DISCUSSION PROPOSAL

INCREASING VACCINE ACCESS IN A SHORTER TIME

Discussing Alternative Regulatory Frameworks
in Response to Pandemics

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Abstract

To prevent pandemic outbreaks or mitigate an evolving pandemic crisis, it is of utmost importance to guarantee timely and global access to safe and effective vaccines. There are multiple variables that can impede timely and global access, ranging from inability to set up production sites to practices of licensing intellectual property (IP). In this discussion paper, we problematize how the regulatory environment of vaccine development, approval, production, and deployment might have detrimental effects on vaccine access. Thus, we look at vaccine access mainly through the lens of vaccine availability determined by regulatory bodies. While the development of mRNA vaccines against Sars-CoV-2 might serve as a prime example of regulatory acceleration for timely vaccine access, this acceleration has not led to acceptable global vaccination rates within a reasonable timeframe. We argue that regulatory approval practices are a key variable for timely and global vaccine access and that it is necessary to improve their build-up into regulatory frameworks to handle the current pandemic and to be prepared for future pandemics. As one potential starting point for discussion, we suggest a *modular approach* to vaccine regulation that allows more flexible combinations of existing, unconventional, or even controversial regulatory practices to respond to evolving pandemic threats. We reflect upon how this modular approach might influence vaccine uptake by the public and, thus, the vaccination rate more generally, and discuss whether certain alternative regulatory practices could influence monopoly dynamics in the pharmaceutical industry.

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INTRODUCTION: QUESTIONING PREPAREDNESS AND THE RELATIONSHIP OF TIME, REGULATION, AND VACCINE ACCESS

For almost three years, the Sars-CoV-2 pandemic (in the following "the pandemic") has had a hold around societies all over the world. After initially fighting the virus through measures of social distancing, testing, and mask obligations, vaccines became the single best option countering the global health crisis. About one year into the pandemic, the first vaccines were proven effective. Approved by regulatory bodies, they made it to market. This was a tremendous and, in this timeframe, unprecedented scientific success (see for instance Hunter et al., 2022). These vaccines were created by private companies, although heavily subsidized with public money (Safi, 2021), revealing "the relation between the capitalist organization of the economy and the organization of society for the reproduction of life" (Zanoni & Mir, 2023: 370) not least in times of crises. The vaccines were protected by multiple layers of intellectual property (Jecker & Atuire, 2021) and, thus, treated as market- and not as public goods (Hunter et al., 2022). Still, already hundreds of thousands had died by the hands of the pandemic when the vaccine rollout in high income countries commenced. Other than in rich countries of the Global North, access to vaccines remained scarce for a long time (Yunus, 2022) and even today there are significant differences regarding vaccine access globally (Ryan & Nanda, 2023). Moreover, an immune evasive variant reduced the efficacy of vaccines drastically. It's emergence came earlier than expected by epidemiologists and, according to some, became possible also due to low global vaccination rates (Welch, 2021). This event makes apparent how vulnerable even widely vaccinated societies are given the uncertainties and rapidly changing circumstances around the virus – not to speak of those still unvaccinated, leading to calls for "rebooting biomedical R&D in the global public interest" (Swaminathan et al., 2022: 207). Timely and global access is of the essence to prevent, but also to mitigate a swiftly evolving pandemic and today the focus of attention is already shifting towards (global) preparedness for future pandemic situations (Perehudoff et al., 2023). Pointing to one specific issue of preparedness, this discussion proposal questions whether our regulatory institutions have been able to make timely and global access a priority for this, but even more so whether they are prepared to do so sufficiently for future pandemic situations.

Two problems are striking in the emergence and the development of the pandemic. Both revolve around the timeline of development, deployment, and accessibility of vaccines: (1) The later vaccines are accessible, the more people die from an infection. (2) The longer populations remain unvaccinated, the higher the probability that new variants emerge therefrom (Welch, 2021). In this discussion proposal, we focus on vaccine testing and regulatory approval processes as the key bottlenecks of temporality and accessibility (e.g., IFPMA, 2019; John Hopkins University, 2022). We acknowledge the legitimacy and trustworthiness of these trial and approval standards during non-pandemic times as well as the increased pace - compared to the regular trial and approval procedure for vaccines - by regulatory bodies approving the Sars-CoV-2 vaccines (Kashte et al., 2021). Still, we consider it vital for future preparedness to pandemic threats to explore existing but rarely used and further unconventional or even controversial approaches to vaccine research and development (R&D), approval, and deployment as means to act in times of crisis.

We consider open-source science, alternative trial designs, and rarely used approval exceptions as potential routes to accelerate the regulation of vaccine development and deployment in times of crises. Building on these practices, we suggest a *modular approach* to vaccine regulation as a possible framework. Allowing for more regulatory flexibility in times of crisis, this approach could foster a decentralized, less monopolized and IP-protected vaccine ecosystem that is prepared to impede the emergence of future pandemics or at least mitigate outbreaks during their early phases of evolvement. This discussion proposal's main goal is to open a public debate about the regulatory environment of vaccine R&D and its influence on timely and global access. Vaccines are very special "drugs" that have a unique medical, economic, and regulatory environment (see for instance Chen & Toxvaerd, 2014). The specificity of vaccines as potential public goods (see for instance Hunter et al., 2022) with the objective of preventing major outbreaks of a pathogen makes them particularly relevant, and therefore suited to broaden the discussion of existing approval exceptions meant to accelerate vaccine access as well as unconventional approaches that go even further. We want to encourage a debate about the relationship between (individual) access to vaccines and regulatory institutions, discussing how access can be facilitated regulatorily and touching upon what impact on global health, particularly on vaccination hesitancy, this could have. Doing so,

we also sensitize for the implications of alternative regulatory practices on refunding the vaccine development costs without strict exploitation of IP (monopolies).

The discussion proposal is structured as followed: first, we summarize the relationship between regulation and the timeline of vaccine development and approval processes. Second, we outline the regulatory practices leveraged to fight the pandemic more rapidly and argue that efforts towards pandemic preparedness urgently need to consider temporality and accessibility as key bottlenecks for mitigating emerging pandemics. Third, we outline potential alternative routes to vaccine R&D, before we, fourth, turn to initiatives like RaDVaC and 1DaySooner that suggest particularly time-sensitive shifts in regulation to counter a pandemic threat and even aim to set up an alternative ecosystem of vaccine R&D. In the last part of this discussion proposal, we first discuss ethical issues concerning alternative regulatory approaches as well as the approaches' potential effects on vaccine hesitancy. We then suggest a *modular approach of vaccine R&D and deployment* to be consciously chosen and applied depending on the urgency the pandemic situation demands. Generally, we argue that it is a fundamental task of health governance to question the current balance of regulating access to vaccines with demands on vaccine safety in situations of health crises to ensure fast and tailored responses to future pandemics.

Regulation and timeline in vaccine development and approval processes

Vaccine approval is regulated by authorized institutions (IFPMA, 2019), often bound to nation-state jurisdictions like the Food and Drug Administration (FDA) in the USA or the European Medicines Agency (EMA) in the European Union. On a global scale, many countries, particularly low- and middle-income countries, do not maintain their own approval institutions, but instead rely on foreign approval and evaluations by the World Health Organization (WHO). To apply for drug approval, pharmaceutical companies need to submit a data package for a treatment based on a clinical trial program. Regulators review the submitted data before making a decision (e.g., EMA, 2022a). There are two main temporal constraints posed by approval institutions: (1) the duration of the clinical

trials program leading up to review and (2) the time elapsing during the review process itself.

Clinical studies usually build upon three trial stages with progressing involvement of human subjects (John Hopkins University, 2022; IFPMA, 2019). Phase I and phase II trials determine initial safety and efficacy of a potential vaccine in small groups. Phase III trials need large patient groups of usually a few thousand individuals to allow for randomized and controlled results of safety and efficacy, known as randomized controlled trials (RCT). These three phases are followed by post-marketing studies in phase IV that aim to detect long-term side effects (IFPMA, 2019). In most cases, phase I to phase III trials are conducted in succession. It is well documented that these trials take up a large chunk of time throughout the R&D process (John Hopkins University, 2022). Clinical studies not only take time, but are very cost-intensive, too. They are central for calculating the costs of drug innovation that serve to justify the necessity for IP-protection (see for instance DiMasi et al. 2016). Gaps in funding slow down R&D processes significantly and though there are many vaccines which could be beneficial to develop, there is regularly not enough venture or public money available to fund their trials (e.g., Fogel, 2018). Undone science and missing results impede approval. Financial bottlenecks often delay or even prevent development of promising vaccine candidates. Vaccine R&D advancing a less exclusive approach to IP might particularly experience these bottlenecks, because of their reduced capacity to secure return on investment.[1]

Trial results need to be submitted to approval institutions for review and time to review varies significantly not only for individual submissions, but also between institutions (IFPMA, 2019). Though approval bodies estimate timelines for review decisions, actual review periods can vary greatly. For example, the cancer drug Opdivo was submitted to the FDA at the end of February 2022, scheduled for a June 2022 decision, and was approved not in four months, but in just five days (Mast, 2022). However, it can well be the other way around. Concerning approval institutions, on average EMA approval time takes longer than FDA approval (Hatswell et al., 2016).

[1] A well-known example is Corbevax developed by theTexas Children's Hospital Center for Vaccine Development that did not receive any funding from the Operation Warp Speed. According to their chief scientist and director Peter Hotez, the refusal of funding led to a significant time delay of more than a year.

Although vaccine R&D and approval times can be lengthy, they can vary significantly, and there is much flexibility in the process. As we learned first-hand during the pandemic, in times of crisis both R&D and approval can be accelerated, while still maintaining high standards of safety.

Acceleration of vaccine approval and access during the pandemic

The pandemic has provided evidence that nation-states and regulatory institutions are able and willing to accelerate timelines to allow vaccines to reach the market more quickly, utilizing several approaches to enable greater efficiency in R&D and regulatory approval processes.

Among the Global North, nation-states generously funded pharmaceutical companies to accelerate their vaccine R&D efforts, applying names like “Operation Warp Speed” (U.S. Department of Health and Human Services, 2020) in the USA or “Project Lightspeed” (Miller et al., 2021) in Germany to underscore the necessity to accelerate time to approval. The funding was mostly directed towards clinical trials of vaccines and was distributed among a few companies that provided early hopes for a successful vaccine design.

One means of accelerating the vaccine R&D process has been the overlapping of clinical trial phases. Instead of the usual practice of conducting phase I, II, and III trials sequentially, we saw an adaptation of these industry standard practices and a leap towards simultaneously conducting different phases of trials (e.g., phase II and phase III in parallel) during the pandemic (Paul-Ehrlich-Institut, 2022). This approach shortened the time needed for the vaccine development significantly. In addition, the FDA and EMA implemented regulatory rolling reviews in which data review was conducted ongoingly during the phase III trials rather than after completion, a technique also mobilized in previous pandemic situations such as the H1N1 outbreak (Marinus et al., 2022), to shorten time-to-approval.

Further, both FDA and EMA have a tool to accelerate the approval process after the trialing has been successfully completed: the ‘emergency use authorization’ (EUA) of the FDA and quite similarly the ‘conditional marketing authorisation’ of the EMA. These regulatory exceptions made rather swift approval of vaccines possible. In the case of

Pfizer/BioNTech's vaccine Comirnaty, the approval process from final submission to the FDA until emergency approval, was 22 days (Alatovic, 2022).

Besides the acceleration of vaccine trial and approval processes, transnational initiatives like WHO's Access to COVID-19 Tools (ACT) Accelerator increase the speed of technological development and deployment of already developed and approved vaccines (WHO, 2022) with the goal to increase timely vaccine access on global scale. This initiative mainly aims at bringing together governments, scientists, businesses, civil society, philanthropists, and global health organizations to secure funding for, but also legal access to IP-protected technology. In connection with WHO's COVID-19 Technology Access Pool (C-TAP), a platform to share IP, knowledge, and data relevant to develop vaccines, these WHO initiatives aimed at minimizing delays in responses to the pandemic. Other proposals were put forth, like the heavily disputed TRIPS waiver which had as its main purpose to suspend IP restrictions and provide neglected countries with the means to create vaccines on their own, and thereby speed up vaccine access for the Global South. Though this proposal has not been leveraged effectively, it has fostered a process to develop a global preparedness treaty emphasizing the relevance of lifting IP restrictions for fighting pandemics globally (WHO, 2023; Perehudoff et al. 2022). Beyond these efforts, "an international group of researchers, scientists, academics and lawyers [were] seeking to accelerate the rapid development and deployment of diagnostics, vaccines, therapeutics, medical equipment, and software solutions" through the Open Covid Pledge Initiative (Open Covid Pledge, 2022). Organizations such as IBM, Amazon, or Microsoft pledged IP.

We see that there has been some effort to accelerate vaccine development and deployment during the pandemic. However, at least two very detrimental shortcomings of these approaches need to be considered. First, though vaccines were created almost immediately after the genetic code of the Sars-CoV-2 virus was released, it took almost a year for commercial vaccine production companies to deploy vaccines. The aforementioned measures undoubtedly accelerated vaccine access, but it remains questionable whether access to vaccines was provided fast enough taking into account the dangers of an infection with the Sars-CoV-2 virus and the number of casualties countries all over the world suffered. Millions died, even in the rich, Western countries that were the first having vaccines at their disposal. Second, in 2022, even more than one

year after the first deployment of vaccines, and with some countries vaccinating segments of their population for the fourth time, large parts of the global population had not received a single dose. While some countries declared the pandemic to be over, many others were still struggling (Ryan & Nanda, 2023). The development of the pandemic has shown that there has not been timely access to vaccines on a global scale, with devastating effects on individual suffering and the progression of the pandemic.

Concludingly, acceleration of vaccine development and deployment during the Sars-CoV-2 pandemic has not been sufficient and has allowed or still allows avoidable suffering. We must find alternative means to further and more sustainably accelerate vaccine R&D and access – if possible for the still ongoing Sars-Cov-2 crisis, but in any case for the next public health crisis bearing the potential to become pandemic. In the reminder of the discussion proposal we focus regulatory practices of increasing timely and global vaccine access.

Alternative regulatory practices to increase speed of vaccine access

There are several existing but rarely used and further unconventional approaches to R&D, approval, and deployment that increase speed of access to vaccines. We conceive of them as *alternative regulatory practices* to accelerate access to vaccines. Table 1 gives an overview of practices and whether they have been used during the Sars-CoV-2 pandemic. Increased speed of R&D, approval, and deployment do not come without cost and trade-offs need to be considered when arguing for accelerating vaccine access. The table indicates the (main) trade-off to accelerate access

Alternative regulatory practices	**used**	**Trade-off to accelerate access**
rolling review	yes	potential sunk costs in case trials are not successful
emergency authorization	yes	less comprehensive long-term population safety and efficacy data
accelerated approval	no	no comprehensive safety and efficacy data
early/expanded access	no	using drugs (and potentially vaccines) in experimental stage
approval without RCT	no	limited clinical data

utilize lower-efficacy vaccines	no	more individuals vaccinated with less efficacious vaccines
challenge trials	no	increasing individual risks for public knowledge
develop multilateral rules	no	strengthen low-income countries at the cost of high-income countries
compulsory licensing of IP	no	decrease potential to maximize profits

Table 1: Alternative regulatory practices to accelerate timely vaccine access

Though bureaucratic requirements and standards of the FDA or EMA are surely also obstacles to accelerating timely access to vaccines, their regulatory frameworks actually offer alternative approval practices that can provide valuable leeway.

Rolling review is a regulatory tool to hasten the time until a vaccine or drug is officially approved by the EMA, FDA, or other regulatory body. Marinus et al. (2022) describe the rolling review as an approach that allows data to be "submitted and reviewed as they become available before the full data package is available. This approach requires a closer collaboration and more intense interaction between the sponsor and the health authority", but offers a great potential of time savings once phase III is finalized (Paul-Ehrlich-Institut, 2022). Rolling review is part of the Fast Track program for drug approval at FDA (FDA, 2018). Furthermore, FDA also offers Priority Review for quicker approvals, the program under which the previously mentioned cancer therapeutic Opdivo was approved in just five days.

Also, **emergency authorization**, or rather emergency use authorization (issued by FDA) or conditional marketing authorization (issued by EMA) have been applied during the pandemic. FDA's emergency use authorization facilitates "the availability and use of medical countermeasures (MCMs) needed during public health emergencies" of "unapproved medical products or unapproved uses of approved medical products" (FDA, 2022). Similarly, EMA's conditional marketing authorization "supports the development of medicines that address unmet medical needs" and allows authorization based on "less comprehensive clinical data", in cases "where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required" (EMA, 2022b).

Similar to emergency authorization is **accelerated approval**. To bring drugs to the market that treat serious conditions and fill an unmet medical need, the FDA offers an

accelerated approval program. This program rests on a “surrogate endpoint,” a kind of early outcome that provides initial evidence for the likelihood of clinical benefits. After approval, drug companies are still required to conduct studies and to confirm those benefits in phase IV confirmatory trials (FDA, 2020).

There is **early/expanded access**, which is similar to the other aforementioned measures, but rather stresses the access of single individuals with specific life-threatening conditions (FDA, 2021). Expanded access allows patients with life threatening conditions and no hope for improvement of their health condition with currently available drugs to access experimental and unapproved drugs as a last resort. Early access can be applied, when “randomization is unethical, for example due to a large unmet medical need" (Polak et al., 2019). Early access is a very constrained program with five conditions that all need to be met: (1) Patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition. (2) There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition. (3) Patient enrollment in a clinical trial is not possible. (4) Potential patient benefit justifies the potential risks of treatment. (5) Providing the investigational medical product will not interfere with investigational trials that could support a medical product’s development or marketing approval for the treatment indication (FDA, 2021). An important example from medical history is access to AIDS treatments, where activists also intensely fought for early access (Epstein, 1997). Although this approach might not have been used for vaccine deployment yet, a transfer into the vaccine sphere would mean providing particularly vulnerable groups with a first prototype of a vaccine.

Vaccines could be **approved without randomized controlled trials** (RCT), which can significantly increase access. Hatswell et al. (2016) argue that “despite the frequency with which approvals are granted without RCT results, there is no systematic monitoring of such treatments to confirm their effectiveness or consistency regarding when this form of evidence is appropriate.” With regard to vaccines, the authors state that the majority of vaccines are licensed based on well-understood technologies and mechanisms of action, which make them appropriate for approval without RCT. However, though they discuss vaccines, there was apparently no vaccine approved without RCT in their data. The scope of treatments that can be approved that way is very constrained and narrow, which is similar to the practice of expanded access. The authors recommend taking on a more

serious debate about regulatory approval without RCT and suggest "the development of guidelines on what constitutes an acceptable data package for regulators" (Hatswell et al., 2016: 1).

Other, unconventional alternative regulatory practices oppose existing regulatory frameworks and to some degree contrast the practices mentioned above.

It has been argued that **utilizing lower-efficacy vaccines** could provide a comparatively early access to vaccines for more people, which in turn would help to decrease severe illness and death (Castillo et al., 2021). Castillo et al. (2021) suggest that "given the value of speed in a pandemic, using a less effective vaccine available now can be better than waiting for the later arrival of a more effective one. Similar logic suggests that lower-dose regimens can have large benefits to a country by getting more vaccines to citizens more quickly (...)." Thus, they either see approval bodies in charge of approving less convincing clinical data or foster a vaccine regimen that cuts dosages to distribute the available vaccine to more people more quickly. A balancing factor we see could be the safety of a vaccine to re-evaluate whether lower-efficacy might still be the overall better way to go.

Another way to support more timely access to vaccines is to rethink the clinical trial design in place. During the pandemic there has been increasing interest in **challenge trials** as a practice to develop further and relevant clinical results. In challenge trials "healthy volunteers are administered a vaccine candidate, and then an infectious dose of pathogen" (Nguyen et al., 2021: 4). This trial design allows to track outcomes of the infection and creates very quickly highly relevant results about a vaccine candidate's performance thereby increasing the speed of vaccine trialing. The British think-tank 1DaySooner (2022) summarizes challenge trials as a historically relevant type of trial practice, where informed consent and building on transparency are key. Through scheduling targeted infections of vaccinated patients, trial planning is facilitated and temporally foreseeable. Yet, challenge trials are accompanied with strong ethical considerations, particularly when there is no effective medication against the specific disease available yet. Though they do not need financial resources similar to phase trials, they are not cheap either. Still, challenge trials can accelerate access to vaccines, since they can prove efficacy of a vaccine candidate much earlier than in RCTs (Manheim et al., 2021).

Further important suggestions challenge regulation rather on a level of governance. Given their international scope and time-intense planning efforts, they are much harder to implement right now, but the pandemic could be the catalyst to rethink practice.

Timely and global access to vaccines can be tackled from a broad perspective of international law. Strengthening authority of global institutions to facilitate waiving of IP-protection in certain situations can be a way to secure access to vaccines and drugs in crises. Velásquez (2022: 60-61) suggests to "**develop multilateral rules** and empower the WHO so that it can exercise a real global coordination on health matters" and "ensure a sustainable long-term R&D and subsequent affordable access to pharmaceuticals" on a global scale. To handle immediate threats and as a central point in the current discussion, initiatives and commentators (e.g., MSF Access Campaign, 2021) demand the use of **compulsory licenses**, under which low- and partly middle-income countries are authorized during times of crisis to produce a patent-protected therapeutic without permission from the patent holder. Both legal mechanisms point to an understanding of general flaws within prevailing business norms in vaccine (and drug) R&D and the need for alternative regulatory practices in vaccine R&D and distribution. As Velásquez (2022: 5) puts it:

> "COVID-19 clearly illustrates the need to use compulsory licensing and, ultimately, the question of how to implement a research and development (R&D) model for vaccines and medicines that ensures equitable access to health for all."

One example for multilateral rules and compulsory licensing in the context of pandemic preparedness is the Zero Draft of the Pandemic Treaty. It is a transnational effort within the WHO to develop multilateral rules (WHO, 2023; Perehudoff, 2022). It very broadly acknowledges the detrimental effects of IP and the handling of TRIPS exceptions during the pandemic and tries to create a transnational regulatory environment that enables countries to more easily draw on these exceptions. However, as their focus is more on equity than on velocity, these commentators do not directly address vaccine approval from a regulatory perspective.

Most practices mentioned above require a comparative risk/benefit perspective into approval or usage of vaccines, where withholding a vaccine likely has a more detrimental outcome for entire societies, than approving or using it without the standard procedures. Compared to use of alternative regulatory practices for specific medications for rare

diseases, the emphasis is on not only the individual patient, but also on public and population health when discussing accelerated vaccine deployment. In the following, we present initiatives fostering novel perspectives on vaccine regulation putting timely, global vaccine access at the core of their operations - on an individual and societal level.

Initiatives fostering novel and alternative approaches to vaccine regulation

We showed in chapter two (*Acceleration of vaccine access during the pandemic*) that during the pandemic many actors (e.g., vaccine developers, politicians, regulatory bodies) turned to be highly time sensitive and tried to increase the speed of vaccine access. For example, the aforementioned initiative 1DaySooner, a very figurative naming to underscore the organization's main purpose to end the pandemic 'one day sooner', or the Rapid Deployment Vaccine Collaborative 'RaDVaC' put temporal considerations first. Thereby, they challenge conventions and the status quo of vaccine R&D and deployment. These organizations encounter considerable criticism and a lot of ambivalent evaluations of their vaccine R&D practice, in particular with regards to their approaches to regulation, for example, the circumvention of official trialing processes. In the following, we focus on RaDVaC as an extreme case of encouraging timely (and potentially global) vaccine access that we see as fruitful to foster a discussion about the temporal dimension of vaccine regulation.

RaDVaC is a small scientific non-profit with the mission of increasing access to vaccines and improving the agility of vaccine development. It was founded in the early days of the pandemic and developed an initially peptide-based vaccine design against Sars-CoV-2 within a few months after the initial outbreak. This vaccine should address the gap until other vaccines were commercially available. RaDVaC, following open-source principles, shared their vaccine design in a White Paper, which is openly accessible online (RaDVaC, 2022a). Building upon the ongoing published research around the world into Sars-CoV-2 and COVID-19 and also informed by insights of a community of (citizen) scientists, RaDVaC has been updating and improving their vaccine designs in numerous further White Papers. RaDVaC describes its vaccine as a "research vaccine" (e.g., RaDVaC, 2022b) and positions it in contrast to commercial vaccines. Vaccines, as RaDVaC envisions them,

serve as public goods. To provide timely access, commercial considerations are of neglectable relevance. As a research vaccine, it can be produced on a smaller, yet ubiquitous scale throughout the globe by people who are able and willing to produce and take it on their own.

Preventing but also engaging with a potentially pandemic situation demands the ability to adapt a vaccine as needed. Encouraging the capability of decentralization and collaboration are two important aspects of RaDVaC's approach. RaDVaC calls for open-sourcing fundamental technology and tools as well as transparent knowledge exchange. The organization fosters incremental adaptation of the vaccine across and outside organizational boundaries and is open to professional and citizen scientists anywhere in the world. Furthermore, they propose accessible production methods to allow scientists in diverse settings and locales to collaborate and improve vaccine designs. These production methods rely on low cost, high safety, and abundant material, which is ideally simple, to give individuals or labs the ability to produce the vaccine for self-administration.

Taken together, RaDVaC's approach puts their vaccine at odds with demands of regulatory institutions, industrial reproduction, and medical professional practice. The approach raises questions regarding safety and efficacy of their vaccine. RaDVaC argues that safety stems from previous published studies about the technologies and materials they utilize. They put details on components and production processes in the public domain, and claim that this transparency enables informed consent. They also point out that vaccines are by far the safest of all therapeutic classes. RaDVaC claims that the efficacy of their vaccine is secured by rapidly updating vaccine designs for newly identified variants. Particularly the practice of rapidly updating puts RaDVaC's efforts seemingly in opposition to approval regulations. Yet, RaDVaC, rather than challenging regulation, sees its model and practice as a form of a pandemic emergency necessity that does not stand in opposition to regulation. Being at the same time in favor of vaccine regulation, and yet developing practices of deploying vaccines without approval creates a conflicting, maybe even paradoxical impression. However, the case of RaDVaC with its potentially paradoxical aspects of balancing speed to access with safety/regulatory approval helps us starting a discussion on how to increase regulatory flexibilities in times of crises.

Starting a discussion for increasing regulatory flexibilities in times of crises

Combining existing regulatory flexibilities with practices of decentralization, we propose a *modular approach to regulation* in times of crises. A modular approach to regulating vaccine approval and access could rely on *alternative regulatory frameworks* that become available under specific (global) health circumstances. We argue that, but at the same ask whether, a modular approach could be helpful to provide timely and global vaccine access, prevent pandemic outbreaks, and prepare for novel global health emergencies. We borrow the idea of modular regulation from the Creative Commons (CC) licensing scheme (Creative Commons, 2022). The CC-licenses allow licensing a knowledge-based good (like a piece of music or a vaccine design) through combining different legal mechanisms to formulate a range of options, from very open (CC0 or CC-BY) to restrictive (CC-NC-ND). We suggest adopting this regulatory modularity and connect the above mentioned (and further) unconventional or rarely used practices as "modules" of alternative regulatory frameworks.

We showed that as of today, vaccine regulation includes a great deal of different existing, but rarely used practices to enable timely access to vaccines in crises. However, these regulation practices are rather fragmented in "bits and pieces" and do not seem to be coherently associated in the regulatory framework. We propose to consider these "bits and pieces" as different "regulatory modules." The challenge we see is to combine these regulatory modules (along with still missing and potentially unconventional pieces) in a meaningful and adaptive manner. A modular approach could allow different sorts of "emergency exits" becoming part of current (FDA, EMA, etc.) regulation to be activated in times of specific health emergencies. As an additional effect, a modular approach could be helpful to foster open-sourcing vaccine R&D, when it lifts the pressure of securing funding and return on investment.

At the heart of a modular approach to regulation is the issue of timeline in different kinds of pandemic situations: *When do we have to act immediately, and when is it the right time for more conventional (scientific and regulatory) consideration?* This could be seen as a purely logistical problem. It might be a problem of scientific evidence. Perhaps it is also a philosophical one that pertains to questions about self-determination in times of global

pandemic threats. Connecting these layers could be one way to further elaborate how a modular approach to vaccine regulation could be imagined. Table 2 sketches very raw alternative regulatory frameworks by linking potential scenarios with regulatory modules that are unlocked to engage with the potential health threat.

Scenario	**Alternative Regulatory Frameworks**
pandemic outbreak of a virus from a well-researched pathogen that spreads slowly and only affects (with death) certain groups of the population	status quo, but develop multilateral rules to facilitate compulsory licensing
pandemic outbreak of a virus from a well-researched pathogen that spreads quickly and only affects (with death) certain groups of the population	develop multilateral rules for waiving IP-protection; compulsory licenses; rolling review; accelerated, early, and extended access
pandemic outbreak of a virus from a not-researched pathogen that spreads quickly and affects (with death) certain groups or some groups more than others	the prior plus: emergency authorization; compulsory licenses; challenge trials; utilize lower-efficacy vaccines; funding phase trials of decentralizing and open-source initiatives
pandemic outbreak of a virus from a not-researched pathogen that spreads quickly and affects (with death) all groups of the population in a similar way	the prior plus: approval without randomized controlled trials; enabling access to vaccine ingredients and administration on an individual basis

Table 2: Initial sketches of alternative regulatory frameworks

Conclusion: Access to vaccines in the early stages of an emerging crisis

There is a saying that good science takes time - this is true for any science. But what if we don't have time for what is conventionally considered to be good science? The pandemic, its evolution, and the potential of emerging pandemics force us to rethink conventions (see also Yunus, 2022) and to imagine a future where vaccines are viewed as public goods, where timely and global access is taken for granted and not simply wishful thinking. Looking into vaccine R&D, approval, and deployment, we reviewed how acceleration of

vaccine access is currently being and could further be achieved and peeked into the efforts of some organizations trying to accelerate access in unconventional ways. There are many questions left unanswered that we think should be addressed more openly: Can good pharmaceutical development happen even under compressed timelines? Can there be good pharmaceutical science (without or) with abridged trials? Are there ways to implement safe and effective vaccines outside of the formal regulatory and approvals process?

Reflecting on timely and global access to vaccines, it is of utmost importance to consider the impact a modular approach could have on vaccine uptake of the public, in other words: the vaccination rate. A vaccine is just as good at mitigating a pandemic as it is effectively vaccinated. A quickly accessible vaccine refused by broad segments of the public might lead to more problems than it solves. This issue surely needs much more scrutiny than the present discussion proposal can provide. However, we collected some arguments that we believe are of value for the debate and that demand further empirical evidence. (1) During the pandemic we witnessed how diverse societies and groups within societies take up vaccines. In some countries (for instance Portugal) there was less skepticism towards vaccines compared to other countries (for instance Germany). As we have seen (and knew already before the pandemic), certain groups of individuals refuse even RCT vaccines. It is very likely they will also refuse more quickly accessible vaccines. This diversity in vaccine uptake, however, could also be seen as a potential benefit for alternative regulatory practices when they are interpreted as means of mobilizing individuals, groups, or even populations that are willing to be vaccinated. Transparency of vaccine R&D process and decision-making as exemplified by RaDVaC's white papers might even have a positive effect on general hesitancy. (2) To mitigate the actual pandemic dispersion early on, also smaller amounts of people willing to get vaccinated could be sufficient. We have also witnessed during the pandemic that second, third, etc. rounds of vaccination comes with decreasing uptake in the population even with RCT and regulatory approved vaccines (European Centre for Disease Prevention and Control, 2023). Timely access to vaccines might lead to a significantly lower spread that decreases necessity for further vaccination rounds.

In heavily vaccinated countries of the Western world the pandemic seems to be over at the moment. Still, even these societies need to reflect upon preparedness for any future

pandemic threat to come. Several millions died in exactly those countries that were allegedly providing their population with vaccines as early as possible. Thus, there is a very general need to discuss the issue of timely vaccine access made available on a broad scale, outside of industrial and regulatory conventions. Extreme cases like RaDVaC could be seen as deterrent examples of unconventional scientific practice. Or, they might offer the starting points for sought-after solutions for highly complex, global issues. In the pandemic, we have seen a rise in appreciation for publishing preprints (at cost of the traditional peer-review system) or even making early scientific results accessible via Twitter. The timelines and regulation of science seem to have been recalibrated in this period of crisis. With this discussion proposal we hope to encourage a broad, and yes, also unconventional discussion around regulation of vaccine access.

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