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Repurposing without purpose? Early innovation responses to the COVID-19 crisis: Evidence from clinical trials

Marvin Hanisch[1,*] **and Bastian Rake**[2]

[1]Department of Innovation Management & Strategy, University of Groningen, Nettelbosje 2, Groningen, 9747 AE, The Netherlands. m.hanisch@rug.nl
[2]School of Business, Maynooth University, Maynooth, Co. Kildare Ireland. bastian.rake@mu.ie

The novel coronavirus has created one of the biggest social and economic challenges in recent decades. Since a critical issue in overcoming a large-scale pandemic involves finding effective treatments for the disease, there is typically urgent pressure on the health-care sector to develop innovations to combat the pandemic. Recently, scholars have argued that repurposing – that is, reusing an existing innovation in a different context – allows for such rapid innovation responses and can reduce costs, as the groundwork has already been laid. In this paper, we compare these benefits with the considerable disadvantages associated with innovation repurposing, including lowered barriers to entry, which can lead to declining average quality and duplicate work. Using data on 2,456 COVID-19-related clinical trials initiated between December 2019 and July 2020, we find that merely one-third of the trials actually investigated drugs or vaccines, whereas the rest focused on diagnostics and crisis management issues. In the trials concerning drug testing, we find that drug repurposing is a predominant innovation strategy, but many trials tested the same (combination of) drugs. This indicates an inefficient use of resources and reductions in the average variety and novelty of clinical trials. Furthermore, the small percentage of biopharmaceutical firms involved in the search for COVID-19 treatments raises the question of whether firms may have insufficient incentives to redirect innovation efforts to respond to the pandemic. Our paper contributes to crisis management research, the nascent debate on COVID-19, and the emerging literature on innovation repurposing.

1. Introduction

The COVID-19 pandemic that started in early 2020 has created major social and economic problems as well as an urgent innovation challenge (Chesbrough, 2020; Wenzel et al., 2021). Due to protective measures imposed by governments around the world, many areas of public and economic life were severely restricted (Pereira et al., 2020). In doing so, most governments were striving to balance the threat of overburdening their health-care systems against the individual and economic freedoms they constrain. A critical part of overcoming the pandemic involves developing an effective drug or vaccine that cures or protects against COVID-19 (Dhama et al., 2020). This is reflected in high expectations on the

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part of the health-care sector to quickly develop appropriate treatments (Baden and Rubin, 2020). From a managerial perspective, the COVID-19 pandemic represents a crucial innovation challenge for the health-care sector, which is called upon to respond to the crisis with effective, innovative solutions.

Despite the wealth of general literature on new product development and innovation management, we have surprisingly little insight into how organizations respond to extreme innovation demands, or 'innovation crises,' as in the case of a pandemic (Rao and Greve, 2018; George et al., 2020). Previous literature on crisis management has focused either on describing how firms can respond to organization-specific crises, such as corporate scandals (Chandler et al., 2020; König et al., 2020), or on macroeconomic challenges, such as economic downturns or terrorist attacks (e.g., Mainiero and Gibson, 2003; Williams et al., 2017). However, this stream of research has not considered how managers can respond to a specific, exogenously induced innovation crisis in which situational requirements demand a versatile organizational response with regard to the development of specific new products or services.

The COVID-19 pandemic offers a particularly intriguing context to further theoretical understanding on innovation crises for three specific reasons. First, the economic incentives for developing a treatment for COVID-19 are unusually high in view of the global need for an effective drug or vaccine. Without such treatment, it would be irresponsible to fully levy the social distancing measures in place (Cohen and Kupferschmidt, 2020; Hill et al., 2020). Second, there is an exceptional time pressure, which is amplified by the fact that the first effective treatment yields the highest economic benefits, while subsequent products are overshadowed by the first mover (Porath, 2018). Third, the otherwise high regulatory hurdles in the industry are minimized due to the public need for medication, which significantly reduces the otherwise lengthy and costly approval process (Rome and Avorn, 2020). Taken together, these factors result in an exacerbated competitive situation coupled with high economic incentives. Thus, COVID-19 represents a novel situation for innovation management that provides unique insights into the responsiveness and adaptability of R&D processes in organizations.

To shed light on how organizations respond to the innovation crisis posed by COVID-19, we draw on and integrate the previous literatures on crisis management (Bundy et al., 2017; Pereira et al., 2020) and innovation repurposing (Toney et al., 2009; Andriani et al., 2017; Neuberger et al., 2019) to argue that reusing existing innovations in a new context (repurposing) can be an effective means of accelerating responsiveness in a crisis. However, this strategy comes at the expense of inefficiency and coordination problems. More specifically, we propose that repurposing is associated with low barriers to entry. When combined with high economic incentives, these low barriers of entry lead to a multitude of uncoordinated actions that cause redundancies and inefficiencies as organizations seek low-hanging fruits and quick wins. As a result, public pressure to promptly innovate can provoke a bustle which, instead of increasing purposeful innovation, fosters mere quantity but deteriorates the average quality of results. Furthermore, the inherent focus of repurposing on application rather than basic research can also prove detrimental for scientific advances in the long run.

We explore innovators' early crisis responses and the trade-offs they faced using a sample of 2,456 manually coded COVID-19 clinical trials that started between December 2019 and July 2020. Our analyses show that slightly above 30% of the clinical trials in our sample test drugs, while only a small fraction of around 2% tests vaccines. The remaining trials often focus on understanding the disease, finding diagnostic tools, or assessing the wider impact of the pandemic. Among the clinical trials related to drug testing, repurposing plays a prominent role and we find that the most frequently tested drugs have either been approved as treatments for other diseases or have been previously tested for other diseases. Repurposing strategies are mainly used in clinical trials that come from countries with lower GDP per capita, and that are sponsored by hospitals, governments, and device manufacturers as opposed to biopharmaceutical firms. An alarming finding from our study is that a large proportion of COVID-19 trials test the same treatments or drugs, creating a thicket of redundant, uncoordinated, and costly testing, while reducing the variety that would be required for an effective, broad-based repurposing strategy (Sleigh and Barton, 2010; Allarakhia, 2013). Another consequence of the high proportion of repurposing trials is the scarcity of research in completely new treatments that could combat the virus in a more targeted and effective way.

Our paper contributes to the literatures on crisis management and innovation repurposing in three important ways. First, in terms of crisis management, we highlight that exceptional innovation pressures can distort incentives toward an unfocused actionism that creates costly redundancies and may reward small wins rather than effective problem solving (Williams et al., 2017). In relation, our paper could also be of interest in the debate on 'grand societal challenges' (Ferraro et al., 2015;

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George et al., 2016) as it shows how a major societal challenge is tackled under enormous time pressure. In addition, we contribute to the emerging literature on innovation repurposing, which has received scarce attention in the management literature (Andriani et al., 2017; Kucukkeles et al., 2019) and is in need of empirical evidence and theoretical development. From an empirical standpoint, we extend the prior focus on repurposing drugs for orphan diseases and accidental discoveries to the context of a large-scale pandemic in which repurposing is used as a purposeful strategy. From a theoretical point of view, our paper demonstrates the double-edged nature of innovation repurposing by highlighting the inherent trade-off between the speed and cost of innovation versus the loss of average variety and novelty. Finally, our findings also contribute to the ongoing public debate on COVID-19, and our analyses can provide decision makers with relevant insights for improving crisis management and creating appropriate economic incentives. In particular, we suggest that a better coordination among clinical trial sponsors could reduce costly duplicate efforts while a clearer prioritization of novel developments could promote more diversity in the types of treatments tested. This applies to testing drugs that have proven ineffective in various studies, such as hydroxychloroquine, but which have been further tested in various subsequent clinical trials with public funding.

2. Innovation repurposing and crisis management

The traditional innovation management literature is primarily concerned with the question of how organizations can innovate to gain a sustainable competitive advantage (Tushman and Anderson, 1986; Lengnick-Hall, 1992). At its core, this literature deals with the emergence of innovation stemming from the purposeful recombination of existing and new elements (Henderson and Clark, 1990; Kaplan and Vakili, 2015) within and outside of an organization (March, 1991; Chesbrough, 2003) to address specific needs of individuals and organizations. A common assumption in this line of work is that the need for innovation primarily stems from competitive pressure and the need for organizations to grow and survive in the marketplace by reaping the benefits of temporary monopoly rents generated by innovations (Schumpeter, 1912).

Significantly less attention has been paid to situations where the pressure to innovate does not arise from an organization's need for growth and profit, but from an exogenous crisis, such as a pandemic, that exacerbates specific innovation needs and imposes significant constraints in terms of timing and the direction of innovation. In the past, such 'innovation crises' have often arisen in times of war. For example, the Manhattan Project, which aimed to develop the first nuclear bomb, was born out of the Second World War (Lenfle, 2011). Other examples are the invention of radar technologies or the precursors of the computer (Rau, 2005). These situations are distinctive from regular innovation processes because they typically force high urgency; often allow access to lavish public funding; and bring together actors across institutional boundaries, such as academia, government, and industry. In turn, this constellation of necessity and the pressure to act, available resources, and recombination of knowledge hold the potential for groundbreaking discoveries.

One solution for responding to innovation needs under time and/or resource constraints lies in innovation repurposing, a phenomenon that has received increased attention in the innovation literature (Andriani et al., 2017; Kucukkeles et al., 2019). Repurposing means that a known solution to a similar problem is transferred to a new context (Allarakhia, 2013). Repurposing has gained considerable traction in recent years, expressly in the context of biopharmaceutical innovation (Chong and Sullivan, 2007; Toney et al., 2009; Neuberger et al., 2019). In view of the considerable risks, time, and costs associated with drug development (DiMasi et al., 2016), biopharmaceutical firms are turning more to such 'exaptations' as a means of speeding up the development process, while simultaneously reducing associated costs and regulatory hurdles (Breckenridge and Jacob, 2019; Polamreddy and Gattu, 2019). A classic example is *Sildenafil*, originally intended for the treatment of *angina pectoris* (chest pain) but re-used as a therapy for erectile dysfunction (*Viagra*®) due to its side effect of prolonged erections (Simsek et al., 2018). Apart from these 'accidental' discoveries, repurposing can also be employed more strategically. For instance, repurposing has been hailed as a solution to urgent innovation needs, especially with regard to rare diseases that are historically underfunded due to the small market size and the resulting difficulty of covering the innovation costs (Muthyala, 2011).

In the context of biopharmaceutical innovation, repurposing an approved drug or vaccine for another disease has the definite advantage that the treatment's tolerability has already been established

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in earlier tests, which allows investigators to focus clinical trials on the treatment's efficacy for another disease (Pantziarka et al., 2018; Pushpakom et al., 2019). Thus, from a clinical vantage point, repurposed drugs or vaccines can leapfrog the first phase of clinical trials, in which the tolerability of the drug is assessed, and move directly to the second phase, in which the focus is on the efficacy of the drug (Oprea et al., 2011). Moreover, the confirmed efficacy of a treatment for a given disease often correlates with the successful treatment for a related disease (Boguski et al., 2009). For instance, it is likely that an antibacterial drug is effective against various bacterial infections.

Despite its advantages, repurposing has a considerable downside resulting from the inherent lack of novelty and focus. In particular, the risk of repurposing is that performance and fit for the problem may be lower because the original innovation was developed with a different objective in mind. There is also the peril that repurposing diverts resources toward incremental innovation at the expense of more novel and radical innovations (Banbury and Mitchell, 1995). Furthermore, repurposing is based on a broad trial and error approach in which a variety of existing solutions are applied to a new problem (Cheng et al., 2018). Thus, repurposing resembles the search for a needle in a haystack and may come at the expense of not developing a profound understanding of the underlying causal mechanisms. In addition, investing in repurposing may be less attractive than *de novo* drug development as repurposed drugs tend to have a shorter exclusivity period (e.g., three instead of 10 years in the United States) and lower profit margins due to the availability of generic drugs (Pushpakom et al., 2019). Finally, biologists and pharmacists may also be deprived of important insights from preclinical basic research, which can provide valuable information about the treatment's underlying mechanisms and a better understanding of the nature of a disease (Oprea et al., 2011; Strittmatter, 2014; Kesselheim et al., 2015).

In assessing the trade-offs associated with repurposing, the scarcity of time and resources plays a crucial role. Particularly in the context of a major pandemic, such as COVID-19, a situation that requires a rapid response, we expect that investigators will weigh the upsides of repurposing more strongly than its potential downsides and will, therefore, resort to drug repurposing as opposed to *de novo* drug and vaccine discovery. In fact, experience shows that repurposing strategies have been deployed in previous epidemics, such as with Middle East Respiratory Syndrome (Dyall et al., 2014). Moreover, given the acute burden on the health-care system induced by COVID-19, we expect that a high number of nontraditional players, such as hospitals and government agencies (as opposed to biopharmaceutical firms and research institutes), will be involved in clinical trials because they are at the forefront of the pandemic. Those nontraditional players will be more likely to resort to repurposing strategies because they represent lower barriers to entry.

Moreover, we expect to see a concentration of clinical trials around the most promising available therapies based on the pathogenic similarities of COVID-19 to other diseases. This approach creates a thicket of partially redundant trials and reduces the average novelty and variety of trials given the inexperience of nontraditional sponsors in clinical trials and the lack of coordination between local actors charged with crisis management. In view of the scarcity of previous theoretical and empirical evidence on this phenomenon, we refrain from developing formal theory-driven hypotheses and instead opt for an explorative study design that focuses on empirical patterns and descriptive analyses.

3. Overview of data and study design

Our investigation of innovation responses to the COVID-19 crisis is based on a comprehensive dataset of clinical trials initiated between December 2019 and July 2020. We obtained the data via the Aggregate Analysis of ClinicalTrials.gov (AACT), provided by the Clinical Trial Transformation Initiative.[1] AACT facilitates access to the protocol and outcome data of all clinical trials registered in the ClinicalTrials.gov database, the official and comprehensive registry of clinical trials maintained by the United States National Library of Medicine. ClinicalTrials.gov contains information on clinical trials conducted in the United States and more than 200 other countries and territories across all disease areas and clinical development stages. Haeussler and Rake (2017) provide further details on the available information, the types of clinical trials registered, and the regulatory requirements related to trial registration in the ClinicalTrials.gov database.[2]

In total, we identified 2,783 clinical trials related to COVID-19. The first clinical trials devoted to COVID-19 started on December 10, 2019, but we identified another 29 clinical trials that started before December 10, 2019, but were reclassified to address COVID-19 after the outbreak of the pandemic. While we included these reclassified clinical trials in our sample, we excluded 327 clinical trials that reported an (expected) start date after the end of July 2020 or did not report any start data,

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because we wanted to focus on the realized clinical trials rather than intended future trials. This leaves us with a sample of 2,456 COVID-19-related clinical trials.

Importantly, each clinical trial lists the sponsors associated with a given clinical trial. Sponsors are organizations (or individuals) that initiate, control, fund, or otherwise support the trial and are typically involved in both planning the trial and the analysis of the results. ClinicalTrials.gov provides only basic information about each clinical trials' lead- and cosponsors, which are referred to as 'collaborators' in the database. To gain deeper insights into the type and provenance of the individuals and organizations involved, we manually classified (co-)sponsors into different finer-grained categories based on publicly available information, such as the sponsors' websites. Specifically, for each of the 2,990 sponsors involved in the trials in our sample, we manually coded the sponsor's country and the institutional type, which includes the categories of hospitals, biopharmaceutical firms, governments, academic institutions, device manufacturers, and others (e.g., individuals and insurance,). For a more granular analysis, we combined our manual coding with Pharm Exec's Top 50 Companies 2019 to identify whether some of the world's 50 largest biopharmaceutical firms were represented in our sample.[3] Table 6 in the Online Appendix provides a detailed description of the different types of sponsors.

Similarly, we manually recoded the type of intervention or treatment based on the clinical trial descriptions to provide more detailed insights into the nature and purpose of the clinical trials, which are given in the full text descriptions at ClinicalTrials.gov. Table 7 in the Online Appendix lists the classifications we used and provides an explanation of the corresponding interventions or treatments. In addition, we consulted the Drugs@FDA database[4] to obtain additional information about the drugs tested in COVID-19 trials, such as the approval status and the primary fields of application to identify repurposed drugs, a vaccine, and biological treatments. In addition, we used information on the number of COVID-19 cases and deaths at the country level provided by the Johns Hopkins University[5] as well as information on GDP per capita and population sizes provided by the World Bank.[6]

In the next section, we present descriptive analyses of clinical trial activities conducted in response to the COVID-19 pandemic. In addition, we employ social network analysis to map the relationship of different treatments (drugs) tested in the COVID-19 trials and present a map of sponsors' geographical origins at the country level. To further explore the phenomenon of drug repurposing, we employ a probit regression comparing *de novo* drug development to repurposing strategies.

4. Analysis and key insights

4.1. Who is responding to the global need for action?

We begin our empirical analysis with an examination of the number of COVID-19-related clinical trials. The number of clinical trials initiated increased exponentially over the first months of the pandemic, as evidenced by a sharp increase in the cumulative number of COVID-19 trials shown in Figure 1. This growth pattern notably accelerated approximately 3 months after the start of the first clinical trial. The considerable growth in the number of COVID-19 trials indicates that clinical investigators are increasingly focusing their efforts on clinical trials related to COVID-19. However, in June and July, the growth rate of the newly initiated trials slowed, indicating that a saturation point had been reached.

To explain the growth pattern, the intriguing question arises as to who is reacting to the global pandemic. Figure 2 shows that COVID-19 trials are mainly (co-)sponsored by hospitals – including university clinics – and academic institutions, such as universities or public and private research institutes. In contrast, only a minority of COVID-19 trials (approximately 12%) are sponsored by biotechnology or pharmaceutical firms. Of the trials sponsored by biotechnology or pharmaceutical firms, only a relatively small proportion (55 out of 293 trials or approximately 19%) is (co-)sponsored by 1 of the 50 largest biopharmaceutical firms worldwide.

We see several explanations for the prominent role of hospitals and academic institutions in COVID-19 clinical trials. One reason for the prevalence of hospitals as sponsors of clinical trial is that they represent a vital conduit through which patients can be recruited for trials. Through their direct contact with patients, hospitals can collect extensive clinical data in the course of their routine services without significant additional costs (Dugas et al., 2010). With the high number of COVID-19 patients being treated in hospitals worldwide, doctors and nurses are at the forefront of the pandemic and under pressure to find safe and effective ways to diagnose and treat the disease. In addition, the

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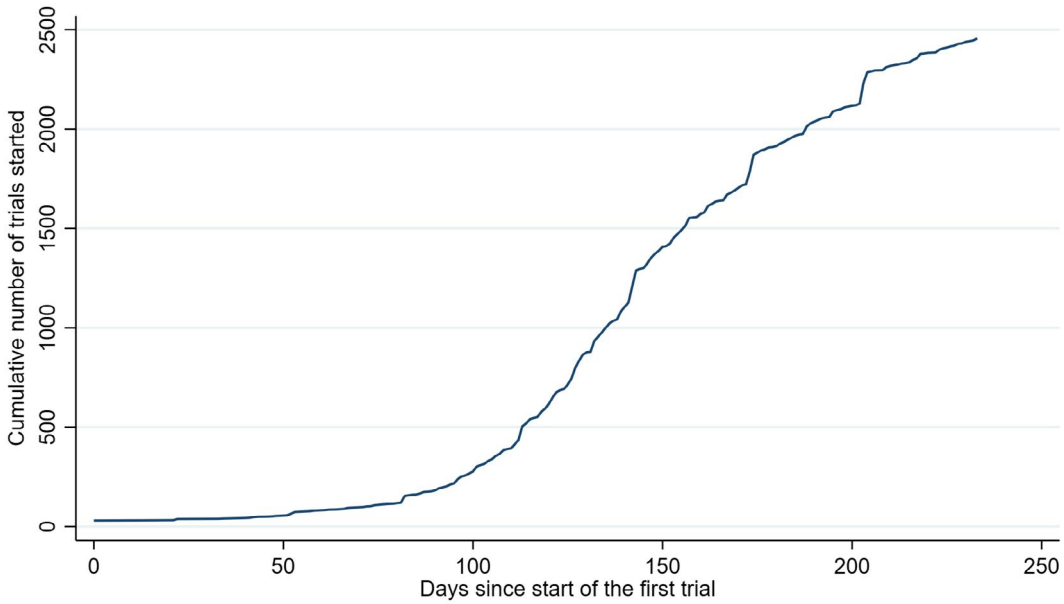


Figure 1. Number of COVID-19-related clinical trials over time. [Colour figure can be viewed at wileyonlinelibrary.com]

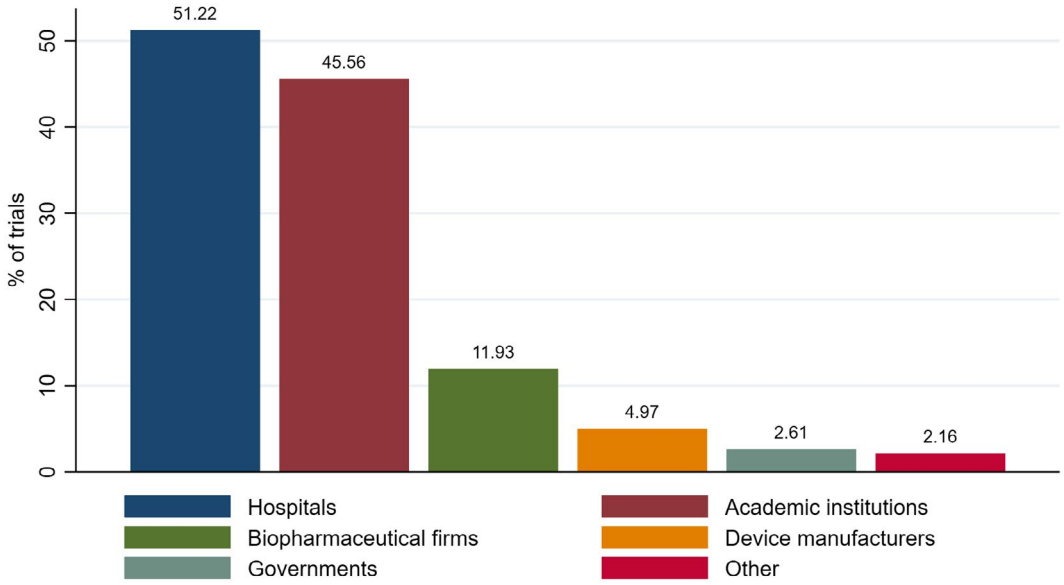


Figure 2. (Co-)sponsors of COVID-19 trials. A single trial can have more than one (co-)sponsor. Therefore, the percentages may exceed 100%. Please see Table 6 in the Online Appendix for further details on our (co-)sponsor classification. [Colour figure can be viewed at wileyonlinelibrary.com]

crisis offers researchers the opportunity to learn more about the causes, mechanisms, and epidemiological consequences of the crisis, stimulated by a number of publicly supported research initiatives, which explains the prevalence of research institutes.

The comparatively modest involvement of biotechnology and pharmaceutical firms (especially the major players in the industry) as sponsors of COVID-19 trials seems especially surprising, as these firms are usually well-equipped financially and knowledge-wise to respond to emerging health-care needs. In particular, these firms have large portfolios of approved drugs and drugs under development that could potentially be repurposed to respond to the pandemic in a timely manner. Moreover, due to the global impact of COVID-19, biopharmaceutical firms can expect large demand, which is a major driver for the speed and direction of biopharmaceutical innovation (Rake, 2017). A

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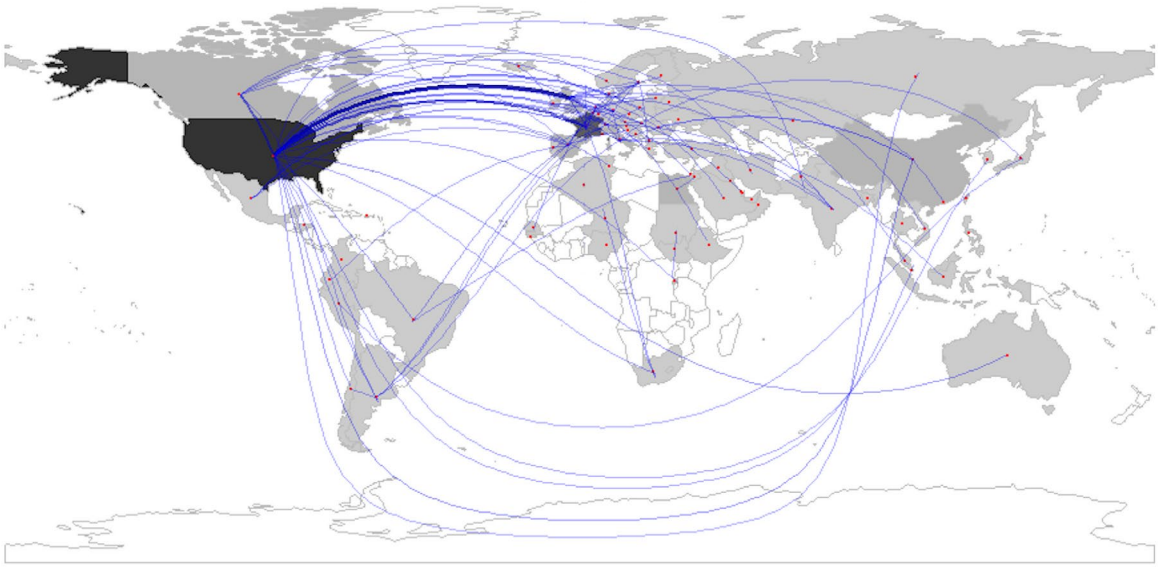


Figure 3. Geographic provenance of COVID-19 clinical trial sponsors. A darker shading of countries on the map indicates a higher number of studies sponsored by organizations from that country (e.g., US sponsors were involved in 581 studies, French sponsors in 432 and Chinese sponsors in 133). The stronger the link between two countries, the more studies that are co-sponsored by organizations from those countries (e.g., 19 studies were sponsored by organizations from the United States and the United Kingdom, 14 by US and French organizations, and 4 by US and Australian organizations). [Colour figure can be viewed at wileyonlinelibrary.com]

potential explanation for the underrepresentation of biopharmaceutical firms is that repurposed drugs tend to have lower financial margins (Pushpakom et al., 2019) and that competition for bringing a treatment for COVID-19 onto the market is particularly high, both of which might discourage market entry. We provide further details on these possibilities in the discussion section.

In relation, we also explored the geographic provenance of sponsors involved in COVID-19 trials in Figure 3. Given the global scope of the pandemic, it is of little surprise that organizations and individuals from around the world sponsor clinical trials aiming to address the health crisis. However, two countries, the United States and France, figure particularly prominently among the sponsors. Taken together, sponsors from these two countries are involved in 41% of all clinical trials related to COVID-19. Figure 3 also shows that international cooperation of clinical trial sponsors through co-sponsoring is rather rare. In fact, only around 7% of the clinical trials in our sample are projects involving sponsors from different countries. The lack of international collaboration might explain the high number of similar clinical trials that test the same or similar interventions. Without international collaboration and exchange, the risk of information residing in isolated pockets increases considerably.

4.2. What kind of medical innovations are being developed to alleviate the pandemic?

In this section, we further examine the types of medical innovations that are being studied in clinical trials in the early stages of the global COVID-19 pandemic. Figure 4 reports the number of different intervention types relative to the cumulative number of trials over time. Overall, Figure 4 indicates that the distribution across different intervention types is stabilizing after some oscillation right after the beginning of the pandemic. The figure suggests that many COVID-19 trials test specific treatments, with the proportion of drug trials, which varies between slightly above 15% and around 30%, increasing over time to reach just over 30% of all clinical trials by the end of July 2020. The consistently high proportion of drug trials reflects the strong need for effective treatments to alleviate the viral symptoms and shorten hospitalization periods. Trials related to monitoring the spread of the disease and describing its symptoms continue to play a prominent role throughout the initial phase of clinical research on COVID-19. However, the share of this type of clinical trial decreases over time and reaches less than 15% of cumulative trials by the end of July 2020. Interestingly, more than 15% of the COVID-19 trials deal with secondary

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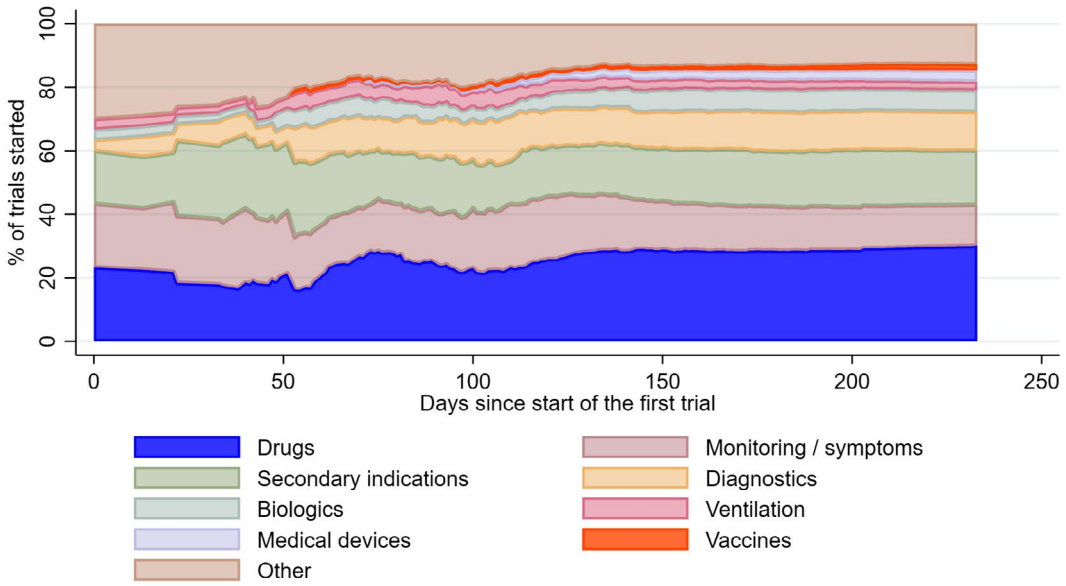


Figure 4. Types of COVID-19 clinical trials. The figure shows the percentage share of the various interventions or treatments in the cumulative number of clinical trials related to COVID-19. [Colour figure can be viewed at wileyonlinelibrary.com]

indications, such as physical and mental health problems, resulting from pandemic-related socio-economic lockdowns, fears of infection, and prolonged hospitalization. While many policy makers and the public hope for the rapid development of an effective vaccine, our results show that by the end of July 2020, only around 2% of COVID-19 trials were testing vaccines. Although the number of clinical trials of vaccines has gradually increased with the progression of the pandemic, the number of such trials relative to the total number of trials remains rather low. This seems to suggest that vaccine development requires highly specialized competencies, which only a few players in the field possess.

4.3. Is repurposing used as an innovation strategy to identify treatments?

We further investigated which drugs are being tested in COVID-19 trials. Table 1 provides information on the 11 most commonly tested drugs in our sample. As shown in the table, we find that many of the frequently tested drugs were approved more than a decade ago so that patent protection and market exclusivity should have expired, allowing for generic alternatives with much lower prices than the original drugs. Notably, the search for safe and effective COVID-19 treatments is not limited to antiviral drugs, and many of the drugs were originally developed for different indications, including parasitic and bacterial infections, hypertension, and cancer.

We also note that many commonly tested drugs are tested in combination with other drugs. To better illustrate this interesting observation, Figure 5 maps the co-occurrence of drugs or pharmaceutically active ingredients in COVID-19 clinical trials. Drugs that are not tested in combination with or compared to other drugs have not been included in the figure to improve readability. The size of the nodes in Figure 5 indicates how often a drug is used, while the position within the network indicates how often the drug is used in conjunction with other drugs. Remarkably, hydroxychloroquine is the most dominant drug in the figure and is used in a variety of combinations with other drugs. Other prominent drugs are azithromycin, ivermectin, favipiravir, and remdesivir, all of which are repurposed drugs.

Our results reveal that many clinical investigators are using repurposing as an innovation strategy in response to the COVID-19 pandemic. However, it remains to be seen whether repurposing will ultimately lead to successful innovations, that is, safe and effective medicines. We are concerned that the high concentration on a few drugs does not exhaust the full range of possibilities and that, despite the large number of clinical trials, the current landscape does not exhibit a sufficient level of breadth. In particular, the concentration on hydroxychloroquine, the most commonly used drug in COVID-19 drug trials, may not pay off. While scientific evidence is developing rapidly, trial results published since April 2020 have raised questions about the safety and efficacy of hydroxychloroquine (Scavone et al., 2020;

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Table 1. Overview of the most prominent treatments tested for COVID-19

Active ingredient or drug	Number of trials	Combinations with other drugs	Earliest FDA approval of drug used in COVID-19 trials	Main conditions treated with drug
Hydroxychloroquine	213	66	April 1955	Malaria
Azithromycin	72	32	November 1991	Bacterial infections
Tocilizumab	43	32	January 2010	Rheumatoid arthritis; systemic juvenile idiopathic arthritis
Lopinavir (Ritonavir)	42	41	September 2000	HIV/AIDS
Ivermectin	33	16	November 1996	Parasite infections
ARB (angiotensin II receptor blocker)	28	18	April 1995	Hypertension; congestive heart failure
Favipiravir	23	10	Not yet approved	Influenza
Remdesivir	20	20	Not yet approved; since May 2020 emergency use authorization as COVID-19 treatment	Virus infections
ACE-I (angiotensin-converting enzyme inhibitors)	18	2	April 1981	Hypertension; congestive heart failure
Nitazoxanide	18	8	November 2002	Virus infections; parasite infections
Ruxolitinib	18	4	November 2011	Myelofibrosis; polycythemia vera

The numbers are based on 743 COVID-19-related trials testing 395 drugs initiated between December 2019 and the end of July 2020.

Wiersinga et al., 2020). In addition, the US Food & Drug Administration (2020b) issued a warning in June 2020 because it fears severe side effects from using hydroxychloroquine. Despite this academic evidence and the regulatory concerns, hydroxychloroquine remains the most widely tested medication for COVID-19 and is being tested in 83 additional new trials that started between May 2020 and the end of July 2020.

Notwithstanding the need for further research, some repurposed drugs are showing promising initial results as effective treatments for COVID-19. Remdesivir is a notable example. The drug has not shown clinical efficacy in trials against Ebola and the Marburg virus, but appears to be an effective treatment for COVID-19, at least for patients with severe symptoms (Rochwerg et al., 2020). In fact, shortly after receiving regulatory approval from the European Union on July 3, 2020, the European Commission signed a 63 million euro supply contract for the treatment of approximately 30,000 patients (European Commission, 2020). The United States followed suit and approved remdesivir as the first treatment for COVID-19 on October 22 (US Food & Drug Administration, 2020a). Based on current evidence, it seems that remdesivir is a successful case of drug repurposing.

To better understand when and why sponsors rely on drug repurposing, we conducted an exploratory probit regression analysis predicting the likelihood that a given clinical trial, studying a single drug or a combination of drugs, uses innovation repurposing. Our dependent variable equals one if a drug is repurposed, that is, the drug has been applied to treat a disease other than COVID-19 before, and zero otherwise (i.e., a *de novo* drug development). The information is based on our manual coding and matching information based on the Drugs@FDA database. We included various covariates as potential predictors, including the cumulative number of COVID-19 cases and COVID-19-related deaths per 100,000 inhabitants in the sponsor country, economic factors (GDP per capita), and indicators for different sponsor types. Table 2 provides a detailed description of the variables used in our probit regression.

Summary statistics and correlations are presented in Table 3, and the results of our regression analysis are presented in Table 4. The results of our probit regression suggest that drugs are repurposed in response to a high number of COVID-19-related deaths per 100,000 inhabitants in the sponsor country. Thus, as external pressure increases, repurposing is becoming more dominant as a crisis response. Moreover, the GDP per capita is negatively related

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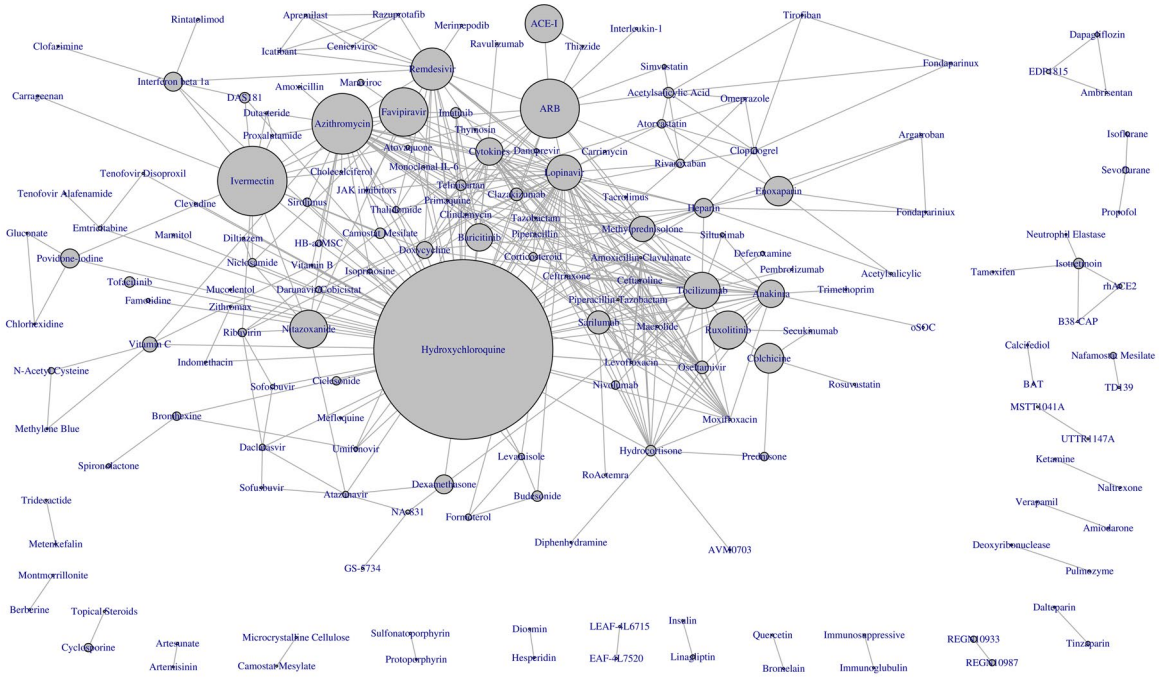


Figure 5. Network of COVID-19 drugs tested. The network is based on 175 active substances. A further 220 tested active ingredients are not shown here because they are not tested in combination with other drugs and are usually tested in isolated clinical trials. [Colour figure can be viewed at wileyonlinelibrary.com]

to the probability that a clinical trial tests a repurposed drug, which indicates that repurposing is a viable strategy for low-income countries where the financial resources for *de novo* drug development may not exist. We also see that the probability of *de novo* drug development increases if the sponsor is a biopharmaceutical firm, whereas device manufacturers, hospitals, or governments will more likely resort to drug repurposing. As drug repurposing presents lower barriers to entry, it invites more nontraditional sponsor types.[7]

5. Discussion of results and policy implications

In this study, we set out to understand how organizations innovate in crisis situations, with a focus on the recent COVID-19 pandemic. Based on data from COVID-19-related clinical trials, we find that organizations are focusing on repurposing drugs as an immediate response to the health-care needs resulting from the viral pandemic. Despite the benefits of repurposing, we also see that many trials are testing the same drugs and pursuing similar strategies, indicating an inefficient use of resources and a duplication of efforts. The sheer mass of clinical trials also creates an impenetrable thicket and makes it difficult to identify truly novel and unique trials that follow high academic and clinical standards, especially since many trials are sponsored by nontraditional and potentially less experienced players. This can be problematic as it may inhibit policy makers from supporting the most promising approaches.

From a theoretical point of view, our study contributes to the emerging literature on innovation repurposing in management (Andriani et al., 2017; Kucukkeles et al., 2019). Although our empirical focus is on the health-care sector, the idea of repurposing could also be relevant in other contexts, including semiconductors (e.g., the use of Raspberry Pi computers in various environments), engineering (e.g., the use of drone technologies for passenger aviation), and software development (e.g., the redeployment of code) (also see Dew et al., 2004; Andriani and Carignani, 2014). Even in the context of biopharmaceutical innovation, our study is instructive because it shifts the focus in existing research on repurposing drugs for rare diseases and accidental discoveries toward the systematic use of repurposing strategies in response to a viral pandemic, thus providing an interesting contextualized comparison. More broadly speaking, understanding when and why organizations are innovating through repurposing can help to understand the dynamics of innovation and provide

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Table 2. Variable description

Dependent variable	
Repurposed drug	Binary variable equaling one if a drug is repurposed, that is, the drug has been applied to treat a disease other than COVID-19 before, and zero otherwise.
Independent variables	
COVID-19 cases per 100,000 population	Number of COVID-19 cases in a sponsor country per 100,000 inhabitants as of mid-August 2020. If multiple sponsor countries are involved, the variable represents the average of the corresponding countries.
COVID-19 deaths per 100,000 population	Number of COVID-19 deaths in a sponsor country per 100,000 inhabitants as of mid-August 2020. If multiple sponsor countries are involved, the variable represents the average of the corresponding countries.
Academic institutions	Binary variable equaling one if the trial is sponsored by an academic institution, and zero otherwise.
Biopharmaceutical firms	Binary variable equaling one if the trial is sponsored by a biopharmaceutical firm, and zero otherwise.
Device manufacturers	Binary variable equaling one if the trial is sponsored by a medical device manufacturer, and zero otherwise.
Hospitals	Binary variable equaling one if the trial is sponsored by a hospital, and zero otherwise.
Governments	Binary variable equaling one if the trial is sponsored by national, regional, or local governments, and zero otherwise.
GDP per capita	GDP per capita in 2019 in current US dollars. The variable enters the analysis in logarithmic form. If multiple sponsor countries are involved, the variable represents the average of the corresponding countries.
Days since first COVID-19 trial	Number of days from the first COVID-19 trial until the start of a trial.
Number of trial sites	Number of sites – such as hospitals or clinics – the trial is conducted in.
International trial	Binary variable equaling one if the trial is conducted in multiple countries, and zero otherwise.
Phase controls	A set of binary variables controlling for the phase of the clinical development process.

a more holistic picture of the potential value of original innovations as they experience late cyclical revivals.

Our study also has important implications for the literature on crisis management (Bundy et al., 2017). Prior research has primarily focused on understanding crisis situations that emanate from specific organizational problems or macroeconomic factors (Mainiero and Gibson, 2003; Bundy et al., 2017). We expand this conception of a crisis by introducing the idea of 'innovation crisis,' which we understand as specific innovation demands that unexpectedly shift organizational attention to a new area. Such situations are particularly interesting because they show how organizations can adapt to unforeseen contingencies to effectuate immediate responses. We show that innovation repurposing is a dominant crisis response strategy and illuminate the value and dangers of applying old technologies in a new context.

A key finding of our study is that the (generally positive) activity level triggered by the crisis may have led to a lack of coordination and variety as evidenced by the large number of highly similar and potential redundant clinical trials. This is problematic because these duplicate clinical trials consume resources that could be better employed in different trials to increase variety and thus the likelihood of finding an effective treatment. A potential explanation for the lack of coordination could be that many clinical trials are confined to individual countries or conducted by a single institution, which may reduce information exchange between actors and explain the number of similar clinical trials. This problem could be spurred on by politically motivated and nationalist pressure from governments to give priority to local research and development. Moreover, as many organizations are working toward the same goal, the competitive landscape is becoming increasingly confusing, making it difficult for actors to keep track of new scientific evidence and promising avenues for future research.

In addition, the concentration on rapid success might also crowd out solutions that are more likely to be long-term oriented and create a 'first-past-the-post' mentality. In the end, this reduces economic incentives for developing truly novel innovations out of a fear of being too slow or having to compete

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Table 3. Summary statistics and correlations

		N	Mean	SD	Min.	Max.	(1)
(1)	Repurposed drug	623	0.8555	0.3518	0	1.0000	1.0000
(2)	COVID-19 cases per 100,000 population	623	891.7808	679.2399	2	4073.6323	–0.1291**
(3)	COVID-19 deaths per 100,000 population	623	37.3321	21.6372	0	86.5896	–0.0305
(4)	Academic institutions	623	0.4366	0.4964	0	1.0000	0.2329***
(5)	Biopharmaceutical firms	623	0.2681	0.4433	0	1.0000	–0.4729***
(6)	Device manufacturers	623	0.0128	0.1127	0	1.0000	0.0469
(7)	Hospitals	623	0.4205	0.4940	0	1.0000	0.1928***
(8)	Governments	623	0.0401	0.1964	0	1.0000	0.0840*
(9)	GDP per capita	623	10.1828	1.4845	2	11.3144	–0.1448***
(10)	Days since first COVID-19 trial	623	148.1974	41.8183	0	233.0000	–0.1416***
(11)	Number of trial sites	623	5.7079	14.9859	1	184.0000	–0.0114
(12)	International trial	623	0.0562	0.2305	0	1.0000	–0.0782
		(2)	(3)	(4)	(5)	(6)	(7)
(2)	COVID-19 cases per 100,000 population	1.0000					
(3)	COVID-19 deaths per 100,000 population	0.5335***	1.0000				
(4)	Academic institutions	–0.0541	–0.0191	1.0000			
(5)	Biopharmaceutical firms	0.1368***	0.0661	–0.3647***	1.0000		
(6)	Device manufacturers	0.0075	–0.0380	–0.0717	–0.0368	1.0000	
(7)	Hospitals	–0.0523	0.0189	–0.2058***	–0.2733***	0.0761	1.0000
(8)	Governments	–0.0954*	–0.0830*	0.0839*	–0.0499	–0.0233	0.0081
(9)	GDP per capita	0.3966***	0.4157***	–0.2039***	0.1998***	–0.0401	0.1053**
(10)	Days since first COVID-19 trial	0.1886***	0.1355***	–0.0433	0.2337***	–0.0295	–0.1398***
(11)	Number of trial sites	0.0680	0.0542	–0.1382***	0.2364***	0.1222**	–0.0980*
(12)	International trial	0.0068	0.0196	–0.0883*	0.2300***	0.0341	–0.1090**
		(8)	(9)	(10)	(11)	(12)	
(8)	Governments	1.0000					
(9)	GDP per capita	–0.0675	1.0000				
(10)	Days since first COVID-19 trial	–0.0129	0.0874*	1.0000			
(11)	Number of trial sites	–0.0501	0.1183**	–0.1056**	1.0000		
(12)	International trial	–0.0499	0.1021*	–0.0303	0.4843***	1.0000	

*$P < 0.10$, **$P < 0.05$, ***$P < 0.01$.

against multiple alternative products. This would be the case, for example, if a sufficiently effective and inexpensive repurposed drug is brought to the market prior to the launch of a novel drug that takes much longer to develop and incurs higher costs. In this scenario, any follow-on product would have to compete and potentially share the market with the first mover, a prospect that reduces the *ex-ante* incentives to enter the market at all. An empirical indication for this problem could be the fact that biopharmaceutical firms, which traditionally introduce the majority of medical innovations, are woefully unrepresented in clinical trials related to COVID-19.

No study is without limitations and ours is no exception. The explorative approach of our study focuses on understanding how organizations respond to an unexpected crisis event that calls for rapid innovation. In view of the limited previous work in this field, we decided against testing a specific theory and instead focused on uncovering latent patterns in a descriptive way. This explorative approach naturally calls for future research to identify the causal

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Table 4. Probit regression estimates predicting innovation drug repurposing

	(1)	(2)	(3)	(4)	(5)
Dependent variable: Repurposed drug					
COVID-19 cases per 100,000 population	−0.0000	−0.0001			−0.0002
	(0.0001)	(0.0001)			(0.0001)
COVID-19 deaths per 100,000 population			0.0098***	0.0061*	0.0081**
			(0.0032)	(0.0036)	(0.0039)
Academic institutions		0.3564*		0.3283*	0.3082
		(0.1879)		(0.1893)	(0.1893)
Biopharmaceutical firms		−1.3322***		−1.3074***	−1.3273***
		(0.1683)		(0.1715)	(0.1701)
Device manufacturers		4.7949***		5.1341***	4.8618***
		(0.3259)		(0.3219)	(0.3274)
Hospitals		0.3669**		0.3784**	0.3572*
		(0.1871)		(0.1892)	(0.1896)
Governments		4.7380***		5.0981***	4.7601***
		(0.2095)		(0.2128)	(0.2092)
GDP per capita	−0.2897***	−0.1709**	−0.4337***	−0.2912***	−0.2382**
	(0.0864)	(0.0823)	(0.0888)	(0.0970)	(0.0942)
Days since first COVID-19 trial	−0.0035*	0.0010	−0.0039**	0.0005	0.0008
	(0.0018)	(0.0020)	(0.0018)	(0.0020)	(0.0020)
Number of trial sites	0.0006	0.0173**	0.0009	0.0179**	0.0175**
	(0.0040)	(0.0079)	(0.0041)	(0.0080)	(0.0080)
International trial	−0.5473*	−0.1915	−0.5170*	−0.1783	−0.2019
	(0.2872)	(0.3222)	(0.2819)	(0.3163)	(0.3173)
Phase controls	Yes	Yes	Yes	Yes	Yes
Constant	4.7006***	2.6140***	5.8806***	3.6297***	3.1792***
	(0.9602)	(0.9173)	(0.9605)	(1.0402)	(1.0067)
N	623	623	623	623	623
AIC	473.1522	379.2301	466.8190	377.8356	378.4225
BIC	526.3668	454.6174	520.0336	453.2229	458.2443

Robust standard errors in parentheses.
*$P < 0.10$, **$P < 0.05$, ***$P < 0.01$.

mechanism of repurposing in light of a specific theory (Hambrick, 2007). The literature on exaptation might be especially promising in this regard (Cattani, 2005; Andriani and Carignani, 2014). Follow-on studies could, for example, explore the role of firms' experience, their internal resources and capabilities, network structures, and international collaborations as potential drivers of repurposing. Apart from studying organizational-level drivers, it might also be interesting to explore how different innovation demands can shape repurposing strategies. This could include factors, such as market pressure and the role of regulators in facilitating repurposing and fast-tracking this process. More specifically, it is likely that repurposing drugs to treat orphan or rare diseases (Kucukkeles et al., 2019) is motived by a strong cost-saving logic and, therefore, might differ fundamentally from repurposing strategies used in the context of a pandemic where speed is much more critical and potentially a major driver for the decision to rely on repurposing.

In addition, we have not investigated why organizations decide to participate in the search for COVID-19 treatments, which is another opportunity for further study. In particular, it would be interesting to investigate how firms balance the trade-off between public incentives to join the race for a drug or vaccine against the threat of high competition and the reduced financial margins for repurposed development versus the development of novel medicines. Understanding these considerations could help to identify the underlying incentives for firms to contribute toward solving a health-care crisis.

Finally, while we descriptively examine the value and caveats of innovation repurposing, a more in-depth analysis could show under which circumstances

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repurposing is more successful. In this regard, a comparison of repurposing efforts in different areas, such as rare diseases and COVID-19, could be particularly promising. It would also be interesting to see which organizations rely on repurposing strategies, whereas others prefer novel development. In untangling the causal mechanisms, organizational resources, and capabilities, as well as intellectual property rights, could play a central role. Therefore, we see our paper as an impetus to further explore the role of repurposing in innovation research.

Despite its limitations, our study carries some relevant implications for policy makers. In view of the relatively small number of biopharmaceutical firms involved in the search for COVID-19 treatments, the question arises as to whether firms have sufficient incentives to enter the market. There are two reasons that suggest this might not be the case. First, firms may not be able to patent a repurposed drug because the knowledge is already in the public domain. Therefore, profit margins are relatively low. Second, the 3-year exclusivity periods for repurposed drugs in the United States, the largest pharmaceutical market, may be too short to provide incentives for clinical trials of repurposed drugs, as firms still have to conduct expensive phase 3 clinical trials (Pushpakom et al., 2019). This suggests that policy makers should consider revising incentive schemes to provide motivations for firms to shift internal resources from alternative options to the development of treatments for an imminent pandemic. In view of the long drug development cycles (DiMasi et al., 2016), it seems to be of paramount importance to provide long-term incentives and public support to conduct continuous and large-scale research for treatments against viruses to be more reactive and more quickly react in the event of a crisis.

From a managerial perspective, our study has three important implications. First, the exponential growth rate and rapid development of clinical trials in a pandemic suggest that managers need to act quickly if they want to enter the market. For example, remdesivir was among the first clinical trials launched for COVID-19 and was the first to receive regulatory approval in the European Union. A late market entry could mean that competitors reap most of the benefits, although a follow-on product might later prove more effective. Second, managers must also be aware of the risks associated with rapid innovation in a health-care crisis. If a treatment shows unexpected side effects that only occur later, the legal and reputational damage could be irreparable. Third, there is, of course, a strong moral responsibility in responding to a pandemic. Although economic benefits play an important role when entering a market, a major crisis in the health-care sector may also require a strong commitment as part of a firm's larger responsibility to society (Jones and Wicks, 1999). In recent years, people have become increasingly aware of how firms respond to a crisis, and the COVID-19 pandemic should be no exception (Wang et al., 2021).

Looking at the crisis situation as a whole, our study shows that innovation activities in a crisis situation follow fundamentally different dynamics than under normal circumstances. This has implications for the type of innovation (e.g., repurposing vs. *de novo*, short term vs. long term, incremental vs. radical), with repurposing being one of the key innovation strategies in a crisis. We show that repurposing is a double-edged sword that increases speed, but at the same time promotes a dynamic that creates inefficiencies and redundancies. The challenge for crisis management is to create selective incentives for innovation and at the same time improve coordination between actors to enable a broad search for repurposed innovation.

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Notes

[1] https://aact.ctti-clinicaltrials.org/.

[2] Every clinical trial in the database contains information about the disease or medical condition that is being studied. We use this information to identify all trials studying COVID-19 by searching for the term 'COVID 19' and its synonyms, such as 'SARS-CoV-2,' among the conditions addressed in the studies and in the titles of the clinical trials. A full list of synonyms used in this study is provided in Table 5 in the Online Appendix.

[3] https://www.pharmexec.com/view/pharm-execs-top-50-companies-2019.

[4] https://www.accessdata.fda.gov/scripts/cder/daf/.

[5] https://coronavirus.jhu.edu/region.

[6] https://databank.worldbank.org/home.aspx.

[7] We focused our regression analysis on drug repurposing. In an unreported robustness check, we also included repurposed biologicals in the analysis. The results from this extended analysis are qualitatively consistent with the results presented in the Table 4.

Marvin Hanisch is an Assistant Professor in the Innovation Management & Strategy Department at the University of Groningen. He studies how individuals and organizations collaborate in knowledge-intensive areas with a focus on the underlying governance mechanisms. He applies qualitative and quantitative methods to contexts such as strategic alliances in the biopharmaceutical industry, the Linux kernel development community, and industry blockchain networks.

Bastian Rake is an Assistant Professor at Maynooth University School of Business. His research focuses on innovation in knowledge-intense industries with a particular focus on the biotechnology and pharmaceutical industries, collaboration and innovation networks, as well as in the internationalization of science and R&D. His research appeared in renowned journals such as Research Policy, Industrial and Corporate Change, Industry and Innovation, as well as the PLoS ONE.

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