to replicate effectively. These may include:

- The ACE2 protein on the target cells, possibly including alternative receptors or receptors which enhance the infection such as lectin, with a view to blocking the entry of viruses into cells (e.g. through ACE2 antagonists; see figure 1, step 1);
- Cellular enzymes required for virus entry (e.g. inhibitors of the TMPRSS2 protease; see figure 1, step 2);
- Host factors which play an essential role in the replication of the virus in the cell. These may include cellular proteins which are involved in protein synthesis (see figure 1, step 5), protein folding, lipid synthesis and modification, intracellular transport between different subcellular organelles (see figure 1, steps 6 and 7) and the chemical modification of viral proteins (phosphorylation, glycosylation, ADP-ribosylation, etc.).⁵⁴

⁵¹ Corti, D., Purcell, L. A., Snell, G., & Vesler, D. (2021). Tackling COVID-19 with neutralizing monoclonal antibodies. *Cell*.

⁵² Owen, D. R., Allerton, C. M., Anderson, A. S., Aschenbrenner, L., Avery, M., Berritt, S., ... & Zhu, Y. (2021). An Oral SARS-CoV-2 Mpro Inhibitor Clinical Candidate for the Treatment of COVID-19. *medRxiv*.

⁵³ As at 9 November 2021. For the latest daily information, including on other medications, see

www.vfa.de/de/anzneimittel-forschung/woran-wir-forschen/therapeutische-medikamente-gegen-die-coronavirusinfektion-covid-19 and <https://clinicaltrials.gov/> (both last accessed: 9 November 2021).

⁵⁴ The different sub-steps of the viral replication cycle (see figure 1) depend on such cellular factors to varying degrees; targeted inhibition of these factors disrupts the replication cycle of the virus or prevents the formation of new viruses which are fully capable of infection. Since these cellular factors generally also possess functions which are important to the

Furthermore, host-targeted therapy deploys naturally occurring antiviral defence mechanisms. For these to be used, however, viral defence factors must first be produced in the infected cell in order to activate the cells prior to viral replication. These defence mechanisms may be stimulated in a targeted manner using specific substances, generally through administration of interferon or short artificial nucleic acids, enabling them to counteract viral replication and the spread of the virus in the organism.

The defence mechanisms are usually activated when specialised receptors in the innate immune system detect viral nucleic acids and then initiate a broad antiviral immune response. Examples of these receptors and defence mechanisms are:

- RIG-I-like receptors (RIG-I, MDA5), which are present in all body cells and recognise certain properties of viral nucleic acids in the cytoplasm;
- Toll-like receptors (TLR7, TLR8 and TLR9), which predominantly occur in or on immune cells and immediately detect viral RNA and DNA upon entry of viruses into the cell;⁵⁵
- Type I and III interferons, messenger substances (cytokines) which are secreted by virus-infected cells to alert surrounding cells and enable activation of antiviral mechanisms.

4. Exploitation and development of antivirals against SARS-CoV-2

4.1 Prerequisites for the development of antivirals

The search for antivirals targeting SARS-CoV-2 initially fell back on medications which had already been tested or approved for the treatment of other pathogens. The effectiveness of these repurposed drugs is often limited, however, as they are not optimised for SARS-CoV-2. A targeted search for and optimisation of other substances against SARS-CoV-2 is therefore of vital importance.

Some of the enzymes which are essential for viral replication, such as the 3CL protease (also known as the main protease M^{pro}) and the RNA polymerase, have been investigated extensively thanks to intensive fundamental research, enabling current active substance development to draw on these findings. In particular, knowledge of the structure and properties of the spike protein of the closely related SARS-CoV, which first emerged in 2002, and of the corresponding specific antibodies has played a decisive role in the rapid development of vaccines targeting SARS-CoV-2. The picture is similar for the SARS-CoV-2 main protease. Here, too, optimised candidate medications against SARS-CoV-2 were developed on the basis of findings in connection with the closely related SARS-CoV enzyme.⁵⁶ These examples show that comprehensive fundamental research will continue to be vital for the identification and characterisation of new viral and cellular targets for antivirals as well as new therapeutic approaches targeting pandemic pathogens.

cell's survival, there is the risk of inhibitors affecting these cellular proteins having toxic side effects. For time-limited administration, such as in the acute phase of a viral infection, such possible toxic side effects can be tolerated in most cases. The very low risk of resistant virus variants developing is generally considered to be a possible advantage of inhibiting cellular (as opposed to viral) factors.

⁵⁵ Khanmohammadi, S., & Rezaei, N. (2021). Role of Toll-like receptors in the pathogenesis of COVID-19. *Journal of Medical Virology*, 93(5), 2735-2739. Paulsen, D., Urban, A., Knorr, A., Hirth-Dietrich, C., Siegling, A., Volk, H. D., ... & Weber, O. (2013). Inactivated ORF virus shows antifibrotic activity and inhibits human hepatitis B virus (HBV) and hepatitis C virus (HCV) replication in preclinical models. *PLoS One*, 8(9), e74605. von Buttler, H., Siegemund, S., Büttner, M., & Alber, G. (2014). Identification of Toll-like receptor 9 as parapoxvirus ovis-sensing receptor in plasmacytoid dendritic cells. *PLoS one*, 9(8), e106188.

⁵⁶ Anand, K., Ziebuhr, J., Wadhwani, P., Mesters, J. R., Hilgenfeld, R. (2003). Coronavirus main proteinase (3CLpro) structure: Basis for design of anti-SARS drugs. *Science*, 300, 1763-1767; Zhang, L., Lin, D., ... & Hilgenfeld, R. (2020). Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. *Science*, 368, 409-412.

In order to successfully translate scientific research into medical practice, scientists require – in addition to expertise on the translation processes at their institution or facility – access to infrastructures which actively and continuously support processes leading to clinical application. These include infrastructures relating to medicinal chemistry,⁵⁷ which are needed to implement concepts pertaining to structure-based inhibitor design and further modify candidate substances identified by means of screening.

In the search for new antivirals, fundamental research needs to be supplemented with an infrastructure for developing and assessing medications, since active substances need to possess suitable toxicological, pharmacokinetic and metabolic properties in addition to antiviral activity. These include good tolerability and sufficient stability in the organism. The necessary expertise in these areas may be obtained through cooperative partnerships with relevant academic institutions, such as those working in the fields of toxicology, pharmacology and pharmacokinetics, or by awarding contracts to external companies which will perform the standardised investigations required against payment. Here, it is also important to ensure that materials for clinical use are manufactured in accordance with internationally valid GMP (good manufacturing practice) regulations,⁵⁸ that stability testing is conducted and that a suitable form of administration is developed. Ensuring access to quality assurance information⁵⁹ and possible means of support with regard to statistics, business development and patent applications, including regulatory issues and professional contract management, is also essential, as are structures facilitating clinical research such as biobanks and patient registries, including medical information infrastructure.

If the results pertaining to a substance permit testing on humans, clinical research centres will be required which have experience in developing and conducting clinical studies (see box 2) and in interacting with the authorities required to authorise such studies. Here, too, the studies may be carried out either at academic institutions or by companies which conduct clinical development activities as contract research.

Significant funding is required to develop or forge links between structures relating to medication development and, in particular, to conduct the clinical studies in question. To successfully launch a medication on the market, costs in the region of approximately 1 billion euros are usually anticipated. This figure also includes the costs associated with the numerous failures which occur during the medication development process; for every 10 medications which are tested on humans (phase I) in a first trial, only one on average ultimately reaches the market. The US government made available 3.2 billion US dollars to the research and development of medications targeting SARS-CoV-2 in June of 2021.⁶⁰

⁵⁷ Medicinal chemistry is a scientific sub-discipline of chemistry which deals with the development and synthesis of medicinal products. It analyses the molecular chemical principles underlying the effects of medicinal products and derives quantitative structure-activity relationships. It also combines aspects of organic chemistry with elements of computational chemistry, pharmacy, pharmacology, physiology, biochemistry and chemical biology.

⁵⁸ GMP is a set of guidelines designed to ensure that medicinal products and active substances are produced in accordance with quality assurance standards.

⁵⁹ GMP in addition to GCP (good clinical practice) and GLP (good laboratory practice).

⁶⁰ Further information is available at: www.nytimes.com/2021/06/17/health/covid-pill-antiviral.html (last accessed: 9 November 2021).

Box 2. Clinical studies

Following the successful conclusion of the preclinical trial and authorisation by the responsible authorities and an ethics committee, new substances are tested on humans within the framework of clinical studies. Clinical studies are divided into a total of four phases. In **phase I**, the new active substance is initially tested on a small number of healthy volunteers to investigate how it is tolerated, at which speed the substance enters the blood, which level it reaches, whether it is converted in the body, how quickly and in which way it leaves the body again and whether interactions with other medication are to be expected. In **phase II**, the substance is first tested for effectiveness and again for safety on a limited number of patients. This phase is also used to find the optimal dose. In **phase III studies**, the effectiveness and safety of the substance are investigated with a significantly larger number of patients. The number of patients depends on the indication. Phase II and phase III studies should, where possible, be carried out as controlled studies. This means that groups of patients are treated differently in a blinded study (in which neither the doctor nor the patient knows which therapy has been administered) and compared with each other. Generally speaking, one group receives the new substance, while the other group receives the current standard preparation or a placebo. Once phases I to III have been successfully concluded, an application for approval of the new medication may be submitted to the responsible authorities (e.g. the European Medicines Agency, EMA). The process from the start of phase I to approval usually takes more than five years.

In exceptional cases, such as in a health emergency due to a pandemic, there is also an expedited process in the form of a rolling review, in which the necessary data is submitted and analysed successively as it becomes available, accelerating the process of obtaining formal marketing authorisation, subject to compliance with the necessary standards and level of effectiveness. In addition to general marketing authorisation, the authorities may also issue emergency use or temporary authorisation. Such authorisation may be subject to additional requirements for the manufacturers, for example the requirement to carry out more in-depth clinical studies (**phase IV**) with a view to better understanding or confirming certain aspects linked to the administration of the medication. In general, manufacturers are required to monitor and report any side effects which occur.

4.2 Study design and infrastructure

Taking into account the course of illness illustrated in figure 2 with an early peak in viral replication, a study design which enables therapy with antivirals to commence rapidly needs to be chosen. This requires an infrastructure which enables the early detection of persons infected with SARS-CoV-2 and their swift access to clinical studies. The need to curb the spread of acute, easily transmissible infectious diseases poses additional challenges. Firstly, infected individuals need to self-isolate and cannot visit a study centre without permission. Secondly, hospitals and central study sites need to be specialised in patients with highly contagious infections and have the necessary infrastructure and protective clothing. This requires resources which may already be massively under strain during a pandemic.

Furthermore, parameters indicating the risk of severe courses must be sufficiently understood in order to reliably interpret the results of studies; the study design must also take into account that, for patients who develop severe courses of illness, swift measures will need to be taken to treat their symptoms (including the option of being transferred to an intensive care unit).

As already shown, early intervention in acute respiratory infections with antivirals is key to the success of the therapy (see Chapter 3.2). The extent and speed of virus shedding may vary considerably in those infected with SARS-CoV-2 for various reasons. This must be taken into account when defining the endpoint and setting the inclusion criteria (with regard to the time between the onset of symptoms and the latest possible therapy start date), as well as the virological parameters

such as “reduction of viral load” and “negative test result”, and the optimal timing for assessing virological and standardised clinical endpoints.⁶¹

With regard to the clinical development of antivirals for treating highly contagious respiratory infections in the academic context in particular, Germany lacks structures for implementing and conducting, in a swift and coordinated manner, early-stage pilot and feasibility studies, but also phase III studies, on an outpatient and pre-admission basis. Forming a network as part of a coordinated study infrastructure, for example between test centres, outpatient care, care facilities and university outpatient departments, would be key to enabling qualified study staff to identify patients with newly diagnosed viral infections on site and, provided they meet the relevant criteria, include them in clinical studies at university hospitals. A high but temporary volume of patients is a particular challenge during pandemics. During this time, the academic institutions leading the studies should remain in close contact with the aforementioned inpatient and outpatient structures, as well as with patients who are self-isolating at home, for example by implementing flying study nurses and virtual study visits with doctors, in order to ensure that studies are being carried out in a qualified manner at various locations at the same time, with high numbers of patients being recruited. This also requires effective IT infrastructure.

4.3 Industrial development of antivirals

Licensing to an industry partner may be an important step in the development of medication by an academic institution or biotechnology company, especially if large-scale clinical studies (phases II and III) need to be carried out, as these are particularly costly and logistically challenging.

The point in time or stage of development at which a partnership should or can be created for a substance depends on the skills and capacity for cooperation of the academic institution or biotechnology company responsible for its development on the one hand, and on industry interest on the other. If there are funds from which an academic institution or biotechnology company can receive funding for later clinical studies, it may make sense for it to initially forge ahead with the development and pursue authorisation itself, and only to look for a partner when required for commercialisation purposes. The later a partnership for a substance is created with large pharmaceutical companies, the higher the value that remains with the institutions and biotechnology companies behind the development of the substances. Such funds would also enable the advancement of substances which are initially of no interest to large pharmaceutical companies. These decisions should, however, always take into account the skills and expertise of the academic institution or biotechnology company in question and its ability to advance the clinical development of the substances in an efficient and targeted manner and raise the relevant funds itself.

Once a substance has obtained initial authorisation in a country, it must be considered whether and to what extent global distribution makes sense and thus whether authorisation should be sought in other countries. In turn, this may mean that an institution or company needs a distribution partner with a corresponding reach, with which it will have to conclude corresponding licence agreements.

The price of the medication in question is another key issue. Higher prices are generally determined in industrialised countries to enable companies to offset the high development costs incurred with the resulting revenue as quickly as possible. In less developed countries, it is commonplace for

⁶¹ Iwanami, S., Ejima, K., Kim, K. S., Noshita, K., Fujita, Y., Miyazaki, T., ... & Wakita, T. (2021). Detection of significant antiviral drug effects on COVID-19 with reasonable sample sizes in randomized controlled trials: A modeling study. *PLoS medicine*, 18(7), e1003660.

medication or licences enabling national companies to produce the medication themselves to be offered at significantly lower prices, thus enabling such medication to also be supplied in these countries. Examples include HIV and HCV infection therapies (see Chapter 3.1). These basic conditions are also important for COVID-19.⁶²

5. Broad-spectrum antivirals as a preparatory measure for future pandemics

5.1 General considerations on broad-spectrum antivirals

Vaccines, diagnostics and medication all play an important role in pandemic preparedness. However, it is not usually possible to predict in advance which of these measures will prove most successful. For example, there are viruses against which, despite years of intensive research to date, it has not been possible to develop an effective vaccine (e.g. HIV, HCV or respiratory syncytial virus RSV).

It is not possible to predict which virus will cause the next epidemic or pandemic. However, it is highly likely that the next pandemic will be caused by a respiratory virus, since these are transmitted particularly effectively via droplets and aerosols. Influenza A viruses have caused devastating pandemics in the past, such as the Spanish flu in 1918 (H1N1), estimated to have resulted in up to 50 million deaths worldwide, the Asian flu in 1957 (H2N2), estimated to have resulted in up to 4 million deaths worldwide, and the Hong Kong flu in 1968 (H3N2). Other virus families also have the potential to trigger a pandemic, such as flaviviruses like dengue and Zika viruses, or other coronavirus types.

The WHO has compiled a corresponding list of possible pandemic pathogens (*Prioritizing diseases for research and development in emergency contexts*), which is regularly updated.⁶³ According to the list, illnesses resulting from the following are to be considered as a matter of priority in terms of the further research and development of active substances:

- COVID-19
- Crimean-Congo haemorrhagic fever
- Ebola and Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome (MERS)
- Severe acute respiratory syndrome (SARS)
- Nipah and henipavirus diseases
- Rift Valley fever
- Zika virus disease

Antivirals available to date against viruses such as HIV and HCV are highly specific and optimised to have the greatest impact against the pathogen in question, whilst having the smallest impact on the cell, in order to achieve excellent tolerability. However, the time frame for developing such substances is usually very long – for HIV it took 10 years from the discovery of the virus to the development of antiviral therapy, and for HCV it took around 25 years to develop a well-tolerated curative therapy. While, in all likelihood, less time will be needed to develop specific medications targeting SARS-CoV-2 owing to numerous research projects, it will remain to be evaluated how

⁶² This was also illustrated in the “Commitments to Expanded Global Access for COVID-19 Diagnostics, Therapeutics, and Vaccines” declaration, which was signed by the Bill & Melinda Gates Foundation and 16 pharmaceutical companies. This established, for example, that top priority should be given to ensuring that antiviral medication is affordable and swiftly available and that innovations in this area should be made available to individuals around the globe. See www.gatesfoundation.org/ideas/media-center/press-releases/2020/09/commitments-to-expanded-global-access-for-covid-19-diagnostics-therapeutics-and-vaccines (last accessed: 9 November 2021).

⁶³ Available at: www.who.int/blueprint/priority-diseases/en (last accessed: 9 November 2021).

effective these substances are in everyday clinical practice, how quickly resistance is built up and how they should be combined.

For future pandemics, this process of developing medication only upon the emergence of a new pandemic virus is too slow. Advancing the development of active substances before the emergence of possible future pandemics is therefore strongly recommended. One approach to preparing for an as yet unknown virus is developing broad-spectrum antivirals, namely substances which not only target one specific virus, but cover an entire group of viruses. This would mean that the substances are not only effective against SARS-CoV-2, for example, but also against any emerging coronaviruses which have sufficiently similar properties and would thus also be covered by this medication. Therefore, in the event of another pandemic with a coronavirus, an initial antiviral therapy would be immediately available and could buy time until more specific and more effective medication becomes available.

5.2 Development of broad-spectrum antivirals

The principle of broad-spectrum agents, known from antibiotics therapy, is still poorly established in the field of virology. This is due to the specific differences between viruses and bacteria. Bacteria have their own metabolism, which differs considerably from that of a human cell. As such, bacterial species offer target sites which are common to several bacterial species. This is in contrast to viruses, which are obligatory cell parasites and primarily use cellular functions and therefore only offer very few virus-specific target sites. In addition, the RNA genomes of viruses in particular change continuously and rapidly owing to mutations. As a result, the structures of possible viral target sites may vary significantly between individual virus types, and in particular between viruses from different virus families.

There are three main approaches to overcoming this challenge to develop broad-spectrum antivirals: The first is to choose those structures and functions of the viruses as a target which are as conserved as possible between different viruses, i.e. targets that are constant over longer periods of time (see Chapter 3.2). These are predominantly **essential virus factors** like enzymes (proteases, polymerases), where changes (mutations) near to the active site essential for enzyme function may lead to considerable loss of function for the virus. Since these enzymes are similar in many coronaviruses which infect humans, inhibitors of these enzymes would have a broad-spectrum effect.

The second approach consists of selecting as target sites those **cellular factors** which are needed for viral replication, such as the main receptor ACE2 on the cell surface. Since this is a cellular component, it remains constant; at the same time, as far as is known, it is used by the SARS-CoV-2 variants as main receptor, with other coronaviruses like SARS-CoV and the “common cold coronavirus” HCoV-NL63⁶⁴ also using this receptor. Substances targeting this receptor therefore have a certain broad-spectrum effect.

A potential third approach to achieving a broad-spectrum effect relates to substances which stimulate the **immune system** in such a way as to make cells less receptive to a viral infection. Such an effect may be achieved through treatment with interferons or other substances which activate

⁶⁴ Hofmann, H., Pyrc, K., van der Hoek, L., Geier, M., Berkhout, B., & Pöhlmann, S. (2005). Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. *Proceedings of the National Academy of Sciences of the United States of America*, 102(22), 7988–7993.

innate immunity.⁶⁵ This strategy would achieve higher levels of resilience against a viral infection, thus promoting considerably milder courses of infection.

The process for developing broad-spectrum antiviral medication is comparable with that for specific antivirals (see Chapter 3.2), the difference being, however, that the selection of target sites is restricted to meet the aforementioned criteria. Here, too, large collections of chemical substances can be analysed with regard to their inhibitory effect on the target structure, or collections of drugs which have already been characterised and authorised (drug repurposing). The substances identified during this search will first be evaluated to determine their effectiveness against analogous structures of closely related viruses (such as SARS-CoV-2 variants and other coronaviruses which may infect humans and certain animal species) and, should their broad-spectrum effect be sufficient, then be optimised further by applying chemical modifications.

In addition to analysing collections of chemical substances, consideration should also be given to the development of antibodies targeting highly conserved viral structures. Detailed analyses of immune response following a SARS-CoV-2 infection have enabled antibodies which are highly effective at binding to the spike protein of the virus and preventing infection to be identified and produced on a large scale within a short period of time.

Developing antibodies or smaller variants thereof (known as nanobodies⁶⁶) which target certain structures in the spike protein, which are highly conserved in coronaviruses, or using ACE2 fusion proteins which are able to neutralise various coronaviruses or Variants of Concern represent additional opportunities for developing broad-spectrum antivirals. In addition, antibodies and particularly nanobodies,⁶⁷ as well as small-molecule antiviral substances can be developed and combined in a targeted manner to achieve a synergetic effect and hamper the development of resistance.

The intended broad-spectrum effect might have a detrimental effect on the antiviral activity against individual members of a virus group. Combining substances with different mechanisms of action is expected to mitigate this effect. When using substances targeting cellular factors, toxicity must also be very closely monitored. Only cell factors where inhibitory effects are tolerated by the cell or organism should be considered. It should be taken into account, however, that the duration of the therapy will be relatively short owing to the acute course of a COVID-19 infection (see figure 2) and that toxic side effects, which occur in particular during long-term treatment, will likely be of less relevance.

⁶⁵ Coch, C., Stümpel, J. P., Lilien-Waldau, V., Wohleber, D., Kümmerer, B. M., Bekeredjian-Ding, I., ... & Hartmann, E. (2017). RIG-I activation protects and rescues from lethal influenza virus infection and bacterial superinfection. *Molecular Therapy*, 25(9), 2093-2103. Bartok, E., & Hartmann, G. (2020). Immune sensing mechanisms that discriminate self from altered self and foreign nucleic acids. *Immunity*, 53(1), 54-77. Loske, J., Röhmel, J., Lukassen, S., Stricker, S., Magalhães, V. G., Liebig, J., ... & Lehmann, I. (2021). Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. *Nature Biotechnology*, 1-6. Paulsen, D., Urban, A., Knorr, A., Hirth-Dietrich, C., Siegling, A., Volk, H. D., ... & Weber, O. (2013). Inactivated ORF virus shows antifibrotic activity and inhibits human hepatitis B virus (HBV) and hepatitis C virus (HCV) replication in preclinical models. *PLoS One*, 8(9), e74605. von Buttler, H., Siegemund, S., Büttner, M., & Alber, G. (2014). Identification of Toll-like receptor 9 as parapoxvirus ovis-sensing receptor in plasmacytoid dendritic cells. *PLoS one*, 9(8), e106188.

⁶⁶ Nanobodies are antibody fragments which occur naturally in certain animal species (e.g. camels), but can also be manufactured using genetic modification. Owing to their small size, nanobodies are particularly well suited to therapeutic applications.

⁶⁸ GMP is a set of guidelines designed to ensure that medicinal products and active substances are produced in accordance with quality assurance standards.

Box 3: Links to the development of symptomatic therapies

Symptomatic therapies predominantly play a role in the later phases of an infection (see figure 2) and must be clearly distinguished from antiviral approaches, which primarily take effect in the early stages. Pathophysiological processes which are common to different viruses with pandemic potential should also be taken into account in symptomatic therapies to the extent possible with a view to achieving a broad-spectrum effect. Such processes include inflammatory responses, which in SARS-CoV-2 and other infections are generally caused by the excessive production of messenger substances (known as cytokines) and can be clinically treated through the use of immunosuppressants (e.g. steroids). Other examples are acute respiratory failure or disorders of the coagulation system or vascular functions. The development of targeted symptomatic therapies requires thorough knowledge of molecular processes and a comparison across different groups of viruses with pandemic potential. Based on this, corresponding therapy concepts can be developed, in line with the process for antivirals.

5.3 Structures required for the development of broad-spectrum antivirals

As a matter of principle, broad-spectrum antivirals targeting several pathogens with pandemic potential are required. Furthermore, more than one single substance is required per virus group where possible, owing to the risk of resistance developing, and substances should be combined to enhance the potentially only moderate antiviral activity against the new pathogen (see Chapter 5.1). The development of medication with broad-spectrum effectiveness is subject to a wide range of requirements, since special expertise and infrastructure are required for each virus family, including high-security laboratories for handling viruses with pandemic potential (BSL-3 and BSL-4 laboratories), appropriately trained staff as well as adequate cell culture systems and animal models.

The infrastructures available at universities and non-university research institutes which could be used in the development of antivirals are currently scattered across Germany; there is no one location at which all of the elements required for this process can be found. Establishing an organisational structure which links the necessary infrastructure therefore appears to make sense as a component of efforts to ensure future pandemic preparedness. This structure could be created through associations of or cooperation between academic institutions (at both the national and international level) and biotechnology companies and supplemented by outsourcing to commercial providers, for example with regard to medicinal and pharmaceutical chemistry and the manufacture of active substances in accordance with GMP regulations.⁶⁸

Box 4: One health approach

In any case, the research and development approaches selected should follow the one health approach. This recognises that the health of humans is closely connected to the health of animals and the health of the environment, and the fact that pandemics are generally caused by pathogens from the animal kingdom.

Around two thirds of infectious diseases affecting humans originally stem from animals, with zoonoses accounting for over three quarters of emerging human infections. SARS-CoV-2, too, is a zoonotic pathogen, meaning that it stems from the animal kingdom, replicates in humans and can also be retransmitted from humans back to animals⁶⁹ – and from these new reservoirs then back to humans again, as documented in mink

⁶⁸ GMP is a set of guidelines designed to ensure that medicinal products and active substances are produced in accordance with quality assurance standards.

⁶⁹ Measures taken to combat infections in animals primarily focus on prophylaxis through vaccination. Vaccines against SARS-CoV-2 infections in animals (e.g. fur animals in breeding farms, susceptible pets such as cats, and zoo animals like big cats and primates) are already in use or under development. Antiviral therapies are primarily of relevance for the individual treatment of animals kept in captivity, though SARS-CoV-2 infections in these animals have only led to severe illness and fatal outcomes in a small number of cases, the majority of which associated with pre-existing conditions.

farms, for example.⁷⁰ The close linkages between the health of humans, animals and the environment (one health approach) must therefore be taken into account when devising preparatory measures for new pandemics.

Furthermore, reducing contact between (wild) animals and humans may help to minimise the risk of transmitting infectious zoonotic pathogens. In this regard, the early detection of chains of infection is also key, since it enables containment measures to be implemented in a timely manner. The newly established *One Health High Level Expert Panel* is currently drawing up proposals on this matter.⁷¹

This network should also include representatives from regulatory bodies – as well as the policy makers responsible in an emergency situation – with the objective of advancing necessary research and development of broad-spectrum therapies up to completion of a comprehensive clinical phase I characterisation (phase I; see box 2) in order to make effective therapies available much more rapidly.⁷² Existing German centres for health research or university hospital networks⁷³ could make significant contributions in this regard.⁷⁴

Since the development of broad-spectrum antivirals targeting future pandemic pathogens which might never emerge poses a financial risk to pharmaceutical and biotechnology companies, most research and development work will need to be funded by the government. Government aid will also be required if a new pathogen emerges to make new medication available as quickly as possible.

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⁷⁰ A wide range of animal species, such as cats, dogs, minks and zoo animals (big cats and primates), have proven to be susceptible to SARS-CoV-2. See Michelitsch, A., Wernike, K., Ulrich, L., Mettenleiter, T. C., & Beer, M. (2021). SARS-CoV-2 in animals: From potential hosts to animal models. *Advances in Virus Research*, 110: 59–102. Retransmission of SARS-CoV-2 from humans to animals has already been observed in isolated cases and should continue to be prevented through vaccination and testing of animal care workers.

⁷¹ Established by the World Health Organization (WHO), the World Organization for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO) and the United Nations Environment Programme (UNEP): <https://www.who.int/news/item/20-05-2021-new-international-expert-panel-to-address-the-emergence-and-spread-of-zoonotic-diseases> (last accessed: 9 November 2021).

⁷² See, for example, the concept proposed by the National Alliance for Pandemic Therapeutics (NA-PATH), available at: www.dzif.de/system/files/document/Konzept%20-%20Nationale%20Allianz%20f%C3%BCr%20Pandemie-Therapeutika_2.pdf (last accessed: 9 November 2021).

⁷³ See, for example, Netzwerk Universitätsmedizin (university hospital network), available at: www.netzwerk-universitaetsmedizin.de/aufgaben-und-ziele (last accessed: 9 November 2021).

⁷⁴ See also www.gesundheitsforschung-bmbf.de/de/deutsche-zentren-6580.php (last accessed: 9 November 2021).

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Please note: The scientists involved are required, under the published “Rules for dealing with conflicts of interest within science-based consulting work” (“Regeln für den Umgang mit Interessenkonflikten in der wissenschaftsbasierten Beratungstätigkeit“, German only), to cite any circumstances which could lead to conflicts of interest. Reference is also made to the rules set out in this document.

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