"A Most Equitable Drug": How the Clinical Studies of Convalescent Plasma as a Treatment for SARS-CoV-2 Might Usefully Inform Post-Pandemic Public Sector Approaches to Drug Development

Quinn Grundy[1], *Chantal Campbell*[1], *Ridwaanah Ali*[1], *Matthew Herder*[2], *and Kelly Holloway*[1]

1. UNIVERSITY OF TORONTO, TORONTO, ONTARIO, CANADA. 2. DALHOUSIE UNIVERSITY, HALIFAX, NOVA SCOTIA, CANADA.

Keywords: Convalescent Plasma, Randomized Controlled Trials, Clinical Trials, Public Sector, Innovation, Pharmaceutical Industry

Abstract: Interventional clinical studies of convalescent plasma to treat COVID-19 were predominantly funded and led by public sector actors, including blood services operators. We aimed to analyze the processes of clinical studies of convalescent plasma to understand alternatives to pharmaceutical industry biopharmaceutical research and development, particularly where public sector actors play a dominant role. We conducted a qualitative, critical case study of purposively sampled prominent and impactful clinical studies of convalescent plasma during 2020-2021.

The world over, the COVID-19 pandemic has wrought uneven sickness and death driven, in large measure, by multiple forms and sources of inequity. In line with Louis Pasteur's prescient warning centuries ago —"the microbe is nothing, its terrain everything" — access to SARS-CoV-2 screening and diagnostic testing tools, antivirals, and vaccines has been delayed and limited in low- and middle-income countries for much of the pandemic. Foreseeing this eventuality, many called for systemic change to laws and systems governing biopharmaceutical knowledge production at the outset of the pandemic, which included demands for transparency around scientific methods, data, and clinical trial costs, intellectual property waivers, and public sector leadership in biopharmaceutical research, development, and access.[1] However, more than 2 years into the COVID-19 pandemic, excepting limited waivers to intellectual property rights related to COVID-19 vaccines, none of the proposed changes had been implemented.

One potential medicine, identified even before the pandemic was officially declared, appeared to offer a set of different possibilities than other experimental leads in the hands of the multinational pharmaceutical industry: convalescent plasma. Unlike other experimental options controlled by those companies, convalescent plasma could be sourced directly from people who had been infected by, and recovered from, COVID-19. As well, convalescent plasma itself is not patentable subject matter (although a host of scientific processes used, for example, to separate out immunoglobulin from other proteins within plasma,[2] have been patented), enhancing researchers' freedom to operate without immediate risk of legal reprisals. In principle, an available human supply, complicated by fewer intellectual property related barriers, made convalescent plasma a plausible, more equitable target for investigation and development even though scientific

Dr. Quinn Grundy, Ph.D., R.N., *is Assistant Professor with the Lawrence Bloomberg Faculty of Nursing at the University of Toronto.* **Chantal Campbell, M.N. R.N.**, *and* **Ridwaanah Ali, M.N., R.N.**, *were Mitacs Accelerate Fellows with the Lawrence Bloomberg Faculty of Nursing at the University of Toronto.* **Matthew Herder, J.S.M., L.L.M.**, *is Associate Professor with the Department of Pharmacology, Faculty of Medicine and Director of the Health Law Institute at Dalhousie University***. Kelly Holloway, Ph.D.**, *is a Scientist with Canadian Blood Services and Assistant Professor (status) with the Institute for Health Policy, Management and Evaluation at the University of Toronto.*

DOI: 10.1017/jme.2024.51

understanding of how and to what extent convalescent plasma conferred immune protection against any pathogen, let alone SARS-CoV-2, was essentially non-existent in early 2020.[3]

Two years into the pandemic, the World Health Organization (WHO)[4] and the National Institutes of Health (NIH)[5] among others, recommended against the use of convalescent plasma among non-severe, immunocompetent hospitalized patients, judging that the benefits did not outweigh the costs of the therapy. The story of convalescent plasma during COVID-19 nevertheless has much to tell us: trusted networks, comprised of government-funded trialists, clinicians, and regulators mobilized at unprecedented speed and, with the aid of public funding and infrastructure, implemented these clinical trials on a national scale, including in lower- and middle-income countries. Drawing on the field of pharmaceutical studies,[6] we conducted a critical, qualitative study of clinical trials seeking to understand the effectiveness of convalescent plasma against SARS-CoV-2 with the aim of understanding the range of approaches to biopharmaceutical research and development, and particularly approaches where public sector actors play a dominant role.

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Currently, the majority of pharmaceutical clinical trials globally are funded, conducted, and disseminated by for-profit industry.[7] The involvement of pharmaceutical companies in industry-sponsored trials varies from the free provision of study drugs to running the entire trial and publishing the results without involvement of academic researchers.[8] Pharmaceutical industry sponsorship of clinical trials is associated with biases in the scientific literature, including the tendency to publish favorable results and to suppress negative findings, safety risks stemming from lack of access to proprietary data, inequities in access to patented treatments, and the unethical treatment of research participants.[9] The existing system of biopharmaceutical innovation is also critiqued for research agenda biases, which result in unmet medical and public health need (e.g. as evidenced by the high proportion of me-too drugs that offer only incremental innovation), inefficient collaboration due to protectionist practices and secrecy arising from the current intellectual property regime, and high drug pricing which creates barriers to medicines access and results in limited re-investment into innovation.[10]

Scholars have thus called for a rethinking of the current status quo for drug development,[11] pointing to the essential and underrecognized role the public sector already plays in the funding, conduct, and implementation of clinical trials.[12] To address current public health challenges, scholars argue for new policy approaches to innovation that envision a leadership role for the public sector involving research direction-setting to address public health challenges, public sector capacity building to enable dynamic collaboration with the private sector that genuinely serves the public interest, and a re-distribution of the risks and rewards associated with innovation.[13]

The global COVID-19 pandemic prompted an unprecedented mobilization of public and private resources for clinical research into the safety and effectiveness of treatments and vaccines. Using publicly available documentary sources, we conducted an in-depth analysis of prominent clinical trials of convalescent plasma and hyperimmune immunoglobulin for the treatment of SARS-CoV-2 that took place globally during 2020-2021. We sought to understand the

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respective roles and interests of public, academic, and private entities within the context of a global market in clinical trials, their inter-relationships, and the implications for health equity and research integrity and to analyze these configurations as a means of identifying promises and challenges of alternative models of biopharmaceutical research and development.

A Critical Case Study of Public Sector Innovation

We conducted a qualitative, critical case study[14] of prominent clinical studies of convalescent plasma for the treatment of COVID-19, collecting and analyzing publicly available documents detailing the processes related to the design, approval, conduct, and dissemination of the studies. We employed a critical interpretive approach to examine biomedical and bioscience regulation which aims to consider the meaning of practices and processes related to decision-making, governance, and allocation of resources that take place across clinical, regulatory, and scientific domains.[15] The methods are reported according to the COREQ guidelines[16] (Supplementary File 1).

In the case of clinical studies evaluating convalescent plasma for the treatment of COVID-19, the recruitment of convalescent plasma donors often meant the integral involvement of a highly regulated, publicly funded blood service. The involvement of blood services organizations in convalescent plasma trials is in some ways analogous to the role of the pharmaceutical company in a clinical drug trial — primarily in that they provided the drug and/or source material (convalescent plasma), but also extending to involvement in clinical trial design, participant recruitment, data collection and analysis, and dissemination. Thus, the efforts to evaluate the safety and effectiveness of convalescent plasma as a treatment for COVID-19 pan-present a unique case to understand the role of public institutions amid the politics and economics of drug development.[17] We approached analysis of this collection of prominent trials as a form of mission-driven public sector innovation[18] with the aim of offering insights into the nature, value, facilitators, and challenges associated with public sector-led clinical trials.

Sampling and Data Sources

We purposively sampled studies of convalescent plasma that were prominent, impactful, and public facing as they were most likely to have relevant and publicly available documents and could provide the most information-rich illustrations of the range of convalescent plasma studies for analysis. We selected studies that had an online presence in the form of a study website, clinical trials registration, or social media activity; that had demonstrable impact defined as publications (including preprints), inclusion or reference in clinical practice guidelines, and/or citation by other trials; and were prominent in terms of media coverage, social media activity, and/or clinical or scientific impact. We also aimed to sample studies that reflected a range of study designs, geographic locations, sponsoring entities, and blood service involvement. To identify the sampling frame, we searched for "convalescent plasma" and "hyperimmune immunoglobulin" study records within ClinicalTrials.gov and the Cochrane COVID-19 database and categorized records returned by design, region, size, enrolment status, and sponsor type. We continued to sample studies until we found frequent cross-references to the previously sampled studies through citations, collective inclusion in systematic reviews and meta-analyses, or mentions in media reports, and determined saturation at this point.

For each study identified we conducted targeted, structured, purposive Google searches, beginning with a search of all ethics and regulatory applications and approvals, study websites, trial protocols, preprints, and publications. Then, we sought ancillary documents related to these including editorials, participant-facing materials (e.g., recruitment posters, consent forms), and first-person accounts of the study (e.g., author blogs) to deepen our analysis of the relationships among key clinical trial stakeholders. Finally, we conducted systematic Google searches with the following: [study name] and [study country] and "trial" and "convalescent plasma." Using this search strategy, we searched Google month by month, restricting hits by date range beginning March 1, 2020. We also used advanced search functions within Google to restrict to geographical region (i.e., Argentina) to sample in a more targeted way. We purposively sampled articles (including blogs, news, journal articles) that pointed to relevant documents, were information rich and returned new information, or answered particularly lines of inquiry (as laid out in the data extraction form). We stopped sampling when articles returned by the Google search returned no new information or consistently cross referenced previously sampled documents. All documents were saved as PDFs and catalogued in Excel and EndNote.

Data Collection and Analysis

Data were analyzed using qualitative, interpretive content analysis.[19] This method involves a systemic classification process of labelling the text using thematic codes and then identifying themes and patterns

The Journal of Law, Medicine & Ethics, 52 (2024): 80-97.

https://doi.org/10.1017/jme.2024.51 Published online by Cambridge University Press

within and across thematic codes.[20] We created a data abstraction instrument consisting of a series of open-ended questions based on the study aims, background literature, and theoretical perspectives on the political economy of drug development (Supplementary File 2). For each sampled trial, four coders working as pairs (QG, CC, RA, KH) used the sampled documents to answer the open-ended questions, including identifying and describing the key entities involved in funding, planning, conducting, and disseminating the trial and their interrelationships and describing salient legal, ethical, and equity issues such as how convalescent plasma was sourced and how participants and donors were recruited and consented.

Through multiple team meetings, we used these data abstraction forms to develop a thematic coding scheme. QG and RA piloted the coding scheme on 10% of the sample and finalized the coding scheme as three groups of codes: the "who" (e.g., blood services, funders), the "what" (e.g., participant recruitment, donor recruitment), and the "how" (e.g., open science, regulatory facilitators/barriers). RA and QG coded all sampled documents independently using NVivo 11, resolving discrepancies through discussion. QG and KH then wrote interpretive memos based on the data compiled under each code to generate overarching themes (e.g. equity-driven approaches, reliance on public infrastructure, primacy of relationships) and comparative analyses. To report on each theme, we then selected and present exemplars, which are particularly information-rich and strong examples of the theme in narrative form, which serve to illustrate the themes in ways that capture rich contextual detail, commonalities, nuance, and variability in experiences across studies.[21]

The Promises and Politics of Convalescent Plasma

We included 245 documents from 8 clinical studies in 6 countries (**Table 1**). The studies, one large-scale, prospective observational study and 7 randomized controlled trials (RCTs), spanned Canada, the United States, Argentina, the United Kingdom, India, and China. These documents included: study protocols and registrations; press releases and media accounts; first-person accounts and journalistic retrospectives; and scientific reports. In the following text, we cite illustrative sampled documents and provide a full catalogue in Supplementary File 3.

Inspired by its use in previous pandemics, in late January 2020, hospitals in Wuhan, China, where the SARS-CoV-2 virus was first detected, began collecting convalescent plasma from individuals recovered from COVID-19 and published the promising outcomes as case studies.[22] Given limited understandings of how convalescent plasma worked, how to select for donors, how to ensure that plasma donation had sufficient quantities of precise therapeutic components (and what these were), or which patients might benefit,[23] the pandemic represented an opportunity to develop a robust body of evidence supporting this historically significant treatment. Building off these early case studies, scientists at the Institute of Blood Transfusion at the Chinese Academy of Medical Sciences (a public institution and the study's funder) designed and launched the first RCT (ChiCTR2000029757) of convalescent plasma on February 14, 2020 and helped launch a pilot program through the Wuhan Blood Centre to recruit donors.[24] The investigators stopped the trial early on March 27, 2020, following an entire week where no new cases of COVID-19 were reported in Wuhan, finding no difference between those receiving convalescent plasma and those who did not.[25]

However, given that the trial was underpowered, and participants received treatment at a late disease stage (at least 14 days after the onset of symptoms),[26] the questions of the effectiveness and clinical utility of convalescent plasma remained open. Interest in convalescent plasma soon caught on globally, and by May 1st, 2020, there were 64 planned and ongoing studies of convalescent plasma in 22 countries;[27] by March 2021, systematic reviewers identified 113 completed and ongoing studies of convalescent plasma.[28]

In our purposive sample, the 8 studies were larger and higher-profile in terms of high-impact publication, influence on national and international clinical guidelines, and media attention per our inclusion criteria (Table 1). Among these prominent and impactful trials, convalescent plasma was collected and tested for two main purposes and involved two different, but often overlapping groups of stakeholders: 1) licensed, publicly-funded, and often nationally-coordinated blood services worked with hospitals, academic researchers, and government funders to collect plasma from donors recovered from COVID-19 for direct transfusion (n=7/8 sampled studies, including the trial in Wuhan); and 2) the for-profit plasma therapeutics and pharmaceutical industry spearheaded the development of hyperimmune immunoglobulin, manufactured from aggregated convalescent plasma donations with high titres of SARS-CoV2 antibodies (n=1/8 sampled studies).

These sampled studies thus offered rich insights into the dynamics of nationally coordinated clinical studies led by the public sector, with the case of the trial of hyperimmune immunoglobulin offering a

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Table 1

Characteristics of included clinical studies of convalescent plasma for the treatment of SARS-CoV-2

Country, Trial	Design	Endpoints *denotes primary	Population	Registered	
China, ChiCTRY2000029757	National, multicenter, randomized, open-label, parallel, unblinded controlled trial	28-day time to clinical improvement*, 28-day mortality, duration of hospitalization, ratio of negative viral test results	Hospitalized adults with severe and life-threatening COVID-19 infection	Y (Chinese Clinical Trial Registry)	
UK, RECOVERY	National, multicenter, adaptive, open-label, factorial randomized, controlled trial	All-cause, 28 day mortality	Hospitalized adults (incl pregnant people) and children with COVID-19 infection	Y (EU Clinical Trials Register; ClinicalTrials.gov; ISRCTN Registry)	
UK/Global, REMAP-CAP	Global, multicenter, adaptive	All-cause, 90 day mortality	Adults admitted to intensive care with severe pneumonia	Y (EU Clinical Trials Register; ClinicalTrials.gov; ISRCTN Registry)	
USA National Emergency Access Program	National, multi-center, open-label, emergency access program	Availability of COVID-19 convalescent plasma, serious adverse events (secondary)	Hospitalized adults with severe or life-threatening COVID-19 disease	Y (ClinicalTrials.gov)	
India, PLACID	National, multi-centre, open label, parallel arm, phase II, randomised controlled trial	Composite of progression to severe disease or all-cause mortality at 28 days	Hospitalized adults with moderate COVID-19 disease	Y (Clinical Trial Registry of India)	
Argentina, PlasmAr Study	National, multi-center, double-blind, randomised, placebo-controlled, trial	Clinical status at 30 days	Hospitalized adults with severe COVID-19 pneumonia	Y (ClinicalTrials.gov)	
Canada, CONvalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness CONCOR-1	Multinational, multi-centre, open-label, randomised, controlled trial	Need for intubation or patient death in hospital at 30 days	Hospitalized patients with COVID-19 infection aged 16 years and older and receiving supplemental oxygen	Y (ClinicalTrials.gov)	
USA/Global, Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC)	Global multi-centre, randomised, double-blind, placebo-controlled trial; remdesivir as standard of care	Clinical status on day 7*	Hospitalized adults at risk for serious complications of COVID-19 infection	Y (ClinicalTrials.gov)	

BARDA= US Biomedical Advanced Research and Development Authority; CAMS=Chinese Academy of Medical Sciences; CIHR= Canadian Institutes of Health Research; HRC=New Zealand Health Research Council; ICMR= Indian Council of Medical Research; NIAID=National Institute of Allergy

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https://doi.org/10.1017/jme.2024.51 Published online by Cambridge University Press

	Sample size	Published protocol? Analysis plan? (Y=Yes, N=No)	Plasma source	Funder	Author affiliations	Data sharing
	103	Y,Y	Wuhan Blood Center	Chinese Academy of Medical Sciences (CAMS)	Institute of Blood Transfusion (CAMS)	Y, deidentified participant data, available by email request
	11558	Y,Y	NHS Blood and Transplant	NIHR	University of Oxford	Y, de-identified participant data, with approved proposal and 3 months after publication
	4763	Y,Y	NHS Blood and Transplant	European Union, NHMRC (Aus), HRC (NZ), CIHR (Canada)	UMC Utrecht	Y
	>20,000	Y,Y	American Red Cross, American Association of Blood Banks, The Fight is In Us	BARDA, NIH	Mayo Clinic	Y, Limited, de-identified data sets available in research data repository and shared under controlled access procedures
	464	Y	Hospital study sites	Indian Council of Medical Research (ICMR)	Indian Council of Medical Research	Y, deidentified participant level data available upon written request with a proposal
	332	Y	Not stated	Research Council of the Hospital Italiano de Buenos and participant institutions (no external funding)	Hospital Italiano de Buenos Aires	Not stated
	921	N	Canadian Blood Services, Héma-Québec (Canada sites); New York Blood Center (US sites)	CIHR Health systems Foundations Canadian Blood Services, Héma-Québec	Hamilton Health Sciences Corporation	Y De-identified individual patient data available upon request if use is concordant with existing REB approvals
	593	N	Grifols (H-IgG) The Fight Is In Us	NIAID/ NIH INSIGHT Network	University of Minnesota	N

and Infectious Diseases; NIH=National Institutes of Health; NIHR=United Kingdom National Institute of Health Research; NHMRC=Australian National Health and Medical Research Council

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counterpoint. Our analysis constructed 6 themes that characterized this group of high-profile clinical studies, which collectively suggest alternative approaches to pharmaceutical industry dominance within clinical research and drug development. The themes are:

1. How research agenda-setting can contribute to equity-oriented health policies;
2. How the values underlying prioritization of clinical research affects the stewardship of health system resources and production of meaningful research results;
3. The primacy of relationship building and trusted networks for mobilizing research networks and capacity building;
4. Understanding the vital role of the public sector for clinical research funding, capacity, and infrastructure;
5. The tensions among transparency, open science, and science hype;
6. The challenges of mitigating political exploitation within public sector clinical research.

Each theme presents key tensions for equitable, accessible drug development that require future research and policy deliberation, which we pursue in the Discussion.

"A Most Equitable Drug": When Access and Affordability Drive Research Agendas

Interest in convalescent plasma rose because of its perceived availability, accessibility, and affordability, as this therapy could be sourced from amongst countries' own populations. Proponents characterized convalescent plasma as an equitable, stop-gap measure while vaccines and other treatments were under development. For example, during early 2020, two influential scientists, Arturo Casadevall, a professor of immunology at Johns Hopkins University, and Liise-anne Pirofski, the Chief of Infectious Disease at the Albert Einstein College of Medicine published high-profile op-eds advocating the promise of convalescent plasma as a rapidly scalable and accessible treatment for COVID-19, and calling for controlled clinical trials to determine efficacy.[29] They also seeded the idea of convalescent plasma programs to ramp up supply, emphasizing the need for key infrastructural elements to ensure recruitment of donors, safety, and quality assurance in donation collection, and regulatory oversight.[30]

The thinking around convalescent plasma as a tried and true therapy echoed among scientists worldwide who noted not only its relative safety and availability, but also, unlike other vaccines or treatments, its relative accessibility and affordability.[31] For example, scientists at the Indian Council of Medical Research (ICMR) examining promising treatments in early April 2020 characterized convalescent plasma as, "a century old friend, tried and tested every time humanity faced a dangerous pathogen."[32] They decided to pursue a trial of convalescent plasma because "unlike all other new treatments which were in uncertain supply, it could be the most equitable drug."[33]

Convalescent plasma thus emerged as a promising therapy, but one without a commercial manufacturer, avoiding issues and complex negotiations around acquisition, pricing, and reliable supply. For example, the United Kingdom (UK) Department of Health and Social Care tasked the therapeutics subcommittee of the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG), a standing expert committee,

> Please will the independent scientists help us come up with a shortlist of compounds it would be sensible to evaluate if possible during the early phases of a UK pandemic. We need a quick answer from a simple trial such that we can then turn our attention to using successful therapies in a widespread way.[34]

The following week, the NERVTAG therapeutics subcommittee made recommendations, prioritizing drugs for acquisition by the Department of Health and Social Care which were currently licensed, widely available, with good safety profiles, and giving weight to therapies with stronger levels of evidence of human efficacy.[35] Among several therapies, they recommended convalescent plasma or hyperimmune serum. While convalescent plasma was not currently available, the group noted the ability and readiness of the publicly funded blood service through the National Health Service.[36]

Through crafting a time-sensitive pandemic response, clinical trial processes located within the public sector could prioritize equity-oriented considerations such as accessibility, availability, and affordability. Further, promising therapies could also be prioritized in the context of wider public health infrastructure such as blood services capacity.

Gaining Priority Status: How Values Drove The Research Approach

In the early weeks of the pandemic, governments sought to rapidly prioritize efforts to identify and evaluate treatments to streamline and conserve health system resources. However, different values appeared

The Journal of Law, Medicine & Ethics, 52 (2024): 80-97.

https://doi.org/10.1017/jme.2024.51 Published online by Cambridge University Press

to guide the policy choices among study designs and the decision to prioritize particular studies. Studies of convalescent plasma thus gained priority status for different reasons — the generation of clear evidence of effectiveness in some cases and access to convalescent plasma as a treatment in others — with crucial implications for the stewardship of health system resources under pandemic conditions and the generation of meaningful research results that could guide health policies.

Prioritizing Clinical Trials

Many governments restricted access to convalescent plasma therapy to participants of clinical trials with the aim of generating clear evidence of safety and effectiveness. These decisions were guided by recognition that many studies conducted during previous pandemics such as SARS were underrecruited and failed to deliver meaningful results.[37] For example, at the first meeting of the NERVTAG therapeutics subcommittee, the minutes reflected the "strong view" that "the primacy and importance of getting a meaningful result from clinical trials is the number 1 priority" as opposed to considering non-clinical trial, salvage, compassionate, or other unlicensed use of therapeutics.[38] Among the three key national trials that the National Institute of Health Research (NIHR) and National Health Service gave priority status were REMAP-CAP (the Randomized, Embedded, Multifactorial, Adaptive Platform trial for critically ill patients) and the RECOVERY trial (Randomized evaluation of Covid-19 therapy). Subcommittee meeting minutes reflected the desire to test therapies "with simple, pragmatic design which can be started, recruited to and analyzed quickly," to "design whatever we can make fit best," that "all parties hold fire on their own research projects and get behind central initiatives" and that they had "<6 weeks."[39] Similarly in Argentina, on the 18th of April 2020 the Ministry of Health of the Nation launched a new Single Registry of Clinical Trials to centralize and create a clearinghouse for sharing results among all trials in both the public and private sphere.[40]

Prioritizing Access

The US favored a different set of priorities, which included maximizing access to convalescent plasma as a therapy and establishing a safety profile. The US Food and Drug Administration (FDA) thus permitted the use of convalescent plasma through an Emergency Access Program, in addition to use within clinical trials.[41] The primary aims of the Emergency Access Program, as a large-scale observational study, were to provide access and establish a safety profile among hospitalized patients with severe or life-threatening COVID-19, though it also aimed to assess a dose response.[42] With the priority of access, an additional goal of the Emergency Access Program was to establish, standardize, and qualify the supply chain for convalescent plasma into the US, in line with its promise as a "rapidly available" treatment.[43] The investigators, a priori, intended to create a control comparator group within the context of the Emergency Access Program [44] but despite planning trials, sites opted to enroll as part of the observational study and did not randomize participants into treatment and control arms as the "vast majority" of study sites "had no infrastructure or experience with clinical trials, and wouldn't be expected to run them."[45] By August 2020, the Mayo Clinic Emergency Access Program had reached massive proportions, enrolling 2,232 sites, 13,019 physicians, and 105,717 patients, and had conducted 94,287 transfusions.[46]

Sharing Within Trusted Networks: The Importance of Being Connected

The convalescent plasma trials were designed, approved, and implemented at unprecedented speed, sometimes going from design to first enrollment in a matter of weeks (see **Table 2** for a timeline of events). Investigators credited the importance of global networks of colleagues and friends in facilitating this mobilization, which resulted in the rapid and wide sharing of clinical trials resources including various protocols, which were adapted to local contexts.

Following publication of their op-eds, Casadevall and Pirofski disseminated these ideas through global networks of friends and collaborators. In the US, on March 21st, Michael Joyner, a physiologist and anesthesiologist with an NIH-funded lab focused on exercise physiology at the Mayo Clinic, and self-identified friend of Arturo Casadevall, organized a conference call of physicians and scientists; this was the first meeting of the National Convalescent Plasma Project (CCPP19):

> A group of colleagues who were already connected through friendships and common interests, instantly recognized the promise and importance of examining whether this mode of treatment might work in COVID-19 and reached out to other colleagues in virology, transfusion medicine, epidemiology, clinical trials and several other disciplines to move these ideas forward.[47]

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Dr. Casadevall went on to chair the CCPP19, while Drs. Joyner and Pirofski served as members of the 7-person leadership team. Dr. Casadevall also helped to seed the idea of convalescent plasma internationally. In the early weeks of the pandemic, he worked with colleagues at Johns Hopkins to connect with clinicians, researchers, and regulators around the world to develop generic treatment, donation, ethics, and regulatory protocols that could be adapted to local settings "in a marathon of selfless, round-the-clock work toward an urgent common goal—to overwhelm and crush the COVID-19 virus."[48]

Table 2
Timeline of key events

Timelines
2020
February **8 –** First patients to receive convalescent plasma for treatment of COVID-19 in China **12 –** ChiCTR2000029757 trial registered with Chinese Clinical Trial Registry **14 –** ChiCTR2000029757 trial recruitment begins
March **3 –** Wuhan Blood Centre convalescent plasma donor recruitment pilot program begins **4 –** Takeda announces intention to develop hyperimmune immunoglobulin (H-IgG) to US Congress **11 –** WHO declares global pandemic **13 –** Editorial on convalescent plasma published in the *J Clinical Investigation* **19 –** UK RECOVERY trial registered with EU clinical trials registry; recruitment begins **19 –** UK NIHR suspends nearly all clinical research to prioritize COVID-19 studies **21-24 –** First meeting of the US national convalescent plasma project (CCPP19) **24 –** US FDA invites applications for investigational new drug (IND) protocols for convalescent plasma **27 –** ChiCTR2000029757 recruitment ends prematurely due to no new infections
April **1 –** Initial IND for the convalescent plasma Emergency Access Program submitted to US FDA by Mayo Clinic **2 –** US FDA approves Emergency Access Program and IND **3 –** FDA announces National Emergency Access Program initiated through the Mayo Clinic **6 –** Announcement of industry collaboration to develop and evaluate H-IgG for treatment of COVID-19 **7 –** FDA releases **"**Investigational COVID-19 Convalescent Plasma: Guidance for Industry" **12 –** Drugs Controller General of India approves protocol for PLACID trial; Indian Council of Medical Research launches call for intent for the study **15 –** Canadian CONCOR trial registered with ClinicalTrials.gov **19 –** REMAP-CAP immunoglobulin therapy domain-specific protocol approved **21 –** PLACID trial registered with ClinicalTrials.gov **22 –** PLACID trial begins recruitment across 39 trial sites
May **7 –** CoVIg-19 Alliance announces ITAC, an NIH-funded trial of H-IgG **14 –** RECOVERY trial adds convalescent plasma as a treatment under evaluation **14 –** Canada's CONCOR trial of convalescent plasma begins recruitment **26 –** Launch of national US campaign "The Fight Is In Us" to drive plasma donation **28 –** PlasmAr trial in Argentina enrolls first patient
June **2 –** Delhi opens the first public plasma bank in India **3 –** RECOVERY trial administers convalescent plasma to first participant, a child **3 –** Results of ChiCTR2000029757 published online in *JAMA* **11–** Grifols starts production of H-IgG in preparation for ITAC trial **11–** Early safety evaluation of convalescent plasma administered through Mayo Clinic Emergency Access Program published in the *J Clinical Investigation* **27 –** Indian Government updates Clinical Management Protocol for COVID-19 to include convalescent plasma as an investigational therapy

The Journal of Law, Medicine & Ethics, 52 (2024): 80-97.

https://doi.org/10.1017/jme.2024.51 Published online by Cambridge University Press

The generic convalescent plasma trial protocol reached Argentina, which had a high burden of COVID-19 disease, an early first wave,[49] and a specific historical experience with convalescent plasma in the 1970s as an effective treatment for Argentine Hemorrhagic Fever.[50] Laura Bover, an Argentine-American researcher and Director of the Monoclonal Antibodies Laboratory of the MD Anderson Center of the University of Texas, contacted her "network of friends in Argentina" to discuss the idea of a trial after witnessing the implementation of the protocol in the US.[51] This network of friends then grew into a team of more

Table 2 (continued)

Timeline of key events

Timelines
2020
July **19 –** Full safety evaluation of convalescent plasma administered through Mayo Clinic Emergency Access Program published in *Proceedings of the Mayo Clinic*
August **20 –** Convalescent plasma Emergency Access Program based at Mayo Clinic ends enrolment **23 –** US FDA issues Emergency Use Authorization for convalescent plasma **27 –** PlasmAr trial in Argentina concludes recruitment
September **8 –** PLACID trial preprint published, followed by national media coverage **24 –** ITAC NIH trial registered on ClinicalTrials.gov
October **8 –** ITAC NIH trial of H-IgG enrolls first patient **22 –** PLACID trial results published in *BMJ*
November **24 –** PlasmAr results published in *NEJM*
2021
January **15 –** RECOVERY trial closes enrolment for convalescent plasma arm on Data Monitoring Committee advice and makes public the preliminary result **29 –** CONCOR trial stops enrolment after meeting defined threshold for futility
March **10 –** RECOVERY posts preprint on convalescent plasma results
April **2 –** CoVIg-19 Plasma Alliance announces that trial did not meet its endpoint; Alliance to be dissolved
May **17 –** Indian Council of Medical Research national COVID taskforce removes convalescent plasma from Clinical Management Guidelines
September **9 –** CONCOR publishes trial results in *Nature Medicine*
2022
January **27 –** ITAC trial publishes results in *The Lancet*

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than 60 Argentine and Argentine-American researchers who organized under the name CPC-19 (Convalescent Plasma COVID-19), most of whom were affiliated with CONICET, the independent, publicly funded National Council for Scientific and Technical Research, who worked to tailor the generic convalescent plasma donation and transfusion protocols and templates for informed consent, with the hope that protocols could be implemented across Argentina.[52]

Investigators of the sampled trials were highly connected individuals whose networks also included health products regulators, health system administrators, and institutional review board leadership, who facilitated review processes, priority status, and trial recruitment efforts. For example, in the UK, the RECOVERY study, whose PI also chaired NERVTAG, gained priority status (as an Urgent Public Health Research study), receiving priority consideration by the Health Research Authority and Medicines and Healthcare products Regulatory Authority and the full support of the National Health Service leadership.[53] Consequently, the RECOVERY study had gone from ideation to enrolment in less than two weeks and enrolled over 7,500 patients in the first few weeks.[54] By July 2020, approximately 15% of all hospitalized patients with COVID-19 in the UK were enrolled in the RECOVERY trial[55] and by August, RECOVERY had become the "dominant" trial in the UK. The RECOVERY platform was then expanded to form "the principal vehicle for all publicly funded phase II studies"[56] in the UK.

A Public Investment: Public Funding, Capacity Building, and Generating Infrastructure

The efforts to mobilize, implement, and scale studies of convalescent plasma relied almost exclusively on public funding and publicly funded infrastructure (Table 1). While governments took interest in transfused convalescent plasma as a potential therapy for COVID-19, the pharmaceutical industry, in parallel, sought to investigate convalescent plasma as source material for drug development. However, despite industry initiative, the clinical trial of H-IgG was also ultimately reliant on public funding, and publicly funded infrastructure. For example, Takeda, a pharmaceutical company with a line of plasma-derived products and a network of for-profit plasma collection centers in the US and Europe, announced the development of an anti-SARS-CoV-2 polyclonal hyperimmune globulin (H-IgG) to treat high-risk individuals with COVID-19[57] and a partnership with "global plasma leaders," including the pharmaceutical companies and fractionators designed to increase plasma supply.[58] A key impetus for the collaboration was the need to collaborate with public and scientific actors. The Executive VP and Head of Research at CSL Behring explained,

> In addition to pooling industry resources, we will also collaborate with government and academic efforts as a single alliance whenever we can, including important activities like clinical trials. This will make it more efficient in these hectic times for these stakeholders as well.[59]

On May 7th, 2020, the company leads christened the alliance the "CoVIg-19 Plasma Alliance," announcing expanded industry membership and a collaboration with the US National Institutes of Health (NIH) to test "the safety, tolerability and efficacy of the hyperimmune therapy in adult patients with COVID-19."[60] The clinical trial was scheduled to start in the summer of 2020 and would form the basis for a regulatory approval if successful. Sponsored by the National Institute of Allergy and Infectious Diseases,[61] the Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) phase 3 clinical trial began enrolling patients in October 2020 through the INSIGHT Network, a global, NIH-funded clinical trials infrastructure originally designed to conduct trials for treatments of HIV and subsequently, influenza.[62]

Clinical Trials Infrastructure

The speed at which governments hoped to identify safe and effective treatments for COVID-19 meant that the studies given priority status and the investigators chosen to lead these efforts were highly established in terms of clinical trials capacity, funding, and connections within the policy, academic, and clinical communities. The existence of publicly funded clinical trials infrastructure enabled the rapid pivoting of existing studies and demonstrated the potential to deliver relatively rapid and conclusive results. For example, the UK NERVTAG therapeutics subcommittee identified REMAP-CAP, a randomized, factorial platform trial examining therapies for people admitted to critical care with pneumonia as having the extensive experience necessary to design, conduct, and report clinical trials that enroll patients who are severely ill[63] and an existing global research infrastructure that facilitated acquisition of approvals, ethics review, and research implementation.[64]

The PLACID trial in India also provided the impetus for national capacity-building around clinical trials. Following protocol approval, the ICMR launched

The Journal of Law, Medicine & Ethics, 52 (2024): 80-97.

https://doi.org/10.1017/jme.2024.51 Published online by Cambridge University Press

a call for letters of intent for participation as trial sites and received 99 applications.[65] The lead investigators explained that their instinct was to implement the study protocol at a "few elite centres of repute," but questioned

> Would it be equitable to restrict clinical trials, an important vehicle for providing access to treatment, to a few hospitals? Would it represent the reality of India, which encompasses both the urbanscapes of Delhi, as well as the rural villages of Bihar?[66]

Thus, the study authors opened recruitment to "every hospital that had the requisite infrastructure and agreed to provide treatment free of cost to all of the participants in the trial."[67] Between April 22 and July 14 464 patients were admitted across 39 heterogenous trial sites with the investigators noting the pragmatic nature of their approach given that these settings likely reflected the nature of real world care in lower- and middle-income countries. On later reflection, the PLACID trial investigators "learnt that reputed elite institutions, first world collaborations, third party organizations, or big funding are a big help if available, but they are not indispensable."[68] The inclusivity of the PLACID trial was coupled with rigorous capacity building and training efforts to ensure the integrity of data collected.

Blood Services Infrastructure

The injection of public funding and resources into convalescent plasma trials served to generate the development of infrastructure for clinical trials, but also public health: in this case, blood services. Among the key conditions outlined by proponents of convalescent plasma at the outset[69] was the availability of a population of plasma donors and the infrastructure to collect and test convalescent plasma donations. In countries with a national blood service, such as Canada and the UK, these institutions mobilized their marketing, outreach, and other resources to collect and distribute convalescent plasma. In countries without national blood service operators, the trialists first relied on the participating study sites to recruit from their own recovered patient population.

However, the interest in convalescent plasma — both within and outside of clinical trials — sparked the development of novel blood services infrastructure. In 2020, the first plasma bank opened in New Delhi based out of the Institute of Liver and Biliary Sciences, an autonomous institute of the National Capital Territory of Delhi.[70] Similarly in Argentina, historically, blood donation was limited and most voluntary donations are familial replacement donors, not altruistic.[71] On June 26th, lawmakers advanced a bill to create a National Programme for the Donation of Blood Plasma to the Senate; the program aimed to promote donation of convalescent plasma, in particular. The legislation, enacted August 11th, declared the collection of convalescent plasma a national public interest and created a series of incentives to encourage voluntary plasma donation such as granting two days paid leave for employees in a dependent relationship, transportation facilities to and from health centers, and an official recognition as "outstanding citizens of solidarity of the Argentine republic."[72]

In contrast, the highly decentralized and eclectic blood system in the US created conditions in which key stakeholders — the Emergency Access Program and the CoVIg-19 Alliance — were in competition for donors. Joyner, the PI of the Emergency Access Program, at one point, floated a plan to coordinate efforts so that those eligible to donate convalescent plasma for transfusion could be funneled into the Emergency Access Program and those ineligible could donate for H-IgG development — however, this did not materialize.[73] Instead, to meet growing demand for source and transfusion convalescent plasma in May 2020, the Emergency Access Program, the CoVIg-19 Plasma Alliance, Grifols, and the American Association of Blood Banks joined forces through "The Fight Is In Us," a national donor recruitment campaign, with celebrity support from the National Basketball Association and Dwayne "the Rock" Johnson and funding from The Bill & Melinda Gates Foundation, the Lasker Foundation, Microsoft, and The MITRE Corporation.[74] These high profile recruitment campaigns raised the profile of convalescent plasma as a treatment, but also created a competitive market within the context of the US blood system where donors are frequently remunerated, resulting in reports of dubious recruitment practices.[75]

Transparency and Science by Press Release

Sampled convalescent trials were characterized by a high degree of transparency, thus, we were able to analyze a wide range of study documents that were made publicly available. The transparent approach had an instrumental dimension in terms of building relationships and capacity among prospective sites and investigators. For example, the authors of the PLACID trial emphasized, above all, the primacy of relationships and a focus on capacity building, training, and respect for local health systems. They attributed this model to a grounding in trust and transparency: "As in other

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areas of life, generating evidence is also best done by fostering trustworthy relationships — with effective communication, clear ownership, and teamwork at their heart."[76]

Transparency around dissemination of study results, justified by the desire to impact care of people ill with COVID-19 in near real-time, were at times criticized as science by press release, due to the speed with which major policy decisions were taken based on these media releases of interim study data, without publication or sharing of trial data. Speaking about the release of preliminary results related to steroids in the RECOVERY trial, a lead investigator told *Science*, "It's very, very rare that you announce results at lunchtime, and it becomes policy and practice by tea time, and probably starts to save lives by the weekend."[77] The urgency of the pandemic crisis, the media savviness of trialists and sponsors, and rapid and highly public forms of dissemination of interim or preliminary study results brought a great deal of transparency, "global recognition" and "intense scrutiny."[78] However, public availability of de-identified patient-level data sets, analytic code, or full results often followed months or years later (Table 1), meaning that truly open science in terms of traceability or replicability was secondary to rapid knowledge mobilization.

The findings of this case study thus add to growing challenges of the dominant discourse that drug research and development is best conducted by the private sector. For example, in the development of a vaccine against Ebola, the pharmaceutical company credited with developing the vaccine did not make any progress until public funds were made available; thus, the vaccine was in fact a product of the combined efforts of government funding and publicly funded institutions.

When Public Support is Vulnerable to Political Exploitation

While all science is political in that it involves normative, social processes related to prioritization, allocation of resources, and power relations, the sampled studies illustrated the vulnerabilities of public sector clinical research to political exploitation. As governments sought to address the global pandemic emergency, convalescent plasma became a high-profile, and promissory treatment, attracting the attention of politicians seeking solutions to the COVID-19 pandemic. For example, convalescent plasma studies attracted the particular attention of then-President Donald Trump and his administration, who sought to frame the Emergency Access Program through the Mayo Clinic as a Trump-led, life-saving initiative.[79]

Politicians' promotion of convalescent plasma therapy in the media was in part responsible for prompting "unrelenting demand" of a scarce resource.[80] For example, the Delhi Health Minister, the first in the country to set up a plasma bank, refuted the ICMR's decision in November 2020 to remove convalescent plasma from the national treatment guidelines following publication of the PLACID study results, reporting to the media that the

> Delhi government has done a lot of work on [convalescent plasma] and we took permission for trial runs, in any case. More than 2,000 people have been administered plasma in Delhi. I myself survived because of plasma therapy.[81]

Politicians' interest in providing widespread access to a promising therapy also threatened the recruitment efforts of clinical trials globally as people could readily access convalescent plasma outside of clinical trials. Recognizing this threat, in early April 2020, the UK NHS and Chief Medical Officers of Health sent out letters to all NHS clinicians urging trial participation, explaining "Use of treatments outside of a trial, where participation was possible, is a wasted opportunity to create information that will benefit others."[82] Similarly, Canadian scientists with the CONCOR trial emphasized the need to prioritize clinical trials efforts to determine safety and efficacy. In the closing remarks of a presentation on August 25th, 2020, the lead scientists concluded that convalescent plasma is a "promising therapy. We are trying to figure out if it works. Ignore everything coming out of the US." They noted that

The Journal of Law, Medicine & Ethics, 52 (2024): 80-97.

https://doi.org/10.1017/jme.2024.51 Published online by Cambridge University Press

> In some countries COVID-19 is becoming politicized. It shouldn't be politicized. It's a medical treatment. Listen to the scientists. Keep Canada out of the political nightmare and stick to the science. Focus on the science. Do the trials. Get answers for Canadians.[83]

By early 2021, the trials in India and Argentina had published their results,[84] and those in Canada and the UK had ended recruitment, noting that trials had reached their defined thresholds for futility and that preliminary analyses had found no significant difference between the treatment and control groups.[85] Finally, the CoVIg-19 Plasma Alliance announced on April 2, 2021 that the NIAID-funded clinical trial (ITAC) did not meet its endpoints; they also reported no serious safety signals were raised.[86] The findings of no benefit were further confirmed through systematic reviews and meta-analyses,[87] and reflected in the ramping down of convalescent plasma donor recruitment programs. Originally envisioned as a stopgap or prophylactic measure, the clinical utility of convalescent plasma was clarified in some respects, though the question of its use as an equitable treatment in future pandemics — including among outpatients, the elderly, the immunocompromised, and those with early stage and mild disease — remains open.[88]

Discussion

This purposive sample of prominent, public-facing, trials of convalescent plasma as a treatment for COVID-19 offer important insights into the dynamics of clinical trials when public actors, including funders, independent scientific advisory groups, government-funded researchers, and institutions such as blood service operators lead and have a substantial place within the process of catalyzing, evaluating, and disseminating health technology innovations. Though these studies of convalescent plasma do not necessarily represent deliberate efforts to develop and implement alternative models for biopharmaceutical research and development, they can be analyzed with attention to that potential. Thus, the findings of this case study point to the nature of public sector innovation and its impact, which should be conceived in the context of wider infrastructure and capacity building developments.[89]

As part of a wider array of efforts to find treatments and vaccines for COVID-19, clinical studies of convalescent plasma and hyperimmune immunoglobulin represented a facet of a mission-oriented approach[90] on the part of governments to address the public health crises posed by the COVID-19 pandemic. In setting a clear direction for efforts to address the anticipated, intense strain that the pandemic would put on health systems, governments could prioritize public health interests,[91] identifying convalescent plasma as a priority candidate therapy because of its perceived availability, versatility, scalability, and affordability.[92] This case study also illustrates the ability of public sector actors to take on risk in terms of health innovation—the trials of convalescent plasma and hyperimmune immunoglobulin could produce negative results, and even in the instance of public-private partnerships (e.g. the ITAC trial), the public sector took on the risk of funding, conducting, and disseminating the clinical trial.

The findings of this case study thus add to growing challenges of the dominant discourse that drug research and development is best conducted by the private sector.[93] For example, in the development of a vaccine against Ebola, the pharmaceutical company credited with developing the vaccine did not make any progress until public funds were made available; thus, the vaccine was in fact a product of the combined efforts of government funding and publicly funded institutions.[94] Further, analysis of the development of the *r*VSV-ZEBOV Ebola vaccine suggests that sole reliance on the private sector for commercialization precluded exploration of alternative pathways to vaccine development and may in fact, have slowed progress. In contrast, the rapid proliferation of rigorous, publicly funded studies of convalescent plasma within the context of diverse national contexts, including diverse regulatory, blood services, and health systems, suggests that public sector innovation can be both expedient and experimental.

Public sector innovation can provide an important counterpoint to the secrecy and proprietary practices of industry-led innovation,[95] illustrated through the transparency of sampled trials and the high degree of sharing within personal and professional networks. However, mission-oriented innovation to address complex public health challenges also requires multiple competing solutions, bottom up experimentation, and public sector capacity characterized by diversity of expertise and skills.[96] The dissemination of generic trial protocols and mobilization of networks of friends, while facilitating rapid development and implementation of rigorous protocols, may have benefited from greater diversity in terms of approach or multi-national collaboration to avoid duplication of effort. Sampled studies were led by highly established individuals who were well connected and influential with policymakers, regulators, the health system, and academia, and represented low risk investments in terms of expertise, skills, and access to resources to

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conduct studies of this magnitude under crisis conditions. Thus, efforts to diversify expertise, skills, and capacity within scientific advisory bodies, clinical trials networks, health research funders, and health system administration need to occur in preparation for the next public health crisis. Public sector innovation offers the opportunity to develop models of knowledge governance that is transparent, open, and premised on sharing in the public interest,[97] however, this case study suggests the need for governance mechanisms that work across national contexts to facilitate prioritization, allocate scarce resources, and avoid duplication of effort globally.

In the search for an equitable and accessible treatment for COVID-19, the clinical trials of convalescent plasma generated knowledge of optimal clinical use, allowing conservation of a scarce and valuable public resource, i.e., convalescent plasma. However, these studies also served to strengthen the wider public health infrastructure. For example, in several contexts, national interest in convalescent plasma prompted the development of blood services infrastructure including a legislative framework and plasma program development. The importance of established clinical trial networks and infrastructure, as illustrated by REMAP-CAP and the INSIGHT Network, also suggests the importance of building public sector capacity,[98] and demonstrated versatility and the ability to rapidly pivot under emergency conditions toward public health priorities, including partnering with industry where applicable.

These studies also shed light on the complicated politics of evidence and the challenges to scientific rigor, trust in health institutions, and ability to address public health problems in a context where clinical trials are vulnerable to political exploitation. The public-facing aspects of these studies suggests a new era for transparency and a democratization of clinical research, with updates released via social media and preprints. However, these forms of transparency also lent themselves to scientific hype, to the detriment of several efforts to evaluate convalescent plasma within the context of an RCT, and do not fulfill the goals of open science in terms of traceability and replicability. This underscores the need to think through new forms of knowledge governance for public sector innovation that ensure transparency, but also accountability and scientific independence.

Strengths and Limitations

While illustrative of a range of ways that trialists conducted studies of convalescent plasma during COVID-19, as a purposive sample and qualitative study, this case is not representative. This study was limited in terms of its reliance on publicly available documents and thus, key developments, decisions, or processes may not have been publicly documented. We sought to analyze the processes related to how convalescent plasma would be allocated, data sharing agreements, and intellectual property arrangements. However, given that these studies found convalescent plasma was not effective, these kinds of considerations did not arise in the sampled documents. Despite these limitations, this case study suggests the importance of studying the dynamics of public sector-led clinical trials for the possibility of rigorous knowledge and infrastructure creation in the public interest.

Conclusion

Global efforts to evaluate the safety and effectiveness of convalescent plasma as a treatment for COVID-19 can be analyzed as a form of public sector innovation given that they were predominantly funded, designed, conducted, and disseminated by public and health system actors. Characterized by an open science approach, efforts to build clinical trials and blood services capacity, and a high degree of collaboration, these trials provide insights into the nature and value of innovation when pursued in the interest of public health. Through an in-depth, document-based case study of convalescent plasma, we abstracted key insights to enhance the likelihood of success of future models of biopharmaceutical production, designed in the service of ensuring equitable access to biopharmaceuticals, should the political will and financing to support such models someday follow.

Note

Availability of data and materials: Supplementary File 3 contains a full catalogue of sampled data sources.
Competing interests: QG, CC, RA, and KH declare no conflicts of interest. From 2018-2023 MH was a member of the Patented Medicine Prices Review Board (PMPRB), Canada's national drug pricing regulator, and received honoraria for his public service. The PMPRB had no role whatsoever in the design or conduct of the research, or the analysis and writing of this manuscript.
Funding: This work was funded by the Social Science and Humanities Research Council (SSHRC) of Canada through a Partner Engage Grant and the MITACS Accelerate Program in partnership with Canadian Blood Services. MH holds funding from the Canadian Institutes of Health Research (CIHR PJT 156256) and has been awarded a chair in Applied Public Health, which is funded by the CIHR and the Public Health Agency of Canada.
Authors' contributions: QG, KH, and MH conceptualized and designed the study. QG acquired funding and provided supervision. QG, CC, KH, and RA performed document sampling, and data collection. All authors performed data analysis. QG drafted the manuscript. All authors performed data analysis, read, and approved the final manuscript.

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