NA-PATH

National Alliance for Pandemic-Therapeutics

A joint initiative of the German Center for Infection Research (DZIF)
and the Helmholtz Centre for Infection Research (HZI)

DZIF
German Center
for Infection Research

HZI HELMHOLTZ
Centre for Infection Research

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Provision of broadly effective and rapid available therapeutics for handling of future pandemics

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Content

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SUMMARY

The current SARS-CoV-2 pandemic shows how devastating emerging, uncontrollably spreading infectious agents can be. Since new major outbreaks of infection in humans are to be expected at any time, better **preparation for future pandemics is imperative**.

Active **substances specifically adapted to the respective infection process** are an essential component for successful pandemic management. Therapeutics are needed as early as possible in the pandemic to limit the number of severe disease progressions and deaths. However, neither the timing nor the causative agent of the next pandemic can be predicted. For that reason, there are substantial challenges in the provision of suitable infrastructures as well as market-based risks that complicate and delay the development of pandemic therapeutics, as has been shown in the current pandemic. These limitations apply to both academic research and the industrial sector, as well as their cross-sectoral cooperation.

We therefore propose to establish a novel strategic alliance of science, industry, regulatory authorities and politics as the „National Alliance for Pandemic Therapeutics" (NA-PATH), charged with providing the necessary research and development (R&D) – up to the first clinical testing – of active substances even in non-pandemic times in order to be able to make available effective therapies much faster in the event of a crisis. This alliance builds on the already successfully established structures and mechanisms of the German Center for Infection Research (DZIF) and the Helmholtz Centre for Infection Research (HZI), specifically strengthening them for the rapid and effective development of a portfolio of pandemic therapeutics through to clinical trials.

NA-PATH focuses on selected and continuously updated **pathogen groups with a high pandemic potential** (at present influenza, corona and flaviviruses). For the optimal preparation against an unknown pathogen from these groups, NA-PATH focuses on therapeutics with **cross-pathogen efficacy, platform technologies** with rapid clinical development potential, and approaches for the **symptomatic therapy** of significant complications. The planned approaches also include treatment concepts that are based on the body's own broadly effective defence principles

(such as immune stimulators) or on the identification of highly specific immune receptors (e.g. antibodies) against particularly conserved pathogen targets. In addition to freely or commercially available drug libraries, NA-PATH will draw on other **drug sources**: Drug repurposing banks that are particularly suitable for the discovery of active ingredients against host target structures, nucleoside-based agents that have achieved outstanding success in the past in the development of antiviral therapeutics, and previously underutilised sources of naturally occurring substances.

The successful establishment of these approaches up to accelerated product approval in the event of a pandemic requires the availability of **technology platforms** that include all work steps from the discovery, optimization and profiling of the active substance to the preclinical and clinical testing of Phases I and IIa. Project-related, flexible funding as well as targeted investments in the specialist and project management expertise of the participating institutions results in the long-term strengthening and professionalisation of R&D for pandemic therapeutics. In contrast to conventional R&D projects, the selection and continuous evaluation of all NA-PATH technology platforms and projects is strictly **guided by purpose** (therapeutics for future pandemics) and flexible prioritisation in relation to the then current global pandemic risk assessment. To this end, recourse can be taken to the mechanisms already developed within the DZIF for project management and success monitoring of large clinical development projects, adapted to the specific requirements of NA-PATH.

At the latest with achieving the milestone of clinical proof-of-concept (Phase IIa), an opportunity arises for the value-based licensing of intellectual property rights to the biotechnology and pharmaceutical industry or for spin-offs and thus **connectivity for the NA-PATH product candidates**. Relevant expressions of interest have already been received from the pharmaceutical industry. In addition, NA-PATH product candidates at various levels of technology maturity are suitable for targeted funding or financing by future planned national or European sponsors, which could be modelled on the US agency BARDA[1]. The overarching goal is the rapid response to an outbreak, i.e. the scaling of manufacturing technologies, the accelerated conduct of clinical trials and the approval of the products by the regulatory authorities.

[1]Biomedical Advanced Research and Development Authority

A. VIRAL EPIDEMICS AND PANDEMICS AS A CENTRAL SOCIETAL CHALLENGE

The **COVID-19 pandemic**, which has been rampant for more than a year, has made it abundantly clear to the population that the world is insufficiently prepared for major outbreaks by new or re-emerging infectious agents, especially viral ones. The pandemic caused by SARS-CoV-2 is the **most severe outbreak** since the Great Influenza of 1918/19; it has caused over 160 million confirmed infections worldwide in just over a year and has already claimed around 3.5 million lives (as of May 2021). The **global economic costs** have exceeded the enormous sum of US$10 billion[2], while the **long-term** health consequences as well as the medium- and long-term societal impacts associated with significant social constraints cannot yet be estimated.

Although the pathogen families with the greatest pandemic potential can be narrowed down reasonably clearly, respiratory-transmissible but also other viral infections in particular pose enormous challenges for globally networked societies of the 21st century due to their variability and dynamics. The observed **globally increasing incidence** of emerging infections is accelerated by urbanization, globalization and the immediate consequences of climate change. In the past 15 years, WHO alone has declared six infection-related global health emergencies. The occurrence of further severe pandemics is thus but a matter of time. We know they will come; we just don‘t know which ones and when.

Despite the gratifying progress in the d**evelopment of preventive vaccines**, such as the record-time introduction of mRNA-based vaccines against SARS-CoV-2, there is still a glaring **lack of effective antiviral therapies**. For example, in the spring of 2021, there are vaccines approved by the EMA, but still no effective antiviral drug against SARS-CoV-2. Despite successful vaccination campaigns, antiviral drugs are an urgent necessity for the effective treatment of viral infections, prevention of severe and fatal courses and for bridging the development time for further vaccines (e.g. against virus mutants).

Currently, no specific therapies are available for any of the viral pathogens[3] prioritized by the WHO, not even against the SARS coronavirus that had already led to epidemic outbreaks in more than 20 countries in 2003. This shows that despite major international efforts (WHO Research and Development Blueprint[4], CEPI[5]), there are still large **gaps in the innovation process**, and that the hurdles of long development times for therapeutics as well as a lack of market incentives for the pharmaceutical industry must be overcome.

In a comprehensive analysis of pandemic preparedness and management[6], the **European Commission** recently made a clear recommendation for the long-term promotion of biomedical innovation in order better to be prepared for future pandemics. Suitable support and acceleration in the field of diagnostics, therapy and prevention is to ensure that short- and medium-term pandemic management strategies are available in time to limit the health, economic and social consequences of a pandemic. In a recent position paper[7], the **German Council of Science and Humanities** also pointed to the need for urgent action for a better handling of future pandemics, especially regarding the faster translation of research results into clinical application.

[2]Dobson *et al.* (2020), Science 369:379-381
[3]https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts
[4]https://www.who.int/teams/blueprint/covid-19
[5]https://cepi.net
[6]Improving pandemic preparedness and management, European Commission, 2020
[7]Impulse aus der COVID-19-Krise für die Weiterentwicklung des Wissenschaftssystems in Deutschland, Wissenschaftsrat, 2021

In recent years, **preparing for the unknown** has proven a powerful approach to accelerated development not only in epidemiology, but also in vaccine research in terms of effective and innovative vaccine platforms. This approach must now also be given the appropriate and necessary status in therapeutic development, in reflection of its **systemic relevance**.

As part of a sustained paradigm shift, a structured cooperation between the various actors from science, industry, regulatory authorities and politics across organisational and national borders is imperative. Long-term funding **formats for the entire value chain** are intended to contribute towards the sustained upgrading and acceleration of drug development.

B. BASIS FOR A NATIONAL ALLIANCE FOR PANDEMIC THERAPEUTICS

Viruses are almost completely dependent on functions of the host cell for their multiplication, with only a few steps in the infection process being directly mediated by the virus. Accordingly, there are only a few targets for antiviral agents that selectively interfere with the function of a particular virus component without affecting the host cell in parallel. For that reason, into the 1990s, the **development of antiviral agents** had been based on accidental discoveries. As a general rule, there was no specific treatment for viral infections. Thanks to the by now significantly improved knowledge of molecular pathogen-host interactions and technological advances, it has been possible, for example against HIV-1 or hepatitis C virus, to develop a large number of specific drugs directly targeted at the virus, resulting in a dramatic decline in AIDS and hepatitis C worldwide. Because of the risk of rapid development, the combination of several active substances has proven its worth. In principle, it is thus possible to develop **effective antiviral therapies with minor side effects** in order to combat major epidemics.

In the two cases mentioned, however, the pathogens were known and very well researched with a large number of chronically infected persons worldwide. In each case, the antiviral drugs are specifically directed against certain structures of the respective pathogen and often show little or no efficacy even against close relatives from the same virus family. So what is different if we want to **prepare for the next pandemic**?

- We do not know the pathogen and can only predict the virus families that currently have the highest pandemic potential. Accordingly, active substances with a broader efficacy range and drug combinations with good effectiveness against various pathogens must be developed and tested.

- There is no or only a **limited market** for the economic development of active substances against emerging and currently unknown pathogens of pandemic potential. So far, this task has therefore been largely limited to basic research activities by individual research groups within academia.

Against the backdrop of these challenges, the following aspects form the essential basis of the **National Alliance for Pandemic Therapeutics**:

1. **Definition of the virus families** with the greatest probable pandemic potential. This is currently mainly seen for **RNA viruses** from the groups of influenza viruses (viral flu), coronaviruses (SARS) and flaviviruses (such as Zika, dengue). The known pathogens of these virus groups

already lead to a high disease burden and mortality worldwide, and they were responsible for the largest epidemics and pandemics of modern times (Table 1). For all these virus families, there are extensive and largely unexplored animal reservoirs that can lead to a new epidemic or pandemic with an as yet unknown pathogen. For that reason, NA-PATH will initially focus on this **zoonotic virus families**.

Table 1 | List of the largest epidemics and pandemics in the past 100 years

Virus	year of the first outbreak	case number	number of deaths	number of affected countries
H1N1 (Spanish flu)	1918	500,000,000	> 20,000,000	worldwide
Ebola	1976	33,577	13,562	10
Dengue	1981	100,000,000	38,000	25
H5N1, H7N9 (Bird flu)	1997	2,429	1,071	18
SARS	2002	8,096	774	29
MERS	2012	2,494	858	28
Zika	2015	900,000	-	87
SARS-CoV-2*	2019/2020	> 167,350,000	> 3,475,000	worldwide

*in Covid-19 case and death rates, status: May 2021

2. **R&D of broadly effective agents** with good efficacy against different viruses and the development of symptom-oriented treatment approaches against severe disease progressions. At present, antiviral agents are directed as precisely as possible against target structures of the respective virus, but often already proven ineffective against closely related pathogens or pathogen mutants; an effect against a new pathogen can thus only be expected serendipitously. By contrast, the NA-PATH conducts research and development of active substances that are effective against as many and as different pathogens as possible from one or more virus families. For a broad efficacy, certain losses in potency may be accepted in turn. As part of the development, the candidates are tested against as diverse a group of pathogens as possible of the respective virus family (from humans and various animal species), with prioritisation of those substances with the ability **to inhibit as many pathogens as possible**. In the case of coronaviruses, tests would therefore be conducted against the seven known coronaviruses of humans[8] as well as against coronaviruses e.g. from bats. **Specific developmental goals** are directed towards (i) inhibitors of viral functions that are as similar as possible in the various pathogens, (ii) inhibitors of cellular functions that are required for the multiplication of as many different viruses as possible, but that at least temporarily are not essential for the host organism, (iii) active substances that stimulate the innate immunity of the host and the individual host cell non-specifically and against a range of pathogens, and (iv) active substances that are derived from the host's pathogen-specific immune response and that are produced synthetically or in a modified form, where required. In addition, symptom-oriented therapies against severe forms of viral infections are to be developed, which are particularly important in the later stages of the disease and which can be similar for different pathogens. The individual approaches are described in more detail in Section D.

3. **Establishment of a product pipeline** from the identification, optimisation and characterisation of individual active substances via preclinical to early clinical development in an organisation specifically and exclusively oriented towards this objective that builds on and is integrated into the established DZIF/HZI structures (Figure 1). NA-PATH will present researchers and

[8]HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, MERS-CoV, SARS-CoV, SARS-CoV-2

developers with broadly coordinated target product profiles, along which product development will be promoted. Candidate connections will be evaluated on the basis of previously agreed detailed requirement specifications and in a formal approval process nominated for the cost-intensive development.

The planned product pipeline requires the direct and intensive cooperation of key stakeholders from academic science, industry, regulatory institutions as well as national and international funding organisations and politics. There will be a direct involvement of research infrastructures - existing ones and those currently under development - within the framework of the Network University Medicine (NUM) and the Medical Informatics Initiative.

The entire optimisation and development process is evaluated in all steps by means of **milestones and Go/NoGo criteria** to determine whether the continuation is expedient and feasible. Key **partners from science and industry** will be contractually involved, and the necessary infrastructures and capacities will either developed within NA-PATH or bindingly secured with the partners. The governance required for this is based on the structures of the Product Development Unit developed within the DZIF, including the regulatory arm, as well as the interdisciplinary and cross-sector Project Advisory Groups with the involvement of representatives from industry, regulators and venture capital, who regularly accompany ongoing development projects, evaluating them with regard to progress and Go/NoGo criteria and issuing recommendations to the executive board as to which projects can be continued and in what manner. In this way, quality-oriented and connectable product development up to clinical Phase I/IIa can thus be carried out within the NA-PATH framework (Fig. 2). For the subsequent phases of the clinical trial up to (conditional) approval, industrial licensees are required and – especially for projects without direct economic sales potential – a support mechanism that is geared to public health requirements (Fig. 1). Within the DZIF, for example, two products have already been brought to approval by in-licensing pharmaceutical companies in a partnership process.

In the case of efficacy against known circulating pathogens, industry can take on the further development to approval of successful product candidates. Should there be no current feasibility for efficacy studies and no market potential, accelerated and parallelised development to approval in the event of an epidemic or pandemic threat could be prepared with the aid of national or European agencies still to be established.

C. ESTABLISHMENT AND FUNCTIONING OF THE NATIONAL ALLIANCE FOR PANDEMIC THERAPEUTICS

The National Alliance for Pandemic Therapeutics is intended to ensure the **necessary paradigm shift** in response management to future pandemic pathogens. The overarching task is the development of broadly effective antiviral therapeutics for the treatment of emerging viral pathogens. This is to contribute to reducing the burden of disease and to the early control and containment of future pandemics. To this end, research and development staff from leading German infection research centres under the **leadership of DZIF and HZI** will be specifically focused on crucial fields of innovation with the greatest potential for the development of effective therapeutics. Na-PATH relies on cooperation between academic research institutions with a special expertise and availability of highly relevant infrastructures in the field of infection research, university hospitals, the pharmaceutical and biotechnological industries as well as regulatory authorities and politics (Fig. 1).

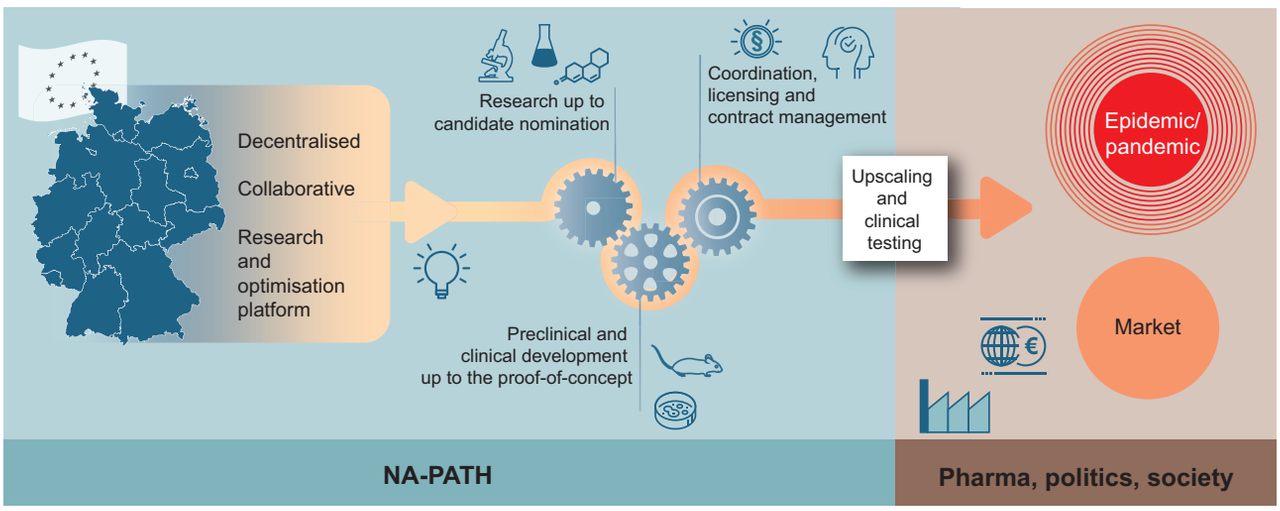


Fig. 1 | Establishment and functioning of NA–PATH

The **decentralised platform** of scientific disciplines and technologies for the research and optimisation of new low-molecular and biological agents forms the basis of the NA-PATH. On this platform, the individual projects are being carried out. Qualified project managers organise the interface between platform and project. It is a **unique combination** of selected infrastructure, expertise and interdisciplinary cooperation between German and European partners (Fig. 1).

NA-PATH will focus mainly on **two indispensable and high-performance product classes** – synthetic molecules or natural products as well as biologic agents (Fig. 2). The platform will give rise to a portfolio of promising preclinical development candidates for future therapeutics; advanced candidates can also be introduced into the portfolio at any stage of development. The further clinical development up to (conditional) approval and their upscaling can then be achieved either by licensing to biotechnology or pharmaceutical companies, by spin-offs or by higher-level national or European organizations.

The work of the platform is managed by a central **governance structure**, involving representatives from politics, industry, higher federal authorities (RKI, BfArM, PEI) as well as DZIF and HZI. All activities of the platform are immediately and directly focused on the development of broadly effective therapeutics against potential pandemic pathogens and are evaluated and assessed at each step with regard to this target orientation.

The accelerated research and optimisation of broadly effective antiviral therapies requires **capacity building** in critical specialist and management areas. R&D output is increased by targeted technical **reinforcements in important key areas**, such as immune cell or receptor engineering, the use of AI approaches in the medical-chemical optimisation of active substances and the modelling and prediction of pharmacological parameters. To this end, the platform will be equipped with **dedicated product developers**. In contrast to fundamental academic research, direct product orientation and entrepreneurial spirit are crucial qualities for these scientists. They operate units that play a decisive role in the preclinical R&D process. Examples are the qualification of active principles in human organoid cultures and predictive animal models. Finally, capacities for project management and technology transfer will be created in order to ensure a **consistently streamlined** project implementation and to coordinate communication between the structures of the NA-PATH platform and external stakeholders. The successful DZIF Product Development Unit can serve as a blueprint and nucleus. In this way, NA-PATH will already significantly accelerate the development, validation and preclinical and clinical development up

to Phase IIa in non-pandemic times in order to provide the most advanced agents against the respective pathogen in the event of a future epidemic or pandemic (Fig. 3).

Wherever scientifically, clinically and economically reasonable and possible, **NA-PATH exploitation partners** will further develop the product candidates through Phases II and III clinical trials for proper approval in commercial indications and markets (example: seasonal influenza therapy) (Fig. 2). **Spin-offs of start-ups** for the further development of early NA-PATH drug candidates are also to be made possible. To this end, NA-PATH will establish a technology transfer office with the remit of creating and publishing meaningful technology offers on behalf of the central governance structure and in close coordination with the patent offices of the NA-PATH member institutions, discussing the NA-PATH product portfolio at conferences and trade fairs and preparing licensing negotiations with third parties. In addition to direct licensing, scientific cooperation between public and private partners in conjunction with an option for subsequent licensing of intellectual property rights by the company can also promote the necessary technology transfer. Preliminary discussions have already been held with VFA[9], who support the present concept. A direct approach of SMEs through the NA-PATH technology transfer ensures that even companies without an active Business Development are provided with cooperation and licensing opportunities. In this process, an important mediating role is given to the interest groups representing biotechnology in Germany, specifically Bio Deutschland, VBU and DIB[10].

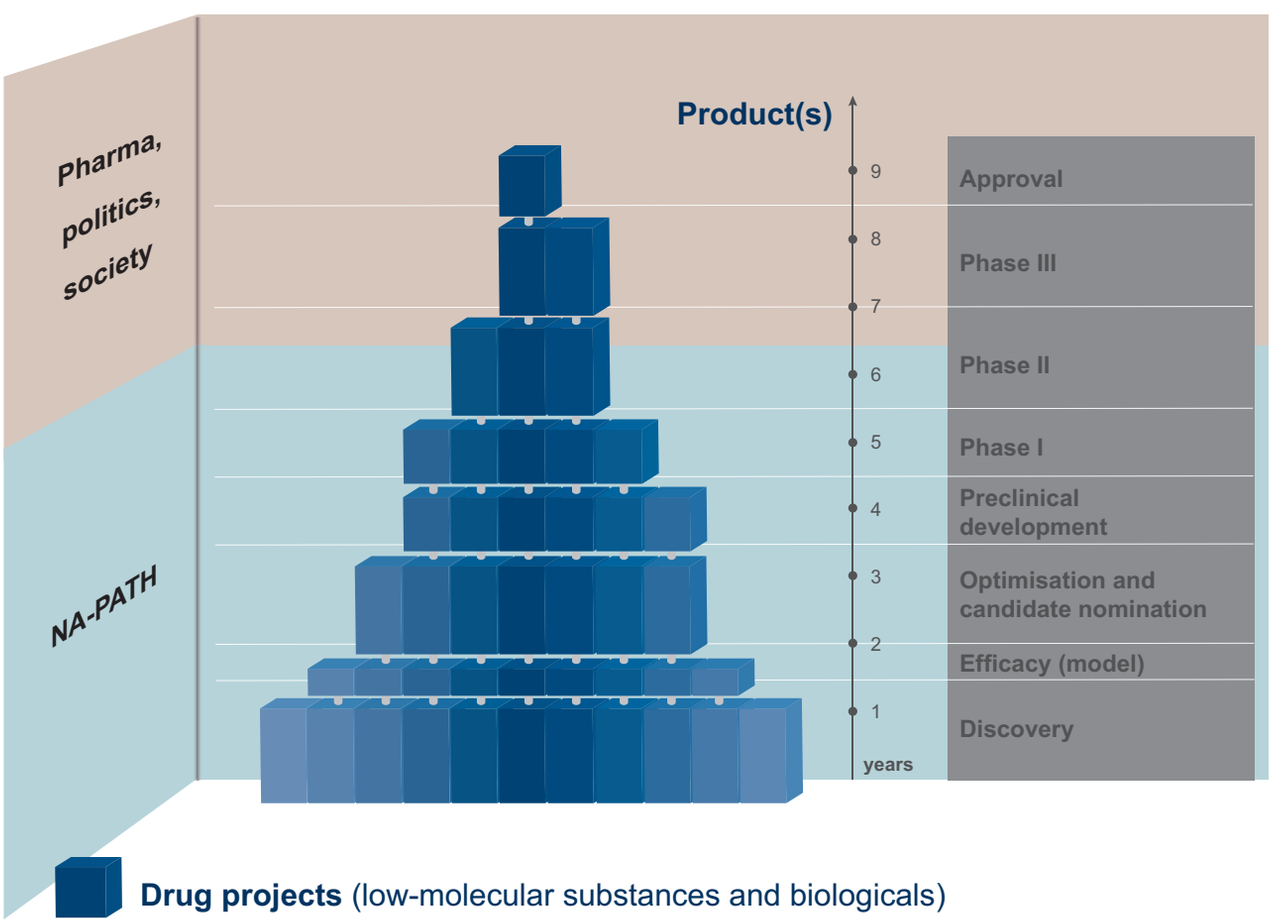


Fig. 2 | Schematic representation of the conventional development phases for low-molecular active substances and biological agents with average duration and success rate; NA-PATH addresses the development up to Phase IIa (light blue shading). In the event of a non-pandemic, successful NA-PATH product candidates can be further developed by exploitation partners until proper approval

[9]Verband Forschender Arzneimittelhersteller
[10]Bio Deutschland, Branchenverband der Biotechnologie-Industrie; VBU, Vereinigung Deutscher Biotechnologie-Unternehmen; DIB, Deutsche Industrievereinigung Biotechnologie

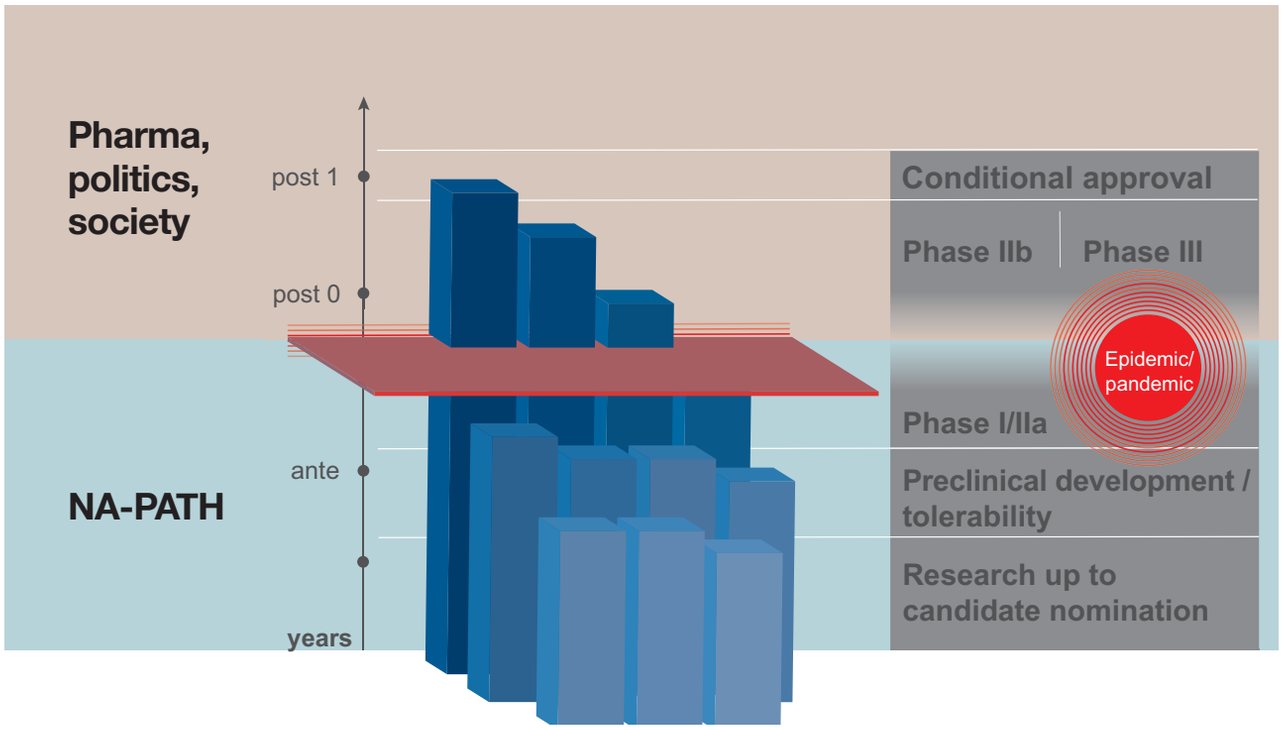


Fig. 3 | How NA-PATH works in the event of a pandemic. The aim is to transfer NA-PATH product candidates that have already successfully completed Phase I (possibly Phase IIa) in a development period of 5 - 7 years into a time-streamlined, possibly parallelised process, which envisages the implementation of the late clinical phases, the upscaling of production and the accelerated (conditional) market approval within one year.

Further product development beyond this in the event of a **pandemic requires** the commissioning of companies by a yet to be created governmental organisation. For this purpose, preclinical and, above all, early clinical product candidates from a significantly accelerated and expanded development (e.g. Phase II/III, this in close coordination with the regulatory authorities) are introduced and brought to (conditional) approval (Fig. 1, Fig. 3). At its core, this involves scaling up the production and release of clinical trial specimens, expanding the production towards market-standard goods and applying for approval.

D. PRODUCT PORTFOLIO FOR THE PROVISION OF ANTIVIRAL THERAPEUTICS

For the development of therapeutics against viral pandemic pathogens, the focus will be on **two complementary areas of intervention**:

(1) Antiviral therapy

In the development of targeted antiviral therapeutics, the main focus is on two complementary areas of potential in order to address the special challenges in the development of therapies against viral pathogens with pandemic potential:

[10]Bio Deutschland, Branchenverband der Biotechnologie-Industrie; VBU, Vereinigung Deutscher Biotechnologie-Unternehmen; DIB, Deutsche Industrievereinigung Biotechnologie

a) The use of unique drug sources for the identification and development of active substances against **conserved target structures of pathogens and host**. All viruses are incapable of reproduction on their own. In receptive body cells, they exploit the body‘s own processes in order to multiply. The **interfaces between pathogen and host** (such as the contact point between the viral envelope protein and a cellular receptor) are obvious targets. In some cases, they are also used simultaneously by several related pathogens. This makes them particularly important targets for therapy development. In addition, drug discovery focuses on crucial **viral enzymes such as polymerases and proteases**, and in particular their conserved active centres. These are often less adaptable and can be very similar in different pathogens. NA-PATH will therefore place a special focus on the development of new inhibitors of viral polymerases based on **nucleoside or nucleotide analogues** with a broad spectrum of action. In the field of active ingredients, **special substance collections** are specifically examined for active substances that address conserved therapeutic goals. On the one hand, this includes **drug repurposing banks** whose molecular targets are known and that are particularly suitable for finding targets in the host. It is known from antibiotic research that new principles of action against bacteria are often found in the field of **naturally occurring bacterial substances**. Bacteria are in constant competition with each other and have developed chemical defences to prevail in the competition. In this process, bacteria are also exposed to numerous viral attacks. In addition, they have developed messengers and defence substances for the colonisation of human tissues or human cells in order to nest and reproduce. For this reason, the unique active ingredient repertoire of naturally occurring bacterial substances is to be systematically searched for **active ingredients against conserved virus/host targets** in emerging pathogens. The use of unique drug sources for the development of innovative therapeutic approaches requires a strong infrastructure in medicinal chemistry that integrates innovative, structure-based and computer-aided processes in addition to preclinical development models.

b) The use of the body‘s own principles of action pertaining to pathogen defence (e.g. antibody and immune cell-based therapy and activators of innate immunity). Immunological defence processes have become honed and differentiated through continuous competition with adaptable pathogens. Defence mechanisms were selected that provide protection against different groups of pathogens while at the same time minimising endogenous damage. These **protective host factors** include highly specific principles of action (e.g. antibodies and immune cells) and, on the other hand, broadly effective defence mechanisms (immune activators such as e.g. interferons). In times of capacity building, selected endogenous principles of action are systematically developed with a view to application against newly emerging pathogens. Collections of **immune activators** are thus specifically tested for their efficacy against viral pathogens with pandemic potential, permitting the quick mobilisation of promising applications for a clinical trial in the event of an outbreak. **Modern technologies**, including targeted genetic engineering techniques involving **gene scissors** (e.g. Crispr/Cas) are used to construct immune cells that mediate highly effective immunity. These approaches of **synthetic immunity** are programmed for **conserved pathogen targets** so that the broadest possible immune protection is created. Ground-breaking new technologies allow rapid identification of neutralising antibodies with great prophylactic and therapeutic potential. NA-PATH will systematically advance the development of broadly effective antibodies. This includes the design and validation of optimised antibodies as well as the profiling of **antibody combination preparations**. Pandemic-relevant optimisation goals such as increasing antibody efficacy and stability, expanding the pathogen spectrum as well as pathogen resistance-breaking properties are being pursued.

(2) Symptom- and pathogenesis-related therapy

The most severe forms of viral infections are often characterised by misregulated endogenous processes. Syndromes such as acute respiratory failure as well as disorders of the blood coagulation system, vascular functions and inflammatory regulation are central occurrences in the **pathophysiology of pandemic pathogens**. Often, the pathophysiological basis of these disorders is the misdirected release of soluble endogenous messenger substances that regulate central bodily functions. For example, the massive release of inflammatory cytokines (cytokine storm) is attributed a causal role in severe progressions of SARS-CoV-2. Accordingly, NA-PATH deals with developing **modulators** of central **pathophysiological regulatory circuits**. For this purpose, organoid and animal models are used to map the relevant processes. Candidates are to be identified primarily in **drug repurposing banks**; these banks include clinically proven or approved agents that influence physiological processes in humans and whose molecular targets are known. In the planned investigations, they will be searched specifically for active substances with the ability to control pathogenesis-relevant key processes. In addition, **antibody-based concepts** are being developed, in which messenger substances or their receptors are specifically addressed in order to intercept uncontrolled metabolic reactions. This **pathophysiological intervention** is systematically combined with antiviral therapy or used staggered over time to avert the most severe progressions.

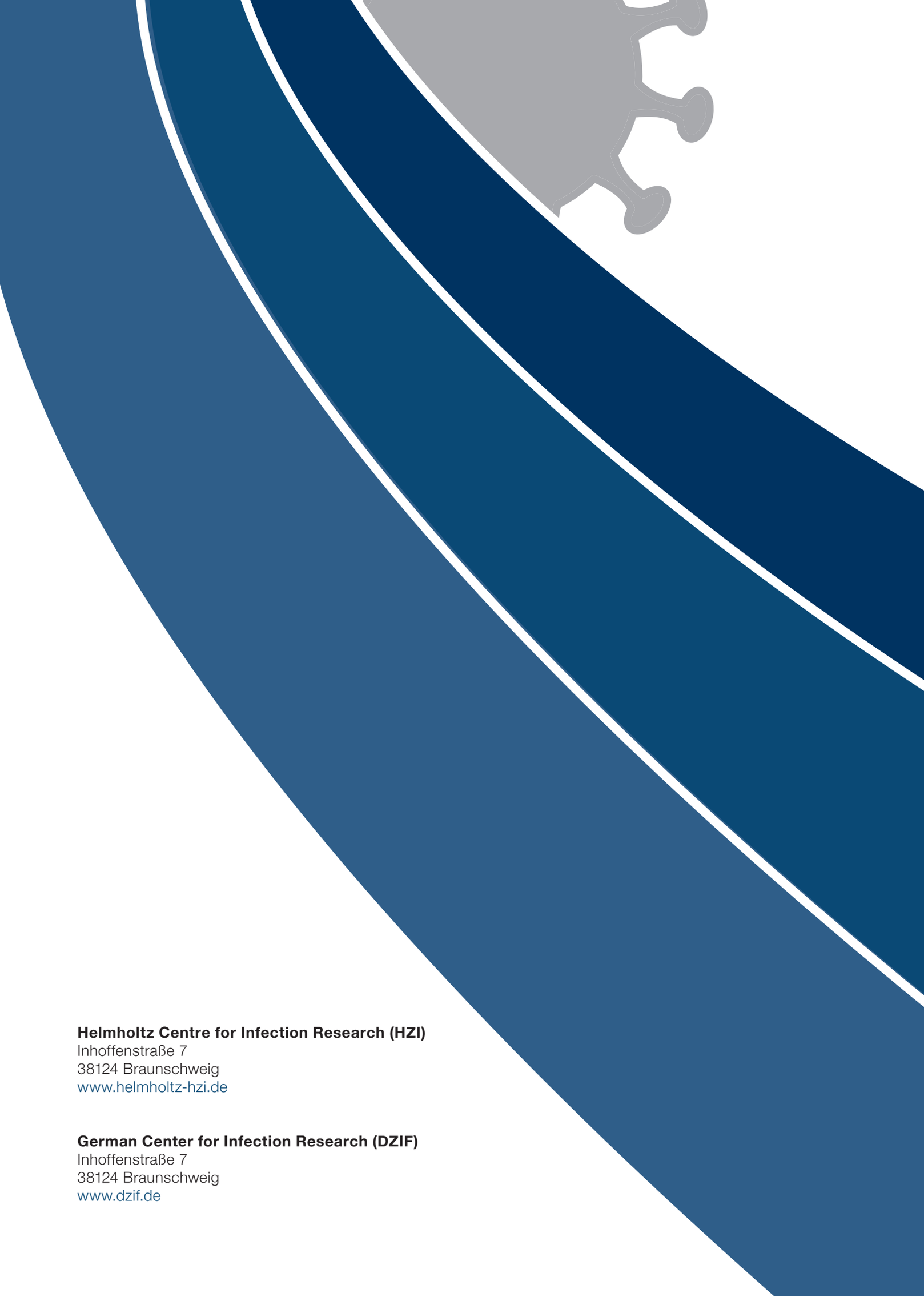
In both areas of development, NA-PATH will prioritize systematically and according to goal-oriented criteria and develop the **best candidates to a high (pre-)clinical maturity level** in order to be able to complete a clinical trial with a short reaction time in the event of a pandemic.

E. RESOURCE PLANNING

The calculation of the necessary budget for NA-PATH essentially depends on the number of therapeutics to be brought **to clinical proof-of-concept**. In order to compensate for the interim failure of product candidates, we have chosen a portfolio approach, underpinning it with **empirical failure rates** (Fig. 2). In our cost estimation, we assume that NA-PATH will launch more than **10 drug projects** in order to be able to provide two, or three in a favourable course of events, early clinical proofs of efficacy. It is possible and an express desire to include advanced projects, e.g. at the transition to preclinical development or clinical trial. This concept is scalable depending on expectations and available budget, but would be subcritical if the volume proposed here were significantly reduced.

For the creation of **translational infrastructures** at the academic research centres, we budget a **financial expenditure** of €15 million per year over an initial period of 7 years. This takes into account existing structures and includes costs for setting up high-performance units for project management and technology. Additional project expenses, in particular for the commissioning of manufacturers of clinical trial samples (CDMO) as well as preclinical and clinical contract research institutes (CRO), amount to €25 million per year for the above funding period. This €175 million is divided into €55 million in project funding for work up to the nomination of preclinical development candidates and €120 million for regulatory preclinical as well as Phase I and II clinical trials.

With these expenses, we will lay a foundation for improved pandemic preparedness and drive an innovation process that can lead to the approval of highly differentiated products. It is impossible at present to provide a reliable estimate of the expenditure up product approval.



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