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Second World War and the direction of medical innovation

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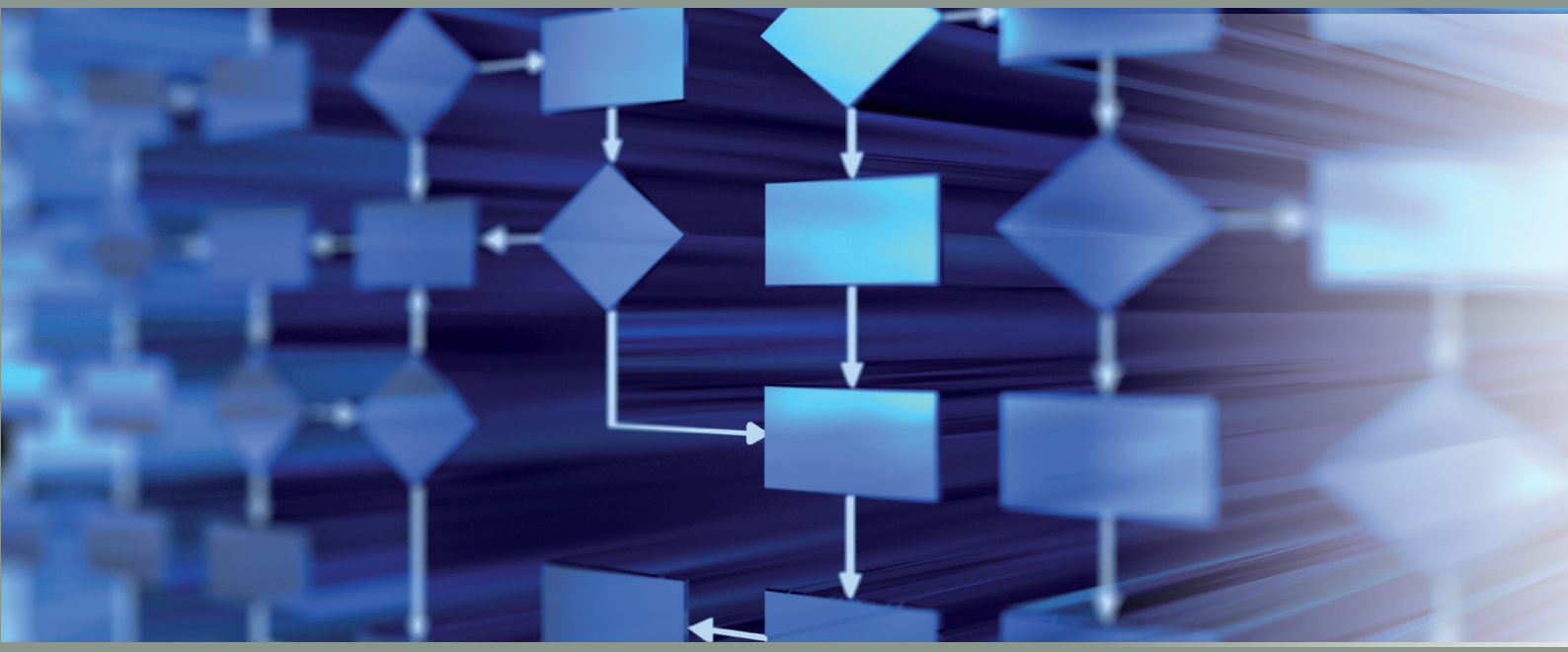

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Second World War and the direction of medical innovation

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Abstract:

This paper provides an overview of the role of the United States of America (U.S.) Second World War research effort on the direction of innovation, with a particular focus on medical research. It provides an overview of the U.S. wartime research program, reviews quantitative evidence on the effects of the overall wartime research shock on postwar patenting, describes the wartime medical research effort, and summarizes case studies of five major wartime medical research programs
(penicillin, antimalarials, vaccines, blood substitutes, and hormones) and their effects on postwar R&D. It concludes by drawing out implications for crisis innovation and the direction of innovation in general, discussing mechanisms through which crises may have long-run effects, and highlighting hypotheses warranting further investigation.

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Keywords: *Second World War; direction of innovation; crisis innovation*

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Disclaimer:

The views expressed in this article are those of the author and do not necessarily reflect the views of the WIPO or its member states.

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1. Introduction

A peculiar fact of history is that crises — unexpected events that impose high costs and demand urgent resolution — are sometimes the sources of valuable innovation. In *The Poverty of Philosophy*, Karl Marx wrote of worker strikes as a source of innovation,[2] and a half-century ago economic historian Nathan Rosenberg (1969) discussed how supply shortages and other constraints, often due to war, can shape the direction of technical change. The Covid-19 pandemic has revived interest in these old questions, with speculation that the innovation and diffusion of technologies induced by the crisis — from mRNA vaccines to telemedicine, to new models of education and business practice — may have long-lasting positive socio-economic effects.

As of this writing, it is too soon to tell what impact the Covid-19 shock will have on the direction of innovation. However, historical evidence may inform speculation on the issue. In this paper, I discuss the role of the U.S. Second World War research effort on the direction of research, with a particular focus on medical innovation. Second World War was the first time the U.S. government seriously invested in funding extramural research, including the first significant federal funding of medical research, and is often described as a watershed event in the U.S. innovation system. During the war, the government supported several important technologies that were central to Allied victory, including radar, the atomic bomb, and the mass production of penicillin. The crash R&D effort has also been credited with fueling the rise of U.S. technological leadership in the postwar era (Nelson and Wright, 1992) and, in medicine, the golden age of pharmaceutical innovation in the 1950s and 1960s (Pisano 2002; Temin 1979).

I begin, in Section 2, by describing the wartime R&D effort, run through the Office of Scientific Research and Development (OSRD). In Section 3 I summarize previous research (with Daniel Gross) on the quantitative impact of the wartime shock on the direction of U.S. innovation. I also discuss why this particular empirical approach is ill-suited to studying the direction of medical innovation. As an alternative, in Section 4 I summarize a series of case studies, drawing from historical accounts, of five major wartime medical research efforts: penicillin, antimalarials, vaccines, blood substitutes, and hormones. I pay particular attention to what the historical literature says about the links between these efforts and the direction of innovation after the crisis. In Section 5, I step back and summarize different mechanisms through which the wartime research efforts may have influenced the direction of innovation. Finally, in Section 6 I discuss potential implications for thinking about the long-term effects of Covid-19 on medical innovation based on insights from Second World War, but also the differences between the two crises that limit the lessons we can draw from history.

2. Scientists at War: the OSRD and the Committee on Medical Research

In 1940, as the German armies advanced in Western Europe, U.S. involvement in Second World War was imminent. Military leaders and policymakers knew that more so than in previous conflicts, this would be a technological war, and that the side that could best marshal the R&D needed by the military — for weapons development, communications and radar, jet propulsion, chemistry, optics, atomic fission, and medicine, among others — would have a major advantage. This was on one hand a source of optimism, since in the period following World War

[2] "[F]rom 1825 onwards, almost all the new inventions were the result of collisions between the worker and the employer. After each new strike of any importance, there appeared a new machine" (quoted in Rosenberg 1969, pages 12-13).

I U.S. firms and universities had improved their scientific and technological capabilities in a range of fields. On the other hand, there was no serious national policy for coordinating or supporting this research. Outside of agriculture, the U.S. government did not seriously fund extramural research before Second World War, and as Vannevar Bush (1945) would later put it, had "no national policy for science."

Recognizing the gap, in June 1940 President Franklin D. Roosevelt authorized the creation of the National Defense Research Committee (NDRC). NDRC was led by Bush (former Dean of Engineering at MIT, and President of the Carnegie Institution of Washington), together with Karl Compton (MIT President), James Conant (Harvard President), Frank Jewett (President of the National Academy of Sciences, and Chairman of the Board at Bell Labs), Richard Tolman (CalTech physics) and the U.S. Patent Commissioner Conway Coe. NDRC was created by Roosevelt to "coordinate, supervise, and conduct scientific research on the problems underlying the development, production, and use of mechanisms and devices of warfare." To do so, it made the momentous decision to support research through contracts to leading firms and universities, which the government had not previously done on a large scale. The effort did not initially include medical research, but in June 1941 Roosevelt signed an Executive Order creating the Office of Scientific Research and Development (OSRD) composed of NDRC and a new Committee on Medical Research (CMR). All this happened before the December 1941 Pearl Harbor attacks, when the U.S. would officially enter the war.

During the war, OSRD entered into over 2,000 R&D contracts with a value of $7.4 billion current dollars, a pittance by today's standards but much more than the U.S. government had previously invested in research. Gross and Sampat (2020b, 2021a, 2021b) describe the OSRD model in detail. Its core features included setting priorities in close cooperation with the military, funding largely applied research activities focused on crisis resolution, designing policies (including patent and indirect cost policies) to engage the most capable researchers, funding multiple rival efforts when there was solution uncertainty, coordinating decentralized R&D efforts, supporting not just research but also downstream production and diffusion, and in general prioritizing time (rapid crisis resolution) over money. This crisis R&D push contributed to the development of a range of technologies that helped win the war, including, famously, radar and the atomic bomb, and communication technologies. The effort was widely considered a success and crucial to the Allied victory. So impressed were policymakers that even before the war was over, Roosevelt asked Bush to reflect on lessons from this experience for peacetime R&D policy, to promote goals of national security, health, and economic welfare. Bush's response, *Science, The Endless Frontier*, is sometimes considered the blueprint for postwar R&D policy.[3]

CMR, though only one-tenth the size of NDRC in financial terms, was also crucial to crisis resolution, helping support the mass production of penicillin, blood substitutes, research on malaria, and numerous other technologies that were crucial for the Allied victory and highlighted in the Bush Report. The Executive Order that created OSRD instructed that CMR would be in charge of determining (and recommending for funding) "the need for and character of contracts to be entered into with universities, hospitals and other agencies conducting medical research activities" (Executive Order 8807, "Establishing the Office of Scientific Research and

[3] The model it prescribed, with a heavy emphasis on basic research and priority setting by scientists, deviated considerably from the OSRD approach (Gross and Sampat 2021b). Mowery (1997) argues that Bush's report had a stronger impact on the ideology of postwar funding than on institutional design or operation. In practice, the postwar funding system was very different from the OSRD model (Gross and Sampat 2021b) but also deviated from many of the specific recommendations in the Bush Report.

Development."). Large-scale federal support for medical research was also radical for its time. Chester Keefer (the "penicillin czar") has described CMR as a "novel experiment in American medicine, for planned and coordinated medical research had never been essayed on such a scale" (Keefer 1969, p 62). While the National Institutes of Health (NIH) had existed going back to the 1930s, it was small, mostly focused on intramural research (conducted at its own labs), and struggled for funding (Swain 1962).

CMR operated slightly differently from NDRC, in particular working closely with pre-existing government committees devoted to wartime medical research that had been formed (but did not have significant funding) a year earlier. Its main divisions were Medicine, Surgery, Aviation Medicine, Physiology, Chemistry, and Malaria, reflecting the range of medical problems where the military sought R&D advances. Stewart (1948, 102) notes that even though the problems CMR dealt with (citing pneumonia, malaria, burns, wounds, shock, etc.) were not as new as those required from the NDRC (citing radar, the proximity fuse, and the atomic bomb):

> The shift in emphasis and even in direction was enormous. Many subjects of minor importance in peacetime become of controlling importance in war. Some subjects are born of war. Tropical medicine had been considered of rather academic interest to the health of the United States. Even the machine age had not adapted our younger generation to flying at 40,000 feet or diving at 400 miles an hour.

That is to say, in most cases (though we will see some exceptions below) there was a sharp shift in the direction of research during the war, not just at NDRC but also at CMR. The following sections discuss the long-term effects of these shifts on the direction of U.S. innovation, first summarizing previous quantitative research on OSRD overall, then delving into case studies of specific medical research efforts.

3. OSRD and the Direction of Innovation

In previous research with Daniel Gross, I quantitatively examined the effects of the wartime shock on innovation (Gross and Sampat, 2020a). We collected, transcribed, and harmonized a complete record of all OSRD contracts and outputs from the National Archives in College Park, MD. The final dataset included 2,254 contracts (to 461 distinct contractors), nearly 8,000 invention reports, and 2,740 patents. For each contract, we observe many features, including contractor name, location, and funding amount. The invention reports include patent application serial numbers, which we then link to issued patents. For the 588 CMR contracts we also observe subject descriptions, extended abstracts, and principal investigators.

We linked the contracts to all patents and examined how patenting in areas where OSRD was active changed before and after the war. Specifically, we collected data on all U.S. utility patents granted from 1920-1979 from the USPTO historical master file (Marco et al., 2015), using the serial numbers for patent applications on the OSRD invention reports. The historical master file includes information on application dates and patent classes. We linked the patent classes to the two-digit NBER patent categories (Hall et al., 2001). We also determined the location of the first-listed inventor on each patent from the Petralia et al. (2016) HistPat dataset.

To understand the effects of the wartime shock on the direction of innovation, we began by comparing U.S. versus foreign patenting in more and less intensively treated classes, before and after the war. The treatment measure is the share of all U.S. patents in a class, between 1941 and 1948, that came from OSRD contracts. Exhibit 1 shows the top 10 treated NBER categories, using this measure:

Exhibit 1: Top 2-digit NBER categories by OSRD rate, 1941-1948

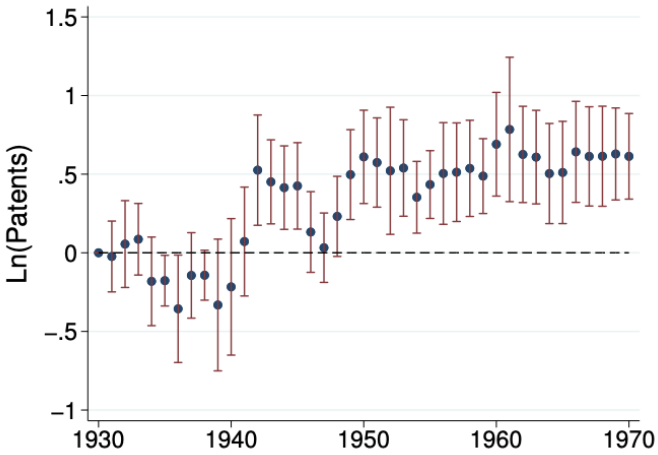
Category	Description	# Patents from OSRD contracts	Pct. of patents from OSRD contracts, 1941-48	Max pct. OSRD in any year, 1941-48
44	Nuclear, X-rays	194	12.5%	24.8%
21	Communications	671	6.9%	16.6%
46	Semiconductor devices	15	5.4%	12.1%
42	Electrical lighting	241	4.2%	10.0%
22	Computer hardware/software	65	4.1%	8.5%
23	Computer peripherals	2	3.9%	12.5%
43	Measuring, testing	187	3.1%	6.8%
41	Electrical devices	308	2.5%	6.5%
45	Power systems	163	1.7%	4.2%
31	Drugs	27	1.7%	6.4%

Notes: This is a reproduction of Table 3 from Gross and Sampat (2020a). The table lists the 10 2-digit NBER categories with the highest fraction of 1941-1948 patents produced under OSRD contracts, in descending order, and the number of patents and the maximum fraction of patents that were OSRD patents in any given year.

Importantly, given the focus of this paper, note that while "Drugs" is among the top 10 treated classes, it is relatively low on the list. This reflects the lower propensity to patent at the CMR than at OSRD overall (and potentially also lower absolute funding levels) meaning the analyses on the effects of medical research will require other approaches as well, described in more detail below.

In one set of analyses, we compared patenting at the USPTO by U.S. versus non-U.S. inventors (based on locations of first-listed inventors on patents), in heavily treated versus less heavily treated NBER categories, before and after the war. Exhibit 2 shows how patenting in the top quartile of treated NBER classes evolved over the 1930-1970 period. Overall patenting is 50-60 percent higher by U.S. inventors in the top-treated classes (relative to the bottom quartile, which includes untreated classes), and this effect is persistent for decades.

Exhibit 2: USPTO patenting by U.S. versus foreign inventors in the top quartile of OSRD treated classes (relative to untreated classes), annual estimates 1930-1970:



Notes: This is a reproduction of Figure B.5 from Gross and Sampat (2020a), which shows annual difference-in-difference estimates of the effects of the OSRD shock on domestic vs. foreign patenting (based on inventor address) at the USPTO, in technology areas (2-digit NBER categories) in the top quartile of NBER treatment. Error bars represent 95 percent confidence intervals.

The paper also reports a strong dose-response relationship in these estimates; i.e., the effects are strongest in the top quartile (those shown above), and weaker in lower quartiles (see Figure 3 in Gross and Sampat, 2020a). In companion analyses using data from PATSTAT, we also compared USPTO patenting versus patenting at the British and French patent offices at the IPC level, showing very similar results and magnitudes of effects as those reproduced above.

The results are suggestive of long-lasting effects on U.S. patenting in technology areas that were subject to the wartime shock relative to those that were not, i.e. a shift in the direction of innovation. This is consistent with a range of qualitative and historical accounts (Mowery and Rosenberg, 2000; Nelson and Wright, 1992; Temin 1979) suggesting the wartime research effort catalyzed innovation in a range of industries in the decades that followed.[4]

For various reasons, the Gross and Sampat (2020a) approach is not ideal for examining the direction of medical research. For one thing, patent classes don't typically map to specific diseases or medical research fields. Moreover, the propensity to patent medical research was low. CMR contracts primarily generated publications (nearly 2,500) rather than patents (just

[4] In other analyses, the core of their paper, Gross and Sampat (2020) also show long-term effects on the geography of innovation and other outcomes, lasting into the 1970s, and explore mechanisms underlying these effects.

81).[5] This reflected a policy choice by OSRD. After long deliberation (Gross and Sampat 2020b, Sampat 2020), OSRD decided that in most cases it would use a "long form" patent clause allowing contractors to retain patent rights and make patent decisions, subject to a government-use license and the requirement to report inventions and patents back to OSRD. This decision was made to incentivize participation by firms in the wartime effort, some of which were concerned these provisions would spill over to research and inventions emanating from their own private investments, including those before the war (Gross and Sampat 2020b, 2021a). However, in medicine and a few other fields, OSRD retained rights to decide whether patents should be filed and the assignment of the resulting patents. Reflecting norms militating against medical patenting at the time (especially by academic institutions, a large share of the CMR contractors), CMR-supported research was not typically patented.

Accordingly, we cannot use "treated" versus "untreated" patent classes to look at the direction of medical innovation, as in the analyses above. Instead, we draw on evidence from case studies of five major CMR research efforts — penicillin, antimalarials, vaccines, blood substitutes, and hormones — to summarize the qualitative literature on the wartime medical research effort and the direction of innovation.[6] Non-random case studies have their limits, but in addition to helping illuminate influences that patent data may miss, another advantage is that they may point to mechanisms through which crises such as wars may influence the direction of research, complementing what we can learn from econometric analysis alone.

4. Wartime Medical Research and the Direction of Innovation: Case Studies

4.1 Penicillin and antibiotics[7]

> In the summer of 1941, when the Committee on Medical Research came into being, there was not enough penicillin in this country to treat a single patient. In the spring of 1942 a sufficient amount had been produced to treat *one* patient adequately. A year later the first group of wounded men returning from the Pacific received penicillin. By D-Day there was enough penicillin available for our armed forces and our allies, as well as a moderate amount for civilians. In 1945, penicillin was removed from government allocation so that it could be used widely in this country and abroad. (Chester Keefer, in Baxter 1946)

The mass production of penicillin is the most celebrated medical accomplishment of the Second World War effort. Like the other technologies discussed in this section, penicillin discovery and development pre-date the war. In 1928 at St. Mary's Hospital in London, the Scottish physician-scientist Alexander Fleming had found that penicillin inhibited the growth of bacteria in mold, in what is now a signal example of serendipity in research. A decade later, in 1939, an Oxford

[5] The majority of these patents are in two of the NBER categories listed above, Drugs and Organic Compounds.

[6] In ongoing work, we are instead linking CMR grants and the universe of medical publications (and potentially other outputs, including drugs) to medical subject categories, using a language processing tool called the medical text indexer (MTI) developed by the U.S. National Library of Medicine. Then we will look at treated medical categories versus others, similar to what we described for patent classes above. The case studies presented here will help guide these analyses, and, we expect, the interpretation of results.

[7] Parts of the penicillin and malaria studies draw on the discussions in Gross and Sampat (2020b).

University laboratory headed by Howard Florey and Ernst Chain (who, with Fleming, would share a Nobel Prize for this discovery in 1945) were first to purify the molecule. However, the Oxford group was unable to produce penicillin in the amounts that would be needed for human testing. In 1941, unable to engage British companies to help with production, Florey and another member of the Oxford team, Norman Heatley, came to the U.S. for help (Baxter 1946).
Soon after arriving, Florey and colleagues met with Alfred N. Richards, the Chairman of CMR. Though this project was more focused on production than the research activities typically supported by CMR (Stewart 1948), Richards assured them he would help. (Since there was uncertainty about the basic feasibility of natural penicillin production, CMR would also support a parallel effort to synthesize penicillin, discussed below.) While scaling up natural penicillin was a production problem, it was not simple. Baxter (1946) wrote: "It is impossible to exaggerate the difficulties and strains of those first eighteen months. The same difficulties encountered [by the British] were now encountered on a larger scale and with more at stake. It was scientists against time in a very real meaning of the phrase" (347).

For natural penicillin, CMR did not itself fund much of the initial R&D needed to produce penicillin, beyond some support to the Department of Agriculture's Northern Regional Research Laboratory (NRRL), where much of the work on fermentation techniques was done (Rasmussen 2002; Neushul 1993). Rather, its most crucial role initially was coordination. This included persuading private firms to get involved, communicating advances from NRRL to these firms, and brokering information flows among the firms (and back to the NRRL).

In one of its earliest meetings, CMR had stated its intention to stimulate "a concerted programme of research on penicillin involving the pooling of information and results" (Richards 1964, 442). Information sharing would be a struggle. In an October 1941 meeting Bush presided over a meeting between representatives of the Department of Agriculture, the National Research Council, and research directors from four firms it viewed as having capabilities for penicillin production: Merck, Pfizer, Lederle, and Squibb, to convince them to become involved in a collaborative program. At that meeting three of the four firms were non-committal about sharing information. The fourth, Merck, expressed willingness but expressed concerns about the legality of doing so under antitrust laws. At the second meeting (in December 1941), Merck announced it would share information (if permitted by the Justice Department); the others remained cautious, "but agreed to make periodic reports to the C.M.R. and to give discretion to C.M.R. to circulate their information" (Richards 1964, 442). In 1942 Merck and Squibb formally agreed on a collaborative research program including "full exchange of research and production information, joint ownership of inventions" and was open to "other firms who have made definite contributions to the solution of the problem." (Richards 1964, 442). In 1942, Pfizer was also included in the agreement, in force until 1945. Importantly, these four firms chose not to work under OSRD contracts (FTC 1958), but to fund research themselves and collaborate with CMR efforts and NRRL, perhaps deterred by the CMR's short form patent clauses or the prospects of excessive government control.

By 1942 the firms were able to produce enough penicillin to conduct trials. CMR then assumed a prominent role in coordinating clinical and field trials, and spent about 8 percent of its total budget on purchasing penicillin for testing during the war. The studies were originally limited to a handful of sites, but once enough penicillin was produced were eventually conducted by investigators at hundreds of clinics and medical centers, studying the effects of penicillin on numerous diseases. Collectively they showed strong positive results of penicillin on combating infections.

Despite considerable improvement in production yield and quality by 1943, reflecting the firms' efforts and NRRL's, Bush was dissatisfied with the extent of know-how transfer that had occurred. Though the drug companies had been cooperating "after a fashion" he remarked in a letter, they "have not made their development of manufacturing processes generally available" and "[u]ndoubtedly there could be expedition if the interchange were complete" (Bush to Elihu Root, quoted in FTC 1958, 38). At the same time, he noted while "it may be to the public interest" to bring in new manufacturers "it would hardly be equitable to ask the pharmaceutical houses that have born the burden of development to make their knowledge freely available" (FTC 1958, 39).[8] The tension between incentivizing participation of firms with requisite capabilities in the crisis resolution effort, and promoting broad diffusion of knowledge to expand production, also needed for crisis resolution would be present in several other CMR efforts as well.

The task of scale-up of production to meet demand was largely coordinated by the War Production Board (WPB). WPB corresponded with 175 potential producers and eventually worked with 20 in the program (Neushul 1993), providing construction assistance and supplies needed for scale-up. In some cases the government built the required production facilities directly; in others the private firms did themselves, knowing there was a large market during the war. The WPB too tried to promote information flow among participants (FTC 1958), working to get approvals for collaboration from antitrust authorities, collecting and circulating reports, and hosting meetings. According to Richards it "obtained and distributed information that greatly increased production effectiveness" (in Andrus, p lii). However, like Bush, WPB leadership lamented that firms were not adequately sharing information with WPB and one another (FTC 1958). The coordinator of the WPB program, Albert Elder (1970) later recalled "Progress could have been made more rapidly with a free exchange of information" (10).

Despite these frictions, the program was successful. By 1943 there was enough natural penicillin for military use, and also to meet civilian demand. During the war penicillin was also profitable for the firms involved, with the government paying cost-plus prices (Achilladelis 1993). Antibiotics would be the major drug market for the quarter-century after the war (Achilladelis 1993), and the focus of dozens of follow-on innovations. Cockburn et al (1999) argue the "technical experience and organizational capabilities accumulated through the intense wartime effort to develop penicillin" helped focus the industry on R&D in the years after the war in general (367). Achilladelis (1993) argues that the investments in antibiotic-specific production techniques and capacity (including fermentation plants) were leveraged to postwar antibiotics research by some firms. There is also a demand-side explanation for the follow-on investment: the market success of penicillin (and its falling price, as the basic process technology diffused and the market for natural penicillin crashed) led firms to explore similar replacement technologies, including those with stronger patent protection (Temin 1979; Achilladelis 1993) and clinical advantages (fewer side effects, better absorption, etc.).

Though CMR had an important coordinating and brokering role in the scale-up of natural penicillin, from the beginning of the war it favored, and more substantially funded, a parallel program to chemically synthesize penicillin. This was viewed by CMR leadership as a surer path to mass production (Swann 1983). CMR funded 9 firms, 2 universities, and a Department of Agriculture laboratory to determine penicillin's structure and synthesize it. Here too there were attempts to promote knowledge flows: companies were to provide progress reports to OSRD,

[8] Bush did suggest that firms may have process patents on the production techniques which they could later enforce, which might make the transfer of information "not only desirable but also equitable" (FTC 1958).

which would distill and pass along general process information to other firms without comprising specific proprietary positions. OSRD also had the right to inspect contractors' work and records (Swann 1983).

More so than natural penicillin (an old unpatented molecule) patent provisions were difficult in this research effort, since some of the firms had been working on synthesis with their own funds prior to the CMR contracts. Ultimately CMR waived the standard "short form" patent clauses for synthetic penicillin contracts, instead reserving a government license for all patents by contractors (before and after the CMR contracts), and the government's right to compel cross-licensing to other CMR contractors. Vannevar Bush himself was to draw the lines and be the "final arbiter" of patent rights and royalties on any inventions that resulted (Richards, in Andrus 1948, page lii). He made clear he had no intention of "inequitable treatment" of the firms that were contributing to the effort, and would seek to balance "reasonable profits" and "reasonable prices" (FTC 1958, 336).

We would never learn exactly how Bush would strike this balance. Despite being CMR's preferred effort, the synthetic penicillin effort was unsuccessful during the war, and the rapid progress in natural penicillin ultimately rendered it moot. However, the knowledge developed through this program "paved the way for [the] general synthesis of penicillins in the 1950s, and this led to the development of the therapeutically invaluable semisynthetic penicillins" (Swann 1983, 189). Indeed several of the investigators funded through the CMR program, including John Sheehan of Merck (later MIT), were central figures in the postwar research efforts. In this case of synthetic penicillin, the wartime effort helped create a general platform that was not useful during the war but would be fully exploited for years to come.

4.2 Malaria

While penicillin is the best-known wartime research program, the CMR invested a much larger share of its budget (over 20 percent) in the search for antimalarial drugs. While malaria had been controlled in the U.S. since the 1930s, during the war it was prevalent in many areas Allied soldiers expected to enter. Morbidity from malaria was a serious impediment to the Allied effort. General Douglas MacArthur would observe in 1942, "this will be a long war if for every division I have facing the enemy I must count on a second division in the hospital with malaria and a third division convalescing from this debilitating disease" (quoted in Condon-Rall 2000, 58).

Anticipating war, the Rockefeller Foundation and National Research Council had supported research on malaria in the 1930s. There were also parallel German efforts, including research on quinine substitutes (perhaps driven by the memory of World War I, when the Allies had cut off German quinine supply routes). One result of the German effort was the drug atabrine, which was reverse-engineered and sold in the U.S. since the early 1930s. However, the U.S.-produced version had a range of side effects, prompting speculation that the patent may have included deliberately misleading descriptions of the drug and the process to produce it (Baxter 1946). There was a fear, justified or not, that atabrine was too toxic to be reliable during wartime.

Thus the U.S. effort focused on identifying a quinine substitute that was better than atabrine. The NRC had created a board for coordinating malaria research in 1941, laser-focused on that goal. After CMR was established it funded this effort. Like many other OSRD initiatives (Gross and Sampat, 2021a) the Board for the Coordination of Malarial Studies included representatives from the military as well as scientists, to focus research on what was both important and feasible. Over the course of the war this and other CMR programs supported the identification

or synthesis of over 14,000 compounds, testing against animal models, in clinical trials, and in the field on soldiers (Keefer 1969). As in penicillin, beyond funding the activities CMR also had an important coordinating role. In this case, since there were thousands of compounds to explore, CMR had to coordinate the research efforts of individual firms and academic laboratories, making sure there was not excess duplication of efforts on any one molecule, but also that there were no major holes. Like the penicillin effort, it also tried to promote information sharing without compromising proprietary interests. There were tensions between CMR leadership (including Richards) who wanted to promote information sharing and ensure that private firms didn't unduly profit from public research, and the leader of the malaria program, William Mansfield Clark, who was concerned about maintaining incentives for cooperation by private firms (Slater 2009).

Despite these thorny issues, according to one account by 1942 "research on the disease moved faster in one year than in the previous ten" (Condon-Rall 2000, 56). Surprisingly, the drug that would eventually be used in the field was none other than atabrine. CMR funded systematic research on the molecule suggesting it was "relatively nontoxic' (Baxter 1948, 313)' after all, and research also identified optimal dosing and administration regimes to balance efficacy with side effects. Baxter (1948) observes: "Had there been, in 1941, the same knowledge of atabrine which existed in 1944, the absence of adequate quinine supplies would have seemed a subject of no concern instead of one of calamitous importance" (316). Once it was determined to be safe and effective in 1943, General MacArthur essentially decreed atabrine be used (Condon-Rall 2000). By 1944 there was a sharp decrease in malaria incidence (Baxter 1948), making the other developments moot during the war itself.

Even before the war was over there was considerable enthusiasm that the effort would contribute to preventing or curing malaria. Baxter (1948) speculated that one of the promising compounds found or modifications thereof "may prove to be the perfect curative and preventative drug" and perhaps "V-M day is at hand" (319). One of the molecules studied, chloroquine, was CMR's focus too late to be useful during the war effort but would become a revolutionary malaria treatment in the years immediately afterward. Research on this and other "lead compounds" identified during the war continued (Slater 2009). Other compounds with links to the wartime effort include primaquine, mefloquine, malarone, and others still used today. In part, future demand from the Korean and Vietnamese conflicts created demand in the U.S. (FTC 1958), even though malaria was no longer a major issue domestically.

In addition to facilitating follow-on research on these specific molecules, the CMR malaria program also had a more diffuse impact on innovation and innovation policy. The research approach, screening molecules from many sources, later was a model for cancer chemotherapy research and other efforts at the NIH (Slater 2009). The program was also allegedly formative in the careers of several future biomedical research policy leaders, including James Shannon, who would later become NIH Director overseeing its massive postwar expansion. Thus, like penicillin, malaria research may have also influenced science policy more broadly, and thus the rate of biomedical innovation beyond malaria.

4.3 Vaccines

The military was also heavily invested in vaccine research during Second World War, and in many cases preferred prevention over treatment on the grounds this would limit soldier days lost. The memory of World War I, when the 1918 influenza pandemic accounted for 80 percent of soldier casualties (Hoyt 2012) was vivid, and focused attention on the need for vaccines. As U.S. involvement in the new conflict became imminent, the government (through the Army

Surgeon General's Office and other departments) began research into vaccines for influenza and other infectious diseases. The military performed basic research on a number of vaccines before the war, including against pneumococcal disease and influenza, and the Rockefeller Foundation also supported academic work on vaccines. For several infectious diseases, the basic etiology, isolation of the virus, and the ability to grow the vaccine were already done before the war (Hoyt 2012).

After CMR was established, it worked closely with the military "to align what was feasible with what was needed" (Hoyt 2012, 43) in the area of vaccine research. The pre-existing understanding helped. For example, for influenza Hoyt (2006) writes: "Once the scientific feasibility of the vaccine had been determined [before the war], targeted research and development of an influenza vaccine proceeded apace. The remaining tasks consisted of determining methods to scale up the vaccine for industrial production and to evaluate it for safety and efficacy" (46). CMR contracted with academics and industry to improve yields, standardize titration, and improve production. It worked with industry to produce enough vaccine for trials, and then funding trials and field testing. Just two years after CMR's efforts began, the U.S. was able to produce 10 million doses of influenza A vaccine for the Army, and several years later an influenza B vaccine was also shown to be efficacious (Hoyt 2012).

A pneumococcal capsular polysaccharide vaccine was also developed during Second World War. Here again, preliminary evidence that such vaccines would work in humans was generated before the war, led mostly by the military. "The remaining challenge" according to Hoyt (2006) was organizational, specifically "coordinating the expertise and activities of the scientists, engineers, epidemiologists, and physicians to identify which serotypes were most prevalent in military populations, and to develop, scale-up, and test a vaccine containing these serotypes" (66). Academics worked closely with firms with the required facilities in production scale-up and in coordinating trials.

Hoyt (2006) calculates that the wartime effort (including CMR but also other government agencies) helped develop new or improved vaccines for 10 of the 28 vaccine-preventable diseases identified in the 20th century. To be sure, not all efforts were successful. In other cases, e.g. anthrax, lack of prewar basic research limited the ability to meet wartime needs. However, the overall success was remarkable. Beyond basic scientific understanding, government funding, coordination, and close collaboration and involvement with the military have been argued to be crucial for success in vaccine development efforts during the war (Hoyt 2006; 2012).

What about the long-term effects on innovation? According to Hoyt (2012, 74), many of the companies involved in the wartime effort "found themselves at an advantage after the war since they had been forced to adopt new production methods" including mass production techniques. Several of the methods developed during the war (e.g. centrifugation techniques) would become "state of the art" to the industry by the 1960s (Hoyt 2006, 47). However, in some cases the postwar commercial market for vaccines was limited; paradoxically, the antibiotic revolution may have shrunk it further for some vaccines (e.g. for pneumococcus). This highlights that absent sustained military demand and funding, continued civilian demand is needed for crisis innovation to have long-term effects. More broadly, a number of individuals involved in the wartime research program would become important figures in postwar vaccine development. Jonas Salk was active in the influenza vaccine effort (though his specific research was funded directly by the Army, not OSRD), and some of the principles from that effort may have been important to the development of the polio vaccine decades later (Oshinsky 2005). Maurice Hilleman, credited with developing more vaccines than any other individual, was involved with

the development of the Japanese encephalitis vaccine (JEV) effort while employed at E.R. Squibb, one of the CMR's major contractors (Offit 2007). Establishing causal linkages between wartime efforts and subsequent vaccine development is hard. But it is notable that, as with antibiotics, a number of the central figures in postwar innovation were involved in the wartime efforts as well.

4.4 Blood

Another critical need during the war was for blood or blood substitutes for the replacement of blood lost to injury, hemorrhage, burns or surgery (Andrus 1948). An important characteristic of any effective solution would be the ability to store it and easily transport it to distant locations (Creager 1989). In preparation for war the Navy had asked Edwin Cohn, a physical chemist from Harvard Medical School, to look for such a substance. Previously, Cohn had been working on the physical chemistry of proteins, funded by the Rockefeller Foundation but not particularly focused on clinical applications (Creager 1989).

He initially did research on bovine antiserum, from cows. Drawing on his previous basic techniques Cohn was able to isolate a transfusable portion of cow blood quickly, but this was ultimately not useful in humans. Nonetheless, the path to extracting serum from human blood was then relatively straightforward. Cohn's lab isolated human serum albumin and tested it in early 1941, so that by the time of the Pearl Harbor attacks that December it was used to treat casualties (Creager 1989).

Once CMR was formed it funded work by Cohn and others comparing the serum extract to human blood, clinical research on how well blood substitutes worked in the body, and improving isolation procedures. CMR also brokered donations from blood banks, including the American Red Cross that facilitated the work, and relationships with firms with production expertise.

Even early on, the "dual-use" nature of the technology was emphasized. In September 1944 the *New York Times* summarized a lecture by Cohn: "The new knowledge, which is already saving countless lives of our fighting men on the battlefields, promises in the generations to come to give back to mankind more lives than the war has taken." In particular, the techniques refined during the war were useful for isolating other proteins from blood as well, and ultimately for treating measles, shock, surgical recovery, clotting issues, and many other medical conditions. Thus in this case the wartime effort helped develop a set of techniques that were useful for other blood-related disorders and blood-derived therapeutics. According to Creager (1989), Cohn’s methods “provided a technical framework for [a] productive research field" after the war (396).

In addition, Creager (1989) emphasizes the effects on Cohn himself, suggesting the wartime effort gave him a taste for more applied endeavors on blood. His eminence also meant he was important in shaping the direction of blood-related work at the NIH. The relationships (between his lab and blood banks, and firms with pilot plants) formed during the war also lasted, with Cohn capitalizing on these for his own research after the war (Creager 1989).

4.5 Hormones

Even before the war, drug companies and academics, sometimes in collaboration, had begun research on isolating, producing, and administering hormones for a range of diseases and conditions, from constipation to obesity (Rasmussen 2002). The research involved removing endocrine organs from animals, extracting different compounds, and seeing if this replicated the

function of the missing organs. Biochemists also studied the chemical structure of the extracted compound. Examples include epinephrine extracts from adrenal glands (marketed by Parke-Davis as adrenaline) and insulin extracted from the pancreas (work done Banting and Best in Toronto, and later marketed by Eli Lilly), each of which was commercially successful.

One of the trailblazers in this work was Edward Kendall, a biochemist at the Mayo Foundation. He had in the 1930s isolated thyroxine (from the thyroid gland), which was licensed to Squibb pharmaceuticals for the treatment of constipation and for weight loss (Rasmussen 2002). He had also been working on recovering cortical hormones from the adrenal glands. Though this was originally focused on treating adrenal insufficiencies, including Addison's disease, the compounds also had some benefits for healthy organisms. Rasmussen (2002) notes: "With cortical hormone injections, normal dogs were found to run much longer on treadmills, 'neurotic' but otherwise normal sheep were calmed, and ... patients reported increased vitality, lifting of depression, improved digestion and sharper vision" (308). Needless to say, results like these were of interest to drug companies, fueling a goldrush of hormone-related research activity in the 1930s, including drug companies' funding of academic research.

The work became relevant during the war as the air war in Britain intensified. There were rumors that both British and German pilots were using cortical hormones to combat fatigue and adapt to high altitudes, and even that these and other hormone-derived drugs were central to the German Blitzkrieg strategies (Rasmussen 2002).

In early 1941 the National Research Council's Committee on Aviation Medicine held a conference to understand the science and military needs, and this effort was taken over by CMR upon its formation later that year. As with malaria, in this case CMR had an organizing and coordinating role, bringing together hormone researchers from across the country, from different sectors and disciplines (e.g. biology, biochemistry, endocrinology), to assess the state of the science and prospects for advancement, and the key bottlenecks to synthesizing usable compounds and producing at scale. In this case, too, CMR was focused on avoiding unnecessary duplication of research but also on making sure all bases were covered. As in penicillin efforts, it also had a brokering role, collecting progress reports and sharing information among participants, with an eye to balancing the benefits of spillovers with the proprietary interests in specific approaches. CMR also funded work on physiology, including "whether treatment of aviators with adrenal cortex hormones would increase their tolerance for high altitude" and whether the compounds could counteract shock from battlefield trauma or surgery (Rasmussen 2002, 314).

In parallel, CMR funded work to synthesize the compounds and produce at scale, including Compound A and Compound E from Kendall's lab. Interestingly, the physiological work ultimately suggested that these compounds did not help much during flight, but by that time several corticosteroids had been identified by Kendall, other academics, and firms (Achilladelis 1999). CMR continued to support synthesis despite the lack of immediate military demand, which Rasmussen (2002) has categorized as a "curious" decision (318). Processes for synthetics were developed and refined, as were bioassays for evaluating the physiological properties of the molecules (Achilladelis 1999). Shortly after the war Kendall's compounds including Compound E (now called cortisone) were tested against several diseases, including arthritis. Cortisone became a miracle drug in the decades after the war, and the methods developed for producing corticosteroids were used for developing similar drugs with fewer side effects. Kendall earned the Nobel Prize in Medicine in 1950 for his work on adrenal hormones. Achilladelis (1999, 62) writes "because the technology had diffused among participants of the OSRD project, all of them introduced corticosteroid drugs in the 1950s."

5. War and the Direction of Medical Innovation: Potential Mechanisms

There seems to be widespread agreement that the wartime medical research effort contributed to the emergence of the postwar research-intensive pharmaceutical industry in the U.S. For example, Achilladelis (1999, 63) claims:

> To a great extent the U.S. government's wartime policies led to the emergence of the American pharmaceutical industry as the undisputed worldwide leader. The American companies had made considerable advances in the 1930s and had come to realize the importance of in-house research. But with the exception of Merck none of them were on par with the German and Swiss companies ... the federal war effort encouraged corporate research and development, widened and deepened the companies' cooperation with academic institutions, and catalyzed the diffusion of new technologies across the industry. By the end of Second World War fifteen American companies could fairly be described as research intensive.

Much as the successes of science and technology during the war bolstered the argument for additional public investment in research (Bush 1945), the "recognition that drug development could be highly profitable" (Cockburn et al 1999, 367) may have spurred drug companies' entry into serious research as well. Cockburn et al (1999), Pisano (2002), Temin (1979), and others also have argued that involvement in the penicillin program itself may have contributed to capabilities to conduct future research.

There are other continuities between the CMR and the postwar innovation system as well. When CMR was disbanded in 1945, the open contracts were transferred to the Public Health Service and were the basis for the emerging extramural research program at the NIH (Swain 1962; Fox 1981). The OSRD contract mechanism itself was novel; historian A. Hunter Dupree (1970) has called it “one of the great inventions” of OSRD “the glue which held the whole system together” (457-458). Unlike standard procurement contracts, the OSRD contracts purchased the research and development itself, rather than specific products, an idea revolutionary for its time (Dupree 1970). This helped balance scientist and university preferences for freedom with the government’s needs for accountability and shifting the direction of inquiry (Fox 1981). Beyond providing a general model for using grants and contracts for funding extramural research, several specific contracting approaches developed during the war (including indirect cost recovery policy; see Rosenzweig 1981; Fox 1981 and elements of patent policy; see Sampat 2020) were adapted by the NIH. Moreover, the NIH peer review system — using external scientific experts in study sections to assess priority — itself was modeled on the CMR model of using NRC scientists to judge the feasibility of projects of interest to the military (Fox 1981). Indeed, some of the specific NIH sections came directly from CMR: in December 1945 the Penicillin panel at CMR became the Syphilis study section at NIH (Fox 1981).[9]

Each of these mechanisms — enhancing firms' capabilities for innovation, demonstrating the value and potential returns from public and private R&D, and increased federal funding for science and infrastructure for supporting it — could potentially explain the effects of the wartime funding program on the *rate* of pharmaceutical innovation.

[9] The treatment of syphilis was one of main uses of penicillin during the war, and even today penicillin remains the main recommended treatment for syphilis.

But what about *direction*? One natural way to operationalize direction in medicine is via disease areas or, in pharmaceuticals, drug classes. Several studies show the importance of market size for this direction of innovation (Acemoglu and Linn 2004; Dubois et al 2015; Blume-Kohout and Sood 2013; Acemoglu et al 2006; Finkelstein 2004), generally showing that diseases with larger markets see more product innovation or research effort. Though crises certainly create sharp demand shock in certain fields, almost by definition demand dissipates after crisis resolution, so the long-term effects must be through other channels. (More on this below.) Another line of research looks at the effects of supply-side factors, including NIH funding that may create scientific opportunities, on disease-specific measures of innovation (e.g. Toole 2012; Toole 2007; Blume-Kohut 2012). But most of this work focuses on the effects of government-funded "basic" scientific research on outcomes. Basic research was explicitly not the focus during the war (Gross and Sampat 2021b).[10] Rather, the government primarily funded (and as a number of the cases illustrate, otherwise supported) applied research, and also provided a large guaranteed market for successful innovations.

Summarizing across the cases, there are several (overlapping) channels through which the temporary crisis of Second World War may have influenced the long-run direction of medical research.

- A first is through **development of technology platforms or research tools and approaches** that lowered the cost of (or equivalently increased technological opportunities for) later adjacent innovations. Synthetic penicillins, vaccines, blood fractionation technologies, and (from a non-medical case) radar are good examples. Note that the more "general purpose" the technologies, the less of an effect we see on direction rather than solely on rate.
- A second is development of **embryonic products and prototypes** that were the basis for future, incremental innovations. "Lead compounds" coming out of the malaria program are good examples.
- A third is **overcoming bottlenecks to development, production and application** of existing technologies or research approaches, improvements that may spill over to adjacent areas. This seems to have been a major contribution of the penicillin program, for example. In this case and others, the need for speed meant the government invested heavily in funding, coordinating, and facilitating (through information sharing, knowledge diffusion) such activities during the war. To the extent these activities were successful, know-how from these efforts could then be leveraged to other similar applications, at least by the firms involved in the effort.
- A fourth way in which the wartime effort may have shaped the direction of innovation is **by providing information on what works and what doesn't, de-risking future development efforts in an area**. Research was not for its own sake; there was a real focus on getting things tested and "in the field" in short order, and there was sharp feedback from users (the military).
- A fifth is through creating **new human capital, organizational capabilities, and patterns of productive collaboration** in the affected areas. As already noted, for this to

[10] There is also important work on how the appropriability regime shapes the direction of medical research (Budish et al 2015). There are anecdotal accounts that within fields firms shifted away from unpatentable substances (e.g. penicillin) to patentable ones (e.g. synthetic penicillin), and avoided compounds where there was considerable knowledge sharing during the war (see Achilladelis 1999). It is unclear how this would play out across diseases or fields, though this seems like an interesting area for future exploration.

explain direction these would need to be sticky across fields, or there would have to be large costs for researchers and firms to switch research areas (see Myers 2020).

- A final potential channel is **political capital** for the institutions and individuals involved. As the cases revealed, a number of the individuals involved in the effort went on to become important players in postwar policy. If they (or the institutions that were involved in the wartime effort) were able to leverage this to benefit from the expansion of postwar R&D funding, securing a larger share of the funding in the areas field could also generate persistence.

These channels blur into one another and may be difficult to distinguish empirically. For example, continued federal funding for researchers involved in the war could reflect the increased productivity of their fields, or pure political capital independent of quality.

Collectively the cases suggest two other points about the wartime effort and the direction of research. First, in almost all cases, the wartime research seems to have been enabled by previous fundamental knowledge, including that funded by Rockefeller Foundation and other philanthropies. It is unclear whether without this base, the crisis innovation effort would have been successful. (Indeed, this is a central part of the argument that Vannevar Bush made in *Science, The Endless Frontier* in arguing for large-scale postwar federal support for research, primarily focused on basic science.) In a few of the cases (mostly notably hormones) there was already ongoing progress in research fields "shocked" by the war. Some historians (Rasmussen 2002) suggest the modes of collaboration between universities and industry during the war have their roots in the 1930s, calling into question the idea of the war as a "watershed" for science.

Second, the vaccine case also suggests that post-crisis demand is necessary for the crisis research effort to influence the direction of follow-on innovation. Without it, the movement along a technological trajectory may be for naught, at least until the next similar crisis comes along. That is to say, pre-existing knowledge may be necessary for crisis innovation efforts to succeed, but post-crisis demand also necessary for it to have long-lasting effects on the direction of innovation. The fact that there was both civilian and military demand for many of the non-medical technology classes "treated" by the wartime effort may help explain the long-term effects found in the Gross and Sampat (2020a) analysis discussed earlier.

Stepping back from the cases, another wrinkle in thinking about the direction of research is that the war may also have disrupted research in certain fields. Swain (1962) writes of the CMR's effect on public health research "In the rush to solve specific problems, such as the development of blood substitutes and the synthesis of malarial drugs, basic medical research studies suffered" (1235). Bush (1945) made the point more forcefully in *Science, The Endless Frontier:*

> We have been living on our fat. For more than 5 years many of our scientists have been fighting the war in the laboratories, in the factories and shops, and at the front. We have been directing the energies of our scientists to the development of weapons and materials and methods, on a large number of relatively narrow projects initiated and controlled by the Office of Scientific Research and Development and other Government agencies … [t]hey have been diverted to a greater extent than is generally appreciated from the search for answers to the fundamental problems.

In addition to a shift in the orientation, research in fields not critical to the wartime effort may also have slowed down, to the extent that scientists shifted direction. In considering the effects of the war on the direction of innovation, this needs to be kept in mind as well.

6. Looking Forward: Covid-19 and the Direction of Innovation

Since the beginning of the Covid-19 pandemic, economists and others appealed to the Second World War model as a successful example of crisis innovation policy to emulate (e.g. Azoulay and Jones 2020). Gross and Sampat (2021b) describe how the Covid-19 response was similar to and diverged from the wartime model in practice. One major difference was the heavy focus by public funders (in the U.S. and globally) on one technology area---vaccines—rather than a broader suite of interventions (therapeutics, testing, surveillance, changes in business practice) that could curtail the pandemic or reduce its socio-economic and health costs (Sampat and Shadlen 2021). What this means is that the scope for public funding shifting direction of research may be more circumscribed compared to Second World War, where the government invested in an array of technologies, determined with input from users (the military) on what exactly was needed to defeat the enemy.

At the same time, reflecting the massive expansion of the biomedical innovation system in the 75 years between the two crises, there was a large pivoting of researchers worldwide to work on a range of Covid-19 problems, often crossing fields to do so. The modes of collaboration have also changed, relying heavily on pre-prints and "open science" approaches, though there has been an accompanying set of concerns about the quality of the research (Yong 2021). It is possible that these transitions will be sticky — perhaps economists will continue to work on epidemiology, and researchers who pivoted from other fields will continue work on infectious diseases. This will depend on both switching costs and the long-term salience of the work in this area, as noted above. As was the case in Second World War the new types of collaboration and new ways of organizing research may also persist, and could plausibly have a long-run effect on productivity in Covid-adjacent fields. Firms too shifted to research on Covid-19 therapeutics (Bryan et al 2020); it is possible that these shifts in research orientation will outlast the pandemic through one or more of the channels discussed in the previous section. Like Second World War, evaluating Covid-19 and the direction of research will also require attention to the "untreated" fields. Other types of socially valuable research (e.g. Alzheimer's, cancer trials) may have stalled with the mass reorientation (Agrawal and Gaule 2021).

Covid-19 also prompted the refinement, adoption, and implementation of other technologies by individuals, firms and other organizations, including electronic communications. In the medical arena the long-awaited promise of telemedicine may finally be close to realization. The extent to which this shifts the direction of innovation, as opposed to productivity, will depend on the remaining technological opportunities in the affected areas.

The area where there has been the most significant public investment, and where the U.S. Covid-19 response most closely resembles the Second World War approach, is vaccines. In several Second World War medical research efforts, most prominently penicillin, the government invested in parallel competing approaches, invested in downstream applied research and development, and provided a large guaranteed market. These all reflected the need for speed in a crisis. Similar approaches were used in the U.S. and global vaccine development efforts during Covid-19 (Sampat and Shadlen 2021; Gross and Sampat 2021).

The apparent speed of progress in treated areas is another parallel. One observer quoted above noted we made more progress against malaria in the first year of the war than in the previous decade. Similarly, the Covid-19 response saw vaccines developed at extraordinary speeds, and in particular may have "unlocked the power" of mRNA approaches that could be the basis for vaccines against malaria, influenza, and myriad other diseases (Dolgin 2021). Like many of the wartime efforts, the Covid-19 vaccine approaches involved developing and applying

existing technologies (supported by a strong pre-crisis scientific base), including working out production issues and providing proof-of-concept for future applications. There is tremendous enthusiasm that these developments will contribute to a new "golden age" of vaccine innovation, a long sought-after goal in health policy globally. One cautionary note from the case studies is that expectations of future demand may also be necessary for private firms to capitalize on these investments. As Xue and Ouellette (2020) show, there are many market failures on the demand side of the vaccine market as well as the supply side, including that many vaccine-preventable diseases don't have large rich-country markets.

There are also important differences between the two crisis responses. In addition to those already noted, Gross and Sampat (2021b) argue that the coordination and priority setting roles of OSRD and CMR were missing in the Covid-19 response, especially for non-vaccine research. Promotion of diffusions to users and implementation of the inventions were central government activities during Second World War; these have proven more difficult for Covid-19 technologies, including vaccines. In part, this may be because the final user during the war was the military, rather than millions of individual consumers (Gross and Sampat 2021). Also, though there have been many calls to do so (e.g. Morten and Herder 2021) it is at this point unclear whether and how the Covid funding and policy efforts actively tried to promote knowledge transfer and information exchange to speed up research and production, issues which CMR aimed to do (though in some cases struggled with) during Second World War. In the synthetic penicillin and other efforts, for example, the government retained government use licenses to relevant patents of participating firms (even if not, per the "short form" clause in standard CMR contracts, title to the patents). By contrast, the Warp Speed contract to Pfizer explicitly states "[a]s between Pfizer and the Government, Pfizer shall hereby retain all of its rights, titles and interests in and to any and all inventions conceived and reduced to practice by Pfizer and/or BioNTech (i) as of the Effective Date of this Agreement...Pfizer does not grant to the Government a license to practice any Subject Inventions on behalf of the Government" (as quoted in Druedahl et al 2021, 3).

And in both the natural and synthetic penicillin efforts, though there were concerns about the actual extent of sharing, firms at least nominally agreed to collaborate and share knowledge with other firms and government researchers to help resolve the crisis quickly (FTC 1958).

Returning to the main theme of this paper, throughout I have discussed the direction of medical innovation as it relates to the disease or scientific areas that are the focus of research. A final speculation is that the Covid-19 experience may lead governments to invest more generally in the types of applied activities (targeted problem-driven research, funding development and manufacturing) that facilitated rapid vaccine development. Or, reflecting the widely recognized importance of pre-pandemic basic research to the success of the vaccine development efforts, they could also redouble national commitments to fund basic research, along the lines Bush advocated. As in Second World War, the long-term influence of this crisis may be not only the direction of research, but also the direction of research policy.

One remaining paradox is that if crises shift the direction of research in ultimately beneficial ways, were these developments, like Dorothy's return to Kansas in the *Wizard of Oz*, possible all long? And if so, what prevented the same effects on innovation from being secured earlier? As Rosenberg (1969) asked, is the observation that crises shape innovation equivalent to saying "constraints are good for you" (19)? While this is possible, there are unique features of crises that may be difficult to replicate. One is that crises can be short-lived, especially when the innovation response is effective (Hoyt 2012). The deputy director of OSRD, Irwin Stewart (1948), observed of OSRD the that temporary nature of the war promoted patterns of participation, collaboration, and information sharing that may not otherwise be sustainable. It

also seems that the level and intensity of government support during the two crises considered here, including for downstream activities, may be difficult to justify in “normal” times. Because the costs of crises (in monetary terms, or existential threats) are so obviously high, extremely large expenditures on finding or rewarding solutions can be cost-effective. But, then again, the value of improved health is in general quite high (Murphy and Topel 2000). What counts as a crisis may lie in the eye of the beholder.

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